

MIGRAINOUS INFARCT: AN UPDATE

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Migraine and stroke have been linked in a complex bi-directional association, though there are quite a few pathophysiological pieces to be found to complete the puzzle. International Classification of Headache Disorders-11 (ICHD-II) has defined a specific term 'migrainous infarct' that can be the crucial link between the two disorders. The authors review the latest developments related to migrainous infarct and present a compilation of case reports from 1988 to 2006.

Migraine is mysterious. It has been described as a disease, a benign condition, a progressive disorder and merely a symptom for some other disorder. Similarly, whether migraine causes stroke or vice versa is a subject of controversy in today's research circles. An important consequence of this debate will be to ascertain if migraine proceeds to ischaemic stroke (IS), hence is a progressive disorder or otherwise. The proponents of either side put the cases very prudently.

On one hand Bousser and Welch¹ argue that migraine, though painful and often detrimental to quality of life, is a primary headache disorder, and an essentially benign condition. They insist that labelling migraine, as a progressive disease is "simplistic and eventually deleterious generalization". On the less bright side is the view that migraine should be conceptualized not just as an episodic disorder but also as a chronic-episodic and sometimes chronic progressive disorder². What is generally agreed upon is the uncertainty about migraine being a single entity, a group of related disorders, or a syndrome.

Migraine and stroke do not have much in common. Migraine typically starts before age 40 years and affects 12% of the population with a 3 to 1 female preponderance. By contrast, stroke is an acute event that occurs in 2 per 1000 people per year at a mean age of 70 years with a 2 to 1 male preponderance. Despite these differences, many studies have suggested a complex bi-directional relation between migraine and stroke including migraine as a cause of stroke, migraine as a risk factor for or as a consequence of cerebral ischaemia, and migraine and cerebral ischaemia sharing a common cause.³⁻⁵

Migraine has been found to precipitate a stroke event. According to the Classification of Headache Disorders-11⁹, a 'migrainous infarct' is described as one or more migrainous aura symp-

toms associated with an ischaemic brain lesion in appropriate territory demonstrated by neuro-imaging. The strict diagnostic criterion is:

1. The present attack in a patient with migraine with aura is typical of previous attacks except that one or more aura symptoms persists for >60 minutes.
2. Neuro-imaging demonstrates ischaemic infarction in a relevant area.
3. The episode is not attributed to another disorder.

Furthermore the ischaemic stroke in a migrainous sufferer may be categorized as follows⁹.

1. A cerebral infarction of other cause coexisting with migraine,
2. Cerebral infarction of other cause presenting with symptoms resembling migraine with aura, or
3. Cerebral infarction occurring during the course of a typical migraine with aura attack. Only the last fulfils criteria for migrainous infarction.

Migrainous stroke is most common in women under 45 years of age, suffering from migraine with aura, especially in the presence of recognized risk factors such as smoking and oral contraceptive use.¹⁰⁻¹⁶

DEFINING MIGRAINOUS INFARCT

Traditionally migrainous infarction has been largely over-diagnosed. It was redefined in a more restrictive way in the IHS classification⁹ as described above. With this redefinition, migrainous stroke has become rare.

It is not known whether this 'rarity' is due to the strict diagnostic criteria or a 'real' low incidence. For instance, Henrich and colleagues¹⁷ found 7 migrainous infarcts among 244 first cerebral infarctions, corresponding to an incidence of 3 per 100 000 per year in the UK. The association

between these strokes and migraine is highly debatable because only one patient had cerebral angiography, one had echocardiography, three were hypertensive, and one had widespread atheroma.¹

On the other hand a WHO study defines migrainous stroke as the existence of headaches in the 3 days before the stroke and concludes that up to 40% of the strokes in migrainous women are migrainous strokes.¹⁴ Many researchers argue that migrainous infarcts are rare and probably over-diagnosed.^{4,6,18-21}

PATHOPHYSIOLOGY

Hypoperfusion or Hyperperfusion

Some experts view migrainous infarcts as being caused by severe hypoperfusion during an attack.^{4,18,19} Occurring mostly in the posterior cerebral-artery distribution and being more common during attacks of MA than of migraine without aura; the precise mechanism of this severe hypoperfusion is unknown. Cortical spreading depression (CSD), a major theory for migraine pathophysiology, is caused by this hypoperfusion according.²² There are others who take a diametrically opposite view. Kobari et al²³ found a pronounced, sustained, diffuse brain hyperperfusion to be a consistent feature of migraine attacks, both with and without aura. Furthermore there is need for more evidence to link CSD and oligoemia.²⁴⁻²⁶

Coagulation Risk Factors

Coagulopathies may play a role in the evolution of migrainous infarct. Etminan et al²⁷ found that users of oral contraceptives had an eightfold higher risk of stroke when compared with those not using oral contraceptives. It is not known whether this is an independent risk factor associ-

ated with migraine with aura¹⁴, or whether it requires the presence of additional risk factors²⁸. A large European case-control study observed a higher prevalence of antiphospholipid antibodies in female migraine subjects who have experienced cerebral ischaemia or transient focal neurologic events²⁹. However, a recent prospective study could not confirm this finding³⁰. Currently, due to deficient evidence, the role of coagulation abnormalities in migrainous stroke is not conclusive.

An interesting aspect of coagulopathies is APL (anti-phospholipid antibodies). APLs are a group of circulating serum immunoglobulins associated with thrombosis. Many neurological diseases have been described in patients with APL.³¹⁻³² They include cerebral infarction, transient ischaemic attacks, optic nerve infarction, vascular dementia, cerebral venous thrombosis, chorea, myelopathy and migraine. The relationships between APL and migraine have been studied both ways: frequency of migraine in APL syndromes and frequency of APL in migraine. There is no good evidence that the frequency of APLs is increased in migraine³³, hence, the role of APLs in migraine remains to be elucidated.

CASE REPORTS

Below is a collection of case reports of adults with migrainous infarct diagnosed from 1988 onwards.

Additionally Oleson et al⁴¹ concluded that ischaemia-induced migraine attacks may be more frequent than migraine induced ischaemic insults (migrainous infarct) and hence migraine is not as strong a risk factor for stroke as indicated by the mere coincidence of the two disorders. Linetsky et al⁴² described six patients, fulfilling ICHD-II criteria for migrainous cerebral infarction, with

Table 1: Case report of migrainous infarcts in a tabulated form

Study	Gender	Risk Factors	Clinical Features	Imaging Results / Other Investigations / Conclusions
Frigerio et al ¹⁵	5 F/median age of 29, range 23-40 1 M/36	At the time of attack OC and smoking in 2 Only smoking in 1 No vascular risk factors in 3	Fulfilled ICHD-II Criteria <ul style="list-style-type: none"> • Homonymous hemianopia in 3 • Lower homonymous quadrantopia in 1 and sensory symptom in 1 	MRI: All showed cerebral infarct (posterior cerebral artery in 4, middle cerebral artery in 1 and anterior cerebral artery in 1).
Tang et al ³⁴	1 F/29 1 M/47		<ul style="list-style-type: none"> • H/o migraine with aura 	Territory of Posterior Cerebral and Anterior Choroidal Anterior involved in F/29

Study	Gender	Risk Factors	Clinical Features	Imaging Results / Other Investigations / Conclusions
			•	Territory of Middle and Posterior cerebral Arteries involved in M/47
Arboix et al ¹⁶	M/39, 30, 49 F/35, 32, 25, 27, 24, 60		<ul style="list-style-type: none"> • Limb weakness in 5, sensory symptoms in 3, hemianopia in 4, nausea and vomiting in 4 and aphasia in 1. • Aura was sensitive when superior cerebellar artery was involved (hemiparesthesia). • Aura was visual in 2 (hemianopia), motor (weakness) in 1. Undetermined topography cases :3 	6 had cerebral infarct (middle cerebral artery in 3, posterior cerebral artery in 3, superior cerebellar artery in 1) Rest 3 with negative neuroimaging
Santiago et al ³⁵	1 F/11		<ul style="list-style-type: none"> • Fulfilled ICHD-II criteria • Referral made on CT showing hypodense area at the level of ganglia of left base 	MRI confirmed ischemic lesion
Demirkaya et al ³⁶	M/38		<ul style="list-style-type: none"> • 2 year H/o migraine • Woke up one day with failure to concentrate or converse • Had experienced bifrontal throbbing headaches associated with nausea and preceded by tingling on left side of body for 5-10 minutes in a month • Mild paresis of left leg, left hyperesthesia and gait ataxia 	CT: Normal MRI: Cortex of paramedian region of frontal and parietal lobes showed ischemic changes (more prominent on the right) Cerebral angiography: No occlusion
Narbone et al ³⁷	3 F/37, 34 and 27 1 M/29	F/37: OC	F/37: MA developed after starting OC Symptoms: Speech difficulty, right hemiparesthesias and weakness. Developed confusion and drowsiness in one	F/37: CT (pre-ischemic episode): Normal CT (post-ischaemic attack): ischemic lesion near the left basal ganglia. Cerebral angiography

Study	Gender	Risk Factors	Clinical Features	Imaging Results / Other Investigations / Conclusions
		F/34: Family history of CVD, OC M/29: Partial epileptic seizures in infancy, had resolved F/27: Family history of migraine Smoking	attack; aura became persistent. F/34: MA developed after starting OC. Frequency of headaches increased within months. Developed motor aphasia and a severe right hemiparesis in one attack M/29: Developed bailar migraine when he was 25 years old. During a typical migraine attack, had left hemiparesthesias and sudden onset of decreased level of consciousness, lasting 12 hours. F/27: Frequent attacks of MA since adolescence. During a typical migraine attack, complained of left-sided hemi-paresthesias followed by a left hemiparesis.	thrombus in the left middle cerebral artery. F/34 CT-MRI: Ischemic lesion near the left basal ganglia. Others: Significant increases of thromboglobulin, platelet factor 4 plasma levels and the presence of PFO M/29: CT: Normal MRI: Ischemic lesion in the right cerebellar hemisphere. Cerebral angiography: Normal Others: Moderate increase of the plasma levels of cholesterol and triglycerides F/27: CT: Normal MRI: Right pontine ischemic lesion Echocardiography: Presence of a PFO.
Rothrock et al ²⁸	310 with migraine 30 with migranous infarct		24 of 30 migranous infarct patients reported H/o MA, poor H/o stroke	Conclusion: MA patients and the ones with prior H/o of strokes, are more prone to developing migrainous infarct
Sanin LC, Mathew NT ³⁹	F/47	Smoking	<ul style="list-style-type: none"> Long history of recurrent episodes of MA Developed a continuous intractable headache during the course of which cortical blindness and quadriparsis occurred 	Arteriogram: Severe diffuse intracranial major arterial vasospasm
Rothrock et al ⁸	20 F (age no mentioned) 2 M (age no mentioned)		Prior 'presumed' history of migrainous stroke	12 showed ischemic / hemorrhagic infarction on CT, MRI/RC 5 showed abnormalities related to acute stroke on cerebral angiography
Bogousslavsky et al ⁷	22 F 5 M (Mean age 32.7)		MA with H/o stroke during a migraine attack	Doppler ultrasound, cerebral angiography, and two-dimentional echocardiography was

Study	Gender	Risk Factors	Clinical Features	Imaging Results / Other Investigations / Conclusions
				done in all patients: They had longer previous attacks of migraine and their infarct was more frequently in the territory involved during the attacks than the controls
Moen et al ⁴⁰	M/37	Smoking Family history of migraine	<ul style="list-style-type: none"> • H/o confusional migraine since 20 years of age • Attacks accompanied by scotoma and confusion • Recent increase in symptom frequency. On one occasion confusion persisted 	CT: Left temporo-occipital infarct Catheter vertebral angiography: Occluded posterior cerebral artery Carotid imaging: Normal

H/o: History of; OC: Oral Contraceptive; CVD: Cardiovascular Disease; MRI: Magnetic Resonance Imaging; RC: Radionucleotide scanning; CT: Computerized Tomography Scan; MA: Migraine with aura; PFO: Patent Foramen Ovale.

decreased headache frequency and severity after stroke. Nanri et al⁴³ reported a 31 year-old man having migrainous infarction accompanying idiopathic thrombocytopenic purpura.

Infrequent cases

Lee et al⁴⁴ describe acute auditory symptoms as part of the prodrome of migrainous infarction in a 40 year old man and a 25 year old woman. They conclude that migrainous infarction should be considered in the differential diagnosis of acute auditory symptoms, including sudden, bilateral hearing loss. Tzoulis et al⁴⁵ found a 93 year old woman with migraine with aura having a migrainous infarct. Prominent features were negative scotoma covering most of her left visual field which persisted in the headache phase, severe nausea and vomiting (more than usual) unsteady gait, left homonymous hemianopsia, hypodense area in the right occipital lobe (fresh infarct) on CT scan. MRI confirmed the presence of fresh occipital infarct.

In **conclusion** it is mentioned migraine seems to be an independent risk factor for stroke, however, the evidence for migrainous infarct is inconclusive. The classification of ICHD-II needs to be put to test in future studies. In case the ICHD-II criterion is too restrictive, many potential positive cases might be missed. Alternatively very liberal criteria lead to over diagnosis. Large and

focused epidemiological studies elucidating the 'true' presence of migrainous infarct are required. Additionally the concepts of CSD, brain hypo or hyperperfusion also need to be standardized. It is only after these steps that the prime question of migraine being a progressive disorder or not can be answered.^{46,47}

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