Chapter 57

The Man with the Red Eye

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Case History

The patient was a 21-year-old man who described attacks of severe right temporal pain, beginning approximately 4 months prior to presentation. For "many" years prior to that time, he had experienced "normal" mild holocranial headaches without associated features, with a frequency of perhaps once per month. The new headache attacks had begun without a clear precipitant or suspicious exposure. They increased in frequency over approximately 2 weeks until he was experiencing them once or twice per day, approximately 10 to 12 days per month.

The headaches could occur at any time of the day without predictability, but would typically occur between 9:00 am and 5:00 pm. The pain would build rapidly over 1 to 2 minutes to a severity of ~7 (on a scale of 0 to 10), and would rarely last longer than 30 minutes; the mean attack duration was 15 to 20 minutes. The attacks seemed to end as abruptly as they started. He characterized the new headaches as a "dry stinging" pain, and placed his palm over his right temporoparietal region to indicate their location. The headaches were typically associated with transient blushing hyperemia of the nasal portion of his right conjunctiva and twitching of his right upper eyelid.

The attacks were often accompanied by a high-pitched buzzing tinnitus, worse in the right ear than the left, although he denied any particular sensitivity to sound or light, hearing loss, or pain localized to his ears. With some attacks, he noted moderate neck tightness. He never noted nausea or vomiting. He believed that drinking alcohol tended to worsen his headaches. He had tried multiple over-the-counter medications including ibuprofen, naproxen, and acetaminophen for the attacks but had not found any that helped significantly to relieve or prevent the attacks. His past medical history, social history, and family history were noncontributory. His general and neurologic examinations were normal.

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 diagnosis of the new headache attacks?
- Which historic features help in diagnosis?
- Is any further diagnostic evaluation warranted?
- What therapeutic interventions are helpful in treatment of these headaches of brief duration?

Case Discussion

The patient gives a history of long-standing, relatively infrequent, attacks of mild headache without associated features. These headaches are consistent with intermittent tension-type headache. He now reports a new headache type that unfolds in a recurrent stereotypical pattern. These new headache attacks are notably short in duration, abruptly severe in intensity, always on the same side of the head, and associated with autonomic features ipsilateral to the pain, such as conjunctival hyperemia. He complained of intermittent eyelid twitching with the attacks, which could be a reflection of intermittent "minor" ptosis from sympathetic hypofunction, although multiple other possibilities exist (eg, tremor, seizures). The headaches seemed to be worse following ingestion of alcohol and were unresponsive to simple over-the-counter analgesics.

Based upon attack duration, location, and associated features, my initial clinical impression of this man was that he suffered from a variant of paroxysmal hemicrania (PH). The attacks of PH are typified by brief severe pain, strictly unilateral without side shift, and associated with cranial autonomic symptoms and signs ipsilateral to the pain. Two other headache disorders share this constellation of characteristics: cluster headache and short-lasting unilateral neuralgiform headache attacks with conjuctival injection and tearing (SUNCT). On the basis of these common clin-

ical features, Goadsby and Lipton grouped PH, cluster headache, and SUNCT together under the term trigeminal autonomic cephalalgias (TACs), and these disorders have now been codified together in the *International Classification of Headache Disorders, 2nd Edition* (ICHD-II). PH differs from the other TACs largely with respect to the attack duration and frequency; the attacks of PH are generally shorter and more frequent than those of cluster headache and longer and less frequent than those of SUNCT. The diagnostic criteria for these disorders allow for some degree of uncertainty in individual cases where the duration and frequency of attacks may reflect either PH or cluster headache. However, the attacks of PH possess an additional key characteristic that typically allows clear distinction from cluster headache: they respond promptly and absolutely to intervention with the nonsteroidal anti-inflammatory agent indomethacin. In the case of this patient, the characteristics of his new headache attacks most closely approximate the diagnostic criteria of PH, although they do not strictly meet the currently accepted criteria in the ICHD-II. Specifically, the attacks occur less frequently than the average of five or more per day as called for in PH, and while not specified in these diagnostic criteria, the attacks of PH also typically occur daily without remission.

Moreover, in this particular case, the headache attacks were also accompanied by some symptoms not typically associated with PH (eg, tinnitus and eyelid twitching). If these brief headache attacks do indeed represent a form of PH, then they should respond to indomethacin prophylaxis at a dosage of ≤ 50 mg three times a day. However, a therapeutic response to indomethacin would not preclude a presumptive secondary cause for the attacks, and PH has been described in association with multiple systemic conditions and intracranial abnormalities (see below). For these collective reasons, it is appropriate to exclude the existence of a causative intracranial lesion with an imaging study such as magnetic resonance imaging (MRI). The impetus for obtaining such a study remains strong, despite the otherwise reassuring presence of normal general and neurologic examinations.

Management Strategies

- Cranial MRI, including gadolinium enhancement sequences, should be obtained.
- Indomethacin 25 mg three times daily should be initiated as prophylaxis. If no therapeutic response is reported following 7 days of therapy at this dosage, then increasing the dosage to 50 mg three times daily for an additional 7 days is appropriate.
- If brain imaging studies are unrevealing, but no therapeutic response to indomethacin is reported, then further diagnostic studies may be warranted (eg, electroencephalogram to assess for epilepsy given paroxysmal eyelid twitching, blood counts for thrombocythemia, lumbar puncture to assess for raised intracranial pressure, central nervous system inflammation, or cytopathology).

Case Summary

- This young man presented with new-onset, recurrent, brief, severe unilateral attacks of headache with ipsilateral autonomic features.
- The working diagnosis on initial evaluation was a variant of PH.
- The patient's MRI study was normal.
- The patient's attacks remitted following a week of 50 mg oral indomethacin three times daily, thus supporting the diagnosis of PH.

Overview of Paroxysmal Hemicrania

PH is a chronic syndrome of stereotypic episodic attacks. The disorder was initially described 30 years ago by Sjaastad and Dale and termed "chronic paroxysmal hemicrania." These authors noted the essential clinical features of the syndrome and, in particular, emphasized that it was unremitting unless the patient was treated with indomethacin. Subsequently, it has become clear that spontaneously remitting forms of the disorder also exist and the disorder is now formally subclassified into episodic and chronic forms (Table 57-1).

PH is rare, with an estimated population prevalence of approximately 2 per 100,000. It preferentially afflicts women (F:M sex ratio of ~2 to 3:1), and typically begins in young adulthood (mean age of onset 34 years); however, both pediatric (age 6 years) and late-onset (81 years) cases have been reported. The disorder has been described among individuals of diverse ethnic and racial backgrounds. Familial forms of PH have not been reported.

An attack of PH usually begins abruptly, without warning or predictability, at any time of day. Attack onset is usually spontaneous and unprovoked, although a minority of patients are able to precipitate attacks by adopting certain head postures or applying pressure against upper cervical vertebrae, nerve roots, or at the occipital notch. Alcohol may precipitate attacks in a small fraction of patients. The attack lasts from 2 to 30 minutes (up to 120 minutes), and usually terminates as abruptly as it began. Between attacks, patients may describe a vague low-intensity ache in the region of the severe pain. Attacks recur frequently, with a mean of approximately 14 attacks per day (range 2 to 40 per day). In ~80% of PH cases, attacks occur daily without remission (chronic form). In the remaining ~20% of cases (episodic form), daily headache attacks may continue for weeks to months before spontaneously, and unpredictably, remitting for

Table 57-1. Diagnostic Features of Paroxysmal Hemicrania

3.2 Paroxysmal Hemicrania

Diagnostic criteria:

A. At least 20 attacks fulfilling criteria B to D
B. Attacks of severe unilateral orbital, supraorbital, or temporal pain, lasting 2 to 30 minutes
C. Headache accompanied by at least one of the following:
   1. Ipsilateral conjunctival injection and /or lacrimation
   2. Ipsilateral nasal congestion and/or rhinorrhea
   3. Ipsilateral eyelid edema
   4. Ipsilateral forehead and facial sweating
   5. Ipsilateral miosis and/or ptosis
D. Attacks have a frequency above five per day for more than half of the time, although periods with lower frequency may occur
E. Attacks are prevented completely by therapeutic doses of indomethacin*
F. Not attributed to another disorder†

Notes:

*In order to rule out incomplete response, indomethacin should be used in a dose of ≥ 150 mg daily orally or rectally, or ≥ 100 mg by injection, but for maintenance, smaller doses are often sufficient.

†History and physical and neurologic examinations do not suggest any of the disorders listed in groups 5 to 12, or history and/or physical and/or neurologic examinations do suggest such disorder, but it is ruled out by appropriate investigations, or such disorder is present but attacks do not occur for the first time in close temporal relation to the disorder.

3.2.1 Episodic Paroxysmal Hemicrania

Diagnostic criteria:

A. Attacks fulfilling criteria A to F for 3.2 paroxysmal hemicrania
B. At least two attack periods lasting 7 to 365 days and separated by pain-free remission periods of ≥ 1 month

3.2.2 Chronic Paroxysmal Hemicrania

Diagnostic criteria:

A. Attacks fulfilling criteria A to F for 3.2 paroxysmal hemicrania
B. Attacks recur over > 1 year without remission periods or with remission periods lasting < 1 month

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

weeks to years. Approximately 25% of patients with the chronic form of PH initially experienced the episodic form. For many patients with PH, it appears to be a life-long condition, although large-scale longitudinal studies of the disorder are not yet available.

The headaches of PH are notably severe to excruciating in intensity, and may have throbbing, aching, or piercing qualities. The pain is localized unilaterally in ocular, periorbital, temporal, and upper facial regions, and typically does not vary in location from attack to attack. Exceptionally, the pain may involve otalgia, other cranial and nuchal regions, shift sides between attacks, occur bilaterally, or radiate into the ipsilateral neck, shoulder, or arm.

Cranial autonomic signs and symptoms are also essential features of the attacks of PH. These autonomic features are ipsilateral to the pain during attacks and typically include increased lacrimation, conjunctival hyperemia, nasal congestion, and/or rhinorrhea. Eyelid edema, ptosis, miosis, and facial sweating may be included less often. Clinical features associated with migraine, such as photophobia, nausea, or even aura (rarely), may be present but are not usually emphasized by patients.

Differential Diagnosis

In spite of its rarity, PH has been reported in association with a wide variety of systemic and intracranial conditions. These conditions include tumors (frontal glioma, sella turcica gangliocytoma, cavernous sinus meningioma, pituitary microadenoma, Pancoast's tumor, cerebral metastatic parotid epidermoid adenocarcinoma, tuber cinereum hamartoma, Meckel non-Hodgkin's lymphoma), vascular conditions (circle of Willis aneurysms, parietal arteriovenous malformations, middle cerebral artery or posterior cerebral artery stroke, vasculitis), infections (herpes zoster ophthalmicus), intracranial hypertension, and thrombocythemia. Current data are insufficient to conclude that any of these various conditions represent causative versus coincident associations with PH. However, a clinical suspicion for secondary causes for PH should be maintained in evaluating new cases.

PH may also be present in the setting of other primary headache disorders including migraine, cluster, cough headache, trigeminal neuralgia ("CPH-tic" syndrome), and tension-type headache (as in the case outlined above). Differential diagnosis of PH with other relatively brief headache disorders may be particularly challenging when the presenting clinical features are somewhat atypical (as above). In particular, cluster and PH are both strictly unilateral severe pains with ipsilateral autonomic features. By contrast to cluster, PH is more likely to occur in women, is typified by briefer and more frequent attacks, is more likely to occur in a chronic rather than an episodic form, and perhaps most importantly, is exquisitely responsive to indomethacin, and is unlikely to respond to therapies effective for cluster (eg, subcutaneous sumatriptan, high-flow oxygen). Moreover, whereas cluster patients often pace or move restlessly during attacks, this feature may be variably present in PH. Cluster headache attacks also tend to occur with circadian and seasonal frequency, features not associated with PH.

Diagnostic Evaluation

At the current time, PH is essentially a clinical diagnosis. Fortunately, a characteristic history of stereotypic attacks, their response to indomethacin, and normal detailed general and neurologic examinations are often sufficient to provide a high assurance of the correctness of the diagnosis. However, given the existence of multiple other conditions (above) associated with PH in individual case reports, a broader diagnostic work-up is typically warranted

regardless of diagnostic confidence. Brain imaging studies are certainly appropriate and should include MRI with and without paramagnetic contrast agents, when available. Other diagnostic tests (eg, chest radiograph to exclude Pancoast's tumor, complete blood count, erythrocyte sedimentation rate, spinal fluid studies) have also been advocated in the evaluation of patients presenting with PH; however, a consensus does not yet exist regarding the precise timing and necessity of these studies. Certainly, the presence of any clinical symptoms or signs atypical of PH should raise consideration of further studies.

The response of PH to indomethacin is useful diagnostically as well as therapeutically. Some controversy exists regarding the appropriateness of a response to a therapeutic agent as a diagnostic criterion for PH, particularly since the basis for the apparent specificity of response to indomethacin is unknown. However, until more specific laboratory diagnostic features are identified (eg, imaging anomalies, genotypes), the indomethacin response will remain central to the diagnostic classification of PH. An acceptable initial diagnostic trial of oral indomethacin should be 25 mg three times daily. If no clear therapeutic response has been noted after a week, then 50 mg three times daily should be continued for an additional week. Subsequent further increases in dosage to 75 mg or 100 mg three times daily for 10 days may be required to conclude that the condition is truly unresponsive to indomethacin. In most cases of PH, attacks are totally resolved within 2 days of initiating the appropriate indomethacin dosage. Intramuscular application of 50 or 100 mg indomethacin has been proposed as a rapid test for PH ("indotest"), with remission from attacks noted for a mean of > 11 hours following 100 mg intramuscular dosing.

Therapeutic Management

The brief duration of PH attacks renders acute interventions with therapeutic agents largely impractical. Moreover, the acute therapies that characteristically relieve the somewhat longer typical attacks of cluster headache (ie, subcutaneous sumatriptan, high-flow oxygen) are rarely effective in PH. Therefore, therapy for PH is directed at prevention of attacks. Indomethacin is typically effective in this maintenance role at 25 to 100 mg daily in divided dosages; however, therapeutic responses necessitating 300 mg daily have been reported. Patients with chronic PH, as well as those with episodic PH during periods of headache activity, may notice prompt return of attacks on missing or lowering indomethacin dosages. Accordingly, the lowest effective dosage of indomethacin should be continued as maintenance therapy. Patients with episodic PH should not require continued indomethacin maintenance therapy while in remission, and trials of tapering off the medication are appropriate when clinical remission is suspected. Patients with chronic PH may also rarely experience durable remission following prolonged indomethacin therapy, and periodic tapering downward of the dosage at 6- to 12-month intervals may be helpful to screen for these rare cases. Patients with PH seldom become refractory to indomethacin maintenance therapy, and such a development would warrant further diagnostic studies for associated disorders.

As with chronic exposure to other nonsteroidal anti-inflammatory drugs (NSAIDs), maintenance indomethacin may induce gastrointestinal adverse effects in up to 25% of patients on long-term therapy. Accordingly, prophylactic co-medication (eg, antacids, proton pump inhibitors, H_2 receptor antagonists) is appropriate for patients on maintenance therapy. For patients intolerant of indomethacin, some other drugs have been reported as showing variable effectiveness in the prophylaxis of PH including NSAIDs (aspirin, naproxen, piroxicam, celecoxib, rofecoxib), calcium channel blockers (verapamil, flunarizine), acetazolamide, and corticosteroids. However, none have shown the consistent beneficial response observed with indomethacin. Patients with PH comorbid with other primary headache disorders (eg, CPH-tic) typically require therapies specific for each disorder.

Selected Readings

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Editorial Comments

Over the past few years, the TACs have entered into the lexicon of the differential diagnosis of headaches, and now are recognized as a group of disorders in the new International Headache Society (2004) classification of headaches. Patients with these disorders are probably seen more often in the offices of neurologists and headache specialists, probably initially being called cluster headache or a "variant" thereof by primary-care physicians. Because of the absolute responsiveness of some of the TACs to indomethacin, it is now necessary to be more diligent in the diagnostic formulation, as effective therapy appears to be at hand. Two other important clinical points need to be stressed when diagnosing the TACs: 1) The clinician must always exclude secondary causes, and 2) treatment with indomethacin must be carefully monitored, and the lowest effective dosage of the medication must be used because of potentially serious adverse effects of the therapy. Finally, this chapter is an excellent example of clinical neurology at its best—the careful analysis of history and differential diagnosis, so important in this particular group of headache disorders. Dr. Shapiro's case and similar ones in this volume help us in the advanced management of headache.

Final diagnosis:

Paroxysmal hemicrania