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Ayesha KK
Aga Khan University

Rushna Raza
Aga Khan University

Sahar Zafar
Aga Khan University

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APPROACH TO SYMPTOMATIC MIGRAINE - A REVIEW OF LITERATURE

Ayeesha Kamran Kamal, Rushna Raza and Sahar Zafar

Department of Neurology, Aga Khan University, Karachi, Pakistan

Correspondence to: Dr Kamal, Assistant Professor, Aga Khan University, Stadium Road, Karachi, Pakistan. Tel no: + 92-021-493-0051 Email: ayeesha.kamal@aku.edu

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INTRODUCTION

Migraine affects as many as 18% of women and 6% of men aged 25-55 years and is under-recognized worldwide.¹ Although majority of the cases are idiopathic, sometimes migraine can also present as a symptom of another underlying pathology or disorder that perturbs the migraine-generating structures, causing secondary migraine headaches. Diagnosis of symptomatic migraine can be made when headaches which satisfy the International Headache Society (IHS) diagnostic criteria for migraine occur due to an underlying pathology and cannot be classified as "idiopathic". We report the causes of symptomatic migraine based on a critical literature review. Symptoms specific to a particular organic disorder are often present but migraine can sometimes be the only clinical manifestation.

Knowledge of these entities will alert the astute clinician to investigate the possibility of an underlying disorder. This may require neuroimaging, genetic testing and often multi-disciplinary input from, for example, vascular surgeons, cardiologists or oncologists.

METHODS

"Symptomatic migraine" is a migraine secondary to an underlying cause and cannot be classified as idiopathic. Our objective was to find causes of "symptomatic migraine" and hence to include the diseases that can present with migraine or where migraine is a prominent associated feature, and diseases where diagnosis of underlying potential etiology can make a difference to the management of migraine or modify the choice of anti-migraine treatment. We performed a detailed librarian assisted Pub Med Boolean search covering articles from Premed-line to March 29, 2007. Entering the keywords "symptomatic migraine" gave us 380 articles from which we initially selected 162 articles including case reports,

whose subject matter was relevant to symptomatic migraine or which described diseases that presented with migraine like symptoms. Articles which dealt only with management of migraine were excluded.

From these search results, we selected 147 relevant articles. The references of these articles were also reviewed and where indicated they were also retrieved. In total we reviewed 164 articles. These articles described diseases which presented with migraine, had migraine as a major feature, or occurred in concurrence with migraine due to another common underlying pathology. We excluded articles in which migraine was described as a primary disorder and those that dealt with management and complications of migraine. Within each identified subsection, relevant section references were searched and selected as well. We sorted the international library (ILL) when the full text article was not available on PubMed. All articles were reviewed between the three authors and points were clarified by mutual discussion. This was to ensure that the review would involve only the predefined characteristics.

We based our classification of symptomatic migraine on the ICHD-II classification for secondary headaches:

1. Head and neck trauma
2. Vascular disorders
 - a. Intracranial
 - b. Extracranial
3. Intracranial non vascular disorders
4. Substance abuse or withdrawal
5. Infection
6. Disorders of homeostasis
7. Disorders of the cranium, eyes, ears, nose, sinuses, teeth, mouth or other cranial or facial structures
8. Psychiatric disorders
9. Cardiac abnormalities
10. Metabolic disorders

REVIEW

As the pathogenesis of migraine begins to be better understood, it appears that disorders that perturb the structures that are involved in generating spontaneous migraine can cause “symptomatic migraine”.

1. Head/neck trauma

Minor head and neck trauma and whiplash injuries can be followed by severe chronic headaches, which may present as classic migraines. Headaches may begin immediately or within the first few days after injury and may respond well to prophylactic anti-migraine treatment.²

Juvenile head trauma syndromes resemble classic migraine.³ Juvenile head trauma syndromes are characterized by four types of attacks; 1) hemiparesis, 2) somnolence, irritability, and vomiting, 3) blindness and 4) brain stem signs, which make the clinical presentation similar to migraine.³ Migraine due to juvenile head trauma and contact sports is usually the result of a minor injury and is not associated with amnesia.⁴ Head injury is followed by a symptom free interval that lasts for several minutes, followed by motor, visual, sensory or brainstem symptoms. These symptoms last for 15 to 20 minutes and are followed by headache, with nausea and vomiting.⁴ There are no significant differences in treatment, however as far as a history of trauma is concerned it is prudent to rule out other associated injuries - which may not be reported in the juvenile cases

2. Vascular Disorders

a. Intracranial vasculopathy

i. Ischemic Small Vessel Disease: CADASIL (Cerebral Autosomal Dominant)

Arteriopathy with Subcortical Infarcts and Leukoencephalopathy

Due to the high prevalence of primary migraine, CADASIL is often overlooked as a potential cause and may therefore not be diagnosed until the first stroke occurs, a symptom more commonly associated with CADASIL.⁵⁻⁸ CADASIL is an autosomal dominant disorder whose gene, *Notch3*, located on chromosome 19, encodes a 300-kd transmembrane protein with a receptor and cell signal transduction function. A typical arteriopathy with electron dense granular depositions in the media of small cerebral arteries underlies this disorder. These arterial lesions can be found, to a lesser extent, in extra-cerebral arteries

such as skin arterioles.⁹ As the disease becomes better understood, migraine with aura is proving to be a common early manifestation of CADASIL patients, reported in 38% to 60% of affected individuals about 15 years before the first stroke.¹⁰⁻¹²

The natural course of CADASIL starts with migraine with aura in the 30s, subcortical strokes at age 45, accompanied psychiatric abnormalities and dementia in the 60-70s.^{13,14} The aura is prolonged, usually hemiplegic, visual, sensory, aphasic and often with “basilar” type features.¹⁵ Retinal migraine has also been reported.¹⁶ Migraine coma is reported as a complication of CADASIL. This is a reversible acute encephalopathy (lasting 7 -14 days) sometimes associated with fits.¹⁷ The head MRI in the younger (<35 years) migraineurs shows confluent white matter hyperintensities in T2 weighted and flair images in the anterior temporal lobes, the frontal lobes, and the periventricular frontal caps.^{14,18} In more advanced cases, the external capsule may be involved.¹⁹ Regardless of the type of migraine phenotype, abnormal MRI is invariably seen.²⁰ These younger patients may not have associated dementia, although neuropsychiatric testing may show a frontal lobe type cognitive disorder.²¹ Ophthalmologic examination may show generalized arterial narrowing and arteriovenous nicking but only minimal functional disturbance.²² The transcranial doppler (TCD) shows reduced intracranial velocities.²³ In addition, CADASIL has been reported in patients with normal brain MRI; these patients have abnormal skin biopsies.²⁴ Aura and migraine in CADASIL may respond to acetazolamide.^{25,26}

ii. Cerebroretinal Small Vessel Syndromes

Cerebral small vessel disease is responsible for about 20% of all strokes and characteristically small vessel strokes are not associated with headaches. However, the cerebroretinal small vessel syndromes are a group of disorders associated with retinal vascular abnormalities, small vessel ischemia, leukoencephalopathy and frequent migraine with aura.

The main hereditary vascular conditions involving both retinal and cerebral vessels include cerebroretinal vasculopathy, HERNs (hereditary endotheliopathy with retinopathy, nephropathy, and stroke), and hereditary vascular retinopathy; all of which are linked to the same locus on chromosome 3p21.²⁷ A novel hereditary autosomal dominant condition affecting both retinal and cerebral vessels has been described as characterized by infantile hemiparesis, migraine with aura, retinal hemorrhage, retinal arterial tortuosity, and leukoencephalopathy with dilatation of perivascular

TABLE 1. Hereditary disorders affecting small blood vessel of the brain

Disorder	Brain MRI			Retinal arteriolar abnormalities	Skin arteriolar abnormalities	Systemic	Migraine
	Leuko-encephalopathy	Lacunar Infarcts	Other findings				
CADASIL	++	++	-	+	++	-	++
HERNS	+	+	Contrast enhancing lesions (++)	++	+	++	++
HVR	+	-	-	++	-	-	++
Hereditary infantile hemiparesis, retinal arteriolar tortuosity & Leuko-encephalopathy	++	+	Dilated perivascular spaces (++) unilateral ventricular enlargement (+)	++	-	-	++

CADASIL= cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; HERNS= hereditary endotheliopathy with retinopathy, neuropathy and stroke; HVR= hereditary vascular retinopathy; * = ultra structural analysis of biopsy material; ++ = prominent sign; + = may be present

spaces and microbleeds on brain MRI.²⁸ Patients with headache that is migrainous with aura and cerebral small vessel disease should receive a gradient echo MRI and retinal fluorescein angiogram to diagnose these disorders. Table 1 summarizes disorders of the small blood vessels of the brain.

iv. Amyloid angiopathy

Cerebral amyloid angiopathy is a disorder affecting the elderly, and usually presents as a non hypertensive intracerebral hemorrhage in a lobar location. A peculiar pattern of its presentation is continuous spread of symptoms. It is important to investigate elderly patients complaining of typical “aura” sans migraine. These auras may be the clinical correlates of petechial hemorrhages induced by the deposition of amyloid in fragile vessels.²⁹ Although there is no cure, strict avoidance of antiplatelets, anticoagulants, Gingko and all agents that prolong the bleeding time is advocated. The diagnosis of probable amyloid angiopathy may be made with a gradient echo MRI in vivo.³⁰

Hereditary amyloidosis is a group of genetically heterogeneous autosomal-dominant inherited disorders characterized by the ubiquitous extracellular deposit of fibrillary aggregated proteins. In the vast majority of cases, the offending protein is variant transthyretin (TTR), of which over 80 mutations are known.³¹ TTR amyloidosis presents with polyneuropathy occasionally accompanied by vitreous amyloid opacities. Rarely, involvement of the

leptomeningeal or meningovascular structures dominates the clinical picture.³² A marked delay in perfusion time and an enlargement of arterioles are found via cerebral angiography, suggesting a disturbed autoregulation of cerebral blood vessels by the amyloid-laden vasculature, which may lead to hemodynamic changes.³³ Arteriography often precipitates prolonged encephalopathy. This altered hemodynamic mechanism results in small areas of cortical ischemic changes, which may then cause fluctuating consciousness, TIA and migraine aura like symptoms.³⁴ Diagnosis may be made by postcontrast T1-weighted imaging which shows smooth leptomeningeal enhancement. Also noted on gradient echo sequences are a few punctate areas due to hemosiderin deposition.³³ Although orthoptic liver transplantation is a cure in Familial Amyloid Polyneuropathy (FAP), its effectiveness in those with CNS manifestations is not known.³⁵

b. Extracranial Vasculopathy

Large Vessel Vasculopathies:

i. Carotid Artery and Vertebral artery dissection

Spontaneous carotid artery dissection may present with aura and headache indistinguishable from migraine and are more common in migraineurs.^{36,37} Headache and neck pain may be the only symptoms of spontaneous carotid artery dissection.³⁸ Marching impairments from one modality to another, scintillating scotoma,³⁹ aphasia

and sensory impairment have been reported.⁴⁰ Odd accompaniments like pulsatile tinnitus, headache accompanied by aura, limb shaking, and Horner's syndrome should raise the suspicion of carotid dissection.⁴⁰ Moreover, carotid artery dissection is more likely to present with migraine with aura, as opposed to migraine without aura.

Vertebral artery dissection often presents with headache mimicking a migrainous attack followed by basilar ischemic symptoms.⁴¹ The presenting symptoms are often characterized by severe occipital headache, followed by nausea, vomiting and vertigo.⁴² Migraine associated with vertebral artery dissection is usually ipsilateral to the side of the dissection and may also be associated with neck pain.⁴³ Vertebral artery dissection appears to be an important consideration in pediatric atypical migraines associated with new onset neurological dysfunction.⁴³

c. Vascular Malformations

i. Sturge-Weber Syndrome

The Sturge-Weber syndrome (SWS), also called encephalotrigeminal angiomas, is a neurocutaneous disorder with angiomas involving the leptomeninges and skin of the face (port-wine stain). Patients may present with cortical, often occipital, calcifications and cranial angiomas without the cutaneous port wine stain.⁴⁴ All patients may not manifest the common symptoms of epilepsy and cognitive retardation but, may have hemiplegic migraines.⁴⁵ In a specific study of headaches in SWS, migraine headache occurred in 28%, and neurologic deficits occurred in 58% of patients during the migraine.⁴⁶ The prevalence of migraine in children younger than 10 years was 31% in children with SWS, much greater than the 5% prevalence in the general population.⁴⁶ In a single report, the migraine aura resolved with aspirin.⁴⁷ In another case celiac disease with folic acid deficiency was found to be the cause of the occipital calcifications.⁴⁸

ii. Intracranial arteriovenous malformations (Occipital AVM)

Occipital AVM may occasionally be confused with migraine.⁴⁹ A report describes a patient whose "symptomatic migraine" fulfilled IHS criteria for migraine, and resolved after resolution of the AVM.⁵⁰ Clinically distinguishing characteristics include late onset, fixed laterality, cranial bruit,⁵¹ concomitant "flashes" or occipital epilepsy like phenomena and crash migraine with homonymous hemianopsia.⁵²⁻⁵⁴

iii. Pontine cavernoma

Studies have shown that the periaqueductal gray, locus ceruleus and the nucleus raphe are the antinociceptive structures of the brainstem whose dysfunction could disinhibit the trigeminal system and lead to a migraine attack. Dorsal pontine activation, has been demonstrated in human PET studies of migraine.⁵⁵ Unilateral migraine can be associated with a pontine cavernoma affecting the contralateral nucleus raphe magnus, with subsequent loss of laterality over time as a result of local spread from microhemorrhages. Thus cavernous malformations of these "migraine generator areas" can act as irritant foci for migraine activation.^{56,57}

iv. Intracranial aneurysms

Migraine may be associated with a higher incidence of dissections and dissecting aneurysms of the posterior circulation in particular.⁵⁸ Sumatriptan may induce clinical relief in real SAH when misdiagnosed and treated as migraine.⁵⁹

v. Moyamoya disease

Moyamoya is a chronic cerebral vascular disease, characterized by occlusion of the arteries around the Circle of Willis, with resultant collateral circulation. This gives rise to a smoky angiographic appearance of the vascular collaterals and hence the name "moyamoya", derived from a Japanese word that means puffy or obscure.⁶⁰ The common clinical presentations include ischemic events, hemorrhagic stroke and epilepsy, and are more prevalent in children than in adults. The vascular stenosis seen in the Circle of Willis in moyamoya disease can impair the posterior circulation. Decreased occipital perfusion has been suggested as a trigger for migraine with aura.⁶¹ Hence patients with atypical migraine should be investigated for underlying vascular diseases including moyamoya.⁶¹

d. Thromboembolic Ischemia (Stroke or TIA)

A bidirectional relationship seems to exist between stroke and migraine.⁶² Migraine-stroke are a group of entities in which migraine and stroke occur simultaneously and include migrainous stroke.⁶³ Cerebral ischemia can induce migraine, and presents primarily as migraine with aura.⁶⁴ Moreover, both stroke and migraine may be the result of a third underlying condition, e.g. a stroke diathesis,^{63,64} and hence these need to be kept in mind when diagnosing and investigating migraine as a consequence of stroke or cerebral ischemia.

e. *Plasma Hypercoagulability*

A higher frequency of underlying prothrombotic conditions have been reported in migraine patients.⁶⁵ Migraine is one of the clinical manifestations of antiphospholipid antibody syndrome.⁶⁶ Patients with SLE and RA may also present with migraine, and antiphospholipid antibody levels are raised in these migrainous.⁶⁷

Ocular migraine, also known as retinal migraine, may occur in antiphospholipid antibody syndrome. It is characterized by transient monocular loss of vision followed by headache.⁶⁸ Visual symptoms may be the result of arteriosclerosis, central retinal artery or vein occlusion, and transient ischemic attacks.⁶⁹ Important clues in the history of a patient with migraine, that may point to antiphospholipid antibody syndrome, or other prothrombotic states, would be recurrent thrombosis especially in young patients, recurrent pregnancy losses or thrombocytopenia.⁶⁸ An ophthalmologic exam would be essential in these patients.

3. *Nonvascular Intracranial Disorders*

i. *SMART Syndrome (Stroke like migraine attacks after radiation therapy)*

This is a rare and probably under diagnosed condition in those adult patients who present with migraines associated with complex prolonged neurologic deficit, and a previous history of childhood cranial irradiation for brain tumour.⁷⁰ These patients often have brainstem cavernous malformations; radiation related capillary telangiectasias and evidence of superficial siderosis on their baseline MRI. They have headaches, photophobia, visual scintillations and neurologic deficits that resolve over a period ranging from 12 hours to days. Ictal FLAIR MRI shows gyral thickening with negative diffusion scans. EEG demonstrates slowing, and PET shows intense ictal hypermetabolism that subsequently resolves.⁷⁰ All patients reported have shown ongoing pathology in the brainstem or posterior circulation, probably areas that trigger the migraine generating mechanisms.

ii. *Lymphocytic Pleocytosis*

Pseudomigraine with pleocytosis is a self-limited and rather a benign disorder, characterized by recurrent bouts of migrainous headaches, prolonged aura and cerebrospinal fluid abnormalities with increased opening pressure. Patients with this condition are between 15 and 40 years of age. The syndrome is more frequent in men. These headaches are described as predominantly throbbing and bilateral with a variable duration (mean of 19 hours). The average duration of the transient neurologic deficit is 5 hours. Sensory (78% episodes),

aphasic (66%), and motor (56%) disturbances are the most common associated features. Migraine-like visual symptoms are relatively rare (18% episodes). Patients are asymptomatic between episodes and after the symptomatic period (duration > 3 months). Lymphocytic pleocytosis (10 to 760 cells mm³) and increased cerebrospinal fluid protein are found with negative bacteriologic, viral, fungal, and immunologic studies.⁷¹ Syphilis must be ruled out in these patients.⁷² Brain computed CT and MRI are normal including DWI,⁷³ but an electroencephalogram frequently shows focal slowing over the symptomatic brain area. SPECT reveals transient focal areas of decreased uptake consistent with the clinical symptoms.⁷⁴

iii. *Neoplasm*

Intracranial neoplasms, can present with migraine along with other focal neurologic deficits and signs of increased intracranial pressure.⁷⁵ In some cases migraine may be the only symptom of intracranial neoplasms, and studies have suggested occipital lobe tumors, including meningiomas, as a cause of migraine with aura.⁷⁵⁻⁷⁷ Cases have described occipital lobe tumors to present with migraine that may be characterized by throbbing headaches, visual auras, nausea, photophobia and phonophobia. The migraines may be refractory to medical management and respond only to surgical removal of the tumor.⁷⁵⁻⁷⁷

iv. *Pineal Cyst*

Pineal cysts are most often seen in women in their third decade of life, and most commonly present with headache.⁷⁸ About half of the headache cases are migraines, which may either be migraine with aura, migraine without aura or chronic migraine.⁷⁹

v. *Septum Pellucidum Cyst*

A septum pellucidum cysts lies between the walls of the lateral ventricles. The walls of the cyst demonstrate lateral bowing and are more than 10 mm apart.⁸⁰ Septum pellucidum cysts are found in approximately 15 % of adult brains.⁸¹ Asymptomatic cysts may expand, causing compression of surrounding structures and producing symptoms. They may cause obstruction of the interventricular foramen, giving rise to hydrocephalus, or compress the deep venous structures of the brain, or the hypothalmo-septal triangle.⁸¹ The most common symptom of septum pellucidum cysts is intermittent headaches, which include migraine.⁸²

vi. *Multiple Sclerosis (MS)*

Migraines are a common feature of multiple sclerosis and

migraine-type vascular headaches may be a presenting symptom in MS patients.⁸³ Migraines also occur during MS exacerbations and relapses, and changes in serotonin function have been proposed as a link between the migraines and MS exacerbations and relapses.⁸⁴ It has been suggested that altered function of the red nucleus, periaqueductal gray matter and substantia nigra, play a role in the pathophysiology of migraine and demyelinating lesions of these regions are seen in MS patients with migraine.⁸⁵ Hence presence of midbrain plaques in MS patients increases the likelihood of migraine type headaches in these patients.⁸⁶

vii. Behcets' Disease

Nervous system involvement is seen in 5 % of the cases of patients with Behcets' syndrome, headache being the most common neurological symptom.⁸⁷ Headaches may even occur in Behcets' syndrome in the absence of any other neurological problem.⁸⁸ Migraine is one of the most common headaches seen in Behcets' patients.⁸⁹ Migraines have a high prevalence of visual or sensory aura, and result in severe disability in many cases.⁸⁸

viii. Idiopathic Hypertrophic Cranial Pachymeningitis

Idiopathic hypertrophic cranial pachymeningitis is a disorder of the dura mater. The pathogenesis is diffuse or localized thickening of the dura mater. The most frequent clinical manifestation is a chronic daily headache, particularly chronic migraine-like headache which is lateralized to the side of the dural lesions. A gadolinium enhanced MRI, which will reveal the dural lesions, is required to rule out the disorder in a patient presenting with chronic migrainous headaches.⁹⁰

ix. Epilepsy

Periictal headaches are a feature of parieto-occipital epilepsy, and may on rare occasion be the presenting symptom.^{91,92} The periictal headaches, may be of migrainous nature and disappear with the treatment of epilepsy. Parieto-occipital epilepsy is also characterized by illusions and visual hallucinations, and needs to be differentiated from a migraine attack.⁹¹

4. CNS Infection

Migraine-like headaches, particularly migraine with aura, are a frequent manifestation of neurosyphilis, and the underlying infection needs to be detected to prevent further complications of the disease.⁹³ A careful neurological examination along with CSF analysis needs to be performed in such patients.

Migraine like headaches have also been described as a

feature of bacterial meningitis, with two cases showing poor response of these headaches to sumatriptan management.⁹⁴ Migraine is also a common manifestation of acquired CNS *Toxoplasma gondii* infections in immunocompromised individuals.⁹⁵

5. Disorders of Cranium, ENT, Eyes Neck, Sinuses and Teeth

i. Schimke immuno-osseous dysplasia

Schimke immuno-osseous dysplasia (SIOD) is a rare autosomal recessive disorder. It is caused by a mutation in the chromatin remodeling protein SMARCAL1 (SW/SNF2 related, matrix associated, actin dependent regulator of chromatin, subfamily a-like 1).⁹⁶ The disease results in steroid resistant nephritic syndrome, spondyloepiphyseal dysplasia, and T-cell deficiency.⁹⁷ One study has shown that about half the patients with this disorder complain of severe and disabling migraine like headaches.¹⁰⁷ It is postulated that the migraines result from vascular, neuroimmune, or neurovascular defects due to the gene mutation.⁹⁷

ii. Progressive Hemifacial Atrophy (Parry Romberg Syndrome)

Parry Romberg Syndrome is a disorder of unknown etiology characterized by gradual wasting of one side of the face due to loss of subcutaneous tissue. It often begins in childhood. The disorder may be manifested by hemiplegic migraines, and one case describes these migraines to be ipsilateral to the facial wasting.⁹⁸

6. Psychiatric disorders

i. Tourette Syndrome

Tourette syndrome is a common childhood movement disorder, featured by motor and phonic tics along with psychiatric abnormalities including obsessive compulsive disorder. The frequency of migraine headaches in Tourette syndrome is almost four times the frequency in the general population.^{99,100} This may be explained by the hypothesis that both conditions are caused by an underlying pathology in the metabolism of serotonin.¹⁰⁰

7. Cardiac Abnormalities

i. Patent Foramen Ovale (PFO)

The possible relationship between migraine with aura and paradoxical embolism from PFO was investigated in a study on 74 patients presenting with acute stroke of undetermined origin. PFO was found in 44 of 74 patients, 36% of whom had migraine with aura (MA) compared to

TABLE 2 Clues to the diagnosis of symptomatic migraine

Historical Features	Suspect	Findings
Aura Sans Migraine , age >60	Microrhemorrhage of Cerebral Amyloid Angiopathy	Gradient Echo MRI showing “ dark spots”
Migraine Precipitated by Long Periods of Fasting	Idiopathic Ketotic Hypoglycemia	Gradient Echo MRI showing “ dark spots”
Prolonged Aura	MELAS , CADASIL , Pseudomigraine with lymphocytosis	MRI posterior occipital WMDx (MELAS) Anterior temporal and External capsule WMD (CADASIL), MRI normal in pseudomigraine
Hemiplegic Aura	MELAS , SMART syndrome	Cavernous malformation and capillary telangiectasia, gyral thickening in SMART
Laterality of Visual Aura Fixed	Occipital AVM	Cranial Bruit, Flow Voids on MR
Migraine coma	CADASIL	As Above
Odd accompaniments: Pulsatile tinnitus, Horners	Carotid Dissection	Abnormal carotid MRA , axial T1 Fat suppressed image showing “flap” of dissection
TIA History	Patent Foramen Ovale, CADASIL	Crochetage Pattern on EKG, cardiac murmur
Valsalva Induced TIA	Patent Foramen Ovale	Crochetage Pattern on EKG, cardiac murmur
History of Cranial Irradiation, Posterior Fossa	SMART syndrome	Cavernous malformation and capillary telangiectasia interictally, Ictal gyral thickening in SMART, EEG slowing
Valproate Induced Rhabdomyolysis	CPT II deficiency	Family History of death in anesthetic accident., decrease serum carnitine or muscle

13% MA patients without PFO.¹⁰¹ Of 25 patients in whom the PFO was considered to play a causal role in the stroke, 52% had MA whereas only 16% of 19 patients in whom PFO was considered unrelated had MA. Patients with MA and PFO, treated either with surgical closure or anticoagulants, noticed complete disappearance of MA attacks.¹⁰¹

Closure of interatrial communications may result in improvement of migraine headaches.^{102,103} In a recent study, 42% of patients undergoing percutaneous closure of an interatrial communication primarily for the secondary prevention of stroke or closure of ASD were migraineurs. At 3 months after closure of the interatrial communication, episodes of migraine headache had

ceased in (60%) of these patients. Among the patients who experienced migraine with aura, 75% had complete resolution. Those who experienced migraine without aura, 31% had complete resolution. Of the remaining patients, 40% experienced significant improvement in frequency and severity of migraine headache. The benefit has been sustained in this population over a median follow-up period of 18 months.¹⁰⁴

It is therefore, imperative to do a thorough neurologic review in patients presenting with migraine with aura who also have a cardiac murmur, or have a crochetage pattern on EKG.¹⁰⁵ A possible history of TIA needs to be ruled out in such patients and a bubble study and antiplatelet prophylaxis need to be considered.

TABLE 3 Causes of symptomatic migraine

	Migraine with aura	Migraine without aura	Not specified
1 Vascular Disorders	Contralateral pontine cavernosa	CADASIL (less common)	Stroke
	CADASIL	Cerebrovascular amyloidosis	PFO
	Plasma hypercoagulability	iAVM (less common)	Intracranial aneurysm
	HERNS		Spontaneous cervical artery dissection
	iAVM		ICAD/VAD Moyamoya disease
2 Nonvascular intracranial disorders	Neoplasm (SHM)	Pineal Cyst	Septum pellucidum cyst
	Pineal Cyst (less common)		Lymphocytic pleocytosis
	Ischemia (stroke or TIA)		Hydrocephalus Schimke immuno-osseous dysplasia Meningioma
3 Infection	Neurosyphilis		
4 Metabolic	Glutathione S-transferase M1 phenotype (less common)	Glutathione S-transferase M1 phenotype	Horners - HC
			Ketotic hypoglycemia
			Progressive facial hemiatrophy- HM
			Carnitine palmityl transferase II deficiency Leigh disease-subacute necrotizing encephalopathy

Intervention should probably be reserved for those with stroke and in the setting of a randomized clinical trial.

ii. *Atrial Myxoma*

Left atrial myxoma may present with migraine-like episodes.¹⁰⁶ The migraine usually lasts for one to two days and are preceded by visual disturbances including scintillating scotomas.¹⁰⁷ The pathogenesis of migraine with aura in patients with atrial myxoma may be due to vasoactive intestinal peptide (VIP) secreted by the myxoma, or because of microembolization.¹⁰⁷ VIP may induce migraine via its excitatory affect on cerebral or trigeminal nucleus caudalis neurons, through the enhancement of cortical glutaminergic neurotransmission, or vasodilation of cortical vessels.¹⁰⁷

8. Metabolic Disorders

i. *MELAS (Mitochondrial Encephalopathy, Lactic Acidosis and Stroke-like episodes)*

Altered mitochondrial DNA has been proposed in the pathogenesis of migraine due to frequent maternal transmission of the disorder.¹⁰⁸ Impaired energy metabolism and mitochondrial function have been noted in patients with migraine,^{109,110} and these defects may contribute to the pathophysiology of the migraine.¹¹² MELAS is a mitochondrial disorder with a wide range of symptoms ranging from seizures, headaches, stroke-like episodes, memory impairment, hemianopsia, hearing loss, diffuse limb weakness, exercise intolerance, nausea and vomiting.¹¹³ Age of onset may range from 2 to 40 years.¹¹³

One of the more common manifestations of MELAS is migraine, which is often cyclical, severe, and associated with vomiting. The migraine may or may not be preceded by aura, and may be accompanied with complex partial occipital lobe epilepsy.¹¹⁴ EEG during a migraine episode may show focal high-voltage delta waves with polyspikes (FHDPS).¹¹⁵

ii. *Carnitine Palmitoyl Transferase II Deficiency*

Carnitine is used by mitochondria for fatty acid transportation. In a recent report the diagnosis of migraine was made according to the International Headache Society (IHS) criteria for migraine, for two adolescent girls who had a history of recurrent fatigue, muscle cramps, and multiple side effects from their prophylactic treatment. Carnitine levels were measured and found to be low. Carnitine supplementation was initiated. Both patients had a reduction in headache frequency, as well as an improvement in their associated symptoms and other complaints. A skin and muscle biopsy obtained from one patient revealed a partial carnitine palmitoyl transferase II deficiency in the muscle only.¹¹⁶ Since valproic acid can induce rhabdomyolysis in patients,¹¹⁷ and carnitine supplementation would alleviate migraines, CPT II deficiency must be suspected in those with exercise intolerance or intolerance to migraine medication.

iii. *Ketotic Hypoglycemia*

Idiopathic ketotic hypoglycemia is an important cause of hypoglycemia in children between 1 and 5 years of age.¹³⁴ The signs and symptoms of hypoglycemia are commonly missed as children may present with migraines triggered by the disorder. Urinary ketones and glucose levels should be monitored in such cases. If left untreated the disease may lead to severe neurological sequelae and intravenous administration of glucose is mandatory as it reverses symptoms.¹¹⁸

iv. *Glutathione S-Transferase*

Migraine has been proposed as a polygenic and multifactorial disorder, and the Glutathione S transferase (GST) M1 gene polymorphism may present in, and is a risk factor for migraine without aura.¹¹⁹

CONCLUSION

Migraine is a common headache syndrome. A careful history and physical examination with testing to exclude "symptomatic" causes should be considered in those with atypical presentations. Awareness and targeted questioning will lead to the correct diagnosis. Table 2 summarizes the clues to diagnosis of symptomatic

migraine, and table 3 revisits the causes of symptomatic migraine.

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