Chapter 12

Headache with Transient Weakness and Positive Family History

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Case History

A 46-year-old patient presented to one of us for a better treatment of her migraine attacks, which had started in her childhood, but have become more frequent since she emigrated from the United States to Switzerland at the age of 27 years. Headache frequency was twice monthly when she presented to one of us. She reported premonitory symptoms consisting of dizziness together with an aching pain in all of her teeth. A few minutes later, visual disturbances begin, gradually starting from the periphery of one of her hemifields, moving to the center in about 5 to 10 minutes. Toward the end of the visual disturbances, the patient feels a weakness in her right arm, starting with a "feeling of heaviness," increasing to pronounced weakness, followed within about 5 minutes by a weakness of her right leg as well. The weakness has a variable duration of 24 hours to 3 weeks, and when maximal, she is unable to hold a glass and able to walk only with support of a person.

The headache usually starts about 5 to 10 minutes after the weakness. At onset, it is nuchal and then extends, over minutes, to a hemicrania with a maximum periorbitally. The pain is pressing and aggravated by movement, such as during walking around, and relieved by lying down in a dark, quiet room. Pain intensity is high, with the patient unable to follow her routine daily activities. There is accompanying phono-, photo-, or osmophobia, but no nausea. When referred to one of us, she treated her attacks with a triptan.

The patient's father suffers from very similar attacks including hemiparesis. A brother and a sister suffer from migraine without aura. One of her children had two attacks of migraine with aura with a mild hemiparesis; another has migraine with visual aura only.

The patient does not smoke and her past medical history is unremarkable. Neurologic and medical examinations between attacks have always been normal. Genetic testing is in process. A magnetic resonance imaging (MRI) scan was unremarkable.

Questions on the Case

Please read the questions, try to answer them, and reflect on your answers before reading the authors' discussion.

- Based on the clinical history only (no family history, no imaging), which differential diagnosis would be possible, and which others (name two) are less likely, but still possible?
- Which investigations, in addition to the MRI mentioned in our case, would you think of to rule out the above differential diagnoses?
- Which are two typical misdiagnoses such patients come across during their diagnostic odyssey?

- Can the diagnosis be made confidently based on International Headache Society (IHS) criteria?
- In patients with similar presentation and the same diagnosis, which abnormality would you expect in the neurologic examination?
- After having made the diagnosis, what would your considerations be concerning the acute treatment?
- Regarding prophylactic treatment, which aspects could be different, in this and other patients suffering from the same disorder compared to patients with the more common related headache syndromes?

Case Discussion

This is a typical case of familial hemiplegic migraine (FHM) with a hemiplegic or, more correctly, hemiparetic aura of variable duration and intensity, which occurs here in sequence with a visual aura. It is accompanied by a hemicrania that is associated with sensory hypersensitivity, fulfilling the IHS criteria for migraine headache. In this patient, the diagnosis of a familial hemiplegic migraine can be made.

Based on clinical history only (with no knowledge of the family history and no investigations), the most likely differential diagnosis would be the so-called syndrome of transient headache and neurologic deficits with cerebrospinal fluid lymphocytosis (HaNDL; *International Classification of Headache Disorders*, 2nd ed. [ICHD-II] code 7.8). HaNDL is a syndrome of unknown etiology. It may mimic migraine with prolonged aura, with the notable exception that there is a lymphocytosis on cerebral spinal fluid (CSF) examination. The episode may start with visual symptoms, but more often, there is one-sided paresthesias and weakness. The headache may precede the neurologic symptoms; it may be uni- or bilateral and accompanied by nausea, vomiting, and sensoriphobia. Although the headache lasts for several days, the neurologic deficits usually take a few weeks to disappear completely. The episodes may recur several times in the same individual and are considered to be benign. In contrast to FHM, HaNDL does not show any familiarity itself, but can be associated in about 30% with a family history of migraine. It could, however, be confused with sporadic hemiplegic migraine (ICHD-II code 1.2.5).

Two other differential diagnoses are less likely, but still possible, considering exclusively the clinical picture: cerebral autosomal dominant arteriopathy with subcortical infarctions and leukoencephalopathy (CADASIL) and mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS), a mitochondrial cytopathy.

CADASIL is a familial disorder that can cause migraine, transient ischemic attacks (TIAs) and, more often, recurrent strokes. The CADASIL mutation has been identified on the notch-3 gene on chromosome 19 and is inherited in an autosomal dominant way. Since its identification, it has been found in over 200 families worldwide. Deep white matter lesions are best demonstrated using MRI. Migraine, sometimes with prolonged aura, is part of the disorder, and typically begins at a mean age of 30 years, about 15 years before the first stroke.

Mitochondrial cytopathies, especially MELAS, are exquisitely rare disorders characterized by maternal inheritance and a disturbance of mitochondrial energy metabolism leading, amongst others, to encephalopathy that may be associated with migraine headaches. The leukoencephalopathic lesions will lead to progressive and permanent interictal neurologic changes, which are not observed in migraine with aura. Mitochondrial cytopathies may present with a multitude of other clinical manifestations.

Brain MRI is normal in migraine as well as in HaNDL syndrome and excludes many secondary headache types, but it is typically pathological in CADASIL and MELAS, showing deep white matter lesions on the T2-weighted images. If HaNDL syndrome is suspected, a spinal tap needs to be performed looking for CSF pleocytosis and mild elevation of protein concentration. Transcranial Doppler during and shortly after attacks was reported to show alterations in blood flow in the middle cerebral artery, and the electroencephalogram may reveal unilateral slowing over the affected hemisphere. If MELAS is suspected, then CSF lactate should be measured and the mitochondrial genome analyzed.

The most common misdiagnosis in FHM is probably that of a cerebrovascular accident (CVA), most often a TIA. Transient motor weakness is a hallmark of TIA, but rare in migraine with aura. In our patient, a strong argument against a TIA is that hemiplegic attacks started in her childhood. Furthermore, they did not change their clinical picture over several decades, which is not usually the case in TIA. A TIA does not usually occur associated with headaches, but it may (and it can) resemble a migraine attack in those with migraine history or susceptibility for migraine. Considering the time course of the aura in our patient, it is typical for migraine, with a *gradual* start, a progression within minutes, and a slow remission, as opposed to the mostly *sudden and simultaneous* onset of all symptoms and signs in TIA, diminishing subsequently. The constellation of neurologic symptoms and signs in a CVA is usually that of a syndrome bound to vascular territories, whereas those associated with migraine can often be explained by spreading symptoms across the cerebral cortex, disregarding vascular territories. Another useful distinction can be that CVAs do not tend to cause positive symptoms such as the illusions of a migraine aura (eg, teichopsia or tingling). A family history of migraine with or without aura may also be helpful.

In cases suspicious for TIA, the appropriate investigations, including clinical and laboratory tests to evaluate the risk profile (eg, cerebral Doppler, echocardiography [ECG], Holter ECG), need to be done, especially at the occurrence of the first attack.

A CVA occurring at the same time as a migraine attack is called a headache attributed to an intracranial vascular disorder (ICHD-II code 6.1.1 for ischemic stroke and 6.1.2 for TIA). A CVA presenting like an aura and occurring in the same topography is called a migrainous infarction (ICHD-II code 1.5.4).

The second most common misdiagnosis would be an epileptic seizure. In our patient, this is very unlikely, since in most cases, epileptic attacks are characterized by obvious positive motor activity consisting of tonic or clonic seizures involving head and limbs, and they are typically short-lasting (seconds to a few minutes). When Todd's paralysis (postictal motor weakness) occurs and persists for hours or even days, its differential diagnosis is a CVA, and not migraine aura.

The syndrome reported by the patient does indeed fulfill ICHD-II criteria for FHM. However, a subset of the attacks, namely those with weakness longer than 24 hours, would not. The reason is that the headache plus accompanying symptoms have to qualify for migraine without aura (ICHD-II code 1.1) in order to fulfill criterion C3 of FHM (Appendix 12-1). This is not the case in our patient, so it only fulfills criteria for "probable migraine without aura." However, as only two hemiplegic attacks are needed to make the diagnosis, this does not cause any diagnostic uncertainty in our patient.

In one-fifth of the FHM families, an association of permanent cerebellar signs like nystagmus and/or cerebellar ataxia is observed, each occurring in about half the patients, as well as dysarthria in about 10%.

Management Strategies

Triptans are contraindicated in FHM, according to the recommendations of all triptan-producing pharmaceutical companies. The main reason is their (small) vasoconstrictive effect, which may theoretically result in an ischemic event in conjunction with the vasoconstriction during the aura. When our patient came to see us, she had already been treated with a triptan. Even though in the absence of vascular risk factors and at the age of 46 years, the risk would probably be small to cause a CVA, we put her off the triptan and switched her to a high-dose nonsteroidal antiinflammatory drug (NSAID), which gave her sufficient relief. There is one report of a beneficial effect of intranasal ketamine on the duration of the FHM aura in some patients.

Familial and sporadic hemiplegic migraine are relatively rare conditions. Therefore, there are no controlled studies on prophylactic treatment, and recommendations are based on small series of patients or on case reports. Prophylactic treatment for hemiplegic attacks is rarely necessary since their occurrence is too infrequent. Frequent nonhemiplegic attacks in the same patients may however be an indication for prophylaxis. In such cases, recommendations follow those for the more common migraine types. FHM with cerebellar signs may respond to acetazolamide.

Case Summary

- This is a typical case of FHM.
- Differential diagnosis can be difficult and includes HaNDL, CADASIL, and MELAS as well as CVAs and epilepsy.
- In general, several investigations need to be done in FHM, in contrast to the more common types of migraine.
- In the acute treatment, vasoconstrictive substances like triptans and ergots are contraindicated; the most important substances to use are high-dose NSAIDs. Ketamine and intravenous verapamil might be beneficial.
- Due to a generally low attack frequency in FHM, prophylaxis is rarely needed.

Overview of Familial Hemiplegic Migraine

Familial hemiplegic migraine is a rare but well-studied disorder that has attracted clinicians and researchers for a long time. Its first description may date back to the seventeenth century. FHM shows an autosomal dominant inheritance pattern. Attacks of FHM are characterized by migraine headache accompanied or followed by transient hemiparesis or even hemiplegia, lasting from minutes to days. Alterations in consciousness ranging from somnolence to coma are not exceptional, can rarely become life-threatening for some individuals, and need to be treated accordingly, in case of doubt, including strict monitoring in an intensive care unit together with appropriate symptomatic treatment. Fever can be another clinical sign that is not to be found in the more common migraine types. Most attacks in FHM patients follow the temporal pattern of the more common types of migraine attacks, such as typical aura with migraine headache, with a duration of the aura of about 1 hour, followed by headache. Interestingly, the hemiparesis during the aura in FHM does not seem to be isolated, but always occurs in association with visual, sensory, or language disturbances. In contrast to the more common migraine with typical aura, where the visual modality is almost always involved, the visual symptoms in FHM are present only in about 3 of 4 attacks.

Another characteristic of FHM patients is their susceptibility to brain injury: even the mildest concussions may

lead to profound vomiting and brain edema, which rarely can be fatal. Furthermore, approximately 20% of the FHM families show permanent cerebellar signs and cerebellar atrophy in brain imaging.

Linkage studies have shown that approximately half the reported FHM families are linked to chromosome 19p13, whereas for a few families, linkage to chromosome 1 was found.

Ophoff and colleagues identified the first four FHM mutations on the gene *CACNA1A*, coding for the α1A subunit of a neuronal voltage-gated P/Q-type calcium channel. Since then, at least 14 different mutations have been reported in a total of 34 FHM families. The *CACNA1A* gene product is found in high concentrations in the cerebellum, cerebral cortex, thalamus, and hypothalamus. The so-called *T666M* mutation seems to be the most prevalent, being detected so far in 14 unrelated FHM families. Mutations on *CACNA1A* are also responsible, apart from FHM, for two other disorders, episodic ataxia type-2 (EA-2) and spinocerebellar ataxia type-6. The second FHM gene is called *ATP1A2* and encodes the α2 subunit of the Na^+/K^+ pump.

For further information on the complex genetic background of FHM, which would go beyond the scope of this clinical chapter, the reader can consult one of the numerous publications on the topic, some of which are cited in the Selected Readings.

Selected Readings

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Editorial Comments

Rare neurologic disorders can teach us a lot about more common entities, and in the field of headache medicine, there is no better example than FHM. What this case does is to challenge us to think broadly and consider other less common but important causes of headache. Furthermore, it broadens our interest in neurology and headache, as FHM is clearly solidly based on a definite genetic abnormality. FHM is the prototype of the future of headache study and research. Importantly, however, there are important therapeutic implications to the diagnosis of FHM. This case deserves very careful study and reflection, as Dr. Sándor and his colleagues have provided us with a challenging case in all respects.

Final diagnosis:

Familial hemiplegic migraine

Appendix 12-1. International Headache Society Criteria, 2004

1.2.4 Familial Hemiplegic Migraine

Description:
Migraine with aura including motor weakness, and where at least one first- or second-degree relative has migraine aura including motor weakness

Diagnostic criteria:
A. At least two attacks fulfilling criteria B to E
B. Fully reversible motor weakness and at least one of the following other aura symptoms: visual, sensory, or speech disturbance
C. At least two of the following:
   1. At least one aura symptom develops gradually over ≥ 5 minutes and/or different symptoms occur in succession
   2. Each aura symptom lasts less than 24 hours
   3. Headache that meets criteria B to D for migraine without aura (1.1) begins during the aura or follows aura within 60 minutes
D. At least one first- or second-degree relative has migraine attacks with aura including motor weakness (fulfills 1.2.4 criteria A, B, C, and E)
E. Not attributed to another disorder

1.2.5 Sporadic Hemiplegic Migraine

Description:
Migraine with aura including motor weakness, but no first- or second-degree relative has aura including motor weakness

Diagnostic criteria:
A. At least two attacks fulfilling criteria B to D
B. Fully reversible motor weakness and at least one of the following other aura symptoms: visual, sensory, or speech disturbance
C. At least two of the following:
   1. At least one aura symptom develops gradually over ≥ 5 minutes and/or different symptoms occur in succession
   2. Each aura symptom lasts less than 24 hours
   3. Headache that meets criteria B to D for migraine without aura (1.1) begins during the aura or follows aura within 60 minutes
D. No first- or second-degree relative has migraine attacks with aura including motor weakness
E. Not attributed to another disorder

Adapted from Headache Classification Committee of the International Headache Society, 2004.