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Autopsy evidence of central and peripheral demyelination in a case of Guillain-Barré syndrome/ Bickerstaff brainstem encephalitis overlap syndrome

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Abstract

We report a case of a 59-year-old male who had acute, severe, rapidly progressive ascending weakness, which progressed to difficulty of breathing in a span of twelve hours. Neurophysiologic studies showed acute denervation compatible with acute motor axonal neuropathy. He was started on intravenous immunoglobulin therapy on the first day of hospitalization and completed five days of treatment but still developed decrease in sensorium and bilateral ophthalmoplegia. Imaging studies of the brain and cervical spinal cord showed findings that are non-contributory to the clinical presentation, leading to the consideration of Bickerstaff's brainstem encephalitis. Pulse therapy with high dose methylprednisolone for five days was given however, despite maximal treatment, he expired on the 12th day of illness. Post-mortem immunohistochemical studies of the pons and sural nerve showed areas of inflammation and demyelination in both areas, suggesting combined central and peripheral demyelination in a single patient. Literature review shows that our patient presents with atypical clinical and diagnostic features, different from Bickerstaff's brainstem encephalitis and combined central and peripheral demyelination, suggesting another disease entity presenting as acute fulminant neuropathy.

Keywords: Central and peripheral demyelination, Bickerstaff encephalitis, Guillain Barré syndrome, AMAN

INTRODUCTION

Bickerstaff's brainstem encephalitis (BBE) is a condition characterized by a triad of decreased level of consciousness, bilateral external ophthalmoplegia and ataxia.[1] It is a post-infectious neurologic condition, where an autoimmune mechanism is triggered by an antecedent infection.[2-5] It has a high incidence in Japan compared to other Western countries.[2] In our review of literature, only two other cases of BBE have been reported in the Philippines, both with benign outcomes and good prognosis.[3,4] Combined central and peripheral demyelination (CCPD) is not well-recognized owing to the difficulty to detect these disease entities concomitantly and has, thus far, been reported only in autopsy studies of patients with multiple sclerosis and chronic inflammatory demyelinating polyneuropathy simultaneously—both of which occur with chronic, and insidious course. We report a case presenting with acute fulminant symptoms of neuropathy, suggesting a different clinical entity.

CASE REPORT

The patient is a 59-year-old male, presenting with bilateral, symmetric lower extremity weakness of twelve hours duration with a 3-day history of non-productive cough. His symptoms progressed to upper extremity weakness associated with difficulty of breathing, prompting immediate mechanical ventilation in a span of a few hours. On neurologic examination, he was fully awake, without any cranial nerve deficits, but had quadriplegia, decreased sensation on both lower extremities and arreflexia. Cranial and cervical MRI on the first day of illness only revealed mild vertebral body compression on C4-C6, without any signs of cord compression, ischemia, or inflammatory processes. Nerve conduction (NCV) study done on the first day of illness showed normal SNAP amplitudes with normal latencies and conduction velocities of the bilateral sural nerves, F-wave latencies and absent bilateral tibial H reflexes while motor conduction studies of median, ulnar, tibial nerves

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could not be elicited. Needle electromyography (EMG) study showed no voluntary activation of MUAPS with decreased insertional activity on all muscles tested. Thus the EMG-NCV findings were evident of the acute axonal motor neuropathy (AMAN). Intravenous immunoglobulin (IVIG) was initiated on the first day of illness (0.4g/kg body weight) and was completed for five days. Upon its completion, he developed lethargy, ptosis and bilateral ophthalmoplegia, leading to a consideration of Bickerstaff encephalitis. Hence, high-dose methylprednisolone therapy (1000mg/dose/day) was given for five days. Repeat needle EMG done on Day 10 of illness revealed diffuse, distal, symmetric motor polyneuropathy of the facial, upper and lower extremities as seen by reduced recruitment activity on the orbicularis oris muscles, and abnormal spontaneous activities on the tibialis anterior, rectus femoris, biceps, and tongue muscles. CSF Studies were unremarkable, acellular, with normal CSF protein, while CSF immunoglobulins IgG and IgM were negative. Despite maximal treatment, the patient deteriorated and expired on the twelfth day of illness.

Post-mortem autopsy revealed micro-hemorrhages dispersed on the corpus collosum and basal ganglia, grossly. Histopathologic studies interestingly showed demyelination seen on the pons and sural nerve (see Figure 1), suggesting presence of combined central and peripheral demyelination.

DISCUSSION

Bickerstaff and Cloake (1951) first reported a syndrome of GBS presenting with ophthalmoplegia, cranial nerve palsies and ataxia, calling it "Brainstem encephalitis".[1] From then on, BBE is defined as a part of a spectrum of GBS for its presentation of arreflexia and albuminocytologic dissociation on CSF studies.[2-6,10] Because of its rarity, the etiology in which it can occur under the spectrum of GBS has not yet been clearly defined. Direct infection, demyelination, autoimmune process, post-infectious and vasculitis are all postulated to be the cause of this disease.[2-5] In 2003, Odaka *et al*. published a diagnostic criteria for BBE with clinical features of: disturbance of consciousness, ophthalmoplegia, hyperreflexia, ataxia. These findings are comparable with our patient, who presented with quadriplegia, sensory loss, ophthalmoplegia and lethargy in a span of five days. However, Koga *et al*. published

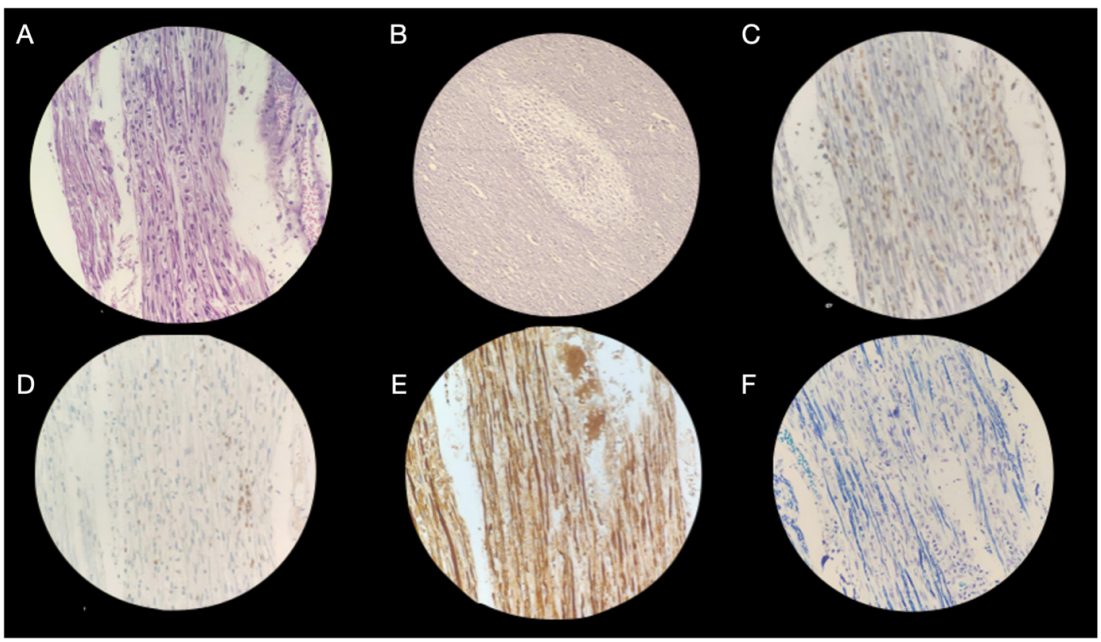

Figure 1. Immunohistologic studies. A. H&E stain of the pons show a plaque of demyelinated nerves infiltrated by macrophages within normal cerebral parenchyma. B. H&E stain of a cross-section of the sural nerve shows fibers infiltrated by macrophages and lymphocytes. C. CD68 stain of the sural nerve shows multiple histiocytes. D. CD3 stain of the sural nerve shows few lymphocytic infiltrates. E. Neurofilament stain of the sural nerve shows a non-infarcted nerve. E. Kluver-Barrera stain on the sural nerve shows abrupt transition of demyelinated and myelinated nerves, confirming a demyelinating process.

another diagnostic criteria for BBE in 2012, highlighting the role of anti-GQ1b. Definite BBE was considered if the patient had the classic clinical features and presence of anti-GQ1b serum antibodies. In our case, anti-ganglioside studies were not done, thus diagnosis of BBE can only be made clinically. However, the fascinating finding in this case was the post-mortem histologic finding of demyelination in the sural nerve and pons—proving the concurrence of peripheral and central demyelination in a single patient. Combined central and peripheral demyelination (CCPD) has been reported in cases of multiple sclerosis and chronic inflammatory demyelinating polyneuropathy.[9,10] This was not the case for our patient, whose clinical presentation and diagnostic findings do not suggest these diseases. Falcone *et al*. (2005) reported 2 cases of central and peripheral demyelination with a common pathology as they share one antigen—peripheral myelin P1 protein.[9] An autoimmune response to myelin P1/BP is thought to cause damage of peripheral nerves and CNS, which would cause secondary response to other myelin antigens, resulting to a spread of autoimmunity from central to peripheral myelin. This pattern of spread is unlikely in our patient, who presented with affectation of the peripheral nervous system, prior to affecting the central organs. Nouha *et al*. (2018), found association of central and peripheral demyelinating lesions specifically in anti-neurofascin-155 antibody.[10] Both studies point to a demyelinating process secondary to an autoimmune pathology and illustrate involvement of other antibodies besides anti-GQ1b.

In conclusion, we present a case of a patient clinically managed as BBE who despite IVIG and steroid therapy, had rapid, severe progression of symptoms and complications leading to his demise. Conversely, neurophysiologic study was atypical of BBE as it did not reveal a demyelinating pathology, but rather, a motor axonal polyneuropathy. Post-mortem studies revealed findings of demyelination in the pons and sural nerve, confirming the diagnosis of CCPD. However, this is usually seen in those with concomitant CIDP and MS, which are both chronic, insidious, demyelinating processes. The contrast of our case to the known features of both BBE and CCPD suggest that this may be a new disease entity — one that presenting with acute fulminant polyneuropathy.

DISCLOSURE

Conflict of interest: None

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