CHAPTER 44

THE OENOPHILE WITH THE DISAPPEARING MIGRAINE

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Case History

This patient is a healthy, athletic 40-year-old wine connoisseur (oenophile) who has suffered from migraine headaches dating back to childhood, when he was also very susceptible to motion sickness. The headaches became quite severe in his twenties, when he noted that the headache might be precipitated by red meat, pizza, and red wine. There was never any prelude or aura and the pain began as a throbbing in the right occipital region that spread forward to the right eye. The eye might tear but he had never noted drooping of the eyelid or alteration of vision. When he was a teenager, the headaches were usually accompanied by nausea and vomiting. As he grew older, vomiting rarely occurred and he had not vomited in recent years. He usually had to lie down in a darkened room and found that acetaminophen with codeine or ibuprofen reduced the intensity of the pain only slightly. Of a number of triggers, red wine was the most potent and he found that even half a glass of red wine invariably induced a headache within an hour and often sooner. He found that particular wines with a high tannin, or oak, or sulfur content were most noxious and certain Bordeaux, Riojas and ports would trigger a headache almost immediately. This lead him to curtail his hobby, although he continued to collect rare wines. In the past few years, his migraine attacks occurred once or twice a month, often precipitated by abrupt changes in the weather or in let-down periods after emotional stress.

His family history is positive for migraine. His mother suffered from severe migraine, also precipitated by red wine. His father suffers from Meniere's disease, but not headache, and his paternal uncle suffers from migraine. His maternal grandmother has continued to suffer from migraine through to her nineties, but her headaches improved after she was prescribed medication for hypertension.

On a very hot day one August the patient and a friend trekked for 4hours up a low mountain and after reaching the top they lifted some heavy rocks to make a cairn. On straining to lift a particularly heavy rock, the patient developed a burning itchy sensation in his right eye and felt light-headed. After a few minutes he noted a tingling in the right side of his lips that spread to the adjacent cheek area. After a further few minutes his left hand developed a crawling tingling sensation and this spread proximally. His left toes went numb and this numbness also spread up the left leg. By the end of 5 minutes his whole left side, from the neck down, felt numb. This was not followed by any headache but he felt faint and profoundly tired. After a further 5 minutes, the symptoms gradually cleared completely and he headed down the mountain. At no time did he have any weakness or loss of function of his limbs. However, as he trekked downhill he experienced the same sequence of events twice again, always starting in the right upper lip and appearing within minutes in the left limbs.

From August through to the following June he experienced many of these stereotyped attacks. By June they were occurring several times a day, often occurring in a flurry where he might experience three or four attacks in a few hours, each lasting only a few minutes. On a few occasions, however, the numbness or buzzing sensation in his right lip and left hand persisted for 20 to 30 minutes. He describes the attacks in detail as follows. First the right upper lip becomes "tingly" and this spreads to involve the right side of the nose, and the nostril stings as if he was about to sneeze. Then numbness spreads to the

adjacent cheek area, and then the lower lip and the inside of the mouth on the right become numb. The right eye develops a burning, itchy feeling but there is no tearing. Then after a few seconds the left fingers and hand become numb. The patient does not think that any one digit becomes numb first, but rather the fingers and whole hand become numb simultaneously and then the left arm and foot are affected, with the whole march occurring over 5 minutes. Eventually his torso is involved and everything is numb from the neck down. The foot feels tingling as if it were "asleep," but when he touches it he can feel the contact and does not appear to have lost touch sensation. He may feel "spacey," which he compares to the "runner's high" he used to get as an athlete. He sometimes feels dizzy and he senses that his hearing is diminished. There may be a vague left frontal discomfort that he says is very different from the old migraine. Pain is not a prominent feature, nor is there nausea. Most of the attacks have been associated with heavy physical activity and he noted that occasionally attacks have been triggered by bending down when picking up a heavy object, particularly when he keeps his neck hyperextended while still in the bending position, as when lifting weights.

The patient was seen by several physicians who carried out an electroencephalogram (EEG) and magnetic resonance imaging (MRI) which were normal, and the attacks were interpreted as an evolution of his migraine. Eventually he was prescribed the β-adrenergic receptor blocker nadolol. This seemed to reduce the frequency of the attacks for a time but after several months they again became more frequent. He himself believed that they were quite distinct from his previously experienced migraine attacks. Indeed during the year since the acute event he has never experienced another episode of what he had previously considered to be migraine attacks. Furthermore he tested himself by consuming four glasses of Côtes de Rhône and two glasses of Rioja. He developed a sensation of nasal stuffiness and flushing, which he had, in the past, interpreted as a warning that he was going to get a migraine. However, on this occasion no other symptoms occurred.

When seen some 9 months after the event on the mountain, the patient was noted to be an exceptionally fit, athletic-appearing man. His blood pressure was normal and no bruits were heard over the head or neck. The only abnormal finding was a slight vertical skew deviation with diplopia when the patient looked up, due to reduced elevation of the right eye. There was no ptosis or pupillary asymmetry. A brief attack was witnessed in which he complained of a numb tingling of the right upper lip that spread in a few seconds to the right cheek area and, within 30 seconds, to his left hand but did not proceed further and lasted only about 2 minutes. During this time there was no change in pulse rate or blood pressure and no alteration of consciousness.

Magnetic resonance imaging scans did not demonstrate any structural changes in the hemispheres or in the brain stem. Magnetic resonance angiography (MRA), however, revealed a narrowed intracranial right vertebral artery, which appeared to end in the posterior inferior cerebellar artery (PICA) without connecting to the basilar artery. A traditional cerebral angiogram demonstrated more clearly the abnormality in the vertebral-basilar territory. The vertebral artery itself showed abnormalities in the intracranial portion with areas of dilation and narrowing of the lumen consistent with a resolving dissection. The left vertebral artery was entirely normal and supplied the basilar artery and the remaining branches including the left PICA, which were well visualized. No abnormalities were seen in the cervical carotid arteries or their intracranial branches. The circle of Willis was intact.

After the angiogram the patient had many daily attacks of ipsilateral face and contralateral limb numbness and he was then started on warfarin sodium and aspirin. He was also prescribed gabapentin at a dose of 300 mg, three times a day. Within a week his attacks lessened and he was then free of all attacks over the next 3 months, by which time it was decided to stop the anticoagulants. In the month subsequent to stopping the warfarin sodium, he remained attack free while taking only gabapentin. One evening he decided to put himself to the test by consuming three-quarters 30of a bottle of his best Bordeaux. He experienced facial flushing but did not develop any symptoms of migraine that evening. The following morning he awoke with a feeling of nasal stuffiness and was certain he was going to develop a migraine. He went back to sleep for another 2hours and then awoke refreshed and headache free. On another occasion he consumed several glasses of port. He has had none of his transient sensory episodes and has had no headache. Needless to say he is delighted that he no longer suffers from migraine and apparently can resume enjoyment of his old hobby, which he had had to put aside for almost 20 years. Repeat MRI and MRA have been done and show no change in the configuration of the vessels and no evidence of brain-stem infarction.

Questions about This Case

- What is the nature of the sensory attacks?
- How does one explain an apparent sensory march in the brain stem ?
- Can spreading depression occur in the brain stem ?
- Why are the sensory attacks no longer occurring ?
- Why does he no longer suffer from migraine ?

Case Discussion

This man's sensory attacks seem to follow a pattern consistent with a localization in the brain-stem. As every medical student knows, any neurologic syndrome that involves one side of the face and the opposite limbs is presumed to have its basis in the brain stem. The ventral spinothalamic tract in the lateral medulla is arranged with the face fibers medial and adjacent to the arm fibers, which are slightly more lateral, whereas trunk and lower limb fibers are arranged still more laterally. The blood supply consists of small arterial branches of the posterior inferior cerebellar artery that penetrate the lateral medulla from the surface. Thus, the face fibers being situated most deeply would be the most susceptible to ischemia. The anatomical localization seems quite clear. However, the problem of pathogenesis is more difficult.

Transient neurologic phenomena are usually either of electrical or vascular origin. The time frame of the attacks would suggest an anatomical progression or march. Since this man had suffered from migraine headaches in the past, one might have wondered whether the march was akin to that seen in migrainous aura where there is spreading depression over the visual cortex. There the rate of depression has been calculated to proceed at a rate of 3 mm per minute. Sensory pathways in the brain stem are very compact and the area occupied by sensory fibres in the spinothalamic tract and the adjacent trigeminal sensory fibers is quite minute. Consequently, a march of depression could appear to be much more rapid. However, spreading depression is presumably a neuronal phenomenon and is not known to occur in bundles of axons. Nevertheless, the time frame seems similar to other marches ascribed to migraine. Andermann reports a woman with migraine (and epilepsy) who described a tingling in the upper and lower lips and tongue that spread over 10 minutes to involve the hand and lasted an hour. The only difference from our case is that it involved the ipsilateral face and hand and presumably arose from cortical structures.

Another explanation must be found for this man's clinical picture. The analogy to amaurosis fugax is more applicable. Patients who experience amaurosis fugax describe a progression of their visual deficit, which presumably indicates an extension of the area of the retina that becomes ischemic as emboli pass through the retinal circulation (curtain sign). Perhaps what this man describes is due to ischemia that is initially localized in the sensory fibers subserving the face area and as the ischemic area spreads sensory fibers coming from the contralateral hand become ischemic, the leg fibres being involved only during a few attacks. As noted, the face fibers would be most susceptible to reduced perfusion through the small penetrating branches of the PICA and might explain why his attacks always start in the face. The nature of these attacks then would seem to be most probably due to decreased perfusion through a precarious blood supply via the PICA and the abnormal right vertebral artery. The supply is particularly precarious in that there is no obvious collateral flow from the opposite vertebral or basilar arteries.

Dissection of cervicocranial vessels is now becoming recognized with increasing frequency, in part due to the ease with which the diagnosis can be established with newer imaging techniques. The underlying cause for most dissections remains obscure, although many have a history of trauma. Even in these cases it may be presumed that there is an underlying defect in the vessel wall. Occasionally patients are known or are found to have fibromuscular dysplasia.

Dissection of the carotid arteries has been reported in patients suffering from migraine, but the association may well be fortuitous. However, a recent study reported migraine in 40 % of a series of 50 patients with dissection versus a 24 % occurrence of migraine in controls suggesting a greater than chance connection. It has been suggested that recurrent attacks of migraine in which there is much vasospasm may render the vessel wall susceptible to dissection. In experimental studies ergotamine may play a role in thickening the arteries. This patient had never taken ergotamine or methysergide.

In this man's case the onset of the dissection presumably occurred when he did some heavy lifting. Whether or not his many attacks of migraine in some way predisposed the particular vessel to dissection is unclear. It is of interest that the previous migraine pain was perceived on the same side as that of the dissection. It may well be that a congenital anomaly, a failure to connect of the terminal vertebral artery on that side with the basilar artery, may have predisposed him to dissection but could it also have in some way determined the side of the migraine?

Dissection may also present with head pain. Indeed pain may be the only manifestation of dissection of either the carotid or vertebral arteries. We have recently encountered a nonmigrainous young serviceman whose only evidence of dissection of a vertebral artery was continuing intense pain behind the mastoid with no neurologic deficit. In the case recounted here, the patient had had migraine all his life until he suffered what was presumably an event that caused brain stem ischemia. The subsequent attacks are difficult to ascribe to a specific diagnostic category. Are they migraine equivalents? Are they transient ischemic attacks (TIAs), due to emboli or transient reduced perfusion? Are they epileptic phenomena? The actual event and subsequent events are most unusual. Two aspects are particularly interesting: the time

frame in which they occur and the apparent anatomical localization of their origin.

The time frame in which the events occur is most suggestive of some sort of "march," as has been discussed already. "Marches" are seen in epilepsy and migraine and possibly in ischemia. The timing of the march of a visual aura in migraine presumably corresponds to the timing of the spread of depression of cortical activity over the visual cortex and usually spans about 20 minutes. The march of an epileptic seizure, either sensory or motor, is presumed to follow the anatomic distribution of cortical representation of peripheral somatic structures but the timing generally is very rapid, the whole process being accomplished in a matter of seconds. The development of a neurological deficit in an acute transient ischemic attack lasts minutes according to the territory rendered ischemic. Amaurosis fugax which is essentially a TIA localized to the retina usually occurs over a few minutes. If the attacks are due to some sort of spreading depression their brief duration would certainly suggest a very small area to be covered as one might expect in the tightly packed brain stem as compared to the relatively extensive cortex-sulci to be covered in a process proceeding over the visual cortex or the postrolandic area.

There is a suggestion that the spreading depression is related to hypoxia in that methods that augment oxygenation may abolish the symptoms. Wolff found that whereas 10 % carbon dioxide inhalation abolished the aura temporarily, adding 90 % oxygen abolished both the aura and the subsequent development of headache. Presumably the hypercapnic hyperoxic state alters the cortical spreading depression. Perhaps then the spreading sensory symptoms in this patient arise in the brain stem from a state of localized ischemic hypoxia.

However, even if the localization can be established, a physiological problem remains in hypothesizing a "march" or at least a spreading depression in the brainstem. Generally a march involves activity in neuronal cell bodies or their immediate dendritic networks. The brainstem structures generally involved in producing a Wallenberg's syndrome are neuronal pathways or axons.

Why have the presumed TIAs stopped? Is this because the warfarin sodium prevented clot formation, thus removing a source for emboli ? Why did the migraine attacks stop ? It would be fascinating to hypothesize that they stopped because of some change in the migraine generator. Recently neurologists have sought the migraine generator with as much enthusiasm as Ponce de Leon sought the fountain of youth. On the basis of observations of patients who had stimulating electrodes inserted into the periaqueductal grey matter in an effort to control pain, Raskin hypothesized that there might be a migraine generator in the brain stem. Work with positron emission tomography (PET) scanning on migraineurs by Weiller and Diener and others have shown that there may well be a center in the brain-stem that sets off and maintains the sequential events of the migraine episode. Their studies show that an area in the mid-dorsal pons remains activated even after the clinical symptoms of the migraine attack have been terminated by sumatriptan, which presumably acts peripherally to block the migraine process. Perhaps in this patient, the migraine generator has been rendered inactive, at least for the present, so that even a previously effective stimulus such as red wine fails to start the process. Space does not permit discussion of the interesting association between wine and headache; why it only happens with certain wines and to certain people and even to them only at certain times. This patient had many ideas on this topic and we can learn a great deal from thoughtful and observant patients. This is the stuff of neurologic armchair philosophers musing over a glass of port, but sober neurophysiologists in the laboratory may soon be able to answer some of these questions and our patients will benefit immensely.

Management Strategies

Management depends almost entirely on the presumed diagnosis. Initially it was thought that this man, having had typical migraine attacks all his life, was now developing a more complex migraine presentation. Consequently the treatment recommended was a medication commonly prescribed for the prophylaxis of migraine, i.e., nadolol at an initial dose of 40 mg per day. When the attacks continued to be very frequent the dose was doubled.

It later became apparent that the patient's attacks were not typical of migraine, not even of "basilar artery migraine," and further investigation was indicated. It is a good general rule that when there is a change in migraine pattern that the patient be carefully re-evaluated and other nonmigraine processes be considered. The second diagnosis considered was transient cerebral ischemic attacks from an as-yet-undiscovered source. Aspirin was then prescribed. When this did not reduce the frequency of the attacks, it was clear that much more extensive investigation was needed such as an MRI. This lead to the discovery of the anomalous posterior circulation and the performing of an angiogram that demonstrated a dissection. Even though it is presumed that the dissection had actually taken place some 9 months previous to the discovery of the dissection, anticoagulants were prescribed. Since there was still some doubt about the actual cause of the symptoms, and on the basis that there might still be some sort of neuronal activity underlying the attacks, gabapentin

was precribed simultaneously, although the justification for its use at this time might be questioned. At the time of writing the patient was very loath to give up the one medication that seemed to bring relief at last. It will be of of interest to see if the attacks return when eventually the gabapentin is also stopped.

Case Summary

A 40-year-old man with lifelong unilateral migraine, readily precipitated by red wine, suffered a dissection of the ipsilateral vertebral artery. Thereafter he suffered frequently recurring attacks of brain-stem sensory symptoms but the migraine attacks no longer occured, even when he drank red wine, an invariable precipitant prior to his dissection. The attacks were reduced by nadolol, aspirin, and warfarin sodium, but only after the addition of gabapentin was he free of both sensory attacks and migraine. This freedom continued when all medications other than gabapentin were withdrawn.

It may be that migraine predisposed the particular artery to dissection but the reason for the cessation of migraine attacks after the dissection can only be surmised. What would be is most intriguing the possibility that the dissection and subsequent brain-stem ischemia in some way altered the hypothesized pontine migraine generator.

Selected Readings

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Editorial Comments

The pathophysiology of migraine is increasingly being defined in more precise neurobiologic terms and concepts, yet remains complex and somewhat enigmatic. Cases such as this one by Dr. Nelson raise many questions about the basic nature of migraine and its genesis. What turns the putative "generator" on, and importantly, what turns it off? Does it really exist? There is a lot of room for speculation and reflection on these matters, a process that has served neurologists particularly well while waiting for definitive answers, which we all hope will come sooner rather than later.