Single Case – Headache

Cluster-Like Headache Revealing Polycythemia Vera: A Case Report

Cyprian Popescu

Victor Pauchet Clinic, Amiens, France

Keywords

Cluster headache · Polycythemia vera · JAK1 and JAK2 inhibitor · Hypoxia

Abstract

Herein, we report on a 44-year-old man who presented with cluster headache (CH)-like pain triggered by polycythemia vera (PV). He had severe unilateral head pain attacks lasting about 30 min not associated with cranial autonomic symptoms. After the exclusion of secondary etiologies, the patient was screened for a neoplastic process through biological markers, and the diagnosis of PV was established. The results of the initial laboratory examination showed hemoglobin at 18.1 g/L and Hct at 54%. JAK2 mutation analysis was positive at 54%, and marrow biopsy confirmed the hematopoietic clonal expansion, without myelofibrosis. He was treated with aspirin and ruxolitinib due to intolerance to interferon and the ineffectiveness of hydroxyurea. The treatment by venesection improved substantially the headaches. Oxygen inhalation was very effective in treating the CH attacks. In contrast, sumatriptan was inefficient at the very beginning of the disease. Among the pathophysiological mechanisms that we can propose to explain these cluster-like headaches are the prolonged hypoxia involving nitric oxide and calcitonin gene-related peptide release.

© 2020 The Author(s)
Published by S. Karger AG, Basel

Introduction

Cluster headache (CH) is a primary headache characterized by severe unilateral head pain attacks lasting 15–180 min associated with at least one autonomic symptom ipsilateral to the pain, circadian and circannual periods. The diagnostic of probable CH is based on all but one criterion for CH defined by the International Classification of Headache Disorder (ICHD) [1]. The prevalence of probable CH without cranial autonomic symptoms is estimated at 12.6% [2]. Autonomic disturbances in CH as lacrimation, redness of the eye, nasal congestion or rhinorrhea may be linked to the intensity of pain in CH patients [3]. The patients with probable CH without autonomic disturbances have clinical profiles almost similar to those with definite CH and thus CH without cranial autonomic symptoms may be considered as a less intense form of CH [4]. We present the clinicopathological case of a patient with episodic severe CH-like headaches without cranial autonomic symptoms. After the exclusion of the secondary etiologies, the patient was screened for a neoplastic process through biological makers, and the diagnosis of polycythemia vera (PV) was established.

Case Report

A 44-year-old man with no previous medical history presented to our outpatient clinic because of headache complaints, hot water-induced pruritus and sometimes limb paresthesia. No vertigo, sweat, or tinnitus were noted. He experienced severe headaches with circannual pattern during 1.5 months per year over the past 4 years. Attacks, of excruciating intensity as stretching or tearing invariably of the right eye, without autonomic symptoms, occurred every day and lasted about 30 min, seldom 1 h, without repeated occurrence headaches in the same day. The headaches had been present for several months, while he reported no previous history of headaches. A second type of headache was characterized by migrainous features with nausea or vomiting, and visual aura described as flies without photophobia. Physical examination results, including neurological examination and consultation by a hematologist, was uneventful. Magnetic resonance imaging (MRI) of the brain including MR angiography was normal. The results of the initial laboratory examination showed the following: hemoglobin 18.1 g/dL, Hct 54%, RBC 5.9 million/ μ L, WBC 11,000/ μ L, platelets 500,000/ μ L, normal hemostasis as well as LDH and iron serum level. Janus kinase 2 gene (JAK2) mutation analysis was positive at 54%. The patient underwent bone marrow biopsy which confirm the hypercellular features with hematopoietic clonal expansion, without myelofibrosis. Initially, the patient benefited from 5 therapeutic phlebotomy sessions. Headache attacks were aborted by oxygen inhalation at a flow rate of 12 L/min over 15 min. At the very beginning of the disease, subcutaneous injections of sumatriptan had no effect, and the treatment by verapamil hydrochloride was declined. The patient was treated with aspirin thromboprophylaxis and hydroxyurea therapy at a dose of 1,000 mg orally daily. In contrast, interferon-alpha as a non-leukemogenic treatment inducing cytogenetic remissions was poorly tolerated, leading to treatment discontinuation. He was further treated with ruxolitinib as JAK1 and JAK2 inhibitor involved in regulating blood and immunological functioning because hydroxyurea was not very effective. Monthly blood count monitoring allowed to optimize the therapy. Laboratory examination 1 month after starting treatment revealed hemoglobin 15.9 g/dL, Hct 45.6%, RBC 5.6 million/ μ L, WBC 9,000/ μ L, and platelets 500,000/ μ L. A close temporal relation of about 10 days between CH relief and phlebotomy was noted by the patient. Therapeutic phlebotomies are periodically repeated in order to maintain the hematocrit below 45%.

Discussion

The etiology and pathophysiology of CH are largely unknown. CH without cranial autonomic symptoms is considered a mild form of CH [4], the trigger of trigeminal autonomic reflex would be mediated by a complex neural network with variable activation state. It was suggested that the autonomic features in CH may be the consequence of the severity of physical suffering in CH patients [3]; therefore, the attacks without cranial autonomic symptoms may represent a distinct phenotype of clinical phenomenology.

We report a rare case of a 44-year-old man with daily CH-like headaches without autonomic symptoms which started 6 months prior to being diagnosed as having PV. CH as well as other trigeminal autonomic headaches may be secondary to structural, infectious, or neurovascular lesions, but the relationship is not necessarily a causal one. CH-like headaches in genetic blood disorders including PV have already been noted [5]. PV involves the myeloproliferation of the red blood cell mass, with associated leukocytosis and thrombocytosis and, for most patients, a V617F mutation of JAK2 in the hematopoietic cells. The proliferation of the hematopoietic cells that are heterozygous or homozygous for the JAK2 (V617) mutation may induce PV, essential thrombocythemia, and even primary myelofibrosis. The gain-of-function of this mutation by progressive enlargement of hematopoietic cell population can cause a wide variety of symptoms including headaches. JAK2 has a crucial role in the signaling pathway of the hematopoietic cytokine receptor family [6]. The JAK-STAT (signal transducers and activators of transcription) pathway is involved in both cellular development and myeloproliferative disorders, and upregulation of STAT led to the proliferation of PV cells [7]. It has been hypothesized that dysfunction of the JAK-STAT pathway induces high levels of proinflammatory cytokines which may increase pain sensitivity [8]. There is evidence to suggest that the suppression of the cytokine (IL-1 β)-induced CGRP release from trigeminal ganglia cells implies a role of cytokine-mediated trigeminal activation in both CH and migraine [9]. The relevant clinical findings support the potential therapeutic value of JAK inhibitors, and indeed our patient was successfully treated with ruxolitinib as one of the first-generation JAK inhibitors. Phlebotomy is also very effective for the increased hematocrit and blood viscosity in PV and resulted in significant improvement of headaches in our patient. Similar to other reports [10], in our case hemodilution led to a rapid disappearance of headaches in a few days and entails the causality between iron overload and headaches by decreasing the threshold for pain [11]. Improvement of the headaches by the venesection in two cousins with secondary CH and increased serum ferritin can account for the iron overload in the brainstem neural circuits involved in the pain transmission [12]. Nausea and vomiting as the most common symptoms associated with migraine and visual aura described by our patient can be observed frequently in the patients with CH, and one must not discard the diagnosis of CH if the criteria for CH defined by the International Classification of Headache Disorder (ICHD) [1] are fulfilled. In contrast to a previously described case of CH showing the efficacy of subcutaneous triptan but not oxygen [5], our patient has responded to oxygen therapy. The benefit of the inhalation of 100% oxygen and lack of response to sumatriptan were reported in CH attacks at high altitudes [13]. Like in our case, the development of cluster-like headaches under these conditions may indicate a causal or effector role of the prolonged hypoxia. The release of nitric oxide and calcitonin gene-related peptide by hypoxia implicated in primary headaches substantiated its etiopathogenic role [14]. Cluster-like headaches reported in PV and the efficacy of the phlebotomy pointed towards a presumed role of microcirculation abnormalities by platelet-mediated thrombosis in the end-arterial circulation induced by hyperviscosity [15].

Limitations

One of the limitations regarding the diagnostic in the case presented here was the lack of all the classical features of CH, notably autonomic symptoms; nonetheless, the efficacy of oxygen therapy was in favor of the diagnosis of CH. Multiple comorbidities, including primary headache disorder cannot be excluded; however, our patient developed the symptoms in close temporal relation to PV, and phlebotomies allow invariably a clear improvement of headaches.

Conclusion

We describe an original case of cluster-like headache revealing PV positive for the V617F mutation of the JAK2 gene. This is a peculiar case involving a secondary CH with atypical features notably without cranial autonomic symptoms. In contrast to the previous report of CH-like induced by polycythemia vera [5], our patient responded to oxygen therapy. We hypothesize that the principal mechanism by which PV could lead to CH is prolonged hypoxia. These atypical features of CH should be regarded as red flags and require quick diagnosis in order to provide adequate care.

Clinical Implications

Even though CH is a very rare consequence of PV, this clinicopathological case report suggests that blood disorders should be considered in the workup of patients with atypical CH features.

Statement of Ethics

The subject gave his written informed consent to publish his case.

Disclosure Statement

The author has no conflicts of interest to declare.

Funding Sources

There was no funding.

References

- 1 Headache Classification Committee of the International Headache Society (IHS). The international classification of headache disorders 3rd edition. *Cephalalgia*. 2018;38:1–211.
- 2 Sohn JH, Choi YJ, Kim BK, Chung PW, Lee MJ, Chu MK, et al. Clinical Features of Probable Cluster Headache: A Prospective, Cross-Sectional Multicenter Study. *Front Neurol*. 2018 Oct;9:908.
- 3 Martins IP, Gouveia RG, Parreira E. Cluster headache without autonomic symptoms: why is it different? *Headache*. 2005 Mar;45(3):190–5.
- 4 Drummond PD. Dissociation between pain and autonomic disturbances in cluster headache. *Headache*. 1990 Jul;30(8):505–8.
- 5 Khalil M, Yoga B, Ahmed F. Cluster-like headache responsive to phlebotomy. *BMJ Case Rep*. 2014 Jun;2014 jun04 1:2014.

- 6 Quintás-Cardama A, Kantarjian H, Cortes J, Verstovsek S. Janus kinase inhibitors for the treatment of myeloproliferative neoplasias and beyond. *Nat Rev Drug Discov*. 2011 Feb;10(2):127–40.
- 7 Röder S, Steimle C, Meinhardt G, Pahl HL. STAT3 is constitutively active in some patients with Polycythemia rubra vera. *Exp Hematol*. 2001 Jun;29(6):694–702.
- 8 Rittner HL, Machelska H, Stein C. Leukocytes in the regulation of pain and analgesia. *J Leukoc Biol*. 2005 Dec;78(6):1215–22.
- 9 Neeb L, Hellen P, Hoffmann J, Dirnagl U, Reuter U. Methylprednisolone blocks interleukin 1 beta induced calcitonin gene related peptide release in trigeminal ganglia cells. *J Headache Pain*. 2016;17(1):19.
- 10 Ickenstein GW, Klotz JM, Langohr HD. [Headache caused by polycythemia vera. Classification of a headache under the heading of metabolic disturbances]. *Schmerz*. 1999 Aug;13(4):279–82.
- 11 Gaul C, Krummnerl P, Tamke B, Kornhuber M. Chronic daily headache in hereditary hemochromatosis treated by venesection. *Headache*. 2007 Jun;47(6):926–8.
- 12 Stovner LJ, Hagen K, Waage A, Bjerve KS. Hereditary haemochromatosis in two cousins with cluster headache. *Cephalalgia*. 2002 May;22(4):317–9.
- 13 Mampreso E, Maggioni F, Viaro F, Disco C, Zanchin G. Efficacy of oxygen inhalation in sumatriptan refractory “high altitude” cluster headache attacks. *J Headache Pain*. 2009 Dec;10(6):465–7.
- 14 Britze J, Arngrim N, Schytz HW, Ashina M. Hypoxic mechanisms in primary headaches. *Cephalalgia*. 2017 Apr;37(4):372–84.
- 15 Aamodt AH, Borch-Johnsen B, Hagen K, Stovner LJ, Asberg A, Zwart JA. Headache prevalence related to haemoglobin and ferritin. The HUNT Study. *Cephalalgia*. 2004 Sep;24(9):758–62.