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Review

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Vestibular Migraine With Brainstem Auras: A Review of Pathogenesis, Clinical Varieties, Abortive and Prophylactic Treatment

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Abstract

Vestibular migraine (VM) is the most common etiology of vertigo in the adults. VM accompanied by brainstem symptoms is not uncommon, but underrecognized so far. It is often misdiagnosed as brainstem infarction. Earlier correct diagnosis could help avoid thrombolysis, intravascular intervention, excessive auxiliary examination, panic and fear, repeated hospitalization, waste of medical resources, early and short-term use of steroid hormone, and antioxidant. Family or sporadic hemiplegic migraine (HM) is a kind of encephalopathy instead of simple hypoperfusion; the pathogenesis, which was not well described, might also account for the neurological symptoms in VM patients. The genomic identification of the migraine could facilitate better understanding on molecular pathogenesis of familial HM. Genetic mutations are believed to be associated with more susceptible alterations of cortical spreading depression in the brain.

Keywords: Hemiplegic migraine; Vertebrobasilar ischemia; Vestibular migraine with brainstem auras; Acute encephalopathy; Abortive treatment; Prophylaxis; Stroke mimic; Thrombolysis

Introduction

Hemiplegic migraine (HM) is a rare subtype of migraine with aura and shows either familial or sporadic occurrence. Both familial HM (FHM) and sporadic HM (SHM) are genetically heterogeneous; majority of them are caused by mutations in *CACNA1A*, *ATP1A2*, and *SCN1A* on rare occasion. The phenotype for FHM is identical to the sporadic type, except for the presence of a first- or second-degree relative also affected [1], which may partly account for the brainstem aura in patients with vestibular migraine (VM). The pathogenesis of HM is still unclear, the clinical presentations vary; it is difficult to diagnose promptly, and treatment needs to be explored further.

VM is the most common neurologic cause of vertigo in adults but remains underrecognized and underdiagnosed. The key to correctly diagnose VM is to identify a relationship between vestibular symptoms and migrainous features, and be aware of the heterogeneity of manifestations of this enigmatic disease [2, 3]. Migraine in patients with acute onset of vertigo, followed by brainstem ischemic symptoms, to our knowledge, has few reports [4, 5]. We herein review the pathogenesis, clinical varieties, abortive and prophylactic treatment of VM.

Mechanisms of Migraine-Related Neurological Dysfunction

Genetic mutation leading to encephalopathy may be the key mechanism in migraine-related neurological deficiency

Several hypotheses for hemiplegic VM had been proposed for the mechanisms and pathophysiological basis of HM, including genetic mutation, hypoperfusion, prothrombotic, oxidative stress, and inflammation.

The identification of the migraine gene mutation may help investigate molecular pathogenesis of FHM [6]. The sensitivity of the brain to cortical depression may be changed due to genetic mutations [7]. The encephalopathy was apt to be triggered in FHM, such as by an uneventful single-dose spinal morphing administration in patients for surgery [8]. Although migraine-related respiratory arrest may result in death while the attack was onset, however, no abnormal findings were discovered from autopsy [9]. It has been indicated that the encephalopathy might be associated with the essential pathophysiology of patients with HM, and the encephalopathogenesis is most likely attributed to hemiplegia as the onset [10].

Several cases of familiar or sporadic migraine with or without aura, experiencing acute encephalopathy, presenting with hemiplegia, consciousness disturbance, fever, progressive

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Table 1. Hemiplegic Migraine and Mutation of Genes

	FHM1	FHM2	FHM3
Chromosome location	19p13	1q23	2q24
Gene	*CACNA1A*	*ATP1A2*	*SCN1A*
Protein	Pore-forming α1 subunit of neuronal Cav2.1 (P/Q type) voltage-gated calcium channels	Catalytic α2 subunit of a glial and neuronal sodium-potassium pump	Pore-forming α1 subunit of neuronal Nav1.1 voltage-gated sodium channels
Location	Both at central synapses and at neuromuscular junction, densely expressed in cerebellar Purkinje cell	During development, predominantly expressed in neurons, but expression shifts to glial cells by adulthood	Expressed primarily on inhibitory neurons
Main function	To trigger the release of neurotransmitters	Utilizes ATP hydrolysis to transport Na^+ ions out of the cell in exchange for K^+ ions into the cell, providing the steep Na^+ gradient for the transport of glutamate and Ca^{2+}. In adults, to modulate the removal of potassium and glutamate from the synaptic cleft into the glial cell	Voltage-gated sodium channels are primarily responsible for the generation and propagation of action potentials in excitable cells
Penetrance	67-89%	63-87%	100%
Type of mutation	Over 50 missense mutations	Over 60 missense mutations	5 missense mutations

FHM: familial hemiplegic migraine.

ataxia, epilepsy, and psychiatric disorder have been reported. Cleves et al reported that siblings with blurred vision and numbness on either side, followed by contralateral headache, unable to answer questions, and with fever, ataxia, developed gradually to lose some memory. *CACNA1A* sequencing showed a mutation in exon 13, designated as A583G (CAA) [11]. Ohmura et al reported a 10-year-old boy with cerebellar vermis atrophy, experiencing dysesthesia, hemiplegia, fluctuating consciousness, intermittent left-sided deviation of both eyes, and fever. A mutation of c.1997C>T (p.T666M) in *CACNA1A* was found in genetic analysis of blood deoxyribonucleic acid (DNA) [1]. Merlino et al reported an 18-year-old case during an attack, experiencing generalized tonic-clonic seizure without gene mutation examination [12].

Mutated genes *CACNA1A*, *ATP1A2* and *SCN1A* encode proteins associated with neuronal voltage-gated sodium, calcium and potassium channels as, well as adenosine triphosphatase (ATPase) [13, 14]. Studies by Ducros et al also found *CACNA1A* mutations in the patients with FHM, who had high variability of symptoms from hemiplegic attacks, atypical attacks with severe diffuse encephalopathy persistently to then of recovery [15].

The mutated FHM genes code for ion transport protein that have associated with disturbed ion homeostasis, which is triggered by environment, causing episodes of headache with neurological deficits [16].

The *CACNA1A* (FHM1) gene encodes the α1 subunit of Cav2.1 (P-Q-type) Ca^{2+} channels that modulate neurotransmitter release. *CACNA1A* is expressed at the neuromuscular junction and throughout the central nervous system, particularly in cerebellar Purkinje cells, enhancing neuronal excitability and increasing neuronal Ca^{2+} influx. Missense mutations in the *CACNA1A* gene account for approximately 50% of all FHM cases. Mutation of *CACNA1A* S218L, causing special attention to "early seizures and cerebral edema after trivial head trauma (ESCEATHT)", may be severe and sometimes fatal [17, 18]. Over 25 HM-associated *CACNA1A* mutations are identified, representing a broad clinical spectrum [19].

The FHM2/SHM2 *ATP1A2* gene on chromosome 1q23 encodes the α_2-subunit of a Na^+/K^+-ATPase, which exchanges Na^+ ions for K^+ ions, creating a steep sodium gradient that facilitates removal of K^+ and glutamate from the synaptic cleft into glial cells. Nearly 50 *ATP1A2* mutations have been discovered. In contrast to FHM1, FHM2 rarely has progressive cerebellar signs. The FHM3 *SCN1A* gene on chromosome 2q24 encodes the α-subunit of voltage-gated Na^+-channel, which is expressed on inhibitory central neurons. The gene penetrance has wide varieties in FHM1 and FHM2, but FHM3 have thus shown 100% penetrance [20]. Mutations in *ATP1A3* gene were found in over 70% of alternating hemiplegia of childhood (AHC) cases occurred before the age of 18 months [21]. Table 1 summarizes the HM and mutations of genes of FHM1, FHM2, and FHM3 [17, 18, 22-24].

Glutamate is the major excitatory neurotransmitter in the central nervous system; and altered brain excitability caused by disturbed glutamate homeostasis plays a role in various paroxysmal neurological disorders. Specifically, glutamate is a potent trigger of cortical spreading depression (CSD); and imbalance of glutamate release and clearance has been shown to underlie HM, a severe monogenic subtype of migraine with transient hemiparesis and other aura symptoms. EAAT1 is a glial glutamate transporter that contributes to glutamate clearance in the cerebral cortex, cerebellum, diencephalon and caudal linked to several neurological disorders. In 2005, Jen et al reported a *SLC1A3* missense mutation in a child with a complex syndrome comprising episodic ataxia, prolonged hemiplegia with migraine and seizures [25]. Kovermann et al identified a novel heterozygous *SLC1A3* mutation as c.1159A>C

in a 22-year-old man from Serbia suffered several episodes of severe migrainous headache accompanied by transient neurological deficits [26].

Episodic ataxia type 1 (EA1) is an autosomal dominant K^+ channelopathy which manifests with short attacks of cerebellar ataxia and dysarthria, interictal myokymia, and migraine. Episodes can be triggered by emotional or physical stress, startle response, and sudden postural change or fever. Maria et al describe a 31-year-old man displaying long-lasting attacks of jerking muscle contractions associated with hyperthermia, severe migraine, and a relatively short-sleep phenotype. A single nucleotide change in *KCNA1* (c.555C>G) was identified that changes a highly conserved residue (p.C185W) in the first transmembrane segment of the voltage-gated K^+ channel Kv1.1. A number of studies have shown that heteromeric Kv1.1/Kv1.2 channels play an important role in the control of neuronal excitability, action potential propagation and synaptic transmission. Headache is also a symptom overrepresented in EA1 individuals [27]. Vries et al identified a missense C186S mutation in 20 patients with EA2 in whom no mutations were found in the *CACNA1A* gene, and a mutation in the *SLC1A3* gene encoding the glutamate transporter EAAT1 was identified. The mutant EAAT1 showed a modest but significant reduction of glutamate uptake [28].

Perfusion changes during the attacks of migraine with neurological symptoms

Migraine with or without aura will experience long lasting hypoperfusion. A 34-year-old female patient was present with migraine headache of right eye and right-sided headache after visual aura with phosphenes in the left visual field. Diffuse narrowing of the retinal vessels was detected by optical coherence tomography angiography imaging. Perfusion weighted imaging at the onset of aura revealed a remarkable drop in relative cerebral blood flow in the occipital cortex [29]. Vallabhaneni et al reported a 48-year-old female patient with migraine accompanying by blurred vision, diploma, and dizziness. Duration one episode, magnetic resonance imaging (MRI) showed a restricted diffusion on diffusion weighted imaging (DWI) in the left cerebellar hemisphere and subtle diffusion restriction in contra-cerebellar hemisphere. An angiogram of the head and neck computed tomography (CT) scan did not find any abnormality. MRI after 56-day follow-up revealed normal image. Therefore, it was proposed that spreading hypoperfusion is the most likely etiology [30].

Hypercoagulability and inflammation

A study found that the large mean platelet volume (MPV) contained 5-hydroxytryptamine (5-HT) in their dense granule, representing the activity of platelet, associated with prothrombotic and migraine headache [31]. Migraine is considered an independent risk factor for vascular dysfunction in central nervous system, especially in the young to mid-aged women. Abnormality in cerebral vessels during attacks included oligemia, activation of clotting system, and vasoconstriction [32]. Red blood cells (RBCs) may function as free radical scavengers preventing oxidative damage, and unique cellular indicators during inflammatory pathogenesis. Free radicals lead to oxidative damage of RBCs, disturbance of the phospholipid bilayer membranes, particularly the asymmetrical distribution of lipids between inner and outer bilayer. Villiers et al observed the hypercoagulability contributed by macrocytosis, poikilocytosis and eryptosis in the migraineurs, and aberrant fibrin polymerisation kinetics [33].

Besides the hypothesis of migraine as a systemic vascular inflammatory disorder characterized by endothelial dysfunction, chronic inflammation may result in an excessive burden of oxidative stress, and cellular dysfunction is critical in the attack of HM. In a case of 10-year-old boy with encephalopathy, high-dose methylprednisolone was administered. His fever subsided, but the hemiplegia, consciousness loss and seizures were improved immediately after treatment with edaravone [1]. Regional activation of inflammation [34], excessive release of neuroexcitatory amino acids [33], and vasogenic edema [35] lead to the disruption of the blood-brain-barrier, which causes brain edema and affects the neuronal excitability. Initial hypoperfusion took place in the affected areas, accompanying by various neurologic symptoms [36, 37]. Residual hypoperfusion in the region may persist a long time in interictal period [33].

Relationship of PFO with migraine

Recently, patent foramen ovale (PFO) closure for cryptogenic stroke was accidently discovered in some patients with aura whose migraine episodes significantly decreased, suggesting micro-embolism might trigger migraine with visual aura. Richmond et al described a 38-year-old male with paroxysmal atrial fibrillation was treated with trans-septal cryoablation, and developed isolated monocular aura phenomena afterwards, however, disappeared right after intervention. Right-to-left shunts led to vasospasms and spreading depression of retinal neurons and cerebral cortical, attributing to exposure to certain venous factors and microembolism due to loss of pulmonary clearance. Cerebral microemboli and vasoactive chemicals such as serotonin trigger CSD were observed in mouse model, yet encephalopathy associated with neurological deficits has not been reported in the literature [38].

It is complicated to identify the relationship between PFO and migraine type headache [39-41]. The improvement of symptoms in the patients with migraineurs post-PFO closure was found unreproducible in randomized studies with a short-term follow-up [42, 43]. The MIST (migraine intervention with STARFlex technology) study did not achieve the endpoint of migraine loss in 6 months, but decreased migraine frequency was found in the PFO closure group. Finally, in the PRIMIUM (percutaneous closure of PFO in patients with migraine) study [44], more than half reduction in migraine attacks as the primary endpoint was achieved in the entire cohort but did not reach in the migraineurs with aura. In a retrospective study by Ben-Assa et al, the absence of residual right-to-left shunt may predict reduction in migraine burden in patients undergoing PFO closure during a long-term follow-up [45]. Strikingly, migraine usually

initiates from childhood, adolescence, or early adulthood but the frequency reduces over time until advanced years [46].

Stimulation of neurovascular mechanisms

Guyuron et al first described in 1999 that corrugator supercilii muscle resection for forehead rejuvenation surgery could improve or cure migraine headache in cosmetic patients. While another study reported cessation of HM aura with greater occipital nerve (GON) blockade. The peripherally injected botulinum toxin also can be abortive treatment of the attack of migraine aura and headache. Nerve compression in some specific areas appears to play a pivotal role in triggering migraine headache episodes. Four major trigger zones were described as follows: 1) frontal: supraorbital and supratrochlear nerves of the trigeminal nerve; 2) temporal: zygomatic-temporal branch of the trigeminal nerve; 3) endonasal: trigeminal end branches; and 4) occipital: GON. Two more trigger sites were reported as well, including the auriculotemporal nerve and lesser occipital nerve (LON). These indicate that the trigeminovasculature or cervical nerve vasculature plays a pivotal role in triggering or in driving the episodes [47-49]. Neuroanatomic findings showed that a number of bidirectional anatomic pathways and feedback loops were recognized; for instance, trigeminal autonomic loop is mainly triggered by trigeminal activation and parasympathetic activation of superior salivatory nucleus. The activity at the trigeminal nucleus caudalis (TNC) can be modulated by blocking GON, leading to termination of CSD and aura symptoms and headache [50].

Migraine headache patterns seem to be localized at the referred pain site due to stimulation of meningeal and cerebral arteries; similarly, as observed in the patients waking up during brain surgery, these pain-sensing structures of anterior cranial fossa and middle cranial fossa are innervated by trigeminal fibers, and posterior cranial fossa is innervated by cervical nerve 1 - 3. Calcitonin gene-related peptide (CGRP) levels are elevated while the patients experienced migraine attacks originating from trigeminal nerve. It is well-known that CGRP is a strong vasodilator in the periphery and a modulator of nociceptive activity centrally. However, on the second order neurons, CGRP can enhance glutamatergic activity and nociceptive activation, thus leading to sensitization of trigeminal system in migraine patients. CGRP is a neuropeptide composed of 37 amino acids. It is involved in the pathophysiology of migraine by regulating nociception in trigeminal vasculature [13, 51].

Diagnosis of VM With Brainstem Auras

HM is uncommonly characterized with aura. HM is usually present in a familial or sporadic manner. Repeated attacks of headache and hemiplegia with an autosomal dominant trait frequently occur in the patients with FHM; on the other hand, those patients with SHM have similar manifestation only for those with family history [1, 51].

Systemic studies on VM date back to the most recent three decades. The diagnosis of VM is largely dependent on the identification of vestibular symptoms related to migrainous characteristics. Heterogeneous clinical symptoms have been addressed nowadays [2, 52]. Migraine can last forever as a hypersensitive symptom. The cycling onsets are present during the intervals of peak attacks, resulting in significantly variable impact on their manifestation. It may be helpful to explain why the patients have persistent dizziness and motion intolerance of VM patients during vertigo attacks. A follow-up study showed that approximately 90% of the patients still suffered from recurrent vertigo after the first diagnosis was made. All patients except one case still experienced migraine headache [3].

The incidence of VM is about 2% overall in adults [53, 54], and the majority are female patients at the age of 30 - 40 years old. The patients used to have a history of migraine headache and motion sickness before occurrence of vestibular symptoms, especially those with family history of migraine [2]. The relationship between migraine and dizziness was initially studied by Edward Living in 1873. It has shown that migraine in the vertigo patients is much more prevalent than in those healthy individuals [55-57]. The incidence of both migraine and vertigo occurrence is about 3% [58]. A study including 57 VM patients indicated that about two-thirds of patients had a central vestibular system deficit, and one quarter of patients presented with a peripheral vestibular system deficit. The flocculus and paraflocculus are essential to control vestibular nuclei and oculomotor functions in terms of the linkage with the migraine pathway. Migraine-like phenomenon can be induced by stimulating the trigeminal ganglia in rat model, simultaneously, leading to partial inhibition of parafloccular Purkinje cells. This inhibitory effect is likely a critical factor to induce VM. Evidence has shown that calcium channel is important to maintain migraine pathogenesis, thus expressing in high levels in Purkinje cells [59, 60].

Different vestibular symptoms in VM patients may coexist, for example, spontaneous vertigo, triggered vertigo, positional vertigo, head-motion dizziness and so on. The term "vestibular migraine" was first coined in 1999, and then the International Headache Society and Barany Society (IHSBS) published consensus criteria for the diagnosis of VM in 2012 [22]. "Vestibular migraine" was adopted by the International Classification of Headache Disorders (ICHD) [61].

A cerebral MRI is recommended in every new HM patient to exclude other (structural) causes, especially when aura symptoms always occur on the same side. Permanent CT or MRI abnormalities are rare in HM. Cerebellar atrophy has been described in FHM1 patients with progressive cerebellar ataxia. In a few cases, cortical cerebral atrophy or diffuse cortical and subcortical hyperintensities on T2-weighted MRI were found. During and shortly after HM attacks, reversible CT or MRI abnormalities have been described, which can be linked to both vascular and neuronal mechanisms. Most often reported is diffuse (cortical) edema of the hemisphere contralateral to the motor deficit [20].

Differential Diagnosis

Migraine-related hemiplegia may be present with stroke-like

episode and trigger "thrombolysis alert", when the patient was taken to hospital within 4.5 h; and endovascular intervention will be considered when the onset-to-door time is within 6 h, if the neurologist and the family neglect the migraine, especially the first episode of neurological deficits [62]. But the migraine-related neurological deficits signs were a kind of encephalopathy, not just ischemia, thrombolysis will not benefit the outcome of the patient, and computed tomography angiography (CTA) usually was normal. The prevalence of stroke mimics varied greatly from 9% to 30%, and about 15% of these patients received intravenous thrombolysis (IVT) [63]. Thrombolysis with alteplase or tenecteplase appears to be safe [64, 65], with a rate of symptomatic intracranial hemorrhage as low as 1% [66, 67]. To reduce potential risk from essential diagnostic procedures, Khan et al proposed a theoretic model with a scoring system to identify stroke mimics parameters. A number of variables such as age, presence of migraine, epilepsy, and psychiatric illness have been applied as a scoring system. It is recommended performing a rapid-sequence MRI for those patients whose scores are higher than 5.0, to rule out a stroke mimic [64].

The most important differential diagnosis for VM with brainstem auras is posterior circulation ischemia. First of all, the syndrome of vertebrobasilar ischemia or posterior circulation stroke has specific clinical features and can be classified according to the location. The clinical symptoms and signs of migraine-related encephalopathy did not confer to any kind of the syndrome. Secondly, the patients did not response to thrombolysis but response to corticosteroids. Thirdly, the MRI rarely found abnormal lesions in brain with serious hemiplegia, and the patients often presented transient consciousness disturbance and loss of memory of the entire event after recovery. Finally, the patients with posterior circulation ischemia often have multiple risk factors of atherosclerosis.

Another important differential diagnosis is autoimmune encephalitis, in which the specific autoimmune antibodies can be found in serum and/or cerebrospinal fluid, such as anti-N-methy-D-aspartate (nmda) receptor [68], and high titers of antithyroid antibodies leading to Hashimoto's encephalopathy [69], anti-GABA-A receptor encephalitis, anti-glycine receptor encephalitis, basal ganglia encephalitis, anti-GAD encephalitis, or herpes simplex virus encephalitis, and enterovirus encephalitis [70].

For differential diagnosis, focal seizures are not considered at the first place, because in VM, headache is usually the main sign, whereas there are very few symptoms related to brainstem in focal seizures.

Headache and neurologic deficits with cerebrospinal fluid lymphocytosis (HaNDL) syndrome is a rare stroke mimicker characterized by moderate to severe headache temporally associated with transient neurologic deficits, typically ascending hemiparesis, hemisensory disturbance, and/or aphasia. Cerebrospinal fluid studies reveal a lymphocytosis and elevated protein. Episodes recur over a period no longer than 3 months. Migraine is almost life time trouble. Leptomeningeal enhancement on MRI was found. Spreading depression (CSD) triggered by a preceding or concurrent viral illness and leading to transient vasomotor changes has been suggested [71].

In mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS), MRI is abnormal in most cases, and complicated with other symptoms; its incidence is significantly lower than migraine with aura.

Mitochondrial encephalopathy involves respiratory chain due to mutation of nuclear and mitochondrial DNA (nDNA, mtDNA) resulting in multiple system disorders, most often included myopathy (weakness, exercise intolerance, ptosis, ophthalmoplegia), brain (stroke-like episodes, migraine-like headache, seizure, psychiatric), lactic acidosis, heart failure, diabetes, and hearing loss; most of them have maternal inheritance, and all differ from VM with brainstem auras. Muscle biopsy in patients finding mitochondrial encephalomyopathy (MERRF) was the golden standard for the diagnosis of mitochondrial disease [72].

Genomic diagnosis of mitochondrial disorders is key to a definite diagnosis [73]. In seven progressive external ophthalmoplegia patients, six levator palpebrae (LP) muscle tissue samples were available for mtDNA testing; three revealed single mtDNA deletions, while one showed multiple mtDNA deletions attributable to *POLG1* gene defects [74]. The patients with mtDNA mutation were definitely diagnosed as mitochondrial disease. Patients with MELAS, with m.3243A>G mutation, had a higher prevalence of electrocardiogram (ECG) abnormalities [75].

AHC is a rare neurodevelopmental disorder, first appears as a rule before the age of 1.5 years, and consists of episodes of hemiplegia, dystonia, quadriplegia, and abnormal eye movements. Developmental delay and epilepsy occur in about half of patients, and it can be found in about 75% of patients a mutation in the *ATP1A3* gene. Some of these patients have other syndromes, such as rapid-onset dystonia parkinsonism (RDP), CAPOS/CAOS syndromes (cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural deafness), relapsing encephalopathy with cerebellar ataxia (RECA), and epileptic encephalopathy [76].

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL) is the most common heritage cause of small vessel disease, in which *NOTCH3* is the gene involved. It encodes a transmembrane receptor primarily expressed in systemic arterial smooth-muscle cells, which alters the number of cysteine residues in the extracellular domain of NOTCH3, and accumulates in small arteries of affected individuals. This disease is characterized by five main symptoms: migraine with visual aura, subcortical ischemic events, mood disturbance, apathy, and cognitive impairment. In early stages of CADASIL, multiple lacunar infarcts and extensive leucoencephalopathy can be found in MRI. The neurological deficits were not followed by migraine, and vascular dementia was early onset during attacks of ischemic events without symptoms of vertigo or brainstem signs, all of which were different from VM with brainstem auras [77, 78].

Abortive and Preventive Treatment

Although HM-related encephalopathy appears to be self-limited in most cases, the signs and symptoms do not necessar-

ily completely recover, or can even be fatal in some patients [79].

Abortive and prophylactic treatment of migraine

Treatment principles of headache include rescue approach, change lifestyle, nonpharmacologic or pharmacologic migraine prophylaxis, and combination therapeutics.

The patients are highly encouraged to get advice from physicians on how to change lifestyle to control migraine attacks, such as to avoid trigger, sleep better, improve eating habit, do exercise and maintain relax [31, 80-82]. Prophylaxis medications, e.g., venlafaxine, propranolol, topiramate, valproid acid, lamotrigine, and acetazolamide have been tried. Nonpharmacologic approaches including riboflavin, magnesium, butterbur extract, and coenzyme-Q10 have shown effective for migraine prevention and perhaps effective for VM as well [2].

Some patients need prophylaxis according to the attack frequency and severity of the episodes. The fluctuations of disease attacks of most patients may relieve over time. The patients should be encouraged to develop a self-care.

Migraine affects about 15% of the population [83]. Approximately 45% of migraine patients developed into chronic state, with neurological deficits, especially those with severe symptoms like sequela, who need preventive treatment [84]. Non-steroidal anti-inflammatory drugs (NSAIDs), usually known as cyclooxygenase (COX)-1/COX-2 inhibitors, could be effective in the patients with mild to moderate migraine headache; therefore, NSAIDs are wildly applied to treat migraine clinically [85-88], to prevent the progression from episodic to chronic migraine [89, 90]. Celecoxib, a selective inhibitor of COX-2, has been indicated to reduce CSD-induced dural artery dilatation and activation of dural and pial macrophages [91]. Sumatriptan is a serotonin 5-HT1B/1D receptor agonist approved in the USA for the acute treatment of migraine with or without aura in adolescents and adult [92], acting as abortive drugs which are used at the initial stage of headache. In patients with mutations of *CACNA1A* gene, which cause a calcium channel disorder and HM, acetazolamide or calcium channel blockers verapamil should be considered for personalized therapy [36, 80]; but caution should be taken to use verapamil or acetazolamide due to their potential cardiac side effect. Erenumab and galcanezumab are the fully humanized monoclonal antibody specifically targeting CGRP [13, 93].

Treatment of VM

For rescue treatment of VM, triptans, vestibular suppressants, antihistaminic drugs, such as diphenhydramine, dimenhydrinate, and meclizine and/or antiemetic agents,metoclopramide and other antidopaminergic drugs can be selected. Patients with chronic attacks and severe nausea are encouraged to be treated in hospital by intravenous infusion of antiemetics and fluid replacement. Methylprednisolone is sometimes required as well [94-96].

For acute encephalopathy with fever, confusion, seizures, and hemiplegia anti-inflammation such as steroid, anti-oxidative, and mannitol can be used to reduce edema, but thrombolysis is resistant in migraine-related thromboembolism. Antivasospasm can improve the hypoperfusion. Another abortive method is to block trigeminal nerve and GON, and LON on the fascia of head, where type A botulinum toxin is injected.

The prophylaxis was also necessary and important for frequent occurrence. Without double-blinded or randomized controlled clinical trials [97], treatment strategies are precisely recommended to those with migraine [98, 99]. Beta-blockers, valproic acid, and lamotrigine have been used as prophylactic treatment for VM [100], as well as tricyclic antidepressants and topiramate [101], and calcium-channel blockers [102]. Until recently, flunarizine [103], propranolol and venlafaxine [104] were being studied in active-control or open-label clinical trials. Evidence has shown that metoprolol was tolerated well, but there was no benefit when compared to placebo in controlling the incidence of vertigo attacks [105].

Surgical approach for migraine

Studies done by Raposio et al included the patients with chronic migraine or tension-type headache with occipital headache. At early stage, local compression can relieve the pain; however at later stage of migraine, nerve compression after vessel ligation checked by a handheld Doppler became tender in this site. In those cases without vascular compression, the occipital, trapezius, splenius capitis, and semispinalis capitis muscles were undermined along with the nerve course. According to the follow-up, over 90% of the patients who had no relief of symptoms were found to have positive response. After receiving contralateral secondary surgery or other trigger point surgery, all patients achieved complete relief from migraine [48]. Two cases treated with GON blockade bilaterally by lidocaine and triamcinolone resulted in symptomatic disappearance without relapse for several weeks [51].

Conclusions

To sum up, migraine is nearly a life span disorder, eventually leading to debilitating condition, poor life quality and low work productivity of the patients. Complications of hemiplegia and vertigo increase the risk of encephalopathy, hypoperfusion and thromboembolism. Despite a benign condition without overt neurological sequela in most migraine cases, detailed assessing may find milder objective signs, like digiti quinti signs (DQS) on the paresis side [106]. Extensive profound evaluation revealed injury in visual, vestibular [107], cognitive [108], motor [109], and various cortical [110] abnormalities in HM patients. Atypical variants are able to present with various symptoms, even respiratory arrest leading to death [9, 14]. Structural changes have been observed afterwards in the white [111, 112] and gray matters [113].

This review calls attention for the risk of migraine imposed on the patients; and it is emergent to propose proper

prophylaxis with or without drugs, or surgery for the patients according to individual severity of the sequela and the frequency of attacks.

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None to declare.

Author Contributions

AJZ conceived the article theme and wrote the manuscript; AYZ participated in revising the manuscript and retrieval of literature; LZG was involved in the manuscript preparation and revising the article; LZ and ANW were involved in the literature retrieval and data preparation. All authors have read the final version of manuscript and approved the publication.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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