Chapter 50

Poison a Headache?

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Case History

A 47-year-old woman was admitted to the hospital with intractable headaches. She had suffered chronic daily headaches for the past 14 years. Prior to that time, she had had 3 to 4 episodes of migraine without aura per month. These headaches began about the time of her menarche at age 12 years. Triggers over the years have included her menses, midcycle (ovulation), and delaying a meal. Her mother had similar headaches.

Her headache pattern changed 14 years ago. She was in a motor vehicle accident and sustained a concussion (10-minute loss of consciousness) and a whiplash event. Due to persisting neck pain, she was begun on acetaminophen with codeine. About 8 weeks later, she developed a predominantly left-sided persistent dull headache, which was constant and moderate in intensity. Her migraines continued to occur as well.

Over the next 4 months, she reported worsening pain down her right arm and weakness. Magnetic resonance imaging (MRI) scan of both her brain and neck was obtained. The brain MRI was normal, while the cervical spine MRI showed a right-sided C5–6 disk herniation. She underwent a diskectomy with good resolution of the arm weakness and pain. Her neck pain persisted, and she was placed on oxycodone and acetaminophen.

For the next 13 years, she remained on oxycodone with acetaminophen. The daily left-sided headaches continued, and her migraines seemed to increase in frequency to 2 to 3 times per week. She was prescribed additional analgesics and muscle relaxants in an attempt to alleviate her neck pain, which clearly seemed to be due to muscle spasm, and to help her headaches, which seemed to worsen despite ever-increasing amounts of pain medication.

Six months prior to the current admission, a neurosurgeon admitted her to the hospital. A left-sided deep computed tomography (CT)-guided C2 root block was performed, which eradicated her left-sided aching headache for over 12 hours. Therefore, the neurosurgeon performed a decompressive procedure on her left C2 nerve root. At the time of operation, he noted impressive scarring around the root. Subsequent to the procedure, the constant left-sided headache was relieved, but she complained of mild holocranial tight headache, with multiple occurrences of her migraine each week. Her neck was persistently tight as well. Over the next 6 months, she was placed on escalating amounts of acute-pain medications.

At the time of her current admission, the patient was desperate. She was taking approximately 12 acetaminophen/caffeine/butalbital tablets per day, 4 to 6 oxycodone with acetaminophen tablets per day, and 10 to 16 (or more) 200 mg ibuprofen tablets per day. She was taking 20 mg of diazepam three times a day. Over the past 10 years, she had failed multiple prophylactic drugs, including beta-blockers, heterocyclic antidepressants, calcium channel drugs, and anticonvulsants. She was complaining of symptoms compatible with gastritis, poor sleep (waking up each night at around 2 to 3 am with a headache), and neck pain. The headaches were causing severe disability, and there was significant palpable posterior cervical muscle spasm. She seemed sedated, and she was dysarthric.

Questions on the Case

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

- What were the diagnoses this patient had?
- Why did she develop persisting headache?
- What are her treatment options now?
- How can her medication regimen be simplified, with a better outcome?
- Does she need further testing, and if so, what tests?

Case Discussion

This patient clearly had a history of migraine without aura (International Headache Society [IHS] category 1.1 by 2004 criteria). She had triggers, as well as a positive family history. The headaches were intermittent. After she suffered both a concussion and a whiplash event (the two usually occur together), she developed new problems. Headache is the most common symptom of postconcussive syndrome. Posttraumatic headaches can mimic any of the primary headache disorders. Neck pain is also a frequent symptom. Both usually resolve in less than a year unless something is perpetuating them.

This lady had numerous perpetuating factors. In the case of posttraumatic headaches, it is important to consider the possibility that more than one process is going on, and to treat all the headache types and etiologies. Her herniated cervical disc was causing a cervical radiculopathy. However, her symptoms only partially improved after it was successfully addressed. While the IHS does not recognize late-onset posttraumatic headaches, many headache experts diagnose and treat such conditions. In this case, the patient had also developed a left-sided C2 dorsal root entrapment. The surgeon had recognized the association with an injury of sufficient severity to cause a herniated disk. He realized there might be associated upper cervical root entrapment, causing a persistent side-locked headache that sometimes has its onset weeks to months after the injury. She had partial loss to pin sensation in the left C2 dermatome when he tested her, and a complete response to a deep CT-guided root block.

Despite the improvement in her radiculopathy and left-sided headache, she continued to have daily headaches, with features of both chronic tension-type headache as a background, and frequent exacerbations reminiscent of her migraine. Her neck was clearly painful, with palpable muscle spasm. She had developed side effects from her acute remedies, including dyspepsia, and intoxication from the diazepam.

Refractory headache has been reported to develop in migraineurs who begin analgesics for other medical conditions, or who overuse them for headache treatment. It may be one of the perpetuating factors in posttraumatic headache. The IHS does recognize medication-overuse headache. Many authors have described analgesic-rebound headache. This patient was consuming ever-increasing amounts of medication without discernible benefit, and accumulating side effects. The likelihood of gastrointestinal bleeding from the ibuprofen, liver damage from the acetaminophen, and encephalopathy/intoxication from the narcotics, barbiturate, and benzodiazepine necessitated her admission to the hospital.

Investigation

Patients with chronic posttraumatic headache and neck pain deserve a comprehensive evaluation. A complete history and examination are mandatory, and prior studies should be reviewed (the actual films if possible, not just the reports). It is important to review which treatments were employed, when, and at what doses. This patient had a normal brain MRI in the past, and an abnormal cervical spine MRI with a problem that had been addressed (the herniated disc).

During her second neurosurgical evaluation, another MRI of the cervical spine was obtained which showed only postsurgical changes. Standard imaging techniques are not expected to reveal upper cervical root pathology. An appropriate history and response to deep CT-guided root block are considered diagnostic. Even though these problems were addressed, her other symptoms continued unabated; in fact, they seemed to progress.

In a patient with a progressive headache pattern, repeat imaging may be warranted. In this case, a repeat brain MRI was in fact obtained, which was again normal. Additionally, a lumbar puncture was performed. The possibility of occult cerebral spinal fluid leak causing headache or of raised intracranial pressure was considered. Her opening pressure was 120 mm H_2O, which is normal.

Management Strategies

It was felt that the patient had clear medication-overuse and possible analgesic-rebound headaches. It was not clear if her cervical posterior paraspinal muscle spasm was due to her old injury, her surgery, her worsening headaches, or some combination of all of these. The attending physician felt that her medication regimen needed to be simplified, and future medications must be limited. It was also felt that a prophylactic agent needed to be chosen that might alleviate both her headaches and her severe neck pain, without significant systemic side effects.

Our patient was admitted to the hospital. She was begun on repetitive metoclopramide followed by dihydroergotamine intravenously three times a day, titrated to the effective subnauseating dose. Her acute symptomatic medications were stopped (the diazepam was slowly tapered). She was placed on 150 mg phenobarbital at bedtime to prevent withdrawal seizures from the butalbital and to improve sleep. This was tapered over 6 weeks. Her headaches rapidly improved, but her neck pain persisted. On hospital day 4, her attending physician injected her with botulinum neurotoxin type A (Botox). This was administered at 25 units in the "wrinkle protocol" (divided into injection in the procerus, corrugators, frontalis, and temporalis muscles), and also at 40 units bilaterally into the

regions of the splenius capitis, semispinalis capitis, and upper trapezius for a total dose of 105 units of botulinum neurotoxin type A. She was discharged on hydroxyzine 25 to 50 mg three times a day as needed for mild headache, and naratriptan 2.5 mg twice a day as needed for migraine.

At follow-up after 1 month, it was noted that her neck pain was completed controlled by the botulinum toxin injections. The benefit lasted approximately 3 months. When the benefit wore off, she developed a recurrence of mild daily holocranial headache, and an increased frequency of her migraine (to 1 to 2 times per week). When the injections were repeated, the daily tension-type headache subsided, and her need to use the naratriptan decreased to 2 to 3 times per month. This benefit has persisted for over 1 year, including four botulinum toxin treatment sessions.

Case Summary

- This patient had a history of migraine with aura, concussion, and whiplash.
- Despite successful surgery for a herniated disc and upper cervical root entrapment, she still had chronic daily headache due to analgesic rebound.
- Residual problematic neck pain responded well to botulinum toxin injections which also improved her headaches, resulting in lessened need for medication.

Overview of Botulinum Toxin for Headache Therapy

Botulinum toxin has been used for many medical conditions. Whereas neurologists recognize its use for dystonia and spasticity, the lay public associates the name with cosmetic applications such as for rhytids (wrinkles). In the course of receiving treatment for facial wrinkles, some patients reported that their migraine headaches were reduced. There have been many reports of its use for various types of headache, including migraine, tension-type headache, cluster headache, posttraumatic headache, and transformed migraine/analgesic-rebound headache. A recent evidence-based review by Evers and colleagues concluded there was a lack of high quality evidence supporting its use in headache.

Despite its lack of proof in the evidence-based medicine arena, there do seem to be patients who respond to this therapy. There is as yet no consensus as to what sort(s) of headache may respond, nor on what dose(s) to use, nor even what injection strategy to use (standardized regimens versus "follow-the-pain" approaches). The literature suffers from a surfeit of anecdotal reports, poorly designed studies, noncomparable patient populations, and incomplete information. There is also no certainty of the mechanism(s) of action for headache relief, unlike dystonia where the temporary chemical denervation caused by injecting botulinum toxin into abnormally contracting muscle seems clearer. Mechanisms of headache relief that have been proposed are numerous, and include reduced muscle spasm (with reduced peripheral input into the trigeminal nucleus caudalis resulting in reduced "central sensitization"); effects on glutamate, calcitonin gene-related peptide, and substance P; and possibly effects on the putative final common mediator of vascular headache, nitric oxide.

Currently, there is no US governmental indication for botulinum toxin in headache, so most insurance companies in the United States refuse to pay for it when used this way. The treatment is expensive, with a 100 unit vial of Botox costing approximately $400 (US). The injection fee varies, but is usually in the $300 to $400 (US) range. Given that the effects seem to last 3 months and then the injection needs to be repeated, this therapy costs about $3,000 (US) per year. It should be noted that there are occasional reports in the lay press and in academic publications regarding worsening pain. This author has had four patients with temporary worsening of their neck pain and headaches after botulinum toxin therapy, as well as several patients with dramatic benefit when multiple other therapies have failed. Benefits, as well as side effects, of botulinum toxin would be expected to be temporary.

The most support in the literature for using botulinum toxin for headaches would seem to be for migraine headaches and perhaps for chronic daily headache, specifically transformed migraine with or without analgesic rebound. It is to be hoped that, over time, the indications for this novel treatment for headache will become clearer.

Recommendations

The use of botulinum toxin for headaches is controversial. Although there are many anecdotal reports of success in the literature, the overall quality of the evidence supporting its use is low. The best evidence may be for migraine prophylaxis and possibly some forms of chronic daily headache. The following recommendations may prove useful to the reader.

- Potential candidates for this therapy should be evaluated by a physician skilled in headache management, as well as in the use of botulinum toxin.
- Prior to the use of botulinum toxin, other more standard forms of treatment should be considered. Also, treatable underlying causes of headache should be addressed, such as analgesic rebound, as many such patients will improve when overused medications are reduced/withdrawn, regardless of any preventative therapy.
- If botulinum toxin therapy is used, there should be informed consent, with the patient being informed that

such therapy does not have a governmental indication (ie, is "off-label"). The possibility of transient worsening of the headache condition needs to be mentioned as well.

- Careful records need to be kept, so that the treating physician can review the overall results of this therapy. If possible, patients should be treated through high-quality study protocols, so that in the future, better information about the efficacy of this form of headache therapy can be made available.

Selected Readings

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Editorial Comments

The history of headache therapy has long included the use of anecdotal therapies and those that have stood the test of time. Many therapies have evolved from the "off-label," and have subsequently been proven in clinical trials to have benefit to headache patients. Obviously, in this century, it would be best if new headache therapies could be subjected to randomized clinical trials, and of course, many are studied that way. However, there are lacunas in our knowledge with respect to certain headache medications, and botulinum toxin treatment is currently being studied further to close such a gap. Until the answer is clear on whether this therapy helps headache patients in a significant way, it would be prudent to use this therapy with full understanding by the patient and therapist of the benefits and risks of treatment. Let us hope that a more definitive answer is forthcoming in the not too distant future.

Final diagnoses:

1. Episodic migraine without aura
2. Chronic migraine and chronic tension-type headache (transformed migraine) with medication overuse (analgesic-rebound headache)
3. Chronic posttraumatic headache
4. Posttraumatic cervical radiculopathy
5. Clinical response to botulinum neurotoxin type A