

Brainstem Encephalitis

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ABSTRACT Brainstem Encephalitis is a rare disease and though it may follow various infections, *inflammatory and non infectious conditions* account for most cases.

Key words: Brainstem Encephalitis

Introduction

Acute demyelinating encephalomyelitis is an immune-mediated disorder localized to the central nervous system which can be localized (clinically isolated syndrome or CIS) or disseminated (acute disseminated encephalomyelitis, or ADEM). When localized to the brainstem, it is known as Bickerstaff's Brainstem Encephalitis (BBE). It is characterized by the acute onset of signs of brainstem involvement, days to weeks after a variety of viral and bacterial infections or vaccinations.

Incidence

The incidence of BBE is higher in Japan compared to the Western nations. The precise incidence and prevalence of BBE in the United States and other Western nations is currently unknown, which can be attributed to the rarity of the disease and confusion and overlap with other Anti-Gq1b antibody syndromes. A recent nationwide survey of patients in Japan with BBE estimated that the annual incidence of BBE is approximately 0.078 per 100,000 individuals. Prevalence is unknown.

Etiology

The exact etiology remains unknown though it is postulated that it has an autoimmune origin. It often follows a preceding illness and its association with herpes simplex, enteroviruses, cytomegalovirus, mycoplasma pneumoniae, listeriosis and C. jejuni has been reported. The Anti-Gq1b antibody may have a role in the pathophysiology of BBE and MFS (Miller Fisher Syndrome); however the absolute underlying

pathogenesis has yet to be discovered. Anti-Gq1b antibody is the one that interacts with the peripheral nerve ganglioside, Gq1b (predominantly expressed at neuromuscular junctions, sensory nerves, and proximal segments of cranial nerves like oculomotor, trochlear and abducens nerves 3, 4, 6 respectively). Binding at these sites by the Anti-Gq1b antibody can be a potential explanation for the presenting symptoms and signs such as ophthalmoplegia and ptosis.

We here report a case of BBE in a girl, who presented with multiple cranial nerve palsies, severe ataxia and incoordination.

Case Report

13 year old girl admitted to Max Superspeciality Hospital with complaints of headache off and on since 1 month (right hemi headache) worsened since 4 days; vomiting since 3 days, 5-6 times/day, non bilious non projectile; altered sensorium; diplopia; slurred speech since 2-3 days; paraesthesias all over the body, right > left since 2 days. The child was not able to walk since 1 day. No history of contact with Koch's; or trauma; or drug intake.

Examination revealed a well built child with normal higher functions; GCS of 11/15 (E3V3M5); dysarthria; diplopia on leftward gaze with left eye ptosis (cranial nerves 3, 4, 6); left 7th nerve palsy; rest cranial nerves normal (good cough and gag reflex). Motor examination revealed normal tone; power > 3/5; DTRs not elicitable; plantars down going. No signs of meningeal irritation were present. She was grossly ataxic; with grossly impaired coordination; pupils were normal size and reaction, no papilloedema. Systemic examination was normal. Her initial blood investigations showed a normal sepsis profile and normal renal functions. MRI brain with contrast was done which revealed T2/FLAIR hyperintensity involving right middle cerebellar peduncle and the adjacent pons and right cerebellar hemisphere.

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No post contrast enhancement is seen in the region of altered signal intensity; probability of focal demyelination/infective process. Lumbar puncture was done which was suggestive of viral meningoencephalitis (TLC = 85 cells; N05L95; sugar = 59/81 mg%; protein = 39mg%; CSF for bacterial meningitis negative; viral studies for enteroviruses and DNA viruses were negative). Nerve conduction velocities in all 4 limbs were done which was normal ruling out GBS. She was started on IV fluids/Inj. Ceftriaxone/Inj. Acyclovir/Inj. Ampicillin/Azithromycin/Gabapentin (for paraesthesias). She showed a gradual stabilization over the next 48 hours. A repeat MRI brain was done after 72 hours which showed a mild increase in the hyperintensity in the previously involved areas though clinically she showed improvement. Repeat CSF study was done on day 5 of admission which was the same as previous one (TLC = 85 cells, N10L90, sugar 60/108 mg%, protein = 44 mg %). Her speech became much clearer; right cranial nerve 6 paresis persisting and all other improved. The coordination also was better but still ataxic. Though no investigation on CSF was positive her medication was continued in view of clinical improvement to the combination. She was investigated for autoimmune diseases but was normal. Her serology for herpes simplex, mycoplasma pneumonia, and antiganglioside antibodies specifically GQ1b was negative. Antibodies to immune markers NMDA receptors and VGKC were negative. CSF for oligoclonal bands was negative. She was given IV acyclovir/ Ampicillin/Ceftriaxone for 7 days and discharged.

Discussion

Brainstem encephalitis is a medical condition that causes swelling and inflammation of the brainstem. BBE is a type of Clinically Isolated Syndrome (CIS) in the consensus definitions proposed by the International Pediatric Multiple Sclerosis Study Group. It is the only CIS that can be associated with encephalopathy.

Bickerstaff's brainstem encephalitis (BBE) is a rare post-infectious neurological disease characterized by the association of external ophthalmoplegia, ataxia, lower limb areflexia, extensor plantar response and disturbance of consciousness (drowsiness, stupor or coma).

Symptomatology of brainstem encephalitis includes visual disturbances, vertigo, and an overall lack of coordination of which ataxia and vertigo are often the first noticeable symptoms. Patients usually present with onset of diplopia and gait disturbance following upper respiratory or gastrointestinal infections. The external ophthalmoplegia is progressive (within 4 weeks of onset) and relatively symmetrical. Flaccid symmetrical

quadriparesis may also be observed in over 50% of the patients, along with deep or superficial sensory impairment, facial weakness, bulbar palsy, internal ophthalmoplegia, oscillopsia (bouncing vision), blepharoptosis and nystagmus. In the acute phase of disease, BBE may be so severe that there is complete ophthalmoplegia, facial diplegia and full paralysis of arms and legs, resembling 'brain-death'. Respiratory problems may develop and can become severe enough that the patient might require ventilatory support. Nausea, vomiting, and persistent headaches may occur due to the abnormal vision. The lesions are located mainly in the brainstem; hence the presentation is related to brainstem dysfunctions.

Diagnosis is based on the clinical findings, patient history, cerebrospinal fluid (CSF) analysis (revealing raised protein levels), detection of anti-GQ1b IgG antibodies (not present in all patients), MRI studies (revealing high-intensity abnormalities in the posterior fossa, white matter or thalami) and neurophysiological examinations (electroencephalogram and electromyography indicative of central nervous system and predominantly axonal involvement).

Treatment

Effective management and treatment of BBE and other variants of Anti-Gq1b syndrome requires prompt recognition and diagnosis. While the majority of patients with BBE and MFS achieve nearly complete recovery, a number of reported cases of recurrence exist. *Surprisingly, despite alarming presenting symptoms, spontaneous recovery is frequently seen both BBE and MFS.* The majority of documented cases of BBE have shown patients to regain baseline functional status within 6 months of diagnosis. Because of frequent spontaneous recovery and rare occurrence, today there is a lack of generalized consensus on the role of specific treatments for BBE. A recent Cochrane review was not able to give any specific recommendations for the treatment of both BBE and MFS because of an apparent lack of randomized trials evaluating treatment in such clinical settings. A few case reports have shown **plasmapheresis** may hasten recovery in patients presenting with high serum titres of Anti-Gq1b antibody and with severe complications such as coma. There has been one reported case of a plasmapheresis and immunoglobulin therapy resistant BBE with eventual resolution with **Rituximab** treatment. Rituximab may have a role in the treatment of BBE based on the effect of anti-CD20 on mice models in countering the immune and complement mediated attack on the pre-synaptic terminal by the Anti-Gq1b antibody. The potential role of plasmapheresis and Rituximab in the treatment of BBE highlights that Anti-Gq1b antibodies

Comparison of Bickerstaff Brainstem Encephalitis; Miller Fisher Syndrome and Guillain Barre Syndrome

	BBE	MFS	GBS
Epidemiology	South east Asia	South east Asia	Worldwide
Diagnostic Criteria	Symmetrical ophthalmoplegia	Symmetrical ophthalmoplegia	Areflexia
	Ataxia	Ataxia	Acute ascending symmetrical limb motor weakness
	Altered sensorium	Areflexia	Dysautonomia
Lab Findings	Anti Gq1b Antibody	Anti Gq1b Antibody	Anti Gq1b Antibody*
	CSF pleocytosis	CSF pleocytosis	CSF pleocytosis
	CSF Albumino-cytological dissociation	CSF Albumino-cytological dissociation	CSF Albumino-cytological dissociation
MRI Findings	High T2 signal with little if any enhancement in brainstem and basal ganglia	Typically MRI Brain findings are unremarkable given the peripheral predilection.	Anterior nerve root thickening and enhancement surrounding the medullary cone extending along the cauda equina

* Can be seen in GBS, however less common than in BBE and MFS

may be a player in the pathogenesis of BBE. Whether BBE is a distinct disease entity or a variant of FS and GBS is still to be clarified. Many authors even consider FS and BBE as the same disease. BBE has a monophasic remitting course, with 2/3rd of patients becoming symptom-free at six months and around **16% patients requiring ventilation**. Deaths have been reported in BBE. Thus *patients with BBE need careful observation and in cases that worsen or have respiratory involvement, immunomodulatory therapy to prevent residual deficit and death needs to be started.* **There are no randomized controlled trials of immunomodulatory therapy in FS or related disorders (BBE) on which to base practice.** Until recently, corticosteroids were the only widely used treatment for acute demyelinating encephalitis. However, there is disagreement regarding their efficacy and there have not been any prospective studies or treatment guidelines. Several reports suggested that *plasmapheresis and IVIG have a beneficial effect on patients with BBE*. Moreover, combined therapy of IVIG and high-dose methylprednisolone should be more efficacious therapy. No advantage of any particular treatment can be inferred from the data available. Controlled clinical trials are needed to test this proposal. Management is based on immunotherapy with intravenous immunoglobulin

(IVIG) or plasma exchange.

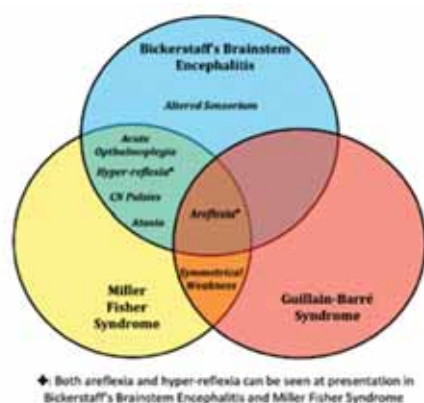
The CSF screen for infections was negative in our patient and markers for vasculitis were normal. The presence of extensor plantar response inspite of areflexia indicated that weakness is caused by brainstem lesion rather than polyradiculoneuropathy. NCV studies were normal though it may suggest peripheral motor axonal degeneration overlapping axonal variant of GBS.

Thus, **the presence of cranial neuropathy (diplopia, dysarthria), disturbed state of consciousness, ataxia, areflexia and dramatic MRI signal abnormalities in brainstem indicated a diagnosis of BBE.** Our patient was managed conservatively and observed over one week. Patient improved partially with dysarthria subsided and ataxia improved; however diplopia and mild facial paresis persisted. Repeat MRI and CSF studies after 7 days showed no progression and patient is under close follow up.

CONCLUSION

Bickerstaff's Brainstem Encephalitis is a rare neurological condition that many general physicians and even neurologists will not encounter during their lifetime. This interesting condition has characteristic signs and

symptoms including altered sensorium that should be kept in mind in the setting of new onset ataxia. Anti Gq1b antibody seropositivity has also suggested that BBE is most likely part of a spectrum of diseases under the umbrella known as Anti-Gq1b antibody syndrome. The similarities between BBE, MFS, and GBS may often cause confusion in reaching a diagnosis especially in the setting of clinical overlap. More epidemiological studies of the incidence and prevalence of BBE should be performed in Western nations. There is also a need for randomized controlled trials to evaluate if certain therapeutic agents or procedures may hasten recovery for patients with BBE.



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