Chapter 25

The Woman with a Continuous Right-sided Headache

Todd D. Rozen, MD

Case History

A 38-year-old woman presented with complaint of daily right-sided headache. She had no significant headache history until 6 years prior, when her headache started as daily from onset. Her headache was always of right frontotemporal and periorbital distribution. Typically, it was of low-grade intensity. At times, it almost felt as if she had no pain, but if she thought about it, the pain was always present. Several times per month, the headache would become severe. It would never move to the left side. The duration of the severe headache could vary from several hours to several days. During the period of pain exacerbation, she would develop nausea and vomiting as well as photophobia. She also noticed that she could develop a right eyelid droop and some lacrimation. Her conjunctiva would never become injected and she did not complain of nasal congestion or rhinorrhea. Her right eyelid would sometimes become swollen and her eye could even swell shut. During these periods of intense pain, the patient could not function at her job and had trouble completing any of her activities of daily living. She would end up lying down in a dark and quiet room. The patient had tried numerous medications for these headaches including large amounts of ibuprofen (twenty 200 mg tablets per day), triptans, corticosteroids, opiates, and butalbital-containing compounds, all without benefit. Past preventives included verapamil, amitriptyline, lithium, valproic acid, and fluoxetine, all with no response.

She also stated that she would have a second type of headache that occurred at irregular frequency. This pain was very short-lasting (several seconds), was extremely severe, and could occur anywhere on her head. It was not uncommon for her to experience over 10 short stabs of pain in a day when they would occur. The pain spikes were so brief in duration that it was impossible to treat each individual attack.

She had no significant past medical history, was a nonsmoker, and there was no family history of headache. Past imaging studies included a brain computed tomography scan with and without contrast, which was negative. General laboratory studies (complete blood count, chemistries, sedimentation rate) were normal. Her general and neurologic examinations were normal except for some tenderness to palpation over the right greater occipital nerve.

Questions on the Case

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

- What is the differential diagnosis of a persistent one-sided headache?
- What type of primary headache disorder should be diagnosed for the patient's second type of headache, and is there any reason to think that the patient's primary and secondary headaches are related?
- Should any other testing be recommended?
- What specific therapies would you suggest?

Case Discussion

The patient presents with a primary complaint of a continuous one-sided headache that appears to have started

daily from onset, and is of mild pain intensity at baseline with pain exacerbation periods of severe headache. Associated symptoms occurring during the exacerbation periods are both migrainous (nausea, vomiting, photophobia) and cluster-like (ptosis, eyelid swelling, lacrimation). The headache always remains one-sided and never switches sides.

There are only a few primary headache disorders that are side-fixed. Each has a very defined presentation. A complete headache history should decipher which type of one-sided headache a patient is suffering from.

Cluster headache is defined by unilateral, severe headaches of fairly short duration with associated autonomic symptoms, including ptosis, lacrimation, conjunctival injection, nasal congestion, and rhinorrhea. The headache can occur daily, but the individual headaches are well defined, each lasting from 15 to 180 minutes (usually about 1 hour). Patients can have up to eight separate headaches in a single day (usually 1 to 3), often with one of them awakening the patient from sleep. Cluster patients are in a state of agitation and cannot lie down or remain still during a headache. Typically a disorder of men, there are two subtypes: episodic cluster, in which patients will have periods of remission lasting weeks to months; and chronic cluster, in which the patient will have daily headaches without periods of remission. In most instances in between the individual cluster headaches, a patient will be pain free until the next headache occurs. Cluster patients will sometimes state that there is a slight twinge of discomfort on the side of the head where the headache occurs between attacks, although this is very mild and almost nonexistent. When this twinge goes away, then the cluster cycle has ended.

The case patient has a daily persistent one-sided headache and pain exacerbation periods that are of severe pain, and have both migraine- and cluster-like associated symptoms. Nausea, vomiting, and photophobia are not typically associated with cluster, but recent studies have suggested that light sensitivity is as prevalent in cluster as in migraine. Nausea and vomiting can occur in cluster, but not frequently. The case patient lacks the typical headache profile of cluster. She has a continuous headache, which is not typically seen in cluster (the twinge between cluster headache attacks is usually so mild that it is not considered a headache), and her exacerbation headaches last longer than typical cluster and have more migrainous features. The patient was not in a state of agitation during the severe headaches. The patient also did not respond to typical cluster preventives. An atypical form of cluster, termed persistent or unremitting cluster, has recently been documented in which individuals have daily, one-sided unremitting pain of very high intensity, and on top of that, true cluster headaches of typical duration. In this form of cluster, unlike what was seen in the case patient, the daily headache is very severe, and the exacerbation headache meets International Headache Society (IHS) criteria for cluster.

Chronic paroxysmal hemicrania (CPH) is a unique headache syndrome that typically affects women. First described by Sjaastad and Dale in 1974, this disorder usually develops in the second or third decade of life but can arise at any age. CPH occurs daily, with attacks of severe unilateral, orbital, supraorbital, and/or temporal pain. Each individual headache lasts from 2 to 45 minutes, and the frequency of attacks can be from 1 to 40 attacks per day. Most individuals will have more than 10 attacks in a 24-hour period. Each individual headache is very severe in intensity, described as boring, pulsatile, or claw-like. Each headache is marked by its associated autonomic symptoms. Unilateral lacrimation is most common, followed by nasal congestion, conjunctival injection, rhinorrhea, and then ptosis. Migrainous symptoms can occur but are rare. The individual CPH attacks closely resemble cluster headache attacks although they are shorter in duration. Unlike in cluster, the patient is not typically agitated during the headache, and there is no true predilection for nocturnal attacks (sleep-induced), although they can occur. Patients can sometimes trigger CPH attacks by rotating the neck or flexing the head to the symptomatic side. Applying pressure to the transverse process of C4–5 or the C2 nerve root can also trigger an attack. In between attacks, the patient is pain free. CPH is one of the indomethacin-responsive headache syndromes, meaning that patients are pain free on indomethacin but have little or no response to most other medications including other nonsteroidal anti-inflammatory drugs (NSAIDs). Like the case patient, CPH patients are typically women. The case patient has one-sided headaches and pain exacerbation periods with cluster-like features. This patient, however, does not suffer from CPH, as she had continuous daily pain, and the exacerbation periods are too long in duration for CPH and far less frequent.

The syndrome of short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) was first described by Sjaastad and colleagues in 1978. With less than 30 documented cases, SUNCT is the rarest of the primary headache disorders. SUNCT is comprised of brief attacks of moderate to severe head pain with associated autonomic disturbances of conjunctival injection, tearing, rhinorrhea, or nasal obstruction. The typical age of onset is between 40 and 70 years. SUNCT pain is normally localized to an orbital or periorbital distribution, although the forehead and temple can be the main site of pain. The pain is normally side-locked and remains unilateral throughout an entire attack. In rare instances, SUNCT pain can be bilateral. Pain severity is

normally moderate to severe, unlike for example, cluster headache pain that is always severe. Pain character is described most often as a stabbing, burning, pricking, or electric shock-like sensation. Pain duration is extremely short, lasting between 5 and 250 seconds, with an average duration of 10 to 60 seconds. This extremely brief pain duration sets SUNCT apart from other primary headache syndromes. Pain onset is abrupt, with maximum intensity being reached in 2 to 3 seconds. SUNCT pain normally plateaus at a maximum intensity for several seconds and then quickly abates. SUNCT can occur at any time of the day and does not show a tendency toward nocturnal attacks. Attack frequency varies greatly between sufferers and within an individual sufferer. The usual attack frequency ranges anywhere from 1 to more than 80 episodes a day. Individuals can experience from fewer than one attack an hour to more than 30 an hour. Mean attack frequency is 28 attacks per day. There have been four documented instances of a SUNCT "status pattern," in which patients experienced a high frequency of hourly attacks (> 30 per hour) continuously for 1 to 3 days. Most SUNCT patients will be pain free between attacks, although there are isolated reports of patients experiencing low background pain interictally. SUNCT is an episodic disorder that presents in a relapsing or remitting pattern. Each symptomatic period can last from several days to several months, and a person with SUNCT will typically have 1 to 2 symptomatic periods a year. All documented SUNCT patients experience conjunctival injection and lacrimation (ipsilateral to the side of the head pain) with each attack. Nausea, vomiting, photophobia, and phonophobia are not normally associated with SUNCT. SUNCT can arise spontaneously, but many sufferers have identified triggering maneuvers, including mastication, nose blowing, coughing, forehead touching, eyelid squeezing, neck movements (rotation, extension, and flexion), and ice cream eating. Thought to be refractory to any medicinal therapy, recent small case series have suggested benefit from lamotrigine, gabapentin, and topiramate. The case patient does not have SUNCT, based on lack of short-lasting, very frequent headaches. The only possible type of SUNCT the case patient could have would be status SUNCT, but again, the temporal profile of each individual attack is very different between what the case patient has and SUNCT syndrome.

The case patient best fits the diagnosis of hemicrania continua (HC). HC is a one-sided headache that is continuous (always present) and is usually of mild to moderate intensity, with added pain exacerbations periods of varying frequency consisting of severe head pain that last for hours to days with associated migrainous and/or autonomic features. HC is felt to be a rare headache syndrome, but more likely, it is one of the most underdiagnosed of all the primary headaches. What makes HC unique is the persistent one-sided head pain. Most of the time, the daily persistent pain is of low intensity, sometimes so low that patients do not recognize that it is present until they concentrate on the presence of pain. HC patients typically present to their physician with a complaint of very severe headaches occurring weekly or monthly with associated migraine and cluster-like features, but will forget to mention the low-level daily pain they experience because they rarely need to treat this pain and feel it is not significant enough to mention it to their physician. An incorrect diagnosis of migraine with autonomic symptoms may be made because the correct follow-up question is not asked. If a patient presents with severe headaches that only affect one side of the head, then the physician must ask the patient if they have a low-level headache always present on that same side, even if the pain is so low in intensity that it is barely noticeable to the patient. If present, then a diagnosis of HC can be easily made. Most physicians do not ask this important question and that is why HC is so underdiagnosed. HC is a very disabling headache that can last for years without remittance (this author's longest case is 38 years), and HC is one of the indomethacin-responsive headaches. If the correct diagnosis is not made, then rarely will the patient ever be given an indomethacin trial. It is common to have HC patients presenting to the physician taking daily NSAIDS, opiates, or triptans, usually without any results, but as the pain is constant, the patient takes something daily to try to find some pain relief.

The case patient also complains of a second type of headache that is short-lasting, severe in intensity, and occurs at varying frequencies. This headache is most consistent with idiopathic stabbing headache, also known as ice-pick headache or jabs and jolts headache. Idiopathic stabbing headache consists of transient stabs of head pain lasting fractions of a second, occurring one time per day up to multiple times per hour. The pain is so severe that it will make a patient stop whatever he or she is doing and grimace. Each individual attack is too short in duration to treat, but if the attacks occur daily in volleys, then indomethacin normally abates them. Idiopathic stabbing headaches can occur in isolation, but have also been found to be more prominent in individuals who suffer from migraine (usually occurring at typical migraine location), cluster headache (may signify end of a cluster cycle), and HC. Most headache specialists look for the presence of ice-pick headaches to help secure a diagnosis of HC when a persistent one-sided headache is present. In a recent study, 41% of HC patients experienced idiopathic stabbing headaches.

When evaluating a patient with one-sided headaches, especially those that are always present, the physician must think about a secondary underlying cause of the head pain. Most cases of HC are idiopathic, but secondary mimics such as cervical disc herniation, mesenchymal tumor involving

the sphenoid bone, and brainstem infarcts can present like HC. Other possible causes of one-sided headaches include carotid dissection, cervical facet disease, and persistent sinus infections. A complete general and neurologic examination is necessary on all patients with one-sided headaches, and should include an examination of the neck, looking for pain or pulling in the neck region when the head is extended and rotated to the right or left side, suggesting facet inflammation; auscultation of the carotid arteries, looking for a bruit suggesting dissection; and palpation over the sinus cavities. HC can start in individuals of any age, but if a 50-year-old or older patient presents with a new one-sided headache, then a presumed diagnosis of giant cell arteritis should be made and a sedimentation rate and C-reactive protein must be obtained. All patients with one-sided headaches need neuroimaging, even if a diagnosis of HC has been made. Brain magnetic resonance imaging (MRI) scan is essential, although one could make a strong case for an MRI of the cervical spine and even an magnetic resonance angiography (MRA) of the extracranial carotids, especially in an individual who fails an indomethacin trial and has positive findings on examination.

As noted, HC is one of the indomethacin-responsive headache syndromes, thus HC patients who are placed on indomethacin will become pain free, and those who take anything other than indomethacin will remain in pain. If a patient presents with a one-sided headache and there is no contraindication to taking indomethacin, then an indomethacin trial should be completed. An indomethacin trial is an at least 6-day treatment. Patients are given indomethacin 25 mg tablets and are told to take one tablet three times per day for 3 days. If the patient is not 100% pain free on this dose, then the dose is increased to 50 mg three times per day for 3 days. If there is no response at that dose, then this is most likely not HC. If there is partial response, then the dose can be increased by 25 mg every 2 to 3 days up to 75 mg three times per day. If the patient is not pain free at a dose of 225 mg, then it is very unlikely the headache is HC, although some patients may need doses up to 300 mg per day to see a full effect. If patients do respond (pain free on indomethacin), they should remain pain free as long as they stay on the indomethacin. The physician needs to instruct the patient to find the smallest effective dose of indomethacin (during the trial, patients are escalating from 75 to 150 mg; thus at 100 mg, they may be pain free). In addition, patients should be prescribed histamine (H_2) blockers, misoprostol, or proton pump inhibitors to help protect against future gastrointestinal disturbances. Outside of the United States, parenteral indomethacin is available, and thus the "indotest" can be carried out on suspected HC patients in the physician office. Indomethacin 50 mg intramuscular injection can prove a headache's indomethacin sensitivity within 90 minutes post injection. Most HC patients will be pain free within 75 minutes of an indomethacin 50 mg injection and remain so up to 13 hours. If there is a positive indotest, then the patient is prescribed oral indomethacin, and the lowest effective dose is utilized. In some instances, patients will be pain free on indomethacin and get infrequent bouts of breakthrough pain. In this scenario, an extra dose of indomethacin 25 to 50 mg will typically alleviate the breakthrough pain.

Patients need to recognize the long-term gastrointestinal and renal risks of being on chronic indomethacin treatment, but as there are so few (if any) effective alternative treatments, most people will choose to remain on indomethacin after the trial has ended. At least once per year, sometimes twice per year, the indomethacin should be tapered off to see if the HC is still present. In some instances, the syndrome will alleviate completely.

Other agents that have been utilized in HC include ibuprofen, piroxicam-beta-cyclodextrin, and naproxen. Even at high doses, the effect is not the same as with indomethacin. Recently, several authors have documented that the COX-2 inhibitors, rofecoxib and celecoxib, have shown effect in HC. Effective doses can be higher than typically utilized in other pain conditions. Rofecoxib in doses from 50 to 75 mg has been at least partially beneficial in HC, and celecoxib in doses of 400 to 800 mg per day has also shown effect. Some HC patients have actually become pain free on COX-2 agents, suggesting a similar mechanism of action to indomethacin but different than other NSAIDs. For individuals with contraindications to indomethacin and the COX-2 inhibitors (past gastrointestinal bleed, on anticoagulation), there is little else to offer. Anecdotally, a number of patients respond short-term to greater occipital nerve blockade, and more recently, several patients with posttraumatic HC have become pain free after cervical facet blocks.

Management Strategies

- Brain MRI is mandatory, and MRI of the cervical spine and MRA of the extracranial carotid circulation should be completed if there are positive findings on examination.
- Medicinal treatment consists of an indomethacin trial, and after positive response, the lowest effective daily dose of indomethacin. If the patient is unable to tolerate indomethacin, then a trial of rofecoxib and celecoxib can be undertaken.
- Indomethacin acts as both a preventive and abortive medication for HC. Daily indomethacin should afford the patient a pain-free status as long as they remain on the drug. Breakthrough pain can be treated with low-dose indomethacin (25 mg).

Case Summary

- This patient represents a case of HC.
- The headache history differentiates HC from other primary headache syndromes that are one-sided, including cluster headache, CPH, and SUNCT syndrome.
- If a patient presents with a one-sided headache and there are no contraindications to indomethacin, then a trial should be initiated.

Overview of Hemicrania Continua

The term hemicrania continua was first introduced in 1984 by Sjaastad and Spierings. Initially, HC was felt to be a very rare syndrome, but it is now felt to be more common and probably routinely misdiagnosed. There are over 90 reported cases in the literature. HC, like migraine and CPH, has a female predominance. There are two recognized forms of HC: a nonremitting form that occurs in about 85% of patients (no remission periods), and the remitting form. The nonremitting form can be continuous from onset or evolve from the remitting form. HC was not recognized in the original IHS criteria published in 1988, but is included in the revised criteria published in 2004.

In regard to the clinical characteristics of HC, there are two patterns of headache. HC patients will experience a continuous daily head pain, which is present 24 hours per day, 7 days per week, and pain exacerbation periods that occur with varying frequency from multiple times per week to every third month or less. The daily continuous pain of HC is usually of mild to moderate intensity, affecting the temple or periorbital region. It is always present on the same side of the head. There are some reports of the pain of HC switching sides or being bilateral, but in those cases, a true diagnosis of HC comes into question. The pain exacerbation periods are marked by moderate to severe pain, lasting hours to days in duration, with associated symptoms that are seen in migraine and cluster patients. Migrainous symptoms include nausea, vomiting, photophobia, and phonophobia. Autonomic symptoms include unilateral lacrimation, ptosis, nasal congestion, and rhinorrhea. Other key symptoms that are commonly seen during a pain exacerbation period include eyelid swelling, eyelid twitching, and "ice-pick" headaches. Many HC patients will also complain of a foreign body sensation in the eye on the same side as their headaches, such as a feeling as if there is a piece of sand in the eye or an eyelash. HC patients can also experience auras, typically occurring just prior to a pain exacerbation period. On indomethacin, both the headache and aura alleviate. One of the best descriptions of the clinical features of HC has come from an observational study from the Jefferson Headache Center in Philadelphia. Thirty-four new cases of HC were identified. The baseline continuous headache was mild to moderate in intensity with no headache-related disability and rare associated symptoms. During the headache exacerbation period, pain was normally severe. Associated symptoms included migrainous photophobia 59%, phonophobia 59%, nausea 53%, and vomiting 24%; autonomic symptoms consisted of lacrimation 53%, nasal congestion 21%, and ptosis 18%. Seventy-four percent of the patients experienced at least one autonomic symptom during the pain exacerbation period. The presence of jabs and jolt headaches occurred in 41%. Interestingly, the exacerbation headache met the IHS criteria for migraine in 71% of patients. The exacerbation periods can awaken a patient from sleep and be short in duration (1 to 2 hours), thus presenting like a sleep-induced cluster-like attack. The entire clinical presentation will help to differentiate HC from cluster or even hypnic headache. The most common form of HC was the continuous pattern from onset (53%), followed by continuous evolving from remitting (35%), and remitting (12%).

HC is defined by its responsiveness to indomethacin. Some authors have suggested an indomethacin-resistant form of HC, but this is controversial. The response to indomethacin is one of the most dramatic treatment responses in headache. Patients can literally become pain free after their first dose of indomethacin, regardless of duration of their headaches. The author had one case of 38 years of undiagnosed HC that was gone by the first morning after taking indomethacin. Why indomethacin works in HC and the other indomethacin-responsive headaches (CPH, idiopathic stabbing headache) is unknown, but may be related to indomethacin's ability to lower cerebrospinal fluid pressure and to reduce resting cerebral blood flow. Indomethacin will greatly enhance the quality of life of an HC patient, but with chronic use comes the risk of developing severe renal and gastrointestinal adverse events. Psychologically, many HC patients worry that indomethacin is only covering up an as of yet undiscovered problem, although in most instances, imaging and laboratory evaluations are normal.

Little is known of the natural history of HC. Studies indicate that some patients are able to taper off indomethacin with no return of symptoms, while in others, HC is a lifelong illness. HC has been shown to recur as fast as 12 to 120 hours after discontinuation of indomethacin. Pareja and colleagues carried out a retrospective analysis of 16 patients with HC, assessing the efficacy and tolerability of long-term indomethacin usage in HC and CPH patients. Follow-up was an average of 3.8 years after the start of indomethacin (range 1 to 11 years). In this group, indomethacin dosing never exceeded 150 mg per day. Complete headache relief occurred within 3 days of an effective dose in all patients. Over time, 42% of the patients had a 56% reduction in the

amount of the effective indomethacin dose, while 55% could not alter the dose amount because of headache recurrence. Those patients able to decrease their dose were older. Thirty percent of patients developed adverse events on indomethacin, but none led to drug discontinuation. No tachyphylaxis was noted.

Selected Readings

Antonaci F, Pareja JA, Caminero AB, Sjaastad O. Chronic paroxysmal hemicrania and hemicrania continua. Parenteral indomethacin: the indotest. Headache 1998;38:122–8.

Newman LC, Lipton RB, Solomon S. Hemicrania continua: ten new cases and a review of the literature. Neurology 1994;44:2111–4.

Pareja JA, Caminero AB, Franco E, et al. Dose, efficacy and tolerability of long-term indomethacin treatment of chronic paroxysmal hemicrania and hemicrania continua. Cephalalgia 2001;21:906–10.

Peres MF, Silberstein SD. Hemicrania continua responds to cyclooxygenase-2 inhibitors. Headache 2002;42:530–1.

Peres MFP, Silberstein SD, Nahamias S, et al. Hemicrania continua is not that rare. Neurology 2001;57:948–51.

Sjaastad O, Spierings EL. Hemicrania continua: another headache absolutely responsive to indomethacin. Cephalalgia 1984;4:65–70.

Editorial Comments

It has been almost 20 years since the original clinical description of hemicrania continua. At first thought to be a rare headache disorder, more defined by its responsiveness to indomethacin than some other features, we now recognize it to be more common than suspected (see Peres et al, 2001, in Selected Readings of this chapter), more clinically distinct, and probably related to the trigeminal autonomic cephalalgias. In fact, the disorder was not included in the initial IHS classification of 1988, but is in the new revised edition. Dr. Rozen and his colleagues have a large clinical experience with this entity, and this chapter exemplifies the approach to diagnosis and management. One suspects that in another 20 years, this disorder will be better defined in neurobiologic terms, and its unique responsiveness to indomethacin will be better understood.

Final diagnosis:

Hemicrania continua