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A very rare case report of baffling, unusual Neuro-Ophthalmology signs and symptoms responsive to thiamine and vitamin B-complex in a confirmed Guillain-Barré syndrome (with CNS involvement) or Fisher Bickerstaff brainstem encephalitis with a comorbid alcohol withdrawal syndrome

[1]Dr. Virti Shah, Assistant Professor MD, DNB (Neurology) Department of Neurology/Medicine

[2]Dr. Prashant Mohan Naik, Medical Officer MD, Emergency Department

[3]Dr. Niharika Sabnis, Senior Medical residents MD, Department of Medicine, MGM Medical College and Hospital. Kamothe, Sector1. Navi Mumbai, Maharashtra.

[4]Dr. Shreyansh Soni, Senior Medical residents MD, Department of Medicine, MGM Medical College and Hospital. Kamothe, Sector 1. Navi Mumbai, Maharashtra.

Corresponding Author: Dr. Virti Shah, Assistant Professor MD, DNB (Neurology) Department of Neurology/Medicine

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Abstract

Lower motor neuron (LMN) bilateral facial nerve palsy with bilateral internuclear ophthalmoplegia (painless) is a relatively rare presentation and often indicates serious underlying medical condition. We present here the complex case of a male in his late 30s who presented with symptoms and signs of bilateral LMN facial paralysis and painless internuclear ophthalmoplegia with positive Magnetic Resonance Imaging (MRI), Cerebrospinal fluid (CSF), and Nerve Conduction Velocity (NCV) findings of Guillain-Barré syndrome (GBS.) The bilateral facial nerve palsy and ophthalmoplegia completely responded to a one-day treatment of intravenous thiamine and Vitamin B Complex with VitB12 (Opti neuron). However, the final outcome of mortality due to the underlying GBS and a possibly undetected other comorbid condition could not be prevented.

Keywords: Alcohol withdrawal syndrome, Bilateral Facial Nerve palsy, Bilateral Internuclear Ophthalmoplegia, Fisher-Bickerstaff brainstem encephalitis, Guillain-Barre' Syndrome.

Introduction

Definition

Acute flaccid paralysis, characterized by symmetrical weakness of the limbs, and hyporeflexia or areflexia may be associated with sensory symptoms, such as paraesthesia or numbness, usually start distally and have a symmetrical pattern in GBS. The most common subtypes of GBS are acute inflammatory demyelinating polyneuropathy (AIDP) and acute motor axonal neuropathy (AMAN). [1,2] A less common subtype referred as Miller Fisher syndrome (MFS), is

characterized by ophthalmoplegia, ataxia and areflexia. [3,4]. Overall, the clinical course, severity and outcomes of GBS are highly variable.

Historical perspectives

The presence of 'cranial neuropathies of the GBS type' has been described in the European literature even before the renowned description by Fisher.[5] Guillain recognised the various presentations in GBS and at a Belgian symposium in 1938 proposed a clinical classification that takes into account the four topographical presentations: (1) involvement of the extremities only ('la formeinferieur'); (2) deficits of both extremities and cranial nerves ('la forme mixte spinale et mésocéphalique'); (3) a syndrome limited to the cranial nerves ('la forme mésocéphalique pure'); and (4) polyradiculopathy and mentation change ('uneforme de polyradiculonéurite avec troubles mentaux').[6] In the 1950s, Bickerstaff and Fisher independently described cases with a unique presentation of ophthalmoplegia and ataxia. The neurological features were typically preceded by an antecedent infection and their majority of patients made a spontaneous recovery. [7,8] Both authors recognised certain similarities to Guillain–Barré syndrome such as the presence of peripheral neuropathy and cerebrospinal fluid albumin-cytological dissociation.[9] In a more recent study of a large BBE and FS population (n=53 BBE; 466 FS), the authors demonstrated that FS and BBE were not distinct conditions but share similar clinical and laboratory profile.[10] The necessary evidence to conclude that both conditions were in fact part of the same spectrum of disease by virtue of their common clinical and immunological profiles was provided by the discovery of immunoglobulin G anti-GQ1b antibodies in patients with Fisher syndrome and later in Bickerstaff brainstem encephalitis.[9] Recently, Shahrizaila N et al published a review article to justify that in pursuing our research into these conditions, we refer to them by the more inclusive term 'anti-GQ1b antibody syndrome' to accommodate these variety of clinical presentation.[9]

Distribution pattern

GBS is a rare disease with an incidence of 0.81–1.89 (median 1.11) per 100,000 person–years, and is more common in men than in women (ratio 3:2).[11] GBS seems to occur less frequently in children (0.34–1.34 per 100,000 person– years) than in adults, and its incidence increases with age.[12] Worldwide, the incidence is variable; for example, a low rate of 0.40 per 100,000 person–years was reported in Brazil, in contrast to a high rate of 2.5 per 100,000 person–years in Curaçao and Bangladesh.[13,14] There are no incidence studies of GBS in Indian population, but some case-based studies have been reported.[15]

Why this report is special

In our opinion, it's a mysterious, extremely rare finding to witness complete improvement of bilateral nuclear facial palsy and ophthalmoplegia following one day treatment with intravenous thiamine and vitamins B complex which was most probably a symptom complex of confirmed GBS, Bickerstaff brainstem encephalitis spectrum disorder overlapped with a possible alcohol withdrawal in this patient. In addition, it is also exceptional to find bilateral facial nuclear palsy, bilateral internuclear ophthalmoplegia, selective disruption of bilateral medial rectus subnuclei of the Oculomotor nerve sparing the other functional components of the Oculomotor nerve as a cluster of signs and symptoms. We present the video recording of these neuro-ophthalmological findings and the case report.

Case presentation

A single, recently divorced, unemployed male of Indian origin, in his late 30s, with a low socio-economic family

background from a local village in Maharashtra state of Indian subcontinent presented to our private teaching, Medical Hospital emergency department (ED) with a seven to eight days history of first episode of gradually progressing symptoms of giddiness and difficulty walking associated with generalised weakness, burning, tingling numbness in the feet, double vision, painless, blurred vision with watering of both his eyes, drooling of saliva from his mouth associated with a change of voice (nasal quality). Though he provided a clear account of his symptoms, he found difficulty narrating the exact chronology of onset and progress of his symptoms. His appetite was decreased but there was no significant weight loss. He denied any bowel or bladder symptoms or any other associated neurological symptoms. There was no preceding or current history suggestive of trauma, head injury, diarrhoea, fever, URTI, minor infection, recent vaccination, confusion, seizures or any other significant current or past medical or neurological illness. He was not taking any prescribed or over the counter medications and denied any known allergies. He was educated up to grade 12 and was married for about ten years. Four months ago, his wife had divorced him. He denied any unprotected sexual exposure outside of marriage. He reported consuming alcohol (country liquor 30-60 ml once in the evening) over the last 18 to19 years, more or less stable drinking pattern with the recent experiences of minor withdrawal symptoms such as tremors in his hands, headaches, but no withdrawal seizures or confusion and memory problems. The patient claimed his last alcohol consumption about seven days prior to his current presentation to our hospital emergency department. He denied any accidents, head injury, intoxication, drink driving, or legal problems related to his alcohol drinks. He refused intake of any other recreational drugs. His regular diet included vegetarian and non-vegetarian food. There was no significant family history of any serious neurological or medical illness in his first-degree relatives. All these details were also confirmed with his younger sister who had accompanied him to the hospital emergency department.

On his first presentation in the emergency department, he came across as a thinly built, average nourished, appropriately dressed, alert, communicating and cooperative man of the stated age. He was apprehensive, anxious and had intermittent watering from his eyes (from inability to blink due to his facial nerve palsy). His initial vital parameters were normal except mildly increased blood pressure (BP) reading of 150/90 mmHg in his right arm. Weight-58kg, random blood sugar was 156mg% and Electrocardiogram was normal. The general examination was unremarkable and there was no sign of alcohol withdrawal or neck rigidity. His focused cardiovascular, respiratory, gastrointestinal system did not reveal any significant findings.

His detailed neurological examination revealed the following- He walked into the ED room with an apparently normal gait. His higher functions were normal with an intact orientation to time, place and person. His voice had a nasal twang quality. The cranial nerve (CN) examination revealed normal sense of smell (CNI), No lid swelling, ptosis, proptosis, or chemosis was noted. Normal near vision (formal Snellen chart not tested in the ED), normal visual field (CN II), normal pupils shape, size with intact direct and consensual light reflex. The voluntary eye movements were painless, all impaired except for the vertical up and down movements (i.e., elevation and depression of his eye balls), resulting in a more or less fixed gaze. An accommodation (convergence) was also not possible, nystagmus could not be elicited, and there was no strabismus or exotropia,

as demonstrated in the video (confirmatory of bilateral internuclear ophthalmoplegia; ruling out wall-eyed bilateral INO-CN III, IV, VI.) His corneal reflex, facial sensation was intact with normal temporalis, masseter feel and jaw jerk (CN V). He had bilateral LMN facial palsy with a bell's phenomenon (CN VII) as demonstrated in the video. His hearing was normal with Rinne and Weber test and there was no dizziness or nystagmus (CN VIII). His Uvular movement was symmetrical and gag reflex was intact (CN IX, X), shoulder shrug, neck turning was normal (CN XI) and tongue movements were normal (CN XII). Motor System- Upper and lower limb- Posture and muscle bulk was normal, no abnormal movements were noted, tone was normal and power was grade 4/5 in the upper and lower limbs. Reflexes- Hyporeflexia (+) was noted in the biceps, triceps, brachioradialis and knee. The ankle jerk was absent bilaterally. The plantar reflex was mute bilaterally. Coordination was normal. Gait was normal including heel-toe walk and Rhomberg negative. Sensory System- Upper and Lower limbs- pain sensation dermatomes- normal; light touch and vibration decreased in the LL up to the knee; joint position was normal.

This patient's blood investigations were sent for all routine investigations including chemistry, serum VDRL, HIV, Hep B, Hep C, Vit B12, and blood culture from the ED. A medical and neurology reference was obtained. A clinical differential diagnosis of GBS (MFS type), alcohol withdrawal (Wernicke) with dry beriberi and alcohol induced Vit b12, thiamine deficiency was suspected. He received intravenous thiamine (500mg) with Vitamin B complex including B12 (Opti neuron 1 ampoule) in the ED and was transferred to the Medical ICU on the same day evening for further management. Fundoscopy was normal. Chest X ray was normal. Urgent Cerebrospinal fluid (CSF) examination was performed and MRI Brain (plain and contrast) was obtained. Anti-nuclear antibodies (ANA), Anti-nuclear Cytoplasmic antibodies (ANCA), Anti-Double Stranded DNA (Anti dsDNA), and extractable Nuclear Antigen test (ENA test), CSF oligoclonal band were planned from the outside private laboratory. The thiamine and Vitamin B Complex with VitB12 (Opti neuron) supplements were started and continued on *day one*. He did not receive any other antibiotics or steroids.

The next day morning *(Day2)* patient's bilateral facial palsy and bilateral internuclear ophthalmoplegia improved completely. The routine investigations revealed no abnormality in the haematological, inflammatory markers, and renal function tests. Liver function test was normal except mild increase in the Liver enzymes (AST and ALT). The vitamin B12 levels were in the low normal range. The CSF study revealed total protein 73.5mg/dl and WBC count of one (suggestive of albumin-cytological dissociation) whereas other CSF parameters (sugar, adenosine deaminase, LDH) were normal; no CSF oligoclonal bands were detected. The Nerve conduction velocity (NCV) and a needle Electromyography (EMG) revealed low amplitude compound muscle action potential from his facial nerve innervated muscle and an absent Soleus 'H' reflex bilaterally. The MRI brain with contrast revealed mild bilateral periventricular white matter T2W and Flair hyperintensities. *On day two*, the intravenous immunoglobulin treatment was planned and the risks of deterioration including a possibility of death were explained in view of hyporeflexia with a confirmed diagnosis of GBS. The patient and his relatives could not afford the ANA screen or costly investigations including the treatment costs of intravenous immunoglobulin despite provision of half of the expenses for this treatment by the hospital Charity funds. Furthermore,

they consented to further continuation of his ongoing supportive management in this hospital medical intensive care unit rather than moving him to another government hospital facility. Tablet lorazepam was added (2mg) twice daily.

On day three, the patient developed sudden onset of severe autonomic instability in the form of hypertension and tachycardia with disorientation which required an emergency endotracheal intubation and ventilatory support. The patient was then started on lorazepam (2mg) injections intravenously three times a day to control underlying suspected delirium tremens. An IV midazolam infusion was continued to maintain his sedation after the endotracheal intubation and a ventilatory support. A prior valid high risk and procedure consent was obtained from his next of kin. The effective nursing care, physiotherapy, adequate IV fluids and nutritional support through the RT based on the input/output was continued. A gradual tapering of lorazepam was ensured over the next three days. Though, his daily focused general, respiratory, cardiac and abdominal physical examination did not reveal anything significant, a comprehensive serial neurological assessment was not possible due to sedation.

On day eight, of his hospitalization, the patient self-extubated and an immediate CPR was ensured. A return of spontaneous circulation (ROSC) was achieved after 2 minutes of successful CPR and an endotracheal intubation with ventilation was re- established with sinus tachycardia rhythm and grossly normal vital parameters on the cardiac monitor. Nevertheless, the patient passed away the next day (day 9 of hospitalization).

Discussion

We discuss the overlapping syndromes and medical conditions causing the symptoms and signs similar to our patient which to our knowledge based on the searched medical literature do not fit categorically in a single syndrome nomenclature.

Internuclear ophthalmoplegia (INO) is an eye movement disorder caused by a lesion in the medial longitudinal fasciculus (MLF) located in the midbrain. Adduction paralysis of the ipsilateral eye and abduction nystagmus in the opposite eye are the main features of the unilateral INO.[16] According to our literature search, it was thought that lesions above the oculomotor nucleus level (anterior internuclear ophthalmoplegia of Cogan) had absent convergence. However, recent studies have disproved this theory, and retained convergence is thought to reflect the innate ability to converge to near targets.[17] Our patient had absent abduction and adduction in both eyes which could be explained by bilateral INO. Concomitant absence of adduction movements including loss of convergence of his both eyes could only be explained based on the neuroanatomy by selective disruption of his bilateral medial rectus subnuclei of the oculomotor nerve in the midbrain. There was no other functional disruption in the oculomotor nerve. No such case studies or case reports are available to us which could explain bilateral absence of adduction and convergence of eyeballs suggesting only selective involvement of the bilateral medial rectus subnuclei of the Oculomotor nerve.

Guillain-Barré syndrome, also known as an Acute Inflammatory Demyelinating Polyneuropathy (AIDP) is an acute demyelinating polyradiculopathy of uncertain aetiology which may present with facial nerve involvement in 27–50% of cases, often bilaterally.[18] In many cases, other cranial nerves may also be involved with the possibilities of ophthalmoplegia, dysphonia. It is regarded as a predominantly motor neuropathy with few sensory features. Although, CNS is rarely involved, GBS associated with CNS manifestations has been described in children,[19] as well as adults.[20] There is extensive

literature suggesting that GBS is associated with autonomic dysfunction in up to two-thirds of patients.[21] This includes blood pressure fluctuations, arrhythmias, vasomotor dysfunction, and gastrointestinal (GI) motility dysregulation. Given that these patients are often stable on initial presentation, it is important to emphasize early monitoring for respiratory or cardiovascular collapse. Mortality can be as high as 7% in this patient population, and early recognition with appropriate management is the key to addressing the number of deaths secondary to dysautonomia.[22]

Ophthalmoplegia, peripheral neuropathy ataxia, altered consciousness and CSF albumin- cytological dissociation has also been described in Bickerstaff brainstem encephalitis. Fisher Bickerstaff syndrome has been described as a continuous spectrum between these conditions presenting with variable central and peripheral nervous system signs (CNS and PNS involvement).[9]

More than 50% of those with a history of alcohol abuse can exhibit alcohol withdrawal symptoms at discontinuing or decreasing their alcohol use. However, only a few (3% to 5%) exhibits symptoms of severe alcohol withdrawal with profound confusion, autonomic hyperactivity, and cardiovascular collapse. This is defined as alcohol withdrawal delirium, more commonly known as delirium tremens (DT).[23] Wernicke's encephalopathy is common, often missed and preventable, with a high morbidity and a 10–20% mortality. Wernicke's encephalopathy ocular abnormalities include nystagmus, bilateral cranial nerve VI palsies, and conjugate gaze palsies. Ataxia is secondary to a combination of polyneuropathy, cerebellar involvement, and vestibular dysfunction.[24]

Though, our patient showed complete improvement of ophthalmoplegia with thiamine infusion and on day three developed severe autonomic instability with disorientation, the bilateral facial nerve palsy and other positive laboratory investigations findings cannot be explained in the context of delirium tremens (DTs) alone. DTs could only be considered as an overlapping comorbid condition in this case. There could be a remote possibility of minimising details of his true alcohol consumption during the formal interviewing of this patient.

We have discussed above, the overlapping syndromes and the not so common medical conditions causing the symptoms and signs similar to our patient's presentation. GBS associated with CNS involvement or Fisher Bickerstaff brainstem encephalitis is the most plausible explanation based on the correlation of the available medical scientific data with the utility of the CSF, nerve conduction velocity, and needle EMG findings. The comorbid alcohol withdrawal syndrome was considered to be present in view of rapid response of ophthalmoplegia to intravenous thiamine administration (a retrospective diagnosis based on the clinical improvement.) It remains doubtful whether thiamine and Vitamin B complex (Opti neuron) was also effective in a simultaneous rapid recovery of this patient's facial nerve palsy.

The Central nervous system involvement here could be suggested by the following findings. The presence of a bilateral medial rectus palsy resulting in an addiction defect and a convergence paralysis in association with an abduction defect of his both eyes could only be explained from a CNS insult located in the bilateral medial rectus subnucleus of the oculomotor nerve and a bilateral lesion in the MLF of his brain stem. The involvement of the central brainstem can be further explained by his bilateral facial nerve nuclear involvement. This patient's MRI with contrast images revealed mild bilateral periventricular white matter T2W and Flair

hyperintensities without brainstem altered signal, signs of demyelination or other structural CNS lesions. The peripheral nerve involvement was suggested by the overall hyporeflexia, sensory involvement in the lower limbs and the NCV studies. There was no laboratory evidence of infection, autoimmune vasculitis, Multiple sclerosis, or malignancy. The disorders of N-M junction were ruled out clinically. The outcome of a severe autonomic instability with death within a short span was a foreseeable future prognosis for this patient from the treating team's perspective due to comorbid alcohol withdrawal and a lack of specific treatment for GBS

Conclusion

We wish to raise the awareness and continue the medical education among the medical fraternity about this exceptionally rare, neuro-ophthalmological constellation of symptoms and signs which cannot be fully explained purely on the basis of neuroanatomical and functional correlates of the MRI Brain imaging findings in this case of Guillain-Barré or Fisher-Bickerstaff Brainstem encephalitis syndrome with a possible comorbid alcohol withdrawal disorder. We also highlight a fact that specific and costly investigations to rule out other very rare causes listed in the medical literature as a part of ruling out differential diagnosis strategy in this case of GBS were not possible due to the financial constraints of this patient's family members and this is one of the limitations of our case report.

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