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Vestibular Migraine and Related Syndromes

Springer

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*To my wonderful wife and to my three
smashing children who make my life serene;
to my parents who gave me the life.*
                                    Bruno Colombo

*To all "friends" who dedicated their time to
the project; my gratitude for their efforts
cannot adequately be expressed.*
                                    Roberto Teggi

Foreword

Migraine is the more frequent neurological disorder, comprising nearly 20 % of outpatient neurological visits, even if worldwide prevalence of chronic disabling migraine is about 1 %. Migraine is characterised by recurrent attacks of headache associated to variable symptoms, including vertigo. Vertigo and dizziness may be associated to migraine in different ways. Vertigo may be the key manifestation of a basilar migraine, it can be an equivalent of migraine, particularly in young subjects, it may be the expression of a higher susceptibility to motion sickness in migraine patients or it may simply reflect the occasional co-occurrence of two frequent neurological disorders, migraine and central or peripheral vestibular pathologies. Quite recently, after long discussions among experts, the term "vestibular migraine" has been proposed to describe a condition where manifestations of vestibular dysfunctions are caused by migraine, constituting a special type of aura.

This book has the great merit to be the first to drive the reader through the different aspects of this new variant of migraine. Some of the major international experts of migraine and vestibular pathologies contribute to delineate epidemiological aspects, pathophysiological characteristics, clinical findings, diagnostic tests and possible treatments. Some chapters dedicated to conditions that may simulate vestibular migraine or share some aspects are of great help in defining the borders of this new pathological entity. To objectivate brain functional changes associated to migraine manifestations, it is fundamental the differential diagnosis from psychiatric manifestations. Different techniques, including electroencephalography, magnetoencephalography, evoked potentials and transcranial magnetic stimulation, have revealed an increased cortical excitability to be of great importance in group studies, unfortunately not really useful in individual patient classification. Finally, the increased importance of neuroimaging is recognized by a chapter dedicated to the contribution of conventional and new magnetic resonance techniques both for the differential diagnosis and for the understanding of the pathophysiology of migraine and related manifestations.

The topic of the book represents a rapidly evolving area, and what is known is widely overcome by the still undefined aspects. Nevertheless, I think that this book should be read by all neurologists and otolaryngologists because

manifestations of vestibular disorders are among the more difficult to correctly diagnose, and as a consequence an adequate treatment is frequently lacking.

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Contents

Migraine: Pathophysiology and Classification

Bruno Colombo

Migraine is a very frequent episodic and reversible primary brain disorder, characterized by recurrent attacks of head pain associated with autonomic nervous system dysfunction [1]. As a form of sensory processing disturbance, mechanisms of migraine could be interpreted as a maladaptive behavioural response to stressors, affecting a genetically determined migraine threshold.

Migraine is one of the most 20 disabling diseases, according to the World Health Organization Ranking. In the Global Burden of Disease study 2010, among 289 classified diseases, migraine was defined as the seventh disabler in terms of years of life lost to disability [2]. One billion people are suffering from migraine, indicating this entity as a major public health concern. Migraine is a very important health problem with relevant costs to economies all over the world (i.e. 18.5 billion/year Euros in Europe, with an annual cost per patient estimated at more than 1,200 Euros) [3]. Costs are mostly indirectly related to reduced productivity and missing days at work. Disability associated with migraine is related to its severity: areas of functioning particularly affected are participation in society, self-care, relationships with family members and others. Psychosocial difficulties are associated to migraine, with a significative impact on mental and physical health, vitality, emotivity and social functioning. Migraine prevalence increased as household income decreased, for both females and males. Despite significant efforts in education, migraine remains an underdiagnosed disturbance.

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1.1   Classification

Migraine is classified according to the gold standard of the International Headache Society (IHS) criteria. A third classification of the International Classification of Headache Disorders (ICHD) is close to being final. This classification is a reliable resource for a correct diagnostic approach, for both medicine practitioners and headache specialists. In 2013, a beta version (ICHD-3 beta) was published in a special number of the international journal *Cephalalgia* ahead of the final version [4]. The aim is to synchronize ICHD-3 with the World Health Organization's revision (11th) of the International Classification of Diseases (ICD-11). This classification is well advanced, and congruence between ICD-11 and ICHD-3 beta is to be ensured.

Classification could be useful in many aspects, particularly for research purposes or if a diagnosis is uncertain. ICHD-3 classification is hierarchical: in general practice, only the first- or second-digit diagnoses are applied. In headache clinics or in specialist practice, a diagnosis at the fourth- or fifth-digit level is used. Each distinct form of headache that the patient has should be separately diagnosed and coded. More than one diagnoses is possible (e.g. 1.2 migraine with aura and 2.1 infrequent episodic tension-type headache). The diagnoses have to be listed in order of importance. To receive a specific headache diagnosis, the patient must, in particular cases, experience a minimum number of attacks. This number is specified in the diagnostic criteria, i.e. five attacks for migraine without aura. The type of headache to be diagnosed must fulfil a number of other requirements listed within the criteria under separate letters. Some letter headings are monothetic (single requirements), whereas others are polythetic (i.e. two out of four specific listed characteristics). Several diagnoses are coded in the appendix of ICHD-3 beta, because of incomplete evidence for their existence. The appendix is basically for research purposes, helping specialists in study orphan entities. The primary goal of the appendix is to present criteria for a number of novel entities that have not been definitely validated by research publications concluded so far. Better scientific evidence must be presented in the next future before these entities can be formally accepted. It is possible that some disorders now in the appendix will move into the main classification (i.e. vestibular migraine). Migraine is basically classified as "without aura (1.1)" or "with aura (1.2)" depending on the presence of transient focal neurological symptoms usually preceding or sometimes accompanying the head pain. They are usually manifested as visual, sensory or speech/language symptoms (but no motor weakness). When a patient fulfils criteria for more than one subtype of migraine, all subtypes should be diagnosed and coded. A patient who has very frequent attacks without aura but also some attacks with aura has to be coded as 1.1 migraine without aura and 1.2 migraine with aura. Migraine without aura was previously described as "common migraine" or "hemicrania simplex". Migraine with aura was previously classified as "classical migraine", "ophthalmic migraine", "complicated migraine" and "migraine accompagnèe". A number of patients have "typical aura without headache" (1.2.1.2): in this form, aura is neither accompanied nor followed by headache of any sort. Patients with aura symptoms localizing a brainstem origin are coded as 1.2.2 "migraine with brainstem aura", but they frequently have additional typical aura symptoms. This entity was

Table 1.1 Migraine without aura: diagnostic criteria and comments

A	At least five attacks fulfilling criteria B–D
B	Headache attacks lasting 4–72 h (untreated or unsuccessfully treated)
C	1. Unilateral location
	2. Pulsating quality
	3. Moderate or severe pain intensity
	4. Aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)
D	During headache at least one of the following:
	1. Nausea and/or vomiting
	2. Photophobia and phonophobia
E	Not better accounted by another ICHD-3 diagnosis

Data from the International Classification of Headache Disorders, 3rd edition, beta version 2013

previously defined as "basilar artery migraine" or "basilar-type migraine". There are typical aura symptoms in addition to the brainstem symptoms during most attacks. Many patients who have attacks with brainstem aura also report often attacks with typical aura and should be coded for both 1.2.1 and 1.2.2. Patients with "Hemiplegic migraine" (1.2.3) have a particular attack with aura associated with characteristic motor weakness (lasting weeks in some patients). This type of migraine is classified as a separate subform because of a genetic basis and a specific particular pathophysiology. Familial hemiplegic migraine (FHM, 1.2.3.1) is a form of migraine with aura including motor weakness, and at least one first- or second-degree relative affected by migraine with aura including motor weakness. This form very often presents with brainstem symptoms. Rarely, disturbances of consciousness, confusion and fever can occur. Epidemiological studies have shown that sporadic cases occur with approximately the same prevalence of familiar cases [5]. Specific genetic subtypes have been identified: in FHM type 1 (1.2.3.1.1, mutations in the CACNA1A gene coding for a calcium channel on chromosome 19), in FHM type 2 (1.2.3.1.2, mutations in the ATP1A2 gene coding for a K/Na-ATPase on chromosome 1) and in FHM type 3 (1.2.3.1.3, mutations in the SCN1A gene coding for a sodium channel on chromosome 2). With 1.2.3.1.4 is coded the FHM, other loci (whereas genetic testing has demonstrated non-mutations on the specific genes listed). With 1.2.3.2 is coded the sporadic hemiplegic migraine, a migraine with aura including motor weakness, and no first- or second-degree relative affected by migraine with aura including motor weakness (no relative fulfils criteria for 1.2.3 hemiplegic migraine). Some apparently sporadic cases have known FHM mutations, and in some a first- or second-degree relative later develops hemiplegic migraine, thus completing fulfilment of the criteria for 1.2.3.1 familial hemiplegic migraine and requiring a change in diagnosis.

The main criteria for migraine are listed in Tables 1.1, 1.2, 1.3 and 1.4 (data from the International Classification of Headache Disorders, 3rd edition, beta version 2013).

At least five attacks are required for a definite diagnosis. If a patient has had fewer than five, attacks should be coded as affected by a probable migraine without aura (1.5.1).

Table 1.2 Migraine with aura: diagnostic criteria and comments

A	At least two attacks fulfilling criteria B and C
B	One of the following fully reversible aura symptoms:

    1. Visual
    2. Sensory
    3. Speech and/or language
    4. Motor
    5. Brainstem
    6. Retinal

C   At least two of the following four characteristics:
    1. At least one aura symptom spreads gradually over >5 min, and/or two or more symptoms occur in succession
    2. Each individual aura symptom lasts 5–60 min (when three symptoms occur during an aura, the acceptable maximal duration is 3×60 min)
    3. At least one aura symptom is unilateral (aphasia is always regarded as a unilateral symptom)
    4. The aura is accompanied, or followed within 60 min, by headache

D   Not better accounted for by another ICHD-3 diagnosis, and transient ischaemic attack has been excluded

Data from the International Classification of Headache Disorders, 3rd edition, beta version 2013

Table 1.3 Diagnostic criteria

1.2.1.2 Typical aura without migraine: *diagnostic criteria and comments*
   A.   Fulfils criteria for 1.2.1 migraine with typical aura
   B.   No headache accompanies or follows the aura within 60 min

1.2.2 Migraine with brainstem aura: *diagnostic criteria*
   A.   At least two attacks fulfilling criteria B–D
   B.   Aura consisting of visual, sensory and/or speech/language symptoms, each fully reversible, but no motor or retinal symptoms
   C.   At least two of the following brainstem symptoms:
      1. Dysartria
      2. Vertigo
      3. Tinnitus
      4. Hypoacusis
      5. Diplopia
      6. Ataxia
      7. Decreased level of consciousness
   D.   At least two of the following four characteristics:
      1. At least one aura symptom spreads gradually over 5 min and/or two or more symptoms occur in succession
      2. Each individual aura symptom lasts 5–60 min
      3. At least one aura symptom is unilateral
      4. The aura is accompanied, or followed within 60 min, by headache
   E.   Not better accounted for by another ICHD-3 diagnosis, and transient ischaemic attack has been excluded

Data from the International Classification of Headache Disorders, 3rd edition, beta version 2013

Table 1.4 1.2.3 Hemiplegic migraine: diagnostic criteria

A	At least two attacks fulfilling criteria B and C
B	Aura consisting of both of the following:
	1. Fully reversible motor weakness
	2. Fully reversible visual, sensory and/or speech/language symptoms
C	At least two of the following four characteristics:
	1. At least one aura symptom spreads gradually over 5 min, and/or two or more symptoms occur in succession
	2. Each individual non-motor aura symptom lasts 5–60 min, and motor symptoms last <72 h (in some patients motor weakness may last for weeks)
	3. At least one aura symptom is unilateral
	4. The aura is accompanied, or followed within 60 min, by headache
D	Not better accounted for by another ICHD-3 diagnosis, and transient ischaemic attack and stroke have been excluded
	1.2.3.1 Familial hemiplegic migraine: *diagnostic criteria*
A	Fulfils criteria for 1.2.3 hemiplegic migraine
B	At least one first- or second-degree relative has had attacks fulfilling criteria for 1.2.3 hemiplegic migraine

Data from the International Classification of Headache Disorders, 3rd edition, beta version 2013

In children and adolescents (aged under 18 years), attacks may last 2–72 h (the evidence for untreated durations of less than 2 h in children has not been substantiated, and attacks are more often bilateral than in adults). Location is usually fronto-temporal. Unilateral pain generally emerges in late adolescence or early adult life. Occipital headache in children is quite rare and calls for diagnostic caution.

A menstrual relationship is often evident for migraine without aura. ICHD-3 beta offers criteria (in the appendix) for A1.1.1 pure menstrual migraine and A1.1.2 menstrually related migraine.

Based on retrospective analysis, prevalence of menstrual migraine ranges from 26 to 60 % in headache clinic patients. Menstrual migraine occurs at the time of the greatest fluctuation in oestrogen levels, particularly during or after the simultaneous fall of oestrogens and progesterone. Pure menstrual migraine is defined if attacks occur −1 to +4 days of menses.

Neck pain is a quite common symptom occurring during a migraine attack. This is possible, due to the overlap and the convergence of pain processing from the trigeminal, occipital and cervical regions in the so-called trigeminocervical complex. For this reason, neck pain may trigger or worsen migraine pain, and migraine may be associated to neck pain. An erroneous diagnosis of "cervicogenic headache" is sometimes the result of symptoms misinterpretation.

Aura may begin after the pain phase has commenced or continue into the headache phase. Visual aura is the most common type of aura, occurring in over 90 % of patients with 1.2 migraine with aura, at least in some attacks. Visual auras vary in its complexity. Positive phenomena, negative phenomena or both may occur. Positive phenomena often occur first and are then followed by negative phenomena. Elementary visual disturbances include phosphenes (simple flashing), scotomata

(starting centrally and migrating—"marching"—peripherally or sometimes vice versa), shimmering or undulation in the visual field. More complex auras included fortification spectrum (an arc of scintillating lights often "C" shaped, migrating across the visual field with a scintillating edge of sometimes zigzag, flashing or occasionally coloured—from grey to purple, often only excessively bright white—phenomena). In other cases, scotomata without positive phenomena may occur. Visual distortions and hallucinations occur more commonly in children, characterized by a very complex disorder of visual perception that may include micropsia, macropsia, mosaic vision and metamorphopsia. When aura presents as distorted images, bizarre visual illusions or spatial distortions, Alice-in-Wonderland syndrome may be considered.

Paraesthesias are the second most common aura phenomenon. It infrequently occurs in isolation and usually follows a visual aura. They typically start in the form of pins and needles in the hand, migrating up the arm and then continuing to involve the face, lips and tongue.

Less frequent are speech disturbances, usually aphasic (17–20 % of patients).

Aura symptoms of these different types usually follow one another in succession, beginning with visual, then sensory and then speech abnormalities (but the reverse and other orders have been described). The typical duration of migraine aura (non-hemiplegic) may be longer than 1 h in 6–10 % of patients with visual symptoms, 14–27 % of patients with sensory disturbances and 17–60 % with aphasic aura. Considering these data, the term "prolonged aura" should be re-established in ICHD-3 as a clinically useful definition.

Premonitory symptoms may begin hours or days before the other symptoms of a migraine (with or without aura) attack in 60 % of cases. They include change in mood or behaviour, fatigue and difficulty in concentrating. In some patients, mental state may become euphoric, talkative and hyperactive. Premonitory symptoms are quite variable among individuals but rather consistent within an individual. Episodic bouts of food craving are quite common and sometimes reported as a part of "migraine complex" premonitory symptoms. They are not to be confused with the aura phase.

When aura occurs for the first time after age 40, when symptoms are exclusively negative (e.g. hemianopia) or when aura is prolonged or very short, other causes, particularly transient ischemic attacks, should be ruled out. "Late life migrainous accompaniments" were described as transient (15–25 min) neurological phenomena not associated to migraine (visual "build-up" scintillating scotoma, dizziness, paraesthesias in "march"), occurring for the first time after age of 45 years in patients with a previous history of recurrent headache. For a correct diagnosis, cerebral thrombosis and transitory ischaemic attacks have to be ruled out (Table 1.5).

Migraine attacks may start at any age, although the incidence peak is in adolescence. The 1-year prevalence of definite migraine in adults is 11 % overall (15–18 % among women, 6 % among men) [6]. The prevalence estimates are quite comparable across the world.

Several recent studies have provides estimates of migraine with aura. The weighted average 12-month prevalence rate is 4.4 %. The aggregate weighted rate

Table 1.5 Differences between transitory ischemic attacks (TIA) and migraine aura

	Migraine aura	TIA
History	Similar attacks in the past	No previous episodes
Onset	Slow evolution over minutes	Sudden (seconds)
Duration	<1 h	>1 h
Timing	Precedes or resolves before onset of typical migraine headache	Occurs with or without headache with no temporal relationship
Visual symptoms	Positive scotoma gradually enlarging across visual field. Scintillating edges	Monocular negative scotoma
Sensory symptoms	Usually in association with visual symptoms	May occur without visual symptoms May include legs Negative symptoms (limb "dead")
Headache	Migraine typically follows resolution of aura	No subsequent headache

of definite migraine in children is 10.1 % (1.6 % migraine with aura). In the past 20 years, the prevalence of migraine has been stable, whereas episodic migraine and chronic migraine remain undertreated [7]. Women are particularly prone to migraine, with different susceptibilities throughout their life influenced by hormonal (oestrogen) fluctuation. Migraine may occur in the first or second trimesters of pregnancy, but they improve as pregnancy progresses parallel with increasing oestrogen levels. About 40 % of women will report their first migraine attack during pregnancy (particularly with aura) or shortly after delivery. Migraines may worsen after delivery as oestrogen levels dramatically drop. The burden of disease may increase in severity and frequency at the onset of perimenopause, but migraine generally lessens after menopause being rare in elderly women [8]. Among all putative triggers (other than sex hormones), stress is the most quoted and food is the second reported cause. The common lists of food triggers include tyramine-containing foods (bananas, avocados, smoked fish, aged cheese as Camembert, red wine), nitrate-containing foods (salami, hot dogs and bacon), monosodium glutamate (soy beans and sauce, pickled and marinated foods) and histamine (especially in seafoods).

However, significative scientific evidence (based on controlled trials) linking consistency of diet with clear improvement in migraine is extremely poor and limited.

Patients who are affected by 1.1 migraine without aura or 1.2 migraine with aura may have episodic syndromes associated with migraine. Although historically noted to occur in childhood (previously used terms were "childhood periodic syndromes"), they may also be diagnosed in adults. Other conditions that may also be associated in these patients include episodes of periodic sleep disturbances (sleep talking, sleepwalking, bruxism and pavor nocturnus) and motion sickness.

Episodic syndromes that may be associated with migraine are classified as (a) 1.6.1 recurrent gastrointestinal disturbance, (b) 1.6.1.1 cycling vomiting syndrome, (c) 1.6.1.2 abdominal migraine, (d) 1.6.2 benign paroxysmal vertigo and (e) 1.6.3 benign paroxysmal torticollis.

Recurrent gastrointestinal disturbance may be associated with migraine. It is characterized by episodic attacks of abdominal pain and/or discomfort, nausea and/

or vomiting, occurring infrequently, chronically or at predictable intervals, with normal gastrointestinal examination.

Abdominal migraine is diagnosed mainly in children and is characterized by recurrent attacks of abdominal pain lasting 2–72 h. Pain is described of moderate or severe intensity (interfering with normal daily activities) with midline or periumbilical location and dull or sore quality. During attacks, at least two symptoms have to be present (anorexia, nausea, vomiting, pallor). Most children with abdominal migraine will develop a definite migraine (with or without aura) later in life. Many of the migraine treatments may also be effective for abdominal migraine.

Older classifications considered "ophthalmoplegic migraine" as a particular form of migraine. It is characterized by repeated attacks of paresis of one or more ocular cranial nerves (in particular oculomotor 3rd nerve) in association with ipsilateral headache. ICHD-3 beta described this head pain as 13.9 recurrent painful ophthalmoplegic neuropathy. Diagnostic criteria are fulfilled if in two attacks the patient presents with unilateral headache accompanied by ipsilateral paresis of one, two or all three ocular motor nerves and orbital, posterior fossa or parasellar lesion has been excluded by neuroradiological examinations. The old term "ophthalmoplegic migraine" was refused because the syndrome is a recurrent painful neuropathy, with headache developing up to 2 weeks prior to ocular motor paresis. With MRI, contrast enhancement (with gadolinium) or nerve thickening can be demonstrated, and steroid therapy is useful in most of patients.

Migraine is reported to be comorbid to many pathologies, in particular other neurological disturbances (epilepsy and Gilles de la Tourette syndrome), vascular pathologies (ischaemic stroke, subclinical brain white matter abnormalities), psychiatric disturbances (depression, anxiety, panic disorder and bipolar disorder), asthma and allergies.

The natural history of migraine is not been well characterized, and the same is for prognosis. Some classical patterns are suggested, such as clinical remissions (attack-free for long periods of time), persistence (attacks continuation over years with or without changes in severity, symptoms profile and frequency) and progression (increase of both frequency and related disability in quality of life). Clinical progression leads to chronicization (2 % of migraineurs, women more frequently than men), including physiological (central sensitization) and sometimes anatomical progression (deep white matter lesions as detected by magnetic resonance imaging). Neuroimaging studies on migraine patients have suggested the prevalence of both structural and functional brain changes between migraine attacks. Severity of white matter lesions correlated with disease duration, type of migraine (with or without aura) and frequency of attacks. They are interpreted as an indirect marker of focal cerebral hypoperfusion induced by migraine attacks, particularly if repeated (i.e. in high-frequency migraine, particularly with aura). Small white matter lesions are not infrequent in both children and adolescents suffering from migraine (without prevalence in patients affected by migraine with aura compared with patients affected by migraine without aura). No relationship between brain lesions and patent foramen ovale was detected in children and adolescents with migraine. Repeated and prolonged oligaemia occurring during migraine attacks

Table 1.6   Chronic migraine: diagnostic criteria and comments

A	Headache (tension-type like and/or migraine like) on >15 days per month for >3 months and fulfilling criteria B and C
B	Occurring in a patient who has had at least five attacks fulfilling criteria B–D for 1.1 migraine without aura and/or criteria B and C for 1.2 migraine with aura
C	On >8 days per month for >3 months, fulfilling any of the following:
	1. Criteria C and D for 1.1 migraine without aura
	2. Criteria B and C for 1.2 migraine with aura
	3. Believed by the patient to be migraine at onset and relieved by triptan or ergot derivate
D	Not better accounted for by another ICHD-3 diagnosis

may affect the more vulnerable small deep penetrating arteries, while local critical hypoperfusion may lead to minor brain injury (ischaemic demyelination and gliosis) revealed as white matter lesions. Other putative mechanisms include endothelial dysfunction (activation and impaired vascular reactivity): if accompanied with platelet aggregation, this process of endothelial changes mediated by radical oxygen species (ROS) may lead to microvascular brain damage [9]. The longevity of clinical history (duration of migraine disease) is associated with increase iron deposition in periaqueductal grey, putamen and globus pallidus. Moreover, reduction in density of both white and grey matter as evaluated with voxel-based morphometry in migraineurs is dependent on both duration of disease and frequency of attacks. Results from longitudinal studies on migraine and cognitive decline consistently show that those who experience any type of migraine (with or without aura) are not at increased risk of cognitive decline. This is confirmed among people affected by migraine and high structural brain lesion load, suggesting that while migraine may be associated with structural brain lesions, the correlation with cognitive decline is lacking [10]. Although these data should provide reassuring evidence, further information are needed (attack frequency and duration) to confirm the conclusions. Risk factors for migraine progression have been supposed such as obesity, snoring and excessive use of caffeine [11] (Table 1.6).

The most common cause of chronic migraine is medication overuse (8.2 medication overuse headache). Modifiable risk factors for headache progression to a chronic form are attack frequency (modifiable with preventive treatment, both pharmacological and behavioural), stressful life events (stress management is to be considered, and psychological support is suggested), the coexistence of other pain syndromes (to be diagnosed and treated) and snoring with sleep apnoea (weight loss is suggested).

1.2   Migraine Genetics

Migraine is a familial disturbance with a strong genetic basis. Different strategies have been employed to search for a "migraine gene", considering that migraine aggregates in the family. Among migraineurs, probands with early onset or more

severe illness are more likely to have affected first-degree relatives [12, 13]. A successful approach leads to the identification of gene mutations in a rare form of migraine, the so-called familial hemiplegic migraine (FHM). As far as migraine is concerned, population-based family studies showed that the familial risk of migraine is increased. A robust contribution of genetic factors was also evident from twin studies that showed a concordance twice as high in monozygotic versus dizygotic twins [14, 15]. Nevertheless, a European study showed that environmental and genetic factors had an almost equally specific contribution [16]. Environmental factors (i.e. female sex hormones and stress) may directly trigger migraine attacks or lower the attack threshold by rendering the brain more susceptible to specific trigger factors [17]. In fact, although many chromosomal regions were identified that seem to harbour migraine susceptibility genes, no specific or exclusive migraine genes were detected. It is likely that many genetic factors are able to induce disease susceptibility together with several environmental factors. Considering classical linkage approach, migraine susceptibility loci that reside on chromosomes 4q21-q24 and 10q22-q23 seem good candidates, particularly because these loci were evaluated and detected in different studies [18–23]. Using candidate-gene association, studies did not yield clear genetic association due to methodological bias. Next-generation sequencing (i.e. whole-genome sequencing) has replaced the classical linkage approach. Gene identification possibilities have advanced in recent years, as large-scale sequencing has become available by new technique known as NGS. Despite the fact that a number of genes were discovered for the classical forms of migraine using a genome-wide association approach, these methodologies are still far from solving the problem. A meta-analysis across 29 genome-wide association studies (including more than 23,000 patients affected by migraine) was able to identify 12 loci significantly associated with migraine susceptibility. Eight of these loci are located in or very close to genes with known functions in synaptic or neuronal regulation, several exerting regulation. We know that eight genes confer an increased risk of migraine. Six of these genes are involved in specific neuronal and glutamatergic pathways, in particular MTDH, LRP1, PRDM16 and MEF2D. At a subthreshold significance, ASTN2 and PHACTR1 are also considered. Two genes are involved in the maintenance of vascular function and integrity (PHACTR1 and TGFBR2), whereas TRPM8 is responsible of pain signalling pathways [24–26]. These data confirm that a complex interrelationship between neuronal, vascular and pain modulating systems is implicated in migraine clinical expression. Nevertheless, mechanisms such as gene-environment interactions, epigenetics (DNA methylation and posttranslational modifications of the tails of histone proteins, affecting chromatin structure and gene expression) and epistasis (variant-variant interactions) have not yet been deeply investigated in migraine. For this goal, large prospective cohorts are needed, particularly to investigate the relationships between epigenetic mechanisms, migraine pathophysiology and chronification of migraine. In this holistic vision of migraine as a multifactorial disease, the interactions between genomics, proteomics and metabolomics have to be evaluated in a synergic and integrated way in order to understand the biomolecular basis of migraine.

1.3   Migraine: A Primary Brain Disorder

Despite the fact that neural events result in the dilation of blood vessels, migraine is not caused by a primary vascular event. It is in fact a form of neurovascular headache, probably resulting from a dysfunction of brainstem or diencephalic nuclei along with hypothalamic (posterior) and thalamic (ventroposteromedial) structures (subcortical aminergic sensory modulatory systems) that are particularly involved in the nociceptive modulation of craniovascular afferents. These networks influence trigeminal pain transmission and specific sensory modality processing. Migraine is probably due to an abnormal central processing of a normal signal. Migraine attacks start in the brain, as suggested by premonitory symptoms (prodromes, i.e. increased emotionality or sensory hypersensitivity) that are highly predictive of an attack in a large percentage of patients, occurring up to 12–18 h before the onset of the migraine attack. Some typical migraine triggers are sleep deprivation or oversleeping, fasting, alcohol, prolonged sensory stimulation (light, noise and smell) and stress (psychological). They may be interpreted as internal or environmental threats for brain homeostasis, and migraine attack is considered as the failure of the complex mechanism controlling an excessive individual allostatic load (the inability of the brain to modulate repeated stress challenges failing to habituate with them). Allostatic load depends on genotype, life experiences and events and lifestyle. It is demonstrated that in the intraictal period (between attacks), people affected by migraine show hypersensitivity to sensory stimuli and abnormal processing of sensory information. This results, i.e. in increased amplitudes and reduced habituation of evoked and event-related potentials [27, 28]. Although we do not completely define the cause and the events linked to migraine pain, we have to consider some major factors. They are the cranial blood vessels, the trigeminal innervation of these vessels and the reflex connections of the trigeminal system with the cranial sympathetic outflow (trigeminovascular system). The intracranial blood vessels are supplied with nerves that emanate from cell bodies in ganglia belonging to the sympathetic, parasympathetic and sensory nervous system. Sympathetic nerves arise from the ipsilateral superior cervical ganglion, whereas nerves supplying the basilar and vertebral arteries originate from the stellate ganglia and inferior cervical ganglia. Activation of these fibres lead to modulation of cerebrovascular autoregulation and vasoconstriction, with responses mediated primarily by noradrenaline and neuropeptide Y. Parasympathetic nerves arise from sphenopalatine and otic ganglia, having acetylcholine as the most important neurotransmitter.

A robust scientific background indicates that migraine headache depends on the activation and sensitization of trigeminal sensory afferents that innervate cranial tissues, particularly the meninges and their large blood vessels [29]. Surrounding both these vessels and large venous sinuses, pial vessels and dura mater are a plexus of unmyelinated fibres arising from the ophthalmic division of the trigeminal ganglion and from the upper cervical dorsal roots in the posterior fossa. The involvement of the ophthalmic division of the trigeminal nerve and the clear overlap with structures innervated by C2 explain the referred pain in migraine attack. In fact, pain is distributed over the frontal and temporal regions, as well as in parietal, occipital

and high cervical zones. In animal models, a dense network of dural nerve fibres is immunoreactive for calcitonin gene-related peptide (CGRP) and substance P (vaso-active proinflammatory peptides) [30]. In the same animal models, cranial perivas-cular fibres have central projections to the trigeminocervical complex (TCC) comprising the caudal division of the spinal trigeminal nucleus and the C1–C2 dorsal horns of the cervical spinal cord. When trigeminal ganglion is stimulated, CGRP and substance P (SP) are released. The TCC receives descending projections from the brainstem and hypothalamic nociceptive modulatory nuclei that mediate descending modulation of trigeminovascular nociceptive pathway [31].

Migraine pain may be caused by a sterile neurogenically driven inflammation in the dura mater, underlying the sustained activation and sensitization of perivascular meningeal afferents. In animal models, the activation of meningeal nociceptors in vivo leads to the release of CGRP and SP from their peripheral nerve endings. These peptides (particularly CGRP, a 37 amino acid vasoactive neuropeptide that is widely distributed in central and peripheral nervous systems in mammals) are able to induce vasodilation of meningeal blood vessels, plasma extravasation and local activation of dural mast cells (producing a long-lasting activation and sensitization of dural nociceptors). All this cascade of events leads to the release of cytokines and other inflammatory mediators in the so-called sterile inflammatory response [32–34]. Human evidence that CGRP is elevated in the headache phase of a migraine attack supports the view of an activation of the trigeminovascular system [35, 36]. The trigeminovascular system seems to be involved at the level of both the brainstem and perivascular nerves and transmits nociceptive information to the central nervous system. During a migraine attack, pain may be due to a combination of different events. Depending on a peripheral or central sensitization, pain could be caused by an altered perception of craniovascular input (i.e. not normally painful), followed by the activation of a feedforward functional neurovascular dilator mechanism specific for the ophthalmic division of the trigeminal nerve. The activation is in fact sequential, involving the second- and third-order trigeminovascular neurons and different areas of the brainstem and forebrain. Being these signalling bidirectional (descending influences to the TCC), a dysfunction in subcortical and diencephalic nuclei that modulate trigeminal nociceptive inputs (in particular the ventrolateral periaqueductal grey (PAG), pontine locus coeruleus (LC), nucleus raphe magnus and rostral ventromedial medulla (RVM)) is suspected in the pathophysiology of migraine (as mediators of pain circuitry). The thalamus has been proposed as a relay centre for handling, processing and modulating incoming sensory information [37]. The so-called pain matrix (including the thalamus as well as amygdala, primary (S1) and secondary (S2) somatosensory areas, prefrontal and anterior cingulate cortex (ACC)) is also involved in integrating and processing sensory, affective and cognitive response to pain [38, 39]. During migraine attack, this circuitry is activated, suggesting that the thalamus and the cortex are both involved in the higher level of processing of migraine pain. Recent demonstrations of altered connectivity between the forebrain/limbic cortex and brainstem nuclei reflect a possible dysfunction of the limbic system, raising the hypothesis of a coexisting altered activity of neurolimbic pain network [40]. This concept may explain the high

Table 1.7 Modular pain processing in migraine

Order	Structures
1st	Trigeminal ganglion (location: middle fossa)
2nd	Trigeminocervical complex via the quintothalamic tract: superficial dorsal lamina of the trigeminal nucleus caudalis and dorsal horns of C1–C2 cervical spinal cord
3rd	Thalamus (contralateral ventrobasal complex and medial nuclei)
4th	Aminergic modulation from dorsal raphe nucleus, periaqueductal grey and locus coeruleus/sex steroids modulation
Final	S1 and S2 somatosensory areas, prefrontal and anterior cingulated cortex, limbic cortex (activation of pain matrix and neurolimbic pain network)

prevalence of mood alterations in individuals affected by migraine. Neurolimbic influence is supposed to be bidirectional, modulating or triggering a brainstem process that promotes a migraine attack, having brainstem dysfunction the capability to alter limbic function in order to influence coping strategies and mood. Sex steroids exert a significative regulation of nociceptive pathways at multiple levels, by modulating expression of a peculiar mediator such as CGRP. The trigeminovascular system, at both functional and expression levels, is clearly modulated by sex steroids and is probably the major determinant of the well-known sexual dimorphism in migraine [41] (Table 1.7).

1.4   Current Hypothesis on Migraine

Despite the advances in knowledge of biochemical and functional aspects of migraine, the nature of mechanisms of the primary brain dysfunctions leading to migraine attack (by the activation of the trigeminovascular system) is still controversial. Furthermore, there are no currently accepted biomarkers (defined as (1) physical signs or laboratory measurements associated with a biological process having putative diagnostic or prognostic utility or (2) characteristics objectively measured and evaluated as an indicator of normal biological, pathological or pharmacological processes) for chronic or episodic migraine. One central issue is the coupling of CSD with the activation of the trigeminovascular system. Animal models support the possibility that cortical spreading depression (CSD) is able to activate trigeminal nociception and thus headache mechanisms [42].

CSD is the putative underlying mechanism of aura, or the aura is the human homologue and counterpart of the animal phenomenon (CSD) so-called by Leao in 1944. Aura may precede the migraine attacks in about 30 % of patients and in some cases occurs as an isolated phenomenon. CSD (a wave of neuronal depolarization) can be induced in animals by focal stimulation of the cerebral cortex. During the aura phase, a wave of neuronal and glial depolarization together with oligaemia passes across the cortex, starting at the occipital lobe, at the slow of 2–6 mm per minute. This oligaemia (a response to depressed neuronal function) is preceded by a short phase of hyperaemia (correlating with the visual phase of aura, i.e. flashing

lights). Oligaemia is present when the headache starts. A direct evidence of CSD has been obtained in human brain. In animal models, CSD can lead to a long-lasting activity of dural nociceptors and central trigeminovascular neurons, mediated by CGRP release from perivascular trigeminal fibres and eventual transient dilation of pial vessels. According to these data, CSD could be able to start the mechanism of migraine cascade. It is supposed that CSD is ignited by local elevations of extracellular potassium as a consequence of hyperactive neuronal circuits in the cerebral cortex [43].

In animal models, data show that CSD does not cause sustained neuronal activity in the trigeminal nucleus up to several hours after a single or a series of CSDs to the cortex. More rostral portions of the trigeminal nucleus are not activated by CSD [44, 45]. It is otherwise conceivable that metabolic changes in the cerebral cortex associated with intracellular calcium overload during CSD could be potential inducers of oxidative stress. The diffusible reactive oxygen species (ROS) generated during oxidative stress are potentially able to activate nociceptive signalling (direct and delayed indirect action) via ion channels (redox sensitive), participating in the coupling of CSD with the activation of the trigeminovascular system and release of CGRP from peptidergic nerves. Oxidative stress may spread downstream, and ROS may promote electrical firing in trigeminal neurons.

Furthermore, the causes of brainstem activation are still debatable. Is this activation just a consequence of the trigeminovascular system firing or the principal driver of migraine pathophysiology? Another possibility is that the alteration of brain state (i.e. the balance in subcortical structures-PAG and RVM-modulating sensory inputs, including trigeminal nociceptive) in terms of responses to stress and homeostatic external triggers results in activation of the trigeminovascular system (ascending pathways via the trigeminothalamic tract). Connections of the salivatory superior nucleus (SuS) with the PAG, RVM and hypothalamus may cause autonomic symptoms. This hypothesis may explain the occurrence of premonitory symptoms in preceding migraine pain outside the possible activation of meningeal receptors. This unbalance is reflected in both levels of neurotransmitters (noradrenaline and dopamine) and neuromodulators (tyramine, octopamine, synephrine) in the pain matrix, confirming the possibility of a top-down dysfunctional process starting from a hyperexcitable and hypoenergetic brain [46].

Admittedly, a specific dysfunction of the brainstem is difficult to demonstrate in patients.

An interesting proof for the involvement of brainstem nuclei in migraine comes from classical positron emission tomography studies during migraine attacks showing both an increased local blood flow in brainstem regions (pons and midbrain) and brainstem activation persisting after injection of sumatriptan [47]. These findings are consistent with the hypothesis that pathogenesis of migraine (and neurovegetative-associated symptoms) is related to an imbalance in the activity of brainstem nuclei regulating vascular control and nociception. It is still unclear whether the brainstem findings reveal an accompanying activation limiting the symptoms of migraine (PAG activity acting as a filter to inhibit the pain) or the origin of the disease. Nevertheless, the particular characteristic of "migraine brain state" suggests that a disorder of brain

excitability characterized by deficient regulation of the excitatory-inhibitory balance during cortical activity is essential for the episodic activation of migraine attack. In addition to all these intriguing lines of evidence, some observations led to the suggestion that the brain energy metabolism is abnormal in all major subtypes of migraine, both between and during the attacks. These energy metabolism deficits could cause impaired cellular ion homeostasis. As a consequence, membrane instability could be the cause of the raise of neuronal transmembrane potential, leading to hyperresponsive and more easily depolarizable neurons when the patient affected by migraine is subjected to particular triggering situations, leading to CSD. Since the metabolic abnormality of migraine extends beyond the brain (as proven with nuclear magnetic spectroscopy techniques), the possible interpretation of migraine as a mitochondrial disorder should be considered [48].

Despite the large body of scientific data regarding pathophysiology of migraine, this disease continues to be one of the most troubling disorders affecting productivity and quality of life around the world. Considering migraine as a bio-behavioural response genetically engendered to restore a disturbed homeostasis of the brain [49], some evolutionary explanations may help us to better understand the persistence of migraine in humans. Migraine could be interpreted as a defence mechanism or a result of conflict with other organism. Moreover, migraine could be the result of novel environmental factor or a trade-off between genetic harms and benefits. The migraine attack may contain behavioural elements which predispose patients to making choices whose end result reduce the susceptibility to, or provocation of, migraine [50].

Migraine is so common that it seems part of the human condition. In this integrated view, migraine is to be considered as a sort of sickness behavioural response, belonging to a physiological adaptive evolutionary conserved attitude and possibly serve the purpose of recovering the full body's homeostasis.

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Neurophysiology of Migraine

<div style="text-align:right">**2**</div>

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Clinical neurophysiological studies in migraine were initially aimed at supporting diagnosis and then, more importantly, at the characterization of the migrainous brain.

There are some recent excellent reviews on these topics [1–3], and here we will summarize and update these reports. We will consider three aspects: neurophysiological testing in migraine diagnosis, neurophysiological features of the migrainous brain and, finally, neurophysiological testing in vestibular migraine.

2.1 Migraine Diagnosis

Recently, the European Federation of Neurological Societies (EFNS) published the guidelines for neurophysiological tests and neuroimaging procedures in non-acute headache [2]. For headache in general, and more specifically for migraine, there are little evidences that neurophysiological testing is a useful support for the diagnosis.

Table 2.1 summarizes the EFNS guidelines for neurophysiological tests, but also for neuroimaging procedure, in non-acute headache [2]. It is noteworthy that the recommendation did not change from the previous guidelines published in 2004, but some of them were supported by an increased level of recommendation.

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Table 2.1 Summary of EFNS guidelines [2]

Method	Routine evaluation	Level of recommendation [4]
EEG	Recommended for basilar/hemiplegic migraine and epilepsy-related migraine	IIB
Evoked potentials	Not recommended	IIB
Reflex responses	Not recommended	IV/IIIC
Autonomic tests	Not recommended	IIIC
Clinical tenderness test and surface EMG	Not recommended for diagnosis; manual palpation useful for classification	IIB
Neuroimaging	MRI recommended in patients with trigeminal autonomic cephalalgias, atypical headache, seizures or focal signs	

2.1.1 Electroencephalography (EEG)

During the attack the background rhythm may [5, 6] or may not [7] be slowed. Some migraineurs show the "H-response", namely, an increased response to photic stimulation; however, a similar finding was reported in normal subjects [8]. The EEG still plays a valuable role when migraine shows epileptic features: unusually brief headache episodes, auras or aura-like phenomena, unusual aura symptoms and headache associated with severe neurological deficits.

2.1.2 Visual Evoked Potentials (VEPs)

The pattern reversal VEP more often proved to be normal, although amplitude could be either increased, between or close to attacks [9, 10], or decreased [11]. Increased VEP amplitudes have been reported with high contrast and spatial frequency stimuli, suggesting an impairment of the magnocellular system [12, 13]. VEP findings are very similar in migraine without and with aura [14].

2.1.2.1 Brainstem Auditory Evoked Potentials (BAEPs)
In contrast with the VEPs, the BAEPs do not originate from the cerebral cortex but from the inner ear, the acoustic nerve and from generators located within the brainstem. These same structures will be considered with more detail when we will focus on vestibular migraine. More frequently BAEPs proved to be normal [14], but a latency delay was reported in some papers [15].

2.1.2.2 Somatosensory Evoked Potentials (SEPs)
The standard SEPs obtained by electric stimulation showed very little abnormalities, but we can mention the cortical N19 latency delay and amplitude reduction reported in migraine with aura [16].

The CO_2 laser SEPs are obtained by selective stimulation of nociceptive A-delta and C fibres, and their amplitude was increased during a spontaneous [17, 18] or nitroglycerine-induced attack [19], and this increase was relieved by symptomatic treatment [20].

2.1.3   Habituation and Sensitization

Habituation consists in a reduction of a response when repeating a constant intensity stimulus. The response depends not only on the stimulus features but also on the "tonic" and "motivational" level within several structures including the monoaminergic nuclei of the brainstem [21]. Habituation is best evaluated by averaging blocks of responses (for instance, by splitting the responses in quartile depending on their trial number) rather than by analysing the single trials.

A reduced habituation occurs for many stimulation modalities: visual [12, 22–29], auditory [30, 31] and somatosensory [32, 33]. The initial response is usually lower than in normal subjects, and it is unlikely to be a factor to explain the lack of habituation as it could be for an increased initial response. Moreover, the "reduced" initial response suggests a lower pre-activation level and argues against sensitization (see also below). Interestingly, the excitatory 10 Hz repetitive transcranial magnetic stimulation over the visual cortex is able to increase the amplitude of the first block and to normalize habituation of VEP [34].

The habituation is reduced in the interictal phase, but normalizes during the attack. The thalamocortical cholinergic drive, and the cortical pre-activation level [35], plays a role in habituation, as pointed out by early high-frequency oscillations (HFO) that are reduced interictally, but normal during the attack [36].

For visual evoked potentials, habituation is related to the degree of short-range lateral inhibition, the behaviour of which is different in the interictal and ictal phases. In the interictal phase short-range latency inhibition is more than normal at the beginning and then becomes less than normal along the stimulation session; the opposite behaviour is observed during the attack.

Finally, a lack of habituation does occur also for nociceptive stimulation as detectable by blink reflex [37–40] or by laser SEP [17, 41–44].

Peripheral and central sensitization mechanisms are able to explain some features of the migraine attack, and these correspond both to a reduced nociceptive threshold and to an increased nociceptive response both to noxious and non-noxious (for instance, tactile or mechanical) stimuli. If we consider sensitization as the counterpart of habituation [1], it should consists in an increased response or in an increased excitability, and in terms of modifications observed with increasing ordinal number of block of response as for habituation, sensitization should correspond to a larger than normal response in the first block.

Considering sensitization there are several aspects that should be considered, and a distinction should be made depending on stimulus features and on the interictal rather than the attack phase.

The reversal from lack of to normal habituation that we mentioned about the attack phase might be considered as a sensitization phenomenon [27, 45, 46].

Sensitization, in association with normal habituation, is detectable by SEP during the attack in episodic migraineurs in medication overuse headache [47].

If we consider noxious stimuli, migraine patients show a reduced pain threshold before and during the attack [48, 49], and this is related to attack frequency [48] and worsens in chronic migraine and in medication overuse headache [44, 50]. During the attack, the R2 component of the blink reflex [51] and the amplitude of the laser SEP [48] are increased in the affected as compared to the unaffected side, and laser SEP does not habituate during the attack [48], which is at variance with the behaviour observed with other, non-noxious, stimulation modality.

In medication overuse headache pain-related evoked potentials proved to be abnormally large after both cranial and extracranial stimulations, and this abnormality is no longer detectable after the discontinuation of medication overuse [52].

Transcranial magnetic stimulation (TMS) is another tool for the neurophysiological evaluation of the migrainous brain. The increased excitability of the visual cortices, usually expressed as a reduced threshold required to generate phosphenes, has been demonstrated in several [53–67], but not all [34, 68], studies. The literature about the motor cortex is small and reports both an increased [61] and a decreased [53, 60] excitability. TMS has been used both to treat [69–76] and to evaluate treatment efficacy in migraine [56, 67, 77–79].

2.2   Vestibular Migraine

For many years, the comorbidity of vertigo and migraine is regarded as not only a co-occurrence by chance [80] and codified by classification criteria [81, 82]. Very recently, Lempert et al. [83] updated the diagnostic criteria for vestibular migraine (VM, Table 2.2), and these criteria have been included in the ICHD3-beta [84].

VM is likely to be the third cause of migraine and to have a life prevalence in the general population of about 1 % [81].

Besides VM, the idea that subjects with migraine may have a vestibular dysfunction is suggested by the findings that about 50 % of them suffer from motion

Table 2.2 Diagnostic criteria for vestibular migraine [83]

A.	At least five episodes with vestibular symptoms of moderate or severe intensity, lasting 5 min to 72 h
B.	Current or previous history of migraine with or without aura according to the International Classification of Headache Disorders (ICHD)
C.	One or more migraine features with at least 50 % of the vestibular episodes:
	Headache with at least two of the following characteristics: one-sided location, pulsating quality, moderate or severe pain intensity, aggravation by routine physical activity
	Photophobia and phonophobia
	Visual aura
D.	Not explained by another vestibular disorder

sickness and in those with VM motion sickness can be relieved by triptans [85]. The motion perception threshold is reduced in VM compared to normal and migraine subjects in the dynamic roll tilt paradigm, that is, in keeping with the idea that patients with VM may have enhanced perceptual sensitivity for head motions that dynamically modulate canal and otolith inputs together [86].

In the interictal phase, the occurrence of vestibular clinical and instrumental signs can be as high as 83 % [82, 87], and the occurrence of these signs can be the same [88, 89] or higher [90] in VM than in patients with migraine but not VM.

The vestibular and ocular motor abnormalities are in keeping with a dysfunction involving the peripheral and/or the central nervous system [80]. The vestibular dysfunction affects both the canal system, as detectable by caloric or rotatory testing [88–93], and the otolith system, as detectable by cervical or ocular vestibular evoked potentials (c- or o-VEMP) [94, 95] and by the evaluation of the subjective visual vertical that proved to be either normal [96] or abnormal [97]. Also the vestibulospinal [93] and the auditory [15] systems can be affected in VM.

Not surprisingly c-VEMPs are abnormal in basilar artery migraine [98] (currently migraine with brainstem aura) that we can be considered as a particular kind of VM. Finally, c-VEMPs by using 0.5 and 1 kHz tone bursts [99] can be used to differentiate VM from Ménière disease.

When VM patients are followed up for a time period of about 10 years, the number of subjects presenting interictal vestibular signs increases from 16 to 41 % [100] or from 20 to 63 % [101], and this progression seems to be prevented by prophylactic migraine treatment [101].

There are two papers on the evaluation of patients during an acute phase of their VM. In one paper the major finding was that all the patients, during but not outside the spell, showed a positional nystagmus [102]. In the other paper, the most interesting finding was that the attack-related signs suggested a central or a peripheral vestibular dysfunction in 50 and 15 % of the subjects, respectively, but in 35 % of them the location of the dysfunction could not be determined with certainty [103].

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Therapy of Migraine

3

Domenico D'Amico and Marcella Curone

3.1 Introduction

Migraine is a relevant public health issue, due to its high prevalence, to the suffering imposed to the individual patients, and to the consequent burden on society as a whole [1, 2]. Although several drugs potentially effective are available, migraine is often undiagnosed, and many patients are not adequately treated [3, 4]. The heterogeneous presentation of migraine among sufferers and between attacks in the same sufferer in different time periods implies that treatment interventions should be tailored to the individual patient [5, 6]. In fact, migraine therapy includes different approaches: avoidance of trigger factors, non-pharmacological and complementary treatments, and pharmacological therapy, which is classically divided into symptomatic (or acute) treatment and prophylaxis (or migraine prevention).

The focus of this chapter is pharmacological therapy. The main indications and goals of pharmacological therapy will be discussed in two parts devoted to symptomatic treatment and prophylaxis of migraine, together with indications on the different drugs whose efficacy is suggested to treat migraine on the basis of scientific evidence and clinical experience.

The discussion of specific issues regarding chronic migraine and medication overuse headache is beyond the scope of the present chapter.

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3.2   Avoidance of Trigger Factors in Migraine Patients

Migraine attacks are not always predictable, but in many patients, at least some factors are able to trigger migraine. The most common reported triggers are environmental factors (weather changes, altitude, bright lights, odours), psychological changes (stressful events, sudden joy), dietary factors (alcohol, chocolate, cheese), and hormonal changes, in women (menstruations). Many of them are in fact related to lifestyle aspects [7]. An important step is to educate the patient to identify and avoid typical migraine triggers that may contribute to the increase in the frequency of migraine attacks, particularly by correcting some particular behaviour, such as irregular sleep schedule (too little/too long sleep in the weekends), irregular or skipped meals, lack of regular exercise, and excessive stress.

3.3   Non-pharmacological and Complementary Treatments

Several behavioural treatments can be suggested to migraine patients, particularly – although not only – to those who prefer them to pharmacological therapy or to those who present contraindication to most of the available drugs. Relaxation training, biofeedback, and cognitive-behavioural therapy are the most used in migraine prophylaxis, and published meta-analyses and reviews have confirmed their efficacy, showing that they may promote a remarkable reduction in migraine frequency and a clear improvement in different clinical and subjective outcomes [8, 9].

Among other non-pharmacological treatments, acupuncture may be effective. A systematic review concluded that there is consistent evidence in migraine, although the evidence for an effect of 'true' acupuncture over sham interventions is not definitive [10].

As for supplements and herbs, evidence for efficacy in migraine prevention exists for magnesium, riboflavin, coenzyme Q10, butterbur, and feverfew. [11, 12].

All of the above-reported approaches can be used alone, but they usually provide additional benefit to patients treated with pharmacological symptomatic therapy and/or prophylaxis.

3.4   Symptomatic Treatment of Migraine

3.4.1   Indications and Goals of Symptomatic Treatment in Migraine

The main goal of symptomatic treatment is to restore patient's ability to function during migraine attacks, particularly by reducing the severity of headache as well as of the associated symptoms (nausea, vomiting, photophobia, phonophobia, etc.). Based on patients expectations as well as data from several clinical trials, the main endpoint to assess success in the treatment of migraine attacks are as follows: rapid and complete effect (pain-free after 2 h) or at least improvement of headache from

moderate or severe to mild or none after 2 h (headache relief), with consistent efficacy through different attacks and without relevant side effects [13–15]. Another critical aspect that clinicians must consider is to avoid headache medication escalation, in order to prevent medication overuse and progression to a chronic headache form [16, 17].

Several studies have demonstrated that symptomatic treatment, particularly with triptans, can reduce the impact of migraine, by limiting impairment in work activities and loss of productivity as well as favouring a better functioning in social and household activities [18]. The prevention of migraine progression from episodic to chronic forms requires adequate prophylaxis for those patients who are at risk. However, the regular monitoring of symptomatic medication consumption and an informed choice of pharmacological classes are critical aspects in migraine management. In fact, medication overuse is a recognized risk factor for chronicity, and published data indicate that the potential for inducing medication overuse may be higher for some classes of symptomatic drugs [17, 19]. Medications containing opioids, barbiturates, and caffeine have the highest risk of inducing migraine chronification, while triptans and NSAIDS are likely to induce migraine progression in patients with high migraine frequency at baseline.

3.4.2 General Principles and Treatment Strategies in the Symptomatic Treatment of Migraine

The choice of treatment should consider the scientific evidence of efficacy as well as some important characteristics of individual patients [13, 14]. Among these are the severity of pain, the presence and degree of associated symptoms, and the level of migraine-related disability. The history of prior response to medications and of occurrence of specific side effects should be reviewed in each patient. Attention should be paid when treating women of childbearing potential for potential teratogenic risks. Realistic expectations should be presented to patients, explaining to them that it may not always be possible to reach complete freedom from pain – or to restore a totally normal functioning. The presence of known allergies and of coexisting conditions which may limit the use of symptomatic drugs must be carefully investigated, particularly heart disease, uncontrolled hypertension, gastrointestinal problems, and renal dysfunction [13, 14].

The regular use of a headache diary and of specific questionnaires assessing migraine-related disability during individual attacks offers the possibility to better monitor the efficacy of symptomatic drugs.

Various treatment strategies may assist clinicians in their efforts to maximize the efficacy of the symptomatic treatment for migraine.

The choice of a particular route of administration may be important. Non-oral formulations (injection, nasal spray, suppository) should be suggested to patients with attacks characterized by the early (or prominent) presence of nausea or vomiting [13, 14].

The term stratified care defines an approach based on the concept that the appropriate initial treatment can be prescribed in most patients after evaluation of each

patient's headache characteristics, and of disability/impact on functioning while having a migraine attack [5, 11, 18], and that the prescription of migraine-specific agents (namely, triptans) should not be delayed in patients with more severe/disabling attacks and should be always offered to those whose headaches had responded poorly to NSAIDs or combination analgesics. As suggested above, the use of headache diaries is essential to have the needed information. Disability measures should be incorporated in these diary cards, and the use of validated self-completed tools (such as MIDAS and HIT-6) may be very useful, as they offer a summary score which can be used in assisting the choice of symptomatic treatments, as well as in monitoring the improvements in migraine-related disability on daily activities achieved with the use of the prescribed symptomatic drugs [5, 11, 13]. In clinical practice, stratified care may be difficult due to the presence of contraindications in using triptans in a given patient and also by the fact that attack characteristics may change over time in individual patient. Stratified care is alternative to stepped care, in which an initial medication is prescribed (e.g. a NSAID) and other medications (another NSAID or a triptan) are subsequently suggested if the patients report insufficient efficacy across several consecutive attacks treated with the first medications. An approach which can be useful in many patients is in fact the stepped care within an attack: a simple analgesic or NSAID may be taken initially for a migraine attack, and if this first medication were not successful, another medication (e.g. a triptan) would be used a few hours later.

Many prospective studies with different triptans have shown that treatment early in the attack (within 1 h of headache onset) was more effective than treatment when migraine attack is fully developed. Early treatment trials reported increases in the success rates for several endpoints, particularly for those in which triptans had relatively poor efficacy in pivotal trials (i.e. pain-free at 2 h, sustained pain-free state during 24 h from triptan dosing) [18, 20, 21].

The probable explanation for this is that triptans may be more effective when taken early in the attack because they can prevent but not reverse central sensitization, which is likely to occur in most migraine patients. In fact, cutaneous allodynia (the clinical expression of central sensitization) occurs in up to 75 % of patients within 20–60 min of migraine onset [22, 23]. However, clinicians should be aware that data from well-designed trials indicate that pain intensity (mild headache) at the time of taking a triptan may influence clinical response more than the timing (early, at the start of the attack) or the presence or absence of allodynia. Furthermore, early triptan intervention carries a risk of medication overuse and requires appropriate education of patients, in order to differentiate migraine attacks from tension-type headache and to avoid an indiscriminate use of early treatment, which may promote medication overuse in patients with very frequent attacks [17, 18].

3.4.3   Drugs Recommended for Symptomatic Treatment of Migraine

International guidelines indicate to use several compounds, whose strength of evidence is demonstrated by published literature and whose clinical utility is suggested

Table 3.1 List of the drugs most commonly used in the symptomatic treatment of migraine, with suggested doses

DRUG (alphabetic order)	Suggested dose (in mg)	Maximum daily dose (in mg)	Pharmacological class
Almotriptan	–	–	Triptan
Oral tablet	12.5	25	–
Acetylsalicylic acid	–	–	Analgesic
Oral tablet	800–1,000	1,000	–
Intramuscular	–	–	–
Injection	500–1,000	1,000	–
Intravenous	–	–	–
Injection	500–1,000	1,000	–
Diclofenac	–	–	NSAID
Oral tablet	50–100	100	–
Orally dispersible tablet	50	100	–
Suppository	100	100	–
Eletriptan	–	–	Triptan
Oral tablet	20–40	40–80	–
Frovatriptan	–	–	Triptan
Oral tablet	2.5	5	–
Ibuprofen	–	–	NSAID
Oral tablet	400–800	800	–
Paracetamol (acetaminophen)	–	–	Analgesic
Oral tablet	500–1,000	2,000	–
Suppository	1,000	2,000	–
Naproxen	–	–	NSAID
Oral tablet	500	1,000	–
Suppository	500	1,000	–
Rizatriptan	–	–	Triptan
Oral tablet	5–10	20	–
Orally dispersible tablet	10	20	–
Sumatriptan	–	–	Triptan
Oral tablet	50–100	200	–
Subcutaneous	–	–	–
Injection	6	12	–
Nasal spray	10–20	40	–
Suppository	25	100	–
Fast-disintegrating-tablets	50–100	200	–
Zolmitriptan	–	–	Triptan
Oral tablet	2.5–5	10	–
Orally dispersible tablet	2.5–5	10	–
Nasal spray	2.5–5	10	–

by expert consensus [11, 13, 14]. Symptomatic medications include "migraine-specific" medications (triptans, dihydroergotamine) and "non-specific" medications (such as ASA, NSAIDS, acetaminophen, antiemetics).

A list of the drugs most commonly used in the symptomatic treatment of migraine, with suggested doses, is reported in Table 3.1.

3.4.3.1 Triptans

Triptans are serotonin 5-HT1B/1D receptor agonists, whose significant role in relieving pain and associated symptoms of migraine are demonstrated by a countless number of large controlled trials. They can also limit disability and improve health-related quality of life [18]. The efficacy of all the marketed drugs of this class has been confirmed by the inclusion with level A evidence in the guidelines from the American Academy of Neurology and from the European Federation of Neurological Societies [11, 13, 14] and by the results of published meta-analyses [24, 25].

There are currently seven triptans available in most countries: almotriptan (oral tablet), eletriptan (oral tablet), frovatriptan (oral tablet), naratriptan (oral tablet), rizatriptan (oral tablet, orally dispersible tablet), sumatriptan (subcutaneous injection, oral tablet, fast-disintegrating oral tablet, nasal spray, suppository), and zolmitriptan (oral tablet, orally dispersible tablet, nasal spray).

Some contraindications must be considered before prescribing triptans: coronary heart disease, Raynaud's disease, untreated arterial hypertension, history of ischaemic stroke, pregnancy, and severe liver or renal problems. The suggested doses of the most widely prescribed triptans are reported in Table 3.1.

Side effects include drowsiness, nausea, dizziness, tightness, or flushing in areas such as the face, the neck, and the chest. Serious adverse events – namely, increased risk of vascular events – were not reported when sumatriptan users were compared with a healthy population. These events have been reported rarely and only when used in patients who had contraindications against triptans or a wrong diagnosis of migraine. According to meta-analyses, each triptan has some specific characteristics, although these are often not confirmed in clinical practice. Subcutaneous sumatriptan has the fastest onset of efficacy.

The effect of rizatriptan, eletriptan, oral sumatriptan, and almotriptan is evident in 30–40 min. Among these drugs, rizatriptan 10 mg and eletriptan 80 are more effective than sumatriptan 100 mg, and almotriptan shows better consistency and tolerability. Naratriptan and frovatriptan may need up to 4 h for the onset of efficacy, but they have a better tolerability profile, and the duration of efficacy is longer as compared with all others.

Clinicians should be aware that an individual patient may respond differently to different triptans, with possible variability as well as the degree of effectiveness and tolerability. Clinicians should be aware that an individual patient may respond differently to different triptans, with an individual variability. Thus, many patients may benefit from switching triptans if they are not satisfied taking into account the degree of effectiveness and tolerability.

Triptans are effective in most patients who do not respond to NSAID, and although they are effective at any time during a migraine attack, there is evidence that their efficacy is better the earlier they are taken. For these reasons, stratified care and early treatment approaches have been proposed (see Sect. 3.4.2).

3.4.3.2 NSAIDS and Analgesics

A list of level A drugs among the most used drugs in this class was included in the European guidelines [11] based on the evidence of efficacy and taking into account

also the level of tolerability and consistency. Among NSAIDS are ibuprofen, oral; diclofenac, oral or rectal; and naproxen, oral or rectal. Among analgesics are acetylsalicylic acid (ASA), in both oral and intravenous administration; and paracetamol (or acetaminophen) in oral or rectal administration. For all the above-mentioned drugs, recent Cochrane Database of Systematic Reviews have confirmed the evidence in migraine patients, with significant effects in relieving pain and associated symptoms, with mild side effects, but with pain-free responses in a minority of patients [26–30]. Tolfenamic acid is rated as a level B drug in the same guidelines.

The suggested doses of the most widely prescribed NSAIDS and analgesics are reported in Table 3.1.

The side effects of drugs in these classes are usually gastric irritation/discomfort, nausea, and vomiting. NSAID-related gastrointestinal adverse effects may be more evident in elderly persons, patients with a Helicobacter pylori infection, and concomitant use of oral anticoagulants and corticosteroids.

Before prescribing these drugs, clinicians must be aware of the presence of contraindications, such as previous allergy to ASA or any NSAID, possible defect of coagulation, and peptic ulcer. The use should be monitored in patients with asthma and liver and renal problems.

3.4.3.3 Ergot Alkaloids

Drugs of this class are considered as "migraine-specific" compounds, as they can act on a variety of catecholamine receptors, with a consequent widespread use before the introduction of triptans. A few placebo-controlled trials, which are often old with relevant methodological problems, demonstrated the efficacy of the two most commonly used ergot alkaloids, i.e. ergotamine tartrate, oral, and dihydroergotamine, suppositories. Furthermore, in comparative trials, ergot alkaloids generally showed lower efficacy than triptans, although the latter showed a lower recurrence rate [11]. More recent trials with dihydroergotamine nasal spray suggested its efficacy, but without conclusive evidence [13]. The prescription of ergot alkaloids should be discouraged for several reasons: the evidence was relatively inconsistent to support their efficacy; they have a high potential to induce medication overuse headache; they have relevant side effects (nausea, vomiting, and paraesthesia; ergotism may rarely occur with chronic use); they could not be administrated together with triptans; and they are often marketed in association with other substances (caffeine, pentobarbital, butalbital, belladonna alkaloids) which can increase the rate of side effects and the risk of medication overuse. Ergotamine may be considered in the treatment of selected patients with moderate to severe migraine with poor response to triptans, particularly in prolonged attacks, status migrainosus, and menstrually related migraine.

A new orally inhalable formulation in which dihydroergotamine is released by an inhaler that incorporates a breath-triggered mechanism with delivery of a standard amount of the drug into the lung. This novel orally inhalable formulation is under consideration for approval for the acute treatment of migraine in adults. It is a promising, practical formulation which is likely to have minimal side effects [31].

3.4.3.4 Other Drugs and Combinations

The use of antiemetics is recommended in attacks with prominent nausea and vomiting, particularly if occurring at the onset of attacks. No prospective, controlled trials are available. These drugs may also improve the resorption of analgesics. Oral metoclopramide can be used, but a better effect is obtained by IM or IV administration; domperidone (oral) or prochlorperazine (oral, IM, IV or in suppositories) may be alternative options; chlorpromazine IM may be required in severe, repeated emesis [13]. All these drugs can cause extrapyramidal side effect, i.e. dyskinesia, and are contraindicated in pregnancy.

Generally, opioids are of only a minor efficacy in migraine. Dependence and addiction are prominent issues. Furthermore, the main concern about the use of opioids is the increased risk for medication overuse headache and chronic migraine, which in fact is higher than other drugs used in the symptomatic treatment of migraine [17]. Opioids should be avoided in migraine patients.

Antiemetics and opioids are associated in some anti-migraine combinations, often with caffeine. Fixed combinations of NSAIDS/analgesics and/or caffeine and antiemetics are available in some countries. The combination of ASA, paracetamol, and caffeine was significantly more effective than placebo in controlled study for various endpoints [11]. Also, an indomethacin/prochlorperazine/caffeine combination is available in some countries, in oral and rectal formulations, and it was found effective and well tolerated in migraine patients in randomized, active-comparator controlled studies [32]. These combination products may represent an option in the symptomatic treatment of migraine. Although the risk of medication overuse is greater than NSAIDs alone [17].

3.5   Prophylaxis of Migraine

3.5.1   Indications and Goals of Prophylaxis in Migraine

The main goal of prophylaxis is the reduction in the negative impact of migraine on patient's daily life, particularly through a reduction in migraine frequency. Other aspects that are hopefully influenced by a successful prophylaxis are as follows: reduction in headache severity and duration and reduction in symptomatic drug consumption, with the consequent prevention of medication overuse [6, 11, 12, 33].

Evidence exists that prophylaxis can reduce the negative influence of migraine on daily life when specific tools to score disability and health-related quality of life were used in open-label studies and in double-blind trials [6, 15, 34–36]. Data from both clinical and population studies indicate that as the number of headache days increases, the risk of migraine daily or nearly-daily headaches (i.e. progression from episodic to chronic migraine) increases [16, 37].

The progressive increase in headache frequency may in turn promote medication overuse, which in turn is a major risk factor for migraine chronification [16, 17, 37]. In patients reporting around 10 days of headache, or 9 days with use of symptomatic medications, per month, the risk for chronification becomes so great, encouraging

adequate prophylaxis to stop the negative progression of migraine. Furthermore, it is well known that the impact on functioning and on quality of life in patients progressing from episodic to chronic migraine is particularly relevant and significantly worse than that caused by episodic migraine. This is particularly true when chronic migraine is associated to medication overuse [36, 38].

The decision to start prophylaxis in the individual patient should therefore be guided by the mean monthly frequency (number of attacks and of migraine days), the effectiveness of symptomatic compounds, the number of days with use of symptomatic drugs and, above all, by the impact of migraine on functioning and well-being in a given patient [6, 12–14, 33]. As discussed for symptomatic treatment, the use of disability measures should be incorporated in the clinical evaluation of a migraine patient. The information obtained by asking specific questions on the degree of impairment in social and familial duties as well as on functioning in work activities or, better, by the use of validated questionnaires (such as MIDAS and HIT-6) is essential to consider prophylaxis in an individual patient. Other circumstances in which prophylaxis is essential are the following: presence of adverse events from symptomatic drugs and/or contraindications to their use, migraine forms with a particularly severe impact (such as prolonged aura, hemiplegic migraine).

In clinical practice, a migraine prophylaxis should be rated as successful when the patient reports a positive change in his/her daily functioning and sense of well-being and when the mean frequency of migraine attacks per month is decreased by at least 50 % within a treatment period of 3 months.

3.5.2   General Principles and Treatment Strategies in the Prophylaxis of Migraine

Particular attention should be devoted to the following aspects. The chosen preventive drug should be started at a low dose, with progressive increase of daily doses, to better control possible side effects. Clinicians should be sure that women of childbearing potential are aware of any potential risks. Patients should be involved in the decisions regarding their migraine prophylaxis, in order to gain their acceptance of prophylaxis. In fact, patient's acceptance and adherence to treatment is often negatively influenced by several factors. Among these are the fact that medications are to be taken every day and for long periods, possible concern about unacceptable adverse events, and unrealistic expectations from therapy – namely, the possibility of experiencing no headache at all after prophylaxis. Physicians must explain the goals of the prescribed prophylaxis, and its schedule, in terms of doses and timing. They should provide the patient a headache diary and discuss with him/her about how to monitor the improvements in migraine-related disability and migraine's negative impact on daily activities, possibly using standard tools (such as MIDAS and HIT-6) [6, 12, 14].

The individual drug should be chosen considering the strength of evidence in migraine prophylaxis as well as the individual patient's characteristics. The

presence or absence of coexisting or comorbid diseases must be always taken into account, as some anti-migraine drugs may have indications for other conditions, while they can worsen other coexisting disorders [6, 39]. As for some examples, in migraine patients with hypertension, a beta-blocker may be suggested; the same drug should be avoided in those with history of asthma; in patients with sleep disturbance and depression, amitriptyline should be considered; but it must be avoided in patients with urinary retention or glaucoma. Also, an accurate evaluation of the lifestyle and the type of working activity should guide in choosing the preventive drug particularly as far as the expected adverse events are concerned. Drugs commonly inducing drowsiness must be avoided in patients who use to drive vehicles; drugs which may cause fatigue or exercise intolerance are not indicated in athletes; those promoting relevant weight gain are not to be suggested to young women who will not tolerate it. Prophylaxis should be used for periods of at least 2–3 months in order to assess its efficacy and tolerability in a clinically relevant period [6, 11, 14]. There is not a general agreement on the duration of a prophylaxis treatment, and recently published data suggest the opportunity of rather long treatment periods (up to 12–14 months) [40].

3.5.3 Drugs Recommended for the Prophylaxis of Migraine

International guidelines indicate the use of several compounds, whose strength of evidence is demonstrated by published literature and whose clinical utility is suggested by expert consensus. However, regulatory approval and availability of anti-migraine prophylactic drugs may vary from country to country. Recent guidelines for the prophylaxis of migraine completed by experts from the American Headache Society (AHS) and the American Academy of Neurology (AAN) [41] and from the European Federation of Neurological Societies [11] were consistent in suggesting for most of the available first-line and second-line drugs, although the two guideline used different rating methods.

A list of the drugs most commonly used in the prophylaxis of migraine, with levels of recommendation according to recent international guidelines, is reported in Table 3.2.

3.5.3.1 Amitriptyline

It is a widely used tricyclic antidepressants which is approved as an anti-migraine drug in many countries (as the UK, in Italy) but not in the US. Generally, 25–50 mg/day – i.e. doses which are lower than those used to treat depression – is effective in migraineurs. The most commonly reported adverse events are sedation, dry mouth, weight gain, and constipation. It should not be used in patients with cardiac dysrhythmia, glaucoma, urinary bladder retention, and hypotension. Amitriptyline is rated as a level B drug both in the US [41] and European guidelines [11].

Evidence supporting the use of other antidepressants (imipramine, nortriptyline, protriptyline, doxepin, as well as selective serotonin reuptake inhibitors) as migraine preventives is poor [11, 41].

Table 3.2 List of the drugs most commonly used in the prophylaxis of migraine, with levels of recommendation according to recent International guidelines [12, 40]

Drug (alphabetic order)	Level of recommendation EU guidelines [12]	Daily dose (in mg) US guidelines [40]	Level of recommendation	Daily dose (in mg)
Amitriptyline	B	50–150	B	25–150
Candesartan	C	16	C	16
Flunarizine	A	5–10	Not available in the US	–
Gabapentin	C	1,200–1,600	U (inadequate or	Up to 2,400
–	–	–	conflicting data to	–
–	–	–	support or refute	–
–	–	–	medication use)	–
–	–	–		–
Magnesium	C	24 mmol	B	1,200
Metoprolol	A	50–200	A	47.5–200
Propranolol	A	40–240	A	120–240
Topiramate	A	25–100	A	25–200
Valproate/ Divalproex	A	500–1,800	A	400–1,000
Venlafaxine	B	75–150	B	150

3.5.3.2 Flunarizine

It is the most widely used calcium channel blocker in migraine prophylaxis. It is not available in the US, although it is one of the most used preventive drugs in some European countries and in Latin America. In published trials comparing flunarizine to placebo, the daily dose of 10 mg was evaluated, but most clinicians tend to prescribe 5 mg before sleep, in order to minimize side effects, the most common being sedation and weight gain. Depression occurs in a minority of treated patients. Flunarizine is rated as a level A drug in the European guidelines [11]. It is not included in the US guidelines [41].

3.5.3.3 Propranolol

It is the most used beta-blocker. It is considered as a level A drug both in the European guidelines [11] and in the US guidelines [41] and registered for migraine prevention in most countries. It is not indicated in the presence of asthma, Raynaud's disease or peripheral vasculopathy, type I diabetes mellitus, severe alterations of atrioventricular conduction, or congestive heart failure. Average daily doses are between 80 and 120, ranging from 40 to 240 mg, and should be adjusted on the basis of blood pressure and cardiac frequency monitoring, as well as on the occurrence of specific side effects: fatigue or exercise intolerance, nightmares, depression, or impotence.

Other beta-blockers may be used in migraine prophylaxis. Metoprolol is a level A preventive drugs in both the US and the European guidelines [11, 41]. Less evidence is available for atenolol, nadolol, and bisoprolol.

3.5.3.4 Divalproex/Sodium Valproate

This antiepileptic drug is approved for migraine prophylaxis in many countries, including the US, but not in all, as in Italy. The level of scientific evidence is considered as A by both the US [41] and the European guidelines [11]. Valproate should not be used as a first-line treatment in young, menstruating women, for possible teratogenicity and development of polycystic ovary syndrome. The most common adverse events are nausea, dyspepsia, asthenia, and weight gain. Alopecia and tremor are less commonly reported. Other, not common but potentially severe, adverse events include hepatotoxicity, pancreatitis, and thrombocytopenia or other bone marrow dysfunctions.

3.5.3.5 Gabapentin

This antiepileptic drug was tested in controlled trials at different daily doses, ranging from 1,200 to 2,400 mg. It is included as a level C compound in the European guidelines [11], while it is considered among those drugs with inadequate or conflicting data to support or refute its use in migraine prophylaxis by the most recent US guidelines [41]. The pooled evidence derived from a Cochrane Database of Systematic Reviews concluded that gabapentin is not efficacious in migraine prophylaxis [42]. Side effects are common, generally mild, and they include fatigue, dizziness, weight gain, and cognitive dysfunction.

3.5.3.6 Topiramate

This antiepileptic drug is registered for migraine prevention in the US and most countries. It has been extensively evaluated in several trials, and its scientific and clinical evidence is rated as A both by the US [41] and the European guidelines [11]. Evidence shows that prophylaxis with topiramate can reduce migraine-related disability and impact on health-related quality of life [35]. Around half of patients report distal paraesthesias. Weight loss, usually around 3 % of the original weight, can be observed in patients receiving the optimal dose of 100 mg/day. Other side effects are fatigue, language or psychomotor slowing, memory difficulty, and taste perversion. Tolerability may be enhanced by slow dose tapering and by an accurate evaluation of the most adequate dose in an individual patient, considering that doses ranging from 75 to 200 mg/day may be effective in migraine prophylaxis. Uncommon, but potentially serious, adverse events include hyperchloraemic acidosis, narrow angle-closure glaucoma, nephrolithiasis, anorexia, aggression, and depersonalization.

3.5.3.7 Other Drugs

With one placebo-controlled trial each, lisinopril at 20 mg/day and candesartan at 16 mg/day were found effective [43, 44]. They are generally well tolerated and may be useful in patients with coexisting hypertension.

Pizotifen may be effective in migraine prophylaxis. It is not available in many countries, and its extensive use is limited by the typical side effects, i.e. weight gain and sedation, which are generally remarkable.

There is no evidence that other antiepileptic drugs such as acetazolamide, clonazepam, lamotrigine, oxcarbazepine, pregabalin, zonisamide, and vigabatrin may

be effective as anti-migraine drugs [42, 45]. With one study each, carbamazepine and levetiracetam were superior to placebo [45].

The placebo-controlled study on carbamazepine is rather old, and although the recent US guidelines rate this drug as possibly effective (level C) [41], it is very seldom used in clinical practice and generally considered as non-effective in migraine.

Levetiracetam was superior to placebo in one trial in reducing headache frequency, although this drug (1,000 mg/day) showed a significantly lower – although little – efficacy than topiramate 100 mg/day in the same cross-over trial in a 28-day treatment.

We note that lamotrigine may be an effective option in patients with frequent auras, as reported in several open-label studies [46, 47], zonisamide 200 mg/day was found substantially as effective as topiramate 100 mg/day in reducing migraine frequency and a controlled venlafaxine is included as a level B drug in recent guidelines [11, 41]. It was effective in reducing migraine frequency when tested versus placebo and also versus amitriptyline 75 mg/day. Possible side effects are nausea, drowsiness, excessive sweating, and irritability.

Aspirin as well as some NSAIDs, such as naproxen and ketoprofen, are sometimes useful for short-term prophylaxis [11, 41].

3.6 Treatment of Migraine in Children and in Adolescents

Most of the available drugs used for the symptomatic treatment and for the prophylaxis in adults are used in the therapy of paediatric migraine, although some of these compounds have not been adequately tested in this group of patients – and most of them are not approved for subjects under 18 years of age.

As for the most common contraindications and side effects, we suggest to refer to the data reported in previous paragraphs. Also the general principles of treatment of paediatric migraine – and particularly the goals, indications, and general rules in choosing an individual drug, are generally the same as for adults. However, we note that clinicians must take into account the possible concerns related to the potential side effects from pharmacological therapy in an even more accurate way than when treating adult patients. The possibility of non-pharmacological approaches should be generally proposed and tested, also considering the preferences and needs of the paediatric patient – as well as of his/her parents.

3.6.1 Drugs Recommended for the Symptomatic Treatment of Paediatric Migraine

According to formal guidelines [48] as well to a recent expert review [49], some drugs among NSAIDs/analgesics and triptans have a sufficient strength of evidence and safety when studied in populations of adolescents and/or children. As for adults, triptans should be the first choice in patients with severe and disabling attacks, while

Table 3.3 List of the drugs most commonly used in the symptomatic treatment of paediatric migraine, with suggested doses and formulations and target population

DRUG (alphabetic order)	Suggested dose (in mg)	Target population	Pharmacological class
Almotriptan	–	Adolescents	Triptan
Oral tablet	6.25–25	–	–
Ibuprofen	–	–	NSAID
Oral tablet	7.5–10/kg	Children, adolescents	–
Paracetamol (acetaminophen)	–	Children, adolescents	Analgesic
Oral tablet	7.5–10/kg	–	–
Suppository	7.5–10/kg	–	–
Rizatriptan	–	Children, adolescents	Triptan
Oral tablet	5–10	20	–
Orally dispersible tablet	10	20	–
Sumatriptan	–	Children, adolescents	Triptan
Nasal spray	5–10	–	–
Zolmitriptan	–	Adolescents	Triptan
Orally dispersible tablet	2.5–5	–	–
Nasal spray	2.5–5	–	–

non-specific drugs should be used for mild to moderate migraines or in those patients who do not tolerate triptans. Side effects and contraindications are generally similar as those found in adults. The suggested doses and formulations are reported in Table 3.3.

3.6.2 Drugs Recommended for the Prophylaxis of Paediatric Migraine

Several compounds among those suggested to treat migraine in adults have been tested in paediatric patients, with sufficient strength of evidence in published literature, although they generally do not have approval from regulatory authorities under the age of 18 years. According to the published evidence [48, 49], some drugs can be recommended in clinical practice.

3.6.2.1 Amitriptyline
It is a widely used tricyclic antidepressant; the suggested dose is 5 mg/day before bedtime, to be reached with a slow titration period.

3.6.2.2 Flunarizine
It is the most widely used calcium channel blocker; the suggested dose is 1 mg/kg/day before bedtime.

3.6.2.3 Topiramate
This antiepileptic drug is generally effective; the suggested dose is 2–4 mg/kg/day, with one or two daily doses, with a slow titration period.

3.6.2.4 Other Drugs

Cyproheptadine and pizotifen are drugs with antihistamine and antiserotonergic effects which may be effective in paediatric migraine prophylaxis. It is not available in many countries, and its extensive use is limited by the typical side effects, i.e. weight gain and sedation, which are generally remarkable.

3.7   Non-pharmacological and Complementary Treatments

Evidence of non-pharmacological treatments in paediatric headache is generally weak, also because placebo effect in clinical trials is more evident than in adults [50].

Behavioural therapies, such as biofeedback training, relaxation techniques, pain coping, and cognitive-behavioural treatment, are optimal treatment choices in young patients.

Also acupuncture may help children and adolescents with migraine, and some dietary supplements (such as magnesium, vitamin B2, coenzyme Q10) and herbs (such as feverfew and butterbur) are suitable also for children, although their efficacy has not been adequately proven.

Information to the patients and their parents about the possible migraine trigger factors is crucial in order to reduce some lifestyle factors which may increase the frequency of attacks. Among children and adolescents, irregularity in meals (e.g. skipped breakfast), insufficient sleeping time, lack of regular exercise, and psychological stress are the most common [51].

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Migraine: The Hypersensitive Brain

4

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Migraine is an episodic disorder with complex pathophysiology, characterized by recurrent attacks of throbbing, unilateral, and moderate to severe headache that typically intensify during physical activities. Migraine pain is associated with vegetative features such as nausea, vomiting, photophobia, phonophobia, and less frequently osmophobia. A migraine attack is characterized by prodromal symptoms, eventually followed by aura, thus a headache phase with pain and nausea/vomiting, and finally resolution and recovery [1]. Hypersensitivity to light, sound, smells, and other stimuli are most prominent during individual migraine attacks, but such features may also occur in-between attacks in many patients. Hypersensitivity to external stimuli and aura suggest an involvement of the cerebral cortex in which hyperexcitability could be the putative basis for physiological disturbances in migraineurs. The reasons for increased neuronal excitability may be multifactorial. Genetic studies introduced the abnormality of ion channels as a potential mechanism of interictal neuronal excitability [2, 3]. During the last decades, clinical neurophysiology and functional neuroimaging shed light on the properties of the cerebral cortex and brainstem in migraine sufferers improving the understanding of migraine pathophysiology.

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4.1 Electrophysiological Studies in Migraine

4.1.1 Electroencephalography

Electroencephalography (EEG) was one of the first electrophysiological methods used to investigate cortical excitability in migraine sufferers even if it is not part of migraine patient's routine evaluation [4]. EEG has provided some insight on neurophysiological research since 1959 when there was an observed enhanced photic driving response in patients suffering from headaches and not in healthy controls. This phenomenon was called the headache or *H-response*. Further studies conducted on this topic confirmed these results [5]. A significant decrease in alpha rhythm power during photic stimulation in migraine group compared to healthy controls and tension-type headache group was described. An increased driving power in patients suffering from migraine with and without aura regardless of patients' age was reported. In an open study conducted on 33 migraine patients and 40 controls, some authors found that high H-response was sensitive (86.4 %) and specific (97.5 %). However, one study reported that photic driving power was higher both in migraine and in tension-type headaches compared with controls. In a longitudinal study conducted on 33 migraineurs without aura, 8 migraineurs with aura, and 32 healthy controls, Bjork et al. showed a depressed photic driving response during and between attacks, and an increased response immediately before the attack in migraineurs without aura: these results supported the theory of hypoactivation of sensory cortices between migraine attacks [6]. Authors concluded that the inconsistency of previous results was due to the inclusion of migraineurs in the preictal phase and to habituation among controls in earlier studies. To summarize, H-response was consistently reported in migraineurs, even though the different studies cannot be compared for their differences in methods.

Prevalence of standard *EEG abnormalities* in migraineurs varies considerably in the literature, although most studies show important methodological flaws [7]. Only few controlled and blinded studies were performed reporting a similar prevalence of focal slow activity and spike activity in migraineurs compared to healthy controls [8]. "Epileptic-like" activity has also been inconsistently reported in migraineurs. These anomalies could be the manifestation of a hyperactive focus supporting the hyperexcitability hypothesis in migraine. Thomaides et al. analyzed the EEG topographic frequency in patients with nitroglycerin-induced migraine and in matched controls 30 min after assumption of sumatriptan, finding that the abnormal EEG rhythm disappeared after the treatment [9]. Sand published a recent review on *quantitative frequency analysis of EEG (QEEG)* with or without topographic mapping applied on migraine [5]. Alpha activity abnormalities and an augmented alpha rhythm variability in migraineurs during interictal phases were found. Comparing migraineurs with aura to controls, an increased alpha total power, an increased delta and theta power, and an alpha asymmetry in temporal regions were reported. An increased slow activity and a decreased alpha band in the posterior regions were also found comparing migraine patients and matched controls. Other authors reported that peak alpha power, as well as its reactivity, was lower among migraineurs

than healthy subjects. In children, no significant difference between migraineurs and healthy controls in interictal EEG activity was found. A reduction of alpha power in occipital regions contralateral to visual disturbances and a subsequent increase in frontal delta power were observed during visual aura. Other studies on pediatric populations reported abnormalities during the interictal period, such an increase in theta-alpha ratio and theta power in children with migraine with aura [5]. Recently, Bjørk and Sand [10] analyzed QEEG of 40 migraineurs before and after a migraine attack, showing (a) an increased frontocentral theta and alpha power within the 36-h interval before the next migraine attack and (b) an occipito-parietal alpha and theta power asymmetry before the attack compared to interictal baseline. These data suggest that cortical neuronal dysfunction in migraine reaches a critical level within a few days before the attack making patients more prone to develop attacks.

Magnetoencephalographic (MEG) studies revealed large amplitude waves and complex direct current shifts in patients with spontaneous and visually induced aura when compared to controls [11]. These results were confirmed in nine migraine patients (five with aura and four without aura) before and after 30 days of daily use of valproate. At baseline, direct current MEG shifts were recorded in the occipital and parietal cortex and in frontal cortical regions in all patients. Thirty days after the treatment, MEG recordings showed a reduction of direct current shifts in three out of four patients remaining in the study [12]. These studies supported the theory that hyperexcitability of the occipital cortex is crucial for the pathogenesis of migraine.

4.1.2 Evoked Potentials

Evoked and event-related cortical responses, especially to visual and auditory stimulations, have been extensively investigated in migraine. Abnormal steady-state response evoked by a sine-wave visual stimulus was reported in migraineurs [3]. One study showed that *visual evoked potentials* were weaker when the clinical state of the patient improved during a double-blind experiment with propranolol. Studies focusing on amplitudes of visual evoked potentials with flash or pattern-reversal stimulation reported controversial results: the majority of studies found normal amplitude in migraine sufferers, while others reported increased or decreased amplitude in patients when compared to controls [13, 14]. Most studies conducted on migraine patients reported normal brainstem auditory evoked responses and long latency evoked cortical potentials [13]. However, some authors showed a strong interictal dependence of *auditory evoked potentials* on stimulus intensity in patients suffering from migraine with and without aura if compared to healthy controls, supporting the abnormality of cortical information processing in patients between attacks [13]. Moreover, an increased intensity dependence of auditory cortical evoked potentials was reported both in migraineurs and their children when compared to healthy volunteers [13, 14]. *Somatosensory evoked potential* abnormalities, such as prolonged N13 latency interictally, reduced P22/N30 amplitude interictally, prolonged N19 latency, and decreased amplitude during aura were also shown in

migraine patients [13, 14]. In a study of somatosensory evoked potentials, the high-frequency oscillations (HFOs) were detected by using an appropriate band-pass filtering. Comparing migraineurs and controls, a reduced early HFOs and a normal late HFOs (thought to be generated by thalamocortical afferents and cortical inhibitory/excitatory neurons, respectively) were reported [2].

The most consistent abnormality found in migraineurs is a *deficit of habituation* during the attack-free phase, expressed by a reduced amplitude of the evoked response to a repeat stimulation.

This phenomenon is a common feature of cortical responses after repeated exposition to any type of stimulus and represents a protective mechanism that prevents the cortex from overflowing inward information, allowing to economize energy balance in a normally functioning brain [2, 15]. The lack of habituation in migraine was first described in visual evoked potentials, but these abnormalities were also found for auditory, somatosensory, cognitive, and painful evoked potentials [2].

Contingent negative variation (CNV) is a slow frontal event-related potential that appears in a reaction-time task between a warning and an imperative stimulus to which the subject has to respond. It reflects expectancy and motor preparation, and it is related to higher mental functions. Studies conducted on migraineurs reported an increased amplitude of CNV, especially for the early component, during the interictal phase. Moreover, a reduction of habituation is reported also in CNV [13]. CNV amplitude and habituation have been shown to normalize after treatment with B-blockers [3], but also with topiramate and levetiracetam [16].

The *blink reflex* is a trigeminofacial brainstem reflex. After electrical stimulation of the supraorbital nerve by means of surface electromyogram, it is possible to distinguish (1) the initial ipsilateral pontine component with brief latency (R1), (2) a late second bilateral medullary response (R2), and (3) a less distinct bilateral ultralate component (R3) [17]. Using a small concentric electrode eliciting mostly the R2 component, Katsarava et al. showed a facilitation of nociception-specific blink reflex responses only in migraineurs and not in patients suffering from frontal sinus pain [18]. These features were observed during acute attacks, mainly on the headache side, and normalized interictally. The authors themselves have showed a lack of habituation of the nociception-specific blink reflex responses in migraineurs outside the attack, supporting an abnormal trigeminal nociceptive processing in migraineurs [19].

Habituation behaves like dynamic parameter changing during migraine cycles. Most sensory ways showing an interictal lack of habituation normalizes during the attack and then get back to the abnormal habituation pattern 24–48 h after the attack [20]. The early CNV component, which is higher during the interictal phase in migraineurs [14, 20], also increases in the days preceding the attack than normalizes during and just before the attack. This periodicity can be explained by dynamic changes in habituation during repetitive stimulation that gets to its highest point in the days before the attack. Some studies highlight as genetic predisposition plays an important role in this interictal dysfunction. A pronounced CNV amplitude and lack of habituation was found in migraineurs and healthy controls with

a family history of migraine in first-degree relatives with respect to those without family history of headache. A reduced habituation of the nociception-specific blink reflex was also described in migraineurs, when compared to first-degree relatives suffering from migraine and to healthy controls without personal or family history of migraine [20, 21].

Recently, Morlet et al. performed an auditory event-related potential study in patients suffering from menstrually related migraine and age-matched controls during three sessions along the menstrual cycle [22]. Authors analyzed brain processes triggered by shorter tones randomly presented among repeated tones in a situation of passive listening condition: in particular they investigated the mismatch negativity reflecting automatic mismatch detection and subsequent N2b and P3a components reflecting attention orienting. No differences in mismatch negativity were reported between groups, while cases showed an enhanced N1 orienting component to all incoming stimuli, a prolonged N2b to deviance, and a different modulation of P3a amplitude along menstrual cycle, which normalized during attacks. These findings evidenced an increased automatic attention orienting processes to auditory changes in migraineurs [22].

4.1.3   Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (TMS) studies conducted on migraine sufferers used single-pulse TMS to investigate the visual or motor cortex activation thresholds or repetitive TMS to activate or inhibit the underlying cortex by means of different stimulation frequencies [20]. *TMS of motor cortex* has the advantage of relying on an objective measure that is the motor evoked potential recorded in peripheral muscles. Global findings of TMS of the motor cortex have observed either normal or increased activity in migraine patients [14]. Comparing migraineurs with aura, migraineurs without aura, and healthy subjects, motor threshold was significantly higher only in the first group mainly on the aura's side. No motor threshold differences were reported comparing migraineurs without aura and controls. Moreover, no differences between the ictal and interictal phases were found. However, these findings were not supported by another study where increased motor evoked potential amplitudes in migraineurs with respect to controls were observed, in migraine with and without aura, whereas no differences in motor threshold was found among the two groups of migraineurs. Comparing patients with migraine with aura and without aura and healthy subjects, a significantly higher motor threshold was found in migraine with aura during isometric contraction [14].

The few studies focused on *cortical silent period* in migraineurs showed conflicting results. Two studies reported that this parameter was normal in patients that were stimulated at high intensity, while another study showed a short cortical silent period in migraineurs with aura at low stimulus intensity [14]. This parameter is a measure of central inhibition of motor pathway, and thus these findings may suggest reduced central inhibition and increased excitability [3]. Curra et al. confirmed

these results reporting shortened cortical silent period in patients suffering from migraine with respect to controls [23].

Occipital cortex excitability has been investigated by *TMS of visual cortex* that used a subjective perception of phosphenes. This technique has taken into consideration different parameters showing conflicting results [14]. A high phosphene prevalence in patients with migraine with aura compared to healthy controls was reported [24]. Focusing on the threshold at which phosphenes appeared, most studies found out that this threshold was much lower in patients suffering from migraine with aura than in controls [13, 14]. On the contrary, other authors reported no significant differences on phosphene threshold among migraineurs with aura, without aura, and healthy subjects. Bohotin et al. comparing migraine without and with aura and healthy volunteers, using a more focal visual cortex stimulation with a figure-of-8 coil TMS, showed that the phosphene threshold was significantly increased in migraineurs without difference between patients with and without aura [25]. Brighina et al. found no significant difference in mean phosphene threshold values between migraineurs and controls [24]. These inconsistencies may be caused by differences in methods, devices, subject recruitment, proximity between the recordings and migraine attack, and individual perception or description of phosphenes [14].

Recently, objective physiological measures to assess differences in cortical excitability were developed [26]. A visual suppression method called magnetic suppression of visual accuracy was used. Timed TMS impulses were delivered to the visual cortex, usually 10 % above phosphene threshold or where suppression was remarked. Subjects were asked to report letters projected at a fixed luminance on a screen in front of them, and visual suppression was calculated on the basis of how many mistakes the subjects made. Authors found that migraineurs did not make mistakes demonstrating a reduction in visual suppression. Moreover the same group collected data on topiramate showing dynamic changes in episodic and chronic migraine in two subjects. Treatment seemed to balance the dysfunction in cortical inhibition seen in chronic migraine [3].

Hyperexcitability of the visual cortex was also evaluated by means of *repetitive TMS*. The phosphene threshold was assessed before and after 15 min of 1-Hz repetitive TMS in migraineurs with aura and healthy subjects [24]. The augmented phosphene threshold found in controls after stimulation was not showed in patients who, conversely, pointed out a reduction in the threshold suggesting that visual cortex in migraineurs may be hyperexcitable. These findings were not confirmed [27] using *repetitive TMS* at 1 and 10 Hz. In controls, lower-frequency stimulation reduced amplitude in the first block of 100 averaged responses and induced lack of habituation over successive blocks. In migraineurs, high-frequency stimulation facilitated the visual cortex, increased first block VEP amplitude, and turned their lack of habituation into a nearly normal habituation pattern [27]. These findings confirm that evoked potential changes, and in particular the habituation deficit found in migraineurs between attacks, were caused by a decreased preactivation level of sensory cortices supporting the theory of an interictal cortical hypoexcitability.

4.2   Neuroimaging Studies in Migraine

4.2.1   Positron Emission Tomography (PET) Studies Investigating Photophobia and Osmophobia

Osmophobia is an increased sensitivity to odors that, during attack, augmented headache pain, nausea, and vomiting. The pivotal role of the olfactory system in migraine is also documented by an altered odor threshold, hypersensitivity to odor between attacks, and odor as trigger factor for headache. Demarquay et al. investigated migraineurs with interictal olfactory hypersensitivity and controls through PET, both during olfactory stimulation and in odorless condition [28]. During both olfactory and nonolfactory conditions, authors found higher regional cerebral blood flow in the left piriform cortex and anterosuperior temporal gyrus in patients than in controls. During stimulation, a stronger activation of the left temporal pole and reduced activity in frontal, temporoparietal, and brainstem regions were observed in migraineurs when compared to controls. Authors suggest that hyperactivity of the piriform cortex (which is a part of the primary olfactory cortex) could result in facilitated triggering of the trigeminovascular system in response to odors during the interictal and preictal period. They speculate further that the altered pattern during olfactory stimulation in patients reflects an altered cerebrovascular response to olfactory stimulation due to the migraine disease or an abnormal top-down regulation related to olfactory hypersensitivity [28]. This study exclusively included migraine patients reporting hypersensitivity to odors, so these findings could not be migraine specific.

Photophobia is defined as hypersensitivity to light, usually causing avoidance. This feature can be represented by an increase of headache when the patient is exposed to light during the migraine attack and an uncomfortable sense of glare between attacks. Boulloche et al. investigated the interaction between the light perception and trigeminal nociception by using PET [29]. Cortical response of migraineurs between attacks and matched controls was studied with three luminous intensities and with or without pain in the trigeminal territory. In order to facilitate habituation, the stimulations were started 30 s before PET acquisitions. When no concomitant pain stimulation was applied, stimulation activated the visual cortex bilaterally in patients but not in controls, while concomitant pain stimulation allowed visual cortex activation in controls and increased its activation in migraineurs [29]. More recently, the same authors investigated photophobia induced by continuous luminous stimulation through PET in migraineurs during spontaneous attacks, after headache relief by sumatriptan, and during attack-free interval [30]. They found that luminous stimulation with low intensity activated the visual cortex during migraine attacks and after headache relief but not during the interictal period. Authors explained that the absence of cortical activation during the attack-free interval in this study was due to the characteristics of the luminous stimuli. Moreover, this activation was statistically increased during attack than after pain relief. The activation during the headache relief phase was still stronger than during the interictal phase, suggesting that photophobia cannot be explained as a phenomenon

produced exclusively by trigeminal pain. Both of these studies showed that migraineurs' visual cortex is hyperresponsive, or hyperexcitable, to light with respect to healthy subjects, and this feature could explain the uncomfortable sense of glare between attacks in patients. During ictal periods, the visual cortex excitability could possibly be enhanced by brainstem activation justifying photophobia. As the activation of visual cortex was potentiated by trigeminovascular system, headache and sensitivity to light increased in a vicious circle during migraine attack.

4.2.2 Imaging Studies Investigating Cortical Spreading Depression

Cortical spreading depression (CSD) is a neurophysiological phenomenon characterized by a self-propagating wave of neuronal hyperexcitability followed by a temporary hypoexcitability, firstly described in the rabbit cerebral cortex. This migrates at a rate of 2–3 mm/min in all directions through gray matter. The depolarization phase is associated with an increase in regional cerebral blood flow, while the phase of reduced neuronal activity is associated with its reduction. The similarity between the velocity of CSD propagation and the march of visual aura was described. Numerous neuroimaging studies on humans have indirectly suggested that CSD underlies migraine [31]. The first evidence was obtained measuring regional cerebral blood flow in 254 areas of the cerebral hemisphere by means of intracarotid xenon *tomography* during migraine aura. Olesen et al. observed that changes in cerebral blood flow start 5–15 min prior to aura symptoms and described as a slowly spreading oligemia which propagates anteriorly from the occipital cortex with a speed similar to that of CSD. In some cases, the oligemia was preceded by focal hyperemia resembling the hemodynamic effects of experimental CSD [32]. Similar results were confirmed also by Woods et al. in a single case of spontaneous migraine with aura imaged with PET [33]. They observed a bilateral decrease in regional cerebral blood that started in the cortical surface from visual associative cortex and spread to parietal and occipitotemporal areas at a relatively constant rate.

   Perfusion- and diffusion-weighted (PWI and DWI) magnetic resonance imaging studies were also performed to investigate migraine aura. These techniques permit to study cerebral tissue ischemia: PWI measures the hemodynamic changes and the degree of the blood flow decrease, while DWI measures local metabolic and structural changes assessing water diffusion by using apparent diffusion coefficient (ADC). PWI and DWI were used during spontaneous visual auras in four migraineurs in a study performed by Cutrer et al. [34]. The authors found a decrease both in relative cerebral blood flow and cerebral blood volume while detected an increase in the tissue mean transit time. No changes in ADC were observed either while the patients were symptomatic or after resolution of the visual symptoms but before the onset of headache. Authors concluded that ischemia, if is present, is less severe or not persistent enough to cause modifications in ADC. This study

elucidated previously reported hemodynamic changes during migraine with aura. Sanchez del Rio et al. studied three subgroups of migraineurs by using PWI techniques: migraine with aura sufferers during spontaneous visual aura and during headache preceded by aura and migraine without aura sufferers [35]. Perfusion deficits were observed only during episodes of migraine with aura and, in particular, in the occipital visual cortex contralateral to the affected hemifield. Authors observed reductions in regional cerebral blood flow and in relative cerebral blood volume and increases in mean transit time. After 150 min, however, there were increases in regional cerebral blood flow and in relative cerebral blood volume and a reduction in mean transit time suggesting a late hyperperfusion phase. In one subject, repeated measurements during four attacks showed that the perfusion deficit evolves over time reaching its maximum during aura. In one patient who experienced migraine both with and without aura, perfusion deficits were observed only during the first one. These findings suggest that the circulatory changes are most characteristic of migraine with aura. Jager et al. investigated four patients using PWI and DWI imaging: two with persistent visual aura and two with a primary persistent visual disturbance [36]. None of the patients showed any abnormalities on the diffusion trace images or ADC maps. The maps of mean transit time, bolus arrival time, and relative cerebral blood volume resulted symmetrical in all patients without regional areas of hyper- or hypoperfusion.

The strongest evidence of CSD emerged from *functional MRI* (fMRI) studies during aura. The most commonly used method is the measurement of blood-oxygen-level-dependent (BOLD) signal. The BOLD signal reflects the balance between oxyhemoglobin (diamagnetic) and deoxyhemoglobin (paramagnetic); the relative reduction in deoxyhemoglobin decreases the paramagnetic influence and produces increased signal intensity on MRI. This augmented signal reflects increase in oxygen perfusing the tissue providing information on brain regions that are activated. Cao et al. investigated visually triggered migraine attacks in ten patients suffering from migraine with aura, two suffering from migraine without aura, and six controls measuring occipital cortex perfusion by means of BOLD-fMRI [37]. After visual stimulation, six patients with migraine with aura and two with migraine without aura developed their typical headache with or without visual changes. Authors described that, in five of these patients, the onset of headache or visual changes were preceded by suppression of initial activation, related to vasodilatation, whose slowly propagated into contiguous occipital cortex at a rate of 2.9–6 mm/min. Hadjikhani and colleagues analyzed three patients during five episodes of visual aura: in one case the attacks were triggered by exercise, while in the other two spontaneous auras were captured 15–20 min after onset, permitting the authors to scan within headache phase and, in the first patient, at the onset of the episode [31]. This study revealed multiple neurovascular events in the occipital cortex that resemble CSD: (1) an initial focal hyperemia lasting 3.0–4.5 min, spreading at a rate of 3.5 mm/min; (2) followed by mild hypoperfusion lasting 1–2 h; (3) an attenuated response to visual activation; and (4) like CSD, in migraine aura, the first affected area is the first to recover.

4.2.3   Functional and Metabolic Neuroimaging of Brainstem Structures in Migraine

Recent studies evaluating changes in migraine brain function by means of *MRI and PET* revealed the crucial role of midbrain both in ictal and interictal phases of migraine. The first observations were reported analyzing patients who underwent electrode implantation in the periaqueductal gray, and more specifically in the dorsal raphe nucleus, who developed head pain with migrainous features [38]. One study used PET to examine the changes in regional cerebral blood flow as an index of neuronal activity during spontaneous migraine attacks, after relief from the headache by sumatriptan and also during headache-free phase. During the attack, authors found an increased blood flow in the cerebral hemispheres in cingulate, auditory, and visual association cortices and in the brainstem with respect to the interictal phase. However, only the activation of this latter region persisted after treatment. The spatial resolution of the PET camera was not enough to identify specific nuclei, but the dorsal-rostral midbrain and dorsolateral pons seem the foci of maximum activation [38]. These findings were confirmed detecting activation in the dorsal-rostral brainstem in a migraine without aura sufferer [38]. Comparing patients with glyceryl trinitrate-induced migraine and controls, a significant dorsal lateral pons activation was observed [39]. This phenomenon both in migraineurs with aura and without aura was ipsilateral in patients with lateralized headache and bilateral in those with bilateral headache. Denuelle and colleagues scanned migraineurs without aura within 4 h of headache onset, after headache relief by sumatriptan injection, and during an attack-free period reporting activations in the midbrain and pons, but also in the hypothalamus [40]. All these areas of activation persisted after treatment, when posttreatment scans were compared to the interictal phase. An increased iron accumulation in the periaqueductal gray in patients with episodic migraine and with chronic daily headache was observed, and it was positively correlated with the duration of illness [41]. A decreased nucleus cuneiform activation was demonstrated comparing brainstem responses to thermal stimuli of migraineurs during interictal phase and controls [42].

To investigate brain activation in visually triggered migraine, *BOLD-fMRI* was used [37]. Most of the patients who develop symptoms during stimulation showed increased intensities in the red nucleus and substantia nigra before occipital cortex activation [37].

Recently investigating brain responses during trigeminal pain processing in migraine patients and control subjects, a significant increased activation of rostral parts of the pons was noted [43]. This activation was found during the attack but not interictally or shortly before attack. Remarkably, the magnitude of the signal intensities in the spinal nuclei was a good predictor of the distance to the next headache attack. The activity of the spinal trigeminal nuclei in response to nociceptive stimulation showed therefore a cycling behavior: it is generally lower than in controls, rises during interictal period toward the attack, and rapidly decreases just before or at acute headache onset. This oscillating behavior may have a key role in the generation of migraine headache modulated by pain control system.

Brainstem activation was reported also in pain conditions other than migraine [44], and PAG alteration in migraine may lead to a lack of modulation of peripheral activators in migraineurs [45].

4.2.4 Magnetic Resonance Spectroscopy Studies in Migraine

Phosphorus magnetic resonance spectroscopy (^{31}P-MRS) has been extensively used to characterize the role of energetic metabolism in migraine physiopathology. This technique allows to assay several metabolites involved in tissue bioenergetic state such as adenosine triphosphate (ATP), phosphocreatine (PCr), inorganic phosphate (Pi), and adenosine diphosphate (ADP) calculated on the basis of creatine kinase reaction. It permits to calculate also intracellular pH and magnesium content. MRS studies have applied to migraineurs both in interictal and in ictal phases (Table 4.1) [46]. The first studies applied ^{31}P-MRS to patients suffering from migraine with and without aura during headache attack or interictally to detect changes in brain pH triggered by vasospasm-induced ischemia. Although both complete and incomplete ischemia cause a reduction of pH, authors did not find significant differences in brain pH between migraineurs during headache attack or in-between attack and healthy controls. The ratios of PCr to Pi (PCr/Pi) and of PCr to total phosphorus were significantly lower during headache attacks. These results indicated that brain bioenergetic deficit in migraineurs during attack is not caused by changes in cerebral blood flow [46].

The role of the interictal impairment of energy metabolism in migraine has been investigated by the Bologna school [46]. Basing on clinical and biochemical results obtained in muscles and platelets of migraineurs that suggested interictal alterations in oxidative metabolism, authors investigated patients with complicated migraine such as patients with prolonged aura and migraine strokes. Comparing all migraineurs with controls, Pcr/Pi and the ratios of PCr to ATP (PCr/ATP) were reduced, suggesting that a deficit of brain energetic metabolism was present outside attack period, representing therefore an intrinsic feature of the migraineur's brain. More recently, some authors compared patients with migrainous stroke with those with migraine with persistent aura without infarction and controls finding that the second group showed reduced cortical PCr/Pi while the first one showed values similar to healthy controls [46]. A deficit of brain energy metabolism was detected also in patients with migraine with and without aura [46, 47].

Skeletal muscle mitochondrial ATP production rate, assessed by the rate of post-exercise PCr resynthesis, is considered an almost pure index of mitochondrial functionality. Its analysis revealed a substantial deficit in patients with complicated migraine, migraine with aura, and migraine without aura [46]. Deficit of brain and muscle bioenergetics similar to adults was detected in pediatric patients suffering from migraine with aura [46].

Low magnesium (Mg^{2+}) content, indicating bioenergetic metabolism deficit, has been demonstrated in serum, saliva, erythrocytes, and mononuclear cells of migraineurs. Comparing migraineurs with and without aura, a reduction of free

Table 4.1 Major results of electrophysiological and functional imaging studies during ictal and interictal migraine phases

	Ictal phase	Interictal phase
Neurophysiology		
EEG [7, 8]	Alpha suppression	H-response in photic driving
		Normal or abnormal alpha activity
		Alpha rhythm variability
Evoked potentials [13]		
VEP	Normal latencies	↑ or ↓ latencies
		↑ or ↓ amplitudes
		Amplitude or latency asymmetries
		Lack of habituation
AEP	Normalized habituation	Lack of habituation
	↑ Latencies	Normal latencies
CNV	Normal amplitudes	↑ Amplitudes
	Normalized habituation	Lack of habituation
Blink reflex		Lack of habituation
Automatic event-related potentials [22]		↑ Activation of attention-related frontal networks
TMS [13]	Normal or ↑ motor thresholds	
	↑ or ↓ motor evoked potentials	
	↑ or ↓ phosphene thresholds	
	↑ or ↓ phosphene prevalence	
Neuroimaging		
PET [27–29, 37]	Hyperactivity of brainstem	Hyperactivity of piriform cortex in pt with olfactory hypersensitivity
		Hyperactivity of visual cortex in pt with light hypersensitivity
PWI and DWI [33–35]	Findings supporting CSD	
BOLD-fMRI [36, 42]	Findings supporting CSD	
	Hyperactivity of brainstem	
^{31}P-MRS and ^{1}H-MRS [46]	↓ PCr/Pi, [Mg^{2+}]	↓ PCr/Pi, PCr/ATP
		↓ [PCr], [Mg^{2+}], [ATP]
		↑ Lac/NAA or no lactate

[ ] concentration, *^{1}H-MRS* proton magnetic resonance spectroscopy, *^{31}P-MRS* ^{31}phosphorus magnetic resonance spectroscopy, *AEP* auditory evoked potential, *ATP* adenosine triphosphate, *BOLD-fMRI* blood-oxygen-level-dependent functional magnetic resonance imaging, *CNV* contingent negative variation, *CSD* cortical spreading depression, *DWI* diffusion-weighted magnetic resonance, *EEG* electroencephalogram, *Lac* lactate, *Mg^{2+}* magnesium, *NAA* N-acetyl-aspartate, *PCr* phosphocreatine, *PET* positron emission tomography, *Pi* inorganic phosphate, *pt* patients, *PWI* perfusion-weighted magnetic resonance, *TMS* transcranial magnetic stimulation, *VEP* visual evoked potentials

Mg^{2+} concentration was found in cerebral cortex during attack but not interictally. Lodi et al. detected an interictal reduction in Mg^{2+} levels in all subtypes of migraine with respect to healthy controls: patients suffering from migraine without aura had higher free Mg^{2+} concentrations than those with migraine stroke or prolonged aura. The Bologna school reported similar findings also in pediatric patients with migraine with aura [46]. Overall, despite the methodological differences and the heterogeneity of migraine patients, brain ^{31}P-MRS studies revealed an association between the

bioenergetic deficit and the reduced free magnesium concentration both ictally and interictally [46]. Low magnesium is known to lead to neuronal instability and hyper-excitability and so may responsible for predisposing the brain to migraine attack [46]. However, the fundamental mechanisms leading to impaired oxidative phosphorylation and reduced brain Mg^{2+} concentration remain unknown.

Proton MRS (^{1}H-MRS) is based on the acquisition of signals from excitation of the nucleus of hydrogen. This technique allows an "in vivo" quantification of brain metabolite concentrations providing metabolic information from definite brain areas and systems. *N*-acetyl-aspartate (NAA), choline (Cho), creatine/phosphocreatine (Cr), myoinositol (mI), and lactate are the metabolites more commonly observed. Lactate represents the end product of glycolysis that typically accumulates when ATP production switches to anaerobic glycolysis. Lactate is normally undetectable in adult human brain and can be detected in diseases associated with an augmented energy request and/or altered cellular capability for oxidative phosphorylation such as malignant tumors, ischemia, and mitochondrial disorders. Some studies evaluated migraineurs with aura by using ^{1}H-MRS focusing on the occipital lobe both at rest and during stimulation, as visual aura is the most frequent form of aura. The first study on this topic compared metabolite levels in the occipital visual cortex in six normal subjects and five migraine with aura patients and in one with basilar migraine, disclosing high lactate levels in the five patients who had experienced a migraine attack within the previous 2 months [46]. Investigating cortical lactate changes during prolonged visual stimulation in healthy subjects and two groups of migraine with simple visual or complex auras, an increased lactate was observed at baseline in the visual cortex of migraineurs with simple visual aura but not in those with more complex aura, whereas during photic stimulation, lactate in visual cortex increased in migraineurs with more complex aura while remained high in migraineurs with simple visual aura [48]. These results were not confirmed by others authors who showed a greater increase in the lactate peak in migraineurs with aura compared to migraine without aura and healthy subjects.

These differences in results could be explained by different methodology and sampling but a more consistent decrease in NAA in migraine with aura patients compared with those without aura and controls was found. These results were interpreted as indirect evidence of mitochondrial dysfunction because NAA is synthesized in neuronal mitochondria and plays a role in mitochondrial/cytosolic carbon transport [46].

Comparing basal ganglia of migraineurs with aura and controls, no association between any of the metabolite ratios (NAA/Cr, Cho/Cr, and NAA/Cho) and type or duration of aura symptoms was found. Recently, Reyngoudt et al. [47] even when a careful absolute ^{1}H-MRS quantification was performed and a photic stimulation was carried out, no significant differences in the visual cortex of migraineurs without aura were observed compared to controls.

^{1}H-MRS study focusing on thalamus found that patients suffering from migraine without aura during interictal period showed a reduced NAA/Cho in the left side when compared to controls. Other brain structures involved in pain processing were

investigated, such as anterior cingulate cortex and insular cortex, finding normal metabolic profile in migraineurs without aura. However, glutaminergic changes on linear discriminant analysis were demonstrated [46].

Conclusions

Neurophysiological studies highlight abnormalities of cortical responsiveness to external stimuli in migraineurs between attacks. The most consistent result obtained by evoked and event-related potentials of different modalities is that migraine sufferers, in contrast with controls, show an unchanged or increased response to repetitive stimulation. This lack of habituation could be explained by a reduced intracortical inhibition or an increased cortical excitability. The lower initial amplitudes during repetitive stimulation, the higher motor and phosphene threshold, and the reduced phosphene TMS stimulation induced in migraineurs supported the "hypoexcitability theory." On the other hand, the increased phosphene prevalence, the lower phosphene threshold reported using TMS, but also the increased CNV amplitude in interictal phase in patients strengthens the theory of hyperexcitability. These contradictory results may derive from methodological differences but also from the fluctuation of cortical responsiveness in relation to migraine attack. It seems more likely that the interaction between inhibitory and excitatory neurons determines the excitability levels of the cortex leading to an oscillation between high and low cortical excitability defining a "neuronal dys-excitability" [49]. Moreover, studies based on somatosensory evoked high-frequency oscillation found decreased early high-frequency oscillations that reflect spike activity in thalamocortical fibers suggesting that the cortical dysfunction in migraine could be caused by thalamic rhythmic activity called "thalamocortical dysrhythmia."

Functional neuroimaging studies report that different brainstem structures play a pivotal role on the migraine pathogenesis, probably lowering the threshold or decreasing the inhibitory nociceptive pathways and making therefore the system hyperexcitable.

MRS studies highlight that migraine is associated with an impaired energy metabolism that could enhance the susceptibility to headache and associated symptoms when brain energy demand increases due to psychological and physiological factors.

As well as, the complexity of migraine symptoms suggests an alteration of extra-nociceptive brain networks indicating migraine as a brain state [50].

Usually, brain determines what is stressful or potentially stressful, responding adaptively through behavioral and/or physiological mechanisms. This ability to protect the body from stressors is called allostasis. In migraineurs stressors may became additive or cumulative leading to a *maladaptive brain* response with possible structural brain changes that may in turn lead to cortical dys-excitability and altered brain homeostasis [51]. Recently, migraine, considered as an inescapable visceral pain that may lead to a behavioral "sickness" response, in a Darwinian perspective view could represent an adaptive response for recovering the brain's homeostasis [52].

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Epidemiology of Vestibular Migraine and Related Syndromes

Andrea Radtke

5.1 Epidemiological Aspects

A causal link between vertigo and migraine has been suspected, based on epidemiological observations indicating a more than chance association of migraine with vertigo and dizziness. Dizziness and vertigo rank among the most common complaints in the general population and are frequently reported by patients with migraine. The prevalence of migraine has been shown to be increased in patients with dizziness [1] and, in particular, among patients with unclassified recurrent vertigo [2, 3]. Conversely, patients with migraine reported more frequently vertigo than patients with tension-type headache (27 % vs. 8 %) [4]. Vertigo was also more common in migraine patients than in headache-free controls in a case-control study [5]. However, the interrelations of migraine and vertigo are complex as different causes may account for an association. First, since both dizziness/vertigo and migraine are very common in the general population, they may coincide simply by chance. The lifetime prevalence of migraine in industrialized countries has quite consistently been estimated at 13–16 % [6], and dizziness and vertigo affect approximately 20–30 % of the general population [7, 8]. In a large population-based neurotological survey, the lifetime prevalence of dizziness/vertigo was estimated at nearly 30 %. Vertigo of vestibular origin accounted for 7.4 % of all dizziness/vertigo symptoms [9]. Thus, assuming a lifetime prevalence of 14 % for migraine [6] and 7.4 % for vertigo, one can expect a chance coincidence of 1 %. However, the actual prevalence of participants reporting both migraine and vertigo of vestibular origin in the neurotological survey was three times higher (3.2 %), suggesting a more than

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chance concurrence [9]. In addition, other vestibular disorders such as benign paroxysmal positional vertigo [10, 11] and Menière's disease [12] show a statistical link with migraine, the basis of this association still remaining uncertain. In an individual patient with dizziness/vertigo and migraine, clinicians must, therefore, determine if vertigo symptoms are causally related to migraine, if they are caused by another vestibular disorder that is statistically associated with migraine or if vertigo and migraine are unrelated.

5.1.1 Prevalence of Vestibular Migraine

The prevalence of vestibular migraine was 7 % in a group of 200 consecutive patients of a specialized dizziness clinic and 9 % in a group of 200 unselected migraine clinic patients [1]. In a large, two-stage population-based study ($n = 4,869$ adults) with screening interviews followed by expert telephone interviews, the lifetime prevalence of VM was estimated at 0.98 % (95 % CI 0.7–1.37) [13]. Of note, VM accounted for only a third of vertigo symptoms in migraine patients, which underlines the importance to also consider other *vestibular diagnoses* in these patients [13]. In a community-based sample of middle-aged women in Taiwan, VM was identified in 5 % and in 30 % of those with migraine [14].

5.1.2 Demographic Aspects

VM may occur at any age [15, 16]. It shows a marked female preponderance with a reported female to male ratio between 1.5 and 5 to 1 [15–17]. Familial occurrence is not uncommon and probably based on an autosomal dominant pattern of inheritance with decreased penetrance in men [18]. In most patients, migraine begins earlier in life than VM [1, 16]. However, vertigo may precede the onset of migraine headaches by several years, and some patients have been free from migraine headaches for years when vertigo attacks first occur, which may obscure the link between the two [16]. In women, vertigo attacks may replace migraine around menopause.

VM typically first manifests in young and mid-adulthood but may already begin in childhood or, rarely, in older age [16]. Early manifestation of vertigo attacks related to migraine has long been recognized by the ICHD (International Classification of Headache Disorders) as benign paroxysmal vertigo of childhood. The syndrome is characterized by brief attacks of vertigo or disequilibrium, anxiety and often nystagmus or vomiting, recurring for months or years in otherwise healthy young children [19]. Many of these children later develop migraine, often many years after vertigo attacks have ceased. A family history of migraine in first-degree relatives is twofold increased compared to controls [20]. In a population-based study, the prevalence of recurrent vertigo probably related to migraine was estimated at 2.8 % in children between 6 and 12 years [20].

5.1.3   Epidemiological and Clinical Link of Migraine with Other Disorders Causing Vertigo and Dizziness

Prevalence of migraine is increased in some well-defined vestibular disorders such as Menière's disease [12] and benign paroxysmal positional vertigo (BPPV) [10, 11]. In addition, there is a more than chance association of migraine with several other dizziness syndromes including motion sickness [4, 5, 21, 22], orthostatic hypotension and syncope [23, 24], panic disorder [25] and depression [26]. These disorders may be the sole cause for vertigo and dizziness in a patient with migraine or may coexist with VM.

5.2   Migraine and Menière's Disease

The interrelations of migraine and Menière's disease are complex. Vestibular migraine and Menière's disease share many clinical features [4, 27], and prevalence of migraine is increased in patients with Menière's disease [12]. Fluctuating hearing loss, tinnitus and aural pressure may occur in vestibular migraine, but hearing loss does not progress to profound levels [17, 27]. Similarly, migraine headaches, photophobia and even migraine auras frequently occur during Menière attacks [12]. An association of Menière's disease and migraine has already been suggested by Prosper Menière in his first description of the disorder in 1861 [28]. A case-control study in 78 patients with idiopathic unilateral or bilateral Menière's disease according to the criteria of the American Academy of Otolaryngology [29] found a twofold increased prevalence of migraine according to the ICDH-2 criteria compared to age- and sex-matched controls (56 % vs. 25 %). Nearly half of the Menière patients always experienced at least one migrainous symptom (migrainous headache, photophobia, aura symptoms) along with their Menière attacks, suggesting a pathophysiological link between the two disorders or reflecting an unsolved overlap of clinical symptoms and current diagnostic criteria [12, 30]. Patients with features of both Menière's disease and vestibular migraine have been repeatedly reported [31]. Migraine, episodic vertigo and Menière's disease may occur in familial clusters, suggesting genetic inheritance [32]. Comorbidity with migraine was found to be associated with a more severe clinical phenotype of Menière's disease, with an earlier age of onset and higher incidence of bilateral cochlear involvement [31]. Common pathophysiological mechanisms that may cause a variable phenotype of vertiginous, cochlear and migrainous symptoms include neurotransmitter imbalances [15, 33] or defunct ion channels which are expressed both in the inner ear and brain [34].

In the first few years after onset of symptoms, differentiation of vestibular migraine from Menière's disease may be challenging, as Menière's disease can be monosymptomatic with vestibular symptoms only in the early stages of the disease. As a rule, the two disorders can be distinguished when a pronounced sensorineural hearing loss becomes evident in Menière's disease within a few years, while cochlear impairment in VM, if present, remains mild even at longer follow-up [27].

5.3   Migraine and Benign Paroxysmal Positional Vertigo (BPPV)

Recurrent episodes of positionally induced, short-lasting vertigo attacks in VM may closely resemble benign paroxysmal positional vertigo (BPPV) [35]. Although clinically two separate entities, there is clinical evidence for a link between migraine and BPPV. Migraine is three times more common in patients presenting with idiopathic BPPV compared to patients with BPPV secondary to trauma or surgical procedures [10]. Similarly, the prevalence of migraine was two times higher in patients with idiopathic BPPV compared to age- and sex-matched controls [11]. Genetic factors and vascular damage to the labyrinth have been proposed as potential pathophysiological mechanisms linking the two disorders [10].

In a patient with migraine and episodic positional vertigo, the clinician must, therefore, determine if positional vertigo is due to vestibular migraine or if BPPV exists as a comorbid condition. When patients present during the acute episode, BPPV is easily diagnosed by the typical nystagmus beating in the plane of the affected semicircular canal, which is elicited on positional testing [36]. In patients with VM, most often a central-type positional nystagmus can be observed during the acute attack [37, 38]. In the vertigo-free interval, episodic positional vertigo in VM may be distinguished from BPPV by its shorter episode duration and greater episode frequency [35].

5.4   Migraine and Motion Sickness

Migraineurs are more susceptible to motion sickness (30–50 %) than patients with tension headache or headache-free controls (about 20 %) [4, 5, 21]. Susceptibility to vestibular stimuli may be most marked in patients with VM who were four times more likely to become nauseous during caloric testing compared to patients with other causes of dizziness [39] and showed the highest motion sickness scores among patients with different types of migraine [22].

Conversely, vestibular stimulation by caloric testing induced migraine attacks in half of 39 migraineurs within 24 h, the effect being most pronounced in migraineurs with VM. Interestingly, migraine headaches were also triggered by caloric stimulation in 12 % of non-migraineurs [40]. Migraineurs also report more 'visual vertigo' while looking at spinning objects [5]. Headache, scalp tenderness and photophobia could be provoked by optokinetic stimulation in a recent study. Migraineurs were more nauseated and had longer-lasting headache and photophobia than controls [41]. Recently, *rizatriptan*, a serotonin agonist effective in treatment of migraine headaches, has been shown to reduce vestibular-induced motion sickness in migraineurs [42]. Pathophysiological models explaining the concurrence of headache, vertigo and motion sickness in migraineurs include common neurotransmitters such as *serotonin* which are active in the inner ear, trigeminal ganglion and brainstem vestibular and trigeminal nuclei and solitary nucleus as well as shared central neuronal circuits for vestibular and nociceptive information processing [43].

5.5   Migraine and Orthostatic Intolerance and Syncope

Transient loss of consciousness has since long been known as a prominent symptom in basilar migraine as described by Bickerstaff [44]. However, orthostatic hypotension and syncope also frequently occur in other subtypes of migraine. Orthostatic symptoms were more common in patients with migraine than in controls (68 % vs. 8 %) [45]. Among 451 females aged 15–44 years, fainting spells were more frequently reported by women with migrainous headaches (11 %) than by those without migraine (2 %) [46]. In the population-based CAMERA study, migraineurs showed an elevated lifetime prevalence of syncope (43 % vs. 31 %), recurrent syncope (13 % vs. 5 %) and orthostatic intolerance (32 % vs. 12 %) compared to non-migraineurs [24]. Syncope during migraine attacks has been reported to occur in 5 [41] to 10 % [47] of migraineurs. In a series of 248 patients with frequent syncope, a high rate of migraine headaches preceding or following syncopal episodes was reported (30 %), leading to the hypothesis of 'syncopal migraine', i.e. recurrent syncopes caused by a primary migrainous mechanism [48].

Case studies on autonomic function in migraine patients have yielded conflicting results, reporting both hypo- and hyperfunction of the sympathetic and parasympathetic systems [24]. However, the CAMERA study, despite the finding of an increased prevalence of syncope and orthostatic hypotension among migraine sufferers, did not reveal clear interictal signs of autonomic nervous system failure in migraineurs [24].

5.6   Migraine and Cerebellar Function

Cerebellar dysfunction causes imbalance, which patients may experience as dizziness. In recent years, several neuronal disorders presenting with a variable phenotype of episodic vertigo, *cerebellar ataxia* and different subtypes of migraine have been identified to be caused by defect ion channels that are expressed in the cerebellum and other brain structures. Patients with *familial hemiplegic migraine* (FHM), a rare subtype of migraine, may develop progressive cerebellar ataxia and nystagmus [49]. Mutations in the CACNA1A gene coding for the 1A subunit of a neuronal Ca2+ channel, which is heavily expressed in the cerebellum, have been identified not only in FHM but also in episodic ataxia type 2 (EA-2) [50] and spinocerebellar ataxia type 6. Episodic ataxia (EA-2) is characterized by short attacks of cerebellar ataxia or vertigo and interictal nystagmus. Approximately half of the patients with EA-2 also have migraine [34]. Both FHM and EA-2 may be associated with typical symptoms of basilar migraine [34, 51]. Subtle interictal signs of vestibulocerebellar dysfunction have also been found in 83 % patients with migraine and were more pronounced in patients with migraine with aura [52]. Similarly, up to two thirds of patients with VM show interictal central vestibular and ocular motor deficits indicating mild cerebellar and brainstem dysfunction which tend to somewhat progress with time [16, 27, 53]. However, the search for genetic mutations of ion channels involved in other subtypes of migraine and progressive cerebellar ataxia has been negative in VM so far [54, 55].

5.7   Association of Migraine and Dizziness with Psychiatric Disorders

Migraine, dizziness and psychiatric disorders are interrelated in a complex way. Migraine has been identified as a risk factor for several psychiatric disorders [25, 26]. Migraineurs carry a three- to fourfold risk to suffer from major depression [26] and panic disorders [25] compared to non-migraineurs. Conversely, a previous history of major depression or panic disorder is associated with an increased likelihood to develop migraine [25, 26], the bidirectional associations being strongest in migraine with aura [25, 26].

Dizziness is the second most common symptom of panic attacks after palpitations and can be a prominent symptom of major depression and somatoform disorders as well. Patients with panic and anxiety show an increased rate of vestibular test abnormalities [56]. Conversely, patients with vestibular disorders carry an elevated risk to develop secondary *anxiety* and depressive disorders [57, 58]. Patients with VM show the highest rate of concurrent anxiety and depressive disorders (up to 70 %) compared to other vestibular disorders [57, 58]. Of note, while a previous history of psychiatric illness increases the risk of emotional distress and anxiety in response to vestibular disorders, the extent of vestibular abnormalities seems to have no impact on the development of secondary psychiatric disorders in these patients [57]. Psychiatric comorbidity is associated with sustained dizziness symptoms in VM [57]. Because of the frequent association of dizziness, migraine and anxiety, a new syndrome named migraine-anxiety-related dizziness (MARD) has been proposed, and hypotheses on neuroanatomical links connecting the vestibular system to neuronal pathways involved in emotional processing have been formulated [59].

Thus, in patients with migraine and vertigo/dizziness symptoms, the clinician has to determine if vertiginous symptoms are caused by VM or if they are due to a primary or coexistent psychiatric disorder. Since psychiatric comorbidity increases the risk for development of chronic dizziness symptoms in VM, early recognition and treatment of underlying psychiatric disorders is essential.

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Vestibular Migraine: Classification and Clinical Features

Thomas Lempert

6.1 Introduction

The interrelations of vertigo and migraine are increasingly recognized by the medical community. The number of published papers on vestibular migraine (VM) has rocketed in the last decades. A PubMed search using the term "migraine" and "vestibular" yields 10 hits before 1980, 70 between 1980 and 2000 and 310 since then. That migraine may present with attacks of vertigo has been noted from the early days of neurology [1]. Starting with Kayan and Hood's classical paper [2], the clinical features of VM have been well elucidated in several large case series [3–9]. Various terms have been used to designate vertigo caused by a migraine mechanism including migraine-associated vertigo, migraine-associated dizziness, migraine-related vestibulopathy, migrainous vertigo, benign recurrent vertigo and basilar migraine. *Vestibular migraine* has been convincingly advocated as a term that stresses the particular *vestibular* manifestation of migraine and thus best avoids confounding with non-vestibular dizziness associated with migraine [10]. Therefore, the Bárány Society and the International Headache Society (IHS) have opted for *vestibular migraine* in their recent joint paper on the classification of the disorder [11].

6.2 Diagnostic Criteria for Vestibular Migraine

In the previous International Classification of Headache Disorders (ICHD-2), vertigo was not included as a migraine symptom in adults except in the framework of basilar-type migraine [12], which leads to vertigo in more than 60 % of the patients [13]. As an aura symptom of basilar-type migraine, vertigo should last between 5

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and 60 min and should be followed by migraine headaches. In addition, at least one more aura symptom from the posterior circulation is required. Less than 10 % of patients with VM fulfilled the criteria for basilar-type migraine [5–8], which makes basilar-type migraine an inappropriate category for most of these patients.

Therefore, the Bárány Society, which represents the international community of basic scientists, otolaryngologists and neurologists committed to vestibular research, mandated a classification group to develop diagnostic criteria for VM. The draught of the classification was extensively discussed with the Migraine Classification Committee of the International Headache Society, which resulted in a joint document defining *vestibular migraine* and *probable vestibular migraine* [11]. These criteria have been included in the third edition of the International Classification of Headache Disorders (ICHD-3), published in 2013 [14]. VM appears in the appendix for new disorders that need further research for validation. In addition, the classification of vestibular migraine is part of the evolving Classification of Vestibular Disorders of the Bárány Society. The new ICHD-3 includes only *vestibular migraine*, while the Bárány classification also contains *probable vestibular migraine* (Table 6.1).

6.3 Prevalence of Vestibular Migraine

Vestibular migraine was diagnosed in 7 % in a group of 200 dizziness clinic patients and in 9 % of 200 migraine clinic patients [8]. In a population-based study ($n = 4,869$) with screening interviews followed by expert telephone interviews, the lifetime prevalence of VM was estimated at 0.98 % (95 % CI 0.7–1.37) [18]. Of note, VM accounted for only a third of migraine patients with a history of vertigo, which indicates the need for a thorough neuro-otological workup for exclusion of other diagnoses [18]. In a community-based sample of middle-aged women in Taiwan, VM was identified in 5 % and in 30 % of those with migraine [19]. VM is still widely underdiagnosed, as shown by a study from a dizziness clinic in Switzerland, where VM accounted for 20 % of the diagnoses in young patients, but was suspected by the referring doctors in only 2 % [20] (for an extensive review on epidemiology of VM, see Chap. 5 in this volume).

6.3.1 Demographic Aspects

VM may occur at any age [4, 5, 7]. It is more common in women with a reported female to male ratio between 1.5 and 5 to 1 [5–8]. Familial clustering may occur, probably based on an autosomal dominant pattern of inheritance with decreased penetrance in men [21]. In most patients, migraine begins earlier in life than VM [7, 8]. Some patients have been free from migraine attacks for years when VM first manifests itself [7]. Not infrequently, vertigo attacks replace migraine headaches in women around menopause.

Table 6.1 Diagnostic criteria for vestibular migraine

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1. *Vestibular migraine*

A. At least five episodes with vestibular symptoms[a] of moderate or severe intensity[b], lasting 5 min to 72 h[c]

B. Current or previous history of migraine with or without aura according to the International Classification of Headache Disorders (ICHD)[d]

C. One or more migraine features with at least 50 % of the vestibular episodes[e]:

    Headache with at least two of the following characteristics: one-sided location, pulsating quality, moderate or severe pain intensity, aggravation by routine physical activity

    Photophobia and phonophobia[f]

    Visual aura[g]

D. Not better accounted for by another vestibular or ICHD diagnosis[h]

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2. *Probable vestibular migraine*

A. At least five episodes with vestibular symptoms[a] of moderate or severe intensity[b], lasting 5 min to 72 h[c]

B. Only one of the criteria B and C for vestibular migraine is fulfilled (migraine history *or* migraine features during the episode)

C. Not better accounted for by another vestibular or ICHD diagnosis[h]

Notes

[a]Vestibular symptoms, as defined by the Bárány Society's Classification of Vestibular Symptoms [15] and qualifying for a diagnosis of vestibular migraine, include:

    Spontaneous vertigo including

      Internal vertigo, a false sensation of self-motion

      External vertigo, a false sensation that the visual surround is spinning or flowing

    Positional vertigo, occurring after a change of head position

    Visually induced vertigo, triggered by a complex or large moving visual stimulus

    Head motion-induced vertigo, occurring during head motion

    Head motion-induced dizziness with nausea. Dizziness is characterized by a sensation of disturbed spatial orientation. Other forms of dizziness are currently not included in the classification of vestibular migraine

[b]Vestibular symptoms are rated "moderate" when they interfere with but do not prohibit daily activities and "severe" if daily activities cannot be continued

[c]Duration of episodes is highly variable: About 30 % of patients have episodes lasting minutes, 30 % have attacks for hours and another 30 % have attacks over several days. The remaining 10 % have attacks lasting seconds only, which tend to occur repeatedly during head motion, visual stimulation or after changes of head position. In these patients, episode duration is defined as the total period during which short attacks recur. At the other end of the spectrum, there are patients who may take 4 weeks to fully recover from an episode. However, the core episode rarely exceeds 72 h [4–8, 16]

[d]Migraine categories 1.1 and 1.2 of the ICDH-2 [12]

[e]One symptom is sufficient during a single episode. Different symptoms may occur during different episodes. Associated symptoms may occur before, during or after the vestibular symptoms

[f]Phonophobia is defined as sound-induced discomfort. It is a transient and bilateral phenomenon that must be differentiated from recruitment, which is often unilateral and persistent. Recruitment leads to an enhanced perception and often distortion of loud sounds in an ear with decreased hearing

[g]Visual auras are characterized by bright scintillating lights or zigzag lines, often with a scotoma that interferes with reading. Visual auras typically expand over 5–20 min and last for less than 60 min. They are often, but not always restricted to one hemifield. Other types of migraine aura, e.g. somatosensory or dysphasic aura, are not included as diagnostic criteria because their phenomenology is less specific and most patients also have visual auras

[h]History and physical examinations do not suggest another vestibular disorder, *or* such a disorder is considered but ruled out by appropriate investigations, *or* such disorder is present as a comorbid or independent condition, but episodes can be clearly differentiated. Migraine attacks may be induced by vestibular stimulation [17]. Therefore, the differential diagnosis should include other vestibular disorders complicated by superimposed migraine attacks

6.4   Vestibular Migraine in Children

Benign paroxysmal vertigo of childhood is an early manifestation of VM which is recognized by the ICHD [14]. It is characterized by brief attacks of vertigo or disequilibrium, anxiety and often nystagmus or vomiting, recurring for months or years in otherwise healthy young children [22]. Many of these children later develop migraine, often years after vertigo attacks have ceased [23]. A family history of migraine in first-degree relatives is twofold increased compared to controls [24]. The prevalence of recurrent vertigo probably related to migraine was estimated at 2.8 % in children between 6 and 12 years in a population-based study [24].

6.4.1   Symptoms

6.4.1.1 Types of Vertigo

Patients with VM typically report spontaneous or positional vertigo. Some experience a sequence of spontaneous vertigo transforming into positional vertigo after several hours or days. This positional vertigo is distinct from benign paroxysmal positional vertigo (BPPV) with regard to duration of individual attacks (often as long as the head position is maintained in VM versus seconds only in BPPV), duration of symptomatic episodes (minutes to days in VM versus weeks in BPPV) and nystagmus findings [25]. Altogether, 40–70 % of patients experience positional vertigo in the course of the disease, but not necessarily with every attack. A frequent additional symptom is head motion intolerance, i.e. imbalance, illusory motion and nausea aggravated or provoked by head movements [5, 26]. Visually induced vertigo, i.e. vertigo provoked by moving visual scenes such as traffic or movies, can be another prominent feature of VM [5, 27]. Nausea and imbalance are frequent but nonspecific accompaniments of acute VM. The combination of different types of vertigo distinguishes VM from other neuro-otological disorders such as benign paroxysmal positional vertigo or Menière's disease, which typically present with monosymptomatic vertigo. Patients with VM are often affected by motion sensitivity even in-between attacks [28], which may lead to a chronic type of vestibular dizziness [25]. Another factor contributing to *chronic vestibular migraine* is secondary psychiatric morbidity, particularly anxiety disorders [29, 30]. These two components of interictal dizziness may not be easily discriminated in individual patients [31].

6.4.1.2 Relation to Headaches

VM often misses not only the duration criterion for an aura as defined by the ICHD but also the temporal relationship to migraine headaches: vertigo can precede headache as would be typical for an aura, may begin with headache or may appear late in the headache phase. Many patients experience attacks both with and without headache [4, 6, 7]. Quite frequently, patients have an attenuated headache with their vertigo as compared to their usual migraine [3, 6]. In some patients, vertigo and

headache never occur together [4, 6, 8]. Misdiagnosis of VM as "cervical vertigo" may occur when accompanying pain is mainly or exclusively localized in the neck, which is quite common in patients with migraine [32].

6.4.1.3 Other Symptoms

Along with the vertigo, patients may experience photophobia, phonophobia, osmo-phobia and visual or other auras. These phenomena are of diagnostic importance, since they may represent the only apparent connection of vertigo and migraine. Patients need to be asked specifically about these migraine symptoms since they often do not volunteer them. A dizziness diary can be useful for prospective record-ing of associated features.

Auditory symptoms, including hearing loss, tinnitus and aural pressure, have been reported in up to 38 % of patients with VM [2, 5, 6, 33, 34]. Hearing loss is usually mild and transient, without or with only minor progression in the course of the disease [6]. About 20 % develop mild bilateral downsloping hearing loss over the years [35]. In contrast, unilateral moderate to severe hearing loss starting in the low-frequency range would rather favour a diagnosis of Menière's disease.

6.4.1.4 Precipitating Factors

Asking for migraine-specific precipitants of vertigo attacks may provide valuable diagnostic information, e.g. provocation by menstruation, deficient sleep, excessive stress, skipped meals, lack of fluid and exposure to sensory stimuli, such as bright or scintillating lights, intense smells or noise. The influence of specific foods and weather conditions is probably overestimated. Sometimes, migraine accompani-ments and typical precipitants may be missing, but VM is still considered the most likely diagnosis after other potential causes have been investigated and appear unlikely. In this case, a favourable response to antimigraine drugs may support the suspicion of an underlying migraine mechanism. However, apparent efficacy of a drug should not be regarded as a definite confirmation of the diagnosis, since spon-taneous improvement, placebo response and additional drug effects (e.g. anxiolytic or antidepressant) have to be taken into account.

6.5   Findings on Clinical Examination

In most patients, the general neurologic and otologic examination is normal in the symptom-free interval [4]. Neuro-ophthalmological evaluation may reveal mild central ocular motor deficits such as persistent positional nystagmus and saccadic pursuit, particularly in patients with a long history of VM [7, 35, 36]. Interictal head-shaking nystagmus was observed in 50 % of VM patients [37]. In one study, patients with VM became nauseous after caloric testing four times more often than migraine patients with other vestibular disorders [38]. A neuro-otologic study of 20 patients during the *acute* phase of VM showed pathological nystagmus in 14 patients, mostly central spontaneous or positional nystagmus. Three patients had a peripheral type of spontaneous nystagmus and a unilateral deficit of the horizontal

vestibuloocular reflex. Imbalance was observed in all patients except one [39]. Another study confirmed the high prevalence of persistent positional nystagmus, which was often horizontal and direction changing, but could also beat in the vertical or torsional plane [40].

Vestibular testing in the interval can be useful to reassure patient and doctor that there is no severe abnormality, such as a complete canal paresis which would rather suggest another diagnosis. MRI is required in patients presenting with central abnormalities and no previous history of similar attacks. Audiometry helps to differentiate VM from Menière's disease. In clinical practice, history will usually provide more clues for the diagnosis than vestibular testing, since there are no abnormalities which are specific for VM. Therefore, in patients with a clear-cut history, no additional vestibular tests are required (for details on vestibular testing abnormalities, see Chap. 7 in this volume).

6.6   Differential Diagnosis

The differential diagnosis of vestibular migraine includes other disorders causing spontaneous and positional vertigo. Again, history taking provides more valuable clues than technical procedures, which rather serve to provide further evidence for or against a clinical working diagnosis.

6.6.1   Menière's Disease

The interrelation of migraine with Menière's disease may cause particular diagnostic problems. Migraine is more common in patients with Menière's disease than in healthy controls [41]. Patients with features of both Menière's disease and vestibular migraine have been repeatedly reported [41, 42]. In fact, migraine and Menière's disease can be inherited as a symptom cluster [43]. Fluctuating hearing loss, tinnitus and aural pressure may occur in vestibular migraine, but hearing loss does not progress to profound levels [6, 44]. Similarly, migraine headaches, photophobia and even migraine auras are common during Menière's attacks [41, 45]. The pathophysiological relationship between vestibular migraine and Menière's disease remains uncertain. In the first year after onset of symptoms, differentiation of vestibular migraine from Menière's disease may be challenging, as Menière's disease can be monosymptomatic with vestibular symptoms only in the early stages of the disease. When the criteria for Menière's disease [46] are met, particularly hearing loss as documented by audiometry, Menière's disease should be diagnosed, even if migraine symptoms occur during the vestibular attacks. Only patients who have two different types of attacks, one fulfilling the criteria for vestibular migraine and the other for Menière's disease, should be diagnosed with the two disorders. A future classification of VM may include a vestibular migraine/Menière's disease overlap syndrome [34].

6.6.2   Benign Paroxysmal Positional Vertigo (BPPV)

VM may present with purely positional vertigo, thus mimicking BPPV. Direct nystagmus observation during the acute phase may be required for differentiation. In vestibular migraine, positional nystagmus is usually persistent and not aligned with a single semicircular canal. Symptomatic episodes tend to be shorter with vestibular migraine (minutes to days rather than weeks) and more frequent (several times per year with VM rather than once every few years with BPPV) [25].

6.6.3   Transient Ischemic Attacks (TIAs)

A differential diagnosis of vertebrobasilar TIAs must be considered particularly in elderly patients. Suggestive features include vascular risk factors, coronary or peripheral atherosclerosis, sudden onset of symptoms, total history of attacks of less than 1 year and angiographic or Doppler ultrasound evidence for vascular pathology in the vertebral or proximal basilar artery.

6.6.4   Vestibular Paroxysmia

Vestibular paroxysmia is a controversial disorder, presumably caused by vascular compression of the vestibular nerve. The presenting feature is brief attacks of vertigo, lasting from one to several seconds, which recur many times per day. Successful prevention of attacks with carbamazepine supports the diagnosis.

6.6.5   Psychiatric Dizziness Syndromes

Anxiety and depression may cause dizziness and likewise complicate a vestibular disorder. Anxiety-related dizziness is characterized by situational provocation, intense autonomic activation, catastrophic thinking and avoidance behaviour. More than 50 % of patients with VM have comorbid psychiatric disorders [47].

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Vestibular Migraine: Vestibular Testing and Pathophysiology

7

Michael von Brevern

The pathophysiology of vestibular migraine (VM) is still a matter of speculation. Up to recently, it was not even known whether the origin of VM is in the peripheral or central vestibular system. Clinical examination of patients with acute VM has now clarified that the vast majority of patients suffer from central vestibular dysfunction.

Neither in the acute episode nor in the interval is there any specific testing abnormality in vestibular migraine. However, laboratory testing can be useful to exclude other diseases and to reassure the patient. It is important to bear in mind that minor signs of peripheral and central vestibular dysfunction are not uncommon in patients with vestibular migraine in the symptom-free interval. Many older studies on laboratory findings in patients with vestibular migraine are limited by the fact that they lack specific diagnostic criteria for VM, control groups, and normative data, but recently studies overcoming these limitations have been published. In the following, findings in the symptom-free interval and during the acute episode are summarized.

7.1 Clinical and Laboratory Testing in the Interval

The most consistent laboratory finding in VM is a unilateral reduced caloric response (Table 7.1). In most studies, about 10–20 % of patients with VM showed a unilateral canal paresis [1–13]. The magnitude of caloric asymmetry has been reported in almost none of these studies. Thus, it is unclear whether a complete or almost complete canal paresis is compatible with a diagnosis of VM. In one study, about a quarter of patients with a canal paresis had a side difference of more than 50 % [10].

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Table 7.1 Prevalence of oculomotor and vestibular dysfunction in patients with vestibular migraine in the symptom-free interval

Reference	n	Spontaneous nystagmus (%)	Central positional nystagmus (%)	Saccadic pursuit (%)	Central oculomotor disorder (%)	Unilateral caloric paresis (%)
Cutrer and Baloh [2]	91	7	7	n.r.	n.r.	21
Cass et al. [3]	100	7	13	3	n.r.	18
Dietrich and Brandt [4]	90	11	11	48	66	8
Bir et al. [5]	53	0	n.r.	24	n.r.	12
Celebisoy et al. [6]	35	0	n.r.	9	12	20
Wang et al. [7]	62	26	n.r.	21	n.r.	21
Teggi et al. [8]	30	3	10	9	23	20
Casani et al. [9]	22	n.r.	9	14	18	18
Radtke et al. [10]	61	2	18	8	28	16
Neugebauer et al. [11]	30	3	n.r.	57	63	7
Boldingh et al. [13]	38	5	19	13	54	16

n.r. not reported

Bilateral caloric hyporesponsiveness has been reported in up to 11 % [1, 10, 14, 15] and an isolated directional preponderance of caloric responses in about 10 % of patients with VM [1, 4, 16]. Interestingly, patients with VM are four times more likely to have an emetic response to caloric stimulation than patients with a vestibular disorder coexisting with migraine [16].

A pathological head impulse test has been reported in up to 26 % of patients with VM [13], but in our experience, it occurs only exceptionally [10].

Rotatory chair testing revealed an isolated directional preponderance in about 20 % of patients [3, 4]. Some authors reported a reduced gain of the horizontal vestibulo-ocular reflex during rotatory chair testing [17, 18], but this finding was confirmed in only 1 % of patients in a large case series [3].

Assessment of cervical and ocular vestibular-evoked myogenic potentials (cVEMPs and oVOMPs) has yielded either unilaterally or bilaterally reduced amplitudes in about two-thirds of patients with VM indicating saccular and utricular dysfunction [19, 20]. Another study found absent cVEMPs in 43 % of patients with VM [21]. Cervical recorded VEMPs were also absent in 35 % of 20 patients with basilar-type migraine, most of them experiencing vertigo [22]. The latencies of the response were only rarely prolonged in patients with VM [23], being normal in most studies [19–21]. VEMPs do not seem to be helpful for the differentiation of VM from Menière's disease, where similar results can be found [19]. One study elicited VEMPs applying tone bursts of various frequencies and concluded that this method may help to separate VM from Menière's disease, but these results await replication [24].

A large case series of patients with VM yielded normal results of posturography in 74 % of patient [3]. Group analysis of posturography demonstrated excessive reliance on somatosensory cues [6] or on visual cues [8, 9] in patients with VM as compared to controls.

Saccadic pursuit has been reported in 3 % [3] to about 57 % [11] of patients with VM. No other ocular motor finding has been reported with such a wide variance in patients with VM. Most authors found that saccadic pursuit occurs in about 10–20 % of patients with VM in the interval (Table 7.1). Assessment of smooth pursuit is problematic as it relies on attention and cooperation of the patient. Furthermore, the vast majority of studies assessed smooth pursuit clinically without eye movement recording. Two case series that described saccadic horizontal smooth pursuit in about half of patients with VM found impaired fixation suppression of the vestibulo-ocular reflex (VOR) in only 3 % of these patients [4, 11]. These are conflicting findings as cancelation of the VOR is typically impaired when smooth pursuit is saccadic [10].

Spontaneous nystagmus is rare in the interval with a prevalence of well below 10 % in most case series (Table 7.1). In contrast, positional nystagmus of a central type is not uncommon and has been described in about 10–20 % of patients (Table 7.1). Gaze-evoked nystagmus occurred in less than 5 % of patients in several case series [6, 9, 10, 13, 25], and only Dietrich and Brandt observed gaze-evoked nystagmus in a large proportion of patients (27 %) with VM [4]. Head-shaking nystagmus has been described in 15–50 % of patients [10, 12, 13, 25] and can be horizontal or downbeating [25]. Vibration-induced nystagmus typically indicating peripheral vestibular hypofunction [26] has been observed in 32 % of patients with VM [12].

It is important to notice that these clinical and laboratory findings are not specific to patients with vestibular migraine but can also be found in migraine patients without a history of vestibular symptoms. A unilateral canal paresis has been described in up to 35 % of migraine patients without vertigo [9, 13, 27]. Clinical examination yielded head-shaking nystagmus in 9–25 % of migraine patients without vertigo [13, 25]. Likewise, central positional nystagmus has been described in patients with migraine without a history of vestibular symptoms [28]. While a high frequency of pathological oculographic findings has been reported by several authors in migraine [5, 9, 27–29], other authors failed to find significant abnormalities [30, 31]. Several studies examined the prevalence of vestibular dysfunction in patients with vestibular migraine as compared to migraine patients without vertigo. In two studies. the prevalence of peripheral and central vestibular dysfunction did not differ between both groups [5, 9], whereas another study reported a higher prevalence of central and peripheral vestibular dysfunction in patients with VM (70 %) than in migraine patients (38 %) [13]. In particular, unilateral caloric hyporesponsiveness has been found with similar frequency in migraine patients with and without a history of vestibular symptoms [9, 13]. Only saccadic pursuit seems to be more frequent in VM as compared to migraine without vertigo [9, 13].

Two studies examined the evolution of interictal vestibular and ocular motor dysfunction in patients with VM over time. In a group of 61 patients with VM, the prevalence of at least one ocular motor abnormality increased from 15 % at initial presentation to 41 % after a median follow-up time of 9 years [10]. The most frequent abnormalities were positional nystagmus and head-shaking nystagmus (Table 7.2). Definite central-type positional nystagmus was present at follow-up in

Table 7.2 Interictal ocular motor abnormalities in 61 patients with definite vestibular migraine at initial presentation and after a median follow-up time of 9 years

	Initial presentation (%)	Follow-up (%)
At least one ocular motor abnormality	15	41
Positional nystagmus	12	28
Head-shaking nystagmus	2	15
Gaze-evoked nystagmus	0	4
Spontaneous nystagmus	2	2
Saccadic pursuit	0	8
Deficit of visual VOR suppression	2	8
Pathological saccades	0	0
Unilateral deficit on head impulse test	2	3

Modified from [10]

18 % of patients. Another 8-year-long observational study with 30 patients found that the prevalence of central ocular motor deficits increased from 20 to 63 % in VM [11]. In this study, the most common finding was saccadic pursuit.

In general, signs of central ocular motor and vestibular dysfunction remain subtle throughout the course and do not worsen over the years [10, 11]. Interestingly, interictal ocular motor abnormalities may show some variation over time [4, 10], and in some patients ocular motor dysfunction may even turn to normal at follow-up [10]. Thus, ocular motor abnormalities observed in the symptom-free interval may partly reflect delayed recovery of vestibular dysfunction after an acute vertigo attack.

Audiometry revealed sensorineural hearing loss not attributable to any cause in up to 20 % of patients [15]. A review on audiometric findings in vestibular migraine summarized results of nine studies and found an average prevalence of unexplained hearing loss of 7.5 % [32]. Thus, hearing loss is rather unusual, and low-frequency, progressive, or fluctuating hearing loss, typical for Menière's disease, is a rare finding in vestibular migraine. In a case series of 61 patients with VM, 18 % of patients had developed mild bilateral sensorineural hearing loss with a downsloping pattern involving also the low-frequency range after a median follow-up time of 9 years after initial presentation [10].

In summary, patients with VM may yield mild signs of peripheral and central vestibular dysfunction in the symptom-free interval. The prevalence of vestibular and ocular motor abnormalities increases with time. These clinical signs and testing results are not specific to VM and may also be found in patients with migraine without vestibular symptoms. However, interictal central-type positional nystagmus may provide an additional clue in diagnosing patients with episodic vertigo. Since central-type nystagmus is clearly not caused by peripheral vestibular disorder, it should raise suspicion of VM as a potential cause of episodic vertigo when other central causes have been excluded. Gross vestibular or ocular motor abnormalities are hardly compatible with VM and should raise the suspicion of another disease.

7.2   Findings During an Episode

Examination during an episode of vestibular migraine usually yields pathological nystagmus, indicating central vestibular dysfunction in most patients. A prospective neurotologic study of 20 patients during the acute phase of vestibular migraine recorded pathological nystagmus in 70 % of patients by means of 3D video-oculography [33]. A peripheral type of spontaneous nystagmus with a unilateral deficit of the horizontal vestibulo-ocular reflex was observed in three patients, a central type of spontaneous nystagmus in three, a central positional nystagmus in five, and a combined central spontaneous and positional nystagmus in three patients during the acute episode of VM. Hearing was not affected in any patient during the episode. Saccadic pursuit was noted in five patients during the attack and in three of them also in the interval. Overall, findings pointed to central vestibular dysfunction in ten patients (50 %) and to peripheral vestibular dysfunction in three patients (15 %) and were inconclusive with regard to the involved structure in 35 %. On follow-up vestibular and ocular motor abnormalities had disappeared in almost all patients.

A retrospective study reported on findings of 26 patients presenting with pathological nystagmus during acute VM [34]. All patients had positional nystagmus, mostly of a horizontal, direction-changing type. Furthermore, 19 % of patients presented with spontaneous nystagmus and 35 % with head-shaking-induced nystagmus always beating in the horizontal plane. As intensity of nystagmus was weak, it could only be observed with fixation blocked. In the interval, nystagmus seen in the acute phase had dissipated in all patients. Caloric testing was normal in all patients. The authors concluded that findings pointed to a central vestibular dysfunction in all patients. Another retrospective study described transient spontaneous nystagmus in eight patients with VM examined in the attack, three of whom also had severe vertical positional nystagmus [4].

7.3   Pathophysiology

The vestibular origin of vestibular migraine has been ascertained by the observation of pathological nystagmus in the acute phase, indicating central vestibular dysfunction in most patients [33, 34]. However, it remains unclear how migraine affects the vestibular system. Several hypotheses have been proposed, all of them derived from the presumed pathophysiology of migraine [35]. Migraine is currently conceptualized as a neurogenic disorder in genetically susceptible individuals that starts in the brain and probably results from dysfunction of brainstem and diencephalic nuclei that activate sensory nerve endings around the extracranial and intracranial arteries of the head [36]. Heterogeneous findings during acute episodes of VM and signs of peripheral vestibular and central ocular motor dysfunction in the interval indicate that more than one mechanism may be involved in this migraine variant.

Spreading depression is the mechanism of a migraine aura and vertigo is the most common aura manifestation in basilar-type migraine [37]. Spreading depression is a

cortical phenomenon and could lead to vestibular symptoms when the multisensory cortical areas processing vestibular information are involved, which are mainly located in the temporoparietal junction. Alternatively, a spreading depression affecting the brainstem has been proposed to account for short-lasting episodes of VM [4]. However, several features of VM such as the duration of most episodes and peripheral vestibular dysfunction cannot be explained by spreading depression.

Secondly, vasospasm of the internal auditory artery could account for peripheral vestibular and cochlear symptoms and dysfunction in migraine with and without vertigo [38]. Vasospasm could account for short attacks of vertigo but hardly for episodes lasting hours or days. Furthermore, central vestibular and ocular motor dysfunction points to another pathomechanism.

Thirdly, the pathophysiology of migraine involves several neurotransmitters such as calcitonin-gene-related peptide and serotonin that are also known to modulate the activity of central and peripheral vestibular neurons [2, 35]. When these neurotransmitters are released unilaterally, static vestibular tone imbalance may result, presenting clinically with spontaneous or positional vertigo; when they are released bilaterally, vestibular signal processing to head motion may become distorted, presenting with head-motion vertigo and dizziness. Reciprocal connections between the vestibular nuclei and the trigeminal system [39] may be the pathophysiological basis of the observation that vestibular stimulation can trigger migraine headache [40].

Fourthly, peripheral vestibular and cochlear symptoms and signs could be explained by activation of the trigeminovascular system during migraine. The trigeminovascular reflex leads to a sterile inflammatory response of intracranial vessels and has shown in animal experiments to affect also the inner ear [41]. In line with this hypothesis, it is interesting that painful trigeminal stimulation can evoke nystagmus in migraineurs [42].

Finally, a deficit of ion channels expressed in the inner ear or in central vestibular structures could account for vestibular symptoms in VM. This last hypothesis is the only one systematically tested thus far and appears to be promising, since other paroxysmal disorders presenting with migraine and vertigo such as familial hemiplegic migraine and episodic ataxia type 2 have been found to result from a channelopathy. However, searching for mutations in various candidate genes was negative in patients with VM [43, 44].

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'Visual Vertigo' and Motion Sickness

8

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8.1 Introduction

'Visual vertigo' and 'motion sickness' are closely related in respect to symptoms and mechanisms. Both derive from essentially normal properties of visual and vestibular mechanisms which, either individually or in interaction, subserve appropriate orientation, balance and movement in the environment. In turn, these two syndromes relate to migraine in a bidirectional way. Some of the symptoms present in a migraine attack (headache, nausea, visual hypersensitivity) resemble those observed during motion sickness and visual vertigo. Reciprocally, migraine increases the susceptibility to motion sickness and visual vertigo.

'Visual vertigo' is the easier to understand in its flagrant form as a false perception of self-motion, termed 'vection', induced by visual motion within the environment; familiar to many in the form of the railway carriage illusion of self-motion induced by a passing train, visual vertigo may also be experienced in *forme fruste* as a sense of unease and imbalance induced by environmental motion in the absence of a definite perception of self-motion. Although visual vertigo may be considered to be a natural phenomenon, deriving from the relativistic properties of visual perception of motion, in highly susceptible individuals, the experience causes distress and disability. In its extreme form, in addition to illusory self-motion, visual vertigo may include symptoms of autonomic activation (sweating, rapid heart rate, etc.), nausea and a host of related symptoms including dizziness and headache, all of which have common symptomatology with motion sickness.

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Motion sickness is provoked by either real self-motion, usually vehicular, or implied self-motion due to optokinetc stimulation (flux within the visual scene), either of which stimulates the vestibular system in ways which are conflicting or ambiguous. The degree of motion sickness provoked by optokinetic stimulation is usually much lower than for actual body movement. Motion sickness is a phenomenon common to all vertebrates, providing that the vestibular apparatus is intact, with individuals differing only in degree of susceptibility. Although the cardinal symptom of motion sickness is thought of as nausea, there are numerous other symptoms, notably including migraine-like headache which may be the prominent feature in certain individuals. Although it is understandable that there should be a vigorous response to movements which challenge interpretation, it is not fully understood why the response should be so potentially disabling in terms of nausea and vomiting.

8.2   Visual Vertigo

8.2.1   Interaction of Vestibular and Visual Mechanisms

The vestibular and visual systems are complementary and may work synergistically or antagonistically. For head rotation, with eyes open, gazing at the stationary environment, the vestibular signal of rotation and visual flow mutually corroborate. However, when a person looks at a visual object rotating with the head, e.g. reading in a vehicle, visual and vestibular signals are in conflict ('visuo-vestibular conflict') and the visual input suppresses the vestibular ocular reflexes to maintain fixation on the page (VOR suppression) (Fig. 8.1).

The intimate relationship between vision and vestibular function implies that visual input may influence vestibular symptoms and modify vestibular function and perception. The interaction between vestibular and visual inputs becomes a significant feature in vestibular disorders in which visual suppression and pursuit mechanisms are evoked to suppress pathological nystagmus and partially restore visual stability. Similarly, absent [1] or altered visual input, as in congenital nystagmus [2] or external ophthalmoplegia [3], modifies vestibular function and perception. The purpose of this section is to review a clinical syndrome in which visuo-vestibular interaction is a prominent mechanism: the syndrome of 'visual vertigo' in which vestibular patients and other individuals with certain pathophysiological and 'psychological susceptibility' experience significant symptoms of malaise and imbalance provoked by visual motion stimuli in the everyday environment. Of immediate, specific relevance, certain individuals with migraine may find themselves highly susceptible to visual motion stimuli.
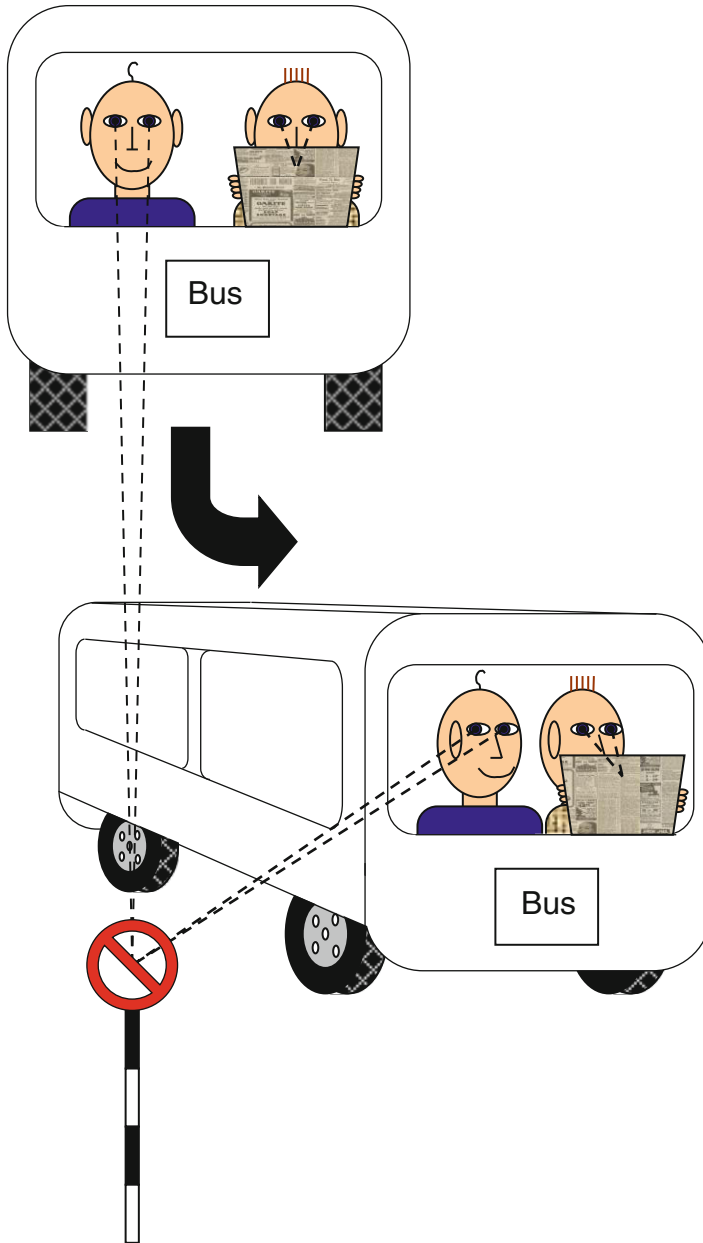
Fig. 8.1 In the passenger looking out of the bus and fixating upon the road sign, vestibular (VOR) and visual (pursuit) mechanisms cooperate to stabilise the eyes on the road sign as the bus turns round. In the passenger reading the newspaper, the VOR takes the eyes off the visual target (the newspaper), but pursuit eye movements are used to suppress the VOR. In the latter situation, visual and vestibular inputs are said to be in conflict (From Bronstein and Lempert [23]; with permission)

8.2.2 Clinical Picture of Visual Vertigo

Some, but not all, 'vestibular' patients report worsening or triggering of dizziness and imbalance in certain visual environments. These patients report a dislike of moving visual surroundings, as encountered in traffic, crowds, disco lights and car-chase scenes in films. A frequent presentation is the development of dizziness and imbalance in specific visual environments such as supermarket aisles. The development of these symptoms in some patients with vestibular disorders has long been recognised [4, 5], see Bronstein (2002) for review [6], and was given various names such as visuo-vestibular mismatch and space and motion discomfort [7–10]. The Classification Committee of the Barany Society now recommends the name visually induced dizziness for this symptom [11]. This syndrome should not be confused with oscillopsia, a perception of oscillation of the visual world wherein the symptom is visual. In visual vertigo, the trigger is visual but the symptom is vestibular in kind, such as dizziness, vertigo, disorientation and unsteadiness.

The symptoms of visual vertigo frequently develop after a vestibular insult. A typical patient is a previously asymptomatic person who suffers an acute peripheral disorder (e.g. vestibular neuritis) and, after an initial period of recovery of a few weeks, discovers that the dizzy symptoms do not fully disappear. Furthermore, their symptoms are aggravated by looking at moving or repetitive images, as described above. Patients may also develop anxiety or frustration because symptoms do not go away or because medical practitioners tend to disregard this syndrome.

The origin and significance of the symptoms of visual vertigo in vestibular patients has been the subject of research. We know that tilted or moving visual surroundings have a pronounced influence on these patients' perception of verticality and balance, over and above what can be expected from an underlying vestibular deficit [9, 10]. This increased responsiveness to visual stimuli is called 'visual dependency', a term used to describe people who use visual input, as opposed to inertial inputs, to organise spatial orientation and postural control [12]. Patients with central vestibular disorders and patients combining vestibular disorders and congenital squints or squint surgery can also report visual vertigo and show enhanced visuo-postural reactivity [9].

Overall, these findings suggest that the combination of a vestibular disorder and increased visual dependence in a given patient is precursive to the visual vertigo syndrome. Ultimately, what makes some vestibular patients develop visual vertigo is not yet known; it may be a natural susceptibility to overreliance on visual signals in response to the challenge of a sensory disorder. The role of the associated anxiety-depression, often observed in these patients, and whether this is a primary or secondary phenomenon are not known. The limited evidence so far does not indicate that anxiety or depression levels are higher in visual vertigo patients than in other patients seen in dizzy clinics [9, 10, 13].

The important differential diagnosis in these patients is, however, one of a purely psychological disorder or panic attacks [12]. An accepted set of criteria to distinguish between psychological and vestibular symptoms are not agreed presently [14–17]; however, in the absence of a clear history of vestibular disease, or findings

on vestibular examination and with visual triggers restricted to a single particular environment (e.g. only supermarkets), a patient with visual vertigo would be more likely to suffer from a primary psychological disorder or a psychosomatic disorder such as chronic subjective dizziness [17]. Reciprocally, a patient with no premorbid psychological dysfunction who after a vestibular insult may develop car tilting illusions when driving [18] or dizziness when looking at moving visual scenes (traffic, crowds, movies) is more likely to have the visual vertigo syndrome. A third diagnostic category comprises certain individuals with migraine who have an exceptionally high susceptibility to whole field visual motion, particularly of the kind which readily imparts vection [19]. These appear not to have been thoroughly studied as a group, but such susceptibility in certain individuals is a familiar encounter in both vestibular and motion sickness studies [20]. By way of illustration; a large rotating disk, viewed by a subject in primary gaze, is a commonplace and powerful device used to reveal visual dependency and challenge postural control. The visual motion readily induces laterally tilting vection and postural leaning in the majority of normal subjects. However, this subgroup of migraineurs is highly susceptible, becoming unstable within a few seconds of exposure to motion, developing nausea and, if exposure continues by merely tens of seconds, developing migraine-like headache. In our experience, these subjects appear also to be highly susceptible to motion sickness, but a full quantitative evaluation of the relationship has not been established.

8.2.3 Treatment of Visual Vertigo

There are three aspects in the treatment of patients with the visual vertigo syndrome. The first is specific measures for the underlying vestibular disorder, e.g. Meniere's disease, BPPV and migraine, and these will be found elsewhere in this book. However, a specific etiological diagnosis cannot be confirmed in many patients with chronic dizziness.

Secondly, patients benefit from general vestibular rehabilitation with a suitably trained audiologist or physiotherapist. These exercise-based programmes can either be generic, like the original Cawthorne-Cooksey approach or, preferably, customised to the patient's needs. All regimes involve progressive eye, head and whole body movements (bending, turning) as well as walking exercises ([21–23]; see video in [23]).

Thirdly, specific measures should be introduced in the rehabilitation programme in order to reduce the patient's hyperreactivity to visual motion. The aim is to promote desensitisation and increase tolerance to visual stimuli and to visuo-vestibular conflict. Patients are therefore exposed, under the instruction of the vestibular physiotherapist, to optokinetic stimuli which can be delivered via projection screens, head-mounted virtual reality systems, video monitors, ballroom planetariums or optokinetic rotating systems [24, 25]. Initially patients watch these stimuli whilst seated, then standing and walking, initially without and then with head movements, in a progressive fashion (Fig. 8.2). Recent research has shown that these patients benefit from repeated and gradual exposure to such visual motion training
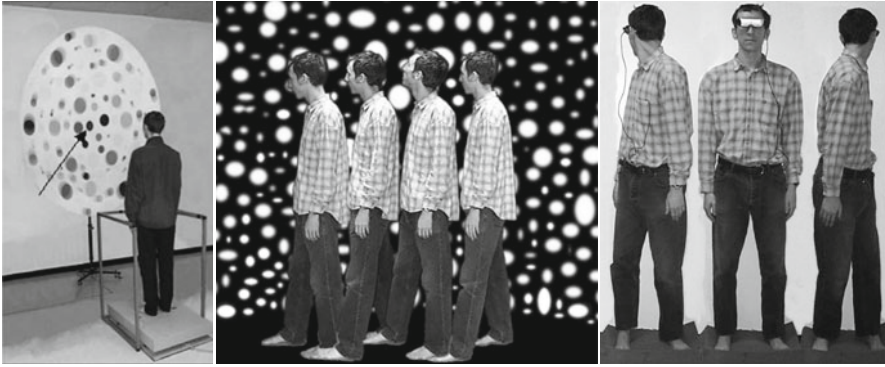
Fig. 8.2 Optokinetic or visual motion desensitisation treatment for patients with vestibular disorders reporting visual vertigo symptoms. *Left*: roll (coronal) plane rotating optokinetic disk; *middle*: planetarium-generated moving dots whilst the subject walks; *right*: 'Eye-Trek' or head-mounted TV systems projecting visual motion stimuli. In this case, in advanced stages of the therapy, the patient moves the head and trunk whilst standing on rubber foam (Based on Pavlou et al. [25], with permission). Patients should look at the central part of the disk (*arrow*) for maximal visual field cover

programmes; both the dizziness and associated psychological symptoms improve over and above conventional vestibular rehabilitation [25].

Finally, although there is not much published regarding the presence of visual vertigo in patients with migraine [19], the fact that migraine symptoms increase on self- and visual motion [26] dictates that patients with visual vertigo and migraine should be treated with prophylactic medication before entering a visuo-vestibular rehabilitation programme. However, on the basis of limited evidence, it seems that migraine patients do benefit from this rehabilitation approach and, in a recent study that would require confirmation, they seemed to respond better to rehabilitation than non-migraineous dizzy patients [27].

8.3 Motion Sickness

8.3.1 Signs and Symptoms

The primary signs and symptoms of motion sickness are nausea and vomiting although migraine-like headache can be a marked feature in a significant number of individuals. Other commonly related symptoms include stomach awareness, sweating and facial pallor (so-called cold sweating), increased salivation, sensations of bodily warmth, dizziness, drowsiness, loss of appetite and increased sensitivity to odours. Motion sickness can be provoked by a wide range of situations – in cars, tilting trains, funfair rides, aircraft, weightlessness in outer space, virtual reality and simulators. The term 'motion sickness' embraces car sickness, air sickness, space sickness, sea sickness, etc. Physiological responses associated with motion sickness

may vary between individuals. For the stomach gastric stasis occurs with an increased frequency and reduced amplitude of the normal electrogastric rhythm [28]. Other autonomic changes include sweating and vasoconstriction of the skin causing pallor (less commonly skin vasodilation and flushing in some individuals) with the simultaneous opposite effect of vasodilation and increased blood flow of deeper blood vessels, changes in heart rate which are often an initial increase followed by a rebound decrease and inconsistent changes in blood pressure [29]. A whole host of hormones are released, mimicking a generalised stress response, amongst which vasopressin is thought to be most closely associated with the time course of motion sickness [30], and the observation of cold sweating suggests that motion sickness disrupts aspects of temperature regulation [31].

Motion sickness is unpleasant, but also under some circumstances, it may have adverse consequences for performance and even survival. Motion sickness preferentially causes decrements on performance of tasks which are complex, require sustained performance and offer the opportunity of the person to control the pace of their effort [32]. For pilots and aircrew, it can slow training in the air and in simulators and even cause a minority to fail training [33]. For survival-at-sea, such as in liferafts, seasickness can reduce survival chances by a variety of mechanisms, including reduced morale and the 'will to live', failure to consistently perform routine survival tasks, dehydration due to loss of fluids and electrolytes through vomiting and possibly due to the increased risk of hypothermia [29].

8.3.2   Causes and Reasons for Motion Sickness

The physical intensity of the stimulus is not necessarily related to the degree of nauseogenicity. Indeed with optokinetic stimuli, there is no real motion. A person sitting at the front in a widescreen cinema experiences self-vection and 'cinerama sickness', but there is no physical motion of the body. In this example, the vestibular and somatosensory systems are signalling that the person is sitting still, but the visual system is signalling illusory movement or self-vection. Consequently, the generally accepted explanation is based on some form of sensory conflict or sensory mismatch. The sensory conflict or sensory mismatch is between actual versus expected invariant patterns of vestibular, visual and kinaesthetic inputs [33]. Benson [29] categorised neural mismatch into two main types: (i) conflict between visual and vestibular inputs or (ii) mismatch between the canals and the otoliths. A simplified model was proposed by Bos and Bles [34] that there is only one conflict: between the subjective expected vertical and the sensed vertical. However, despite this apparent simplification, the underlying model is necessarily complex and finds difficulty in accounting for the observation that motion sickness can be induced by types of optokinetic stimuli which pose no conflict concerning the Earth vertical [35]. A useful set of rules was proposed by Stott [36], which, if broken, will lead to motion sickness: *Rule 1*. Visual-vestibular: motion of the head in one direction must result in motion of the external visual scene in the opposite direction; *Rule 2*. Canal-otolith: rotation of the head, other than in the horizontal

plane, must be accompanied by appropriate angular change in the direction of the gravity vector; and *Rule 3*. Utricle-saccule: any sustained linear acceleration is due to gravity, has an intensity of 1 g and defines 'downwards'. In other words, the visual world should remain space stable, and gravity should always point down and average over a few seconds to 1 g.

The above describes what might be termed the 'how' of motion sickness in terms of mechanisms. By contrast it is necessary to look elsewhere for an understanding of the 'why' of motion sickness. Motion sickness itself could have evolved from a system designed to protect from potential ingestion of neurotoxins by inducing vomiting when unexpected central nervous system inputs are detected, the 'toxin detector' theory [37]. This system would then be activated by modern methods of transport that cause mismatch. This theory is consistent with the observation that people who are more susceptible to motion sickness are also more susceptible to emetic toxins, chemotherapy sickness, and postoperative nausea and vomiting (PONV) [38]. In addition, this theory has been experimentally tested with evidence of reduced emetic response to challenge from toxins after bilateral vestibular ablation [39]. Less popular alternatives to the toxin detector hypothesis propose that motion sickness could be the result of aberrant activation of vestibular-cardiovascular reflexes [40] or that it might originate from a warning system that evolved to discourage development of perceptual motor programmes that are inefficient or cause spatial disorientation [41].

8.3.3   Individual Differences in Motion Sickness Susceptibility

Individuals vary widely in their susceptibility, and there is evidence from twin studies that a large proportion of this variation can be accounted for by genetic factors with heritability estimates around 55–70 % [42]. Some groups of people have particular risk factors. Infants and very young children are immune to motion sickness with motion sickness susceptibility beginning from perhaps around 6–7 years of age and peaking around 9–10 years. Following the peak susceptibility, there is a subsequent decline of susceptibility during the teenage years towards adulthood around 20 years which may reflect habituation. Women appear somewhat more susceptible to motion sickness than men; women show higher incidences of vomiting and report a higher incidence of symptoms such as nausea and vomit more than men (surveys of passengers at sea indicate a five to three female to male risk ratio for vomiting) with susceptibility varying over the menstrual cycle, peaking around menstruation [43]. The elevated susceptibility of females to motion sickness, postoperative nausea/vomiting or chemotherapy-induced nausea/vomiting may serve an evolutionary function. Thus, more sensitive sickness thresholds in females may serve to prevent exposure of the foetus to harmful toxins during pregnancy.

8.3.4   Special Groups: Vestibular Disorders and Migraine

Individuals who have complete bilateral loss of labyrinthine (vestibular apparatus) function are largely immune to motion sickness. However, this may not be true

under all circumstances since some bilateral labyrinthine defective individuals are still susceptible to motion sickness provoked by visual stimuli designed to induce self-vection during pseudo-coriolis stimulation, i.e. pitching head movements in a rotating visual field [44]. Certain groups with medical conditions may be at elevated risk. Many patients with vestibular pathology and disease and vertigo can be especially sensitive to any type of motion. The well-known association amongst migraine, motion sickness sensitivity and Meniere's disease dates back to the initial description of the syndrome by Prosper Meniere in 1861. Patients with vestibular migraine are especially susceptible to motion sickness [45]. The reason for the elevated motion sickness susceptibility in migraineurs (without overt vestibular disease) is not known, but may be due to altered serotonergic system functioning [46]. Support for this possibility was provided by the observation that the serotonin 1B/1D agonist rizatriptan provided significant anti-motion sickness effects in migraineurs [47]. However, rizatriptan did not provide significant protection against exposure to more provocative vestibular stimulation, suggesting that the role of rizatriptan in this context is more likely to be as a modulator of susceptibility rather than a direct 'blocker' of motion sickness. It is possible that there are several underlying and overlapping mechanisms for this link, including pain pathways and autonomic reactivity [48]. The complexity of any association between migraine and motion sickness is illustrated by Bosser et al. [49] who surveyed the general population (i.e. unselected for severe migraine as in migraineurs requiring medical help or attending migraine clinics). This survey demonstrated the expected significant bivariate association between elevated motion sickness susceptibility and migraine. However, when these data were reanalysed using multivariate techniques, the existence of any independent association of motion sickness with migraine disappeared and was replaced by other more important predictors such as syncope and autonomic reactivity [49].

8.3.5   Mal de Debarquement

Mal de debarquement is the sensation of unsteadiness and tilting of the ground when a sailor returns to land. A similar effect is observed in astronauts returning to 1 g on Earth after extended time in weightlessness in space. This can lead to motion sickness but symptoms usually resolve within a few hours as individuals readapt to the normal land environment. In a minority of individuals, symptoms persist and can be troublesome. Customised vestibular exercises have been proposed as a treatment [50]. Some temporary relief can be obtained by reexposure to motion, but this is not a viable treatment. Standard anti-motion sickness drugs appear ineffective.

8.3.6   Behavioural Countermeasures

Habituation offers the surest counter measure to motion sickness but by definition is a long-term approach. Habituation is superior to anti-motion sickness drugs, and it is free of side effects. The most extensive habituation programmes, often denoted

'motion sickness desensitisation', are run by the military with success rates exceeding 85 % [51] but can be extremely time consuming, lasting many weeks. Critical features include the following: (a) the massing of stimuli (exposures at intervals greater than a week almost prevents habituation); (b) use of graded stimuli to enable faster recoveries and more sessions to be scheduled, which may help avoid the opposite process of sensitisation; and (c) maintenance of a positive psychological attitude to therapy [52]. Habituation may be specific to a particular stimulus, for example, tolerance to car travel may confer no protection to seasickness. Anti-motion sickness drugs are of little use in this context, since such medication may speed habituation compared to placebo in the short term, but, in the longer term, it is disadvantageous.

Immediate short-term behavioural countermeasures include reducing head movements, aligning the head and body with the gravito-inertial vector or laying supine [53]. However, such protective postures may be incompatible with task performance. It is usually better to be in control, i.e. to be the driver or pilot rather than a passenger, and obtaining a stable external horizon reference is helpful. Controlled regular breathing has been shown to provide increased motion tolerance and may involve activation of the known inhibitory reflex between respiration and vomiting [54]. Some report acupuncture and acupressure to be effective against motion sickness; however, well-controlled trials find no evidence for their value [55]. For habitual smokers, acute withdrawal from nicotine provides significant protection against motion sickness [56]. Indeed this finding may explain why smokers are at reduced risk for postoperative nausea and vomiting (PONV), whereas nonsmokers have elevated risk, since temporary nicotine withdrawal peri-operatively and consequent increased tolerance to sickness may explain why smokers have reduced risk for PONV [56]. Any effects of ginger and diet are contradictory.

8.3.7 Pharmacological Countermeasures

Drugs currently used against motion sickness may be divided into the categories antimuscarinics (e.g. scopolamine), H_1 antihistamines (e.g. dimenhydrinate) and sympathomimetics (e.g. amphetamine) and have improved little over 40 years [57]. Commonly used anti-motion sickness drugs are shown in Table 8.1. Other more recently developed antiemetics are not effective against motion sickness, including D_2 dopamine receptor antagonists, and $5HT_3$ antagonists used for side effects of chemotherapy, nor do the neurokinin 1 antagonist antiemetics appear effective against motion sickness. This is probably because their sites of action may be at vagal afferent receptors or the brainstem chemoreceptor trigger zone (CTZ), whereas anti-motion sickness drugs act elsewhere perhaps at the vestibular brainstem nuclei.

All anti-motion sickness drugs can produce unwanted side effects, drowsiness being the most common. Promethazine is a classic example. Scopolamine may cause blurred vision in a minority of individuals, especially with repeated dosing. The anti-motion sickness combination drug amphetamine + scopolamine

Table 8.1 Common anti-motion sickness drugs

Drug	Route	Adult dose	Time of onset	Duration of action (h)
Scopolamine	Oral	0.3–0.6 mg	30 min	4
Scopolamine	Injection	0.1–0.2 mg	15 min	4
Scopolamine	Transdermal patch	one	6–8 h	72
Promethazine	Oral	25–50 mg	2 h	15
Promethazine	Injection	25 mg	15 min	15
Promethazine	Suppository	25 mg	1 h	15
Dimenhydrinate	Oral	50–100 mg	2 h	8
Dimenhydrinate	Injection	50 mg	15 min	8
Cyclizine	Oral	50 mg	2 h	6
Cyclizine	Injection	50 mg	15 min	6
Meclizine	Oral	25–50 mg	2 h	8
Buclizine	Oral	50 mg	1 h	6
Cinnarizine	Oral	15–30 mg	4 h	8

Adapted from Benson [29]

(so-called scopdex) is probably the most effective with the fewest side effects, at least for short-term use. This is because both scopolamine and amphetamine are proven as anti-motion sickness drugs, doubtless acting through different pathways so they have additive efficacy, and their side effects of sedation and stimulation cancel each other out. Unfortunately, for legal reasons, the scopdex combination is no longer available apart from specialised military use, and alternative stimulants such as modafinil seem ineffective.

Oral administration must anticipate motion since motion sickness induces gastric stasis consequently preventing drug absorption by this route. Injection overcomes the various problems of slow absorption kinetics and gastric stasis or vomiting. Other routes such as transdermal also offer advantages providing protection for up to 72 h with low constant concentration levels in blood, thus reducing side effects. However, transdermal scopolamine has a very slow onset time (6–8 h), which can be offset by simultaneous administration of oral scopolamine enabling protection from 30 min onwards. Buccal absorption is effective with scopolamine, but an even faster route is via nasal scopolamine spray, and this is effective against motion sickness.

Investigations of new anti-motion sickness drugs include re-examination of old drugs, such as phenytoin, as well as the development of new agents. The range of drugs is wide and the list is long. Such drugs include phenytoin, betahistine, chlorpheniramine, cetirizine, fexofenadine, benzodiazepines and barbiturates, the antipsychotic droperidol, corticosteroids such as dexamethasone, tamoxifen, opioids such as the u-opiate receptor agonist loperamide, neurokinin NK_1 receptor antagonists, vasopressin V_{1a} receptor antagonists, NMDA antagonists, 3-hydroxypyridine derivatives, $5HT_{1a}$ receptor agonists such as the anti-migraine triptan rizatriptan and selective muscarinic M_3/m5 receptor antagonists such as zamifenacin and darifenacin. So far none of these drugs have proven to be of any major advantage over those currently available for motion sickness. The reasons are various and include relative

lack of efficacy, complex and variable pharmacokinetics or, in those that are effective, unacceptable side effects. Future development of drugs with highly selective affinities to receptor subtypes relevant to motion sickness may produce an anti-motion sickness drug of high efficacy with few side effects. A good candidate would be a selective antagonist for the m5 muscarinic receptor.

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Therapy of Vestibular Migraine

9

Alexandre R. Bisdorff

9.1 Introduction

Associations between migraine and vertigo have been recognized for a long time, but the nature of this relationship is multifaceted and controversial [1].

At a general population level, epidemiological studies in Germany and France have shown a co-occurrence of migraine and vertigo way beyond chance [2, 3]. Case–control studies have also found an association between migraine and vertigo/dizziness greater than chance. Patients with migraine have significantly more vertigo compared with patients with tension-type headache [4] and headache-free controls.

The relationship of migraine and vertigo has several aspects, which are also important to recognize when designing a treatment plan. Experimental vertigo induced during a caloric stimulation [5] and probably any other kind of vertigo can trigger a migraine attack, just as other strong sensory stimulations (like exposure to bright light).

A specified vestibular disorder can occur in a migraine patient, and it has been shown that two common peripheral vestibular disorders (benign positional vertigo and Menière's disease) even co-occur more often than expected by chance in migraine patients [6, 7].

Migraine patients are also recognized to have a higher susceptibility to motion sickness [8]. Anxiety is recognized as the most important psychiatric comorbidity of migraine, and anxiety is also often a complication or comorbidity with vertigo [9] and defined vestibular disorders [10].

Nevertheless, the above-mentioned aspects only explain the minor part of the co-occurrence of migraine and vertigo.

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The major part of episodic vertigo is thought to be a migraine phenomenon akin to other neurological symptoms known in migraine like scintillating scotoma or paraesthesia and is mostly labelled as vestibular migraine (VM). The concept implies a causal relationship between migraine and vertigo even if, in a migraine patient, some or most of the vertigo attacks occur in the absence of other simultaneous migraine manifestations and if no better explanation can be found.

The terms and the definitions have evolved over time. The first operational diagnostic criteria for "migrainous vertigo" were proposed about 10 years ago [11, 12] and represented an important progress in the harmonization of diagnostic standards for a diagnostic entity lacking biomarkers. An updated definition was recently proposed jointly by the International Headache Society and the Bárány Society [13].

The pathophysiology of vestibular migraine is not established. The observations done during the episodes and the interictal eye movement abnormalities suggest that it is in general a central vestibular disorder, but peripheral vestibular causes are also discussed [14, 15]. Cortical spreading depression is supposed to be the mechanism for migraine aura, and in theory this mechanism is also possible in the cerebellum [16]. The vascular theory of migraine is no longer considered valid; instead, migraine is considered to be a brain disorder [17]. For vestibular migraine, the concept of an ion channel disorder is particularly attractive as different mutations of the *CACNA1A* gene coding for a transmembrane component of a neuronal calcium channel can provoke familial hemiplegic migraine or episodic ataxia type 2 [18].

Recent reviews on treatment of vestibular migraine are available [9, 19].

9.2 General Considerations

Migraine in general and vestibular migraine in particular is a chronic, non-life-threatening condition with varying severity over time.

9.2.1 Importance of Diagnosis

As migraine is so common in the general population, chance co-occurrence with an independent vestibular condition has always to be considered, actively explored and ruled out, as they require a different treatment. If left with a condition of episodic vertigo unexplained by other specified vestibular disorders, the question of diagnostic certainty of VM arises. In the appendix of the latest classification of headache disorders, only the entity of definite VM is included, whereas in the Bárány Society's definition, also an entity of probable VM is included [13]. Beyond these two entities, there are quite a few patients with episodic vertigo not fulfilling those criteria nor those for other diseases (like Menière's or TIAs), so they can only receive a diagnosis of "benign recurrent vertigo" NOS (not otherwise specified). So far it is not known how important for the treatment choice the distinction of these three entities is; future research will need to address this question.

9.2.2 Patient Adherence

A first obstacle is usually the acceptance by the patient of the diagnosis of VM. As VM is still a controversial diagnosis not generally accepted in the medical community, patients are often surprised at the announcement of the diagnosis and have usually been confronted with competing and contradictory interpretations of their symptoms. Although migraine is part of general public knowledge, recognizing headache as migraine is still a problem and even more so for VM. A main hurdle, which is probably also a reason why physicians often miss the diagnosis, is when most attacks of vertigo are not accompanied by headache. Additionally, the diagnosis is syndromic, without an available independent diagnostic standard, and test abnormalities are, if present at all, mild and unspecific. Patients' scepticism about the diagnosis will impact on their adherence of treatment recommendations.

Another barrier to patient adherence to treatment is the kind of drugs usually used. As many were originally developed for other indications, patients are often taken aback by the proposal to take drugs for cardiovascular diseases, epilepsy or depression.

9.2.3 Outcome Measures

No standard exists so far to measure treatment outcome in VM. In vestibular disease, most tools have been developed in vestibular rehabilitation for non-episodic conditions, like vestibular neuritis [20]. In episodic disorders, usually attack frequency and intensity have been used but also global measures of the physical and emotional impact like the Dizziness Handicap Inventory [21].

9.2.4 Need for Treatment

After a diagnosis of VM has been established, the issue of the need for a treatment needs to be addressed with the patient. Vertigo is nearly always a worrying symptom but not always debilitating enough to warrant treatment. It is obviously important to establish at least approximately attack frequency, duration and severity as the need for treatment will depend on these factors. Some patients are reassured to know what they have, and if attacks are rare/mild/short, they might just decide to get on without treatment.

But what is considered as rare, mild or short, and what is the degree of suffering and the impact on their lives will vary from patient to patient, such that it is important to take into consideration patient preferences and needs.

Need for treatment will often be present as studies have shown that VM patients are often more handicapped than other vestibular patients [22, 23]. On top of this VM is the vestibular disorder leading most often to complications like chronification [10, 24], anxiety and avoidance behaviour. It is therefore important to try to control VM in order to be able to address better these complications.

Another aspect is that the "activity" of VM varies naturally over time, just like migraine, and the needs for treatment, in particular the daily administration of prophylactic drugs, are usually limited in time.

9.2.5   Quality of the Available Studies

Most studies so far have been uncontrolled; only recently few controlled interventions for drugs and physical therapy have been published.

9.3   Treatment of the Individual Attack

The spectrum of the duration of individual attacks of vestibular migraine varies widely, from seconds to days, mostly from minutes to hours. The duration can vary within and across patients. In the case of short attacks (<30 min), it is not useful to consider a rescue treatment a patient could apply himself, as for pharmacokinetic reasons, the attack will have abated before the drug reaches the brain.

In the case of prolonged and severe attacks, a symptomatic rescue treatment should be considered and general principles of treatment of acute vertigo apply. Acute antivertiginous and antiemetic drugs are considered useful for suppressing vestibular symptoms [14] like promethazine 25 or 50 mg combining antivertiginous, antiemetic and sedating properties; metoclopramide or domperidone helps to control nausea and vomiting associated with both headache and vertigo and promotes normal gastric motility that may improve absorption of oral drugs. Antihistaminic drugs such as dimenhydrinate and meclizine are useful for treating milder episodes of vertigo and for controlling motion sickness. Acetyl-DL-leucine, which has been tested in acute unilateral vestibular loss [25] and cerebellar ataxia [26], has also been used in VM.

Most of these drugs exist in oral and injectable form; they can therefore be used by the patient himself or in the emergency department.

9.3.1   Are There Any More Specific Treatments for Attacks of VM?

Triptans are a class of drugs developed to treat acute migraine headache. In a retrospective study based on patient records, sumatriptan was found to work independently if the vestibular symptom was or was not with accompanied by headache [27].

In a placebo-controlled study with zolmitriptan as primary outcome measure a clear relief of symptoms after 2 h was successful in 38 % for zolmitriptan versus 22 % for placebo [28] in ten patients with altogether 17 attacks, which was inconclusive.

So far it is not established if the vestibular symptoms in VM arise from migraine aura mechanisms. It is however interesting to look what the experiences were, when specifically targeting the treatment of migraine auras.

Sumatriptan 6 mg administered subcutaneously was found ineffective to shorten visual auras and was ineffective in preventing headache if taken during the aura [29]. A small study found that rizatriptan does not consistently reduce visually induced motion sickness in migraineurs but might have diminished motion sickness potentiation by cranial pain [30].

Ergots are not recommended for the treatment of migraine preceded by major aura because of potential vasoconstriction [31] and are contraindicated for hemiplegic and migraine with brain stem aura [32]. It is therefore reasonable not to try them in attacks of vestibular migraine.

Non-steroidal anti-inflammatory drugs have so far only been reported in one study [27] to be useful to treat vertigo attacks but were ineffective for migraine aura [31].

Altogether it seems that drugs effective in treating migraine headache (triptans, NSAID) do not work so well for vertigo or might be hazardous to use (ergots). If a treatment of attacks is needed, it is safer to use a generic strategy to relieve vertigo and nausea as in other causes of acute vertigo.

9.4 Prophylactic Treatment

Episodes of vertigo in VM are often short (<30 min) and/or frequent. In this case, the strategy to treat individual episodes does not make much sense and prophylactic drug treatment should be considered.

Non-pharmacological measures like general recommendations for migraine headache prophylaxis like diet, sleep hygiene and avoidance of trigger factors are probably also beneficial for VM [33].

The drug treatment is essentially aimed at reducing handicap and improving quality of life; it is neither life-saving nor life prolonging. Patients' threshold for taking drugs daily for a "benign" condition varies; it is therefore important to gauge the patients' needs and preferences. If a patient is willing to try a treatment, it should be made clear that each drug will be tried for an adequate amount of time to be able to assess the balance between benefits and side effects before prolonging or changing. The use of many drugs for the prophylaxis of migraine is off label, and for VM, this is even more the case. It is therefore essential to warn patients because they might think the prescription was erroneous.

Prophylactic medication in migraine has an important role if attacks are frequent or insufficiently controlled by rescue medication and seem to converge on two targets, inhibition of cortical excitation and restoring nociceptive dysmodulation [34]. In VM, prophylactic drug treatment is considered the mainstay of the medical management although only a few controlled studies have been published. The drugs used are largely those also in use for the prevention of migraine headaches such as beta blockers, calcium antagonists, anticonvulsants and antidepressants.

Some reported a polypragmatic approach testing sequentially a variety of substances until eventually most patients found a drug they tolerated and felt relief. These studies used an outcome measure consisting of a global appreciation of the impact of VM in the patients' life.

In one study [35], the sequence was a beta blocker (propanolol or metoprolol) followed by flunarizine, clonazepam and finally amitriptyline, eventually finding substantial relief for the vestibular symptoms and the headaches. In another study [33], the steps were dietary intervention, followed by nortriptyline, followed by atenolol. Diet alone helped 27 %; diet plus antidepressant, 24 of 31; and diet and beta blocker, 21 of 37. Nortriptyline and atenolol were considered efficient, parallel responses to headache and vertigo observed in 95 % of patients.

In a retrospective review of 89 patients diagnosed with migraine-related dizziness or vertigo [36], 79 were treated pharmacologically. Medications used included benzodiazepines in 90 % (mostly clonazepam), tricyclic antidepressants in 42 % (amitriptyline or nortriptyline) and beta blockers in 35 % (propanolol); six patients received selective serotonin reuptake inhibitors (fluoxetine, sertraline or paroxetine) and five patients received calcium channel blockers (verapamil or diltiazem). With this approach, substantial response (defined as improvement of symptoms such that they would no longer interfere with daily activities) was seen in 92 % of patients with episodic vertigo, 89 % of patients with positional vertigo and 86 % of patients with nonvertiginous dizziness. None of the patients responded to the calcium antagonists used. At the moment of improvement, 44 % of patients were on a single medication, 33 % on two and the rest on three up to six drugs.

A survey of 58 patients in a headache clinic with a history of symptoms of dizziness or vertigo [27] found that prophylactic medications targeting the treatment of headache (beta blockers, calcium channel blockers, tricyclic antidepressants [individual substances not specified] or methylsergide, valproic acid, cyproheptadine) were also effective in treating the vertigo/dizziness. Responses were graded from 1 to 4, with four being the most effective treatment, and were based on patients' recall of the effectiveness of the therapeutic intervention. A median efficacy score of two for treating migraine headaches was found and one for treatment of vertigo or dizziness. The temporal relationship of the dizziness to the migraine headache did not influence therapeutic efficacy.

In a retrospective study on 100 patients [37], 26 received non-pharmacological intervention and 74 received drugs that are mainly beta blockers (propanolol, metoprolol) and anticonvulsants (valproic acid, topiramate, lamotrigine), or butterbur root extract noticed a reduction of frequency, duration and severity of vestibular attacks as well as headaches. The effect was more marked for the pharmacological treatments.

In a randomized, double-blind placebo-controlled crossover design study [38], sodium valproate affected neither vestibuloocular responses in rotatory chair test nor vestibular complaints but was effective in reducing migraine attacks in 8 of the 12 patients.

Celiker et al. [39] treated 37 patients with migraine (13 with vertigo, 13 with dizziness and 11 without vestibular symptoms) with valproic acid (500 mg/d) for 3 months; improvements were found in migraine and vertigo/dizziness frequency but not in ENG findings.

A study with topiramate 100 mg in ten patients observed a remission over an average follow-up period of 9 months [40].

A retrospective study in 19 patients treated with lamotrigine 25 mg every morning for 2 weeks, then 50 mg for 2 weeks, to reach a target dose of 100 mg after 4 weeks had a significant reduction of the vertigo but not their headache frequency [41].

Although the mechanism of the vestibular symptoms in migraine is not established, it is reasonable to hypothesize a similarity to other neurological (non pain) symptoms in migraine. Most studies in migraine focus on the headache as the main outcome or do not distinguish between migraine with and without aura [42], but some studies report more specifically on aura.

Several studies have shown efficacy of lamotrigine on migraine with aura [43] with an effect not only on visual aura but also on sensory, motor, phasic [44] visual, hemiplegic [45] and brain stem aura. In a controlled 3-year prospective open study in 59 patients, lamotrigine was highly efficient for all types of aura (vertigo not specified) and for headaches [46].

In a report of two cases of persistent visual aura, lamotrigine was reported effective [47]. In a small study on 12 patients with migraine with aura, topiramate was not efficient on aura but was on headaches [48].

A Cochrane Review on anticonvulsants in migraine prophylaxis [42] found superiority over placebo for valproate and topiramate; no difference to placebo for acetazolamide, clonazepam, lamotrigine and vigabatrin; and inconclusive results for gabapentin. In this review, no distinction was made for migraine with and without aura.

From the studies reported above, there seems to be a differential effect for some drugs on the headaches versus aura symptoms, and there also seems to be tendency for anticonvulsants that are effective for aura also to have more potential for vestibular migraine.

This impression is also supported in an experimental study in which lamotrigine was superior to valproate and riboflavin in suppressing cortical spreading depression in the rat [49].

9.4.1 A Fresh Look at Old Studies Can Also Give an Interesting Perspective

The term "vestibular Menière" was dropped in the second revision of the American Academy of Otolaryngology Head and Neck Surgery Committee on Hearing and Equilibrium criteria on Menière's disease, and the differential diagnosis of VM is not even mentioned in the 1995 document [50].

The terms "vestibular Menière's", "recurrent vestibular vertigo" or "benign recurrent vertigo" have been used interchangeably. Recent studies have shown that benign recurrent vertigo is strongly associated with migraine and usually does not evolve to become Menière's disease [14, 51]. Many of these cases would nowadays probably be considered to have VM.

Betahistine, a histamine analogue, and flunarizine, a calcium antagonist, have been extensively investigated in recurrent vertigo without hearing loss with controlled

studies and shown to be effective [9]. The observations on flunarizine are coherent with those done in vestibular migraine, whereas betahistine is still considered as a classical drug for Menière's disease, but it might also relief the vestibular symptoms of migraine.

A recently published controlled study using modern inclusion criteria for VM compared a combination of flunarizine 10 mg plus betahistine and paracetamol against betahistine and paracetamol and found to reduce significantly attack frequency and severity for vertigo but not for headache [52].

9.5   VM and Psychiatric Comorbidity

The relationship between anxiety and vertigo is complex. Anxiety can be a primary cause of vertigo (defining symptom in panic attacks), but anxiety is often a secondary complication of vertigo [53].

VM seems to be the vestibular disorder with the highest risk of secondary psychiatric complications, mainly anxiety [10]. The entity "MARD" (migraine-anxiety-related dizziness) was proposed [54], if balance symptoms predominate a combination of an antidepressant, such as imipramine, and a benzodiazepine, such as clonazepam, is recommended by the authors. For patients with MARD in whom anxiety symptoms predominate, an SSRI such as paroxetine or sertraline is preferred. Vestibular rehabilitation might be beneficial particularly in patients with additional space and motion discomfort.

9.6   Vestibular Rehabilitation

Vestibular rehabilitation plays an important role in the management of vestibular conditions. Rehabilitation targets the impairment level rather than a diagnosis. The aim is to achieve compensation of unilateral vestibular deficits, strategies to cope with bilateral deficits independently of their aetiology, repositioning manoeuvres for benign positional vertigo and addressing wrong strategies like visual dependence. Traditionally vestibular disorders rehabilitation is indicated in stable, non-fluctuating central or peripheral disorders [20]. In episodic disorders like Menière's disease, the value of vestibular rehabilitation is not to reduce attack frequency or severity. Patients may lose parts of peripheral vestibular function during an attack and have therefore residual symptoms after an attack, which can be addressed in a similar fashion as in other peripheral disorders.

VM is considered a fluctuating central vestibular disorder and therefore not a classical target of vestibular rehabilitation. The issue of vestibular rehabilitation in VM has though a special interest as migraine patients often have a higher perception of their impairment with a similar level of performance compared to non-migrainous patients [22]. A retrospective chart review of 14 patients with migraine-related vertigo and migraine headache demonstrated improvement in physical performance measurements and self-perceived abilities after vestibular physical therapy. Patients

with vestibular disorders with or without a history of migraine (30 in each group) demonstrated improvements in both subjective and objective measurements of balance after physical therapy [20].

Physiotherapy seems to have its place if residual symptoms persist between attacks like visual dependence, increase head motion intolerance or loss of confidence in your balance system. These VM patients need more intervention than the classical vestibular patient, and improvements in functional outcome measures could be shown [22]. Studies did not aim at investigating if this intervention can reduce the frequency or severity of the vestibular episodes.

Conclusions

The entity of VM is more and more accepted in the vestibular and headache community. It is the most common episodic vestibular disorder with spontaneous attacks.

The quality of the data on VM management is still relatively poor despite its enormous importance in daily practice. Studies published before 2003 used variable definitions of vestibular migraine and only few are controlled. Studies from the 1980s on recurrent vertigo without hearing loss probably included may patients, which would be considered today to have VM.

Although the condition can have a considerable psychosocial and functional impact, it is medically "benign".

After always include establishing the diagnosis and ruling out mimics, the next step should always an appropriate announcement of the diagnosis to have it accepted by the patient.

The need for treatment will depend on the degree of suffering and patient preferences; some might be happy with an explanation for their symptoms, while others might need long-lasting intervention of a multidisciplinary team if psychiatric complications and persisting vestibular symptoms between attacks have developed.

Prophylactic drug treatment is the most important aspect and drug choice is mainly guided by comorbidities and side effect profiles.

The most important comorbidities to consider are arterial hyper- or hypotension, anxiety and depression, asthma and body weight and how prominent migraine headaches are on top of vertigo.

Flunarizine can be quickly installed, whereas most other drugs require titration.

If anxiety or depression is present, flunarizine or topiramate are best avoided.

In case of obesity, valproate and flunarizine should not be the first choices.

Sedation can be a problem for most drugs, least for lamotrigine and verapamil.

In case of coexisting hypertension, a beta blocker should be considered if bronchospasm or bradycardia is not a problem.

If headaches are prominent, consider anticonvulsants like topiramate in obese patients and valproate in nonobese or beta blockers.

In case of coexisting sleep disturbance and anxiety, consider amitriptyline or nortriptyline; if the psychiatric aspect is very prominent, benzodiazepines and

serotonin reuptake inhibitors and/or a referral to a psychiatrist or behavioural therapist should be considered.

If headache is rare compared to vertigo and/or the vertigo is part of an aura, lamotrigine might be a first choice. Always respect titration steps because of the risk of severe skin rashes.

In all cases, referral to vestibular rehabilitation should be considered, particularly if secondary complications like deconditioning, loss of confidence in one's balance or visual dependence have developed.

All drug treatments should be limited in time or reviewed in appropriate intervals.

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Vertigo as a Migraine Precursor

10

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10.1 Introduction

Vertigo and dizziness are uncommon in childhood, although they are likely to be more prevalent than commonly thought. Often disabling, these symptoms are not easy to be studied in a pediatric age; both clinical history and neurotological assessment present objective difficulties and often are a challenge for the physician. Despite a large number of possible causes, benign paroxysmal vertigo of childhood (BPVC) is the most frequent distinctive clinical entity responsible for vertigo in pediatric patients. It was first described by Basser in 1964 [1], although a previous description of the disorder was given by Lerique-Koechlin et al. in 1961 [2]. BPVC is at present is considered to be the unique form of vertigo that is unanimously recognized and officially defined as a precursor of migraine in the first (1988), second (2004), and third beta version edition (2013) of the International Classification of Headache Disorders [3–5].

Nonetheless, in this chapter, other forms of childhood periodic syndromes, probably related to malfunction of the vestibular system, have been included, specifically benign paroxysmal torticollis (BPT), motion sickness, and cyclic vomiting. The term "periodic syndrome of childhood" was first introduced in 1933 by Wyllie and Schlesinger [6] to describe recurrent episodes of pyrexia, headache, vomiting, and abdominal pain in childhood. The authors reported that the signs persisted in adult life as migraine and that the affected children often present a family history of migraine.

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Finally, it should be underlined that migraine in pediatric patients is not rare and often presents characteristic features: migraine attacks, for example, may last less than 1 h, while in adults they are normally more prolonged; subjects do not generally describe a throbbing unilateral pain but rather a moderate bilateral headache; phono- and photophobia are often difficult to assess; and, more frequently, children migraine may be suspected above all through child behavior [7].

10.2   Benign Paroxysmal Vertigo of Childhood (BPVC)

BPVC is the most common cause of vertigo in a pediatric age and has been included among childhood periodic syndromes. In different studies, the prevalence rate has been estimated to be from 2 to 2.6 %, and both sexes are equally affected [8–10]. The age of onset is normally between 2 and 4 years old, although cases in earlier (13 months) [8] or later ages (11–12 years) have been reported by different authors [8, 10].

BPVC is characterized by recurrent episodes of true vertigo and postural imbalance of sudden onset lasting from few seconds to several minutes; more rarely vertigo may last hours. Auditory symptoms are typically absent. More frequently, the duration of attacks is quite stereotypical for any given child [11–19]. In some cases, a potential trigger can be identified, for example, games with rotating movements that are capable of stimulating the vestibular system (roundabouts, swings) or walking, a period of fever, or stress.

The patient has often been described as unable to move, stand up, or sit down without aid; he/she grasps the person standing nearby and remains immobile, wants to be picked up, and, if put down, may sway and refuse to stand. He/she is often accompanied by increased anxiety; smaller children often cry, while older ones try to explain their sensation of spinning of falling. There is never any loss of consciousness and episodes end with complete recovery and return to normal activity and well-being, sometimes with falling asleep. The vertigo attack is more frequently associated with additional symptoms such as pallor, sweating, nausea and vomiting, and phono- and photophobia; sometimes headache, normally of migrainous type, is reported. The frequency of the episodes is extremely variable, ranging from once a day to once a year; more frequently, episodes are clustered within a period of few weeks or months [20–23]. Normally, the attacks are more frequent at the beginning of the syndrome and progressively decline over a period of years, although in long-term follow-up studies, persistence in adolescence in 50 % of cases and occasionally until adulthood has been reported [19].

Neurotological examination outside the attack is more often normal [8, 12], although some authors have reported the presence of unilateral or bilateral vestibular hypofunction with caloric stimulation [9]. The presence of nystagmus, of peripheral or central type, has been reported during the attack [8, 9], while hearing loss, ear fullness, tinnitus, and neurological symptoms are absent.

Since neurotological examination outside the attack is more often normal as well as vestibular exams, diagnosis is mainly based on symptoms. The International

Table 10.1 International Classification of Headache Disorders, 2nd Edition, 2004 [4]

1.3.3 Benign paroxysmal vertigo of childhood
1. At least 5 attacks fulfilling criterion 2
2. Multiple episodes of severe vertigo,[a] occurring without warning and resolving spontaneously after minutes to hours
3. Normal neurological examination; normal audiometric and vestibular functions between attacks
4. Normal electroencephalogram

[a]Often associated with nystagmus or vomiting; unilateral throbbing headache may occur in some attacks

Headache Society established the diagnostic criteria for BPVC in 2004, which are summarized in Table 10.1 [4].

The most frequent evolution of this syndrome is towards migraine, reported by different authors to range from 21 to 80 % of cases [8, 14, 17, 18]; a less frequent evolution may be towards some forms of periodic syndrome [18].

These subjects often present a familial history of migraine, reported between 39 and 53 % [16–18, 24], and often present comorbidities such as atopy, kinetosis, previous episodes of benign paroxysmal torticollis, and other forms of childhood periodic syndromes, including abdominal pain and cyclic vomiting [10, 23, 25].

Cyclic vomiting syndrome (CVS) is characterized by episodic nausea and non-bilious vomiting in otherwise healthy children; the onset of relentless vomiting often begins in childhood and is associated more frequently with abdominal pain and fatigue lasting several hours. Occasionally, they are preceded by nonspecific prodromal signs, such as behavioral or mood changes or anorexia. Normally episodes resolve spontaneously with little or no treatment. Diagnosis is mainly based on clinical history and exclusion of other gastrointestinal, metabolic, or structural neurological disorders possibly related to symptoms [26]. Patients may experience headache during both CVS and abdominal pain; although a direct correlation between CVS and migraine has not been definitively demonstrated, a possible relationship between the two disorders has been widely investigated in epidemiological studies [27, 28]. In a recent work, a higher incidence (35 %) of subsequent migraine in CVS subjects was reported compared to the general population, in accordance with previous studies [27]. Moreover, in a retrospective analysis, some differences in clinical parameters were found between migraine-associated and non-migraine-associated CVS, since abdominal pain, headache, photophobia, and presence of triggering events during vomiting are more frequently associated with the possibility of developing migraine [28]. Finally, a younger age of onset of CVS and the presence of headache during attacks are positively correlated with the risk of developing migraine [26].

CVS has often been reported to occur in association with motion sickness.

The International Headache Society included CVS among migraine precursors and established the following diagnostic criteria [5]:

A. At least five attacks of intense nausea and vomiting, fulfilling criteria B and C.

B. Stereotypical in the individual patient and recurring with predictable periodicity.

Table 10.2 International Classification of Headache Disorders, 3rd Edition (beta version), 2013 [5]

1.6.2 Benign paroxysmal vertigo
A.   At least five attacks fulfilling criterion B
B.   Vertigo occurring without warning, maximal at onset and resolving spontaneously after minutes to hours without loss of consciousness

C.   At least one of the following associated symptoms or signs:
   1. Nystagmus
   2. Ataxia
   3. Vomiting
   4. Pallor
   5. Fearfulness

D.   Normal neurological examination and audiometric and vestibular functions between attacks
E.   Not attributed to another disorders

C. All of the following: (1) nausea and vomiting occur at least four times per hour, (2) attacks last 1 h up to 10 days, and (3) attacks occur 1 week apart.

D. Complete freedom from symptoms between attacks.

E. Not attributed to another disorder.

The association between vertigo, migraine, and psychiatric disorders in adults has been widely studied. In contrast, only a few studies have focused on the same problems in a pediatric age; according to these authors, psychological assessment of patients referred for BPVC is similar to that of children suffering from migraine. Taken together, the available data suggest that most BPVC patients have scores within a normative non-pathological range at most questionnaires. Nonetheless, the Child Behavior Checklist, a widely used method for identifying behavioral problems in children and based on the evaluation of respondents who know the child well, demonstrated the presence of symptoms of emotional and behavioral difficulties in these patients compared to normal controls. Moreover, higher ratings using this test have been correlated with an increased risk for developing future psychopathological disorders [29].

Since attacks of BPVC are normally brief, no treatment is usually suggested. Nonetheless, management of triggering factors, if present, is recommended. Treatment of a single attack may include symptomatic medications such as paracetamol, antiemetics, or vestibular suppressants. If attacks are frequent, prophylaxis, e.g., with cyproheptadine or cinnarizine has been suggested.

Diagnostic criteria for BPVC included in the International Classification for Headache Disorders, Second Edition and, with minor modifications, Third Edition, are reported in Tables 10.1 and 10.2.

10.2.1 Benign Paroxysmal Vertigo of Childhood and Migraine

The possibility of a close relationship between BPVC and migraine and the idea that BPVC may be considered as a "migraine variant" or "migraine precursor" or "migraine

equivalent" were first suggested by Fenichel in 1967 in a report of "two siblings who displayed a syndrome of benign paroxysmal vertigo and in whom the attacks progressively converted into classical migraine". Fenichel's hypothesis was in contrast with that of Basser [1] who considered "benign paroxysmal vertigo of childhood a variety of vestibular neuronitis." Basser's opinion was mainly based on the observation that in BPVC children, "the caloric tests typically demonstrated moderate, severe or complete canal paresis"; however, this finding was not confirmed in the large majority of subsequent studies [30].

In the following years, Fenichel's hypothesis ("the suggestion is therefore made that "benign paroxysmal vertigo of childhood" may at times be an early manifestation of migraine rather than a form of vestibular neuronitis") was confirmed in a series of following publications in which the terms of "migraine equivalent" or "migraine precursor" were expressly used [8, 13, 24, 31, 32]; this idea is more or less accepted in all studies related to BPVC that have been published in the last three decades. In our opinion, the contributions of population-based studies [16, 24] and studies in which long-term follow-up has been possible are of particular significance [14, 17, 19].

Epidemiological, clinical, and genetic findings support the hypothesis of a relationship between BPVC and migraine.

First, a higher rate of familial history of migraine in children with BPVC than in normal population has been demonstrated, ranging between 53 and 100 %, while motion sickness in parents was reported in 83 % of cases [10, 18, 33]. In a population-based study on 2,165 children [24], the authors described a prevalence rate of BPVC of 2.6 % and of migraine of 8 %; BPVC patients also presented clinical features in common with children with a diagnosis of migraine, including triggering and relieving factors, associated gastrointestinal and sensory symptoms, motion sickness, and a similar pattern of associated recurrent disorders (such as headache, abdominal pain, and cyclical vomiting). Finally, these children presented a twofold increase in the prevalence of migraine (24 %) compared with the general childhood population (10.6 %), while the prevalence rate of BPVC in children with migraine was three times higher than in the general childhood population. In another study [10], the presence of migraine equivalents was assessed on a population of 108 children with periodic syndromes followed over a 8-year period; BPVC was reported in 38 % of cases, while CVS in 18.5 % and benign paroxysmal torticollis in 10.2 %. Other studies have focused on an association between BPVC and other forms of periodic syndromes (atopy and motion sickness above all); moreover, migraine and BPVC often present the same triggering and relieving factors [14, 17, 18]. Finally, headache provocation tests with nitroglycerin, histamine, and fenfluramine were demonstrated to be positive in 9 of 13 patients with BPVC and in 4 cases induced a typical vertiginous attack instead of headache [13].

Several investigations have reported that a high rate of BPVC children develop migraines as adults. In a follow-up of seven BPVC children, Lanzi et al. [14] reported that six developed migraine after the age of 20 years; in studies based on larger patient cohorts, the development of migraine after the age of 15 years was reported to occur in 21–100 % of BPVC patients [17, 19].

Genetic factors underlying common pathophysiological mechanisms between migraine and BPVC have been studied [34, 35]. In a small sample of four BPVC patients, two of who originated from a kindred with familial hemiplegic migraine linked to CACNA1A mutation [36]; in another study, a novel variant of CACNA1A mutation was found in a patient displaying a changing, age-specific phenotype that began as benign paroxysmal torticollis of infancy, evolving into benign paroxysmal vertigo of childhood, and later becoming hemiplegic migraine [37].

These considerations led the International Headache Society (IHS) to include BPVC, together with cyclical vomiting and abdominal migraine, in the first International Classification of Headache Disorders under the chapter "Migraine (1)" and the subtype "Childhood periodic syndromes that are commonly precursor of migraine (1.3)," without modifications in the second edition [3, 4]. The third edition, now in progress (ICHD-3 beta version, 2013) [5], includes minor modifications in the denomination and classification of these disorders under the code "Migraine (1)": "Episodic syndromes that may be associated with migraine (1.6)," "Recurrent gastrointestinal disturbance (1.6.1)," comprising "Cyclic vomiting syndrome (1.6.1.1)" and "Abdominal migraine (1.6.1.2)," "Benign paroxysmal vertigo (1.6.2)," "Benign paroxysmal torticollis (1.6.3)."

However, the official description and clinical features of BPVC (finally called simply benign paroxysmal vertigo) is unvaried: "This probably heterogeneous disorder is characterized by recurrent brief episodic attacks of vertigo occurring without warning and resolving spontaneously in otherwise healthy children." In the Appendix of the ICHD-3, the possible relationship between BPV and the new entity "Vestibular migraine (A1.6.5)" is discussed.

Some authors have hypothesized two distinct forms of BPVC:

- The first is characterized by an earlier onset of vertigo attacks; vertigo spells are rarely associated with headache and spontaneously totally recover after puberty; this form very rarely evolves into migraine.
- The second form presents a later onset of vertigo attacks, is frequently associated with headache, and more often persists after puberty and frequently evolves into migraine.

The first form has been defined as "classic BPVC" or "classic Basser" and considered as a migraine precursor; the second group was defined as "atypical" or "migrainous" paroxysmal vertigo and considered as a migraine equivalent [14, 17, 20, 21]. According to these authors, the first form of BPVC could be expression of a neurodevelopmental anomaly that resolves spontaneously, while the second form is linked to a functional chronic neurological disorder, although both may have the same genetic basis and similar pathophysiological mechanisms. However, this difference is based on a limited number of cases and the distinction between the two forms, in our opinion, is as yet unjustified; in our experience, the terms "precursor," "equivalent," or "variant" may be considered to be mostly synonyms.

The theory that BPVC is a form of childhood migraine is a compelling one. Migraine is a complex polygenic disorder [38] with clinical heterogeneity, and in different individuals or in different ages in the same individual life span, it may occur with different clinical manifestations, depending on its targets within the

nervous system: classic migraine headache in case of involvement of the trigemino-vascular system (typical migraine or, preferred, migrainous headache or trigemino-vascular migraine, with or without aura); paresthesias, ataxia, and visual disorders when the brainstem and cerebellar system is involved (basilar-type migraine); vertigo and/or dizziness in case of involvement of the vestibular system (vestibular migraine); scotomata and/or blindness in case of involvement of the visual system (retinal migraine); and vomiting and/or motion sickness in case of involvement of the neurovegetative system (cyclic vomiting).

10.3   Benign Torticollis of Infancy

Benign paroxysmal torticollis (BTP) is a rare clinical disorder characterized by recurrent episodes of cervical dystonia. It was first described by Snyder [39] in 1969, who reported 12 cases, and in 11, the onset was in infancy; since in nine of 12 subjects the author found abnormal caloric tests, he considered this disorder as a possible clinical manifestation of labyrinthitis in infancy. To date, around 100 cases have been described in the medical literature, although in some the final diagnosis is missing. Among various causes of torticollis, benign paroxysmal torticollis is far from being frequent: in a study on a large sample (700 cases of primary torticollis in developmental age), only 7 had a final diagnosis of benign torticollis of infancy [40]. A female preponderance has been reported, ranging between 58 and 70 % of cases [23, 41]. According to previous reports, the age of onset of clinical symptoms ranges from 1 week to 30 months, with a mean of 5.9 months; in 75 % of cases, the first episode begins within the 7th month of life, and in 95 %, within the first 14 months.

The average duration of attacks has been reported to vary widely, from 10 min to 30 days; in 75 % of cases attacks lasted less than 6 days, and in 90 % less than 14 days. The frequency of periodic attacks is also reported to vary greatly, from 1 every 7 days up to 1 every 5 months [41]. Typically, the frequency and duration of attacks decline as the child grows older.

Episodes of benign torticollis are characterized by the sudden onset of abnormal inclination or rotation of the head on one side; usually the side is reported to be the same in subsequent attacks. Other torsional or dystonic features have been described to be associated with torticollis in some cases, including truncal or pelvis asymmetrical posturing or retrocollis [42]. Other authors described the occurrence during the attack of an abrupt turning of the head and eyes from one side, rapid blinking, flexing of the upper limbs, and upward-diverted gaze [43].

Several associated symptoms have been reported to occur during the attack, including, in order of frequency, vomiting, irritability, vertigo and/or ataxia, pallor, and less frequently apathy or drowsiness, gaze abnormalities, and nystagmus [41].

Although the disorder is distressing for parents, the episodes normally remit after several months (typically at an age between 4 and 60 months).

Clinical tests are often inconclusive; after the first report by Snyder, and with one exception [44], caloric tests are frequently reported to be normal. When performed,

radiological studies and magnetic resonance imaging of brain are normal. Electroencephalograms were normal except in two reported cases: in the first, occipital spikes during attacks were described, while in the other, EEG demonstrated "nonspecific abnormalities." Electromyographic studies are generally normal; in one case continuous electrical discharges were recorded from the ipsilateral sternocleidomastoid muscle and contralateral trapezius muscle, a finding that is consistent with the possibility that this patient could be categorized as having an idiopathic paroxysmal dystonia in infancy [45].

Clinical diagnosis is mainly based on symptoms and exclusion of other possible causes; differential diagnosis includes gastroesophageal reflux (Sandifer's syndrome), idiopathic torsional dystonia, complex partial seizure, tumors of the posterior fossa, and dysfunction of the craniocervical junction. Different authors have reported how patients with benign paroxysmal torticollis frequently develop BPVC, CVS, motion sickness, and migraine at later ages [23].

The International Headache Society included benign paroxysmal torticollis among periodic syndromes and established the following diagnostic criteria [5]:

A. Recurrent attacks in a young child fulfilling criteria B and C
B. Tilt of the head to either side, with or without slight rotation, remitting spontaneously after minutes to days
C. At least one of the following associated symptoms or signs:
    1. Pallor
    2. Irritability
    3. Malaise
    4. Vomiting
    5. Ataxia
D. Normal neurological examination between attacks
E. Not attributed to another disorder

Since patients recover after a few months, usually no treatment beyond reassurance is required; in selected cases, characterized by painful episodes, some authors have suggest a trial with cyproheptadine [46].

The etiopathogenesis of the disorder is still under debate and different possibilities have been proposed:

- Since some authors reported abnormalities by vestibular tests, a peripheral [39, 44] or central vestibular involvement as well as of the vestibulo-cerebellar connections has been proposed [43].
- Immaturity of the brain or involvement of some neurotransmitters could be hypothesized during a limited period of life. Moreover, disorder of the axial tone has been suggested, which increases in a paroxysmal and asymmetric fashion ipsilateral to the side of the torticollis; such changes might be supposed to be related to a disorder of the basal ganglia [23].
- Genetic factors have been studied; since the CACNA1A gene is abundantly expressed in the cerebellar cortex, a mutation of this gene might contribute to the onset of the disorder [36].
- A decrease in glucose metabolism in the cerebellum and basal ganglia or a decrease of perfusion in the basal and temporal cortex may be a causal factor of the disorder [47].

On the basis of different vestibular findings, some authors speculated on the possibility of two different forms of torticollis: the first with a vascular etiology (with a familial history of migraine) and the second with a vestibular etiology (without relationship with migraine).

Different publications have underlined the possibility that benign paroxysmal torticollis is an age-sensitive neurodevelopmental disorder that is a forerunner to migraine. First, subjects with benign torticollis often have a familial history of migraine; around 38 % of all cases described in different reports have at least one parent suffering from migraine, while 10 % have motion sickness. In another work based on a sample of 10 subjects, all had a familial history of migraine in at least 2 other family members; moreover, in 8 of 10 patients at least 1 parent had migraine [41]. The same author referred that motion sickness was present in 6 cases, while in 7 of 10 subjects at least one family member reported episodic dizziness or vertigo, more often associated with migraine. Another investigation reported the presence of a positive familial history of migraine in 54.5 % of cases [48]. Second, patients with benign torticollis more easily develop BPVC, CVS, motor sickness, and migraine at later ages. Evolution towards other episodic syndromes and migraine is reported to occur in over 33.3 % of cases [48].

Conclusions

The prevalence of periodic syndromes of childhood has been widely documented; nonetheless, at present they are probably under-recognized. It should be mentioned that a correct diagnosis may spare the family anxiety and/or costly diagnostic procedures.

Among these, the single form of vertigo unanimously and officially recognized as a precursor of migraine is BPVC. On the basis of epidemiological, clinical, and genetic findings, BPVC may today be simply considered as a form of migraine, typical of infancy, starting earlier or later, characterized by episodic vertigo attacks, and with possible evolution, in adolescence or adulthood, towards spontaneous complete recovery, towards typical headache migraine, towards vestibular migraine, or towards less common forms of migraine. Nonetheless, among other childhood periodic syndromes, benign torticollis of infancy and cyclical vomiting could be hypothesized as other migrainous disorders similarly related to an involvement of the vestibular system.

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Ménière's Syndrome and Migraine

11

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Ménière's disease (MD) is a chronic progressive disorder characterized by recurrent spells of spontaneous vertigo with fluctuating sensorineural hearing loss associated with tinnitus and aural fullness. The disease affects both ears in 25–40 % patients and bilateral involvement appears to increase over time [1].

Although the etiology is unknown, endolymphatic hydrops (EH) is a common finding in postmortem histopathological examinations of temporal bone specimens from individuals with a previous diagnosis of MD. EH consists of an enlargement of the endolymphatic space with a characteristic distension of the Reissner membrane into scala vestibuli as well as other membranous structures in the labyrinth.

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The classical hypothesis sustains that ruptures in the membranes and subsequent mixing of endolymph and perilymph conducts to alterations in the homeostatic equilibrium that finally lead to clinical symptoms. Some authors have considered that EH is not the causative process but a final consequence of diverse changes in the inner ear and even represents an epiphenomenon [2, 3].

MD is a complex disorder where genetic, epigenetic, and environmental factors probably contribute to its pathophysiology. A genetic susceptibility is supported by the report of familial occurrence in around 8 % of cases, mostly with an autosomal dominant mode of inheritance with incomplete penetrance [4].

There is no specific biological marker of MD, so the diagnosis of MD is based upon clinical criteria, being the Committee on Hearing and Equilibrium of the American Academy of Otolaryngology – Head and Neck Surgery (AAO-HNS) 1995 guidelines the most widely used for MD [5]. However, these criteria do not consider migraine as a symptom of MD, and criteria for vestibular migraine (VM) have been recently developed [6] and according to both definitions, VM and MD can be comorbid conditions. This comorbidity has a major interest for the clinician for several reasons: the understanding of its pathophysiology, the differential diagnosis between MD and VM, and their therapeutic management.

We have tried to find the answers to these three questions we have asked ourselves:

A. Is there a link between MD and migraine?
B. Why is there a link between MD and migraine?
C. How can we differentiate VM from MD?

11.1   Is There a Link Between Ménière's Disease and Migraine?

Headache is a common complaint in about 70 % patients with MD as reported by several investigators [7–9]. Of note, a relation between migraine and MD was first described by Prosper Ménière himself in 1861 [10]:

> Les personnes qui sont sujettes à la migraine offrent souvent des phénomènes analogues à ceux que nous avons signalés; mais il faut dire que certaines hémicrânies accompagnées de vomissements se terminent très-fréquemment par la surdité. Il y a bien longtemps que j'ai observé et indiqué le fait. Je n'hésite pas à regarder ces migraines comme dépendant d'une lésion de l'oreille interne; elles s'accompagnent de bruit, de vertiges, d'affaiblissement graduel de l'ouïe, et le plus souvent cette surdité résiste a tous les moyens de traitement.

Since then, many authors have speculated about this relationship.

Vertigo occurs frequently in patients with migraine. In fact, vestibular symptoms and current or previous history of migraine are the key features of vestibular migraine as it is described elsewhere in this book. Phonophobia is a characteristic auditory symptom commonly referred by patients having migraine and vestibular migraine, usually during the migraine headache or the vertigo spell. But tinnitus,

aural pressure, and low-frequency fluctuating sensorineural hearing loss have also been documented in patients with migraine and vestibular migraine [11–13]. Likewise, migrainous headaches, photophobia, and aura symptoms appear in patients with MD [13]. So, it is clear that there is an overlap of symptoms and signs between migraine and MD.

Migraine affects 18–25 % of the general population, whereas the prevalence of MD ranges 17–205 cases per 100,000 in European descendent population. Currently, there is growing epidemiological evidence that endorses a link between both disorders. Kayan and Hood [14] reported six patients with MD in a series of 80 migraine sufferers who complain of vestibulocochlear disturbances. On the other hand, several authors have found a high incidence of migraine in patients diagnosed of MD.

Rassekh [15] found a much greater prevalence of migraine (81 %) in patients fulfilling the 1972 AA-OHN criteria for vestibular Ménière's disease than in patients with (unilateral) classic MD (22 %) or in control subjects (33 %), the differences between these two last groups were not significant, but the age and sex distribution were not specified. It is interesting that Rassekh emphasized that a high proportion of the patients initially diagnosed as having vestibular MD do not progress to classic MD. He stated that these two facts argued against the concept of vestibular MD as a variant of MD and that the vertigo could be caused by migraine itself. Today, we know that the majority of those patients with migraine and vestibular MD would fulfill the criteria of VM.

In 1995, Parker reported in a retrospective uncontrolled case series that 34 % of the patients with MD suffer from migraine [16].

Radtke, according to the 1995 criteria of the AAO-HNS for MD and 1988 of the International Headache Society (IHS) for migraine, found a lifetime prevalence of migraine of 56 % in patients with MD as compared to 25 % in age- and sex-matched controls [13]. Interestingly, during an attack, 28 % of the patients with MD described concurrence of migraine attacks, 52 % reported photophobia, and 10 % aura symptoms. The authors appreciated that 45 % of patients with MD experienced at least one migraine symptom during the vertigo episode. Cha et al. found that migraine was found in a subset of patients with MD and these patients have concurrent bilateral aural symptoms and a family history of episodic vertigo [17], so it seems that familial vertigo is associated with migraine.

Shin et al. [18] have found that 31 % of the patients with MD had migraine headaches associated with their vertigo attacks, but the familial history of migraine or MD was not reported.

A recent epidemiological study in 423,400 individuals on the National Health Interview Survey performed in the USA during the years 1986–1988 and 1994 found that the incidence of migraine in the general population and in patients with MD were 3.8 and 4.5 %, respectively [19].

We have investigated the prevalence of migraine in Spanish patients with MD. Our series have a prevalence of migraine of 11.3 and 21.4 % in sporadic ($N=496$) and familial cases ($N=98$), respectively (OR$=2.14$ (1.23–3.74), $p=0.01$). Our data did not found a higher prevalence of migraine in patients with bilateral
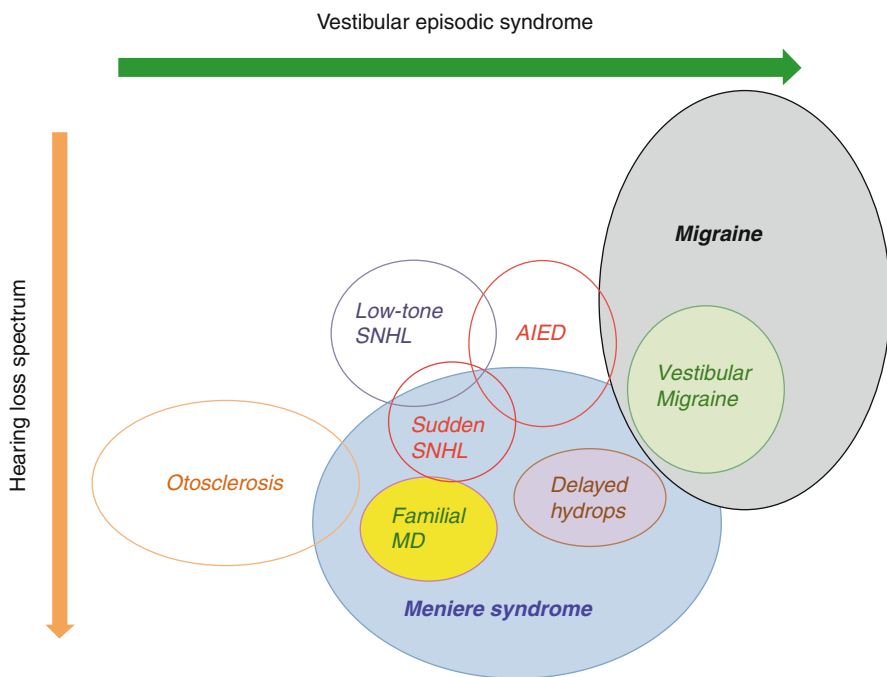
Fig. 11.1 Vestibular episodic syndrome includes several clinical entities which may overlap in the same patient and their relatives resulting in intermediate or complete phenotypes such as MD with migraine. *SNHL* sensorineural hearing loss, *AIED* autoimmune inner ear disease

sensorineural hearing loss when they were compared with unilateral sensorineural hearing loss (Fig. 11.1).

This high prevalence of migraine in familial MD when it was compared to the general population, and the frequent occurrence of migraine symptoms during the vertigo spells suggests a common pathophysiological link between migraine and MD.

11.2   Why Is There a Link Between Ménière's Disease and Migraine?

The clinical practice indicates that some common triggers (stress, menstruation) may facilitate a migraine attack or an episode of vertigo in patients with Ménière's disease or migraine [20, 21]. These triggers could be epigenetic factors which will enhance the risk of suffering the disease. Moreover, overlapping clinical features among MD, migraine, and vestibular migraine suggest a shared pathogenic mechanism in a multifactorial disease. Of note, acetazolamide is effective in rare genetic disorders related to migraine-like episodic ataxia [22], several patients with VM,
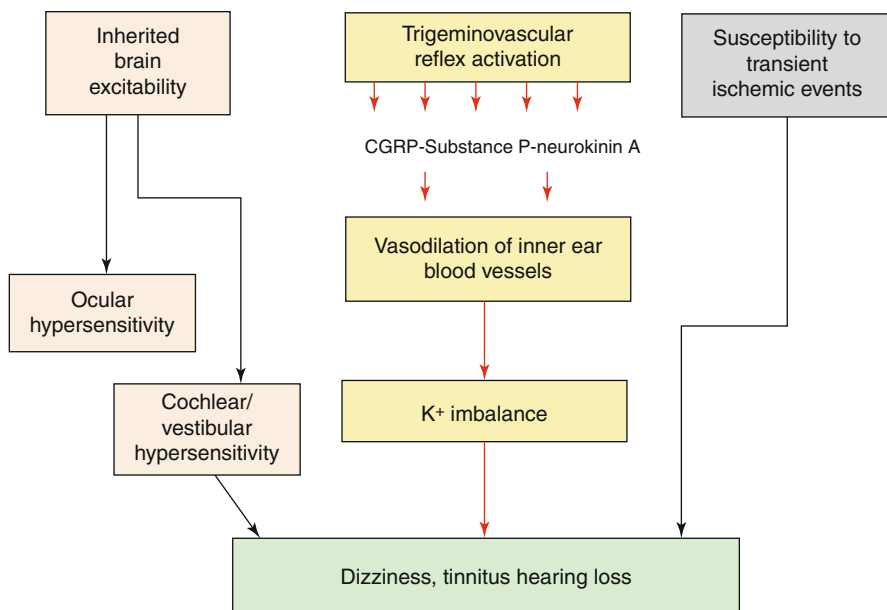
Fig. 11.2 Neurobiological mechanisms associated with migraine which could be associated with MD

and also in some MD patients who do not respond to betahistine [23], suggesting that the membrane homeostasis and its threshold of excitability are crucial to control an attack of migraine or vertigo.

There are several neurobiological or molecular mechanisms to explain the reported association between MD and migraine. These mechanisms include (Fig. 11.2):

(a) Inherited alteration of brain excitability which can be observed as hypersensitivity to visual, auditory, or vestibular stimulation
(b) Sensitization of the trigemino-vascular pathway with release of neuropeptides
(c) Neurogenic vasodilation of meningeal and inner ear blood vessels
(d) Susceptibility to transient ischemic events

Neurogenic vasodilation and extravasation from meningeal vessels is a well-studied mechanism in migraine [24]. The release of neuropeptides such as calcitonin gene-related peptide (CGRP), neurokinin A, and substance P from dural and cerebral blood vessels produces a local inflammatory response contributing to pain [25]. Furthermore, the electrical stimulation of the trigeminal nerve and the chemical stimulation of cochlear and vertebrobasilar arteries with substances such as capsaicin, histamine, or serotonin produce the extravasation of these neuropeptides in the inner ear [26, 27].

However, the activation of the trigemino-vascular pathway itself is not enough to explain the cochlear-vestibular dysfunction observed in MD. So, an alteration in the

ion transport mediated by voltage-dependent channels in the inner ear and brain cortex maybe the common genetic susceptibility leading to variable phenotypes in migraine, MD, or overlapping migraine-Ménière's disease complex.

Both MD and migraine are multifactorial disorders and the interaction of genetic, epigenetic, and environmental factors contribute to the clinical phenotype. This interaction has been observed in the hypersensitivity to vestibular stimulation found in some individuals with migraine where rotatory or caloric vestibular testing can specifically trigger a migraine attack [28].

Familial clustering has been described in patients with MD and migraine [17, 29]. Moreover, familial MD shows an autosomal dominant inheritance pattern with incomplete penetrance and most of these families have multiple members with migraine [30]. However, familial MD shows genetic heterogeneity [4] and migraine does not segregate with MD in all pedigrees [31]. Currently, it is not clear if there is a genetic basis to explain the association between migraine, episodic vertigo, and MD. Since both disorders seem to be heterogeneous and several genes may contribute to its development, it is likely that genetic or epigenetic factors confer susceptibility to this association, rather than be deterministic [29].

Several cross-sectional and population-based studies using MRI have demonstrated an increased incidence of brain white matter hyperintensities, silent infarct-like lesions, and volumetric changes in gray and white matter regions in migraineurs. These findings suggest that migraine is related with posterior circulation territory ischemic stroke, probably as an independent cerebrovascular risk factor [32].

The risk of transient ischemic events is increased in patients with migraine and sudden sensorineural hearing loss (SSNHL) [33–35]. A population-based study indicates that migraine could be associated with SSNHL, but migraine is comorbid with several cardiovascular risk factors, i.e., diabetes and hypertension, and they probably can explain this comorbidity. Combined audio-vestibular symptoms are also a hallmark of transient ischemic attack and such symptoms typically results from ischemia in the anterior inferior cerebellar artery [36]. Vascular risk factors are probably the common link between migraine and transient episodic symptoms of vertigo, tinnitus, or hearing loss that can culminate in stroke with permanent hearing or vestibular loss, or both mimicking Ménière's disease [37].

If patients with migraine have an increased risk of cerebral ischemic events, this ischemic risk could affect the cochlear blood flow [38].

11.3   How to Differentiate Vestibular Migraine from Ménière's Disease?

The clinical picture of VM and MD often overlaps, especially in the early stages of MD; so, it is a real diagnostic challenge to distinguish between both diseases in a patient with recurrent spells of spontaneous vertigo who suffer from migraine. Until now, we do not rely on clinical criteria for VM thereby hindering the differential diagnosis. Undoubtedly, the new definition of VM facilitates the distinction. But anyway, there is no specific diagnostic test for MD or VM; in both conditions, it is

a diagnosis of exclusion based on clinical history and a documented fluctuating progressive hearing loss in the case of MD.

The necessity to differentiate between both entities is particularly relevant in a patient with a known MD, who also has migraine and whose symptoms do not respond to conservative medical treatment. In this situation, it is imperative to rule out a VM before attempting a destructive and irreversible procedure.

We need to distinguish between VM and MD, first, because they have a different therapeutic approach and, second, because they also exhibit a different prognosis.

We can try to differentiate between MD and VM according to a combination of their clinical features, the results of functional testing, and magnetic resonance imaging (MRI).

11.3.1   Clinical Features

First of all, the diagnostic criteria for MD [5] and VM [6] are not enough and a follow-up of several months is usually required to distinguish both syndromes. So, fluctuating hearing loss, tinnitus, and aural pressure may also occur in VM, but hearing loss does not progress to profound levels. Susceptibility to motion sickness may be associated with VM; however, as it also occurs with various other vestibular disorders, it is not included as diagnostic criteria.

According to the 3rd edition of the International Criteria for Headache Disorders (ICHD-III beta), "when the criteria for MD are met, particularly hearing loss as documented by audiometry, MD should be diagnosed, even when migraine symptoms occur during the vestibular attacks. Only patients who have two different types of attacks, one fulfilling the criteria for VM and the other for MD, should be diagnosed with both disorders. A future revision of ICHD may include a VM/MD overlap syndrome" [39].

Phonophobia is the most common auditory symptom associated with migraine attacks [11, 14]. Sometimes it is difficult to distinguish phonophobia from hyperacusis.

Tinnitus and aural fullness, both unilateral and bilateral, have been described in migraine and VM patients [14, 40]. More recently, Brantberg and Baloh [2011] found that 68 % of the patients of a group with MD described two or more of the three characteristic auditory symptoms (unilateral hearing loss, unilateral tinnitus, and unilateral aural fullness) with at least half of the vertigo spells as compared with 18 % of a group of patients with benign recurrent vertigo. Furthermore, none of the three auditory symptoms were reported by 19 % of MD patients and 68 % by benign recurrent vertigo patients. A multivariate analysis revealed that the association of unilateral auditory symptoms is the most useful clinical differential characteristic to distinguish between MD and VM [12].

A longitudinal study in patients with VM has demonstrated that auditory symptoms during the vertigo spells increase from 16 % initially to 49 % after a median follow-up of 9 years, and cochlear symptoms in the interictal interval change from 26 to 77 % at the same time interval [41]. Specifically, hearing loss in the free interval varies from 15 to 38 % (Table 11.1).

Table 11.1 Comparison between Ménière's disease and vestibular migraine

	Ménière's disease	Vestibular migraine
Age of onset	35–60 years	Any age (20–60)
Gender	Equal	Female preponderance
Duration of attacks	20 min to hours	Seconds to days
Triggers	+	++
Family history of vertigo or hearing loss	+	+
Family history of migraine	+	++
Present or previous history of migraine	+/++	+++
Interictal hearing loss	+++	+
Symptoms during an attack		
Vertigo	++	+++
Photo-/phonophobia	++	+
Headache	+	++/+++
Auditory symptoms	+++	+/++
Aura	−/+	+
Interictal vestibular function abnormalities	+ (early stage)/+++ (advance stage)	++

11.3.2   Functional Testing

11.3.2.1   Hearing

The exact determination of hearing thresholds is crucial to distinguish VM and MD. Typically, MD begins with a low-frequency fluctuating unilateral sensorineural hearing loss coincident with spells of vertigo. As the episodes of vertigo recur and the disease progresses, the hearing loss worsens, involving all frequencies, until it stabilizes, no longer fluctuates, and becomes permanent [42]. The initial presentation of MD is highly variable and may be apparent initially only with episodic vertigo or fluctuating hearing loss.

Sensorineural hearing loss is uncommon in patients with VM although several patterns of hearing loss have been described: unilateral/bilateral and fluctuating/permanent [40, 43]. Fluctuating sensorineural hearing loss is not specific of MD as it has also been observed in VM [41] and other disorders such as autoimmune inner ear disease, Cogan's syndrome, otosyphilis, and enlarged vestibular aqueduct syndrome. When hearing impairment is present in VM patients, audiometry usually demonstrates a low-frequency, mild-moderate, bilateral sensorineural hearing loss; but permanent unilateral hearing loss and even SSNHL have also been associated with migraine and vestibular migraine [33–35]. Unlike MD, hearing loss is usually episodic and it progresses much more slowly.

11.3.2.2   Vestibular Bedside Examination

The presence of vestibular abnormalities in bedside examination and vestibular function testing is well recognized in MD. Head-shaking nystagmus and vibration-induced nystagmus are the more common vestibular signs in patients with MD

[44, 45]. The head impulse test yields positive result in less than half of MD patients. Spontaneous nystagmus is often detected during an attack, but its direction varies, beating both toward the affected ear (irritative nystagmus) or the healthy ear (paralytic nystagmus), so it cannot be considered a localizing finding. In the intercrisis period, the frequency of spontaneous and positional nystagmus varies widely among different series.

Patients with migraine and VM also exhibit abnormal results in clinical examination and vestibular function testing both during and between the attacks: spontaneous nystagmus, positional nystagmus, gaze-evoked nystagmus, saccadic pursuit, and unilateral vestibular hypofunction [41, 46, 47]. However, these findings are not specific for VM and can indicate either a peripheral or central origin.

Recently, Shin et al. [18] have compared interictal vestibular function in both patients with MD and VM. They have found that patients with MD show significantly more abnormal results than patients with VM using head-shaking nystagmus, vibration-induced nystagmus, or bithermal caloric tests. Overall, abnormal result was found on at least one of these three tests in 84 % of MD patients and 66 % of patients with VM. It should be noted that in patients with VM, 50 % had abnormal head-shaking nystagmus, 32 % abnormal vibration-induced nystagmus, and 25 % abnormal canal paresis [48].

11.3.2.3   Instrumental Testing

Although instrumental vestibular examination is not usually recommended to distinguish MD and VM, it may yield relevant information and anticipate the diagnosis of MD. Recently, Neff et al. (2012) has found differences statistically significant in the following vestibular tests when comparing MD patients and VM group: head thrust test, head-shaking nystagmus, vibration-induced nystagmus, abnormal caloric asymmetry, rotatory chair gain, abnormal rotatory chair phase, symmetry and summary, and VEMPs [45].

Unilateral vestibular hypofunction in caloric testing is observed in up to 75 % of unilateral MD patients [48], although it is worth noting that a normal bithermal caloric response has been reported in up to 50 % of patients in some series. Unilateral canal paresis usually indicates the involved ear, but it has also been demonstrated in 19 % of patients on the normal side [49].

Electrocochleography (*ECoG*) is a neurophysiologic technique in which an auditory evoked potential is obtained in response to brief sound stimuli and recorded by an intratympanic or extratympanic (noninvasive) electrode. The cochlear microphonic and the summating potential (SP) are generated by the hair cells of the organ of Corti whereas the compound action potential (AP) of the auditory nerve represents the summed synchronized response of many individual nerve fibers. Testing parameters include latencies and amplitudes of SP and AP, and SP/AP amplitude ratio.

Changes in the SP response can reflect pressure differences between the scala media and the scala vestibule, indicating excessive fluid pressure thus deforming the basilar membrane toward the scala tympani, so that enhanced amplitude SP is thought to reflect EH. However, normal ECoG responses have also been reported in patients with EH.

Increases in SP amplitude with an enlarged SP/AP ratio and a prolonged AP latency shift have been observed in patients with MD [50]. Nevertheless, there were no statistically significant differences in SP/AP ratios between MD and migraine-associated dizziness. Moreover, the sensitivity and specificity for detecting MD are variable, although it is increased with duration and severity of disease [51].

Vestibular-evoked myogenic potentials (*VEMPs*) are otolith-mediated, middle-latency reflexes which are recorded from sternocleidomastoid or infraocular electromyography in response to high-intensity auditory stimuli or high-frequency vibratory stimulation. Cervical or ocular VEMPs show a biphasic waveform with a positive and a negative peak. The short-onset latency of the cervical VEMPs is generated by primary vestibular afferents projecting to the vestibular nuclei and hence via the ipsilateral medial vestibulo-spinal tract to the accessory nucleus. Cervical VEMPs evaluate the integrity of the sacculus and the inferior vestibular nerve, while ocular VEMPs test utriculus and superior vestibular nerve. The response parameters commonly used are latencies and interpeak amplitude of the response. Interaural differences are usually determined by comparing the amplitudes between both sides and calculating the asymmetry ratio.

The VEMPs test is currently a standardized technique and it provides a quick and noninvasive method of assessing vestibular-otolith function in patients with an episodic vestibular syndrome. Zuniga et al. (2012) performed a comparative study with 20 patients with MD and 21 patients with VM, but they were not able to find differences between both groups [52]. However, another study comparing 60 patients with VM, 60 patients with MD, and 30 controls found significant differences in the corrected amplitudes in cervical VEMPs between patients with MD and VM [53]. While patients with VM usually present a normal interictal response, unilateral MD shows abnormalities in air-conducted cervical and ocular VEMPs in the ipsilateral ear, and this provides a relevant method to separate VM and MD [53].

11.3.3   Magnetic Resonance Imaging

In the last few years, some investigators have advocated the use of MRI to evidence EH [54]. In particular, intratympanic and/or intravenous administration of gadolinium chelate together with the use of three-dimensional (3D) fluid-attenuated inversion recovery (FLAIR) and 3D real inversion recovery (IR) sequences in 3-T scanner has allowed not only in vivo visualization of membranous labyrinth but also the demonstration of EH in humans diagnosed of MD [55]. Various authors have shown EH in 100 % of the patients with definite MD when these specific inner ear MRI protocols were performed [54, 56], but this tool does not exclude migraine or VM in patients with MD.

11.4   Final Remarks and Conclusions

Migraine and MD can be comorbid conditions. MD and VM can also coexist in the same patient according to the current diagnostic criteria. Epidemiological and genetic information suggest that the episodic vestibular syndrome could be a

multifactorial disorder where bilateral MD and migraine without aura will be the extreme phenotypes. So, several intermediate phenotypes could be considered such as unilateral MD, VM, or migraine with aura, and they will be a continuum between both extremes. According to this model, epigenetic or environmental factors could act as modifiers of brain excitability or neurogenic vasodilation, being the triggers for episodic pain, vertigo, or hearing loss.

This new paradigm has no cut-off point to separate each endophenotype, since these symptoms (migraine, episodic vertigo, or hearing loss) are clustered in families, and extreme and intermediate phenotypes are observed in the same family. In the context of a spontaneous episodic vertigo, the ascertainment of a progressive sensorineural hearing loss favors a diagnosis of MD whereas a history of migraine points to VM. Nevertheless, there is no clinical feature or vestibular function testing capable of differentiating both disorders.

The challenge is to obtain very detailed clinical information from each patient and their relatives and to integrate this information with genomic data for a better understanding of the relationship between MD and migraine.

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Benign Paroxysmal Positional Vertigo and Migraine

12

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12.1 Introduction

The first point of contact between benign paroxysmal positional vertigo (BPPV) and migraine is that both diseases excel in terms of frequency of presentation. BPPV is the most frequent cause of vertigo in adults and migraine is the most frequent cause of headache in humans. Furthermore, both diseases are more prevalent in the female sex. In the last 15 years, interesting relationships between the two disorders have been studied and proposed. In this chapter, the clinical features of BPPV and its correlations with migraine will be described.

12.2 Benign Paroxysmal Positional Vertigo

BPPV is a labyrinthine disorder characterized by positional vertigo and paroxysmal positional nystagmus, both provoked by changes in the position of the head with respect to gravity. It is caused by a mechanical stimulation of the vestibular receptors within the semicircular canals. The pathogenesis of signs and symptoms of BPPV is quite well known, while little is known about its etiology.

12.2.1 Epidemiology

According to data based upon a representative German neurotological survey, the lifetime prevalence of BPPV in the general adult population is 2.4 %, the 1-year

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incidence is 0.6 %, and the 1-year prevalence is 1.6 % [1]. This means that, in Germany, about one million people are affected by BPPV every year. The diagnosis was obtained by a validated telephone interview, not from diagnostic maneuvers, but the estimates were conservative since the diagnostic criteria were based mainly on specificity rather than sensitivity. In that survey, BPPV accounted for 8 % of individuals with dizziness or vertigo.

In an epidemiological study performed on 2,270 patients in whom the diagnosis was obtained by specific diagnostic maneuvers, the results were not too dissimilar: BPPV accounts for about 14 % of all equilibrium disorders, with an annual incidence of about 0.1 % [2]. Women are more affected than men in a ratio of about 2:1. The mean age of onset is about 50 years, with a decreasing incidence under 35 years. The disease is also seen in children but very rarely. About one in every two patients is prone to recurrences [1]. The *posterior semicircular canal* (PC) is usually responsible for BPPV. Indeed about 70 % of BPPV patients receive a diagnosis of unilateral PC-BPPV. The right PC is more often involved than the left, with a ratio of about 1.5:1. This may be related to the habit of most patients of sleeping on their right side [3]. Bilateral involvement of the PC affects 7.5 % of patients, and almost 90 % of these are posttraumatic. Lateral canal (LC) BPPV accounts for 17 % of all BPPV patients, with no difference in gender or side involved.

12.2.2 Etiology and Pathogenesis

Clusters of calcium carbonate crystals, similar to the otoliths attached to the utricular macula, have been observed inside the semicircular canals during surgery in patients affected by BPPV [4]. It is likely that otoconia detach from the utricular macula and enter the semicircular canals moving in the endolymph when the head changes its position with respect to gravity. Only when the cluster reaches a critical mass it is able to alter the endolymphatic pressure enough to displace the cupula. The debris can fall toward or away from the ampulla, creating ampullopetal or ampullofugal deflection of the cupula by a pumping or suction mechanism, or by hydrodynamic drag (canalolithiasis theory). Clusters may also adhere to the cupula rendering it sensitive to gravitational forces (cupulolithiasis theory). Otoconia can be attached to the cupula both on the side of the short arm and on the side of the long arm of the canals, or both. Otoconial debris should eventually dissolve in the endolymphatic fluid, and the concentration of calcium in the endolymph may be important in this clearing action, since otoconia are composed of calcium carbonate crystals [5]. Free-floating otoconia are common in the utricular endolymph, especially in older people. The syndrome is activated when the head of the patient is positioned such that the debris can enter the semicircular canals. Once in the canal, the particles move under the force of gravity, tending to settle to the bottom. This explains why the first episode of vertigo generally occurs in bed or on getting up.

In about 15 % of cases, BPPV initiates in close relationship with a trauma. Trauma, sometimes minor and not necessarily of the head, provokes the detachment of otoconia. The post-traumatic etiology also includes whiplash injury, high-impact

exercises, scuba diving, or surgery on the head in which a drill is used (nasal, dental). In the remaining 85 % of cases, no definite etiology is indicated even though many conditions are considered to be predisposing factors for the "spontaneous" detachment of otoconia from the utricular maculae. The first important condition is aging, since the disease is rare in childhood and frequent in the elderly. In some patients, a viral cause seems likely, as the disease begins during or after a flu-like episode. Disorders of calcium metabolism and hormonal effects may justify the higher incidence of BPPV in females [6, 7]. Migraine, as a causative factor, will be discussed later. Sometimes BPPV begins after a prolonged bed rest, giving rise to the hypothesis that motionlessness may predispose to detachment of otoconia. Prolonged positioning with the head back at the hairdresser and dentist or even after intubation for general surgery can determine the entrance of otoconia into the semicircular canals. Ménière's disease also seems to predispose to BPPV [8]. Associations of BPPV with diabetes [9], hypertension, hyperlipidemia, and stroke [1] have been suggested, but need to be confirmed.

12.2.3   Symptoms

Diagnosis in typical BPPV can also be made over the phone, by asking the patient if vertigo is transitory and triggered by lying down or turning in the bed. If yes, there are very few alternative diagnoses to BPPV, and in this way we also exclude orthostatic dizziness. Vertigo is also provoked by head movements in the pitch plane (getting up in the morning, looking up, bending forward) when the vertical canals are responsible. If the lateral canals are involved, the attacks of vertigo are longer and more intense and provoked mainly by rolling onto a side while lying down. Vertigo is often a spinning sensation, since it is due to the semicircular canals, and generally subsides after many seconds maintaining the provoking position. BPPV is one of the most common causes of falls, especially in elderly patients.

Positional vertigo is recurrent, since attacks occur whenever a critical movement is performed or a critical position is assumed. Initially, the episodes of vertigo are more intense and often accompanied by nausea and vomiting, so that patients may overestimate the duration of the attack. BPPV is quite often a self-limiting condition, with a symptomatic period lasting for days or weeks. On the other hand, there are patients in whom the symptomatology can last for many months if not treated. Recurrences of the symptomatic periods are frequent. Patients with BPPV are generally free of symptoms when standing up and can safely drive a car since turning the head from side to side does not provoke vertigo. Some of them complain of a mild sensation of floating and postural instability. By definition, the disease is not associated with hearing loss or neurological symptoms, unless secondary to other diseases. However, vertigo is often a stressful event and can easily lead to anxiety, phobic behavior, and a reduction in the quality of life [10]. The habit of sleeping in a semi-sitting position or avoiding turning in bed to prevent the vertigo can give rise to neck discomfort that is often considered the cause of vertigo, by general practitioners as well.

Patients with atypical BPPV and particularly those with positional downbeating nystagmus (pDBN) complain of less specific symptoms, with more prolonged and less intense vertigo, especially when getting up. Some of these patients complain of dizziness and unsteadiness when walking, which is a feature not detected in those with typical BPPV [11].

12.3   Diagnosis and Pathophysiology

Hypothetically, otoconial debris can enter any canal in the labyrinth or adhere to any cupula. In this way, they sensitize the endolymph and cupulae to linear acceleration and gravity and generate incorrect information on angular acceleration. The diagnosis is made on the finding of positional nystagmus induced by specific diagnostic maneuvers that act in planes parallel to each semicircular canal. The characteristics of nystagmus are crucial to identify which semicircular canal is involved and sometimes in which part of the semicircular canal the debris are located.

12.3.1   Posterior Canal BPPV

The PC is by far the most commonly affected because of its anatomical position. When the patient lies in the supine position, the common crus is lower than the utricle, and debris can enter the non-ampullar orifice of the canal. PC-BPPV is generally diagnosed by the Dix-Hallpike test. The patient is seated on an examination bed and the head is rotated 45° in the direction of the examiner. The patient is then brought into the supine position with the head hyperextended. With this maneuver, the lowermost PC is specifically stimulated because the canal is aligned with the plane of movement. In the diagnostic position, the ampulla of the PC is placed in a higher position with respect to the canal. In this way, the particles fall away from the ampulla and, by a plunger effect in a narrow canal, cause an endolymphatic flow that deflects the cupula away from the utricle (Fig. 12.1). The ampullofugal displacement is an excitatory stimulus for the PC that provokes a mixed torsional-upbeating paroxysmal nystagmus consistent with the excitatory connections of the PC to the vertical extraocular muscles. The fast phase of the torsional component is directed such that the upper pole of the eyes beats toward the affected lower ear. The patient is then returned to the sitting position with the head straight. With this movement, the particles fall in the opposite direction and cause an ampullopetal flow, which produces an inhibitory response and a less intense nystagmus in the opposite direction, i.e., downbeating with the torsional component directed such that the upper pole of the eyes beats away from the left affected ear. The paroxysmal positional nystagmus of the PC in its typical form has some features that are shown in Table 12.1. The latency between reaching the diagnostic position and the beginning of positional nystagmus is explained by the delay in setting the clot in motion. Paroxysmal means that positional nystagmus is characterized by a rapid increase in intensity and then by a slow decrease. Positional nystagmus is typically transitory,
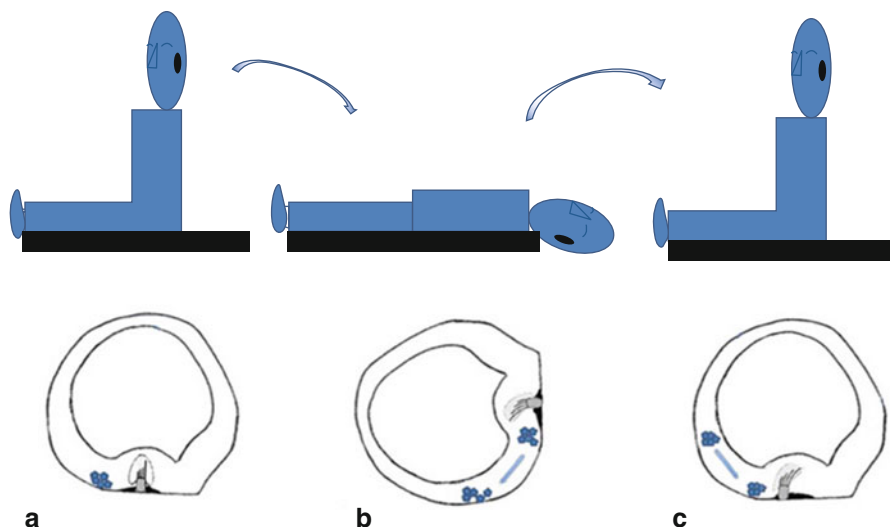
Fig. 12.1 Pathomechanism in left posterior canal canalolithiasis. (**a**) In the sitting position, the head is turned 45° to the left and debris are located in the lower part of the PC. (**b**) The patient is then rapidly brought into a left head hanging position and particles fall in ampullofugal direction, provoking a mixed upbeating-torsional nystagmus (upper pole beating toward the affected left ear). (**c**) The patient is next returned to the upright position and debris fall back in ampullopetal direction, provoking a less intense nystagmus in the opposite direction

Table 12.1 Main features of typical paroxysmal positional nystagmus due to posterior canal canalolithiasis (Dix-Hallpike maneuver)

Direction and plane	Torsional with the upper pole of the eye to the lower ear and vertical (to the forehead). Reverses its direction when returning to the sitting position
Latency	1–10 s
Duration	Usually 20–30 s (<1 min)
Fatigability	Reduction of intensity by repeating the maneuvers
Temporal profile	Paroxysmal (rapid "crescendo" – slow "decrescendo")

that is, it dissipates in 10–40 s, because once the clot reaches its lowest position in the canal, the cupula returns to the primary position with its time constant, primarily due to its elasticity. Another important feature is the fatigability, i.e., the reduction in nystagmus intensity when the maneuvers are repeated. This is explained by dispersion of particles from the clot, making the plunger less effective.

If otoconial debris are attached to the cupula of the PC (cupulolithiasis), the Dix-Hallpike maneuver will similarly provoke a positional nystagmus. The cupula is deflected down, toward the canal, by gravity, because adherence of debris makes it heaviest with respect to the endolymph. Positional nystagmus due to PC cupulolithiasis should have the same features as those due to canalolithiasis according to plane and direction but will be less intense and more prolonged, as reasonable to expect but also deduced from mathematical models [12].

12.3.2 Lateral Canal BPPV

Positional nystagmus from the lateral canal is reliably elicited by the "Pagnini-McClure test," also called the "supine head roll test," a maneuver that acts in a plane parallel to that of the lateral canal [13, 14]. The patient is first brought from the sitting to the supine position, with the head straight (nose upward) and bent about 30° forward, looking for the appearance of any positional nystagmus. Then the patient's head is rolled 90° to one side. After that, the head is rotated 180° to the other side, looking for changes in the direction and intensity of nystagmus. According to the different locations of otoconial debris in the canal, LC-BPPV can be divided into two variants, the more common one with geotropic nystagmus and the less common one with apogeotropic nystagmus.

12.3.3 Geotropic Variant

Once otoconial debris have entered the lateral canal, they move under the force of gravity, tending to settle at the bottom of the canal, far from the cupula. When the patient is moved from the sitting to the supine position with the head straight, the debris gravitate downward to the lower portion of the canal, away from the ampulla. This causes an inhibitory ampullofugal endolymphatic flow and a mild horizontal nystagmus toward the unaffected ear [15] (Fig. 12.2). The subsequent rotation of the head toward the affected ear causes the particles to fall toward the ampulla, producing an excitatory flow and an intense horizontal nystagmus beating toward the lower ear. It is named *geotropic* because it beats toward the ground. When the head is then rolled to the other side (to the unaffected ear), the particles fall in the opposite direction and cause an inhibitory ampullofugal stimulus. This provokes an inversion of nystagmus direction, i.e., beating toward the opposite, healthy ear (again geotropic) (Fig. 12.3).

Geotropic positional nystagmus, when paroxysmal, is always due to canalolithiasis and does not require differential diagnosis. There are reports of horizontal positional nystagmus, geotropic, stationary, and long lasting, attributed to light cupula [16].

12.3.4 Apogeotropic Variant

The apogeotropic variant is due to a different position of particles inside the lateral canal. According to cupulolithiasis theory, they can be attached to the cupula, on the canal side, on the utricular side, or both, and when the head is turned on its side, the heavy cupulae are deflected by gravity. When the head is rotated so that the affected side is down, the deflection will be toward the ground, and the resulting nystagmus will result from an inhibitory stimulus, that is, toward the opposite, normal, side (apogeotropic). In contrast, when the head is rotated so that the affected ear is up, the heavy cupulae will deflect toward the utriculus and the resulting "excitatory" nystagmus will be directed toward the uppermost affected ear (again apogeotropic).
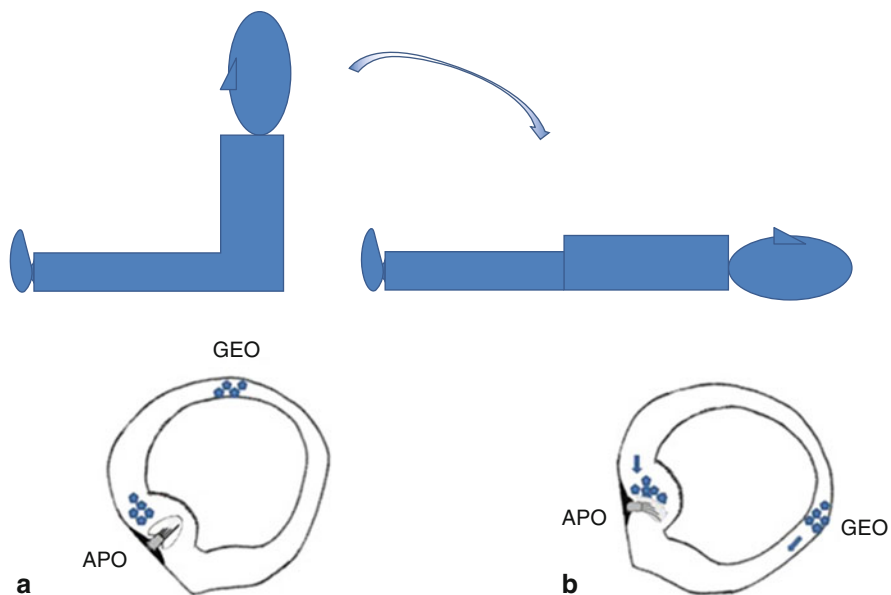
Fig. 12.2 Sitting-supine positioning test in lateral canal BPPV. The patient is rapidly moved from the sitting (**a**) to the supine (**b**) position with the head straight. The maneuver causes otoconial debris to gravitate away from the ampulla, to the most dependent part of the lateral canal, provoking an ampullofugal flow and positional nystagmus beating toward the normal ear (geotropic). If located close to the ampulla, particles move toward the cupula, provoking an ampullopetal flow and nystagmus beating toward the affected ear (apogeotropic)
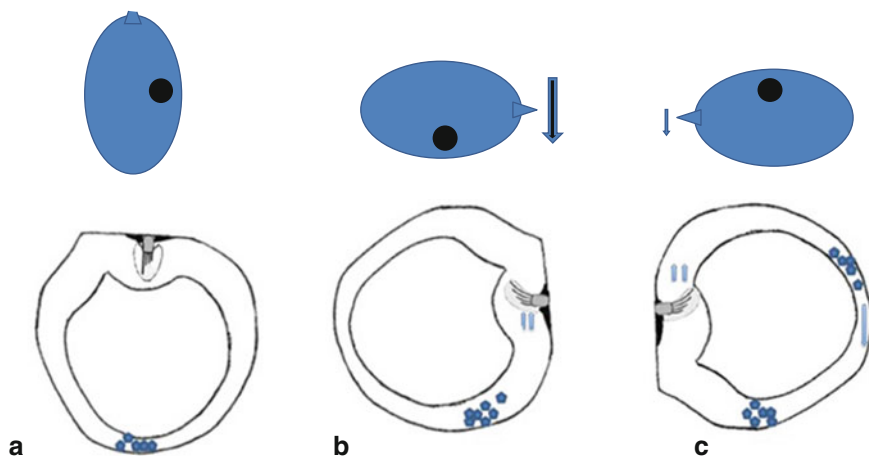
Fig. 12.3 Right lateral canal BPPV: supine head roll test. Geotropic positional nystagmus. (**a**) The patient lies in supine position with the head straight and the debris in the most dependent part of the right lateral canal. (**b**) Rolling the head to the right side, particles fall toward the ampulla, producing an ampullopetal flow and intense right-beating (geotropic) nystagmus. (**c**) Rolling the head to the left side, particles move in the opposite direction, producing ampullofugal flow and left-beating (geotropic) mild nystagmus
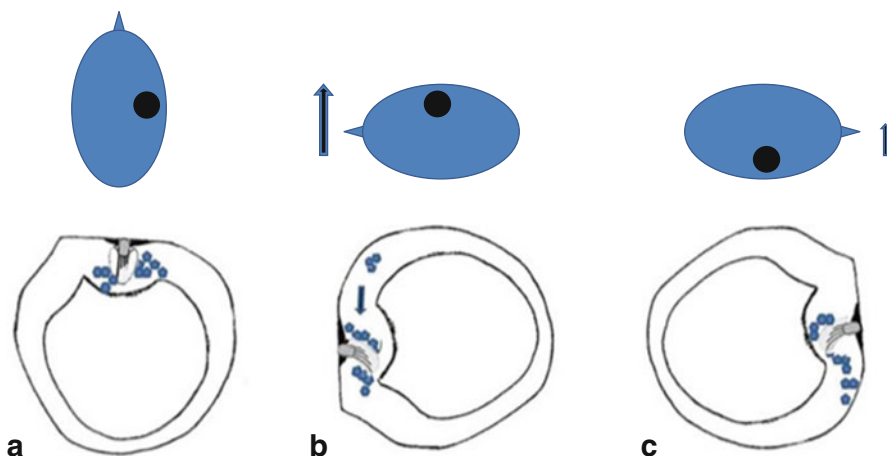
Fig. 12.4 Right lateral canal BPPV: supine head roll test. Apogeotropic positional nystagmus. (**a**) The patient lie in supine position with the head straight and particles located close to the ampulla of the right lateral canal. (**b**) Rolling the head to the left side causes the particles to fall toward the cupula, triggering an intense right-beating (apogeotropic) nystagmus due to the excitatory stimulus (canalolithiasis). The same nystagmus could be elicited to be the deflection of the ampulla caused by the weight of particles strictly close or attached to the ampulla (cupulolithiasis). Positional nystagmus due to cupulolithiasis should be less intense and more prolonged. (**c**) Rolling the head to the right side, the particles move in the opposite direction, producing less intense left-beating (apogeotropic) nystagmus

The intensity of nystagmus again reflects the difference in the stimulation (excitatory/inhibitory) of vestibular end organs, with the strongest nystagmus beating toward the affected ear.

There is also the possibility that the apogeotropic variant is due to canalolithiasis. If debris are located near the ampulla of the lateral canal, on its anterior part, they can move in the opposite direction with respect to the geotropic variant (Fig. 12.4).

Cupulolithiasis should be characterized by less violent and more persistent positional nystagmus. Canalolithiasis is more likely when positional nystagmus is very intense and when the apogeotropic variant is easily transformed into the geotropic one, by diagnostic or therapeutic maneuvers. The characteristics of positional nystagmus due to LC-BPPV are shown in Table 12.2.

The diagnostic key for LC-BPPV is the finding of a horizontal and direction changing positional nystagmus evoked by the supine head roll test. Its latency is usually shorter than that of the PC-BPPV; it is generally more intense and lasts longer, usually less than a minute. It is sometimes necessary to repeat the diagnostic maneuvers, because the first rotation may not have evoked the positional nystagmus. Repetition of the rotation is also helpful to identify the more intense nystagmus and the pathological ear. Patients with LC-BPPV may also exhibit a mild "spontaneous" horizontal nystagmus while in the sitting position [13]. This pseudo-spontaneous nystagmus is strongly modulated by head position and movement [17, 18].

Table 12.2 Main features of typical paroxysmal positional nystagmus due to lateral canal canalo-lithiasis/cupulolithiasis (supine head roll test)

Direction and plane	Horizontal, geotropic (toward the lower ear), or apogeotropic (toward the upper ear). Reverses its direction when rolling the head to the opposite side
Latency	0–10 s
Duration	Usually 30–40 s (<1 min). More prolonged with cupulolithiasis
Fatigability	Probable (difficult to assess)
Temporal profile	Paroxysmal (rapid "crescendo"-slow "decrescendo"). Not paroxysmal with cupulolithiasis (low "crescendo"-slow "decrescendo")

Unlike the geotropic variant, the apogeotropic variant requires a differential diagnosis with dysfunction of the central vestibular system, especially if positional nystagmus is not paroxysmal. The best way to obtain a correct diagnosis is probably by exclusion. Posterior fossa lesions quite often produce symptoms that are difficult to ignore and lead to additional ocular motor abnormalities such as gaze-evoked nystagmus, impaired smooth pursuit or saccades, and other neurological abnormalities. A clinical history of previous episodes of PC-BPPV is often a clue. In cases of doubt, especially if apogeotropic nystagmus does not disappear in a few days or does not change its direction, an MRI of the brain is necessary.

12.3.5 Anterior Canal BPPV

Anterior canal (AC) BPPV is much rarer than LC- and PC-BPPV because of the superior anatomical position of the canal. It is improbable for debris to enter this canal, and self-clearing is facilitated because the posterior arm of this canal descends directly into the common crus. AC-BPPV can be detected with both Dix-Hallpike maneuvers since the anterior canals are coplanar to the PCs of the opposite side. In fact, the best way to elicit a positional nystagmus due to the ACs is with straight head hanging, by bringing the patient to the supine position with the head 30° (or even more) below the earth horizontal [19, 20]. When the Dix-Hallpike maneuver provokes a mixed vertical-torsional nystagmus and the fast phase of the vertical component is downbeating, anterior canal involvement may be responsible. The torsional component beats with the top pole of the eye toward the upper ear. This is because the Dix-Hallpike maneuver on one side acts on the plane of the AC of the contralateral side. Otoconial debris will fall away from the ampulla, provoking an excitatory stimulus to the ipsilateral superior rectus and to the contralateral inferior oblique muscles, that is, the antagonists of the muscles connected to the PC.

In fact, canalolithiasis of the AC is still debated because patients with positional downbeating nystagmus (pDBN) show some features that are difficult to justify. Nystagmus can be vertical-torsional but is often purely vertical, relatively sustained, and of low intensity. Very often, the nystagmus does not reverse its direction when the patient is returned to the sitting position, in spite of the contemporary presence of important vertigo or unsteadiness. Some of these features may be justified [19], some not. Moreover, patients with pDBN are more common than previously

reported [11], probably with the same frequency of presentation as LC-BPPV in the geotropic form, in contrast to the anatomy of the labyrinth. Many of them were previously affected or will develop a typical PC-BPPV. The course of the syndrome, often characterized by a rapid and spontaneous remission, is benign, but its relationship to canalolithiasis of the AC needs to be confirmed. Other pathomechanisms must also be considered. Theoretically, pDBN can also be observed in atypical forms of PC-BPPV, when the debris are located in the non-ampullar arm of a PC and move in a direction opposite to the expected one, similar to the pathomechanism of apogeotropic nystagmus in the lateral canal [21]. Furthermore, debris could also be located in the short arm of a PC [22], causing deflection of the cupula due to debris falling into the utriculus.

On the other hand, it must be emphasized that a pDBN can be due to damage to the vestibular cerebellum even though this is improbable when positional nystagmus is the only sign and/or there is a rapid resolution.

12.4 Treatment of BPPV

The therapy of choice for BPPV is physical treatment. Physical therapy aims to eliminate the episodes of positional vertigo by forcing the otoconial debris to come out of the semicircular canals. Special movements and positions of the head and body are used to trigger a series of clinical events which are consistent with the canalolithiasis hypothesis. Therapies for PC- and LC-BPPV have been validated. On the other hand, specific diagnostic criteria and effective treatment for the anterior canal variant of BPPV are still illusive. Surgery and medications play a minor role in BPPV. Below, we summarize the main therapeutic maneuvers for BPPV, details of which can be found in the references.

12.4.1 Physical Treatment of PC-BPPV

PC-BPPV is effectively treated by Epley's canalith repositioning procedure (CRP) or Semont's liberatory maneuver. The aim of CRP is to allow the particles to come out of the canal using gravity, while with Semont's maneuver the flushing of particles is strongly influenced by the acceleration of the head (centrifugal inertia). An evidence-based review by the American Academy of Neurology considered CRP to be an effective and safe therapy to be offered to patients of all ages with PC-BPPV [23]. A recent class I study on the short-term efficacy of Semont's maneuver [24] indicated that the efficacy of both treatments is similar, with remission rates of 80–90 %.

12.4.2 Physical Treatment of LC-BPPV

Lateral canal BPPV is also treated by physical maneuvers that allow the flushing of otoconial debris by centrifugal inertia and/or gravity. In the authors' opinion, the

most effective options are the forced prolonged position of Vannucchi et al. [25] and Gufoni's maneuver, which was recently validated with a randomized double blind study [26]. Several studies have reported success using these maneuvers with remission rates ranging from 75 to 90 %.

The treatment of LC-BPPV in its apogeotropic form is performed by the same therapeutic maneuvers, with the aim of changing the position of debris in the canal and transforming the apogeotropic nystagmus into geotropic nystagmus (two-step treatment), or by one-step treatment with a modified Gufoni's maneuver [27].

12.4.3   Treatment of AC-BPPV

Many physical treatments have been proposed for the treatment of AC-BPPV (for a review, see [28]) with good results in terms of efficacy. Unfortunately, at present, no controlled studies are available and their effectiveness is sometimes questionable considering that in about 50 % of patients with pDBN, there is a spontaneous remission within a few days, without any specific treatment [11].

12.5   Correlations Between BPPV and Migraine

The main correlation between BPPV and migraine is epidemiological since both are frequently encountered diseases with a higher prevalence among woman. Furthermore, migraine could have a role in BPPV pathogenesis as a result of damage to the inner ear and subsequent detachment of otoconia [29]. Positional vertigo is both the main symptom of BPPV and a frequent complaint in migraine subjects. In this review, the criteria for differential diagnosis between these two diseases are suggested.

One of the first reports on the possible existence of a correlation between BPPV and migraine dates back to 1998 when Baloh and Honrubia [30] described three members of a family who developed BPPV before the age of 13 years. All three had migraine headaches and two had spontaneous episodes of vertigo. The relationship between the two diseases was subsequently confirmed by a subsequent study where migraine was found to be three times more common in patients with idiopathic BPPV than in those with posttraumatic BPPV. Also, the age of onset in patients with BPPV and migraine was different from that in BPPV patients without migraine. About 50 % of patients with onset of positional vertigo under the age of 50 years met the diagnostic criteria for migraine and only 15 % of patients with onset of BPPV after the age of 50 years were also migraine sufferers [31]. It was also suggested that BPPV is more prone to recurrences in migraine patients, since more than three-quarters of these had recurrent bouts of positional vertigo. The threefold higher incidence of migraine and motion sickness in patients with BPPV, with respect to the general population, was confirmed in a later study [32]. In 2007, von Brevern et al. [1] performed an epidemiological study on BPPV to assess its incidence, prevalence, clinical presentation, social impact, and comorbid conditions in

the general population. The survey comprised a validated telephone interview performed by medical students and an experienced neurotologist. The results of this survey indicated that the strongest association of BPPV was with migraine (prevalence 34 %; OR 7.5). This study also confirmed a marked female preponderance among BPPV patients. The authors concluded that the association between BPPV and female sex reflects to a considerable extent the association of migraine and BPPV but without excluding an additional independent association of female sex and BPPV.

On the other hand, in a survey performed to looking for comorbidities of vertiginous diseases, there was no elevated prevalence of migraine in comparison to the general population [33]. Some doubts also arose from the results of another study assessing the evolution of clinical symptoms and vestibular function. In a cohort of 61 patients with a specific diagnosis of definite vestibular migraine and a median follow-up time of 9 years (range 5.5–11), only one patient received a diagnosis of typical PC-BPPV during the follow-up period [34]. This result seems to be at odds with the high prevalence of BPPV (34 %) in migraine sufferers.

In conclusion, migraine may be a risk factor for BPPV, though the mechanism is unknown. Vasospasm of the terminal vestibular arteries was suggested to be a possible mechanism, since vasospasm is a well-known phenomenon in migraine. The resulting ischemic damage to the utricular macula would result in a recurrent detachment of otoconia and the development of recurrent BPPV in these patients [30, 31].

12.6 Differential Diagnosis Between BPPV and Vestibular Migraine

Since vestibular migraine (VM) is characterized, inter alia, by recurrent episodes of positional vertigo, differential diagnosis with BPPV may be necessary. It is well known that there is no specific diagnostic marker or pathognomonic sign for the diagnosis of VM. Moreover, most patients are sign and symptom-free when the neurotological examination is performed; therefore, diagnosis is based on history and the exclusion of other causes. If the patient is male, with onset of positional vertigo after the fifties and without a history of migraine, BPPV is probable, even though positional nystagmus (PN) has not been detected. If the patient is female and of perimenopausal age or younger, with a history of migrainous headache, episodes of recurrent spontaneous and positional vertigo, and head-motion dizziness, VM is very likely. The duration of the symptomatic period is quite different: hours to days in VM patients and weeks to months in BPPV patients, if not treated [35]. Also the duration and intensity of a single episode of vertigo are presumably different. Positional vertigo is usually intense and short-lasting (seconds) in typical LC- or PC-BPPV and less intense and longer lasting in VM patients. This temporal feature is sometimes difficult to assess because patients tend to avoid or to quickly leave the provoking position. Positional vertigo as the only symptom of VM is very rare and the accompanying symptoms are naturally

Table 12.3 Main criteria used to differentiate typical positional nystagmus in BPPV from that in vestibular migraine

	Positional nystagmus in BPPV	Positional nystagmus in VM
Temporal profile	Paroxysmal, transitory	Stationary, persistent
Intensity	High SPV	Low SPV
Direction	Direction changing	Direction fixed
Latency	Present	Absent

BPPV benign paroxysmal positional vertigo, *VM* vestibular migraine, *SPV* slow-phase velocity

important since headache, photophobia, and phonophobia are very often complained of by migraine sufferers in combination with vertigo episodes. On the other hand, in idiopathic BPPV, there is, by definition, no other neurological symptoms. Mild cervical pain is possible in long lasting symptomatic BPPV patients, probably arising from avoidance behavior.

In the few patients seen during an acute episode of VM, PN is the most frequent finding [36] as an isolated sign or in combination with spontaneous nystagmus [37]. PN due to migraine commonly results from dysfunction of vestibular structures in the brainstem or vestibulocerebellum, so differential diagnosis with BPPV should be easier than in asymptomatic patients. In most VM patients, PN persists as long as the precipitating head position is maintained [37], while in BPPV patients, PN is transitory, lasting less than one minute, with the exception of those with prolonged duration, probably due to cupulolithiasis. From surveys performed on patients examined during the acute episode of VM, there is consistent evidence that PN is persistent, not paroxysmal, and with low velocity of its slow phase, so that it is difficult to detect without removing visual fixation. Conversely, typical PN in BPPV is often so strong that it can be easily seen without Frenzel glasses [36]. PN in VM is more often horizontal, geotropic or apogeotropic, and direction fixed, that is, it does not reverse its direction when the supine head roll test is performed. This kind of PN is not removed or modified by liberatory maneuvers [38]. LC-BPPV is instead characterized by a direction-changing horizontal nystagmus which is often easily treatable with physical therapy. In a lower number of VM patients, PN is rotatory, upbeating, or downbeating. The most difficult differential diagnosis with BPPV is probably in patients with atypical positional nystagmus, namely, those with pDBN. As already mentioned in this chapter, BPPV with pDBN is more common than previously thought. Nystagmus can be vertical-torsional but more often purely vertical; it is relatively sustained and of low intensity, and very often it does not reverse its direction when the head position is changed. These features correspond quite well with those arising from a dysfunction of the central vestibular structures, like those of VM. In these cases, the differential diagnosis is again helped by the presence or absence of migraine accompanying symptoms. Moreover, pDBN of BPPV is often fatigable and many patients have already received a diagnosis of typical BPPV in the past. The main criteria used to differentiate typical positional nystagmus of BPPV from that of VM are shown in Table 12.3.

References

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Dizziness Anxiety and Migraine

13

Roberto Teggi

Abbreviations

BPPV	Benign paroxysmal positional vertigo
CSD	Chronic subjective dizziness
DRN	Dorsal raphe nucleus
LC	Locus coeruleus
MARD	Migraine anxiety-related dizziness
MD	Menière's disease
PBN	Parabrachial nucleus
PD	Panic disorder
PPV	Phobic postural vertigo
SMD	Space and motion discomfort
SSRIs	Selective serotonin reuptake inhibitors
VM	Vestibular migraine
VN	Vestibular neuritis
VR	Vestibular rehabilitation
VV	Visual vertigo

13.1 Introduction

Dizziness and vertigo are unpleasant sensations occurring in around 5–10 % of all patients seen by a general practitioner. For many years, dizziness and unsteadiness have been included mainly among symptoms related to a neurological or

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psychological disorder, and Freud himself included both symptoms among manifestations of an anxiety neurosis. The clinical spectrum of vertigo is broad, ranging from the *sensation of spinning* to *light- or heavy-headedness* and imbalance; frequently, aetiological diagnoses of vertigo rely mainly on phenotype. It has been stated that dizziness is an individual experience and that verbal labelling has no social validation; as a consequence, different individuals may describe their sensations in different ways, and emotional factors may also play a role in this [1].

Dizziness is commonly reported by patients suffering from anxiety, and in 30–50 % of patients referring dizziness, no identifiable disorder can be demonstrated; in these patients, high prevalence of phobic or panic disorders, anxiety and other somatoform disorders has been described. In these subjects, psychotherapy has been reported to be useful [2].

Epidemiological data support the possibility of an association between vertigo and psychiatric disorders, and above all anxiety and *panic disorders* (PD). In a recent questionnaire-based study on over 2,000 randomly sampled outpatients, it was referred that more than 13 % of subjects had experienced dizziness during the last year, 10 % anxiety without vertigo and 11 % with both symptoms; moreover, almost 50 % of dizzy patients also reported anxiety and/or *avoidance behaviour*, compared to only 13.3 % of subjects without dizziness. Above all, patients with comorbidity for dizziness and anxiety/avoidance behaviour had the highest level of handicap [3]. Patients presenting vertigo, anxiety, agoraphobic avoidance and *feeling faint* more frequently develop chronic dizziness [4].

For a long time, the only overlapping between dizziness and psychiatric disorders was a clinical syndrome called "psychiatric vertigo", characterised by dizziness without true rotational vertigo and arising in subjects with anxiety, PD or depressive disorders. It was also characterised by highly frequent onset of dizziness in open spaces, and a psychiatric diagnosis should precede the dizziness which may be often reproduced with hyperventilation; bedside examination should be negative. According to various authors, the prevalence of "psychiatric vertigo" (variously defined as "functional symptoms", "psychogenic vertigo" or "hyperventilation syndrome") is present in 20–48 % of cases [5–8]. Some criticisms may arise from this definition: hyperventilation, for example, is a useful test to reveal a panic attack in patients suffering from PD but may also provoke nystagmus in patients with a previous vestibular disorder [9]. Moreover, the underlying idea in the definition of this disorder is that one symptom should be provoked by a single disease.

On the other hand, dizziness related to an incomplete central adaptation is commonly reported by patients after an acute vestibular loss; it normally increases in scarcely illuminated places and in all conditions in which a good head-eye movement coordination is required or with a rich visual environment, more typically in places such as open squares or shopping malls. This condition sometimes causes *avoidance*. In these subjects, a greater increase in respiration rate following random head movements has been demonstrated [10].

Moreover, anxiety has been reported to be three times more elevated in patients after a first attack of vertigo than in a group of subjects with non-vestibular neurologic deficit of acute onset, despite the fact that premorbid anxiety was similar in

both groups [11]; in another study, it was observed that anxiety with any evidence is one of the most important factors preventing adaptation [12].

These considerations obviously do not rule out the possibility that dizziness can be a simple somatoform symptom in psychiatric subjects.

13.2 Anxiety and Panic Disorders

Some considerations on the pathophysiology of anxiety and panic (above all phobia, anticipatory anxiety and panic attacks) may be helpful to understand the relationship with dizziness. The constitutive character of *phobia* is a marked, persistent, excessive and often unreasonable fear of circumscribed conditions. The physiological role of fear is to signal a danger for survival and to allow *adaptive responses* such as "fight or flight"; an inappropriate modulation of fear mechanisms, involving the amygdala and limbic system, could lead to phobia, a clinical condition that interferes significantly with a person's daily routine [13]. Exposure to the phobic situations almost invariably provokes an immediate anxiety response that may take the form of situationally bound or situationally predisposed panic attacks and leads to anxious anticipation and avoidance behaviours. We can speculate that the subjective discomfort experienced during a vestibular loss may act as an *emotional trauma* on vulnerable fear mechanisms of predisposed individuals, leading to excessive fear of becoming dizzy, fainting and being left helpless on the ground; thus, situations such as being outside the home alone, being in a crowd or on a bridge and travelling on a bus, train or car are avoided or endured with marked anxiety (agoraphobia). Westphal coined the term *agoraphobia* in 1871 for patients troubled in navigation in open spaces and busy market places; he described the disorder as characterised by distorted spatial perception that was mainly related to anxiety. On the contrary, his contemporary Benedikt suspected that a neuro-ophthalmologic deficit was the core disorder leading to anxiety and agoraphobia.

Anticipatory anxiety is the anxious expectation of physical symptoms or anxiety. It can lead people to avoid situations that trigger it, thus influencing avoidance of phobic situations; moreover, the physical and psychological discomfort provoked by *anticipatory anxiety* may in itself trigger or increase symptoms, such as dizziness/vertigo/fear of falling down, in phobic situations. Finally, symptoms of feeling dizzy, unsteady, light-headed or faint are included in diagnostic criteria of panic attacks. A panic attack is a discrete period of intense fear or discomfort in which several physical and cognitive symptoms develop abruptly reaching a peak within a few minutes. Experimental evidence has suggested that a malfunction of the respiratory-cardiovascular-vestibular system connections may be involved in the pathogenesis of panic attacks and thus underlie the occurrence of vestibular symptoms during panic attacks [14]. About 70 % of patients with PD develop agoraphobia and thus experience situational panic attacks, i.e. almost invariably or more likely occurring on exposure to, or in anticipation of, a situational trigger. It has been demonstrated that 92 % of patients who experienced dizziness during panic attacks were agoraphobic, compared to 54 % of patients without dizziness during

panic attacks; it can be speculated that these subjects might be more vulnerable to the development of agoraphobic avoidance as a result of fears of falling down or fainting as a consequence of postural instability [15].

Overall, these considerations suggest that, at least in some groups of patients, dizziness may be linked to complex mechanisms involving connections between balance system dysfunction and neural circuits underlying anxiety symptoms [16].

13.3 A More Complex Reality

Different investigations over the last 30 years have focused on a possible overlap between dizziness and psychiatric disorders. The terms *street neurosis*, *supermarket syndrome* and *space phobia* [17, 18] proposed in the early 1980s describe disorders including environmental fears and agoraphobic avoidance arising in subjects after a vestibular disorder. More recent papers refer that patients with PD often complain of dizziness, instability and heavy- or light-headedness, and this cluster of symptoms is an important source of functional impairment and significantly impact their quality of life [19, 20].

Firstly, epidemiologic data support the hypothesis of common pathways between mechanisms related to anxiety and vestibular disorders. Among patients presenting long-lasting dizziness, the rate of PD is 5–15 times higher than in the general population [21].

On the other hand, many experimental studies have investigated the possibility that dizziness in patients with psychiatric disorders may be linked to a malfunction of the vestibular system; with one exception [22], all of the studies have reported a higher prevalence of vestibular abnormalities in patients with PD both when selected and unselected for vertigo [23, 24]. It is still under debate if agoraphobia is a symptom predicting vestibular anomalies in dizzy patients; above all, it could be of some importance to the consideration that dizzy patients with depressive disorders without PD presented a lower prevalence of vestibular abnormalities [25, 26]. Clinical history may be helpful, and above all the presence of dizziness between panic attacks can be predictive of the presence of vestibular disorders in PD patients [19].

Clinical evidence supports the possibility of a link between PD and vestibular disorders; *selective serotonin reuptake inhibitors (SSRIs)*, widely used in the therapy of PD, have been demonstrated to be useful in the treatment of dizziness [27]. Moreover, the abrupt interruption of these drugs provokes a so-called SSRI discontinuation syndrome, mainly characterised by vertigo or dizziness that increases with head movements [28].

The relationship between panic and vestibular disorders is still under debate, and different possible pathophysiological mechanisms have been proposed:

- A primary vestibular disorder may impact subjects who are vulnerable to anxiety and PD. PD subjects show signs of a malfunction of homeostatic mechanisms, such as decreased global heart rate variability and irregularity in the respiratory pattern [29]; the onset of a vestibular disorder, widely connected to the cardiovascular and respiratory system, might act as a disrupting factor on the homeostatic

instability of overanxious patients, possibly influencing the onset of PD. Moreover, since serotonin is involved in the pathophysiology of PD but is also an important neurotransmitter in the vestibular system [30, 31], vestibular loadings might also influence PD by affecting the serotoninergic system in these patients.

- The findings of *vestibular abnormalities* might be the consequence of PD; for instance, the mechanism might be related to increased vestibular responses for hyperventilation.
- The onset of vestibular abnormalities might influence the appearance of agoraphobic symptoms in subjects already affected by anxiety and PD, rather than being involved in the pathophysiology of PD per se; it should be underlined that agoraphobia is the psychiatric condition mainly correlated with navigation in open spaces and in which non-misleading vestibular information is required [19].

In conclusion, *chronic dizziness* is often a puzzling dilemma in which the paradigm "one symptom – one disease" may be misleading, and the co-occurrence of vestibular and psychiatric disorders should be always considered. Moreover, it is often complicated, and probably not essential, to assess which of the two disorders appeared first. As a consequence of these considerations, in recent years different authors have proposed clinical entities whose definitions mainly rely on symptoms rather than the aetiology. This could be considered as a more practical approach to the problem.

13.3.1 Phobic Postural Vertigo (PPV)

This condition was firstly proposed by Brandt to identify patients referring subjective dizziness, balance disorders while standing or walking despite poor values in balance tests. The authors consider PPV to be one of the most frequent causes of chronic dizziness, and it often has substantial impact on the quality of life of patients. Instrumental analysis of postural control in these subjects has demonstrated some abnormalities; above all, during quiet standing subjects present increased high-frequency body sways and muscular energy expenditure. In contrast, while performing more demanding balance tasks such as a single leg stance on rubber foam, the results are similar to those of healthy subjects. During postural tasks, patients often refer increased anxiety level and autonomic activation. This discrepancy between self-estimated postural resources and posturographic data has been defined "anxious postural control". Authors underline that a primitive vestibular disorder may be the disrupting factor, as well as stressful life periods; nonetheless, they should be considered more important to diagnose PPV rather than as a diagnosis of a single component leading to PPV [32].

13.3.2 Visual Vertigo (VV)

VV is a clinical condition defined by Bronstein in which symptoms such as dizziness and vertigo are triggered by specific conditions characterised by a *rich visual*

environment, typically shopping malls or open squares. Patients with VV during a mismatch rely mainly on visual rather than on proprioceptive-vestibular cues in postural control. Studies have demonstrated that these patients present a high rate of vestibular disorders, anxiety trait and dizziness during visual stimulation overlapping those of subjects after a recent onset of a vestibular loss. However, a self-administered questionnaire demonstrated a higher rate of handicap in subjects with VV. As a consequence, diagnosis of VV relies more on questionnaires as Situational Vertigo Questionnaire or Vertigo Symptoms Scale rather than on clinical tests; nonetheless, once again, the clinical situation is more important than disorders underlying VV. Finally, rehabilitation techniques with moving visual stimuli like optokinetic stimulation has been demonstrated to be useful in these patients [33, 34].

13.3.3   Space and Motion Discomfort (SMD)

SMD is a clinical condition characterised by dizziness or imbalance often associated with anxiety that typically occurs in places characterised by certain spatial characteristics or triggered by motion. Studies on subjects with SMD have established a high rate of vestibular disorders; moreover, dizzy patients with PD and agoraphobia present with higher levels of SMD. A primitive vestibular dysfunction may be the causal factor of SMD, and SMD subjects may develop a postural strategy in which visual or proprioceptive cues replace the defective vestibular function. Static and dynamic posturography has confirmed increased visual or proprioceptive dependence in these subjects. Conversely, a group of patients with anxiety disorders and SMD presented greater sensitivity for optic flow stimuli compared to a normal control group [35, 36].

13.3.4   Chronic Subjective Dizziness (CSD)

Previous studies of VV and SMD have identified conditions arising from the co-occurrence of vestibular and psychiatric disorders; in the definition of CSD, as well as in previous definition of PPV, the somatoform component is emphasised. As in previous conditions, diagnosis mainly relies on anamnestic criteria, above all the sensation of non-rotational vertigo or unsteadiness and heavy- or light-headedness present for most days for 3 consecutive months. In these patients, neurotological assessment is usually unremarkable, although clinical history may demonstrate previous otoneurological disorders like benign positional paroxysmal vertigo or *vestibular migraine*; nonetheless, vestibular disorders do not explain the full extent of symptoms. Recently, some authors have attempted to redefine CSD using the psychiatric definition of *health anxiety*, a condition in which patients maintain high levels of attention to physical symptoms or misinterpret bodily sensations; healthy anxious subjects often avoid situations or activities that they believe could impact on their physical condition. In these subjects, the clinical presentation of an acute vestibular disorder such as BPPV may be troublesome and interpreted as a

life-threatening symptom [37, 38]. We underline that the treatment of these patients should include a multimodal plan, with vestibular habituation exercises to reduce the sensitivity to movement in addition to SSRIs and/or cognitive behavioural therapy.

In almost all these clinical conditions, a rich visual surrounding may trigger dizziness and instability. Different studies in the last 20 years have focused on an increased rate of vestibular abnormalities in at least one vestibular test in patients with PD and agoraphobia, although a peculiar pattern of these anomalies was not identified. On the contrary, studies of integrated balance function with static and dynamic posturography showed more consistent results in these subjects. For example, these subjects swayed more than normal individuals during static and dynamic posturography, and increased sways were correlated with severity of anticipatory anxiety and fearful avoidance of situations possibly provoking dizziness; moreover, therapy with SSRIs is reported to improve postural control. Patients with anxiety and PD during dynamic *posturography* relied more on visual and somatosensory cues in postural control, and results with these tests were worse than those of subjects with a vestibular deficit; finally, agoraphobic patients have an increase in body sways during peripheral visual stimulation [39, 40].

13.4   An Overview on Psychiatric Disorders in Different Vestibular Syndromes and in Migraine

Until now it has been underlined how patients with a vestibular dysfunction normally exhibit a higher rate of psychiatric disorders than the general population, although often vestibular findings show no correlation with the amount of psychological strain.

Recent investigations have explored whether patients with different organic *vertigo syndromes* and the elderly exhibit different singular psychological features. In a recent study, psychological features were assessed in four groups of patients with vestibular organic disorders, respectively, vestibular neuritis (VN), *BPPV*, *Ménière's disease* (MD) and vestibular migraine (VM), and a control group of normal subjects [41]. Overall, patients with VM and MD demonstrated higher levels of psychological disorders (65 and 57 %, respectively), while the results in patients with VN and BPPV overlapped those of the group of normal patients (ranging between 15 and 22 %).

Some considerations can be made on these data. Firstly, VN is a stressful life event and is often accompanied by increased levels of anxiety; nonetheless, most individuals cope successfully with the event, and it may be argued that only overanxious subjects maintain high anxiety levels after 6-month follow-up and present increased possibilities to develop chronic dizziness. BPPV patients generally do not present higher levels of anxiety than the general population; nonetheless, even after successful repositioning manoeuvres, some patients report *imbalance* without positional vertigo for some days afterwards. Among causal factors for this *residual dizziness*, increased anxiety levels have been considered. Above all, anxiety has been

correlated with residual dizziness in the elderly, in which vertigo presents adverse physical, psychological and social consequences, since it increases the risk of falls and fear of falling, decreases performance in activities of daily living and reduces participation in social activities [42].

Migraine per se also exhibit a comorbidity with anxiety, depression and PD. Longitudinal studies have shown that among migraineurs anxiety and depressive disorders are two to five times more common. The relationship between psychiatric disorders and migraine is bidirectional, so that in many patients depression is subsequent to the onset of migraine, while in others depressive disorders may precede migraine attack. Around 51–58 % of migraineurs meet criteria for lifetime diagnosis of anxiety disorders; previous studies have demonstrated that anxious symptoms are frequently comorbid with depressive disorders. Several investigations have shown that the presence of anxiety and depressive disorders in these patients is also associated with a lower quality of life than migraine alone; moreover, anxiety disorders have a negative impact among migraineurs since they predict long-term persistence of migrainous attacks, increased headache-related disability, reduced perception of satisfaction with acute and prophylactic migraine therapy, poorer long-term outcomes and response to headache treatments, increased risk of acute medication overuse and possible development of medication overuse headaches.

Among all anxiety disorders, PD has been the most widely studied in migraineurs. It may be argued that migraine, as well as vertigo, shares several characters with PD, all being chronic disorders with episodic manifestations; all are characterised by common autonomic and affective symptoms, with nausea fear and anxiety above all. According to some authors, the lifetime prevalence of PD among episodic migraineurs ranges between 5 and 17 %, while in samples of *chronic migraineurs* a prevalence of PD around 25–30 % has been reported. Above all, the prevalence of PD is significantly higher in patients suffering from migraine with aura than migraineurs without aura. The relationship between PD and migraine can be considered bidirectional; some authors have reported that the presence of PD also confers increased risk for migraine and around 60 % of PD subjects also fulfil diagnostic criteria for migraine. Comorbidity with PD has often been associated with more frequent and longer migraine attacks, above all in males; moreover, the impact of anxiety and PD on the evolution and symptoms of migraine is greater than depression alone. Finally, psychiatric disorders, PD above all, have been described as a factor that influences the progression of migraines from episodic into chronic forms [43].

The possibility of an increased rate of *personality disorders* among migraineurs is still under debate and variously reported in around 26 % of chronic migraineurs, while borderline personality disorder has been reported to be more frequent [44].

As previously stated, migraine, anxiety and dizziness share different features, and comorbidity among them has been reported at varying frequency. Recently, some authors proposed a clinical entity characterised by the co-occurrence of all three disorders, called *migraine anxiety-related dizziness (MARD)* [45]. It was underlined how MARD may be considered as both a syndrome, i.e. a constellation of clinical signs and symptoms, and a disorder, which in clinical practice identifies

a specific pathophysiological mechanism. Epidemiologic data support the possibility of a link among the three disorders and above all suggest that in a subgroup of patients the three disorders coexist. MARD is unlikely to be the simple by chance association of anxiety, migraine and dizziness, but all three disorders share common pathways in the brain. The clinical implications of MARD should be underlined. MARD may be misdiagnosed and unrecognised if the physician mainly relies diagnosis on the prevalent symptom referred by the patient, while all other components should be studied and treated. MARD subjects present some common features with patients diagnosed with SMD. Above all, they present an excessive reliance on visual cues in balance control and navigation. Conversely, migraineurs or overanxious subjects are also known to present hypersensitivity to rich visual environments even without head movements (i.e. stimulation of the vestibular system); as a consequence, they can develop discomfort in certain places such as shopping malls and avoid them.

Clinical implications of a diagnosis of MARD necessitate that each component of the disorder should be considered and treated; above all, patients diagnosed with MARD may benefit from therapy with antidepressants such as SSRIs and *prophylactic migraine therapy*, although *vestibular rehabilitation* should always be considered.

13.5   Neuroanatomical Bases Underlying the Relationship Between Vestibular and Psychiatric Disorders

Recent studies have focused on the possibility of overlap in the central nervous system between pathways implied in anxiety and balance control, focusing on three different networks: the *vestibulo-parabrachial*, the *coeruleo-vestibular* and the *raphe nuclear-vestibular projections*.

Several animal studies in the last two decades have identified central pathways contributing to vestibular autonomic interactions. Projections from vestibular nuclei to the nucleus of the solitary tract, the nucleus ambiguous, the ventrolateral medullary reticular formation, the nucleus raphe magnus and the lateral medullary tegmentum are the anatomical substrate of the vestibule-autonomic reflex.

Vestibular nuclei also present ascending connections with *parabrachial nucleus* (PBN). The PBN in turn have connections with the amygdala, infralimbic cortex and hypothalamus; PBN and these connections have been widely reported to play a central role in the formation of conditioned fear and anxiety responses and may be the anatomical substrate linking anxiety and balance disorders. In particular, the vestibular system may provide information related to the safety or danger of one's position in the external world, and the presence in particular, the presence in the PBN of neurons responding to both whole body rotation and gravity acting on the body has been demonstrated. It should be mentioned that PBN also receive different somatic and visceral information. The purpose of this network is likely to regulate motor responses after vestibular stimulation as well as increasing attention towards sensorial stimulation.

The *locus coeruleus* (LC) has been demonstrated to have a central role in physiological responses to stress. LC is the main brain area involved in the production and release of noradrenaline, which has an excitatory effect on most of the brain by mediating arousal and producing increased brain responses to different sensorial stimuli. Different studies have demonstrated connections between the caudal pole of the LC and the vestibular nuclei in animals. It may be assumed that the LC-vestibular projections mediate increased vestibular responses during movements of the body as well as altered vestibulo-ocular movements during anxiety.

Finally, it rather than this has been demonstrated in animal projections from *dorsal raphe nucleus* (DRN) to vestibular nuclei. DRN is the largest serotoninergic nucleus in the brain, located in the periaqueductal grey matter. Immunohistochemical studies demonstrated serotoninergic fibres from DRN to vestibular nuclei in rats. On the other hand, DRN axons project in different brain sites including PBN; the amygdala and the infralimbic cortex are involved in both regulation of vestibular responses to movement and anxiety. It is important to mention that serotonin receptors have been recently demonstrated in the inner ear and in the vestibular nuclei, and serotonin levels are increased in the median vestibular nucleus in rat in the first 5 min after caloric stimulation [31].

Finally, the *hippocampus* is a brain region in the *limbic system*; various anatomical connections join the vestibular nuclei and hippocampus, which also receives information from other sensorial end organs. It has been demonstrated to play an important role in spatial memory and navigation. Regarding possible overlap between anxiety and dizziness, brain imaging studies reporting *hippocampal atrophy* after a bilateral vestibular loss in human are worthy of mention [46].

13.6 Cognitive Disorders in Patients with Vestibular Impairment

We have seen how an acute vestibular loss is a traumatic occurrence, implying adaptive processes in different parts of the central nervous system, while other functions maintain a deficit that is long-lasting; consider, for example, the vestibulo-oculomotor reflex for high-frequency stimulations which has been demonstrated to have a reduced gain even after years from the onset of the vestibular disorder.

Several studies have pointed out a possible role of *cognitive impairment* in patients with vestibular loss; for some of these functions, related to *spatial memory* or navigation, the implication of vestibular loss seems somehow logical. In other cases, above all attention and nonspatial learning, it hardly seems to be correlated directly to vestibular function. We have previously reported how patients, after bilateral vestibular loss, present atrophy of the hippocampus, while in the same subjects no atrophy was demonstrated in vestibular nuclei. In these patients, a deficit in spatial learning has been demonstrated that was proportional to the level of hippocampal atrophy; few differences, moreover, were described when subjects could use visual information for this function. Other animal studies have demonstrated a decrease in electrical excitability in hippocampal neurons. In animals,

hippocampal atrophy has been reproduced after chronic stress or repetitive acute stressful events, while in other studies the degree of atrophy has been correlated with cortisol plasma levels during stress. It is useful to remember that the hippocampus is a part of the limbic system which is particularly important in long-term memory and connecting emotions with senses.

Other studies have focused on possible *disorders in attention* and time of reaction during the execution of different tasks in patients with a vestibular disorder. For example, around 85 % of patients with a perilymphatic fistula demonstrated memory disorders, and most of these also presented emotional disorders including anxiety and depression. In patients after a vestibular loss, simple tasks like counting backwards 2–7 numbers at a time is slower than in a control group matched for age and level of instruction; moreover, no differences could be seen when patients were performing the task alone or while asked to perform exercise requiring good equilibrium. After a vestibular loss, even with a good adaptation, patients have demonstrated a reduced *capacity to organise information* from different sources or to learn new information.

Such subjects, moreover, demonstrated an increased reaction time after a sound stimulus, both during the execution of a stabilometric exam and while sitting compared with a control group; none of the subjects presented hearing impairment.

It is under debate whether *cognitive impairment* may be the result of the vestibular disorder on the central nervous system (i.e. hippocampal atrophy) or if it is linked to increased attention that is necessary for postural control tasks.

Finally, recent studies have reported that after bilateral vestibular loss, rats show decreased interest in exploring the surrounding environment and prefer to remain in well-known places even if stimulated with the necessity of finding food [47].

13.7 The Role of *Rehabilitation* and *Cognitive Behavioural Therapy*

Dizziness is a common symptom with a lifetime prevalence of around 25 %. In up to 30–50 % of subjects reporting chronic dizziness, the symptom cannot be fully explained by a well-identifiable medical disorder. Dizziness, for example, can occur after an organic vestibular disorder, especially in subjects suffering from VM or MD. Nonetheless, vestibular impairment cannot fully explain the persistence of chronic dizziness. In previous parts of this chapter, the possibility of concomitant anxiety and PD has been widely reported, and these patients often refer a similar burden of symptoms: dizziness increases in particular environments, spatial disorientation, anxiety and often avoidance for places triggering symptoms. Patients often present increased visual dependence in postural control.

Both vestibular rehabilitation (VR) and cognitive behavioural approaches have been proposed in these subjects. VR has been widely recommended in patients after vestibular function loss; the central element of VR is a set of physical exercises promoting central adaptation, mainly consisting in eye-head and body movements and requiring active collaboration of the patient. The final result should be a

reprogramming of the balance function in the brain. Conversely, in different clinical conditions, including VV and SMD, VR has been proposed with habituation techniques, and patients are subjected to series of stimulations moving in the visual field such as *optokinetic stimuli*. During VR, a good patient compliance is required. VR also present implicit psychotherapeutic ingredients and have been demonstrated to positively influence the emotional condition of subjects and improve independence in daily activities, thereby ameliorating the quality of life.

Cognitive behavioural therapy has the main purpose of developing an integrative explanation model for the disorder; the approach tries to define the disorder of the patient and how the problem affects actual life and thoughts. This therapy can help patients to change what they think about the dizziness (the cognitive part) and what they can do to improve their condition. During cognitive behavioural therapy, the first attack of dizziness should be widely explored in addition to situations that trigger or intensify the dizziness. A significant part of the treatment consists in exposure to dizziness triggering situations so that exercises are often a part of this treatment [2].

Conclusions

Chronic dizziness is a clinical condition characterised by a burden of symptoms rather than a single causal factor. All clinical entities previously described as VV, SMD, PPV and CSD share some common points among them:

- Patients present increased visual dependence in postural control, which in some cases does not differ from that of subjects after vestibular neuritis.
- Patients also present increased anxiety levels and may develop avoidance for conditions provoking or increasing dizziness.

It should be noted that after vestibular loss patients often present increased anxiety levels. More anxious subjects frequently develop chronic dizziness. After an acute vertigo attack and above all in syndromes characterised by an episodic vertigo (especially VM), a burden of changes occurs in various levels of the CNS.

Common brain pathways related with both anxiety control and navigation have been studied extensively and have focused on a central role of the *limbic system* and *hippocampus*. Further studies should assess the central role of serotonin in both pathways. For example, recent studies demonstrated the presence of *serotonin receptors* in both the inner ear and vestibular nuclei; a vestibular caloric stimulation produced an increase of *serotonin levels in medial vestibular nuclei* in the guinea pig. In our opinion, assessment of chemical factors linking anxiety and dizziness might be a goal for future research.

A potential limit in the research of the last 20 years is that the relationship between anxiety and dizziness has been conceptualised in a bidirectional manner: a vestibular disorder may raise anxiety levels and anxiety disorders may cause vestibular symptoms. A newly proposed integrated model conceptualises *threat assessment* as the central integral component of spatial perception, postural control and navigation in both health and disease. For example, related to the fear of fall, when standing or walking on an elevated platform,

normal humans reduce the range of motion, thus reducing movement of the ankles; as a consequence, postural adjustment has lower amplitude and higher-frequency body sways. Healthy people standing at heights also demonstrate *autonomic activation*, which even occurs in a virtual reality environment mimicking the real condition. However, threats unrelated to gait and stance demonstrated fewer effects on postural control and the autonomic system. Obviously, anxiety during the execution of the task may depend on the anxiety trait; in an experimental setting, mice with a mutation of the serotonin transporter showed locomotor deficits, which could support the hypothesis that serotoninergic activity modulates both threat responses and the sensitivity of neurons in the vestibular system. According to this theory, both balance disorders and dizziness might be conceived more as a "continuum" rather than as a "present or absent" symptom that could be related to normal responses to threatening situations [48].

Finally, a more practical conclusion is warranted. Agoraphobic patients also referring dizziness seem, in the author's opinion, the most challenging subjects for a clinician; it should be mentioned that agoraphobia is the disorder in the panic spectrum that is most closely related with postural control and navigation; these functions are often a challenge for patients with a recent vestibular loss. In patients with PD and agoraphobia who also refer dizziness, a full neurotological assessment should always be done, especially in subjects referring dizziness outside anxiety or PD. In these subjects, a multidisciplinary approach is strongly suggested, and both disorders must be treated whenever demonstrated. Concerning drug therapy, SSRIs are useful in the treatment of both PD and chronic dizziness. Vestibular rehabilitation and cognitive behavioural therapies must always be considered, and the strict relationship between the two therapies has previously been underlined.

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Dizziness and Cognitive Processes

14

Giorgio Guidetti and Riccardo Guidetti

Our equilibrium is the result of perfect control of the relationship between the body and the environment in every life conditions.

It is an essential function and cannot be entrusted to a single organ or apparatus, but it requires an entire system, the balance system and a set of communicating structures and processes. This complex system exhibits several constants and a multitude of subjective variables. Some of the balance system's correlations are still unknown, but they appear more and more complex. Their progressive knowledge will allow to identify new therapeutic strategies for vertigo and balance disorders.

The main functions of the balance system are maintaining a good visual and motion control, ensuring spatial-temporal orientation, regulating autonomic reflexes, always without any psychological distress. The ability of the human body to balance or maintain an upright posture is performed by analysing reality and integrating the inputs received from the vestibular, visual, proprioceptive, acoustic and tactile peripheral receptors. A constant flow of information about the events occurring in the environment and from the body reaches the central nervous system (CNS) to allow the adaptive balance strategy.

The inputs from various receptors in the human body are normally processed by the CNS with a certain degree of preferentiality, due to both habituation and the need to use one afference more than the other. The vestibular afferences are preferred at all

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ages, and the vestibular system becomes fundamental for maintaining equilibrium. Vestibular input can be processed by the CNS in different ways for varied outcomes. It can either be upregulated with an exciting result (typical games in the amusement park) or downregulated with a sedative effect (cradling a newborn).

The CNS processes, compares, integrates and modulates the sensorial inputs; it stores the experiences and finally it programmes the responses to adapt to the ongoing reality.

Responses of the CNS may be automatic or voluntary with three possible levels of integration.

At the first level the segmentary reflexes activate only a minimum number of neurons. At the second level the motor synergies activate also the related muscles and joints of the neighbouring segments. At the third level the final strategy involves the cognitive and emotional processes.

The information processing time of the cerebellum is much more rapid than at the cortical level.

Therefore, a motor response based on automatic processes is generally faster as it requires lower levels of integration and greater speed of decision.

However, especially when facing a new situation or condition a higher level of processing inputs and a new more complex adaptive strategy are necessary and desirable.

Initially, the single afferences are recognised by recalling specific experiences and memory for each condition so that the present situation may be compared to the previous experience indicating adaptation not only to ongoing reality but also to predict the expected forthcoming reality. This is followed by comparison and integration of the individual afferences and modulation to regulate their interference with the entire CNS. Incoherent inputs from the sensory systems or a disruption of the central processing causes vertigo and balance disorders. In case of contradictory input from the afferent sensory systems, the input from one of the systems can be downregulated or suppressed to avoid a mismatch in signals received [1].

Hence, maintaining equilibrium is a real cognitive process [1].

14.1 Vestibular-Cognitive Interaction

The vestibular system is crucial for the balance function, and its inputs must be therefore integrated with the highest brain functions.

The vestibular-cognitive interaction is supported by the neuronal projections between the vestibular centres in the brainstem and both the cerebral and cerebellar cortex [2]. Actually the vestibular system is connected to the whole CNS: the spatial-temporal pattern of vestibular information processing after brief caloric stimulation implies a functional decoupling of cortical and subcortical activity [3] with prolonged involvement especially of both neurons in the brainstem and those in the cerebellum, thalamus and insula.

The most important connections between the labyrinth and the brain cognitive areas concern the cerebellum, the so-called vestibular cortex, the thalamus and the limbic system.

Vestibular inputs reach the *cerebellum* directly and indirectly, and the modulating activity of the cerebellum on the vestibular function is well known.

The cerebellum, however, also has various cognitive functions such as control of sensory data acquisition, neural representation of moving system, timing, attention coordination and anticipatory control, context–response linkage, linguistic processing, associative learning, verbal working memory, skill and visuomotor learning, visual selective attention, spatial event processing and the mental simulation of motor acts [4].

It is immediately involved in cognitive predictive processes as a result of visual signals and integrates and improves the timing of events in connection with the cortex. It is especially important for motor and spatial learning, including the oculomotor, thanks to the remarkable ability of long-term memory storage that allows it to generate motor outputs in accordance with the previous experiences.

The trace of motor memory is initially acquired in the cerebellar cortex and later transferred to the cerebellar nuclei for consolidation.

Motor and spatial learning becomes very important in the early days after an acute vestibular deficit to facilitate recovery of the balance function. In addition, new features emerge during the adaptation time thanks to the implications of the cerebellum with psyche, behaviour and emotions, in particular as regards the storage of negative events and "fears" and the emotional and behavioural patterns, with possible dysfunctions characterised by dysmetria of thought, mental disorders, even obsessive-compulsive, and even schizophrenia and autism. In fact the so-called cerebellar cognitive affective syndrome is characterised by impaired executive functioning (planning, verbal fluency, abstract reasoning, working memory), reduction of skill in visual–spatial tasks, impaired visual memory and logical sequence and inappropriate affection. Therefore, this condition would be able to interfere negatively on the vestibular adaptation.

Studies in animals have focused on several structures of the *cerebral cortex* that receive vestibular inputs: the area 2v at the tip of the intraparietal sulcus, the area 3aV in the central sulcus, the parieto-insular vestibular cortex (PIVC) located posterior to the dorsal end of the insula, the ventral intraparietal area, area 7 in caudal inferior parietal lobule, the primary motor cortex (area 4) and the premotor cortex (area 6).

Functional imaging studies have demonstrated that the so-called vestibular cortex is a multisensorial cortex because it receives not only vestibular inputs but also somatosensory and visual inputs.

In humans the vestibular system projects to the primary somatosensory cortex; to the anterior parietal cortex; to the inferior parietal lobule; to the lateral superior parietal lobule; to the precuneus; to the "parieto-insular vestibular cortex" and temporoparietal junction; to the frontal cortex including the primary motor cortex (precentral gyrus), the premotor cortex and the inferior frontal gyrus; to the anterior and posterior cingulate cortex; to the anterior and posterior insula; to the temporoparietal junction; to the striate and extrastriate visual cortex and to posterior intraparietal sulcus.

A recent meta-analytical neuroimaging study concluded that the cytoarchitectonic area OP2 in the parietal operculum, embedded in a joint vestibular network, should be the primary candidate for the human vestibular cortex [5].

The anterior insula has been proposed as a main region for interoception and bodily awareness and vestibular signals could thus interact with this region to influence various aspects of spatial and bodily perception.

Relatively few human studies have revealed occipital lobe contribution to vestibular processing. Several visual and somatosensory regions have been reported to be "deactivated" during vestibular stimulation and reciprocal inhibitory visual–vestibular interactions have been hypothesised.

It is difficult to conclude about the presence of a primary vestibular cortex, or a core vestibular region in humans, based on existing PET and fMRI studies because the poor temporal resolution of PET and fMRI makes it difficult to determine the time course of subcortical and cortical vestibular processing.

Several neuroimaging studies have revealed that vestibular projections are bilateral, with a significant blood flow increase in both cerebral hemispheres.

Hemispheric dominance was revealed depending on both the stimulated ear and the participant's handedness with a predominant activation of ipsilateral vestibular cortex following right or left caloric ear irrigation. This pattern of cortical activation after unilateral caloric ear irrigation appeared additionally and strongly modulated by the handedness of the subjects. The right hemisphere in right-handers and the left hemisphere in left-handers showed the strongest vestibular cortical activations, respectively, and that this was further modulated by which ear was stimulated. Based on the interaction with handedness, it was argued that the vestibular system and its cortical projections may influence the development of handedness in humans.

Vestibular inputs activate both the contralateral cortex and ipsilateral cortex and hence stimulate the related functions. Stimulation of the left ear can affect the functions of the brain in the right side (including insight, imagination, left hand control, 3-D forms and art and music awareness), whereas right-ear activation plays a role in left brain functions (including number skills, written and spoken language, reasoning, scientific skills and right hand control). In healthy individuals, caloric stimulation of the left ear can improve the activity of the right hemisphere by affecting the recalling ability or recollection of the objects in the environment. Similarly, the activation of the right ear can stimulate the capability to memorise words [6]. In patients with left cortical stroke who exhibit spatial hemineglect and failure to recall complete image, caloric stimulation can rectify cognitive deficits such as asomatognosia, hemineglect, aphasia and hemiplegia for 3–5 min [7].

Hemineglect patients exhibit diminished awareness of stimuli arising spatially contralateral to the side of a cortical lesion.

Caloric vestibular stimulation can lessen the severity of hemineglect, including its cognitive deficits not restricted to awareness of extrapersonal space, a recognised vestibular function, like the ability to recall items on the affected side of a visual image held in memory [8].

The hemineglect symptoms are improved also by somatosensory stimulation of neck muscles, by reorientation of the gravitational vertical, by galvanic vestibular stimulation and by optokinetic stimulation, and all these are mediated, at least in part, through the vestibular nuclei.

On the other hand, no modification of neglect was observed after bilateral vestibular stimulation. These results support the idea that caloric vestibular stimulation may improve neglect through a specific effect; bilateral stimulation making the putative activation bilateral and symmetrical does not affect the lateral bias of neglect.

Probably vestibular signals can contribute to the ability to organise spatially common cognitive operations such as arithmetic, sentence comprehension and short-term memory, and although the cognitive effects of a vestibular disorder are perhaps not as severe as those of hemineglect, any disruption of vestibular function or spatial organisation will have related (if more subtle) effects on cognitive operations.

Cold caloric stimulation in the left ear improves thalamic Dejerine–Roussy Syndrome, while treatment with placebo had no effect probably because vestibular stimulation is able to activate also the posterior insula, which in turn inhibits the generation of pain in anterior cingulate.

Recently some studies have demonstrated the dominance of the right hemisphere after vestibular stimulation. The activation in the right hemisphere is the same for both right- and left-ear stimulation [9].

Some degree of hemispheric specialisation can be attributed to the cortical processing of vestibular inputs as in right hemisphere patients, poor sensitivity for rotation towards contralesional hemispace and overestimated rotation towards ipsilesional hemispace exists, while in left hemisphere patients rotation is more appropriately scaled for both directions.

The corticofugal influence on vestibular nuclei by polysynaptic pathways is supported by electrophysiological recordings in vestibular nuclei while different vestibular cortical areas are electrically stimulated. These responses are complex and can manifest as facilitation or inhibition of the vestibular neuron response or by a combination of these effects. The neural mechanisms of the corticofugal influence on vestibulo-oculomotor and vestibulospinal commands remain to be clarified.

A regulatory control of frontal regions over posterior systems for sensation and autonomic functions in a dense, interconnected network was suggested, and an associative relation within the right hemisphere was proposed to explain links among dizziness, nausea and negative emotion.

Lesion of the vestibular cortex in the human posterior insula leads to a tilted perception of visual vertical but not to tilted body posture and loss of lateral balance.

Following unilateral injury to the human vestibular cortex, asymmetrical perception of body rotation is present.

14.1.1 Thalamus

The thalamus is an important station of the vestibulo-cortical projections. However, the vestibular inputs reach the cortex not only through the thalamic pathway but also via the extra-thalamic pathway.

Thalamic responses to vestibular stimulation have been recorded in animals, and several neuroimaging studies describing the location of the vestibular cortex in healthy participants have also revealed thalamic activations during caloric and galvanic vestibular stimulation.

Vestibulothalamic projections terminate in various thalamic nuclei, but correlation between animal and human thalamic nuclei receiving vestibular inputs remains somewhat problematic because of differences in thalamic anatomy across species and multiple nomenclatures [10]. On the basis of neuroimaging studies in healthy humans and neurological observations in epileptic patients and patients with focal thalamic lesions, the thalamic nuclei involved in vestibular processing are the nucleus medialis, nucleus habenularis and the nucleus pulvinaris. These nuclei contain multisensory neurons that process and relay vestibular, proprioceptive and visual signals to the vestibular cortex. Clinical data also suggest that the posterolateral thalamus is a major relay station for vestibular signals.

Despite the evidence of multisensory convergence in some thalamic regions, the exact nature of the sensory processing taking place in the human vestibular thalamus is poorly understood.

The vestibulothalamic pathway is associated with self-motion cues for updating motor behaviours, spatial representations and self versus object motion distinctions. The mammillotegmental pathway supplies vestibular input to create a cognitive representation of head direction.

Interaction of the vestibular–thalamic–cortical projections may explain dysequilibrium, a common and reversible stimulation-associated side effect. Thalamic infarctions have been shown to suppress vestibular cortex activations which are side-specific. The presence of thalamic lesion reduces the homolateral cortical activation during caloric vestibular stimulation with only a small area in homolateral inferior insula becoming activated (extra-thalamic pathway).

Lesions of the posterolateral region lead to the presentation of vestibular signs such as ipsi- or contralateral tilts of the subjective, visual vertical and corresponding deviations of stance and gait.

14.1.2 Vestibular Inputs

The vestibular system is tightly connected to the *limbic system*, which in turn regulates emotions, homeostasis and storage of experiences. In particular, vestibular inputs are basic for the activity of the *hippocampus*.

A predominant ipsilateral activation of the hippocampus and of the subiculum during caloric vestibular stimulation has been demonstrated with also an additional activation of the parahippocampal gyrus.

The possible routes through which the vestibular inputs reach the hippocampus include the thalamocortical route, the theta rhythm-generating structures leading to the medial septum and the head direction system.

The vestibular signal is essential to generate the directional signal and the metric proprieties of representational space although the proprioceptive signals are equally important [11].

Vestibular stimulation during spatial navigation activates a hippocampal theta rhythm which enhances spatial processing and motor response.

Spatial information activates the prefrontal and posterior parietal areas in the right hemisphere. In humans, the hippocampus is not only essential for memory processing facets such as early encoding, consolidation and retrieval, but it also has a role to play in spatial memory functions along with the subcortical regions. The navigation requires first an accurate perception of spatial orientation with respect to the environment, which consists in the knowledge of where you are and what direction you are taking.

Navigating animals and humans encodes properties of the environment, including its objects and landscapes, and they use that information both to identify significant locations and to maintain or recover a sense of their own position and orientation. Thus, the spatial representations of the environment that guide navigating animals are best revealed when path integration is pushed beyond its limits or disabled altogether by disorientation.

Several cognitive strategies and several types of reference frames can be used by the brain to establish relations between our body and the environment. Parietofrontal and temporal brain areas have been considered involved in egocentric and allocentric coding on one hand and on the other hand the areas involved in the "route" like and the "survey or map" like strategies used during tasks in which subjects had to mentally remember a path by mental navigation or mental scanning of a map. Berthoz [12] coined the term "topokinetic" or "topo-kinesthetic" memory which defines a particular type of spatial memory involved in the memory of routes and movements.

The navigation in the environment is ensured in mammals by cells located mainly in the limbic system.

A study [13] in a taxi driver of London with bilateral hippocampal lesions demonstrated that the hippocampus in humans is essential for facilitating navigation in places that were memorised long time ago where complex large-scale spaces are concerned. Detailed spatial representation is required for a successful navigation. Greater grey matter volume was noted in the mid-posterior hippocampi in London taxi drivers when compared with London bus drivers, as observed in the coronal section from the standard SPM canonical MRI.

Even an only unilateral resection of the hippocampus causes a significant deficit in learning and spatial memory, regardless of which side of the ablation.

The hippocampal formation of mammals and birds mediates spatial orientation behaviours consistent with a maplike representation, which allows the navigator to construct a new route across unfamiliar terrain [14, 15].

Its mediation by the hippocampal formation and its presence in birds and mammals suggests that at least one function of the ancestral medial pallium was spatial navigation.

Active movement is a critical factor in determining place-specific firing of hippocampal neurons.

This could explain why passive displacement is not an effective way of acquiring spatial knowledge for subsequent active navigation in an unfamiliar environment. The existence of two populations of neurons signalling the animal's location or head

direction: place cells found primarily in the hippocampus and head direction cells found in brain areas anatomically and functionally related to the hippocampus.

The place cells (PC) are mainly used for localisation. Place cells collectively map spatial locations, with each cell firing only when the animal occupies that cell's "place field", a particular subregion of the larger environment. In fact, these cells are activated in one place of the environment.

The head direction cells (HD) are needed, especially for discriminating the direction, and are located mainly in the thalamus (post-subiculum, dorsal thalamic nucleus, mamillar lateral nucleus)

Head direction cells encode directional heading, with each cell firing when the rat's head is oriented in that cell's particular "preferred firing direction".

Both place cells and head direction cells are usually coupled, and they are controlled by a complex interaction between external landmarks and idiothetic cues.

The hippocampus PC and HD cells generally work in pairs to control the complex interaction between body and space.

Grid cells and border cells support spatial navigation.

The entorhinal grid cells, upstream of the place cells in dorsomedial entorhinal cortex, are the likeliest source of the continuous attractor dynamics in the system. Grid cells are space-modulated neurons with periodic firing fields. In moving animals, the multiple firing fields of an individual grid cell form a triangular pattern tiling the entire space available to the animal. Collectively, grid cells are thought to provide a context-independent metric representation of the local environment. The firing of grid cells is spatially localised, but firing fields from a given cell are multiple. Grid cells have a number of interesting features which make them plausible candidates for the long-postulated continuous attractor system that underlies place cell activity and the ability of place cells to update their activity in response to movement. Like place cells, grid cells change their firing patterns following environmental change, but the exact nature of the remapping is different. Grid cells are always active, so they do not switch fields on and off as place cells do.

Border cells are border-sensitive entorhinal neurons, reacting when a border is present in the proximal environment.

The right hippocampus seems to be more required for the acquisition of new spatial information than when the environment is highly familiar.

The hippocampus likely works in concert with anatomically connected regions, including parahippocampal areas and retrosplenial cortices, to create a map of environment. In humans the parahippocampus is more activated than the hippocampus during a searching phase and in case of visual–spatial discontinuities.

In particular the parahippocampal gyrus distinguishes between objects that were previously encountered at navigationally relevant locations (decision points) and irrelevant locations (nondecision points) during simple object recognition.

Complementing hippocampal place coding, prefrontal representations provide more abstract and hierarchically organised memories suitable for decision making.

The posterior parietal cortex is crucial for accessing remote spatial memories within an egocentric reference frame that enables both navigation and reexperiencing, and it was found to be necessary to implement specific aspects of allocentric

navigation with high demands on spontaneous retrieval. A role of cerebellum in the construction of hippocampal representation map is suspected [16].

Vestibular inputs are critical for topokinetic memory, navigation and spatial learning [17, 18].

Vestibular inputs must be transformed considerably in order to signal head direction, and the neuronal circuitry that accomplishes this signal processing has not been fully established.

Both the semicircular canals and the otolithic signals seem to be the indispensable component for the activity of HD Cells.

Temporary inactivation of the vestibular system led to the disruption of location-specific firing in hippocampal PC and direction-specific discharge of postsubicular HD cells, without altering motor function. PC and HD cell activity recovered over a time course similar to that of the restoration of vestibular function.

Damage to the vestibular inner ear causes long-term changes in neuronal nitric oxide synthase expression in the rat ipsilateral hippocampus, suggesting a long-term effect of loss of vestibular input on hippocampal function.

Neurochemical effects of a peripheral vestibular lesion can include a reduction of hippocampal NMDA receptor expression [19], and these receptors are important for memory, learning and long-term potentiation.

The vestibular damage can also result in the ipsilateral hippocampus deficit of glutamine, glycine, taurine and threonine and increase in norepinephrine in contralateral hippocampus.

Changes in the expression of N-methyl-D-aspartate receptor subunits, synaptosome-associated protein of 25 kDa, the serotonin transporter and tryptophan hydroxylase were observed.

Bilateral labyrinthectomy completely abolishes the spatial learning in the rat because spatially dependent firing fields of PC are larger and less uniform compared with controls, both in the light and in the dark (vision independent phenomenon). This long-term cognitive hippocampal deficit is partially improved in the course of time by a specific training.

Even animals with unilateral vestibular lesion maintain a deficit of navigation for at least six months.

These results indicate that vestibular signals provide an important influence over the expression of hippocampal spatial representations and may explain the navigational deficits of humans with vestibular dysfunction.

Hippocampal atrophy (a 16.7 % loss in size compared with controls) was found [20] in patients with acquired bilateral vestibular loss, accompanied by spatial and navigation deficits, while the nonspatial functions were unaffected.

In patients with bilateral vestibular failure due to NF2 with bilateral neurectomy, significant spatial learning and memory deficits were shown as compared to healthy controls but nor general memory deficits nor atrophy of the whole brain [21].

Also unilateral suppression of vestibular information would induce transitory spatial memory disorganisation at a high level of information processing: Meniere's disease patients after monolateral neurectomy were tested one day before surgical treatment and during the recovery time course [22]. In the acute stage (1 week) after

unilateral vestibular lesion, navigation error was greater in patients than in controls for the highest level of mental representation (spatial inferences or reversing routes). Impairment at making accurate rotations had disappeared by 1 month after vestibular lesion.

In our study [23] in patients suffering from chronic only partial unilateral vestibular deficit and "well compensated" (without vestibular symptoms) the Navigation Ability test showed the route times walked with eyes closed are always longer than in normal people. The mistakes improved with training. Corsi's test also showed a deficit of topokinetic working memory.

Subjects with left unilateral vestibular lesion seem to have a deficit of topokinetic memory and navigation smaller than those with right deficit [24].

14.2   The Reorganisation of the Balance System After Acute Vestibular Lesion

Acute vestibular lesions produce a sudden change in information to the balance system which provoke a complex syndrome: oculomotor syndrome (nystagmus, skew deviation and ocular cyclotorsion), postural syndrome (ataxia, head–body tilt and loss of stabilisation of the head), vegetative syndrome (nausea and vomiting) and perceptive syndrome (emotional involvement and spatial disorientation) [25].

In nature this is a dangerous condition because a subject with vertigo becomes an easy prey.

In an experimental study in baboons [26] Lacour demonstrated that dynamic stimulations in the first 7 days improve the final level of balance performances.

The presentation of the vestibular symptoms is linked to the ability of the CNS to adjust to the development of new dangerous conditions. Hence, adaptation to a vestibular loss is neither a simple nor a homogeneous process. Functional recovery results from neurochemical and neuronal plastic events and from cognitive mechanisms in CNS like those of habituation, storage of experiences, learning and the modulation of inputs.

Plasticity of the CNS and cognitive resources play a continuous role during compensation for unilateral vestibular loss [27]. Therefore adaptation to unilateral vestibular loss requires continued cognitive resources also in patients with no more symptoms [28, 29].

The brain may select different sensory or motor strategies for adapting to vestibular deficit, and in each patient, the nature of the adaptive mechanism is distinctly related to the type of experience, training, life span and cognitive style and other individual characteristics before and after the vestibular loss. So the adaptation mechanisms are partially different for each patient.

The two main mechanisms involved in reorganisation of balance are sensory substitution (compensation) and the new strategies and relearning processes (adaptation).

Sensory vicariant compensation is dependent on neuronal plasticity with neurotrophin re-expression, newborn neurons and neuronal sprouting of new terminals,

sensory reweighting with up- and downregulation of the synaptic activity and increased sensitivity of the surviving receptors [30] which increase the compensatory role of other inputs such as the contralateral vestibular, visual and the proprioceptive.

Progressive compensation of vestibular nuclei asymmetry involves initial inhibition of nuclei contralateral to the affected side, leading to subsequent slow recovery of bilateral neuronal activity.

The increase of the influence of the vision depends on experience, training, life span, presetting, cognitive style and perceptual factors, and it is very difficult to predict.

Deactivation of visual cortex during vestibular stimulation is most likely to reduce the effects of nystagmus but in the post-acute phase fMR demonstrated a visual substitution cortical mechanism with an upregulation of visual inputs in visual cortical areas in patients suffering from bilateral vestibular deficits [31].

The reweighting of visual input is partially related also to the type of visual experience after the vestibular loss.

Greater reliance on visual information can greatly affect the patient with vestibular deficit.

Vestibular-deficient subjects can experience decreased sensitivity to visual movement or visually induced vertigo without movement of the head and therefore without any stimulation of the vestibular end organs [32].

At the same time vestibular patients are particularly susceptible to imbalance in conditions of visual–vestibular discord. It has been noted in multiple works that patients with balance disorders commonly experience discomfort in environments with repetitive or moving visual patterns, such as those encountered in supermarkets, automobile traffic, tunnels or aisles.

In some cases the substitution role of visual cues gradually decreases.

Adaptation is a more complex phenomenon which requires new strategies, new operative modes mimicking the lost functions, relearning processes and cortical map remodelling

It includes mechanism of habituation, storage, learning and modulation. The recurrence of abnormal conditions every day can lead to habituation, which typically involves a reduction in the gain of the concerned reflexes.

The habituation of the patient is situation specific without complete satisfactory adaptive transfer.

In fact, habituation to a particular sensory pattern of quality or frequency does not guarantee the stability of the function in the event of a change in the frequency of inputs or other characteristics of the environmental situation.

The habituation becomes therefore often environment-specific. Patients usually become accustomed quickly to domestic conditions and maintain over time a greater level of disability in other living conditions.

Novel strategies involve activation of learning and biological memory processes of non-declarative procedural memory.

Activation of learning leads to increase in branching of dendritic extensions and synapses in the cerebellum and neocortical and hippocampal neurons. In order to

adapt to ongoing reality, continuous modulation of the vestibular response is essential followed by memorisation of the experience for behavioural adaptation and retrieval. Comparison to previous episode will enable in predicting a response to the expected event.

Memory is an active and plastic mechanism consisting of acquiring, holding, consolidating and recalling the inputs. Functional adaptation mechanisms are essentially similar to those characterising sensory-motor learning which is based on procedural memory, a kind of memory activated through practice. Traditionally these have been motor skills, such as those used when playing golf or tennis. Procedural learning is slow and incremental and requires immediate and consistent feedback. Individual peculiar cognitive feature and the specific neuronal networks are able to modify the time course, the type and the results of the adaptive mechanisms.

The adaptation to vestibular deficit is usually satisfactory, but a "cognitive-vestibular cicatrix" remains forever.

Perturbations in autonomic regulation are transient and largely dissipate over time [33].

In some tests of cognitive abilities, vestibular patients perform significantly worse than normal patients, and cognitive deficits are greater in patients who are not well compensated.

Loss of vestibular sensory inputs may negatively impact the cognitive processing ability to assimilate spatial and nonspatial information [34].

A topokinetic memory disorganisation at a high level of information processing, a spatial working memory deficit and a reduction of navigation ability are evident.

Abnormal levels of anxiety and depression have been observed in patients suffering from chronic vestibular deficit [35, 36]. It constitutes a kind of chronic alerting state able to cause a significant impact on daily activities and psychological well-being.

In several cases, the psychological distress is similar to that of traumatic memory. Probably acute rotatory vertigo is a true emotional visual input that can activate the amygdala which acquires lasting memories of emotional anger and fear experiences.

In traumatic memories induced by acute disorder, affected brain circuits are extended and unstable, while chronic diseases are characterised by circumscribed and stable neurofunctional abnormalities. Reactivation occurs in the cerebellum storage of the relatively defensive programmes with possible dysmetric phobic behaviour.

Panic disorders and agoraphobia may be linked to chronic vestibular deficit [37] probably due to these mechanisms.

In well-compensated patients increased attention is demonstrated by slower forced choice reaction time for cognitive tasks.

Vestibular-deficient subjects perform worse on cognitive tasks such as backward counting, especially when these must be carried out in a posturally demanding or disorienting environment [38]. It was also suggested that compensation requires continued cognitive resources especially in case of concurrent reaction time task. This interference with cognition occurs as a result of the sensory integration required for resolving inputs from multiple sensory streams.

14.3   Cognitive Factors Interfering with Functional Adaptation

In our experience some vestibular symptoms (transient vertigo with rapid head movements or slight unsteadiness) can recur or persist for some months or years.

Actually some individual factors (age, gender, psychological distress, stress) seem to interfere with vestibular adaptation processes.

Processing speed, visuospatial working memory and procedural learning, related to vestibular adaptation, are more affected by ageing than verbal cognition.

When instability increases, older adults allocate more attentional resources to posture control than to cognition to avoid fall accidents.

The level of neurogenesis in the hippocampus gradually attenuates with age, resulting in damage to learning and spatial memory.

Older subjects show reduced or absent hippocampal activation in performing navigation tasks and prefer an egocentric route strategy [39]. However the older subjects certainly seem to achieve the same performance levels as the younger ones, but they do not fully automate the procedure.

Even in the elderly the adaptation is generally able to lead to a functional normalisation in a longer term, thanks to vestibular rehabilitation.

Also the interference of gender seems important in navigation [40]. On average, men tend to rely more on an allocentric cognitive map strategy and to activate the hippocampus than women.

Ill people experience more psychological distress if they have a strong illness identity (i.e. attribute many symptoms to the illness), have a stronger emotional response to illness, feel that they do not understand their illness well and believe that their illness has serious consequences, will last a long time and cannot be easily controlled.

Furthermore symptoms of vertigo, dizziness and imbalance often appear to be inexplicable, unpredictable and uncontrollable. The combination of unpredictable vertigo attacks and accompanying severe vegetative reactions was considered as a causative factor for anticipatory anxiety, phobic fear and social avoidance.

It has been shown that the more strongly an individual perceives the vertigo sensation at the time of hospital admission and the higher the fear of body sensations within the first 10 days after admission, the higher the risk for developing a secondary persistent dizziness [41] and panic or somatoform disorders [42]

It is likely that the emotional responses related to vestibular dysfunction are mediated by the noradrenergic outflow from the locus coeruleus and the monoaminergic inputs to the vestibular system, the limbic system and the parabrachial nucleus network.

The cerebellar storage mechanisms and mechanisms of traumatic memory can make serious psychological distress, facilitate the fact to become chronic and lead to avoidance behaviours that further reduce the dynamic experience needed to make more stable adaptation to the new condition.

Release of stress hormones is essential for adaptation to change but persistent elevated levels of physical (pain, noise exposure, etc.), psychological (apprehension

to impending events, acoustic conditioning, etc.) or due to homeostatic disturbance (hunger, blood pressure, inner ear pressure, etc.) stress can lead to disease states.

Stress steroids modulate the synaptic and neuronal plasticity involved in vestibular compensation [43–45]. Neurosteroid modulation of glutamate neurotransmission might be involved in the longer-term compensation of neuronal activity, through the induction of long-term potentiation (LTP) and depression (LTD) in the vestibular neurons.

Stress not only induces neuronal cell death and atrophy in the hippocampus, but also inhibits the ability to induce LTP in the hippocampus and the medial prefrontal cortex activity. Chronic stress also enhances amygdala-dependent unlearned fear and fear conditioning with related LTP [46].

The activation of the stress axis in the paraventricular nucleus of the hypothalamus (PVN) is more evident after unilateral labyrinthectomy than in sham operation [47].

Based on the timing of occurrence of stress, opposite effects are observed on the learning process [48].

During the first day of adaptation, stress can facilitate the ongoing learning processes; however, after adaptation, stress can impair such processes [49]. Retrieval of spatial learning is modified by the high level of stress which is deleterious for any kind of spatial explicit information processes [50]. Normal level of stress activates spatial learning. Therefore, we need a middle level of stress to improve our reaction to the acute vestibular deficit, more specifically to promote the learning process on the first day. The compensatory increase in intrinsic excitability of vestibular neurons in the brainstem failed to occur in animals that were labyrinthectomised under prolonged anaesthesia so that they did not experience the stress normally associated with the vestibular deafferentation.

Conclusion

In conclusion we must be confident in the CNS adaptive mechanisms and in the ability of our mind to adapt to new conditions of vestibular deficit. In the great majority of cases a strategy to calm the patient and to facilitate cognitive and physiological processes of neuronal plasticity that underlie adaptation to the vestibular lesion will be able to guarantee the return to a normal balance function.

If symptoms persist, you should identify and limit the factors that interact with processes of adaptation and thus reduce stress, remove other sensory problems affecting the visual or proprioceptive apparatus, which should have vicarious compensatory activity, search possible to reduce the high levels of anxiety and depression, psychological conditions that interact negatively, to continue the use of nootropics and/or neuromodulators and possibly use a customised rehabilitation training.

Cognitive-behavioural approaches are also very useful in cases of chronic illness because cognitions about illness and its consequences are important in how the risk people emotionally respond to their chronic illness is particularly high.

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Imaging of Migraine and Vestibular Migraine

15

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15.1 Introduction

Migraine is one of the most common neurological diseases, affecting around 15 % of the population and being associated with a substantial personal and social burden. According to consensus expert guidelines, neuroimaging procedures are not recommended for routine use in the workup of patients with a certain diagnosis of migraine [1]. However, during the past few years, the extensive application of advanced functional and structural magnetic resonance imaging (MRI) techniques has contributed to improve the understanding of the pathophysiology of this condition and to elucidate novel mechanisms which might become target of future therapeutic interventions [2].

What is now established is that migraine is not simply a disease related to pain occurring intermittently, but a process that over time either affects the brain or acts on a predisposed brain that may have an underlying difference in function or structure [3]. The role played by different MR techniques to build up such a theory is the main topic of this chapter. Given the fact that criteria for the diagnosis of vestibular migraine have been proposed only recently [4] and the relative rarity of this condition [5], only a few studies have applied neuroimaging techniques in patients suffering of vestibular migraine. However, the potential of the use of these techniques, in the context of the current knowledge on migraine, will be discussed.

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15.2 Conventional MRI

15.2.1 MRI and the Diagnosis of Migraine and Vestibular Migraine

The use of neuroimaging in patients with migraine varies widely in the clinical settings. MRI examinations are often obtained in migraine patients because of fear of missing serious underlying diseases (e.g., stroke, tumors, infections), especially in patients with migraine with aura (MWA) or vestibular migraine. MRI is indeed the most useful technique for the evaluation of the labyrinth, internal auditory canal, 8th cranial nerve, and brain parenchyma [6], and its use is mandatory in the differential diagnosis of acute headache versus symptomatic headache. However, in patients suffering of non-acute headache, the use of MRI should be indicated only in patients with atypical headache patterns, a history of seizures, and/or focal neurological symptoms or signs, as specified in the 2011 revision of the EFNS guidelines [1].

15.2.2 Migraine and Brain White Matter Hyperintense Lesions

Numerous MRI studies have described an increased risk of harboring white matter hyperintense lesions (WMls) on dual-echo and fluid-attenuated inversion recovery (FLAIR) scans in patients with migraine compared to healthy individuals (Fig. 15.1): a meta-analysis of published case–control studies found a pooled increased risk of 3.9 in migraine patients [7]. WMls of migraine patients are usually small, punctuate, round, or oval-shaped lesions located in the deep or periventricular WM.
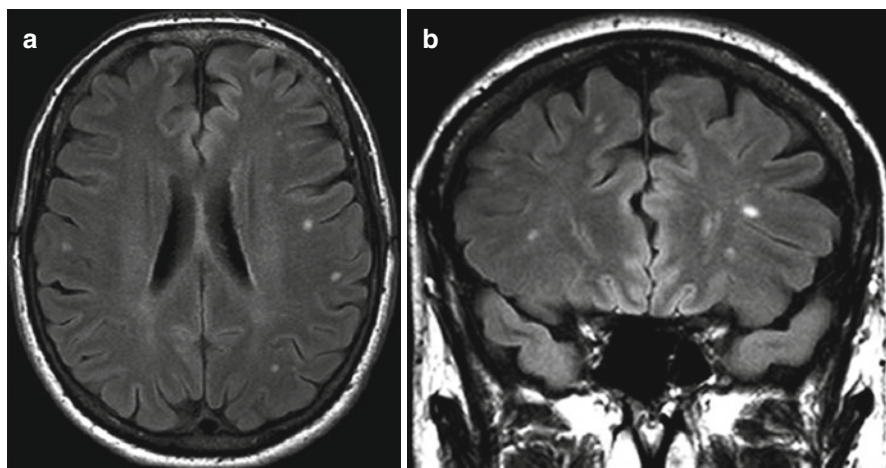
Fig. 15.1 Axial (**a**) and coronal (**b**) fluid-attenuated inversion recovery magnetic resonance images of the brain from a 61-year-old patient with migraine without aura. Multiple hyperintense, small, punctuate lesions are visible in the deep and juxtacortical white matter

However, focal T2 lesions in the brainstem are also frequent in these patients, without significant differences between patients with and those without aura [8]. Infarct-like lesions involving the posterior circulation territory, in particular the cerebellum, have been described in MWA patients [9]. Increasing headache frequency and age, longer disease duration, a familial history of migraine and female gender have been associated with an increased incidence of WMls [10].

Several theories have been considered to explain the increased susceptibility to form WMls of migraine patients. Some authors have suggested that hemodynamic changes detected during the attacks, including oligemia and focal hypoperfusion, may lead to such a damage [10, 11]. Other mechanisms include atherosclerotic causes, such as common cardiovascular risk factors, endothelial dysfunction, medications with vasoconstrictor activity taken to treat headache (e.g., triptans), local excessive neuronal activation, and cardiac abnormalities including patent foramen ovale (PFO) [11]. The association between WMls and PFO in patients with migraine has been the argument of several investigations, with controversial results. Indeed, some studies have reported that migraine patients, especially those with MWA, had a higher prevalence of PFO and right to left shunt (RLS) than non-migraineur controls with a relationship between these cardiac abnormalities and WMls [12], whereas other studies did not confirm these results [10].

Neurogenic inflammation has also been considered in the pathogenesis of WMls of migraineurs. Increased neuropeptides and proinflammatory cytokines have been reported during ictal and interictal periods in these patients [10]. In addition, in many cases the imaging features of WMls of migraine patients resemble those of WM lesions of patients with multiple sclerosis (MS), satisfying MS diagnostic criteria for disease dissemination in space in up to 34 % of the patients [13, 14]. Clearly, these patients with migraine and multiple WMls may represent a diagnostic challenge, particularly when neurological symptoms (even if reversible) and/or signs are present. A recent study has shown that double inversion recovery sequences may provide important pieces of information in the diagnostic workup of these patients, since, differently from what is usually observed in MS, no cortical lesions are detected with these techniques in migraineurs [13].

The definition of how early WMls occur in patients with migraine and the evaluation of their rate of progression over time may provide further insights into the mechanisms responsible for their formation. Recent studies in pediatric patients with migraine have demonstrated that WMls occur in a relatively high proportion of these patients (more than 30 % in some studies) [15], have imaging features similar to those of adult patients, and are not associated with stroke, migraine type, the presence of PFO, or the degree of RLS [16, 17]. Recent longitudinal studies have shown that the rate of progression of WMls, in both adult [18] and pediatric [17] patients with migraine, is similar to that found in individuals without migraine.

The clinical relevance of WMls in migraine patients remains unknown. Camarda et al. [19] have suggested a potential association between the presence of executive deficits and WMls in migraine patients. However such an association has not been confirmed by other investigations [20].

15.3 MRI and Pathophysiology of Migraine

15.3.1 MR Imaging of Cerebral Vasculature

Early MRI studies have supported the conceptualization of migraine as a vascular disorder. Numerous MR angiography (MRA) studies have shown that patients who undergo imaging examinations during an aura characteristically have hypoperfusion associated with vasoconstriction, whereas those who undergo imaging examinations during the headache phase show vasodilatation and hyperperfusion. Decreased cerebral blood flow (CBF) and venous dilatation during a migraine attack have also been confirmed using susceptibility-weighted imaging (SWI) [2]. However, other studies have suggested that modifications of vascular diameter might not occur, or might not be required, during migraine pain [2, 21].

15.3.2 Functional Imaging Techniques

Functional imaging techniques allow one to assess hemodynamic abnormalities in migraine patients and are not only improving the understanding of the mechanisms responsible for initiation and propagation of migraine attacks but also contributing to shed light on the cyclic aspect of the disease and the modifications in cortical and subcortical regions during the different phases of migraine.

15.3.2.1 Positron Emission Tomography and Single Photon Emission Computerized Tomography

Positron emission tomography (PET) and single photon emission computerized tomography (SPECT) are two imaging techniques that use radiolabeled molecules to provide information about function and metabolism of different tissues. These techniques are based on the detection and quantification of gamma rays emitted indirectly by a radionuclide (tracer), which is introduced into the body on a biologically active molecule. Three-dimensional images of tracer concentration within the body are then constructed by computer analysis. Using both SPECT and PET, a focal reduction of regional CBF (rCBF) in the occipital cortex was reported in migraine patients during the aura phase. Posterior cerebral hypoperfusion has been reported also in migraine patients without aura (MWoA) during a spontaneous migraine attack [2]. Hypoperfusion in migraine patients is not restricted to posterior regions of the brain, but may also involve regions located in the frontal and temporal lobes, which have been variously implicated in nociception [22].

By defining the patterns of neuronal activation involved in migraine, numerous PET studies have contributed to move from a purely vascular hypothesis of migraine pathophysiology to a neurovascular or a CNS theory. An important early study revealed an increased blood flow in the brainstem, cingulate, auditory, and visual association cortices during spontaneous migraine attacks. However, only the contralateral brainstem activation persisted after relief from headache and phono- and photophobia induced by sumatriptan injection, thus suggesting a role of brainstem

nuclei (involved in antinociception) in the pathogenesis of migraine [23]. The activation of brainstem nuclei, in particular in the midbrain and dorsal pons, has been confirmed by subsequent studies in both episodic and chronic migraine, thus supporting its role as "migraine generator" [2, 3].

Repetition of migraine attacks leads to metabolic abnormalities of brain regions belonging to the central pain matrix, such as the insula, anterior and posterior cingulum, and prefrontal and primary somatosensory cortices. Indeed, hypometabolism of these regions has been negatively correlated with disease duration and lifetime headache frequency [2].

The application of PET to investigate patients with medication-overuse headache (MOH) [5] has allowed to demonstrate that metabolic abnormalities may be reversible, since abnormal metabolic activity of cerebral regions involved in pain processing recovered to almost normal levels after the medication was withdrawn. The only exception was found in the orbitofrontal cortex, which showed a further reduction of activity after medication withdrawal, indicating a role for this structure in the predisposition to analgesic overuse.

Brain metabolism alterations in patients with vestibular migraine have been studied only recently using PET in two patients during and between attacks [24]. Compared with interictal images, ictal PET showed increased metabolism in the bilateral cerebellum, frontal and temporal cortices, posterior insula, and thalami and deactivation of the bilateral posterior parietal and occipitotemporal areas. These results suggest that patients with vestibular migraine activate the vestibulothalamo-vestibulocortical pathway during the migraine attack. In addition, decreased metabolism in the occipital cortex may represent reciprocal inhibition between the visual and vestibular systems.

15.3.2.2 Perfusion MRI

Brain tissue perfusion can be estimated using either exogenous tracers (e.g., gadolinium chelates) or endogenous arterial water (arterial spin labeling – ASL). Several perfusion-weighted MRI studies have reported a reduced rCBF in brain regions contralateral to the side of aura symptoms (e.g., occipital regions contralateral to the affected visual hemifield during visual aura) and a subsequent cerebral hyperperfusion during pain in migraine patients [2, 25, 26]. Such perfusion abnormalities regress over time without permanent sequelae or cerebral ischemia on follow-up [26, 27]. Studies of interictal patients showed both hyper- and hypoperfusion of brain areas that are not specific for migraine pathophysiology [2].

15.3.2.3 Functional MRI

Functional (f) MRI is a noninvasive technique which allows to study (CNS) function and to define abnormal patterns of activation and/or functional connectivity (FC) caused by injury or disease. The signal changes seen during fMRI studies depend on the blood oxygenation level-dependent (BOLD) mechanism. Local increases in neuronal activity result in rise of blood flow and oxygen consumption. The increase of blood flow is greater than the oxygen consumption, thus determining an increased ratio between oxygenated and deoxygenated hemoglobin, which
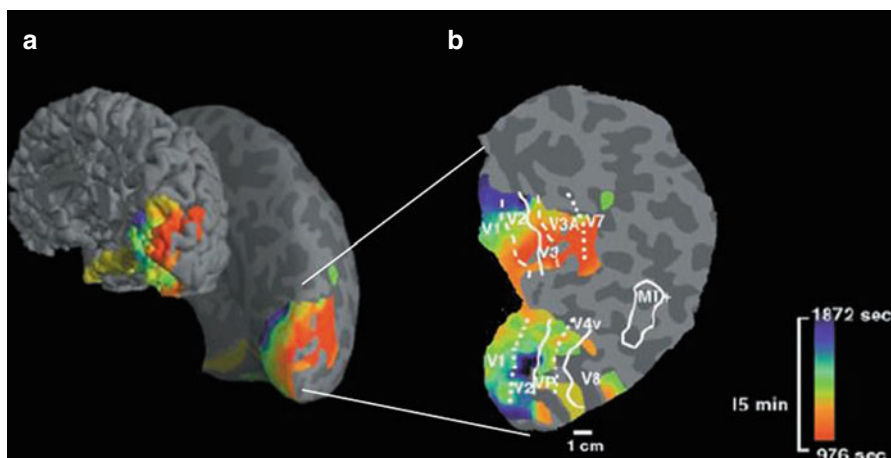
Fig. 15.2 Source localization and time of onset of the blood oxygenation level-dependent (BOLD) signal changes during induced and spontaneous visual aura attack in patients with migraine: (**a**) data are represented on inflated cortical surface shown from a posterior-medial view; (**b**) a fully flattened view of the cortical surface of the involved region. Cortical regions showing the first BOLD perturbations are coded in *red* (according to the color-coded scale representing variation in time), and locations showing the BOLD perturbations at progressively later times are coded by *green* and *blue* (according to the color-coded scale representing variation in time). The aura-related changes appeared first in extrastriate cortex (area V3A) and then progressed contiguously and slowly over the cortex following the same retinotopic progression of visual disturbance (Reproduced with permission from Hadjikhani et al. [30]. Copyright (2001) National Academy of Sciences, USA)

enhances the MRI signal [28]. By analyzing these data with appropriate statistical methods, it is possible to obtain information about the location and extent of activation as well as connectivity of specific areas involved in the performance of a given task in healthy subjects and in patients with different neurological conditions. Recently, a completely task-free approach, based on the assessment of functional correlations of neural networks at rest (resting state [RS] fMRI), has been developed (for a review see [29]).

In line with PET investigations, several fMRI studies have contributed to the classification of migraine as a neurovascular or even a brain disorder. The pioneering study by Hadjikhani and coworkers [30] has shown that during induced and spontaneous visual aura, a focal increase of BOLD signal (possibly reflecting vasodilation) developed within occipital extrastriate cortex (area V3A) (Fig. 15.2). This BOLD change progressed contiguously and slowly over the cortex, congruent with the retinotopy of the visual percept, and, then, following the same retinotopic progression, it diminished (possibly reflecting vasoconstriction). This spreading signal disturbance had striking similarity with cortical spreading depression (CSD) phenomenon, thus supporting the theory that CSD was the electrophysiological correlate of visual aura. Notably, a spreading neural activity suppression has also been described in MWoA patients during triggered migraine attacks [31].

FMRI studies have also confirmed dysfunctional activity of brainstem nuclei involved in pain modulation during both the ictal and interictal phases [2]. Stankewitz et al. [32] confirmed an increased activation of the dorsal pons in migraine patients during induced migraine attacks. This study also revealed a selective gradient-like activity in the spinal trigeminal nucleus: after trigeminal nociceptive stimulation, interictal migraine patients exhibited lower activations of this nucleus; however, shortly before the migraine attack, patients had an increased activation at this level. Of interest, the time interval to the next headache attack could be predicted by the amplitude of signal intensities in the spinal trigeminal nuclei, suggesting that this oscillating behavior may represent a key phenomenon in migraine pathogenesis.

Studies which have explored cerebral activity within the pain network in migraine using experimental pain stimulation have shown abnormalities of a widespread sub-cortical and cortical brain network involved in pain processing in these subjects. However, one of the main challenges in the interpretation of these results is to differentiate findings consistent with a general pain response from those that might be specific to migraine [33]. Using a contact thermode as a noxious stimulation paradigm, migraine patients were found to exhibit a greater activation in the anterior cingulate cortex at 51 °C and less activation in the bilateral somatosensory cortex at 53 °C [34], thus supporting the presence of an increased antinociceptive activity in these patients, which could represent a compensatory functional reorganization aimed at modulating pain perception to the intensity of healthy controls. Other fMRI studies have demonstrated alterations in pain modulatory/inhibitory circuits, which may be related to the lack of habituation after repetitive painful stimulation and increased cortical excitability to painful stimuli that may lead to the development of allodynia [3]. The thalamus is now considered to play a pivotal role in the manifestation of allodynia. Burstein et al. [35] showed that brush and heat stimulation at the skin of the dorsum of the hand produced larger BOLD responses in the posterior thalamus of patients undergoing a migraine attack with extracephalic allodynia than the corresponding responses registered when the same patients were free of migraine and allodynia.

An increased activation of cortical regions mediating the affective dimension of pain has also been demonstrated in migraineurs. During spontaneous and induced migraine, these patients had increased BOLD signal intensities in limbic structures (e.g., the amygdala and insula) and exhibited a stronger recruitment of affective cortical areas when exposed to emotional inputs [3]. Based on these data, a model of migraine as a dysfunction of a "neurolimbic" pain network has been proposed [36].

Abnormalities of function of pain-processing regions have also been investigated in patients with chronic migraine, particularly those with MOH. Before the withdrawal of the offending medications, these patients had reduced pain-related activity in areas of the lateral pain pathway, including the primary and secondary sensorimotor areas. Such abnormalities regressed after treatment withdrawal [37]. In addition, patients with MOH presented dysfunctional activity of the meso-cortico-limbic dopamine circuit, including the ventromedial prefrontal cortex and the substantia nigra/ventral tegmental area complex, during the execution of a decision-making under risk paradigm. The ventromedial prefrontal cortex dysfunctions were

reversible and attributable to the headache, whereas the substantia nigra/ventral tegmental area complex dysfunctions were persistent despite treatment withdrawal, suggesting that MOH may share some neurophysiological features with addiction [3].

It is well established that migraine patients show also hyperresponsiveness of the primary visual cortex and a lack of habituation to visual stimuli [2]. These phenomena are more pronounced in patients with MWA [10]. Hyperresponsiveness of the visual cortex in migraine extends beyond primary visual areas, even in the interictal period. Antal et al. [38] demonstrated significantly stronger activation of the extrastriate, motion-responsive MT area, representing the medial-superior temporal area, in migraine patients versus healthy controls in response to coherent/incoherent moving dot stimuli. This cortical hyperexcitability may represent the biological basis for the clinical observation of heightened vulnerability to motion sickness that migraine sufferers often report [2].

Numerous studies provided a conceptual framework for understanding vestibular migraine as a variant of MWA produced by the convergence of vestibular information within migraine circuits. Several fMRI studies showed that vestibular stimulation activate cerebral regions that are generally involved in migraine and pain perception, such as the posterior and anterior insula, orbitofrontal cortex, and the posterior and anterior cingulate gyri, thus suggesting that central constituents of the migraine circuit might include components of central vestibular pathways [5]. However, so far, fMRI has not been applied yet to investigate functional cortical abnormalities in patients with vestibular migraine.

RS fMRI studies have shown that FC is generally increased in pain-processing networks in migraineurs, whereas it is decreased in pain modulatory circuits [39]. In particular, migraineurs with a history of allodynia exhibit significantly reduced RS FC between PAG, prefrontal regions, and anterior cingulate cortex compared with migraineurs without allodynia [40]. These RS FC abnormalities have been related to the frequency of migraine attacks and disease duration [39]. Significant abnormalities of RS FC occur also in affective networks [39], the default mode (DMN) [41], and the executive network [33].

15.3.3 Quantitative Structural and Metabolic MRI Techniques

The notion that patients with migraine might have structural abnormalities in association with the previously described functional imaging abnormalities is relatively recent and is prompting the extensive application of modern, quantitative MRI techniques. The results obtained by this effort have consistently demonstrated that, similar to what has been observed in other neurological conditions, brain damage in patients with migraine extends beyond abnormalities detectable with conventional MRI sequences.

15.3.3.1 Morphometric Techniques
Several approaches are currently available to define the regional distribution of morphometric abnormalities among different cohorts of subjects, including voxel-based

morphometry (VBM) (which allows an automatic comparisons of regional WM and GM volumes, on a voxel-by-voxel basis) and surface-based morphometry (SBM) (which allows a more precise and direct measurement of cortical thickness [CT] and cortical surface area [CSA], on a vertex-by-vertex basis) [10]. As extensively reviewed elsewhere [42], while a pioneering VBM study [36] did not find any significant morphometric abnormality of WM and GM in patients with episodic migraine, several more recent studies question this negative finding by showing that, similar to other chronic painful conditions, migraine patients exhibit a reduction of GM volume [2], CT, and CSA [43] in a network of areas that are involved in pain processing, including the insula, cingulum, and frontal, parietal, and temporal cortices. In some of these studies, GM atrophy was significantly associated with longer disease duration, higher frequency of attacks and higher T2 lesion load (in those patients with WMls), thus supporting the view of migraine as a progressive disorder. However, this hypothesis is in part contradicted by the fact that migraine is a self-remitting disease, which usually resolves with age, and by the results of other VBM and SBM studies which found no correlation between morphometric abnormalities and the number of attacks, disease duration, and WM lesion load, which has led some authors to postulate that the observed cortical abnormalities might represent a phenotypic biomarker of the disease [43]. As a consequence, longitudinal studies are needed to clarify this point. At present, only one study has applied VBM to track longitudinal modifications of GM volume in MWoA patients and found significant reduction of GM volume of the superior frontal gyrus, orbitofrontal cortex, hippocampus, precuneus, and primary and secondary somatosensory cortices after 1 year, which were not associated with changes in headache activity parameters [44]. It is important to note that recent longitudinal studies have shown that the GM volume reduction found in chronic pain syndromes can be normalized by treatment [45, 46], suggesting that it may represent a reversible aspect of chronic nociceptive transmission.

Concomitantly with such a diffuse pattern of GM volume reduction, several morphometric studies in patients with migraine have also reported increased GM volumes in regions of the brainstem (such as the PAG GM and the pontine nuclei), regions involved in visual processing (such as the MT/V5 complex and V3A), and the primary sensorimotor cortices. Whether these abnormalities contribute to the triggering of migraine attacks, or, conversely, are the consequence of repeated attacks, is still a matter of debate [2].

A recent VBM study of pediatric patients suffering of migraine [15] has shown that morphometric abnormalities occur relatively early in the course of this disease, since GM atrophy of frontal and temporal regions involved in nociception was detected also in this population (Fig. 15.3). Notably, pediatric patients with migraine had also an increased GM volume of the right putamen, which was inversely correlated with disease duration, suggesting that the involvement of the putamen likely occurs early in migraine patients with a pediatric onset of the disease.

The application of morphometric techniques is contributing to identifying structural correlates of some of the clinical deficits that are typically detected in migraineurs in clinical practice. For instance, significant correlation has been found between decreased GM volume of the frontal lobes and deficits of executive functions [2].
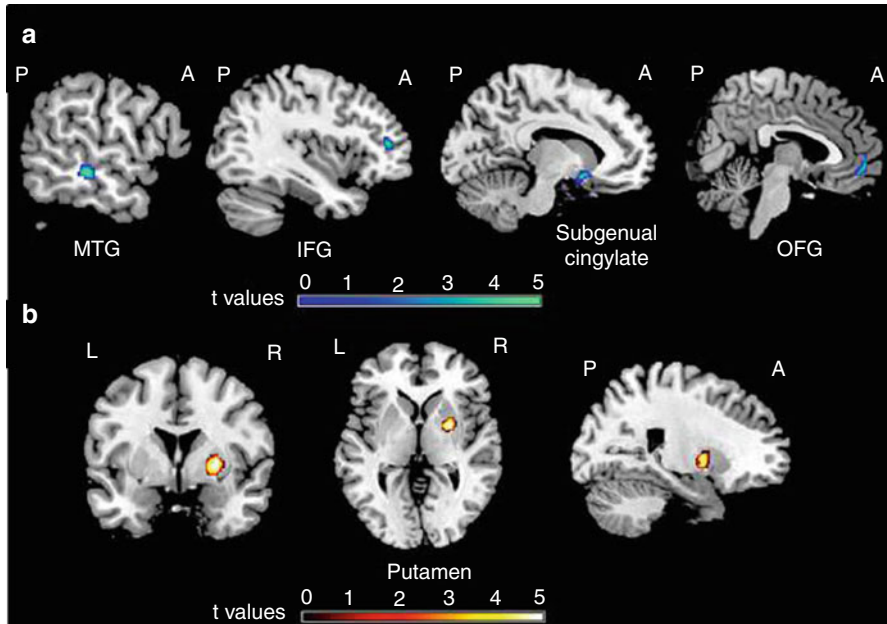
Fig. 15.3 Differences of regional gray matter (GM) volume between pediatric patients with migraine and healthy controls: (**a**) compared to healthy controls, pediatric patients had reduced GM volume of the left middle temporal gyrus (*MTG*), inferior frontal gyrus (*IFG*), subgenual cingulum, and right orbitofrontal gyrus (*OFG*) (*blue-green* scale according to *t* values); (**b**) compared to controls, pediatric patients had an increased GM volume of the right putamen (*red-yellow* scale according to *t* values). The GM differences have been superimposed on a high-resolution T1-weighted template (neurological convention) (Reproduced with permission from Rocca et al. [15])

15.3.3.2   Diffusion-Weighted MRI

Diffusion-weighted (DW) MRI is a quantitative technique that exploits the diffusion of water within biological tissues [47]. The diffusion coefficient measures the ease of this translational motion of water. In biological tissues this coefficient is lower than that in free water because the various structures of the tissues (membranes, macromolecules, etc.) impede the free movement of water molecules [47]. For this reason, the measured diffusion coefficient in biological systems is referred to as the "apparent diffusion coefficient" (ADC) [47]. Pathological processes that alter tissue integrity typically reduce the impediments to free water motion, and, as a result, these processes tend to increase the measured ADC values. A full characterization of diffusion can be provided in terms of a tensor [48], which has a principal axis and two smaller axes that describe its width and depth. The diffusivity along the principal axis is also called parallel or axial diffusivity (AD), while the diffusivities in the two minor axes are often averaged to produce a measure of radial diffusivity (RD). It is also possible to calculate the magnitude of diffusion, reflected by the mean diffusivity (MD), and the degree of anisotropy, which is a measure of tissue organization that can be expressed by several indexes, including a dimensionless one named fractional anisotropy (FA).

DW MRI is sensitive to the transient disturbances of cerebral water distribution occurring during CSD [49]; as a consequence, its application to image patients during the migraine attack might contribute to improve the understanding of its pathophysiology. Nevertheless, studies which have applied this technique in migraine patients during the attack have provided contradictory results. Indeed, while some studies [50] found no ADC abnormalities during the migraine attack, others [51] described an increased ADC in the red nuclei, supporting the role of the brainstem in the pathogenesis of migraine episodes. Reversible DWI signal abnormalities have also been shown at the level of occipital and temporoparietal regions during aura in patients with MWA [52].

In patients in the interictal phase, seminal diffusion tensor (DT) MRI studies used histogram-based methods of analysis and provided a global estimation of "occult" CNS damage in migraineurs. By using this approach, Rocca et al. [53] showed that brain damage in these patients extends beyond T2 lesions and involves diffusely the normal-appearing (NA) brain tissues. The correlation found in this study between diffusivity abnormalities of the NA brain tissues and T2 lesion volumes suggested that secondary Wallerian degeneration of fibers traversing macroscopic lesions might be one of the mechanisms responsible for the observed DT MRI abnormalities. A subsequent study from the same group [54] revealed that DT MRI abnormalities, as reflected by an increased MD, involved mainly the GM, with a relative sparing of the NA white matter (NAWM).

More recently several approaches, including DT MRI tractography and the quantification of abnormalities at a voxel level (voxel-based analysis), have been developed to investigate damage to selected WM fiber bundles [2]. Based on these approaches, a decreased FA along the thalamocortical tracts has been found in migraineurs, with lower FA in the ventral trigeminothalamic tract in MWA patients and lower FA in the ventrolateral periaqueductal GM in MWoA patients, indicating an involvement of the trigeminal somatosensory and pain modulatory systems [2]. Microstructural abnormalities of frontal WM tracts, the corpus callosum, and internal capsule (which connect cortical areas of the pain network) have also been reported, with conflicting findings among studies concerning the correlation between these abnormalities and patients' clinical characteristics (disease duration and frequency of the attacks) [2, 55]. In line with morphometric studies, an involvement of visual-processing areas has also been demonstrated as reflected by FA abnormalities in WM areas in the vicinity of regions that are part of the motion-processing visual network, including V3A, MT/V5, the superior colliculus, and the lateral geniculate nucleus [2]. These WM FA abnormalities might be due to a chronic dysfunction of these cortical areas, which in turn might be the consequence of repetitive migraine attacks. Using DT MRI tractography, reduced FA of the optic radiations and increased MD of the right optic radiation have been shown in MWA patients in comparison to healthy controls and MWoA patients [56]. Such abnormalities have been interpreted as a phenotypic biomarker of the disease, given the lack of a correlation between clinical and structural MRI metrics.

The 1-year longitudinal study of Liu et al. [44] found that, differently from what happens in terms of GM volume, WM abnormalities tend to remain relatively stable

over such a follow-up, suggesting that WM damage is likely to evolve slowly in the course of migraine chronification and alterations of GM and WM may take place at different pace.

Dynamic modifications of DT MRI indexes have been recently described at the level of the thalamus in MWoA patients [57]: during the interictal phase, patients had higher FA and lower MD values of the thalami compared with controls, whereas during the attacks, DT MRI indexes did not differ between patients and controls. Remarkably, thalamic FA values were positively correlated with the number of days since the last migraine attack, suggesting that these modifications could represent the anatomical counterpart of the cyclical functional fluctuations previously observed in the neurophysiology of migraine.

Recent advances in MRI enable imaging of both the structural and functional connections of large-scale neural system, thus enabling efficient mapping of connectivity across the entire brain. Network-based analysis of brain connections has provided a new technique to study the brains of healthy people and patients with neurological disorders. Graph theory analysis provides a powerful method to quantitatively describe the topological organization of brain connectivity (for review see [58]). Using DT MRI tractography and graph theory approaches, Liu et al. [59] showed reduced/strengthened anatomical distances of WM networks, leading to a tendency for clustered connections in migraine patients. Such network features could distinguish patients with migraine from healthy controls with high accuracy of 90.4 %.

15.3.3.3 Magnetization Transfer MRI

Magnetization transfer (MT) MRI is based on the interactions between protons in free fluid and protons bound to macromolecules [60]. MT MRI allows the calculation of an index, the MT ratio (MTR), which, when reduced, indicates a diminished capacity of the protons bound to the brain tissue matrix to exchange magnetization with the surrounding free water. Early MT MRI studies did not find any change in the brain and cervical cord of patients with migraine, suggesting that this technique might not be sensitive enough to detect abnormalities in this condition [56]. Recently, Granziera et al. [61] have found higher thalamic MTR values in MWA compared to MWoA patients. These broad microstructural alterations in the thalamus of MWA patients may underlie abnormal cortical excitability control leading to CSD and visual aura. However, these findings were not confirmed by a further study [62]. Decreased MTR values have conversely been reported at the level of the cerebellum and pars orbitalis of the frontal lobe in patients with MWoA versus healthy controls and patients with MWA, providing evidence of microstructural alterations in the cerebellar-prefrontal circuit, which could promote increased excitability of the prefrontal cortex and cerebellum, leading to "silent CSD" [63].

15.3.3.4 MR Spectroscopy

Water-suppressed, proton (^{1}H) MR spectra of the healthy human brain at long echo times reveal four major resonances: choline-containing phospholipids (Cho); creatine and phosphocreatine (Cr); N-acetyl groups, mainly N-acetylaspartate

(NAA); and lactate (Lac). Because NAA is a metabolite that is found almost exclusively in neurons and neuronal processes in the normal adult brain, a decrease in its concentration is thought to be secondary to axonal dysfunction, injury, or loss. By contrast, increases in Cho and Lac are thought to reflect acute inflammatory and demyelinating changes. ^{1}H-MR spectroscopy (MRS) with shorter echo times can detect additional metabolites, such as lipids and myoinositol (mI), which are also thought to indicate ongoing myelin damage and glial proliferation, respectively.

Using ^{1}H-MRS, several studies postulated an abnormal cerebral cortical energy metabolism in patients with headache. Following visual stimulation, MWA patients showed a consistent decrease of NAA levels and a slight increase of Lac peak in the occipital cortex compared to patients with MWoA and healthy controls, suggesting a diminished mitochondrial functioning in the first group [56]. Recent studies have also shown a "metabolic" dose-response relationship with aura duration or its severity. Using phosphorus (^{31}P) MRS, a reduction of magnesium levels has been found in migraine patients with neurological symptoms (e.g., aura or hemiplegic migraine), suggesting that disturbances of magnesium homeostasis may contribute to cortical hyperexcitability in migraineurs [3].

15.3.3.5   Imaging Iron Deposition

T2 hypointense areas and reduced T2 relaxation time (RT) are thought to reflect iron deposition, which is believed to be a marker of neurodegeneration.

High-resolution MR techniques have shown increased iron deposition in the PAG in migraineurs, suggestive of a disturbed central antinociceptive neuronal network. Iron deposition has also been described at the level of the basal ganglia and pain regulatory nuclei in patients with various subtypes of migraine, suggesting that this measure might contribute to distinguish patients with episodic and chronic migraine. Moreover, patients with higher attack frequency or longer disease duration experienced higher risk to have iron deposition in deep GM nuclei, suggesting a causal relationship between migraine and these abnormalities. The observed association between repeated migraine attacks and increased iron accumulation in deep GM nuclei involved in central pain processing raises the intriguing possibility that migraine has cumulative effects on brain structure and homeostasis. The increased iron levels in the antinociceptive network may constitute a physiological response to repeated activation of nuclei involved in central pain processing, which may play a role in the chronification of migraine [2].

15.3.4   Correlations Between Structural and Functional Abnormalities

Considering the large amount of functional and structural modifications described in patients with migraine, the dynamic nature of these changes and the phasic course of migraine, one of the main questions is what is the relationship between these abnormalities and which comes first and drives the other.

In a seminal study, Rocca et al. [64] showed that, during the performance of a simple motor task, compared with healthy controls, migraine patients had a larger activation of the contralateral primary sensorimotor cortex and a rostral displacement of the supplementary motor area. Interestingly, the extent of the supplementary motor area displacement correlated with the degree of subcortical brain damage detected by DT MRI, suggesting that structural damage might influence fMRI reorganization in this condition.

Recently, Maleki et al. [65] found that, compared to patients with low frequency of migraine attacks (LF), response to pain in high-frequency (HF) migraine sufferers is significantly lower in the basal ganglia. Surprisingly, this lower response in HF patients was associated with larger volume of the bilateral caudate nuclei relative to LF patients. The same group reported that patients with HF attacks have higher CT in the face of the postcentral gyrus, which correlates with a stronger functional activation, suggesting adaptation to repeated sensory drive. A reduced CT, corresponding to a lower activation, was observed at the level of the cingulate cortex of this group of patients. Significant structural and functional differences (HF>LF) were also observed at the level of the insula, potentially reflecting alterations in affective processing. These results point to differential response patterns in the sensory versus affective processing regions in the brain that may indicate an adaptive response to repeated migraine attacks [2].

Conclusions

Neuroimaging studies have changed the way we understand migraine. Conventional and advanced MR techniques have been applied extensively to the study of patients with this condition, both in the course of an acute attack and during the interictal phases, and such an effort has contributed to improve our understanding of its pathophysiology. Migraine can no longer be considered a purely vascular disorder, but it should be thought as a CNS disease. Moreover, it has become evident that it is not simply a disease of recurrent pain attacks but a process that over time might influence the brain structure and function. Further studies are needed to determine specific biomarkers of migraine and identify new targets for improving effective therapies.

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