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Varicella-zoster virus and exertional headache: Evidence of viral vasculopathy in Valsalva maneuver-related headache syndrome

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Abstract

Exertional headache is one entity of Valsalva maneuver-related headache syndrome. It is usually idiopathic, but has occasionally been reported to be associated with secondary causes. However, central nervous system infection has not been mentioned before. We encountered a young man who suffered an isolated exertional headache and was found to have an active varicella-zoster virus central nervous system infection without typical intracranial hypertension or outflow obstruction. Intracranial vasoconstriction was detected during headache when the patient performed acute lifting or heavy exertion. The findings in this patient suggest a specific relationship between varicella-zoster virus-related vasculopathy and exertional headache from other Valsalva maneuver-related headache syndrome.

INTRODUCTION

Exertional headache is one entity of Valsalva maneuver-related headache (VMRH) syndrome, with a lifetime prevalence of 1%. Secondary disorders, such as subarachnoid hemorrhage, arterial dissection[1-3], brain metastasis, pansinusitis, Arnold-Chiari malformation, platybasia, subdural hematomas, Eagle syndrome, acute myocardial infarction, and coronary artery disease (or cardiac cephalgia)[4] have been reported in 10% to 42% of exertional headache patients. Conversely, the pathophysiology is still unknown in over half of exertional headache patients. Herein, we report a patient who suffered an isolated headache with exertion that was compatible with exertional headache associated with a varicella-zoster virus (VZV) central nervous system infection. The role of VZV-related vasculopathy in exertional headache is discussed.

CASE REPORT

A 26-year-old male mechanical engineer, experienced a subacute onset of headache lasting for two weeks after a mild sore throat. The headache was paroxysmal, bilateral, pulsating, and moderate in magnitude, and was located at the suboccipital, vertex, or, on occasion, the frontal area. It was absent when the patient was not active, minimal when he slowly performed dynamic strenuous exercises, such as coughing, sneezing, running, prolonged walking, or stair climbing, but moderate to severe during exertion, especially acute lifting. Sexual activity did not provoke his headache, and the severity of the headache was only attenuated when he discontinued exertion. His headache did not occur at night during sleep or after awakening in the early morning. Aura or associated symptoms, such as photophobia, nausea/vomiting, and dysautonomia were entirely absent. The pain usually lasted from 15 minutes to one hour, and could be partially relieved by over-the-counter analgesics or caffeine-containing drugs. He denied having migraine, other headache syndromes, systemic disease, allergy, recent craniofacial trauma, recreational drug usage, exposure to toxins or chemicals, or consumption of tobacco or alcohol.

He had received cranial computed tomography and a complete blood count examination at a local hospital, but none of the tests showed any abnormal changes. He contacted our medical service 21 days after the onset of his headache. During this interval, his headache waxed and waned but did not worsen. No fever or chills were found. On presentation, his vital signs were stable, and he was conscious and oriented. The fundus did not show papilloedema or retinal changes.

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There was no tenderness of the scalp, temporal artery, mastoid, or sinuses, and no vesicles were seen on the skin, in the ear canal, or on the oral mucosa. His neck was soft, and Kernig's sign and Brudzinski's sign were negative. Cognition, speech, language, cranial nerves, motor activity, sensory function, coordination, and equilibrium were normal. Pulsating pain was rapidly induced at the suboccipital and vertex areas when he lifted a heavy object, and exertional headache was diagnosed. Laboratory tests including biochemistry, hematology, coagulation tests, infection index, autoimmune indices, cortisol, corticotrophin, thyroid function, serology to *Hemophilus influenzae*, *Neisseria meningitides*, and *Streptococcus pneumoniae*, virology to Cytomegalovirus, human immunodeficiency virus (HIV), herpes simplex virus and mumps virus, and urinalysis were within reference ranges, except that C-reactive protein was 11.6 μg/ml (normal: < 6 μg/ml), blood IgM-VZV titer a ratio of 2.18 (normal: negative), and blood IgG-VZV titer 5,062 mIU/ml (normal: < 250 mIU/ml). Head magnetic resonance imaging and a venogram did not reveal remarkable abnormalities in parenchyma or outflow obstruction, or any pachymeningitis. Magnetic resonance angiography disclosed an ambiguous focal luminal narrowing at the right middle cerebral artery and left posterior cerebral artery (Figure 1A and B). Transcranial Doppler revealed a normal middle cerebral artery mean velocity (48–50 cm/s; maximum < 70 cm/s) during rest (Figure 1C), mild cough, or slight exertion when lifting slowly, but a 1.2 to 1.7-fold increase during headache under acute heavy lifting, indicating overactive vasoconstriction in response to exertion (Figure 1D). The velocity then declined to the reference range within minutes, before a subsidence of the headache. CSF analysis showed lymphomonocytic pleocytosis with an opening pressure of 160 mmCSF, cytology 140 cells/HPF, lactate 17.4 mg%, glucose 48 mg%, $glucose_{CSF}/glucose_{blood}$ 0.53, albumin 26.61 mg%, $albumin_{CSF}/albumin_{blood}$ 0.0064, total proteins 44 mg%, IgG 8.31 mg%, IgG_{CSF}/IgG_{blood} 0.0082, VZV-IgG 15 mIU/ml, $VZV\text{-}IgG_{CSF}/VZV\text{-}IgG_{blood}$ 0.003, and a VZV-IgM titer of 0.02. Intrathecal VZV-IgG synthesis was indicated. Accordingly, a non-febrile VZV central nervous system infection was established. Indomethacin was administrated, and the middle cerebral artery mean velocity normalized after four days. His headache recurred with mild severity after discontinuation of indomethacin, but ceased completely after re-administration of indomethacin for one week. The total time from index headache onset to a resolution of symptoms was 35 days. Three weeks later, his blood IgM-VZV titer was 0.25 in ratio. After three months, his blood IgM-VZV titer was undetectable and his blood IgG-VZV titer had dropped to 315 mIU/ml. At the 1-year follow-up visit, the patient remained free of headache. Transcranial Doppler performed during the follow-up disclosed a normal mean velocity at the middle cerebral artery on lifting or exertion.

DISCUSSION

Infection is responsible for a few typical[5-6] and specific headache syndromes.[7] It may occasionally provoke VMRH[5-7], mostly due to intracranial hypertension or outflow obstruction. Generally, infection-related VMRH presents with more than one provoking cause, but has rarely been reported to occur singly as an isolated exertional headache without other VMRH, such as sexual headache, similar to our patient. An important finding in our patient was the absence of typical intracranial hypertension or substantial outflow obstruction. Therefore, the findings in our patient illustrate the diverse and protean relationships between infection and headache syndromes, and also identify an infection-related vascular abnormality specific for exertional headache.

An abnormal vasoconstriction was found during headache after exertion in our patient. Reviewing the literature, overactive cerebral vasoconstriction has been identified in a couple of headache syndromes. We may categorize them into two classes based on the proximate cause. Class I headache is reversible cerebral vasoconstriction syndrome[8] that can be related to subarachnoid hemorrhage, selective serotonin reuptake inhibitors, ergotamine, vasospasm inducers, postpartum, orgasm, acute mountain sickness, bathing, and benign intracranial vasospasm. Headache in reversible cerebral vasoconstriction syndrome usually simulates thunderclap headache, a high-intensity headache of abrupt onset that peaks within 1 min and lasts from 1 hour to 10 days.[6] Although not the rule, vasospasm is usually diffuse and segmental, occurs spontaneously, lasts for days to weeks, and reverses after headache recovery.[9] It was obvious that our patient's headache not of this type.

Class II headache is due to activation of the vascular calcium channel as in VMRH[10], in which more than one clinical entity is seen. Regarding the isolated exertional headache in our patient, cerebral vasoconstriction is a common mechanism

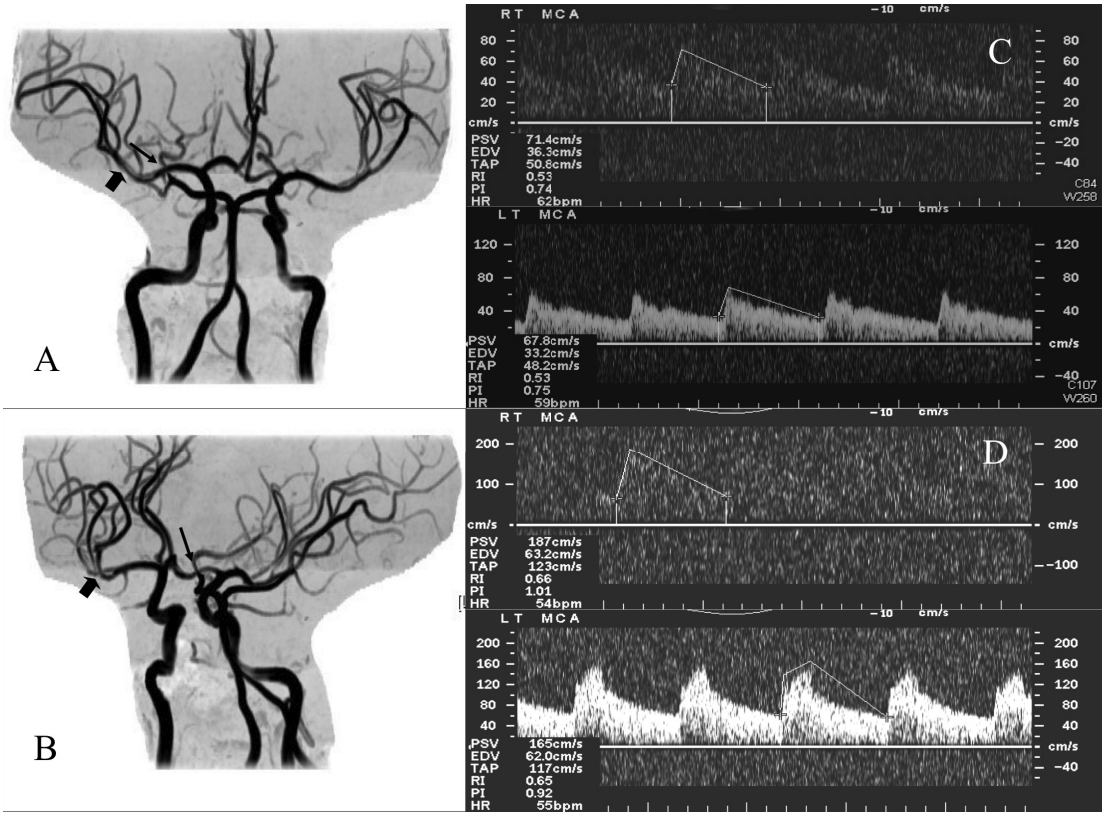

Figure 1. A head magnetic resonance arteriogram showed an equivocal stenotic change at the right middle cerebral artery (thick arrow) and right posterior cerebral artery (thin arrow) (A, anterior view; B, oblique view). This change was not fully compatible with the classic picture of reversible cerebral vasoconstriction syndrome. The mean velocity of the left and right middle cerebral artery was normal during rest without headache (C), but was abnormally elevated and associated with the headache after heavy lifting (D).

between exertional headache and other VMRH, but a different etiology and pathogenesis specifically serves for different types of VMRH.

The trigeminal nerve densely innervates the intracranial vessels and can modulate cerebral autoregulation as well as the pain threshold of cerebral vasculature through a number of mechanisms, such as calcitonin gene-related peptide. A viral modulation of the trigeminovascular system by VZV[11] or in other viral central nervous system infection [12] has been identified in the short-lasting unilateral neuralgiform headache. The responsible virus is proposed to raise the excitability of the trigeminal nerve, and that transmits the excitatory impulse to the trigeminal sensory nucleus to cause pain sensation. The impulse is then conveyed through the parasympathetic fibers in the facial nerves to target tissues to cause autonomic features.

Although a transient increase of intracranial pressure is postulated to be the common underlying mechanism for VMRH,[13] we hypothesize that other potential causes are present in different types of VMRH, as in our patient. Cerebral autoregulation counterbalances a rise in the mean arterial pressure and central venous pressure[14-15] to provide normal cerebral blood flow during acute exertion such as heavy lifting. With regard to exertional headache, impaired myogenic cerebrovascular autoregulation with aberrant vasodilatation during or following exercise has been postulated.[16] Therefore, we propose that the VZV impairs the vasodilatation and instead activates the parasympathetic fibers to induce vasoconstriction through trigeminal nerve autonomic fibres during acute exertion. The findings in this patient warrant further investigations of the acute and chronic viral modulation of vascular response in headache syndrome.

DISCLOSURE

Conflict of Interest**:** The authors declare that there

are no actual or potential conflicts of interest in relation to this article.

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