Bruno Colombo
Roberto Teggi *Editors*

Vestibular Migraine and Related Syndromes

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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

1

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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 frontotemporal. 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