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CASE REPORT

Migrainous Infarction And Cerebral Vasospasm: Case Report And Literature Review

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Abstract: Migrainous infarction (MI) is a rare complication of migraines that accounts for 0.5–1.5% of all ischemic strokes. Although the pathogenesis of MI is still debated, cortical spreading depression and the consequent biochemical cascade and hemodynamic changes are presumed to play an important role. Here we describe a case of MI and systematically review the literature on the complex and possibly bidirectional relationship between migraine and stroke. A 44-year-old female with history of migraine with visual aura presented at the Emergency Department due to a sudden onset of left limb paresis and hypoesthesia. Brain magnetic resonance imaging revealed right fronto-parietal ischemic stroke. Two days after hospitalization, the patient experienced a prolonged visual aura and showed ultrasound evidence of intracranial artery vasospasm. To date, there have been 33 published articles on a total 119 patients with MI, although intracranial vasospasm has rarely been reported. Sustained hyperexcitability of cortical neurons, impairment of γ-aminobutyric acid inhibitory circuitry, altered serotonergic transmission, release of vasoconstrictive molecules, and cerebral blood flow changes have been proposed as pathogenic mechanisms of MI. The present case provides insight into the pathophysiological link between stroke and migraine, thus aiding clinicians in therapeutic decision-making although additional studies are needed to clarify the clinical, neuroradiological, and ultrasound findings that link MI and stroke-related migraine.

Keywords: biochemical change, migrainous cerebral ischemia, pathogenesis, vasospasm

Plain Language Summary

The pathophysiology of migrainous infarction is not well understood, although biochemical cascades and cerebral blood flow changes — namely, arterial vasospasm consequent to cortical spreading depression — may play a critical role. Transcranial color Doppler sonography is a non-invasive and effective tool for the early detection and monitoring of intracranial blood flow changes in migraine and its complications, providing new insight into the pathophysiological link between stroke and migraine.

Introduction

The International Classification of Headache Disorders (ICHD), Third Edition (beta version) defines migrainous infarction (MI) as a stroke developing during an attack of migraine with aura together with neuroimaging evidence of infarction in a relevant area.[1] MI is a rare condition, accounting for approximately 0.5–1.5% of all ischemic strokes, although this fraction may be as high as 13% in young people with cerebral ischemia, with an estimated incidence of 0.8 per 100,000 individuals.[2,3] MI is more common in women and in the posterior

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vascular territory (70.6%) and usually causes small strokes (64.7%), while multiple lesions are observed in 41.2% of cases.[3]

The pathogenesis of migraine-associated cerebral infarction remains unclear, although cortical spreading depression (CSD), biochemical alterations, hemodynamic changes, arterial vasospasm, cerebral edema, and platelet aggregation have been proposed as possible mechanisms.[4,5] Vasospasm is caused by focal or diffuse reversible narrowing of vessel caliber consequent to the contraction of smooth muscle within the artery wall that is detectable by several methods, including transcranial color-coded Doppler sonography (TCCD), computed tomography (CT), magnetic resonance imaging (MRI), and cerebral angiography. TCCD is a portable and non-invasive tool that is useful not only for diagnosis but also for on-site in vivo and real-time monitoring of cerebral blood flow velocity;[6,7] it is used to evaluate acute stroke as well as hemodynamic changes in chronic cerebrovascular disease.[8–10]

Although the temporal and causal relationship between migraine and stroke has been widely documented, the opposite situation—ie, the contribution of stroke to migraines—has rarely been investigated. Here we describe the case of a young woman who first developed ischemic stroke after a prolonged migraine followed by MI soon after hospitalization. Given the rarity and complexity of the clinical presentation, we carried out a systematic review of the literature on MI, paying particular attention to the underlying biochemical changes and relationship among migraine, vasospasm, and stroke.

Case Report

A 44-year-old woman presented at the Emergency Department with a sudden onset of difficulty in verbal expression, left facial tingling, and omolateral arm weakness following a prolonged migrainous attack that had developed two days earlier. She had a history of migraine with aura presenting with visual sensations (oscillopsia and photopsia), although she had also experienced attacks without aura, especially during her adolescence. Since starting prophylactic treatment with flunarizine within the previous 12 months, she had experienced approximately two attacks per month. The current migrainous episode was not preceded by aura, but was more severe than previous attacks and did not respond to oral triptan intake, which was repeated two hours after the first dose. The patient was not taking any oral contraceptive drugs and had no history of other illnesses, except for an episode of paroxysmal atrial fibrillation after percutaneous closure of a patent foramen ovale (PFO) three years earlier that had been successfully treated, without any further evidence of cardiac arrhythmia in repeated electrocardiogram (ECG)-Holter recordings.

At admission, a neurological examination revealed mild paresis and hypoesthesia of the left arm, resulting in a National Institute of Health Stroke Scale (NIHSS) score of 2. Brain MRI showed an acute cortico-subcortical ischemic lesion in the right fronto-parietal region within the vascular territory of the right middle cerebral artery (MCA) (Figure 1A). TCCD revealed increased blood flow velocity in the right proximal MCA segment, with a mean value of 210.2 cm/s (Figure 1B) [cut-off flow velocity for vasospasm: >120 cm/s in the anterior circulation][6,7] and

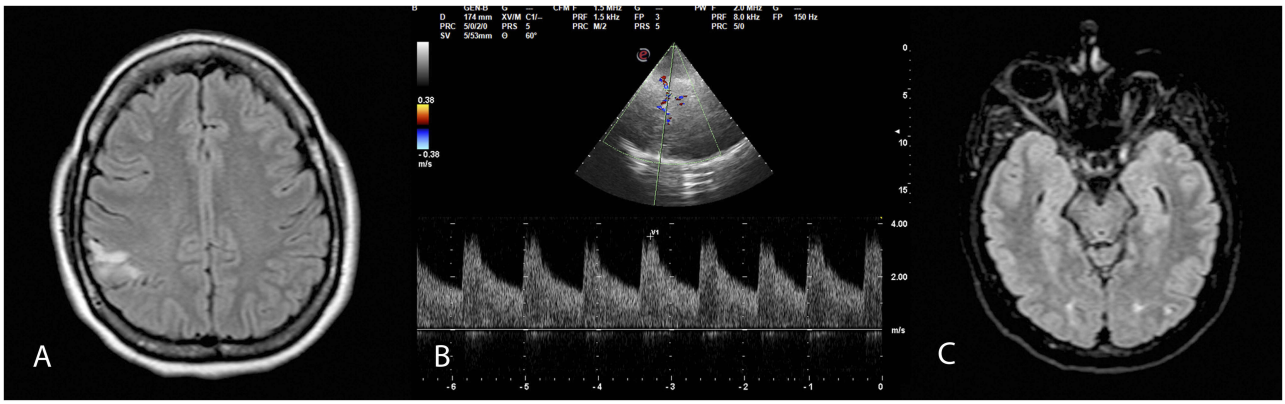

Figure 1 Brain MRI scan of the study subject at the time of admission. (**A**) Right fronto-parietal cortico-subcortical hyperintensity in fluid-attenuation inversion recovery (FLAIR) axial images. (**B**) TCCD revealing increased blood flow velocity (mean value: 210.2 cm/s) with turbulence in the right M1 MCA segment, indicative of vasospasm. (**C**) Control brain MRI showing newly developed bilateral occipital focal hyperintensities in FLAIR axial images, indicative of ischemic stroke.

normal values in the other major brain regions. The Lindegaard ratio (LR) of 5.3 was indicative of vasospasm. Data from instrumental and laboratory tests, including thrombophilia, autoimmunity, and infectious disease screening, ECG and blood pressure monitoring, echocardiography, supra-aortic vessels sonography, and transcranial Doppler bubble test were all unremarkable.

Two days after hospitalization, the patient experienced a prolonged episode of visual aura characterized by a "fortification spectrum" with a "zigzag-type" figure and scintillating scotoma. The control TCCD showed a slight increase in blood flow velocity (mean value of 85.1 cm/s) with turbulence at the top of the basilar artery (BA) segment and a LR for posterior circulation (modified LR) of 2.9. The control MRI revealed two new bilateral lacunar strokes in the occipital lobes (Figure 1C). Treatment with antiplatelet drugs (300 mg followed by 100 mg acetylsalicylic acid)[11] was initiated at admission; paracetamol was used for migraine and verapamil (120 mg three times a day) for migraine prophylaxis and vasospasm. At discharge, the patient was fully recovered from neurological deficits (NIHSS score of 0). A two-week follow-up TCCD examination showed normal blood flow velocity.

Data Source And Selection

The following Medline terms were searched in different combinations: "migrainous cerebral infarction", "migrainous infarction", "acute migrainous infarction", and "migrainous stroke". Original articles, case reports, and case series on adult patients published in English between 1990 and February 2019 were critically analyzed. Full-texts and references from relevant papers were reviewed to identify additional data sources.

Systematic Review

We identified 33 articles including 26 case reports and 7 case series describing a total of 119 patients (41 males and 78 females; mean age: 42.2 ± 18.2 years, range: 15–93 years). Clinical and demographic features and vascular territory of the stroke are summarized in Table 1.

Aura was reported as visual (49.6%), sensitive (15.1%), motor (5.9%), or brainstem (2.5%) disturbances. In some patients, aura symptoms were not specified (30.3%) or were absent (4.2%). Neurological manifestations consisted of visual deficits (57%; as hemianopsia, visual distortions, and phosphenes), sensory disturbances (31.9%; hypoesthesia or paresthesia), motor deficit (28.6%), ataxia (8.4%), dysarthria (8.4%), aphasia (4.2%), diplopia (2.5%), and dizziness and hearing disorders (1.7%). In one report the MI had a fatal course.[12]

A review of neuroimaging correlates of MI revealed lesions in the posterior circulation in 77.3% of cases and in the middle/anterior vascular territory in 22.7%. Intracranial artery evaluation was performed in 22 studies: 13 by MR angiography (MRA; 32 patients), three by conventional angiography (5 patients), one by TCCD (9 patients), and four by more than one technique (4 patients).

Vasospasm was detected in seven studies; the diagnosis was made by MRA in two patients,[12,13] by angiography in three,[14–16] and by TCCD in two.[17,18] TCCD revealed vasospasm in the right MCA (segment M1)[17] in one patient and in both vertebral arteries in another,[18] with evidence of acute ischemic lesion in the corresponding vascular territory. One subject had normal TCCD values[19] and there was no narrowing of the artery lumen or enhanced resistance detected in the other six cases, although the authors did not specify whether this was determined by TCCD or by carotid duplex sonography. The same authors found reduced TCCD values for the breath-holding index in two subjects, indicating an impaired arterial response to vasodilating substances in the affected cerebral territories.[20] PFO was detected in 12 patients in two studies by TCCD.[3,21] One of these articles used MRA or TCCD, but the number of examined patients and obtained results were not specified.[22]

Some investigators have explored the biochemical mechanisms underlying MI (Table 2). One group proposed that migraine-related neuronal injury causes glial cell multiplication and accumulation of protein and fat macrophages, which restricts the motion of water molecules in MRI and yields hyperintensities in the T1-weighted image of the affected cerebral region;[23] this is supported by a recent report.[24] Others have demonstrated cortical hyperexcitability in the primary visual cortex, possibly due to impairment of the γ-aminobutyric acid (GABA)ergic inhibitory network and hypoactivity of thalamo-cortical circuits.[25] Cortical hypermetabolism was also proposed in a case of MI with laminar necrosis.[26] In another patient with MI and vasospasm, a biochemical origin was suggested for the latter based on evidence of enhanced intracellular calcium concentration and vasoactive agents such as serotonin, angiotensin II, hydroperoxides, adenosine diphosphate, and prostaglandins.[16]

Discussion

We described a patient who experienced a first stroke after prolonged migraine without aura. Although this episode

Table 1 Literature Reports Of Migrainous Infarction

Authors and year	Patient n./sex/age	Aura Symptoms	Neurological Features	Stroke Vascular Territory
Mancini et al 2019[27]	1/M/32	Visual, sensitive, motor dysfunction and aphasia	Right hemihyperesthesia and hemiparesis	Left frontal-parietal-occipital regions
Campagna et al 2018[28]	1/F/47	Visual	Left homonymous hemianopsia	Right occipital cortex
Khardenavis et al 2018[29]	1/F/27	Visual	Dysarthria, right paresis and hypoesthesia	Left temporo-parietal cortex
Morais et al 2018[24]	1/F/37	Scintillating scotoma	Left homonymous superior quadrantanopsia	Occipito-temporal gyrus and lingual gyrus with hypoperfusion
Serrano et al 2018[22]	15/8F 7M/18–55	Visual	Visual field deficits (53.3%), hemiparesis (13.3%)	Vertebrobasilar arterial territory
Kreling et al 2017[30]	1/F/16	Blurring and scotoma in right visual field	Diplopia, dysarthria, imbalance	Paramedian right dorsal midbrain
Renard et al 2015[31]	1/M/47	Visual	Visual disturbance	Left occipital cortex and cerebellum bilaterally
Parks et al 2014[32]	1/F/59	Scotoma, left leg numbness	Visual distortion, transient Cotard's syndrome, hypoestesia	Right temporal-parietal-occipital cortex.
Thissen et al 2014[25]	1/F/74	Left zigzag lines and flashing	Visual spots	Right occipital cortex
Arboix et al 2013[23]	1/F/29	Visual	Dysarthria, left paresis and hypoesthesia	Right temporo-parietal cortex
Lai e Hong 2012[33]	1/M/60	Blurred vision, right limbs numbness and weakness, dysarthria and diplopia	Right hemiparesis, hypoesthesia	Left posterior medial pons.
Wolf et al 2011[3]	17/4M 13F/20–71	Oscillopsias, photopsias, fortification spectra, or scintillating scotomas (82.3%), sensory dysfunction (41.2%), and aphasia (5.9%)	Visual field deficits (88.2%), hypoesthesia (47.1%), imbalance (35.3%), hemiparesis (11.8%), aphasia (11.8%), dysarthria (5.9%)	Posterior circulation (70.6%), MCA territory (29.4%). Reduced (23.5%) or more prominent flow (11.8%) in ischemic territory
Laurell et al 2011[33]	33/13M 20F/16–76	Not specified	Visual field deficit (42%), paresis (33%), sensory deficit (% not specified)	Posterior circulation (82%), anterior circulation (18%)
Tsai et al 2010[17]	1/F/42	Nil	Left facial palsy, dysarthria, left hemiparesis	Right basal ganglion and corona radiate territory.
Decima et al 2009[21]	1/M/41	Not specified	Flashes and blurred vision, spatial disorientation	Occipital cortex
Caballero 2009[35]	1/F/21	Fortification spectrum, scotoma	Left homonymous hemianopia, metamorphopsias, dysarthria, left hemi-paraesthesias	Thalamus and right occipital cortex
Schulz et al 2009[36]	5/3M 2F/21–58	Visual (80%), hemiplegia (20%)	Visual symptoms (80%), dysphasia (20%), hemiparesis (20%)	Occipital (80%), internal capsule (20%).

(*Continued*)

Table 1 (Continued).

Authors and year	Patient n./sex/age	Aura Symptoms	Neurological Features	Stroke Vascular Territory
Arai et al 2008[37]	1/M/64	Left-side hemianopsia	Left-homonymous hemianopsia, unilateral visual spatial agnosia, and topographical agnosia	Right occipital lobe.
Marshall et al 2007[12]	1/F/57	Blurred vision	Delirium, right arm weakness, near total visual loss	Parieto-occipital and insular cortex.
Liang e Scott 2007[26]	1/F/57	Photopsia and paresthesias	Left homonymous hemianopsia, hypoesthesia	Right temporal, parietal, and occipital cortex
Tzoulis et al 2006[19]	1/F/93	Fortification spectrum, scotoma	Left homonymous hemianopsia	Right occipital cortex
Matsuo et al 2006[38]	1/F/35	Nil	Homonymous bilateral upper visual field defects	Bilateral occipital cortex
Frigerio et al 2004[39]	6/1M 5F/23–40	Visual (83.3%)	Homonymous hemianopia/ quadrantopia (80%), sensory symptom (16.7%)	Posterior (80%), middle (16.7%), and anterior (16.7%) territory
Tang et al 2004[40]	2/1M 1F/29–47	Not specified	Not specified	Posterior cerebral and anterior choroidal territory; middle and posterior territory
Lee et al 2003[41]	2/1M 1F/40–25	Vertigo, hearing loss, hemiparesis	Hearing loss, tinnitus, vertigo, speech disturbance, right hemiparesis, dysarthria, diplopia, sensory symptom	Pons and cerebellum bilaterally
Arboix et al 2003[42]	9/3M 6F/24–60	Hemianopia, speech difficulty, hemiparesthesia/paresis	Hemianopia (66.7%), motor (33.3%), sensory (66.7%) symptoms, aphasia (11.1%)	MCA (33.3%), SCA (11.1%), PCA (22.2%), undetermined (33.3%) territory
Linetsky et al 2001[20]	6/1M 5F/15–46	Visual (83.3%), paresthesias (16.7%)	Visual field defect (33.3%), hemiparesis (83.3%), hypoesthesia (50%), dysartrhria (33.3%), dysphasia (16.7%), ataxia (16.7%)	Frontoparietal, MCA and cerebellar territory
Demirkaya et al 1999[43]	1/M/38	Nil	Left hemiparesis, hypoesthesia	ACA territory bilaterally.
Meschia et al 1998[12]	1/M/43	Nil	Right homonymous visual defect	Left occipito-parietal cortex.
Mendizabal et al 1997[13]	1/F/47	Numbness, speech disturbances, vertigo, gait instability, diplopia	Nystagmus, gait ataxia, confusion and agitation	Posterior thalami, left occipital cortex and cerebellum.
Sanin et al 1993[15]	1/F/47	Scintillating scotoma	Blindness, left-sided hemiparesis and hemineglect	Fronto-parietal and occipital cortex.
Gomez et al 1991[18]	1/F/33	Flashing	Imbalance	Right cerebellum
Solomon et al 1990[16]	1/F/36	None	None	Not specified.

Abbreviations: MCA, middle cerebral artery; PCA, posterior cerebral artery; SCA, superior cerebellar artery; ACA, anterior cerebral artery.

Table 2 Biochemical Implications Proposed In Migrainous Infarction

Morais et al 2018[24]	Deposition of fat laden macrophages, higher protein concentration and glial cell proliferation in the cortical area affected
Thissen and Koehler 2014[25]	Damage to inhibitory GABAergic cells in the occipital lobe and low cortical preactivation in thalamocortical tract
Arboix et al 2013[23]	Fat macrophages and glial proliferation due to selective neuronal damage
Schulz et al 2009[36]	Phosphocreatine/inorganic phosphate ratio lower in patients with persistent aura than in Migrainous infarction and controls
Liang and Scott 2007[26]	Blood-brain barrier disruption, cytotoxic edema secondary to focal hypermetabolism
Solomon et al 1990[16]	Intracellular calcium increase, catecholamines and prostaglandins release leading to vasoconstriction

did not meet all of the criteria for MI diagnosis, soon afterward she had a second stroke that completely satisfied the ICHD-3 beta diagnostic criteria for MI,[1] with one or more otherwise typical aura symptom that persisted beyond one hour with neuroimaging confirmation of an ischemic infarction in the affected territory. The main finding of the present study is the possible bidirectional relationship between migraine and stroke, which is based on the hypothesis that vasospasm serves as a link between migrainous attack and cerebral ischemia. Indeed, the patient showed a vasospasm in the related ischemic territory.

TCCD demonstrated a high positive predictive value for detectingspasm.[7,44–46] Mean flow velocity >120 cm/s in the MCA or 90 cm/s in the posterior circulation and an increase of >50 cm/s within 24 h usually indicate a vasospasm, which is generally accompanied by typical disturbances in blood flow (turbulence and musical murmurs). The LR and modified LR are often used to reliably distinguish between hyperdynamic flow and vasospasm by comparing MCA/extracranial carotid artery velocities for the anterior circulation and BA/extracranial vertebral artery velocities for the posterior circulation, respectively.[6,47] Our patient had elevated blood flow velocity, suggesting vasospasm; on the other hand, she did not meet the clinical and neuroimaging diagnostic criteria for reversible cerebral vasoconstriction syndrome.[48]

A retrospective study of more than 130,000 migraineurs found that treatment with ergot alkaloids but not triptans was associated with increased risk of ischemic events.[49] Some studies have suggested that vasospasm arises from transiently enhanced sympathetic neuronal activity through the release of noradrenaline (and consequent activation of adrenergic receptors) or vasoconstrictive molecules such as serotonin and endothelin, resulting in vasoconstriction, thrombosis, and ischemic lesions.[16,50,51] A positron emission tomography study demonstrated a reversible reduction of 40% in cerebral blood flow during a migraine attack that was confirmed bysingle-photon emission computed tomography (SPECT) in a subject with basilar migraine.[52,53] Similarly, extensive hypoperfusion of brain regions involved in the development of prolonged aura was reported in another SPECT study[27] and in a case of cortical laminar necrosis detected by perfusion MRI.[24] Hence, vasoconstrictive drugs such as ergotamines and triptans should be avoided during the acute phase of MI.

Propranolol should be prescribed with caution for migraine prophylaxis as it can limit compensatory vasodilator capacitance, and should be avoided altogether in cases of prolonged aura or migraine with aura presenting with brainstem symptoms.[4] Calcium channel blockers, angiotensin receptor blockers, or angiotensin receptor antagonists are alternative choices for migraine prevention and have been shown to promote endothelial repair and decrease the level of von Willebrand factor.[4,54,55] Among calcium antagonists, verapamil was shown to be particularly effective in rapidly reducing cerebral vasospasms, as detected by TCCD.[56] Treatment strategies also need to take into account patients' co-morbidities, vascular risk factors, and drug interactions. Given that pro-thrombotic alterations and platelet activation are presumed to play a role in MI, it is generally recommended that antiplatelet therapy be initiatedto prevent ischemic events.[2]

Except for one case with a fatal course,[12] the functional outcome of MI is usually favorable. In particular, patients with posterior circulation stroke improved or recovered from neurological deficits in about 47.9% and 18.5% of cases, respectively, although mild visual field defects

persisted in cases of more severe occipital infarct (approximately 32.4%). Similar results were recorded in cases of anterior circulation ischemia: approximately 74% of patients showed improvement from neurological disturbances, with 17% achieving total recovery; whereas around 26% of those with larger cerebral lesions had persistent deficits. Consistent with these data, our patient showed clinical improvement and full recovery from MI-related deficits.

The precise etiology of MI is largely unknown, although different pathomechanisms have been proposed.[5] Migraine aura is generally attributed to CSD, which is a brief depolarizing wave moving at 3–5 mm/min across the cortex followed by sustained neuronal depression. During prolonged aura, long-lasting cortical neuronal hyperexcitability can result in reverberating CSD.[25] Thus, inhibitory control may be lost in the primary visual cortex due to perturbation of the GABAergic system. Accordingly, a transcranial magnetic stimulation study of the human motor cortex of migraineurs found that the duration of the cortical silent period was shortened, which is a well-known index of intracortical inhibition mainly mediated by GABA-B receptor activity.[57,58] Furthermore, a reduction in regional cerebral blood flow in the visual cortex during aura may lead to impairment of the GABAergic inhibitory circuitry comprising spinous stellate cells that spread horizontally and generate an inhibitory network in lamina IV of the primary visual cortex.[59] Clinical studies have demonstrated that migraineurs have altered serotonergic transmission from the brainstem to the thalamus and cortex;[60] this so-called "thalamo-cortical dysrhythmia" results in dysfunction of both inhibitory and excitatory cortical neurons,[61] as observed by electrophysiological recordings in other neurological disorders.[62–65]

Activation of CSD induces cortical spreading hyperemia, followed by long-lasting oligoemia, hypoperfusion, vasoconstriction, and severely limited oxygen delivery to tissues.[4,34,66] Thus, CSD leads to marked metabolic and hemodynamic changes in neurons, creating supply/demand mismatches for adenosine triphosphate, oxygen, and glucose. Consequently, the brain of migraineurs is more

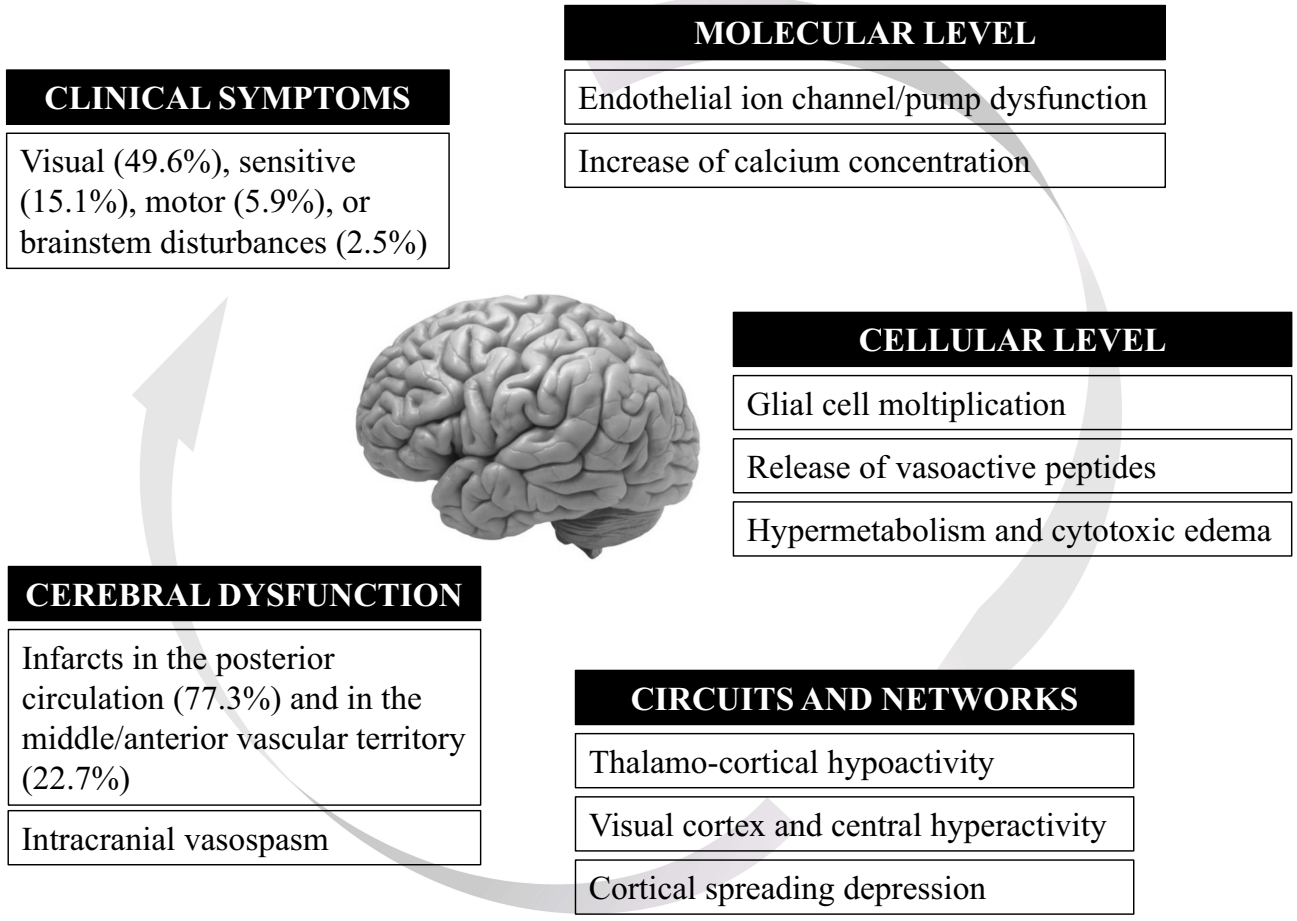

Figure 2 Summary of possible interactions among neurochemical and neurophysiological changes and clinical phenotype in MI patients.

vulnerable to ischemia even after a mild and transient hypoxic state.[27] The triggering of a chain reaction of detrimental processes including prolonged vasoconstriction due to reduced nitric oxide, increased extracellular K^+, and endothelial ion channel/pump dysfunction eventually lead to vasospasm[2] and brain infarction.[66] CSD may also induce the release of inflammatory mediators, vasoactive peptides, and adhesion molecules, which predisposes to intravascular thrombosis.[50]

The neurochemical changes, pathological mechanisms, and phenotypic alterations in MI are schematically depicted in Figure 2. Interestingly, the endothelium may play a major role by inducing vasoconstriction and inhibiting vasodilatation upon neuroinflammation, suggesting that impaired cerebral endothelial function contributes to the development of ischemic stroke in migraine. This is supported by clinical evidence from studies reporting an over-representation of asymptomatic ischemic lesions in the posterior circulation of patients with migraine, especially those with aura.[67] A more recent transcranial Doppler study showed that patients with migraine exhibit impaired endothelial function in the posterior cerebral circulation, implying that direct endothelial impairment contributes to posterior circulation infarcts.[68] Decreased diameter and compliance of the muscular artery have also been observed in migraine patients, likely reflecting enhancedarterial tone and increasing susceptibility to vasospasm.[69]

Taken together, the evidence presented here indicates that arteries of migrainous patients are more likely to develop vasospasm, thereby increasing stroke risk. Indeed, some studies have shown a transient narrowing of the left middle and posterior cerebral arteries during migraine attacks,[70,71] and microvascular vasospasm in cortical regions related to the topography of aura symptoms has been reported.[72] Vasospasms of varying intensity can occur during migraine attacks and may precede or accompany a headache, obstructing focal cerebral blood flow.[73,74] However, further studies are needed to clarify the role of vasospasm in migraines and in the occurrence of MI.

Conclusion

Clinicians should immediately perform neuroimaging and a TCCD evaluation of migraineurs with prolonged aura for early detection of vasospasm or cerebral ischemia. If the clinical suspicion of MI is confirmed, comprehensive clinical and instrumental analyses should be carried out for accurate diagnosis and therapeutic management. Prospective multicenter studies are needed to obtain insight into the pathogenic mechanisms underlying MI and to standardize diagnostic and treatment approaches.

Ethics Approval And Informed Consent

Given that this study reports a single patient's clinical description and instrumental exams that are routinely performed within the conventional diagnostic work-up of these subjects, it did not need ethical approval. The study subject provided written, informed consent for the publication of data and images.

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Disclosure

The authors report no conflicts of interest in relation to this work.

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