

# THE MAN WITH INTRACTABLE HEADACHE

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## Case History

A 39-year-old right-handed man had suffered excruciatingly painful headache attacks since 1995. The attacks lasted 30 minutes to 4 hours, occurred 2 to 5 times a day, and were associated with striking oculo-facial phenomena: lacrimation, reddening of the eye, massive eyelid edema, rhinorrhea, and nasal congestion, all ipsilateral to the pain. The patient became extremely agitated during an attack. Ninety percent of the attacks were on the right side and the rest on the left; they were never bilateral. Attacks often awakened him during the night at fixed times. In the beginning, these headache episodes occurred in periods lasting about a month; but for a subsequent period of 3 years, there were no remissions and attacks occurred every day. He smoked a pack of cigarettes a day. No other illnesses were reported. No similar cases were known in his family.

## Questions on the Case

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

- What are your diagnostic considerations in this case, and do you agree with the diagnosis proposed?
- Would you think that this patient requires any investigational procedures, and if so, what and why?
- How would you manage this patient's headaches, and what specific therapies would you suggest? If your initial therapies are not successful, then what would you plan for the future?

## Case Discussion

We have a male patient suffering from a unilateral headache. When approaching a patient with unilateral headache, it is

vital to note whether the pain is continuous or occurs in distinct episodes. The most common diagnoses of the former are chronic daily headache, chronic migraine, chronic tension-type headache, and hemicrania continua; all may be accompanied by drug overuse. When the pain occurs in episodes, two options are possible: the "long-lasting" or the "short-lasting" headache forms. The former lasts more than 4 hours and basically includes migraine with duration of 4 to 72 hours and episodes of hemicrania continua. The latter lasts less than 4 hours and includes cluster headache, paroxysmal hemicrania, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT), trigeminal neuralgia, hypnic headache, and other minor forms (Table 17-1). Occurrence of ipsilateral oculo-facial autonomic features during the pain, including red eye, lacrimation, rhinorrhea, block of the nostril, facial reddening and sweating, are also important for the diagnosis, since short-lasting primary headaches are divided into forms with and without autonomic manifestations. Cluster headache, paroxysmal hemicrania, and SUNCT have massive accompanying autonomic phenomena (the so-called "trigeminal autonomic cephalalgias" or TACs); trigeminal neuralgia, hypnic headache, and others do not have autonomic manifestations (see Table 17-1).

Our patient suffers from headache attacks lasting less than 4 hours and therefore is in the short-lasting primary headache group. He also has striking oculonasal phenomena during the pain and therefore has one of the TACs (Table 17-2). In this group, the duration of individual episodes is crucial for final diagnosis (see Table 17-2). The final diagnosis in our patient is therefore cluster headache.

The prevalence of cluster headache is less than 1 in 1,000. Men are more often affected than women in the ratio 3:1. The mean age of onset is 25 to 35 years. There are two forms: episodic (80%) and chronic (20%). In the former, pain attacks occur in periods lasting about a month;

**Table 17-1. Short-lasting Primary Headaches (Duration < 4 Hours)**

With autonomic phenomena (trigeminal autonomic cephalalgias)	
Cluster headache	
Paroxysmal hemicrania (episodic and chronic forms)	
SUNCT (short-lasting neuralgiform headache attacks with conjunctival injection and tearing)	
Hemicrania continua (in this form, the pain is long-lasting; ie, lasts more than 4 hours)	
Without autonomic phenomena	
Trigeminal neuralgia	
Idiopathic stabbing headache	
Headache associated with sexual activity	
Benign exertional headache	
Hypnic headache	
Benign cough headache	
Cold stimulus headache	

in the latter, there is no remission period (attacks occur for more than 1 year without remission or with remission lasting less than 14 days). Our patient suffered from chronic cluster headache that had evolved from an episodic form (secondary cluster headache). When the course is chronic from the beginning, it is called primary chronic cluster headache. Table 17-3 summarizes the diagnostic criteria for cluster headache attacks.

The stereotyped nature of the pain attacks renders cluster headache rather easy to diagnose; however, at the very beginning of the illness, symptomatic headache must be excluded by neuroimaging. In particular, the excruciating pain of cluster headache, felt in the orbital region in association with massive reddening of eye, may indicate dissection or fistula of the ipsilateral internal carotid artery in the cav-

ernous sinus, which can be confirmed by computed tomography and/or magnetic resonance (MR) imaging scans.

When the patient has a long history (years) of typical cluster headache attacks, neuroimaging does not usually add information. However, cases with atypical presentation (listed below) may require a neuroimaging study:

- First episode
- Unilateral pain attacks lasting more than 3 to 4 hours
- Absence of autonomic features
- Unusual pain location
- Unresponsive to drugs
- Unusual age at onset
- Abnormal neurologic examination

Because our patient could have attacks longer than 3 hours and he developed complete drug refractoriness (see below), he received a complete neuroimaging study including cerebral MR, MR angiography, and catheter angiography, which excluded other conditions and confirmed the diagnosis of chronic cluster headache.

The attacks in our patient were exceptionally painful, and he became so agitated during them that his wife and children were afraid of him. At the beginning of the illness, the crises improved after subcutaneous sumatriptan injection (several times a day); fortunately, he had no coronary artery disease or hypertension, the conditions contraindicating sumatriptan.

However, he gradually ceased to respond to sumatriptan (administered subcutaneously, orally, as suppository, or intranasal). He also became refractory to oxygen, indomethacin (orally, as suppository, intramuscularly) and nonsteroidal anti-inflammatory drugs. At this point he

**Table 17-2. Main Differences between the Most Frequent Short-lasting (Duration < 4 Hours) Primary Headaches**

	Cluster Headache	Chronic Paroxysmal Hemicrania	Episodic Paroxysmal Hemicrania	SUNCT	Idiopathic Stabbing Headache	Trigeminal Neuralgia
Sex ratio (M:F)	3:1	1:3	1:1	5:1	F > M	F > M
Pain quality	Lancinating	Dull/pulsating	Pulsating	Stabbing	Stabbing	Sudden-stabbing
Pain intensity	Excruciating	Excruciating	Excruciating	Severe	Severe	Excruciating
Pain location	Orbital temporal	Orbital temporal	Orbital temporal	Orbital temporal	Head (any part)	V2-V3 (V1 rarely)
Attack duration	15-180 min	2-45 min	1-30 min	5-240 sec	< 1 sec	From less than 1 sec to 2 min
Attack frequency	1-8/day	1-40/day	3-30/day	From 1/day to 30/hour	From few to many/day	From few to many/day
Autonomic phenomena	++	++	++	+++	—	—
Indomethacin response	+	+++	+++	—	++	—
Common triggers	Alcohol	Alcohol	Alcohol	Chewing and touching face, etc	None (commonly associated with migraine)	Chewing and touching face, etc

F = female; M = male; SUNCT = short-lasting neuralgiform headache attacks with conjunctival injection and tearing.

+ = mild; ++ = moderate; +++ = massive.

**Table 17-3. Diagnostic Criteria for Cluster Headache Attacks**

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- A. At least five attacks fulfilling criteria B to E
- B. Severe or very severe unilateral orbital, supraorbital, and/or temporal pain, lasting 15 to 180 minutes if untreated
- C. Headache associated with at least one of the following signs, which have to be present on the pain side:
1. Conjunctival injection and/or lacrimation
  2. Nasal congestion and/or rhinorrhea
  3. Eyelid edema
  4. Forehead and facial sweating
  5. Miosis and/or ptosis
  6. A sense of restlessness or agitation
- D. Frequency of attacks: from 1 every other day to 8 per day
- E. No evidence of organic disease
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Adapted from Headache Classification Subcommittee of the International Headache Society, 2004.

obtained slight relief with intravenous dexamethasone (up to 48 mg per day!) but only if given at the beginning of an attack.

## Management Strategies

Everything was tried in this patient. One of the most effective drugs for cluster headache prophylaxis is verapamil. First, an electrocardiogram was performed to exclude atrioventricular block, and then verapamil was started at the dosage of 360 mg per day. Blood pressure and heart rate were monitored. The drug was well tolerated and the dose was increased to 960 mg per day, but with no benefit. Lithium was then initiated at 900 mg per day; FT3-FT4 and thyroid-stimulating hormone remained normal, as did electrolytes and renal function, but there was no improvement even when increased at 1,200 mg per day. Methysergide was then given, up to 6 mg per day (to avoid vasoconstriction, sumatriptan administration was always distant from methysergide administration). Again, there was no improvement.

Neither valproate (up to 1,500 mg per day) nor topiramate (up to 300 mg per day) produced any benefit. During the latter treatments, transaminases, hemochrome, ammonium, lipases, and amylase all remained normal.

We next tried prednisone up to 100 mg per day with no benefit. We then tried associations of drugs, verapamil plus lithium, verapamil plus prednisone, lithium plus prednisone, all with no benefit. A full list of the prophylactic and acute treatments tried in this patient is given in Table 17-4. Benzodiazepines were also administered because of difficulties in sleeping.

Thus, our patient eventually developed a form of chronic cluster headache totally refractory to drugs alone or in combination. In fact, about 20% of chronic cluster headache cases are totally unresponsive to medication, and they are among the most difficult medical conditions to deal with. Cluster headache is probably the worst pain

human beings can suffer from, and when unresponsive to drugs, patients become so desperate that they frequently try to kill themselves; cluster headache has been called suicide headache. Our patient attempted suicide three times.

What is to be done in such cases?

Surgery must be considered. A number of operations have been tried both on the trigeminal nerve and parasympathetic nerve structures. The best results are achieved by radiofrequency gangliorhizolysis (thermocoagulation) on the trigeminal nerve. This produces pain relief in about two-thirds of treated patients, but this is rarely permanent and the benefit of a second procedure is less certain. The best pain relief results are obtained when accompanied by complete loss of facial sensation and corneal reflex. Anesthesia dolorosa and keratitis are the most feared secondary effects of trigeminal nerve procedures.

Two balloon compressions on the right trigeminal nerve were performed on our patient, but they produced no benefit. Only after the second percutaneous thermal rhizotomy, in March 2000, did the right-side headaches disappear. Because of repeated surgical damage to the trigeminal nerve, the patient had complete loss of sensation on the operated side, and a few months later, he developed intractable anesthesia dolorosa on that side.

Unfortunately, from that moment, the left-side attacks worsened to exactly mirror those on the right. Left trigeminal surgery was contraindicated by the risk of corneal sequelae, which could have left the patient totally blind, since he was already blind on the right as a result of vitreous humor hemorrhage. For months he suffered from 3 to 8 completely refractory left-sided attacks per day.

## Case Summary

- This is a typical case of cluster headache in which attacks occurred in bouts (cluster periods) at the beginning of the story (episodic cluster headache) and then developed a chronic course.
- Among the headache types occurring in separate episodes, it is important to distinguish the long-lasting from the short-lasting headache forms. In the case of the latter, the presence of accompanying autonomic features will suggest a form of TACs. To differentiate among the various TAC forms, attack duration is the main criterion.

**Table 17-4. List of the Acute and Prophylactic Treatments Tried in This Patient**


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Sumatriptan, oxygen, steroids, ergotamine, indomethacin, other nonsteroidal anti-inflammatory drugs, intravenous dexamethasone as abortive agents and as preventatives, verapamil, lithium, prednisone, intravenous dexamethasone, indomethacin, methysergide, valproate, topiramate, dihydroergotamine, lamotrigine, clonidine, pizotifen, flunarizine, propranolol, tricyclic antidepressants, levomepromazine, promazine, lorazepam.

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- No specific investigation is warranted when faced with a patient suffering from typical cluster headache attacks responding to usual treatments. Our patient had chronic cluster headache; confounding variables in this case were that 1) attacks could last more than 3 hours, and 2) he became completely drug refractory.
- When a chronic cluster headache patient does not have benefit from drug therapies, then surgery has to be considered.
- In the last few years, better understanding of cluster headache pathophysiology has led to a new neurosurgical approach that has been successfully tried in patients suffering from intractable chronic cluster headache.

## Overview of Cluster Headache: A Step Back

Until a few years ago, cluster headache was considered to be a *vascular headache*; that is, primarily due to vasodilatation of cranial vessels. In recent years, this view has changed profoundly. One of the main characteristics of cluster headache is the clockwise regularity of attacks at fixed hours of the day or night, and the typical seasonal recurrence of the bouts. These clinical observations led to the hypothesis that a biologic clock in the hypothalamus might be involved in the pathogenesis of cluster headache. Positron emission tomography has shown activation of the ipsilateral posterior inferior hypothalamus during cluster headache attacks, and voxel-based morphometry has shown increased neuronal density in the same area. These findings suggested that the hypothalamus might be the “cluster headache generator,” or the site of the brain lesion responsible for the condition.

In Parkinson’s disease, knowledge of the cerebral lesion site led to the successful treatment of drug resistant cases by electrode stimulation of the affected areas. We therefore surmised that electrical stimulation of the hypothalamus might benefit intractable chronic cluster headache.

After the fully informed consent of our patient and approval of the local ethics committee, we performed the first ever electrode implant of the posterior inferior left hypothalamus in July 2000. One month after electrode insertion, the attacks disappeared (stimulation parameters at that time were frequency 180 Hz, amplitude 3 V, pulsewidth 60  $\mu$ s). Twice, unknown to the patient, the stimulator was switched off and the attacks reappeared 48 hours later. When the stimulator was turned on again, the attacks disappeared 48 hours later. Three years after the operation, the patient remains pain free unless the stimulator is switched off. No major side effects have been observed or reported.

Up to now, we have performed 16 hypothalamic electrode implants in 14 people for chronic intractable cluster headache, all with similarly good results. Our current pol-

icy is to offer patients with severe intractable chronic cluster headache the option of either trigeminal surgery or hypothalamic electrode implant, explaining the advantages and disadvantages of both. We suspect that electrode implant may be more effective, and associated with fewer side effects, than conventional surgical approaches, particularly since electrode implantation is reversible. However, only a large series of cases with long follow-up will provide more definite information.

## Selected Readings

- Goadsby PJ. Pathophysiology of cluster headache: a trigeminal autonomic cephalgia. *Lancet* 2002;1:251–7.
- Headache Classification Subcommittee of the International Headache Society. The international classification of headache disorders: 2nd ed. *Cephalalgia* 2004;24 Suppl 1:1–160.
- Leone M, Franzini A, Bussone G. Stereotactic stimulation of posterior hypothalamic gray matter for intractable cluster headache. *N Engl J Med* 2001;345:1428–9.
- May A, Leone M. Up to date on cluster headache. *Curr Opin Neurol* 2003;16:333–40.

## Editorial Comments

Few cases in clinical neurology are as important as this particular one by Dr. Leone. Intractable cluster headache can be almost impossible to manage by medical means, and as the last resort, surgical interventions have to be employed in selective patients. However, destructive procedures can be associated with significant morbidity and may not prevent the recurrence of cluster headache. In this remarkable case, an electrode implant placed in the hypothalamus aborted the patient’s symptoms when stimulation was maintained and recurred when the stimulation was off. The site of the implant was designed to be in the precise anatomic localization of the putative cluster generator, determined by prior imaging procedures. In the hands of Dr. Leone and his colleagues, this has been a most successful and remarkable therapeutic intervention. This case is the cornerstone of a new era of headache therapy, utilizing stimulation therapies to modify the pain of cluster headache. Follow this story carefully in the future, as it may lead to other innovative therapies.

### FINAL DIAGNOSIS:

Severe cluster headache, requiring hypothalamic implant therapy

Note: Methysergide is no longer available in the United States, and readers should be reminded that it is an ergot and therefore a triptan cannot be used with methysergide in that country.