Ministry of Defence

Synopsis of Causation

Migraine

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Disclaimer

This synopsis has been completed by medical practitioners. It is based on a literature search at the standard of a textbook of medicine and generalist review articles. It is not intended to be a meta-analysis of the literature on the condition specified.

Every effort has been taken to ensure that the information contained in the synopsis is accurate and consistent with current knowledge and practice and to do this the synopsis has been subject to an external validation process by consultants in a relevant specialty nominated by the Royal Society of Medicine.

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1. Definition

1.1. **Migraine** is a syndrome of cerebral origin, which normally has primary headache as its central feature, and which consists of any or all of 4 phases:[1]

- A **prodrome** which can occur hours or days before the headache
- An **aura** (see 2.2.2) which usually precedes, and may accompany, the headache
- The **headache** itself
- A **postdrome**[2, 3, 4]

1.2. Migraine is usually divided into **migraine with aura** (classic migraine), and **migraine without aura**. Most attacks consist of more than 1 phase. No phase is obligatory for the diagnosis. The diagnostic criteria are as follows:

1.2.1. **Migraine with aura**. At least 2 attacks fulfilling at least 3 of the following:

- 1 or more fully reversible aura symptoms
- At least 1 aura symptom lasting more than 4 minutes or 2 or more symptoms occurring in succession
- No single aura symptom lasting more than 60 minutes
- Headache following the aura within 60 minutes (may begin prior to or concurrently with the aura)

1.2.2. **Migraine without aura**. At least 5 attacks fulfilling the following criteria:

- Headache (untreated) lasting 4-72 hours
- Headache has at least 2 of these characteristics:
  - Unilateral
  - Pulsating
  - Severe enough to interfere with daily activities
  - Aggravated by mild or moderate physical exertion
- Nausea and/or vomiting
- Photophobia and/or phonophobia

1.2.3. **Both disorders**

- The headache must be **primary**. History, physical examination and investigations must exclude any condition which produces headache as a secondary phenomenon
- There are many causes of secondary headaches, and some of the headaches may be migrainous in nature. Causes include:
  - Systemic infections (usually with fever). This is by far the most common cause of secondary headaches
  - Vascular malformations
  - Subarachnoid haemorrhage
  - Intracranial infarctions and thromboses

- Idiopathic intracranial hypertension (raised cerebrospinal fluid [CSF] pressure)
- Low CSF pressure syndromes (including post lumbar puncture)
- Brain tumours

1.3. If a possible cause of secondary headache is discovered, the diagnosis of migraine can only be made if there is no close temporal relationship with the other condition.

2. Clinical Features

2.1. **Migraine** is a common disorder, occurring in almost 20% of women and some 5% of men.

2.2. There are 4 possible components to an attack:

2.2.1. **Prodromal (premonitory) symptoms** occur in some 60% of migraine sufferers. These symptoms may be:

- **Psychological**, including depression, hyperactivity, euphoria, irritability, restlessness and drowsiness
- **Neurological**, including photophobia, difficulty in concentrating, phonophobia, dysphasia, hyperosmia and yawning; and
- **Constitutional and autonomic**, including stiff neck, food cravings, anorexia, diarrhoea or constipation, thirst, fluid retention or excessive urination

2.2.2. **The aura** consists of focal neurological symptoms, developing over 5-20 minutes and lasting less than 60 minutes. There may be an interval of up to 60 minutes between the end of the aura and the beginning of the headache, during which the patient generally feels unwell. These symptoms are variable in nature, and include:

- **Visual disturbances**, which may take the form of flashing lights, fortification spectra (bright sparkling zig-zags), undulations of vision, areas of temporary localised blindness, distortions of colour, shape or size, or mosaic vision
- **Abnormalities of sensation and movement.** These often take the form of numbness or prickling feelings (paraesthesiae) which may spread from a hand, up the arm and then to the face over a few minutes and are usually accompanied by visual symptoms. Other symptoms include abnormalities of spatial perception, speech disturbances, alterations in consciousness such as déjà vu (a sense of repeating exactly events that have happened before) or trance-like states, or a sense of weakness of part of the body

2.2.3. **The headache** of migraine is typically initially unilateral, throbbing, severe and exacerbated by physical activity. In the course of the attacks, however, it may be felt on both sides. It usually starts slowly, rising to a peak and subsiding over a period of 4-72 hours. The headache is almost always accompanied by other symptoms including anorexia, nausea and vomiting, undue sensitivity to light, sound and/or smell, blurred vision, nasal stuffiness, and sweating. The patients often retire to a dark and quiet room.

2.2.4. In the **postdrome** phase, patients are usually left with feelings of listlessness, tiredness and irritability. There may be impairment of concentration, scalp tenderness, or mood change often depressive in nature.

2.3. **Migraine with aura** may occur without headache, but **migraine without aura** must (by definition) include a headache phase.

2.4. Migraine has a number of subtypes in additional to the 2 most common variants described above:

2.4.1. ***Status migrainosus*** describes attacks that are of greater than 72 hours in duration. These are often accompanied by severe nausea and vomiting and are exceptionally unpleasant for the patient.

2.4.2. **Basilar-type migraine** occurs more often in women. Headache is usually severe, and follows visual disturbances. The posterior (basilar) part of the brain is affected and this gives rise to dizziness, tinnitus, diplopia, nausea and vomiting, paraesthesiae and changes in consciousness.

2.4.3. **Hemiplegic** migraine has both familial and non-familial forms. It may cause coma or paralysis of one side of the body during the aura phase. It may begin in childhood and often continues into adult life.

2.4.4. **Ophthalmic (ophthalmoplegic) migraine** consists of attacks of unilateral eye pain and paralysis of some eye muscles. The paralysis can last for some hours to a matter of months. This is a difficult diagnosis to make and it is vital that all other possible causes are excluded.

2.5. **Other causes of primary headache.** [5] Migraine is only one of a considerable number of causes of primary headache. The commonest type is tension-type headache, which affects approximately 90% of adults. The others are much less common, but may be confused with migraine. They all have specific diagnostic features, which enables the differentiation to be made.

2.5.1. **Tension-type headache**.[6] This differs from migraine in that there are no associated autonomic features, and no prodrome, aura or postdrome. Like migraine, it is more common in women than in men. Unlike migraine, it usually has no family history.

2.5.2. **Cluster headache**. Cluster headache is uncommon and occurs three times as often in men as in women. It is characterised by the severity of the pain and by autonomic activation, with lachrymation, conjunctival injection and rhinorrhoea. Attacks are unilateral and usually last between 15 minutes and three hours, once daily on groups of eight successive days for eight to ten weeks a year. In between clusters, most patients are perfectly well. In episodic cluster headache, a small proportion of patients suffer daily attacks without longer remission.

2.5.3. **Syndromes responsive to indomethacin**. This is a disparate group of conditions, which includes paroxysmal hemicrania, idiopathic stabbing headache, benign cough headache, benign exertional headache, and hypnic headache (occurring a few hours after onset of sleep in the elderly). SUNCT syndrome (short-lasting unilateral neuralgiform headache attacks) is not responsive to this agent.

2.5.4. **Benign sex headache.** This is characteristically a throbbing bilateral headache which occurs during sexual activity and may become severe as orgasm approaches. It is more often found in women than in men.

2.5.5. **Thunderclap headache**. This (as its name suggests) is a suddenly occurring, very severe headache which is usually, but not always associated with intracerebral vascular malformations.

3. Aetiology

3.1. For many years, it was thought that the migraine aura was caused by constriction of cerebral vessels followed by headache due to painful reactive vasodilatation. This theory does not explain the presence of a prodrome or why some anti-migraine drugs have no effect on the cerebral vasculature,[7] and it has not been substantiated by cerebral blood flow (CBF) studies. It is now more generally believed that a better explanation can be offered by the comprehensive neurovascular theory, which is based on studies of cerebral blood flow, magnetic resonance imaging and other research. This theory suggests that prodromal symptoms originate in the hypothalamus and limbic system, and that nerve cell dysfunction with secondary vascular changes cause the aura and the headache. Activation of the central midbrain region during migraine has been demonstrated and it has been suggested that this region may be the generator of migraine attacks.[8] Reduction in cerebral blood flow follows a wave of cortical spreading depression (excitation followed by depression of nerve cell activity) in migraine with aura. This may also produce the aura and activate trigeminal nerve endings. There is an increase in CBF after the headache begins, and this continues until the headache passes. In migraine without aura there are no changes in cerebral blood flow.

3.2. Inflammatory mediators such as substance P and neurokinin A may play some role in migraine attacks by producing neuronal inflammation.

3.3. Serotonin can increase cerebral blood flow, and some anti-migraine drugs act as serotonin inhibitors or antagonists. Other neurotransmitters such as catecholamines, histamine, some peptides, endorphins and prostaglandins may have some part to play in the pathogenesis of migraine, but their possible mechanisms of action have not been elucidated.

3.4. Various foodstuffs such as cheese, chocolate and red wine can precipitate migraine attacks in particular patients. Some of these substances contain bioactive amines, but some do not. The mechanisms are not yet well understood and must often be viewed as individual susceptibilities and intolerances.

3.5. There is very often a family history of migraine with aura, but this inheritance is polygenic and complex. Genome-wide screening has identified loci indicating possible genes for migraine on chromosomes 4, 6, 11 and 14, and a recent study has found single nucleotide polymorphisms in the insulin receptor/INSR gene which may be linked to migraine. In contrast, the inheritance patterns of familial hemiplegic migraine are much clearer and 2 single gene abnormalities have been demonstrated, one (Type 1) affecting calcium ion channel pumps and the other (Type 2), sodium-potassium pumps.[9] A different third type has recently also been identified.[10]

3.6. Pregnancy usually lessens the frequency of attacks. This may be related to hormonal changes.

3.7. There is a definite relationship between migraine and affective illness. People with migraine have a 3-fold increased risk of major depression, a six-fold increased risk of manic episodes and a 3-fold increase in anxiety disorder. Patients with either migraine or affective symptoms (not both) develop the other at three times the rate found in the general population.[11] The association between migraine and major depression could result from influences in both directions.

3.8. It is commonly believed that stress may predispose to migraine attacks,[12, 13] possibly by activation of mast cells.[14] There is a positive correlation between the neuroticism score and headache duration (number of hours per week), and people with migraine rate themselves as less calm, less capable of relaxing, and more irritable than healthy control subjects.[15] Although stress may be an important factor in migraine, individual susceptibility to external stressors is a key factor and is extremely variable. Feeling under pressure seems particularly relevant.[16] Management of response to stress is often suggested as an intrinsic part of the overall management of migraine, and therapeutic intervention in this area has been shown to be effective.[17]

4. Prognosis

4.1. Migraine usually begins before the age of 30 years, and the greatest prevalence occurs in the 35-45 age group.

4.2. Improvement commonly occurs during pregnancies, particularly in the later stages.[18]

4.3. Migraine tends to improve over the years, possibly more so in women who have had children.[19]

4.4. Patients (mainly women) may have **transformed migraine**, now referred to as chronic daily migraine, which usually begins in an episodic form in the second or third decades. As the headaches become more frequent, the associated symptoms may occur less often and with lower intensity.

5. Summary

5.1. Migraine is an episodic cerebral disorder, usually characterised by a headache phase preceded by a prodrome and an aura, and followed by a postdrome during which the patient feels tired and unwell.

5.2. Migraine normally starts in the first 3 decades of life, peaks in prevalence in the fourth decade and may improve subsequently.

5.3. There is often a family history, and there is an association with affective disorders and with stress.

5.4. Changes in nerve cell function and cerebral blood flow have been demonstrated and are associated with chemical alterations in the brain, but no single cause has been demonstrated.

6. Related synopses

Stroke

Depressive Disorder

Bipolar Affective Disorder

Generalised Anxiety Disorder

Vertigo

7. Glossary

autonomic	Relating to the autonomic nervous system, concerned with unconscious control of physiological functions.
cerebral	Pertaining to the brain.
diplopia	Double vision.
dysphasia	Non-mechanical difficulties with speech, problems with finding or understanding words.
euphoria	Inappropriately elevated mood.
hemiplegia	Paralysis of one side of the body.
hyperosmia	Enhanced sense of smell.
idiopathic	Of uncertain origin.
infarction	Death of tissue due to interruption of blood supply.
intracranial	Inside the skull.
neurotransmitter	Signaling molecule that alters the behaviour of neurons or effector cells.
ophthalmic	Pertaining to the eyes.
ophthalmoplegia	Paralysis of the eye muscles.
phonophobia	Dislike of sound.
photophobia	Dislike of light.
postdrome	Symptoms occurring after the main feature of a syndrome.
prodrome	Symptoms occurring before the main feature of a syndrome.
temporal	Pertaining to time.
tinnitus	A sensation of ringing or hissing in the ears.
vascular	Pertaining to blood vessels.

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