CASE REPORT

Cluster-like headache responsive to phlebotomy

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SUMMARY

We report the first case of cluster-like headache secondary to polycythaemia vera (PV) that responded to phlebotomy as part of PV treatment.

BACKGROUND

Cluster headache (CH) is one of the most interesting neurological conditions in clinical practice; however, for CH sufferers it is one of life's worst torments they could possibly go through.

Although primary CH is the most common type of disorder, secondary CHs are well recognised (pituitary macroadenomas and meningiomas are common causes for secondary CH) and potentially treatable.

As far as we are aware cluster-like headache secondary to polycythaemia vera (PV) has not been reported in medical literature.

CASE PRESENTATION

A 52-year-old Caucasian man, a life-long smoker, presented with a 4-month history of recurrent right periorbital excruciating headaches on a background of continuous dull ache. The excruciating attacks would come on between 4 and 6 times a day, each lasting 30–75 min with ipsilateral lacrimation, conjunctival injection, rhinorrhoea and ptosis as well as extreme restlessness. The attacks were more common in the early hours of morning.

The patient suffered with migraine without aura between the age of 13 until 47 when they stopped completely.

The diagnosis of CH was made and the patient was prescribed prednisolone 60 mg/day for 5 days tapering the dose by 5 mg/day for 10 days. The patient was also started on verapamil 80 mg three times a day and the dose was titrated up to 240 mg three times a day with ECG monitoring. He was advised to use high-flow oxygen (100%) with or without subcutaneous sumatriptan injections as an abortive treatment.

INVESTIGATIONS

As a new diagnosis of CH, the patient was subjected to investigations looking for a secondary cause. An MRI of the brain was normal, the full blood count showed a haemoglobin (Hb) of 18.5 g/dL (13.5–17.5; with picture of microcytosis and hypochromia), white cell count of $14 \times 10^9/L$ (4–11), platelets of $520 \times 10^9/L$ (150–400) and haematocrit of 0.59 (0.41–0.53); his biochemical profile showed raised alkaline phosphatase of 175 U/L (30–125), all other parameters including serum lipids were normal. Serum copper and ceruloplasmin levels were also normal.

The patient was referred for a haematological opinion and further investigations. He was found to have increased red cell mass, low erythropoietin, low normal serum iron and ferritin while the total iron-binding capacity was at the upper limit of normal. Abdominal ultrasound showed splenomegaly without any other organ involvement and the bone marrow showed hypercellularity with expansion of all cell lines, megakaryocytes proliferation and myelofibrosis. He was tested positive for JAK2 mutation and was formally diagnosed with PV.

TREATMENT

The patient did not experience any improvement of his CH with steroids or verapamil, although the acute attacks responded to subcutaneous triptan but not to oxygen; however, there was a dramatic response following phlebotomy with complete remission.

OUTCOME AND FOLLOW-UP

It was observed that the recurrence of cluster-like attacks coincided with increasing Hb at a level of 18 g/dL that would subside following phlebotomy and achieved complete remission on hydroxyurea treatment for his PV.

DISCUSSION

CH is the most painful condition that affects mankind and is the most frequent type of trigeminal autonomic cephalalgias.

CH prevalence is around 0.1%¹ and typically affects one side of the head with ipsilateral significant autonomic symptoms; however, 'side-shifting' pattern of cluster has been reported.²

A typical CH victim is a male smoker³ (male to female ratio is 3:1) with peak age of onset at 30 years.⁴

CH comes in bouts of attacks, hence the name, which could last anything from 1 week to 3 months with a remission period that can last for a year. During a cluster, the patient could have eight attacks in a day each lasting 15–180 min and some patients' attacks follow certain circadian/circannual pattern as they tend to occur at around the same time in the early hours of the morning.⁵

Diagnostic criteria for CH, as per the International Classification of Headache Disorders, are illustrated in box 1.

The vast majority of CHs are primary; however, a secondary CH disorder is well reported in pituitary macroadenomas, meningiomas, brain arteriovenous malformations, posterior cranial fossa tumours and other intracranial pathologies.⁷

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Box 1 The International Classification of Headache Disorders (ICHD-3) (β) diagnostic criteria for cluster headache⁶

- A. At least five headache attacks fulfilling criteria B–D:
 - B. Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting, untreated, for 15–180 min.
 - C. Either or both of the following:
 1. At least one of the following symptoms:
 - a. Conjunctival injection and/or lacrimation
 - b. Nasal congestion and/or rhinorrhoea
 - c. Eyelid oedema
 - d. Forehead and facial sweating
 - e. Forehead and facial flushing
 - f. Sensation of fullness in the ear
 - g. Miosis and/or ptosis
 2. A sense of restlessness and agitation
 - D. The attacks have a frequency from one every other day to eight per day for more than half of the time when the disorder is active
 - E. Not better accounted for by another ICHD-3 diagnosis
- Episodic cluster headache:* at least two cluster periods lasting 7 days to 1 year separated by pain-free periods lasting 1 month or longer.
- Chronic cluster headache:* attacks occur for more than 1 year without remission or with remission in less than 1 month.
- Probable cluster headache:* attacks fulfilling all but one of the criteria for cluster headache.

Treatment of such conditions can improve CHs but its causative relationship is not understood.

Headaches are common neurological manifestations in patients with PV⁸ although they are non-specific and cluster-like headaches have not been reported. However, it is possible that our patient may have a genetic predisposition which was exacerbated due to the underlying trigger of PV pushing up the threshold. It is difficult to say whether such attacks would have ever occurred if the patient did not develop PV although it remains possible that some other provoking factor could have triggered it. Screening new onset CH and cluster-like headache disorder is very important to rule out such potentially treatable causes.

Pathophysiology

The pathophysiology of CH is not elucidated; however, the most accepted theory behind CH is related to the trigeminal autonomic reflex activation as a subsequent phenomenon to hypothalamic activation in a genetically predisposed individual. The genetic link in CH comes from monozygotic twins with CH⁹ as well as epidemiological studies that showed having one first-degree relative with the condition increases the risk for CH by up to 39-fold.^{10 11} The pathophysiology of the development of CH in those with an underlying disorder remains uncertain. Those with pituitary pathology may have triggered the hypothalamus generator in a genetically susceptible individual but this remains hypothetical. The development of cluster-like headaches in hyperviscosity syndromes where headache has been

described as a non-specific symptom is interesting. It is postulated that hyperviscosity can lead to 'microcirculation disturbances'¹² that could lead to certain headache type development in a genetically susceptible individual. Occurrence of hypoxia in PRV may be the trigger as lack of response to sumatriptan with cluster attack at high altitudes has been reported,¹³ although such hypothesis has been rejected by others.¹⁴ A low iron level as a precipitating cause remains unlikely with reports of CH in patients with haemochromatosis.¹⁵

Learning points

- ▶ Secondary causes of cluster-like headache are uncommon but must be looked for in those with atypical features or new diagnosis.
- ▶ Cluster headache is an interesting neurological condition; further studies are needed to fully understand its pathophysiology in order to establish an associative relationship with other medical conditions.
- ▶ Cluster Headaches cause excruciating unilateral pain with autonomic features. Always consider a secondary cause with first presentation of cluster headache. Investigate when clinical features are atypical.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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