Migraine is amongst the oldest of diseases known to mankind. Migraine is a heterogenous entity, usually characterised by periodic attacks of headache on one or both sides of the head. These may be accompanied by nausea, vomiting, increased sensitivity of the eyes to light (photophobia), increased sensitivity to sound (phonophobia), dizziness, blurred vision, cognitive disturbances, and other symptoms. Migraines are not always preceded by an aura and some migraines may not include headache. If migraine does not manifest itself in the form of headache but in some other form such as paroxysmal episodes of prolonged visual auras, atypical sensory, motor, or visual aura, confusion, dysarthria, focal neurologic deficits with or without a headache, it is labelled a Migraine Variant (MV). MV is therefore diagnosed by the history of paroxysmal symptoms with or without cephalgia and a prior history of migraine with aura, in the absence of other medical disorders that may contribute to the symptoms. Many of the MVs have been included and redefined in the revised edition of The International Classification of Headache Disorders (ICHD-II) 2004 classification. These include hemiplegic migraine, basilar migraine, childhood periodic syndromes, retinal migraine, complicated migraine and ophthalmoplegic migraine. Even though conditions such as vertiginous migraine, acute confusional migraine of childhood and nocturnal migraine are well recognized entities, they have not yet been included in ICHD-II, but will be discussed here in brief because they are relatively common conditions.

Migraine Aura Without Headache or Acephalgic Migraine (1.2.3) -

Some migraine patients may experience an aura without accompanying headache. This presentation is more common in older patients who have had a history of migraine with aura earlier on. Symptoms may include scintillating scotomata, formed stereotyped visual hallucinations in a single visual field or bilaterally, micropsia, and tunnel vision. Other auras may include paroxysmal vertigo, hemisensory dysesthesias and rarely auditory hallucinations. Acephalgic migraine should be differentiated from transient ischemic attack, occipital lobe seizures and temporal lobe seizures.

Hemiplegic Migraine

Hemiplegic migraine is a very rare but well described form of MV. It was initially described as a type of migraine consisting of recurrent headaches associated with transient unilateral hemiparesis or hemiplegia, at times accompanied by ipsilateral numbness or tingling, with or without a speech disturbance. The focal neurologic deficit may precede or accompany the headache, which is usually less dramatic than the motor deficit. Other migraine symptoms may be present. Patients may also experience disturbances of consciousness and rarely go into coma. The neurologic deficit is transient and usually clears in minutes to hours or resolves with the beginning of the headache phase.

Two forms of hemiplegic migraine have been described: familial and sporadic. Both familial hemiplegic migraine (FHM) and sporadic hemiplegic migraine (SHM) are phenotypically similar subtypes of migraine with aura, differentiated only by the family history.

**Abstract**

Migraine is amongst the oldest of diseases known to mankind. Migraine is a heterogenous entity, usually characterised by periodic attacks of headache on one or both sides of the head. These may be accompanied by nausea, vomiting, increased sensitivity of the eyes to light (photophobia), increased sensitivity to sound (phonophobia), dizziness, blurred vision, cognitive disturbances, and other symptoms. Migraines are not always preceded by an aura and some migraines may not include headache. If migraine does not manifest itself in the form of headache but in some other form such as paroxysmal episodes of prolonged visual auras, atypical sensory, motor, or visual aura, confusion, dysarthria, focal neurologic deficits with or without a headache, it is labelled a Migraine Variant (MV). MV is therefore diagnosed by the history of paroxysmal symptoms with or without cephalgia and a prior history of migraine with aura, in the absence of other medical disorders that may contribute to the symptoms. Many of the MVs have been included and redefined in the revised edition of The International Classification of Headache Disorders (ICHD-II) 2004 classification. These include hemiplegic migraine, basilar migraine, childhood periodic syndromes, retinal migraine, complicated migraine and ophthalmoplegic migraine. Even though conditions such as vertiginous migraine, acute confusional migraine of childhood and nocturnal migraine are well recognized entities, they have not been classified by the ICHD-II, but will be discussed here because they are relatively common conditions.

**Introduction**

Migraine is amongst the oldest of diseases known to mankind. It is a heterogenous entity characterised by periodic attacks of headaches on one or both sides of the head. These may be accompanied by nausea, vomiting, increased sensitivity of the eyes to light (photophobia), increased sensitivity to sound (phonophobia), dizziness, blurred vision, cognitive disturbances and other symptoms. 80% of patients suffering from migraine have migraine without aura, 15-20% of patients have migraine with aura and migraine aura without the typical headache may be seen in a small percentage of patients. This is known as Acephalgic Migraine. The term ‘Migrant Variant’ is not used in the Classification of the International Headache Society (IHS), but it includes those forms of migraine that are not typical of migraine with or without aura.

**Migraine Variants**

If migraine does not manifest itself in the form of headache but in some other form such as paroxysmal episodes of prolonged visual auras, atypical sensory, or motor aura, confusion, dysarthria, focal neurologic deficit, gastrointestinal manifestations or other constitutional symptoms with or without a headache, it is known as a Migraine Variant (MV). MVs are less recognized and poorly understood. MV is diagnosed by the history of paroxysmal symptoms with or without cephalgia, a prior history of migraine with aura, in the absence of other medical disorders that may contribute to the symptoms. Many of these conditions are familial. They are less common than typical migraine without and with aura, and they usually affect children and young adults. Many MVs have been redefined and included in the International Classification of Headache Disorders (ICHD-II) 2004 classification. These include hemiplegic migraine, basilar migraine, childhood periodic syndromes, retinal migraine, complicated migraines, and ophthalmoplegic migraine. Even though conditions such as vertiginous migraine, acute confusional migraine of childhood, and nocturnal migraine are well recognized entities, they have not been classified by the ICHD-II, but will be discussed here because they are relatively common conditions. In this article, description of MVs follow the rubrics as listed in ICHD-2.
Familial Hemiplegic Migraine (1.2.4)

Familial hemiplegic migraine (FHM) is an autosomal dominant migraine subtype that typically includes hemiparesis during the aura phase. It can be accompanied by other symptoms such as ataxia, coma and epileptic seizures. There is clinical overlap in some FHM patients with episodic ataxia type 2 and spinocerebellar ataxia type 6, benign familial infantile convulsions and alternating hemiplegia of childhood. FHM is a channelopathy. There are 3 known loci for FHM. FHMI, which accounts for approximately 50% of FHM patients, is caused by mutations in a gene coding for the P/Q-type calcium channel subunit, CACNA1A. FHMI is also associated with cerebellar degeneration. FHMI, which accounts for <25% of FHM cases, is caused by mutations in the Na+/K+-ATPase gene ATP1A2. FHMI is a rare subtype of FHM and is caused by mutations in a sodium channel a-subunit coding gene, SCNA1. These three subtypes do not account for all cases of FHM, suggesting the existence of at least one other locus (FHM4). Many of the non-familial cases of hemiplegic migraine (sporadic hemiplegic migraine) are also caused by mutations at these loci. 1

Sporadic Hemiplegic Migraine (1.2.5)

Sporadic Hemiplegic Migraine (SHM) is defined as migraine attacks associated with motor weakness in the absence of a family history of similar attacks. Cases of SHM have also been linked to the CACNA1A and ATP1A2 genes. Diagnosis of FHM is usually confirmed with repeated stereotyped reversible episodes, particularly in the presence of positive family history of similar attacks. The absence of first- and or second-degree relatives with similar disorder raises suspicion of SHM. Differential diagnosis includes focal seizures with postictal paralysis, mitochondrial cytopathies, intracranial hemorrhage, mass lesion, infection, or cerebral infarction. 2

Basilar-type Migraine (1.2.6)

Basilar migraine (BM), also known as Bickerstaff syndrome consists of headache accompanied by dizziness, ataxia, tinnitus, decreased hearing, nausea and vomiting, dysarthria, diplopia, loss of balance, bilateral paresthesias or paresis, altered consciousness, syncope and sometimes loss of consciousness. BM is observed most frequently in adolescent girls and young women. Localized vertebrobasilar vasocnstriction leading to transient posterior circulation ischemia is said to contribute to the symptomatology of the disorder.

Cyclic Vomiting Syndrome (1.3.1)

Cyclic vomiting syndrome (CVS) is a chronic functional disorder of unknown etiology that is characterized by paroxysmal, recurrent episodes of vomiting and was first described by Samuel Gee in 1882. Although the pathophysiology is unknown, various mechanisms such as abnormal corticotropin-releasing factor (CRF) and a heightened sympathetic response may play a role. Cyclic vomiting of childhood is characterized by recurrent attacks of violent or prolonged vomiting without headache which may last for hours. Attacks may be precipitated by infection, menstruation, or physical or emotional stress. During attacks, patients characteristically show other symptoms of migraine such as nausea, lethargy, yawning, and drowsiness. Cyclic vomiting is thought to result from abnormal activity in the area postrema. 3

Abdominal Migraine (1.3.2)

Abdominal migraine most typically occurs in children, although it has been reported in adults also. Patients usually complain of paroxysmal mid-abdominal pain associated with nausea and vomiting, flushing, or pallor. Like cyclic vomiting, attacks may be associated with other migraine prodromes such as fatigue and drowsiness. Aura and headaches are frequently absent or minimal. Patients may develop migraine late in their life and a family history of migraine is common. 4 Gastroenterologic evaluation and workup is unremarkable.

Benign Paroxysmal Vertigo of Childhood (1.3.3)

Benign paroxysmal vertigo of childhood (BPVC) is characterized by brief episodes of vertigo and disequilibrium lasting for hours, without headache, aura, hearing loss, or tinnitus. Benign paroxysmal vertigo of childhood is a vestibular migraine with aura but without headache. Probably the most frequent form of episodic vertigo in childhood, it has a prevalence of 2.6% and the commonest presentation is one of sudden brief attacks of vertigo associated with nystagmus. It normally begins between ages 1 and 4 years and remits spontaneously within a few years. There are frequently transitions to other forms of migraine with and without aura. Children usually complain of a spinning sensation during the attack. Typical migraine is common later in life and a family history of migraine is helpful in confirming the diagnosis.

Retinal Migraine (1.4)

Retinal migraine (ophthalmic, ocular) is not an uncommon cause of transient monocular blindness in young adults. It manifests as recurrent attacks of unilateral visual disturbance or blindness lasting from few minutes to 1 hour, associated with minimal or no headache. Patients describe a gradual visual disturbance in a mosaic pattern of scotomata that gradually enlarge producing total unilateral visual loss. Postural changes, exercise, and oral contraceptive agents may precipitate attacks. The condition is thought to result from transient vasospasm of the choroidal or retinal arteries. A personal or family history of migraine confirms the diagnosis. The condition needs to be differentiated from amaurosis fugax due to ischemia of the retinal arteries and ocular or vascular causes of transient monocular blindness, mainly carotid artery disease.

Persistent Aura without Infarction (1.5.3)

The typical duration of a migraine aura, predominantly visual, is up to 30 minutes. In rare cases, the aura could be prolonged, lasting up to 60 minutes, raising concerns of possible stroke.

Migraine Infarctions (1.5.4)

The relationship between migraine, mostly migraine with aura, and ischemic stroke has been well recognized. Migraine, generally a benign condition, has been recognized as an independent risk factor for ischemic stroke. Additionally, migraine, predominantly migraine with aura, is associated with the presence of silent infarctions or white matter changes on brain MRI. When a cerebral infarction occurs during a typical migraine aura attack, the term migrainous infarction is used.
The mechanism of migrainous infarction is complex. Whether the relationship between migraine and stroke is the consequence of other underlying etiologies or the presence of similar ischemic risk factors or whether migraine is associated with conditions that could potentially cause stroke is yet to be determined.

Other Variants

Ophthalmoplegic migraine (13.17)

This is a very rare condition seen more commonly in children and is characterized by a migraine like attack, followed within days by periorbital pain and diplopia secondary to cranial neuropathies. The oculomotor nerve is most commonly involved, with pupillary abnormality and ptosis, followed by the abducens, and rarely the trochlear nerve. The attack usually lasts from days to months and resolves spontaneously. A number of adult cases have been reported. Although previously considered a MV, the condition has been classified as a neuralgia in IHCD-II. The condition is thought to be due to a recurrent demyelinating cranial neuropathy. Differential diagnosis includes conditions involving the parasellar, orbital and posterior fossa leading to headache and ophthalmoplegia.

Alternating Hemiplegic Migraine (primarily in childhood)

Alternating hemiplegia of childhood (AHC) is a chronic progressive disorder, associated with high prevalence of neurologic deficit. It is distinguished from familial hemiplegic migraine by its infantile onset and by its characteristic associated neurologic deficit. It is distinguished from familial hemiplegic migraine by its infantile onset and by its characteristic associated neurologic deficit. It is distinguished from familial hemiplegic migraine by its infantile onset and by its characteristic associated neurologic deficit. It is distinguished from familial hemiplegic migraine by its infantile onset and by its characteristic associated neurologic deficit. It is distinguished from familial hemiplegic migraine by its infantile onset and by its characteristic associated neurologic deficit.

Migraine-triggered seizures (1.5.5)

Migraine and epilepsy are highly comorbid conditions probably sharing the same pathophysiology, but the nature of their association is unclear. Migraplexy is the term used when a seizure occurs during or within 1 hour of a typical migraine aura attack. Reversible brain MRI abnormalities have been reported in a patient with migraine-triggered seizure, possibly due to supratentorial focal cerebral edema. Electroencephalographic (EEG) findings are usually normal interictally, although various abnormalities, mainly diffuse slowing have been reported in migraine patients.

Vertiginous migraine

Growing evidence suggests that recurrent episodes of vertigo are related to migraine. Vertigo, a common complaint among migraine patients, has been reported in one third of cases. Recurrent episodes of vertigo lasting between 5 minutes and 1 hour, with or without nausea, vomiting, photophobia, or headache, in the setting of a previous personal history or a positive family history of migraine supports the diagnosis of vestibular or vertiginous migraine. The pathophysiology of migraine-related vertigo is not fully understood. Differential diagnosis includes vertebrobasilar insufficiency and paroxysmal vestibular syndromes.

Nocturnal migraine

Although not a true MV, nocturnal migraine is unique because of its occurrence during the middle of the night or early morning hours. Its nocturnal occurrence is thought to be related to circadian activation of certain neurotransmitters during sleep, which are known to trigger a migraine attack.

Migraine Variants - Physical Examination

The neurologic examination in between attacks is nonfocal. Ictally, hemiparesis, ophthalmoplegia, or altered consciousness may be observed. Abnormalities of oculomotor nerve with pupillary involvement are seen in ophthalmoplegic migraine, followed by the abducens, and less commonly trochlear nerve palsy. Children with abdominal migraine or cyclic vomiting may show subtle clumsiness, attention deficit, or developmental delay. In migrainous infarction, some form of neurologic deficit with abnormal neuroimaging is present. Rarely, when patients with retinal migraine are evaluated and examined during an attack of visual loss, optic pallor or narrowing of the retinal vessels can be seen.

Migraine Variants - Neuroimaging

Neuroimaging (CT, MRI) is indicated when the patient presents with the first attack of a focal neurologic deficit or altered mental status, or when focal findings persist between attacks. Neuroimaging studies are frequently obtained to exclude other acute causes of the symptoms and to exclude migrainous infarction in patients with persistent aura. MR imaging of the brain and MR Angiogram of the circle of Willis is indicated in ophthalmoplegic migraine to exclude posterior fossa or orbital pathologies associated with ophthalmoplegia. Abnormal enhancement on MRI and enlargement of the cisternal portion of the oculomotor nerve, have been reported. Further assessment may include a CT angiogram or lumbar puncture.

The yield for diagnostic testing in basilar migraine is low. Transient abnormalities on CT scan and MRI have been reported during or immediately following attacks. SPECT studies suggest decreased regional cerebral blood flow in the posterior circulation in basilar migraine during attacks, but transcranial Doppler studies have not revealed changes in blood flow velocities. Invasive testing in children with periodic syndromes with a strong family history of migraine is unnecessary. A high-resolution MRI and magnetic resonance angiography (MRA) are indicated in suspicious cases in the absence of supportive family history.

In retinal migraine, it is important to rule out eye disease or vascular causes, especially when risk factors for arteriosclerosis exist. Carotid Doppler sonography, transcranial Doppler study, MRA, or CT angiography examinations of the brain are helpful. Flourescein or cerebral angiographies are rarely necessary. Hypercoagulability workup and sedimentation rate may be useful in excluding other coagulation disorders associated with retinal vasculopathy.

Other Tests

EEG is considered in conditions where seizure disorders need to be excluded, such as migraine-triggered seizure, and in patients with recurrent episodes of confusion. EEG generally does not offer additional information in migraine patients. In general, nonspecific interictal EEG abnormalities, including epileptiform activity are reported with higher frequency in migraine patients during or immediately after an episode, with slowing in focal or generalized patterns, and occipital spike-wave complexes. Continuous ambulatory or video EEG may be useful in patients with episodic confusion or recurrent focal neurologic deficits to exclude partial seizures or nonconvulsive status epilepti. Genetic testing is now available for familial hemiplegic migraine using polymerase chain reaction to detect point mutations in the CACNA1A and ATP1A2 genes using and
DNA sequencing is now available. Genetic testing may also be performed for other conditions associated with migraine such as CADASIL, an autosomal dominant disorder in which patients may present with migraine, multiple subcortical strokes, and dementia in early adulthood. In children with cyclic vomiting, a serum lactate level is helpful in excluding mitochondrial disorders. Other tests including, upper and lower gastrointestinal series and vagal autonomic function testing, are rarely indicated.

More recently, functional neuroimaging studies during and immediately after an attack of migraine have demonstrated abnormalities of perfusion and have helped in understanding the pathophysiology of auras. Similarly, SPECT might show hypoperfusion during the aura phase.

Treatment

Medical Care

The first step in treatment is to establish the diagnosis. Once the syndromes are recognized, MVs respond to typical migraine preventive medications.

Treatment is divided into eliminating particular triggers, acute management of the specific attack, and long-term preventive approach. Patients should follow risk factor modifications including smoking cessation, and they should avoid the use of hormonal replacement therapy and birth control pills, all of which could potentially increase the risk of hypercoagulability in migraine patients. In hemiplegic migraine, acute treatment options include antiemetics, nonsteroidal anti-inflammatory drugs, and nonnarcotic pain relievers. Triptans and ergotamine preparations are contraindicated because of their potential vasoconstrictive effects. Prophylactic treatment is generally warranted because of the severity of the attacks. No data are available to support the use of any particular antimigraine agent. Beta-blockers, low-dose tricyclics, anticonvulsants, and calcium channel blockers can be administered. Acetazolamide has been frequently prescribed to patients with hemiplegic migraine, but its benefit in decreasing the frequency or severity of the attacks is questionable. No data support the use of antiplatelet therapy to decrease the risk of stroke. In ophthalmoplegic migraine, prednisone has been used with mixed results. The data on the benefit of prophylactic therapy with beta-blockers, such as propranolol are anecdotal. In retinal migraine, vasoconstrictive agents such as triptans and ergots should be avoided. The use of prophylactic therapy is also anecdotal; when considered, calcium channel blockers are preferred. In migraine-triggered seizures, antiepileptic agents are drugs of choice because of their dual benefit in migraine prevention and seizure control. In childhood periodic vomiting syndrome, early use of intravenous fluids containing adequate glucose (to prevent a catabolic state) and analgesics may abort the attack. Some patients respond to the triptans or ergotamine classes of medication. Antiemetic medications such as cyproheptadine and tricyclic antidepressants are preferred in children. Abdominal migraine symptoms are usually relieved with sleep. Antiemetics may help aborting an acute attack. For chronic prevention, low doses of tricyclic antidepressants and flunarizine, a calcium channel blocker, are effective. Other migraine prevention medications are occasionally of some benefit. Triptans, ergots and dihydroergotamine are contraindicated in patients with migraineous infarction. These patients may respond to nonsteroidal anti-inflammatory drugs (NSAIDs), antiemetics, and non-narcotic pain relievers. Prophylactic therapy is recommended, with tricyclics, beta-blockers, calcium channel blockers, or antiepileptic drugs. Long-term antiplatelet therapy is indicated in patients with migraineous infarction. Patients with vertiginous migraine rarely respond to migraine prophylactic therapy. Anecdotal data are available on the benefit of verapamil, a calcium channel blocker and amitriptyline, a tricyclic antidepressant, because of their anticholinergic properties, which may help control the vertigo.

Additionally, non pharmacological techniques enables the patient higher responsibility and self-efficacy in coping with migraine. Counselling, relaxation training, biofeedback and cognitive-behavioural treatments are employed. In case of headache in children, behavioural therapy should be the method of first choice.

Conclusion

Migraine Variants are important to recognise in practice. Awareness leads to correct diagnosis. Investigations are often necessary to rule out other closely similar neurological disorders. Most variants respond well to treatment with antimigraine prophylaxis. If diagnosed correctly, treatment response is always satisfying.

References