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REVIEW

Migraine with Brainstem Aura Accompanied by Disorders of Consciousness

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Abstract: Migraine with brainstem aura (MBA) accompanied by disorders of consciousness (DOC) is a rare subtype of migraine. The pathophysiology of MBA with DOC has not been elucidated yet. Some patients have a family history of migraine, and women are more affected than men. The aura symptoms are diverse; however, when MBA is combined with DOC, the clinical manifestations are more complicated. Coma is the most common clinical manifestation. The overall duration of the patient's DOC is short and can often return to normal within half an hour. Headache often occurs after regaining consciousness and can also occur at the same time as DOC. The most common headache is located at the occipital region. Although DOC is reversible, considering the current small number of cases, we still need to improve our understanding of the disease to avoid misdiagnosis. The MBA patient's electroencephalogram and cerebral blood flow perfusion may have transient changes and may return to normal in the interictal period or after the DOC. Although triptans have traditionally been contraindicated in MBA under drug instructions, the evidence of basilar artery constriction, as postulated in MBA, is lacking. Lasmiditan is currently the first and only 5-HT 1F receptor agonist approved by the Food and Drug Administration. The calcitonin gene-related peptide receptor antagonists and monoclonal antibody therapies may be the most promising for future consideration. Here, the pathophysiology, clinical manifestations, diagnostic tools, and treatment progress for MBA with DOC are reviewed.

Keywords: migraine, brainstem aura, coma, calcitonin gene-related peptide

Introduction

Migraine with brainstem aura (MBA) is a rare migraine subtype[1–15] and accounts for about 1.5% of headache and 6.6–10% of migraine with aura.[16,17] The aura features include vertigo, dysarthria, diplopia, tinnitus, ataxia, and disorders of consciousness (DOC).[18] Hiccups[19] or exploding head syndrome (EHS)[14] may also occur in some patients. In 1961, Edwin reported for the first time a subtype of migraine with brainstem dysfunction and proposed the concept of basilar artery migraine.[20] Since then, impairment of consciousness in migraine was considered as a prominent aura symptom.[1] At present, Headache Classification Committee of the International Headache Society (IHS) has renamed basilar artery migraine to MBA.[18] It is notable that the complex symptoms and signs of DOC can negatively affect the differential diagnosis for the DOC-accompanied primary disorder.[21] Therefore, more attention should be paid to achieve early recognition, rapid diagnosis, and timely treatment.

Pathophysiology of MBA with DOC

The pathophysiology of MBA has not been elucidated yet.[22] It mainly includes three hypotheses: vasomotor dysfunction,[23] cortical spreading depression,[24,25] and

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neurogenic inflammation.[26–28] Regarding the MBA with DOC, abnormal neurotransmitter secretion may cause reticular activating system (RAS) dysfunction.[5,10] Increased secretion of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) in migraine patients[29] may be involved in the dysfunction of RAS, thereby changing the state of consciousness.[30] The hypothalamus plays an important role in migraine. Resting regional cerebral blood flow decreases in the lateral hypothalamus immediately prior to a migraine headache.[31] Moreover, resting functional connectivity strength decreases between the lateral hypothalamus and the pain processing pathways (such as the midbrain periaqueductal gray, dorsal pons, rostral ventromedial medulla, and cingulate cortex) before a migraine episode. Abnormal cerebral cortex function can also cause migraine aura symptoms.[32] Abnormal neural activation within specific consciousness networks, including the prefrontal and posterior parietal cortices, can lead to the alteration of consciousness. Most MBA with DOC patients have a family history of migraine. A variety of mutations in genes (such as *CACNA1A, ATP1A2, SCN1A, KCKN18, PRRT2*, and *CSNK1D*)[33] and rare functional gene network abnormalities (such as thyrotropin-releasing hormone receptor and oxytocin receptor signaling pathways, Alzheimer's disease pathway, serotonin receptor pathway, and general heterotrimeric G-protein signaling pathways) are related to migraine.[34] However, there are no reports of genetic susceptibility in patients with DOC.

The etiology of MBA with DOC is unclear; therefore, patients can only avoid exposure to MBA with DOC-inducing factors to reduce the frequency of attacks. The most common predisposing factors[17] are strong emotional stimulation and sleep disturbance, followed by weather changes, direct sunlight, cold air, high-intensity stress, alcohol consumption, and fatigue.

Clinical Manifestations

The aura symptoms of MBA are diverse, and when MBA is combined with DOC, the clinical manifestations are more complicated. In this review, we used PubMed, Scopus, Web of Science, and Google Scholar to collect case reports of migraine with DOC from 1961 to 2020 (Table 1).[1–15] To improve the recall ratio of the literature, we used different search terms besides "migraine with brainstem aura" (including previously used terms: "basilar artery migraine", "basilar migraine", or "basilar-type migraine"). Then, we review the relevant literature to further determine whether there was a MBA with DOC. We found that only five cases (5/27, 18.5%) meet the current diagnostic criteria according to the third edition of the International Headache Classification (ICHD-3).[18] This was related to the update of the diagnostic criteria released in 2018. However, this cannot accurately calculate the incidence of MBA with DOC.

Aura Symptoms

The premonitory symptoms of migraine include, among others, blurred vision, distorted vision, flashing light, nausea, vomiting, photophobia, and sound fear; these can occur several hours to several days before the onset of migraine,[35] and usually last no more than one hour.[36] The typical aura symptoms of MBA include vertigo, dysarthria, diplopia, tinnitus, ataxia, and/or DOC, with the most common being diplopia, followed by vertigo, tinnitus, ataxia, and dysarthria.[17] Notably, motor and retinal symptoms are not considered aura symptoms of MBA according to the ICHD-3 criteria released in 2018.[18] MBA diagnoses previously reported in the literature may be outdated according to the current diagnostic criteria (Table 1). Most patients have difficulty in accurately describing the duration of aura symptoms due to their discomfort. The duration is mostly estimated by the time periods in medical records. The aura symptoms can be short for some patients (few seconds), while for most of them, the duration ranges from a few minutes to 30 minutes. The longer aura durations reported, ranged from several hours to days (Table 1).

Disorders of Consciousness

Drowsiness, stupor, and coma are the main terms describing a decreased level of consciousness in MBA with DOC patients, with coma being the most common. The duration of DOC can range from a few seconds[14,15] to two weeks.[7] The majority of patients gradually regain consciousness within a few hours; most commonly within half an hour. In coma patients, DOC lasts from a few seconds to a few minutes (Table 1). In general, the duration of DOC in MBA patients is short, and consciousness levels can often return to normal within half an hour.

Headache Characteristics

Headache often occurs after regaining consciousness or at the same time as DOC.[2,13] Headaches are frequently severe, accompanied by unbearable, throbbing pain. The most common type of headache is the occipital. About half of the patients have headache symptoms relieved within

Table 1 Previously Diagnosed MBA with DOC Cases

Author/ Date	Gender/ DOC Age	DOC/Duration	Brainstem Aura	Retinal Aura	Other Aura	Aura Duration	Accompanying Symptoms	Headache Location	EEG	Family History
Bickerstaff[1] 1961	F/14	Coma/2 min	No	Blurred vision, flashing light, blindness	Hands and feet tingling	NA	Vomiting	Occipital	Normal	Yes
	F/14	Sopor/30 min	Vertigo, ataxia	Visual distortion, blindness	No	15–30 min	No	Occipital	Normal	Yes
	F/12	Coma/2 min	Vertigo, ataxia	Visual discoloration	Body numbness, hands and feet tingling	5–20 min	Vomiting	Occipital	Normal	NA
	F/15	Coma/1 min	Vertigo, tinnitus	Flashing light, blurred vision	No	5 min	No	Occipital	Normal	Yes
Lee[2] 1977	★F/7	Coma/2 h	Vertigo, diplopia, ataxia	No	No	NA	Mental disorder, vomiting	Left side	Normal	Yes
	M/14	Stupor/3–18 h	Vertigo, ataxia	Blurred vision, flashing light, amaurosis	No	6 h	Vomiting, confusion	Frontal	Excess slow activity	NA
	F/17	Stupor-coma/2 d-3 d	Vertigo, ataxia	Left homonymous hemianopia	Hysteria	5 d	Photophobia, vomiting	NA	Normal	NA
	F/29	Coma/2 h	No	Left homonymous hemianopia	Cheeks and mouth numbness	NA	Left ptosis, pupillary dilatation	NA	Normal	NA
	F/25	Stupor-coma/2 h-5 d	Dysarthria, ataxia	Blurred vision	No	1–3d	Vomiting	Unilateral or bilateral	Normal	NA
	F/44	Drowsiness-coma /minutes-24 h	Diplopia, ataxia, dysarthria	Blurred vision	No	Several minutes	Nystagmus	Occipital	Normal/excess slow waves	NA
Hockaday[3] 1979	M/1 $\frac{9}{12}$	Drowsiness/30 min-hours	Dysarthria	No	Tingling and weakness	Hours	Vomiting	NA	Normal	Yes
	M/5	Coma/1 min	Ataxia	Blindness	No	35 min	Vomiting	NA	Normal	Yes
Smith[4] 1989	F/14	Coma/1 min	Vertigo	Blurred vision	No	Seconds	Photophobia	Occipital	Normal	Yes
Frequin[5] 1991	M/25	Coma/10 d	Vertigo, dysarthria	No	Left hemiparesis	Several hours	Abdominal discomfort	Occipital	Suppression-burst pattern	NA
Ganji[6] 1993	M/54	Coma/24 h	No	No	No	NA	No	Occipital	Slow waves	NA
Muellbacher[7] 1994	★F/35	Drowsiness/NA	Vertigo, dysarthria, ataxia	No	Dysesthesias of both hands and feet	NA	Nausea, vomiting, photosensitivity	Occipital, frontal	Slow waves	Yes

(*Continued*)

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Table 1 (Continued).

Author/ Date	Gender/ DOC Age	DOC/Duration	Brainstem Aura	Retinal Aura	Other Aura	Aura Duration	Accompanying Symptoms	Headache Location	EEG	Family History
Maytal[8] 1998	M/17	Drowsiness/24h	Vertigo, dysarthria, ataxia	Blurred vision	Perioral and fingers numbness	Several hours	No	Left posterior	Slow waves	NA
Li[9] 2011	M/10	Coma/5–30 min	Dysarthria, diplopia, vertigo	Flashing light	No	30 min-6 h	Nausea, photophobia, phonophobia	NA	Slow waves	Yes
	★F/8	Coma/10 min-2 h	Vertigo, diplopia, hypacusis, ataxia	No	No	10 min	Photophobia	Temples, forehead	Normal	NA
Marsala[10] 2012	F/16	Drowsiness/ several hours	No	Left lateral homonymous hemianopsia	No	10 h	Nausea, vomiting	Right frontal parietal-occipital	NA	Yes
Inoue[11] 2013	★M/6	Coma/30 s-1 min	Vertigo	No	No	Several hours	Nausea, vomiting, intense fear	NA	Normal	Yes
Nesbitt[12] 2016	F/41	Hypersomnia/16 h	Diplopia, ataxia	Micropsia, macropsia	Bitter dysgeusia	5–20 min	Photophobia	Left infraorbital	Normal	Yes
	M/12	Drowsiness 12–14 h	Dysphasia, hyperacusis	No	Osmophobia	5 min	Photophobia, phonophobia	Vertex	Normal	Yes
Chou[13] 2018	F/12	Coma/30–60 min	Vertigo, diplopia	Visual disturbance	Lip tingling	10–15 min	No	Occipital	δ wave	Yes
	★F/15	Coma/20–60 min	Diplopia	No	Heat, numbness, tinnitus	5–10 min	No	Occipital	δ wave	NA
Rossi[14] 2018	M/47	Coma/a few seconds	Vertigo, tinnitus, ataxia, dysarthria,	Visual flashing, bilateral visual impairment	Hearing loss, exploding head syndrome	5 s	Nausea, photophobia, phonophobia	Right occipital-parietal, bitemporal	Normal	No
Chirchiglia[15] 2019	M/17	Coma/transient	Vertigo, dysarthria, diplopia	Metamorphopsia	Perceptual distortions	30 min	No	Diffuse or occipital	Normal	No

Note: ★These cases meet the current diagnostic criteria of MBA with DOC according to the ICHD-3 criteria.
Abbreviations: F, female; M, male; NA, not available.

a few hours, while others can relieve headache symptoms by vomiting[1,3,4] or sleeping.[12,13,37]

Diagnostic Tools

Routine blood tests and cerebrospinal fluid tests for MBA with DOC patients yield normal results,[1,3–15,37–39] except for a single case that reported elevated blood ammonia.[2] Abnormalities in MBA with DOC patients are usually reversible, as indicated by studies employing electroencephalogram (EEG), transcranial Doppler (TCD), magnetic resonance imaging (MRI), single-photon emission computed tomography (SPECT) and neuroelectrophysiological examination. In 30% of patients, EEG[2,5–9,13,38] showed a diffuse slow-wave rhythm during a DOC attack; a result commonly obtained from the occipital lobe, followed by the frontal or bilateral temporal lobe. There are no sharp waves, sharp-slow complex waves, or other epileptic waves. EEG becomes normal after recovery or in between the DOC episodes. TCD and MRI can detect basilar artery spasm,[5] abnormal signals in the occipital lobe,[8] and brain stem capillary dilation during the attack.[37] SPECT can detect hypoperfusion of occipital cortex and cerebellar hemisphere.[38] The above abnormal signs are reversible and are related to aura symptoms and headaches. Moreover, studies have shown abnormal brainstem auditory evoked potentials in MBA patients,[6] which are mainly manifested as the prolonged latency between the III–IV waves, and this abnormality can be normal with the recovery of the clinical symptoms. A case report of MBA with vertebrobasilar dilatation (VBD),[39] suggested that VBD may cause chronic pathological changes in the brainstem followed by the corresponding symptoms.

Treatment and Outlook

The main treatments for MBA with DOC aim to relieve symptoms in the acute phase and prevent the recurrence of an attack. Traditional drugs administered during the acute phase include non-steroidal anti-inflammatory drugs,[12] ergotamines[2] and 5-HT receptor agonists.[40] Administration of 5-HT receptor agonists is currently the most common treatment of acute migraine. The 5-HT 1B/1D receptor agonists (triptans) were used to treat MBA patients.[41] Triptans can induce vasoconstriction, which leads to cardiocerebrovascular side effects; therefore, their use in MBA treatment has ceased.[7,9] Although triptans have traditionally been contraindicated in MBA under drug instructions, as the understanding of migraine has evolved substantially, multiple publications have suggested the relative safety of triptans in related patient populations.[42] Evidence of basilar artery constriction as postulated in MBA is lacking. This prohibition of triptans is being reconsidered in the face of evidence suggesting that their use may be safe.[43]

A recent study found that administration of Lasmiditan does not induce the aforementioned side effects; hence, it can be used to relieve the acute symptoms of MBA.[44] It is currently the first and only 5-HT1F receptor agonist approved by the Food and Drug Administration.[45] In addition, analysis of the drug's efficacy found that a dose of 200 mg is more effective than a dose of 100 mg.[46] The prevention of migraine should be combined with non-drug measures,[47] such as avoiding triggers,[17] controlling weight,[48] and maintaining a good lifestyle; cognitive behavioral therapy[49] can also reduce the frequency of migraine attacks. The pharmacological treatments for migraine prevention include β-receptor antagonists,[2] calcium channel blockers,[8,13,15,37,38] anti-epileptics,[37,39] and tricyclic antidepressants.[8,38] Recent studies[50] have found that vitamin B12 and folic acid levels are low in patients with migraine. Thus, vitamin B12 and folic acid supplementation can also play a preventive role in migraine. It was recently found that the calcitonin gene-related peptide (CGRP) is involved in the pathophysiology of migraine.[51] CGRP monoclonal antibodies and receptor antagonists[52] are now used as a treatment for the acute phase and the prevention of migraine.[53,54]

The first-generation CGRP receptor antagonists, gepants, were effective for abortive treatment of migraine.[55] However, they were not fully developed because of hepatotoxicity.[56] Ubrogepant, also known as MK-1602, is an oral, small-molecule CGRP receptor antagonist for acute migraine treatment.[57] A study found that 2 hours after ubrogepant administration, the patient's headache and aura symptoms were relieved.[58] Unlike other gepants, ubrogepant has no hepatotoxicity at therapeutic doses.[59] The most common adverse reactions are nausea, somnolence, and dry mouth. The ACHIEVE II Randomized Clinical Trial study found that both 50-mg and 25-mg doses can significantly relieve migraine.[60] However, only a 50 mg dose helped to reduce the aura. A Phase III, randomized, 52-week extension trial further confirmed the safety of long-term intermittent use of ubrogepant 50 and 100 mg doses.[61] Short-term use of ubrogepant was not related to an increased risk for adverse events.[62] The time course of ubrogepant efficacy was demonstrated out to 48 h,[63] providing evidence of the long-lasting effect. For the subjective feelings of patients,

the potential benefits of ubrogepant could improve patient-centered satisfaction.[64]

Rimegepant received FDA approval in February, 2020, for acute migraine treatment.[65] A randomized, phase III, double-blind, placebo-controlled trial found that 75 mg rimegepant, given via orally disintegrating tablets, were more effective than placebo in the acute treatment of migraine.[66] The 75 mg dose of rimegepant had good tolerance and safety for acute treatment of migraine.[67] The patients were free of pain attack and free from the most bothersome symptom compared to placebo treated patients.[68] For migraine prevention, a recently published Phase 2/3, randomized, double-blind, placebo-controlled trial of oral rimegepant indicated the tolerability was similar to that of placebo, and no unexpected or serious safety issues were noted.[69]

In addition to CGRP receptor antagonists, European headache federation guideline recommended monoclonal antibodies (mAbs) targeting the CGRP receptor (erenumab) and the CGRP (eptinezumab, fremanezumab, and galcanezumab) for migraine prevention.[70] A small sample study found that rimegepant with CGRP mAbs, as preventive treatment, was safe and well tolerated.[71] This suggests that CGRP mAbs combined receptor antagonists have a promising future in the prevention and treatment of migraine. However, it is still necessary to pay attention to the consequences of long-term CGRP blockade, especially when combined with ischemic diseases and when other anti-migraine drugs are used.[72]

In recent years, there have been some potential biomarkers that can be measured in plasma for migraine patients: (1) the abundance of CD4+ effector memory helper T lymphocytes;[73] (2) high serum cystatin C level;[74] (3) elevated plasma CGRP level;[75–77] (4) increased Apo E protein levels;[78] (5) mRNA expression of prostacyclin receptor in peripheral blood lymphocytes;[79] (6) increased interictal vasoactive intestinal peptide level;[80] (7) decreased serum S100B level.[81] Among the abovementioned biomarkers, CGRP seems to be a popular target. However, there were also conflicting studies that found serum CGRP concentration may not be a feasible biomarker for chronic migraine.[82] Unfortunately, there is no research on the MBA with DOC subtype.

Conclusion

The basilar artery is less likely to be involved in the onset of MBA and the third edition of the International Headache Classification (ICHD-3) released by IHS has proclaimed that the term "migraine with brainstem aura" will replace the original term "basilar artery migraine" or "basilar-type migraine".[18] Many MBA patients have multiple typical aura symptoms.[32] At this time, migraine with typical aura and MBA should be diagnosed simultaneously. Notably, many patients exhibiting motor or retinal symptoms were diagnosed with MBA; however, these symptoms are excluded in the diagnostic criteria for MBA and therefore the diagnosis was outdated according to the ICHD-3 criteria (Table 1).

MBA is a rare disease with complex and diverse aura symptoms. Patients may be referred to the relevant departments when the first symptoms of aura start. Coma is the most common clinical manifestation in MBA with DOC patients. Although the overall duration of the patient's DOC is short and can often return to normal within half an hour, it is still necessary for clinicians to improve their understanding of the disease to avoid misdiagnosis. Although triptans have traditionally been contraindicated in MBA under drug instructions, the evidence of basilar artery constriction as postulated in MBA is lacking. This prohibition of triptans is being reconsidered in the face of evidence suggesting that their use may be safe. Lasmiditan is currently the first and only 5-HT 1F receptor agonist approved by the Food and Drug Administration. Calcitonin gene-related peptide receptor antagonists and monoclonal antibody therapies may be the most promising for future consideration.

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Disclosure

The authors report no conflicts of interest in this work.

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