Hemiplegic Migraine

This document was created with the intent of creating a comprehensive introduction to hemiplegic migraines, using peer-reviewed studies and current medical practices. Due to the confusing and contradictory information online regarding HM, newly diagnosed sufferers often struggle to both find accurate information as well as understand the dense terminology. It is my hope that this document is a resource for all. Sources are listed at the bottom.

I. Introduction

A. Hemiplegic migraine is a rare chronic disorder in which affected individuals experience a migraine headache along with weakness on one side of the body (hemiplegia). Hemiplegic migraine attacks comprise an aura phase and a headache phase. Aura refers to additional neurological symptoms that occur with, or often shortly before, the development of the migraine headache. Additional aura symptoms usually affect vision, but also can affect speech, sensation, and mental status. Other typical aura symptoms like visual field defects, scotoma, hemianopia, tingling, numbness, ataxia, fever, or lethargy may occur. Motor symptoms often start in the hand and gradually spread up to the arm and face. The unilateral weakness may switch sides between or during attacks. The symptoms can last for a few hours to days and rarely can last up to 4 weeks

B. Hemiplegic migraine attacks can range from about one a day to fewer than five in a lifetime. There can often be long episode-free periods during life. Generally, episodes become less frequent as a person ages. Individual episodes can vary in severity and duration.

II. Types

A. Familial hemiplegic migraine (FHM)

1. In some affected individuals, hemiplegic migraine occurs because of a change in a specific gene. Abnormal variations in three genes, the CACNA1A gene, the ATP1A2 gene, and the SCN1A gene, have all been shown to cause familial forms. Some affected individuals are believed to develop the disorder because of an abnormal variation in an as-yet-unidentified gene. There is usually a family history of hemiplegic migraines in affected individuals. There are three types of FHM linked to specific gene mutations:

a) FHM1 is associated with mutations in the CACNA1A gene. FHM1 is the most common type and accounts for around 50% of cases of

FHM. FHM1 is commonly associated with cerebellar degeneration.

b) FHM2 is caused by mutations in the ATP1A2 gene, and it accounts for less than 25% of cases of FHM.

c) FHM3 is caused by mutations in the SCN1A gene.

d) FHM4 is diagnosed if no known genetic mutation linked to FHM is identified.

2. Some studies have associated mutation in the gene PRRT2 with familial hemiplegic migraine. More studies are needed to make this determination.

3. The risk of passing the altered gene from affected parent to offspring is 50% for each pregnancy. The risk is the same for males and females.

4. It is the only variety of migraine characterized by an autosomal dominant pattern of inheritance and transient hemiparesis followed by migraine headache

5. FHM patients are not hypersensitive to CGRP exposure, unlike most [1]

B. Sporadic hemiplegic migraine (SHM)

1. The sporadic form is defined as "a migraine with aura including motor weakness but with no first or second degree relative with aura including motor weakness". SHM clinical characteristics are very similar to those of FHM, consisting of motor aura usually followed by other typical auras (mostly visual and sensory) and headache. Motor deficits are usually unilateral, and most of them resolve in less than an hour.

2. SHM occurs only in an individual without a family history of hemiplegic migraine. These individuals may or may not have a family history of migraine with aura. SHM is strongly associated with other conditions (see Associated Conditions).

III. Diagnostic Criteria

A. Diagnostic criteria for a hemiplegic migraine as per International Classification of Headache Disorders-3 are as follows:

1. At least 2 attacks fulfilling the criteria 2 and 3

2. Aura consisting of both of the following:

[1]https://doi.org/10.1212/01.wnl.0000325482.64106.3f

a) Fully reversible motor weakness

b) Fully reversible visual, sensory and/or speech/language symptoms

3. At least 2 of the following 4 characteristics:

a) At least one aura symptom spreading gradually over at least 5 minutes, and/or at least 2 symptoms occurring in succession

b) Each non-motor symptom lasts 5 to 60 minutes, and motor symptoms last less than 3 days

c) At least one aura symptom is unilateral

d) Aura is accompanied or followed by a headache within 30 minutes

B. No other explanation of the symptoms are available, and stroke and transient ischemic attack have been excluded.

C. Doctors may request MRIs, EEGs, CT scans, CSF analysis, and nerve tests to rule out other possible diagnoses like seizure disorders, stroke, meningitis, or brain tumors, especially if the attacks are new in onset, have prolonged symptoms, and have no family history. Brain imaging (CT or MRI head) during attacks is usually normal.

D. Genetic testing is not recommended in all cases. It may be useful for patients with early-onset FHM associated with atypical neurologic manifestations and in patients with FHM when attack severity and neurologic manifestations diverge from other affected relatives.

IV. Symptoms

A. Hemiplegia: Mild to severe weakness on one side of the body during the aura, either just before or during the migraine headache.

B. Hemiparesis: Weakness or the inability to move on one side of the body, making it hard to perform everyday activities like eating or dressing.

C. Aura: A precursor to a migraine with aura that includes sensory symptoms like dizziness, ringing ears, zigzag lines in vision, or sensitivity to light.

D. Paresthesia: Numbness or a prickly sensation of the face or arms and legs

E. Fever

F. Ataxia: Impaired balance or coordination

G. Dizziness

H. Drowsiness or lethargy

I. Confusion

J. Aphasia: Inability to understand or express speech

K. Dysarthria: Muscle weakness in the tongue, mouth, or voice box, causing slurred words

L. Nausea or vomiting

M. Phonophobia: Extreme sensitivity to sound

N. Cold hands or feet

O. Loss of consciousness

P. Changes to vision:

1. Temporary loss of vision
2. Temporary blindness
3. Double vision
4. Foggy vision
5. Scintillating scotoma: Sudden appearance of a bright light in the center of the field of vision causing blind spots
6. Photopsia: Flashing lights
7. Photophobia: Extreme sensitivity to light
8. Fortification Spectra: Bright, shimmering, jagged lines
9. Irregular or uneven pupil sizes

V. Common Triggers

A. Stress

B. Alcohol

C. Minor head trauma

D. Irregular sleep cycles

E. Some medications

F. Hunger

G. Allergies

H. Hormonal changes

I. Bright lights

J. Caffeine

K. Nitrites in some foods, like sandwich meat, bacon, and processed foods

L. Overdoing physical activity

M. Weather or altitude

N. Angiography: An X-Ray used to visualize blood vessels

VI. At-Risk Populations

A. Hemiplegic migraine affects females three times more than males.

B. Onset of the disorder is usually within the first or second decade of life (specifically 14-17), but has ranged from early infancy to the elderly.

C. Studies in a population of Denmark placed the prevalence at 1 in 10,000 individuals in the general population. The prevalence was the same for the familial and sporadic forms.

VII. Complications

A. In rare cases, sufferers may have prolonged weakness, seizures, confusion, memory loss, and personality or behavioral changes. Although uncommon, hemiplegic migraine attacks can be severe enough to cause coma. During such severe hemiplegic migraine attacks, weakness and speech troubles can last for several days or weeks but usually fully recover.

B. About 20 percent of people with this condition develop mild but permanent difficulty coordinating movements (ataxia), which may worsen with time, and rapid, involuntary eye movements called nystagmus.

C. In rare instances, permanent complications can develop including intellectual disability, permanent brain injury, cerebral atrophy, infarction, and death.

VIII. Medications and Treatments

A. There are no uniform recommendations regarding treatment, although drugs such as propranolol, verapamil, ketamine, flunarizine and naloxone have been used with variable degrees of response. No acute treatment has a proven efficacy to reduce the intensity and the duration of the aura, though.

B. CGRP inhibitors (also known as CGRP antagonists) are a new class of preventive medicine for treating most common migraines, but indications suggest this treatment would not be effective for hemiplegic migraines.

    1. The monoclonal antibodies CGRP inhibitors on the market are Aimovig (erenumab-aooe), Ajovy (fremanezumab-vfrm), Emgality (galcanezumab-gnlm), and Vyepti (eptinezumab-jjmr).

C. Abortives are medications that when taken at the onset of an aura, can stop migraines.

    1. Ubrelvy (ubrogepant) is a calcitonin gene-related peptide receptor antagonist used for the acute treatment of migraine with or without aura in adults.

    2. CGRP inhibitors are also available as abortives. The current available ones are Ubrelvy (ubrogepant), Nurtec ODT (rimegepant sulfate), and Qulipta (atogepant).

D. Analgesics and non-steroid anti-inflammatory drugs can reduce the migraine headache.

E. SHM attacks in some cases can be treated with Verapamil.

IX. Contraindicated Medications

A. Triptans and ergotamines are contraindicated in the treatment of hemiplegic migraine because they tend to cause blood vessels to narrow and there is a risk of stroke. There is anecdotal evidence that triptans, beta blockers, and ergotamine derivatives may lead to ischemia in patients with hemiplegic migraine.

    1. However, some doctors do use triptans on patients with hemiplegic migraines with great success.

B. Some specialists also recommend avoidance of beta blockers as preventive therapy for patients with hemiplegic migraine.

C. Hormonal birth control is also typically contraindicated due to increased risk of stroke.

X. Treatments and Procedures

A. Transcranial magnetic stimulation (TMS) is a noninvasive procedure that uses magnetic fields to stimulate nerve cells in the brain.

B. Individuals who experience a severe migraine episode may require hospitalization, particularly for high fever, depressed consciousness, or seizures.

1. Anti-seizures medications (both anticonvulsant or anti-epileptic) may be used to treat seizures, such as those seen in FHM2.

XI. Associated Conditions

A. It is associated with a number of medical conditions, such as tumors, vascular disorders, and autoimmune diseases.

B. Strokes are associated with hemiplegic migraines. As the symptoms for both are nearly identical, it is difficult to discern whether it should be a cause for concern.

C. Transient ischemic attacks (TIA), also known as ministrokes, are temporary periods of symptoms similar to those of a stroke. A TIA usually lasts only a few minutes and doesn't cause permanent damage. A transient ischemic attack may be a warning for an impending stroke. Due to their similarity to and possible warning of strokes, anyone experiencing TIA should go to the emergency room immediately to ensure they receive proper diagnosis and care. About 1 in 3 people who has a transient ischemic attack will eventually have a stroke, with about half occurring within a year after the transient ischemic attack.

D. Other types of migraines

1. A large subset of HM patients also met the clinical criteria for basilar migraine during the attacks.

a) Migraines with brainstem aura, also known as basilar migraines, Bickerstaff's syndrome, brainstem migraine, or vertebrobasilar migraine, are headaches that start in the lower part of the brain, called the brainstem. They cause symptoms such as dizziness, double vision, and lack of coordination. The headache pain of a basilar migraine often starts on one side of the head and then gradually spreads and gets stronger. This type of migraine can last anywhere from 4 to 72 hours.

2. HaNDL (transient headache with neurological deficits and CSF lymphocytosis)

E. Epilepsy

1. FHM has associations with epilepsy. The occurrence of epilepsy was highest for patients with FHM1 (60%), and lower in those with FHM3 (33.3%) and FHM2 (30.9%).

2. Seizures independent of hemiplegic migraine attacks have been reported in some patients with FHM, with higher rates in patients with FHM2.

3. Focal motor seizure, focal sensory seizure, and complex febrile seizure have all been associated with hemiplegic migraines.

F. Neuropathy

1. A few cases of permanent neurologic deficits associated with hemiplegic migraine have been reported. Herein we present the case of a patient with permanent impairments due to hemiplegic migraine despite normalization of associated brain MRI abnormalities. Cases like these suggest the need to consider aggressive prophylactic therapy for patients with recurrent hemiplegic migraine attacks.

G. Vascular Disorders

1. Cavernomas are clusters of abnormal blood vessels, usually found in the brain and spinal cord.

H. MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes)

1. Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) is a condition that affects many of the body's systems, particularly the brain and nervous system (encephalo-) and muscles (myopathy). The signs and symptoms of this disorder most often appear in childhood following a period of normal development, although they can begin at any age. Early symptoms may include muscle weakness and pain, recurrent headaches, loss of appetite, vomiting, and seizures. Most affected individuals experience stroke-like episodes beginning before age 40. These episodes often involve temporary muscle weakness on one side of the body (hemiparesis), altered consciousness, vision abnormalities, seizures, and severe headaches resembling migraines. Repeated stroke-like episodes can progressively damage the brain, leading to vision loss, problems with movement, and a loss of intellectual function (dementia).

I. Rheumatological diseases

1. SHM is associated with various rheumatological diseases, including but not limited to:

    a) Rheumatoid Arthritis

    b) Scleroderma: A group of rare diseases also known by the acronym CREST syndrome for its symptoms: calcinosis, Raynaud’s phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia

(1) Compared to the general population, the prevalence of migraine is 2–4 times higher in patients with primary Raynaud's syndrome.[2] In addition, Raynaud's syndrome appears to be more prevalent in patients with migraine. There is also an increased prevalence of migraine in other diseases associated with Raynaud's, namely, Systemic lupus erythematosus.

XII. Sources

A. Headache Classification Committee of the International Headache Society (IHS). "The International Classification of Headache Disorders, 3rd edition (beta version)." *Cephalalgia : an international journal of headache* vol. 33,9 (2013): 629-808. doi:10.1177/0333102413485658

B. Black, David F. "Sporadic and familial hemiplegic migraine: diagnosis and treatment." *Seminars in neurology* vol. 26,2 (2006): 208-16. doi:10.1055/s-2006-939921

C. Pelzer, N et al. "Recurrent coma and fever in familial hemiplegic migraine type 2. A prospective 15-year follow-up of a large family with a novel ATP1A2 mutation." *Cephalalgia : an international journal of headache* vol. 37,8 (2017): 737-755. doi:10.1177/0333102416651284

D. Hansen, Jakob Møller et al. "Coexisting typical migraine in familial hemiplegic migraine." *Neurology* vol. 74,7 (2010): 594-600. doi:10.1212/WNL.0b013e3181cff79d

E. Grecco, Martin Pablo et al. "Sporadic hemiplegic migraine and CREST syndrome." *The journal of headache and pain* vol. 11,2 (2010): 171-3. doi:10.1007/s10194-010-0188-1

F. Prontera, P et al. "Epilepsy in hemiplegic migraine: Genetic mutations and clinical implications." *Cephalalgia : an international journal of headache* vol. 38,2 (2018): 361-373. doi:10.1177/0333102416686347

G. Vanmolkot, K R J et al. "Severe episodic neurological deficits and permanent mental retardation in a child with a novel FHM2 ATP1A2 mutation." *Annals of neurology* vol. 59,2 (2006): 310-4. doi:10.1002/ana.20760

[2] Headache Classification Subcommittee of the International Headache Society (2004) The International Classification of Headache Disorders, 2nd edn. Cephalalgia 24 (Suppl 1):9–160

H. Jen, J C et al. “Prolonged hemiplegic episodes in children due to mutations in ATP1A2.” *Journal of neurology, neurosurgery, and psychiatry* vol. 78,5 (2007): 523-6. doi:10.1136/jnnp.2006.103267

I. Klopstock, T et al. “Mitochondrial DNA in migraine with aura.” *Neurology* vol. 46,6 (1996): 1735-8. doi:10.1212/wnl.46.6.1735

J. Blicher, Jakob Udby et al. “Perfusion and pH MRI in familial hemiplegic migraine with prolonged aura.” *Cephalalgia : an international journal of headache* vol. 36,3 (2016): 279-83. doi:10.1177/0333102415586064

K. Kingston, William S, and Todd J Schwedt. “The Relationship Between Headaches with Epileptic and Non-epileptic Seizures: a Narrative Review.” *Current pain and headache reports* vol. 21,3 (2017): 17. doi:10.1007/s11916-017-0617-9

L. Ducros, A. “Migraine hémiplégique familiale et sporadique” [Familial and sporadic hemiplegic migraine]. *Revue neurologique* vol. 164,3 (2008): 216-24. doi:10.1016/j.neurol.2007.10.003

M. Joutel, A et al. “Les migraines hémiplégiques” [Hemiplegic migraine]. *Presse médicale* vol. 24,8 (1995): 411-4. PMID: 7899422

N. Haan, J et al. “Is familial hemiplegic migraine a hereditary form of basilar migraine?.” *Cephalalgia: an international journal of headache* vol. 15,6 (1995): 477-81. doi:10.1046/j.1468-2982.1995.1506477.x

O. Kumar, Anil, et al. “Hemiplegic Migraine.” *StatPearls*, StatPearls Publishing, 12 December 2020. https://www.ncbi.nlm.nih.gov/books/NBK513302/

P. Nilanjan R., Arpita M. “Biocomputational Analysis Establishes Genetic Association of Rheumatoid Arthritis (RA) and Migraine.” *bioRxiv*, (2020). doi:10.1101/2020.02.05.936534

Q. Hemiplegic Migraine - NORD

R. Basilar Artery Migraines: Causes, Symptoms, Tests, and Treatments

S. Disease Info- Hemiplegic Migraine

T. Familial or sporadic hemiplegic migraine | Genetic and Rare Diseases Information Center (GARD) – an NCATS Program

U. Rare Disease Database • Hemiplegic Migraine.

V. National Library of Medicine- Studies on Sporadic Hemiplegic Migraine

W. US National Library of Medicine Clinical Trials for Hemiplegic Migraines

X. Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes

Y. Mutations described in ATP1A2 gene related to FHM.

Z. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4220590/

AA. Hansen, J. M., Thomsen, L. L., Olesen, J., & Ashina, M. (2008). Calcitonin gene-related peptide does not cause the familial hemiplegic migraine phenotype. *Neurology*, *71*(11), 841–847. https://doi.org/10.1212/01.wnl.0000325482.64106.3f