Headache in Guillain–Barré Syndrome: Diagnostic and Management Implications

Anas Alrohimi, Rajive Jassal

ABSTRACT: Headache is an uncommon symptom in Guillain–Barré syndrome (GBS). We review four clinical settings related to GBS in which headache may be present. We focus on pathophysiological explanations, alerting the clinician to further potential investigations and treatment. Most reports of headache in GBS occur in the context of the posterior reversible encephalopathy syndrome, an increasingly recognized dysautonomia-related GBS complication. Less frequent is headache in the setting of increased intracranial pressure and papilledema (secondary intracranial hypertension), Miller Fisher syndrome, and cerebral venous sinus thrombosis. Rarely, headache can occur secondary to aseptic meningitis from IVIg use.

RÉSUMÉ: Les maux de tête associés au syndrome de Guillain-Barré : implications en matière de diagnostic et de prise en charge. Souffrir de maux de tête demeure un symptôme peu fréquemment associé au syndrome de Guillain-Barré (SGB). Nous avons ainsi passé en revue quatre cadres cliniques liés au SGB dans lesquels il est possible que des patients souffrent de maux de tête. À cet égard, nous avons mis l'accent sur des explications de nature physiopathologique et tenté d'alerter le médecin clinicien quant à l'importance de pousser plus loin ses examens et d'offrir d'autres traitements. La majorité des maux de tête liés au SGB est survenue dans le contexte du syndrome d'encéphalopathie postérieure réversible, une dysautonomie liée au SGB de plus en plus reconnue. Ces maux de tête sont moins fréquents lorsqu'il est question d'une augmentation de la pression intracrânienne, d'un œdème papillaire (hypertension intracrânienne secondaire), du syndrome de Miller-Fisher et d'une thrombose veineuse cérébrale. À noter qu'il n'est guère fréquent que des maux de tête soient associés à une méningite aseptique consécutive à un traitement d'immunoglobulines intraveineuses.

Keywords: Guillain–Barré syndrome, headache, posterior reversible encephalopathy syndrome, secondary intracranial hypertension, Miller Fisher syndrome, cerebral venous sinus thrombosis

doi:10.1017/cjn.2017.247 Can J Neurol Sci. 2018; 45: 240-242

Introduction

Guillain–Barré syndrome (GBS) is characterized by acute immune-mediated polyneuropathies with resultant progressive limb weakness, diminished/absent reflexes, sensory disturbance, and variable autonomic dysfunction. The association of headache with GBS has been described in the literature. In a large prospective study of pain in GBS, Moulin et al.[1] cited a 2% headache incidence. Headache onset is variable, as it can exist prior to, concurrent with, or following the onset of weakness. Headache in GBS appears to occur in dysautonomia (posterior reversible encephalopathy syndrome [PRES]), secondary intracranial hypertension, Miller Fisher syndrome (MFS), cerebral venous sinus thrombosis (CVST), and aseptic meningitis from IVIg use.

Dysautonomia and PRES

The first description of PRES was in 1996, with many case reports in the PRES literature complicating the acute phase of GBS thereafter. The incidence of PRES and GBS cooccurrence is not known.

There are currently 15 adult cases reported in the literature,[2,3] most being female, older than 55 years of age, and with symptoms of PRES appearing 5 days after the onset of GBS symptoms.

The mechanism of PRES in the context of GBS remains uncertain. A potential explanation is that hypertension due to autonomic dysfunction can exceed the limits of cerebral blood vessels in regulating blood flow, leading to vasogenic edema. Endothelial injury could lead to increased vascular permeability and thus a predisposition to vasogenic edema.[3]

The diagnosis of PRES in the setting of GBS consists of typical magnetic resonance imaging/fluid attenuation inversion recovery (MRI/FLAIR) T2 findings of focal symmetric posterior cerebral hemisphere predominant vasogenic edema/hyperintensities.

The cornerstone of PRES treatment is blood pressure control and treatment of seizures. In most cases, this is an acute and self-limited syndrome.

Secondary Intracranial Hypertension

Secondary intracranial hypertension has been reported in association with GBS. Papilledema has been reported as a rare complication of GBS, and it has been associated with elevated cerebrospinal fluid (CSF) protein in most reports. Taylor and

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Received August 30, 2016. Final Revisions Submitted July 15, 2017. Date of Acceptance July 20, 2017.

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McDonald (1932)[4] reported the occurrence of blurred discs during the course of GBS. However, the first report of definite papilledema was by Gilpin et al. (1936).[5]

Based on the reported patients, the spectrum of headache in this group seems to be severe, throbbing, and associated with vomiting and visual complaints. Symptoms of intracranial hypertension symptoms tend to occur 1–2 weeks prior to GBS symptoms.[3,6]

The pathophysiological basis of headache in such cases remains uncertain, with two main competing theories. The most frequently cited cause is that the increased CSF protein concentration slows reabsorption in the arachnoid granulations, leading to increased intracranial pressure (Denny-Brown in 1952).[7] However, there are cases in the literature of disc edema with normal-range CSF protein concentrations. This remained unchallenged until Joynt (1958)[8] suggested that the basis for papilledema was cerebral edema, rather than impaired absorption of CSF.

Investigating for elevated intracranial pressure includes brain MRI along with MR venography (MRV) to rule out structural causes for the increased pressure.

This condition is extremely rare, and updated literature on this topic is lacking. Thus, general guidelines on intracranial hypertension management should probably be applied. Many patients from previous case reports showed spontaneous improvement as the motor symptoms resolved.[3] However, in cases of impending vision loss, interventions including optic nerve fenestration, repeat lumbar punctures, ventriculoperitoneal shunts, and lumbar drains in consultation with neuro-ophthalmology and neurosurgical colleagues are needed.

Headache in MFS

Since 2007, based on case reports, headache has been considered as one of the variations in clinical manifestation in MFS.[9] Two of the three patients in Dr. Miller Fisher's original report had headaches.[9]

In a case series of 27 patients with MFS,[10] 6 patients (22%) reported having pain early in their disease course, 2 of whom had headaches.

Headache in MFS is periorbital, severe, pulsatile, and induced by cough (Valsalva maneuver). The onset is variable, as it can occur before, concurrent with, or after the onset of motor dysfunction.[9,10]

The pathogenesis of headache in patients with MFS is uncertain. There are several possible explanations for the headache. First, there are the effects of increased protein including CSF outflow obstruction at the level of arachnoid granulations, and, second, activation of the trigeminovascular pain pathway from the serum autoantibodies that cause the disease process.[9] Chiba et al.[11] in 1997 showed that GD3 and GD1b are major ganglioside components of all 12 cranial nerves along with the nerve roots. They also studied[12] the antibodies associated with MFS and found some with activity toward either GD3 or GD1b in conjunction with the typical GQ1b antibodies in a minority of patients' serum (4 of 28). Based on this observation, Friedman and Potts[9] hypothesized that headache in MFS may be explained by these antibodies. This remains a speculation, and it requires further evaluations of these antibodies in MFS patients with headache.

In reviewing the case series, the mainstay of headache treatment in MFS is symptomatic. Oral nonsteroidal antiinflammatory drugs (NSAIDs) have been used, but they did not provide adequate pain relief for most patients. Those patients typically had spontaneous headache improvement parallel to resolving the manifestations of MFS.[9,10]

Aseptic meningitis due to IVIg in GBS:

Aseptic meningitis associated with IVIg therapy is an uncommon phenomenon occurring in about 11% of patients treated with high-dose (2 g/kg) IVIg, the dose typically used for treatment of GBS.[13]

The risk factors for IVIg-induced aseptic meningitis include rapid infusion, over a short time period, and in high doses (2 g/kg). Symptoms appear within 48 hours of initiation of therapy and include neck stiffness, headache, photophobia, and nausea and vomiting.

The pathogenesis of IVIg-induced aseptic meningitis is uncertain. There are several suggested mechanisms, including the IgG itself, various stabilizing components within each of the preparations, cytokine release triggered by the therapy,[13] and leaking of small quantities of IVIg into the CSF. IVIg-induced aseptic meningitis is frequently associated with polymorphic pleocytosis upon examination of the CSF.[13]

Treatment of aseptic meningitis associated with IVIg should require administration of all IVIg treatments over a longer time period (every other day or over 7 days), with each infusion delivered at a slower infusion rate (several hours), and supplemented with regular pre- and post-hydration, prophylactic antihistamines (cetirizine), and analgesic (paracetamol).

Conclusions

Headache in the setting of GBS is a rare but serious symptom that requires further investigation and careful consideration of treatment. Five clinical settings include dysautonomia (PRES), secondary intracranial hypertension, MFS, CVST, and aseptic meningitis from IVIg use. Careful fundus examination, repeated CSF studies, with measurement of opening pressure, and a low threshold for intracranial imaging (brain MRI/MRV) are the cornerstones of management. Future studies focusing on evaluating the antibody composition of patients with headache in conjunction with MFS will be necessary. Collaboration with neuroradiology, neuro-ophthalmology, and neurosurgery may be required.

Acknowledgments

Dr. Alrohimi would like to thank King Saud University, Saudi Arabia, for their sponsorship and funding.

Disclosures

Dr. Alrohimi is a funded resident. He receives his funding from King Saud University, Saudi Arabia, through the Saudi Arabian Cultural Bureau in Canada. This funding is not related to the present article.

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https://doi.org/10.1017/cjn.2017.247 Published online by Cambridge University Press

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https://doi.org/10.1017/cjn.2017.247 Published online by Cambridge University Press