Headache
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ISSN 0017-8748
doi: 10.1111/j.1526-4610.2011.01924.x
Published by Wiley Periodicals, Inc.

Expert Opinion

The Sexagenarian Woman With New-Onset Cluster Headaches

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Key words: cluster headache, misdiagnosis, migraine, corticosteroid

(*Headache* 2011;51:995-998)

This headache type has had many different names in the past including ciliary neuralgia, erythroprosopalgia of Bing, hemicrania periodic neuralgiforms, histaminic cephalalgia, Horton's headache, migrainous neuralgia, Sluder's neuralgia, and sphenopalatine neuralgia. Kunkle and colleagues observed the tendency of the headaches to cluster in time and proposed the term, "cluster headache," in 1952.[1]

CLINICAL HISTORY

This is a 61-year-old woman with a history of headaches since the age of 20. One type of headache occurs rarely and was more frequent in the past. She describes a 1-sided severe throbbing with nausea and light sensitivity without aura lasting about 4 hours after taking an over-the-counter medication and sleeping. A second type of headache, which has been present for many years occurring perhaps once a month, is described as a bifrontal and back of the head pressure with an intensity of 6-7/10 with light and noise sensitivity but no nausea or aura. She takes an over-the-counter medication and the headache lasts a couple of hours. There are no triggers.

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Starting 3.5 months ago, she developed a new type of headache occurring twice a day, about 10-12 hours apart with one awakening her from sleep and occasionally 3 times daily. She describes a left temporal and behind the left eye and sometimes a left parietal stabbing with an intensity of 10/10 with noise sensitivity but no nausea or aura. She has tearing and redness of the left eye. She is not sure if there is nares congestion or drainage. She has not noticed if there is ptosis or miosis. The headache lasts about 45 minutes and she takes an over-the-counter medication. She has to move around during a headache.

She initially saw an ophthalmologist and had a normal eye exam. She then saw an otorhinolaryngologist who found a normal exam and obtained a normal Westergren erythrocyte sedimentation rate (ESR). He started prednisone 10 mg daily for 1 week without improvement. She then saw her primary care physician who queried whether she might have temporal arteritis despite the normal ESR and placed her on prednisone 80 mg daily for 3 weeks starting 7 weeks ago with relief of the headaches. When she tapered off the prednisone, the headaches recurred within 1 week. She then saw a neurologist who obtained a magnetic resonance imaging of the brain without contrast 3 weeks ago with normal findings and an ESR of 20 mm/hour. He discussed a superficial temporal artery biopsy to further consider the possibility of temporal arteritis although he thought it possible she may have temporomandibular disorder and suggested trying naproxen, which did not help.

There was a past medical history of mild depression on duloxetine. She smokes 1 pack of cigarettes per day for over 40 years. Family history reveals her mother with cluster headaches starting in her 40s and her sister with migraines. Neurological examination is normal. The headaches responded well to 100% oxygen through a non-rebreathing mask at a flow rate of 10 L/minute. She was placed on verapamil 240 mg daily and the headaches were gone within several weeks.

Questions: How often are cluster headaches misdiagnosed? How often is the onset of cluster over the age of 50? Are cluster headaches co-morbid with migraine or sleep apnea? What is the genetics of cluster? Is cigarette smoking a risk factor and would quitting change the natural history? As transitional therapy, are oral corticosteroids more effective than corticosteroids administered as a suboccipital injection in the region of the greater occipital nerve (greater occipital nerve block)? What dose of corticosteroids would you recommend? What is her prognosis?

EXPERT OPINION

Misdiagnosis, Self-Diagnosis, and Age of Onset.—Headache specialists know that cluster headache is often mis- or underdiagnosed.[2] Although cluster headache, in its typical form, is unmistakable, there are no valid data regarding the percentage of patients with cluster headache who are misdiagnosed when first consulting a physician, but it is probably more than 80% or 90%. Most patients will initially see an ophthalmologist or rather a dentist as the attacks often start in the eye or with a twitching pain in the upper teeth. Twenty years ago, the average time between first symptoms and correct diagnosis was more than 10 years, and since then a drastic reduction in mean time to diagnosis over the years took place in the UK[2] although 22% were still not diagnosed for 10 years or more according to 1 US survey.[3] Despite the reduction in mean time to diagnosis, the mean number of general practitioners seen prior to neurological referral has not changed and about two-thirds have already been seen by at least 1 other specialist.[2] This situation certainly improves compared to 20 years ago, and at present most patients need less than 2 years to get the correct diagnosis. I would think there are at least 2 main reasons: (1) doctors know more about the pathophysiology of this syndrome and have more treatment options available; and (2) patients get better in diagnosing themselves. The first issue is important as a disease which is better known is more accepted and this makes it more comfortable for doctors to diagnose in primary care and may also be a reason for the increase in the diagnoses of cluster headache in women.[4] The second issue is particularly interesting, as we seem to see more and more patients who use the internet and self-help groups ending up diagnosing themselves. Doctors seem to have no concept yet how to deal with this phenomenon although the potential consequences (eg, adherence) not only in cluster patients should not be underestimated.

In this particular case, even a neurologist misdiagnosed the patient, which is astonishing given the distinct history. At least he has done the right thing initiating a cranial magnetic resonance given that the patient had her first ever episode and is already over 60 years of age. This is not completely unusual as cluster headache may start between the age of 7[5] and 83[6] (usually in the third decade) and in women sometimes later[7] but should trigger further diagnostics[8] as cluster headache, particularly at older ages may have underlying structural abnormalities.[9]

Obstructive Sleep Apnea, Migraine, Genetics, and Cigarette Smoking.—As cluster headache often occurs during the night, obstructive sleep apnea has been proposed as a trigger or an associated abnormality,[10,11] for which it may be clinically useful to diagnose and treat. However, others have not found cluster to improve with treatment of the sleep apnea.[12]

Cluster headache was once considered to be a variant of migraine, a view which has fundamentally changed. Although up to 30% of patients report a family history of migraine,[13] only a few patients suffer from both headache syndromes[14] as in the case presented. Before 1990, cluster headache was not generally considered an inherited disorder. However, the observation of cluster headache in monozygotic twins and a report on the familial occurrence of cluster headache in 7% of the families, resulting in a 14-fold increase in risk of cluster headache in first-degree

relatives, underscores the importance of considering genetic factors in the etiology. To date, one must conclude that the increased familial risk strongly supports the hypothesis that cluster headache has a genetic component at least in some families.[15]

The question whether cigarette smoking is a risk factor cannot be answered on the basis of valid data but it is remarkable that up to 85% of cluster headache patients are chronic cigarette smokers.[16] The question arises if chronic nicotine consumption is needed as a trigger to initiate the syndrome, possibly on the basis of some genetic background.[4] The cessation of smoking usually does not affect the frequency of cluster headache as such but may have profound effects on the future prescription of effective abortive medications, given that a coronary heart disease or stroke are contraindications for, eg, triptans.

Treatment With Corticosteroids and Prognosis.—The treatment of cluster headache is based on empirical data rather than on a pathophysiological concept of this disease.[7] It has to be said that although the headache attacks are unusually excruciating, drug treatment in cluster headache shows a placebo rate of around 30%.[17] The importance of an effective preventive regimen cannot be overstated. Since many patients have between 1 and 8 short-lived attacks a day, repeated attempts at abortive therapy may result in overmedication, toxicity, or medication overuse headaches.

In this specific case, glucocorticoids were given twice: 10 mg without effect and 80 mg daily with immediate effect. This is well in line with all available studies confirming the clinically well-known efficacy of steroids given in different regimes (30 mg prednisone/day and higher; 2×4 mg dexamethasone per day). They are a very effective initial prophylactic option, rapidly suppressing attacks during the time required for the longer-acting preventive agents to take effect. As with verapamil, no evidence for the best regime of steroid administration exists. For the beginning of steroid treatment, 60 to 100 mg of prednisone given once a day for at least 5 days is recommended, then decreasing the dosage by 10 mg every day.[18] About 70% to 80% of all cluster headache patients respond to steroids. It is my impression that most patients will have attacks again when the medication is tapered down to around 30 mg daily. Intravenous and oral application of steroids can also be successfully combined.[19] There is no consensus about the dosage of the parenteral application and certainly no sufficient randomized, placebo-controlled trials available. However, 250 or 500 mg intravenous is probably a good dose for the first 2 days and then the above mentioned dosage of oral prednisolone may be introduced. Because of the side-effect profile, corticosteroids should only be given as an interim solution until another medication (such as verapamil or lithium) is effective.

In addition, suboccipital injection of long-acting steroids (GON-block) was shown to be effective in the prophylaxis of cluster headache in a double-blind, placebo-controlled trial, where 13 episodic and chronic patients were injected with 12.46 mg betamethasone dipropionate and 5.26 mg betamethasone disodium phosphate mixed with 0.5 mL Xylocaine 2% and compared to 10 controls injected with saline.[20] In the first week after treatment, 85% of patients injected with corticosteroid became headache-free (with remissions for at least 4 weeks for most) compared to none in the placebo group. This is a good alternative and certainly worthwhile trying before more invasive treatments are introduced. However, corticosteroids are more effective and give immediate relief. When glucocorticoids are not effective one should in fact reconsider the diagnosis and, if it is still cluster headache, this is usually not a good sign regarding any preventative medication to be effective. The GON-block has certainly less side effects than the systemic administration of corticosteroids but is not recommended as first line therapy due to lack of valid data.

It has been observed that greater occipital nerve stimulation resulted in a significant reduction of cluster headache attacks in about 50-60% of patients.[21,22] This is certainly something to be considered if all drug treatments[18] are ineffective and a secondary cluster headache has been excluded.

The last question is tough because it cannot be answered. In this specific case, it is not even clear whether the patient will have an episodic or chronic cluster headache. In both cases, one of the most urgent questions patients put to their doctors is the

question whether, like in migraine, the cluster attacks decline with age. Longitudinal data for cluster headache have been anecdotal and only recently have larger epidemiological studies become available.[13,23] Altogether, the authors of these studies assume that within the natural course of the condition, the symptoms remit with age. This seems not to be the case in this specific patient but it may well be that her cluster attacks suddenly stop and never reoccur. We have to admit that we still do not know enough about this devastating headache syndrome.

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