Chapter 47

A Woman with Rebound Headache and Intermittent Paralysis

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Case History

A 44-year-old woman was referred by her local neurologists for management of chronic migraine headache. The patient developed headaches for the first time at age 12 years. The attacks were sporadic and ranged in severity from mild to severe, and could be associated with a variety of associated symptoms including photophobia, phonophobia, osmophobia, nausea, and vomiting. Beginning in her late teens, she began to experience an aura consisting of zigzag lines that spread across the visual field from medial to lateral. The aura was most commonly unilateral and bore no correlation to the sidedness of the subsequent headache. The patient believed that her auras would persist for approximately 20 minutes.

The headache began either at the end of the aura phase or shortly thereafter. The pain was not consistent in location, but most commonly occurred on the left side of the head. The pain, if it progressed to more severe levels, was associated with exacerbation by physical activity. The headache ranged in duration from 4 hours to 24 hours and was commonly alleviated by sleep. Over-the-counter and other medications allowed the patient to remain functional for the majority of her headaches. She had used a variety of agents both over-the-counter and by prescription for treating her headaches through her thirties, including aspirin, ibuprofen, and an analgesic combination containing butalbital and caffeine and another combination agent containing isometheptene mucate. These were of variable success. Eventually, she was given an ergotamine preparation with caffeine by mouth, which was more likely to produce benefit. At about age 35 years, she began to utilize medication in the triptan class, with increasing levels of success and with good tolerability.

Beginning at age 39 years, the patient underwent a change in her pattern of headaches. The attack frequency increased to three severe attacks per week. The patient continued to experience intermittent visual auras as she had in earlier life. The occurrence of aura did not correlate with the intensity of the headache attack save for consistently preceding the more severe episodes of headache. She continued to experience exertional worsening of her headaches as well as the previously associated symptoms with the attacks. She rarely progressed to vomiting with her headaches, and the intensity of the photophobia had abated somewhat. The attacks responded to rizatriptan 10 mg tablets. The degree of pain relief was related to the severity of the headache at the time of taking the medication. The more intense the headache and the longer its duration, the less the degree of relief the patient experienced. There had been no appreciable diminution in this response pattern despite the increased frequency of the headaches.

At about this time of the increasing frequency of her headaches that had begun in adolescence, she began to experience a new type of headache, which started in the occipital region and spread across the scalp. These headaches were rarely interfering with activity and were not made worse by physical activity. There were no asso-

ciated symptoms with these headaches. While the headache could last for up to 24 hours untreated, they typically responded to simple analgesics. She estimated that these headaches occurred on an average of 2 to 3 times per month. Although she had tried medications in the triptan family for these headaches, they failed to produce a reduction in this headache's severity or duration.

At age 42 years, the patient began to experience another new headache type. These headaches were strictly unilateral and only occurred in the right temporal and parietal areas. The pulsatile pain gave way to a deep aching after a matter of several hours, and persisted for the remainder of the attack. The attack of headache lasted at least 5 days and could persist for a week or more. The attacks were quite rare and occurred 3 to 4 times per year. During the headache, the patient was incapacitated and could not be left unattended by family members, since she would have the development of a left hemiparesis that spread from the periphery to central, and almost always began in the left upper extremity but invariably involved the entire left side, including a partial facial paresis. Her speech was described as garbled by family and she was often incoherent. She felt that she was unable to find proper words and the proper sounds. She was able to eat solid foods and drink liquids with minimal difficulties. She would develop photophobia and osmophobia during the headache phase; however, this fluctuated during the attack and commonly resolved in the first 48 hours of the attack. Anorexia and nausea were also common during headache, but again, typically only occurred in the first day or two of an attack.

The patient would develop a transient amnesia for the events of the attack, but was able to recall details within several days of the attack abating. The patient had not experienced any residual symptoms after the headache had subsided. These attacks of severe headache associated with hemiplegia were currently being treated with a nasally delivered opioid, butorphanol. Use of rizatriptan had failed to lead to resolution of the headache despite early intervention and repetitive dosing. She has also been treated with intravenous dihydroergotamine mesylate, without resolution of either the headache or any change in her associated symptoms.

The patient had a family history of incapacitating headaches, which had been diagnosed as being migraine, occurring in her mother and maternal grandmother.

She noted that her health had otherwise been good, without hospitalizations other than for childbirth and headache treatment. She was gravida III para III. Her menses were regular, occurring approximately every 32 days. She noted no correlation between her headaches and menstruation. While she experienced headache during pregnancy, they were neither frequent nor severe. She was taking no other medications other than those prescribed for her headaches. She had a college education and was currently employed outside the home in a business occupation. She consumed alcoholic beverages in modest amounts and did not make use of tobacco. She consumed on average approximately 150 mg of caffeine from all sources on a daily basis. She was in a stable marriage of 18 years duration. Other than for what the patient described as the usual life stresses associated with work and raising three teenagers, she denied any psychological factors contributing to her headaches.

In addition to the acute medication noted above, the patient had been treated with a variety of preventive medications, with either a failed response or poor tolerability. These included propranolol, atenolol, verapamil, divalproex sodium, amitriptyline, fluoxetine, and paroxetine. She had been given corticosteroids for her prolonged headaches, which she felt made an improvement in the duration of her attacks.

Her physical and neurologic examinations were within normal limits.

Standard laboratory values were obtained, and included Westergren sedimentation rate and antilupus antigens. A magnetic resonance imaging (MRI) scan with and without gadolinium contrast and a magnetic resonance angiography (MRA) of the internal carotid circulation were ordered on admission. These revealed evidence of multiple old infarcts in the distribution of the left middle cerebral artery. The MRA revealed a 50% stenosis of the left internal carotid artery, just distal to entering the skull. The patient was started on a course of preventive medications for her migraine and tension-type headaches, including nimodipine and protriptyline.

On the second hospital day, the patient developed her headache attack associated with hemiparesis. Analgesics and corticosteroids were begun within several hours of headache onset. The patient failed to respond and had significant hemiparesis and marked difficulty with word finding, comprehension, and speech on examination the following morning. The headache was still severe. The patient was given intravenous valproic acid 1 g over 7 minutes. Within 30 minutes, the headache had improved partially. By 2 hours postinfusion, the patient had complete resolution of the headache as well as complete resolution of all neurologic symptoms and signs on examination. Approximately 8 hours later, the patient began to experience recurrence of the headaches and hemiparetic symptoms. Another dose of valproic acid 1 g by intravenous administration was given. The patient had complete resolution of the headache and other symptoms within 30 minutes. There was no recurrence of the headache or other symptoms during the remainder of the hospitalization.

Questions on the Case

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

- What are the differential diagnostic entities to be considered?
- What is the role of the triptans in this patient's clinical presentation and treatment?
- Are all migraine headaches related to the same pathophysiologic basis?

Case Discussion

This patient presents with an evolving pattern of headaches of long-standing duration. Her initial presentation history is suggestive of a migraine with typical aura. She had a family history of migraine headaches, and her own headaches had the key diagnostic features of migraine and the migraine aura. That is, she had episodic headaches of at least moderate severity, unilateral in location, and exacerbated by physical activity. With these headaches, she experienced both gastrointestinal and neurologic migraine-associated symptoms in the forms of nausea, vomiting, photophobia, phonophobia, and osmophobia. Medications and other treatments, such as rest, had proven useful for her over the years to variable degrees of success, depending on the agent used.

In her late thirties, she underwent an evolution in her headaches. The headaches continued to meet the criteria for migraine headache, however the possibility of medication-overuse headache needed to be entertained since she was taking a triptan, rizatriptan, 3 days a week. This continued for a period of time, sufficient from a time-course to be associated with medication-overuse headache, but failing to demonstrate other features typical of this process; namely, the headache pattern continued at the same frequency of three per week and still continued to respond consistently to the rizatriptan. In medication-overuse headache, it would typically be expected that there would be a pattern of continuing escalation of her headaches in frequency, coupled with a clear reduction or loss of response to the acute medication. There was some variability in her response to the triptan during parts of her migraine headache history. The nature of the variability could not be clearly determined. It may have occurred because of diminution in response to the triptan, as would occur with medication overuse or if this was related to an increase in the intensity of some of her headaches. Along with this, we see a new headache being described that is distinct from her migraines in the nature and location of the pain. The evolution of migraine headache after a long stable pattern, especially with a new headache occurring unrelated to the migraines, is cause to investigate in greater detail. The change in both the frequency of the migraine as well as the development of the new headache may have been related to the patient having life issues that are impacting on her headaches; medication overuse would also need to be considered, although difficult to credit for this change, given the previously discussed issues. Although the patient would be considered relatively young to be entering menopause, occasional patients who approach this lifepoint will have changes occurring in their migraine attacks as a part of this physiologic change. The need to rule out a secondary cause of headache should be entertained, although there was nothing in the history to warrant investigation of this issue.

A likely working diagnosis at this time would be a combination of both migraine headache with prolonged aura and tension-type headache. This double diagnosis is more appropriate for several reasons, rather than using the diagnosis of chronic migraine. First, the headache frequency is marginal for the diagnosis of chronic migraine headache with 2 to 3 attacks per week of headache, translating into 8 to 12 migraine headaches per month with an additional 2 to 3 of the new headache variety. Fifteen headaches per month is the generally accepted headache frequency for chronic migraine. Second, the new headaches are distinct from her migraines in the nature and location of the pain, and devoid of the typical migraine-associated symptoms at any point in their occurrence. Thirdly, these headaches were nonresponsive to triptans, as was the case for her migraines. While there are many migraine patients who experience tension-type like headaches, these are differentiated from the headaches the patient experienced by their severity and their response to triptans.

Last, in her early forties, after a period of renewed stability of her headaches (although still occurring with frequency of several per week and having both migraines with aura as well as the tension-type headaches), the patient developed a third and more distressing variety of headache. This last headache possessed migraine-like components. It was a headache of significant severity, pulsatile in nature, and unilateral. The headaches were also associated with nausea, vomiting, photophobia, and phonophobia. It is here that issues related to her symptoms give concern for a secondary etiology to her headaches. The patient developed a variety of neurologic symptoms associated with these headaches that she had not experienced with her other headaches. The headaches are side-locked and have with them the occurrence of hemiplegic findings that are contralateral to the headache. These events were sporadic, occurring only several times a year, but were prolonged. The patient had complete resolution of her neurologic symptoms in the time period surrounding the events.

Hemiplegic migraine can occur in both a familial as well as a nonfamilial form. The patient has no relatives who have a history of headache associated with hemiparetic spells; therefore, a familial etiology to the hemiparetic-associated headaches is not viable. Although familial hemiplegic migraine is most often discussed, there are also nonfamilial forms and what has been termed sporadic hemiplegic migraine. The failure of the headaches to respond to triptans and dihydroergotamine is both reassuring as well as distressing. There is a paucity of data on the response of hemiplegic migraine to either class of medications she had used that are migraine specific. On the other hand, transient ischemic episodes tend to be repetitive and may be associated with significant headache prior to the development of permanent vaso-occlusive neurologic loss. Case reports suggest that the triptans and dihydroergotamine may both precipitate stroke in patients. Since the patient has a normal examination interictally, both hemiplegic migraine and transient ischemic attacks are considered as possible diagnostic entities.

The first step in elucidating the diagnosis in this patient after obtaining the history is a carefully performed physical and neurologic examination. This was undertaken with care to determine if there were any interictal neurologic findings, as well as to ascertain the status of her cerebral circulation and the potential for a cardiac source to play a contributing factor in this clinical picture. No evidence of organicity was found to underlie the presentation by examination. Despite the negative examination, the severity of the symptoms and their potential consequences suggested the need for neurodiagnostic testing and additional testing. A sedimentation rate was obtained to check for evidence of a connective tissue process such as giant cell arteritis or a lupus anticoagulant-associated vascular process. Atypical presentations of giant cell arteritis may occur, although rare, and certainly the episodic and fully resolving nature of her features would be most unusual for giant cell arteritis. Her age, considerably below that associated with giant cell arteritis, also minimizes this likelihood. The patient had no history of previous clotting disorders such as thrombophlebitis or pulmonary embolism, and she had not had a history of repetitive miscarriages, making the issue of a lupus anticoagulant process unlikely.

A change in the migraine pattern and the development of a new type of headache would by itself constitute a reasonable cause for obtaining a neurodiagnostic procedure. The choice of the MRI over computed tomography (CT) scan was based on the amount of clinical information that can be obtained from the MRI over the CT scan. The CT would only have been preferred if one were looking for acute hemorrhage. Despite a negative examination of the cardiovascular system, the occurrence of a vaso-occlusive process distal to the carotid artery in the neck remained a possibility. The possibility of vasculitis, major vessel occlusive disease, and diffuse small vessel disease remained possible etiologic candidates of her presentation. Patients with hemiplegic migraine additionally show evidence of diffusion changes on MR, but not stroke. However, stroke is always possible in a patient with migraine. It usually occurs in the territory producing the aura.

This patient had used triptans for several years and had also been treated with dihydroergotamine for her headaches. She recalls no incidence of headache that she treated with either of these groups of medications that resulted in the occurrence of new neurologic symptoms, even on a transient basis. The hemiparetic spells not only were not aggravated or made persistent by the use of these agents, but she also had never had neurologic symptoms in the distribution of the MRI and MRA findings of previous multiple infarcts or the vaso-occlusive disease in the distribution of the left carotid artery. There was no evidence for vasculitis, arteritis, or coagulapathy from her diagnostic testing. Her neuroradiologic testing failed to reveal an organic etiology for her hemiparetic spells, nor did they reveal any evidence that would have suggested the development of permanent cerebral changes related to these attacks or to treatment of the episodes with triptans and dihydroergotamine.

The 5-hydroxytryptamine 1 agonists are believed to act on the serotonin B receptors in the vascular system to contribute to their antimigraine effect, the mechanism being potentially to close arteriovenous anastomoses, reduce middle cerebral blood flow, but without diminishing cortical blood flow. Their activity at other receptors, such as the 1D and 1F receptors, may also play a role in terminating migraine but on an inflammatory versus a vascular basis. This vascular effect is notable since there have been cases of patients with headache who have developed stroke related to their use, as well as patients with subarachnoid hemorrhage who have had resolution of their headache pain following the use of a triptan. In this case, not only did the triptans not exacerbate her clinical situation, but they also failed to provide relief of the headache other than for her long-standing migraine attacks with typical aura.

In past decades, it was believed that the vascular changes associated with migraine were the preeminent factor, and that they were responsible for the occurrence of the neurologic events associated with migraine in the form of the aura and the neurologic symptoms associated with hemiplegic migraine. Older, less accurate technology supported these findings. Recent studies have led to a rethinking of the pathophysiologic basis for migraine headache. Migraine is now considered a neurologically generated process with secondary vascular effects, including changes in blood flow in the cerebral cortex associated with the wave of cortical spreading depression believed to be a possible initiating event in migraine. During

the aura phase of migraine, while there is a decline in cerebral blood flow, this occurs after the development of the aura and persists into the headache phase, suggesting that a neurologic basis for the migraine aura is occurring and that the blood flow changes are an unrelated event.

Divalproex has been used primarily as a treatment for the prevention of migraine headache, although a number of small studies have suggested that the intravenous bolus administration of valproic acid may terminate even a prolonged migraine attack. The mechanism by which valproic acid works to treat migraine is not well understood, but may involve a variety of potential physiologic targets associated with the process. These include increasing brain gamma-aminobutyric acid, an inhibitory neurotransmitter, and decreasing aspartate and glutamate, both excitatory neurotransmitters. It may increase brain serotonin as well as both leu-enkephalin and met-enkephalin. It also produces a decrease in *N*-methyl-D-aspartate receptor activity. These processes may modulate the pain of migraine as well as play a role in the migraine-generating system and in the periphery, with action inhibiting the development of neurogenic inflammation.

Although the patient was refractive to the oral administration of divalproex this may also have been related to the dosage administered. Patient dosing is often limited by adverse events precluding the achievement of adequate levels to produce effect. However, the action of valproic acid may have acute effects that modulate migraine that are not evident with the oral formulation because of the pharmacokinetics of the drug and the potential this may have to modulate the above process. The slow administration of valproic acid over 30 minutes has little if any effect to modulate migraine in the experience of the Clinic, yet when it is given in adequate dosages of approximately 1 g over a period of less than 10 minutes, it produces highly rapid resolution of migraine and the associated migraine features in many patients. Such was the case for this patient, who had failed to respond to agents often used for treating migraine with prolonged aura, or hemiplegic migraine, corticosteroids, and opioid analgesics. However, she had rapid resolution of her migraine headache and the associated hemiplegia for a short period following the administration.

The recurrence of the migraine was not unanticipated since her hemiplegic spells of headache had lasted approximately 5 days in the past, and therefore, it was anticipated that if the valproic acid was acting only symptomatically, then repetitive doses over this 5-day period would prove necessary. However, after the second dose, the patient had complete resolution of her symptoms roughly 34 hours after the onset of the first symptoms.

Given the history of repetitive episodes of these hemiplegic spells that had been unaffected by the use of the triptans, it would be tempting to allow the patient to continue their use. The contralateral findings, however, of a moderate carotid stenosis and suggestion of multiple infarcts potentially related to this finding would make it questionable if they should be continued. The patient had experienced no neurologic events with or without headache that would have suggested these findings to have clinical significance. Therefore, the continued use of a triptan might be allowed if the patient were aware of the risks and was carefully monitored.

The use of valproic acid as an acute therapy to be used as a self-administered treatment is rendered difficult, since it can be given intravenously but not by intramuscular or subcutaneous injection secondary to muscle toxicity. The alternative that was attempted was to give the original oral sodium valproate at a 1 g dose. This did not prove to be a successful treatment for follow-on headaches, but the intravenous form continued to provide successful treatment.

In patients with hemiplegic migraine, the use of preventive medications should be entertained if the episodes are significant in their recurrence and severity of the associated symptoms. In this patient's case, not only did we need to prevent the hemiplegic migraines, but we had to prevent her migraine with aura episodes as well. Given the failure the patient had experienced with other treatments, it was decided to use the cerebral-specific calcium channel antagonist nimodipine, despite cost issues, since it has been the experience at the Clinic that this agent was far more successful in reducing or eliminating the occurrence of the neurologic symptoms associated with complicated migraine as well as migraine with and without aura, than other calcium channel antagonists. The use of the nonsedating tricyclic was also added to the regimen. The tricyclics by themselves are useful preventive agents in migraine, but again from an experiential view, have tended to be more effective in high-frequency migraine and in migraine of long duration, where they appear to reduce the duration of the attacks.

This patient did not have a concomitant sleep disorder; therefore the need for a sedating tricyclic for prevention was not needed. Protriptyline, despite having the typical anticholinergic effects and alpha-agonists effects typical of this class, is devoid of the issue of weight gain; weight loss is a more common occurrence. Agents such as the beta-blockers are believed to be at least relatively contraindicated in hemiplegic migraine and other complicated migraines, because of the reports of permanent neurologic symptoms following their use.

Selected Readings

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Thomsen LL, Ostergaard E, Olesen J, Russel MB. Evidence for a separate type of migraine with aura: sporadic hemiplegic migraine. Neurology 2003;60:595–601.

Yu W, Horowitz BH. Familial hemiplegic migraine and its abortive therapy with intravenous verapamil. Neurology 2001;57:1732–3.

Editorial Comments

Drs. Freitag and Feoktistov present a most interesting case of what appears to be nonfamilial hemiplegic migraine with true episodes of hemiplegia. Many patients are called hemiplegic, when in fact, they have mainly sensory symptoms such as a numbness, but this appears to be a special case. One cannot disagree with the diagnostic formulation here and the excellent discussion, including the fact that the patient probably had an element of medication-overuse headache. However, the role of ongoing use of vasoconstrictive agents such as the triptan class or ergotamines can be debated at length. Generally, it would be wise to avoid these classes of medication in patients with "stroke," and this is the general recommendation on their usage in practice. They are contraindicated in the United States in patients with hemiplegic migraine, even though Drs. Freitag and Feoktistov cite some literature and personal experience suggesting that patients can still receive these medications without harm. The presence of radiologic infarction in the left hemisphere with or without migraine would be sufficient to make triptans and ergots contraindicated, even if the "migraine attacks" were not affected by these medications. Of course, individual consideration must be given in each case, and this is the result of a risk-benefit analysis and discussion with each patient, so different approaches are possible in some cases, as suggested by Drs. Freitag and Feoktistov. This case demonstrates the borderland of migraine and stroke.

Final diagnoses:

Nonfamilial hemiplegic migraine and medication-overuse headache