Chapter 16

The Young Man with Recurrent Severe Headache

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Case History

This 43-year-old male had been referred by his primary-care physician to a tertiary headache clinic. He had a 20-year history of almost yearly periods (2 to 3 months) of short-lasting very severe headache attacks. He had a strong family history of migraine on his father's side, where his father, grandfather, and his father's cousins have migraine. His mother had also developed autonomic features with her headaches in association with a muscle disease, later diagnosed as fibromyalgia, and she became free of her headaches during treatment with cortisone. He has an older sister and two children who are in good health. He works at a petrochemical industry as an instructor and enjoys his work. He smokes occasionally, but is regularly using tobacco snuff. His consumption of alcohol is low.

His latest period of recurrent severe headache attacks started 1 month ago, and he now suffers from two episodes per day, which generally last about 2 hours, one at night occurring 90 to 120 minutes after going to bed, and one in the afternoon around 2 pm. The pain during the attacks is strictly unilateral and starts in the region of the right eye and radiates toward the temple and his maxilla, reminding him of a bad toothache. Within 10 minutes, the pain becomes very intense and he describes it as unbearable, 10 plus on a 10-pain intensity scale. He paces back and forth in the room during the attack. He also develops associated symptoms such as a red eye (conjunctival injection), unilateral tearing (lacrimation), nasal congestion/secretion (rhinorrhea), and he has also noted that his right eyelid and eyebrow become swollen and tender. Sometimes, he has also developed sensitivity to light, but found no change in his headache when exposed to sound and smell or any aggravation by routine physical activity. He knows that any intake of beer or alcohol during his headache period immediately will precipitate an attack. He uses a combination of 1,000 mg acetylsalicylic acid and 100 mg caffeine as effervescent tablets in an attempt to relieve the pain, but this meets with little success. He had previously tried ergotamine as prophylaxis, but had to stop using this medication due to severe side effects such as nausea and impaired blood circulation in his lower limbs. His attack duration without treatment varies between 1 to 3 hours.

His physical and neurologic examinations, as well as two previous computed tomography (CT) scans, were found to be normal. His blood pressure was 115/75 with 65 bpm. The electrocardiogram indicated normal sinus rhythm. Finally, he recalled that as a teenager he suffered from a concussion when he fell over while riding his bike.

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 most likely diagnosis, and what would be an appropriate differential diagnosis?
- If his symptoms were the result of cluster headache (CHA), how would you differentiate it from chronic paroxysmal hemicrania (CPH)?
- Does the fact that he has strong family history of migraine help you with the diagnosis?
- Is the fact that he fell on his head and suffered from concussion important information?
- What investigations should be done?
- What would be your advice to him with regard to the acute treatment and prevention of his attacks? If initial therapies are not successful, then what would you plan for the future?

Discussion

Diagnosis

The most likely diagnosis for this patient with periods of daily brief attacks of very severe, strictly unilateral pain in the orbital region associated with local autonomic symptoms and signs would be episodic CHA (category 3.1.1, using the classification of the International Headache Society [IHS]; Table 16-1).

Table 16-1. IHS Classification of Cluster Headache

3.1 Cluster Headache

3.1.1 Episodic cluster headache
3.1.2 Chronic cluster headache

Description:
Attacks of severe, strictly unilateral pain that is orbital, supraorbital, temporal, or in any combination of these, lasting 15 to 180 minutes and occurring from once every other day to 8 times a day. The attacks are associated with one or more of the following, all of which are ipsilateral: conjunctival injection, lacrimation, nasal congestion, rhinorrhea, forehead and facial sweating, miosis, ptosis, eyelid edema. Most patients are restless or agitated during an attack.

Diagnostic criteria:
A. At least five attacks fulfilling criteria B to D
B. Severe or very severe unilateral orbital, supraorbital, and/or temporal pain lasting 15 to 180 minutes untreated
C. Headache is 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
   6. A sense of restlessness or agitation
D. Attacks have a frequency of 1 every other day to 8 per day
E. Not attributed to another disorder

3.1.1 Episodic Cluster Headache

Description:
Cluster headache attacks occurring in periods lasting 7 days to 1 year, separated by pain-free periods lasting 1 month or longer

Diagnostic criteria:
A. Attacks fulfilling criteria A to E for 3.1 cluster headache
B. At least two cluster periods lasting from 7 to 365 days and separated by pain-free remission periods of > (at least) 1 month

Comment:
Attacks occur in series, lasting for weeks or months (so-called cluster periods), separated by remission periods usually lasting months or years. About 10 to 15% of the patients have chronic symptoms. In a large series with good follow-up, 27% of patients had only one period. Cluster headache may be autosomal dominant in about 5% of cases.

Differential Diagnosis

Chronic paroxysmal hemicrania and idiopathic stabbing headaches are two primary headache disorders that also are characterized by brief, short-lived attacks of head pain, which may recur multiple times throughout the day. Another differential diagnosis to episodic CHA is trigeminal neuralgia. These pain syndromes are much less prevalent than migraine and tension-type headaches, but are significantly more disabling. Recognition of these uncommon disorders is important because their management differs from standard headache therapies.

The characteristics of CPH are very similar to CHA. Decisive diagnostic features of CPH in the differential diagnosis versus episodic CHA seem to be the presence of headache every day, a high maximum daily attack frequency, and an absolute indomethacin effect. The frequency of the attacks varies from 5 to 30 per 24 hours, the single attack having a typical length of 2 to 30 minutes. As in CHAs, nocturnal attacks are common in patients with CPH. There is increasing evidence for a female preponderance in CPH (for further information, see Chapter 31).

CHA has been associated with cigarette smoking, head trauma, and a positive family history for migraine. However, the fact that our patient uses tobacco, has a strong heredity for migraine, and that he, as a teenager, fell on his head and suffered from concussion are not indicative or helpful in making the diagnosis. His strong family history of migraine should make us more observant before ruling out hemicranial migraine with unilateral tearing and nasal congestion/secretion as signs of autonomic dysfunction.

In this case, however, there is no need for further investigations. The patient history is very clearly indicating the primary headache CHA. Furthermore, the present physical and neurologic examinations, as well as two previous CT scans, were found to be normal.

Management Strategies

Disappointingly, this CHA patient has not had access to any effective symptomatic and prophylactic treatments for many years. He is informed that the subcutaneous injection of sumatriptan has been found to be very effective for acute cluster attacks, and that verapamil is the first choice with respect to prophylactic treatment (Table 16–2). Accordingly, sumatriptan (12 mg/mL) subcutaneous injection (6 mg per attack) and verapamil 120 mg slow-release formulation (120 to 240 mg twice per day) are prescribed for him, and he is carefully informed about the injection technique, dosing, and possible side effects. The dose of verapamil is titrated over the first week until the attacks disappear, but not exceeding a dose of 720 mg per 24 hours. He is encouraged to keep a headache diary and is given a specific time for a follow-up visit.

Case Summary

- This is a typical case of episodic CHA.
- Sumatriptan 6 mg subcutaneously is the drug of choice in the treatment of acute cluster attacks.
- The calcium antagonist verapamil is the first option in the prophylactic treatment of episodic CHA.

Table 16-2. Attack and Preventive Treatment Alternatives in Cluster Headache

Attack Treatment
I. First-line alternatives
Sumatriptan injection 6 mg × 1–3 alternatively
Oxygen (100% O_2) inhalation through a facemask, 6–8 L/min during 10 to 15 minutes
Use of oxygen is associated with a number of precautionary measures!
II. Second-line alternatives (optional for convenience but less effective)
Sumatriptan nasal spray 20 mg × 1–3 alternatively
Zolmitriptan tablet 5–10 mg × 1–3* or
Zolmitriptan nasal spray 5 mg × 1–3 alternatively
Lidocaine spray 10 mg/dose alternatively†
Ergotamine tablet 1–2 mg × 1–2
Preventive Therapy
I. First-line alternative
Verapamil tablet 360–720 mg per day
Short-term prophylaxis
Prednisolone tablet 45–60–(80) mg per day during 3 days, which is gradually tapered by 10–20 mg per week
Ergotamine tablet 3–4 mg per day
Long-term prophylaxis
Lithium sulfate tablet 42 mg × 2–3‡
Lithium carbonate tablet 800–900 mg per day‡
II. Second-line alternatives (optional)
Methysergide tablet 3–6 mg per day alternatively
Pizotifen tablet 2–3 mg per day alternatively
Sodium valproate tablet 500–1,500 mg per day alternatively
Melatonin tablet 6–12 mg at bedtime§

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

*Oral zolmitriptan was effective against placebo only in those patients with episodic disease.

†Ipsilateral application of nasal spray.

‡Therapeutic plasma concentration 0.3–0.8 mmol/L.

§The melatonin works only in episodic, but not in chronic, cluster patients.

Overview of Episodic Cluster Headache

CHA, also know as Horton's headache, is an uncommon but well-defined neurovascular syndrome occurring in both episodic and chronic varieties. CHA is occurring in about 1 per 1,000 (0.1% of the population), and the mean age of onset is between 20 and 40 years. Inheritance plays a role, and a 14-fold increase in the risk of CHA among first-degree relatives has been reported. The condition is episodic in 85% and chronic in 15% and may change into either direction. For unknown reasons, males are affected more often than females. However, a decreasing male:female ratio has also been noted, from 6.2:1 for patients with CHA onset before 1960, to 5.6:1, 4.3:1, 3.0:1, and 2.1:1 for patients with CHA onset in the 1960s, 1970s, 1980s, and 1990s, respectively. This is perhaps attributable to the adoption by more women of lifestyle trends that were previously associated with men, such as tobacco use, alcohol consumption, and working outside of the home. The reasons for evolution of episodic CHA to chronic are still unknown. Late onset, the presence of sporadic attacks, a high frequency of cluster periods, and short-lived duration of remission periods when the headache is still in its episodic form all correlate with a possible worsening of the clinical picture over time. Also, other factors such as head trauma, and other lifestyle factors such as cigarette smoking and alcohol intake, have been suggested as having a negative influence on the course of CHA over time.

The most striking feature of CHA is the unmistakable circadian and circannual periodicity with chronobiologic features. The attacks are of extreme intensity, of short duration, occur unilaterally, and are accompanied by signs and symptoms of autonomic dysfunction such as cranial parasympathetic activation and sympathetic impairment. In contrast to migraine, the cluster patient prefers to pace about during an attack, but may also experience nausea, photophobia, behavioral agitation, or restlessness. Nocturnal attacks are a characteristic feature in a subset of patients; generally, 2 to 3 hours after the individuals have taken to their supine position and/or fallen asleep.

Although the important pathophysiology of CHA remains to be fully elucidated, decisive observations have recently been made. Neuroimaging has revealed primary defects in the hypothalamic gray matter. Local homolateral dilatation in the intracranial segment of the internal carotid and ophthalmic arteries during attacks is the result of generic neurovascular activation, probably mediated by trigeminal parasympathetic reflexes. Head trauma, coronary artery disease, and migraine appear to be present in more patients with CHA than can be explained by chance alone.

Treatment Recommendations

The medical treatment of CHA includes both acute therapy aimed at aborting individual attacks and prophylactic therapy aimed at preventing recurrent attacks during the cluster period. Needless to say, the treatments should be tailored to the individual patient, taking into account available drugs, efficacy versus side effects, and contraindications. Management of CHA has greatly changed in recent years, although most of the drugs used have not received approval for this indication. In addition, it seems that many CHA patients have not been prescribed nor used the best symptomatic and prophylactic treatments for CHA.

A subcutaneous injection of sumatriptan has been found to be remarkably effective and is the drug of choice in the treatment of acute attacks. This drug continues to exhibit efficacy for long periods of use (up to several months) and has no serious adverse effects if used according to recommendations. A sensation of pressure or tight-

ness in the chest is a well-documented adverse effect with sumatriptan, which for the subcutaneous injection occurs in about 20% of patients in clinical trials but is more frequently perceived in clinical practice. These symptoms may be alarming to patients and physicians because they can mimic the pain of angina pectoris and myocardial infarction. However, data from extensive clinical trials, together with information from nearly 10 years of experience in clinical practice, demonstrate that sumatriptan is generally well tolerated, with an acceptable risk-benefit ratio when used properly.

Nasal administration of oxygen (100% O_2) inhaled through a facemask continues to be an adjuvant treatment for patients with a contraindication for sumatriptan or for those with several acute episodes per day.

With respect to prophylactic treatment during the cluster episode, the calcium antagonist verapamil appears to be the drug of choice. Constipation is a common side effect that the patient should be informed about. In short-term prophylaxis, however, ergotamine may still be a useful drug, if the timing of the attacks allows planned use of the drug shortly before the attack. If the headaches are of very severe and high attack frequency, steroids may at least temporarily break a cluster episode (eg, prednisolone 60 or 80 mg per day, gradually tapered to zero in 3 to 4 weeks). If more long-lasting prophylaxis is needed, lithium carbonate (alternatively, sulfate) can be tried, but was no different from placebo in a recent double-blind, placebo-controlled trial of lithium in episodic CHA. As for chronic CHA, lithium probably will still be the drug of choice, but methysergide and sodium valproate may also be employed.

In some patients, melatonin or pizotifen may be useful adjunctive therapies. For a very limited group of patients with chronic CHA, surgery may be a last resort. The best options are probably percutaneous radiofrequency retrogasserian rhizotomy (PRFR) or percutaneous retrogasserian glycerol blockade. The significance of the latter technique, as an alternative to PRFR, is that it should provide an acceptable degree of pain relief, but result in a lower rate of both corneal and facial anesthesia. Electrical stimulation of implanted electrodes in posterior hypothalamic gray matter has been demonstrated to provide remarkable pain relief in a few patients with intractable chronic CHA.

Selected Readings

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Editorial Comments

Cluster headache is the prototypical short-lasting primary headache disorder. In its classical presentation, it is not difficult to miss the diagnosis, and in that setting it is appropriate to avoid investigations. However, such is not the case when there are atypical features or if the headache is actually another trigeminal autonomic cephalalgia. Furthermore, when therapy is initiated, it is wise to have acute short-term and long-term strategies at hand, and Dr. Dahlöf deals with these in a logical manner. A full-blown CHA is one of the most dramatic neurologic disorders in medicine. The promise of newer treatments based on etiopathogenesis is much welcomed in this particular headache disorder.

Final diagnosis:

Episodic cluster headache