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Case Report

Acute encephalitis with flaccid paralysis following an adenoviral infection presenting as a rare variant of Guillain Barre syndrome in a school-age child

Ramaning Loni[1]*, Aysha Mohammed Alsindi[2], Amina Ali Alfaw[2], Gabriel Padraigh Fox[1], Ittrat Abbas[1], Imlelda Mary Lambert[2], Bryan Lynch[3]

[1]PICU, King Hamad University Hospital, Bahrain
[2]Department of Paediatrics, King Hamad University Hospital, Bahrain
[3]Childrens Health at Temple St, Dublin, Ireland

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***Correspondence:**
Dr. Ramaning Loni,
E-mail: raj2031979@gmail.com

ABSTRACT

Guillain-Barre syndrome (GBS), Miller-Fisher syndrome (MFS), and Bickerstaff's brainstem encephalitis (BBE) are syndromes which represent a spectrum of post-infectious inflammatory immune-mediated diseases. They may share a common autoimmune pathogenetic mechanism presenting with progressive ascending weakness or flaccid paralysis affecting both pediatric as well as adult populations. MFS and BBE are rare variants of GBS that should be part of the differential diagnosis when relevant features are present. We present a case of a 6-year-old boy, presenting with a sore throat of one-day duration, associated with difficulty in swallowing, increased salivation and drooling, inability to speak or swallow following an adenoviral upper respiratory infection with exudative tonsillitis and diarrhea. Clinical evaluation showed weak gag reflex and cough reflex, hyperreflexia without clonus, upgoing Babinski reflexes, and hypotonia. A diagnosis of BBE was made based on specific neurological manifestations of hyperreflexia and drowsiness, serological studies, and MRI findings.

Keywords: Bickerstaff encephalitis, GBS, Child, Bulbar palsy, Ganglioside GM2 antibodies

INTRODUCTION

Guillain-Barre syndrome (GBS) is an acute autoimmune progressive insult that affects motor, sensory, cranial, and autonomic function. It typically presents as a post-infectious reaction, and it is one of the leading causes of flaccid paralysis in adults and children.[1] The most serious presentation is flaccid paralysis which leads to respiratory failure. Although hyporeflexia or areflexia is typically present in GBS, hyperreflexia does not exclude the diagnosis of GBS.[1]

BBE is part of a spectrum with MFS and GBS. They are part of a wide range of clinical disorders presenting with variant central nervous system (CNS) and peripheral nervous system (PNS) involvement.[2] They are autoimmune disorders with common clinical features such as ophthalmoplegia and ataxia.[3] MFS and BBE are less common than GBS. MFS is characterized by a triad of ophthalmoplegia, ataxia, and areflexia. BBE is characterized by an altered level of consciousness or other clinical features beyond the classical manifestation which is not constantly reported.[3,4] BBE typically begins with the involvement of the peripheral nerves and/or the cranial nerve, which progresses quickly to alter consciousness in a varying degree until coma.[3-5]

The majority of GBS cases recover within 28 days with a mean time of full recovery at two hundred days in 80% of patients. Sixty-five percent of cases show minor residual

signs and symptoms with incomplete recovery and 10-15% have clear major residual neurological manifestations. In an adult study, 79 cases were followed up for one year after GBS diagnosis, 8% had died, all were older than 60 years, 4% remained bedbound or ventilator dependent, 9% were unable to walk unaided, 17% were unable to run, and 62% had made a complete or nearly complete recovery.[6]

With reference to the BBS and MFS variants, there is diversity in clinical presentation that could be missed easily and may lead to delayed diagnosis and treatment.[7] Hence, an early index of suspicion and intervention is essential while treating such patients.

CASE REPORT

We report a case of a 6-year-old school going boy, born at term by normal vaginal delivery, who has presented to the emergency department of King Hamad University Hospital, Bahrain with a complaint of a sore throat of one day duration, associated with difficulty in swallowing, increased salivation and drooling, and inability to speak or swallow. Eleven days prior to the current admission, he had been admitted to our pediatric ward with an impression of upper respiratory tract infection in the form of exudative tonsillitis with parenteral diarrhea that resolved after treatment and discharged. The respiratory panel was positive for adenovirus.

On clinical examination he appeared unwell, but he was alert, afebrile, had muffled voice, and was moderately dehydrated. His oral cavity was filled with sputum and excessive saliva. A neurological examination showed drowsiness with a Glasgow coma scale (GCS) of 13/15, a weak gag and cough reflex. The rest of his physical examination was normal. He was referred to ENT and pediatric surgery team for possible foreign body ingestion/aspiration. Bronchoscopy and esophagoscopy revealed no foreign body.

He was very drowsy and lethargic, his vital signs were normal, and he was afebrile, and he continued to have drooling, dysphagia, and dysarthria. He was intubated and ventilated. The neurological examination showed generalized hypotonia, hyperreflexia without clonus, upgoing Babinski reflexes with normal sensory examination, and the presence of weak gag and cough reflex. A provisional diagnosis of brainstem encephalitis/autoimmune encephalitis was made. An immune-mediated etiology was suspected. Investigations including urgent CT brain were normal, he was empirically treated with iv antibiotics, antivirals, and a pulse dose methylprednisolone, which was given for first 3 days and later switched over to enteral prednisolone with tapering doses. Additionally, he received intravenous ((IV) human immunoglobulins of a total 2 grams per kg over 48 hours in two divided doses after nil response with IV pulse dose methyprednisolone initially. During his hospital course, he had recurrent vomiting, nausea, intermittent pain in the abdomen. A nasogastric tube was inserted initially but he kept on vomiting. He underwent an upper GI study which showed significant gastroesophageal reflux. A Naso-jejunal tube was inserted by interventional radiology for enteral feeding and enteral proton pump inhibitor therapy.

MRI of brain and whole spine was repeated on multiple occasions and (after 1 month of admission) revealed minimally thickened and symmetrically enhancing cauda equina roots which remained stable compared on follow-up imaging (Figure 1). This finding is supportive of a diagnosis of GBS. Brain MRI with gadolinium showed millimeter-sized nonspecific white matter lesions (Figure 2). Repeated lumbar puncture for cerebrospinal fluid (CSF) analysis was unremarkable. The baseline blood investigations were normal and the markers for inflammatory syndrome were negative. Ophthalmoscopy showed no papilledema, and the EEG result was normal. Repeat CSF analysis after 4 weeks of admission and serum analysis were sent for autoimmune serology, results were as follows; ganglioside GQ1b Ab (IgG), Oligo clonal bands in CSF, anti MOG in CSF, oligo clonal band in serum all were negative. However, serum ganglioside GM2 (IgG, IgM) antibodies were positive; 53%, which is detectable in cases of GBS.

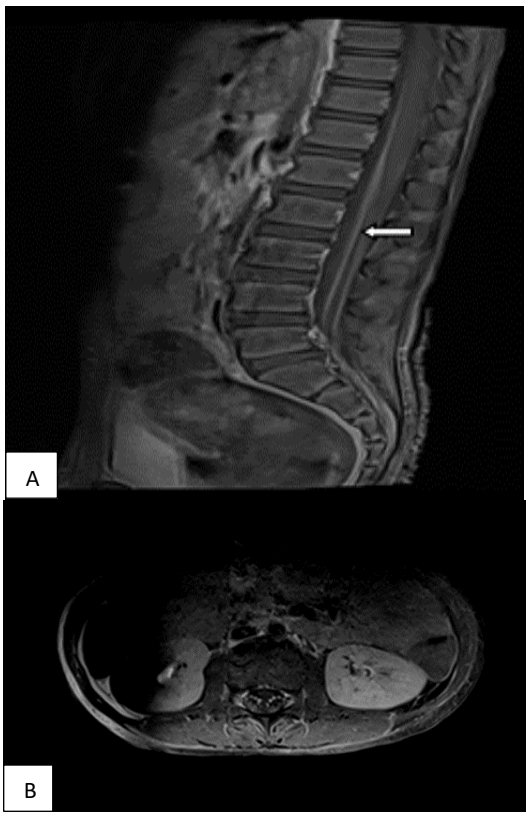

Figure 1: (A) Sagittal T1 weighted fat-saturated image with gadolinium contrast enhancement shows thickened enhancing roots of cauda equina (arrow) and (B) axial T1 weighted fat-saturated image with gadolinium contrast enhancement shows thickened enhancing roots of cauda equina.

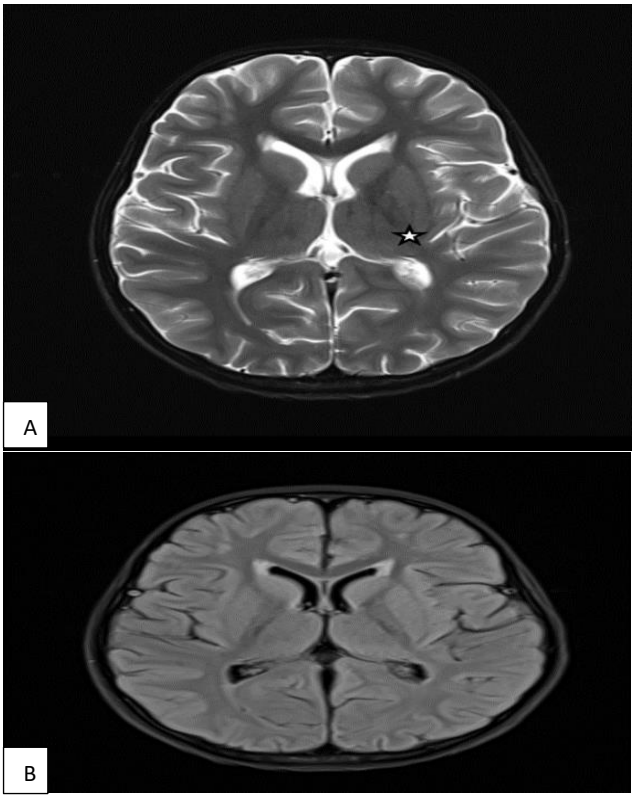

Figure 2: (A) Axial T2-weighted fat-saturated image shows bilateral frontoparietal, periventricular white matter hyperintense foci and (B) axial FLAIR image shows bilateral frontoparietal (frontal is shown here) periventricular white matter hyperintense foci.

Autoimmune encephalitis workup was negative, normal immunoglobulin profile, and a negative autoimmune screen. ESR, C3, C4. ANA and DsDNA, AFB, ANCA, SSA and SSB, Cryoglobulins were normal. Other infectious etiologies, such as *M. pneumoniae*, *M. tuberculosis*, Epstein-Barr virus, cytomegalovirus, coronavirus 2 (SARS-CoV-2), influenzae A and B were excluded. Furthermore, a rheumatology panel was sent, and it was within normal limits. Peripheral blood smear did not indicate hematological malignancy. Diagnosis of Bickerstaff's encephalitis with acute bulbar palsy, a rare variant of GBS with atypical presentation of hyperreflexia was made based on the clinical evaluation, serological studies, and MRI findings. It is a combined atypical presentation of brain stem involvement with signs of upper motor nerve lesion along with bulbar weakness. He had initial hyporeflexia then later developed hyperreflexia with decreased tone (hypotonia) with tendo Achilles tightness.

He was ventilated for 4 weeks, and, later, he was extubated and continued high-flow nasal cannula O_2 therapy followed by O_2 by nasal prongs for 2 weeks. He underwent tracheostomy tube insertion for long term ventilation with extubation failures. He began improving gradually in form of increased spontaneous movements, better mental function, and communications via facial expression and body language. He continued to vomit intermittently. He was given a second dose of IVIgG 3 months after the first treatment, because of slow recovery with latest follow-up) and OPD after 12 months, he still walks with an ataxic gait, has normal sensorium, and responds to communication via body movements with facial expressions. He still has a tracheostomy tube in place due to persisting weak gag reflex and impairment of swallowing. He is fed via nasogastric tube. He can swallow liquids with some difficulty, and he can use his hands for daily activities. His language comprehension is good, and his social skills are fine.

Table 1: CSF analysis.

Tests	Result	Reference range
Glucose	4.28 mmol/l	2.2-3.9
Protein total	14.54 mg/dl	15-45
RBC	0.0 cells/cumm	
WBC	0.0 cells/cumm	

Table 2: CSF culture.

Test	Result	Reference range
Culture	Negative	Negative
Gram pos. cocci	Not seen	Not seen
Gram pos. rods	Not seen	Not seen
Gram neg. cocci	Not seen	Not seen
Gram neg. rods	Not seen	Not seen
Yeast/hyphae	Not seen	Not seen
WBC	Not seen	Not seen
Epith. cells	Not seen	Not seen

Table 3: CSF and serum (s) analysis.

CSF and serum	Result	Unit	Reference range
Oligoclonal bands (CSF)	Negative		Negative
Albumin (CSF)	95.6	mg/l	100-300
Immunoglobulin G (IgG/ CSF)	27.10	mg/l	<34
Oligoclonal bands (serum)	Negative		
Albumin (s)	31.8	g/l	35-52
Immunoglobulin G (IgG/serum)	15.5	g/l	No reference ranges. This analysis is only qualified for immunoglobulin quotient calculation
Albumin-ratio (CSF/s)	3		≤4.5
gG intrathecal synthesis	Not detectable	%	Not detected

Table 4: CSF and serum (s) auto-immune serology panel.

Auto-immune serology	Result	Unit	Reference range
Potassium channel antibodies			
CASPR2 abs (IFT HEK 293 cells) (CSF)	<1:1	Titer	<1:1
LGI1 abs (IFT HEK 293 cells) (CSF)	<1:1	Titer	<1:1
DPPX Abs (IFT) (CSF)	<1:2	Abs titer	<1:2
GABA B-receptor abs (IFT) (CSF)	Negative		Negative
AMPA one-half receptor abs (IFT) (CSF)	Negative		Negative
Glutamate receptor abs (NMDA type) (IFT) (CSF)	<1:1	Titer	<1:1
MOG abs (Myelin oligodendrocyte glycoprotein) (IFT) (CSF)	Negative		Negative
MOG abs (Myelin oligodendrocyte glycoprotein) (IFT) (CSF)	<1:1	Titer	<1.1
Ganglioside profile			
MAG-(IgM) abs. (s)	<30	% AK-ratio	≤30
Ganglioside GM1 (IgG, IgM) abs (s)	≤30	% AK-ratio	≤30
Ganglioside GM2 (IgG, IgM) abs (s)	≤53	% AK-ratio	≤30
Ganglioside GD1a (IgG, IgM) abs (s)	≤30	% AK-ratio	≤30
Ganglioside GD1b (IgG, IgM) abs (s)	≤30	% AK-ratio	≤30
Ganglioside GQ1b (IgG, IgM) abs (s)	≤30	% AK-ratio	≤30
Interpretation			< 30% negative 30-50% borderline 51-100% positive >100% highly positive
Ganglioside IgG/IgM abs (Immunoblot) (CSF)			
Sulfatide IgG abs (CSF)	Negative		Negative
Sulfatide IgM abs (CSF)	Negative		Negative
Ganglioside GM1 IgG abs (CSF)	Negative		Negative
Ganglioside GM1 IgM abs (CSF)	Negative		Negative
Ganglioside GM2 IgG abs (CSF)	Negative		Negative
Ganglioside GM2 IgM abs (CSF)	Negative		Negative
Ganglioside GM3 IgG abs (CSF)	Negative		Negative
Ganglioside GM3 IgM abs (CSF)	Negative		Negative
Ganglioside GM4 IgG abs (CSF)	Negative		Negative
Ganglioside GM4 IgM abs (CSF)	Negative		Negative
Ganglioside GD1a IgG abs (CSF)	Negative		Negative
Ganglioside GD1a IgM abs (CSF)	Negative		Negative
Ganglioside GD1b IgG abs (CSF)	Negative		Negative
Ganglioside GD1b IgM abs (CSF)	Negative		Negative
Ganglioside GD2 IgG abs (CSF)	Negative		Negative
Ganglioside GD2 IgM abs (CSF)	Negative		Negative
Ganglioside GD3 IgG abs (CSF)	Negative		Negative
Ganglioside GD3 IgM abs (CSF)	Negative		Negative
Ganglioside GT1a IgG abs (CSF)	Negative		Negative
Ganglioside GT1a IgM abs (CSF)	Negative		Negative
Ganglioside GT1b IgG abs (CSF)	Negative		Negative
Ganglioside GT1b IgM abs (CSF)	Negative		Negative
Ganglioside GQ1b IgG abs (CSF)	Negative		Negative
Ganglioside GQ1b IgM abs (CSF)	Negative		Negative

Table 5: CSF infectious diseases panel.

Infectious diseases	Result	Reference range
Measles RNA (PCR)	Negative	Negative
Masern RNA transkription	Negative	Negative
Masern RNA amplifikation	Negative	Negative
Masern RNA identifizierung	Negative	Negative

Table 6: Meningitis panel.

Tests	Result	Reference range
FilmArray meningitis/encephalitis panel	Not detectable	Not detectable
***E. coli* K1**	Not detectable	Not detectable
Streptococcus agalactiae	Not detectable	Not detectable
Streptococcus pneumoniae	Not detectable	Not detectable
Enterovirus (EV)	Not detectable	Not detectable
Herpes simplex virus 1	Not detectable	Not detectable
Herpes simplex virus 2	Not detectable	Not detectable
Human herpesvirus 6	Not detectable	Not detectable
Human parechovirus	Not detectable	Not detectable
Varicella zoster virus (VZV)	Not detectable	Not detectable
Cryptococcus neoformans/gattii	Not detectable	Not detectable
Haemophilus influenzae	Not detectable	Not detectable
Listeria monocytogenes	Not detectable	Not detectable
Neisseria meningitidis	Not detectable	Not detectable
Cytomegalovirus (CMV)	Not detectable	Not detectable

DISCUSSION

GBS is a progressive immune-mediated neuropathy with disparate clinical variants in children which may be difficult to diagnose. Atypical variants of GBS may present with rapid onset, severe disability, cranial nerve involvement, urinary incontinence and respiratory impairment requiring the need of ventilator support in some cases.[7] The features of BBE may include disturbance of consciousness or hyperreflexia, several other neurological manifestations are commonly but not frequently reported, including weakness of the limbs, superficial or deep sensory disturbances, facial weakness or palsy and oculomotor impairment, blepharoptosis, internal ophthalmoplegia, bulbar palsy, nystagmus, and mydriasis.[4] Our patient presented with altered sensorium, bulbar weakness with swallowing and respiratory difficulty, and ataxia.

BBE is a rare form of both Miller Fisher syndrome (MFS) and GBS that is diagnosed based on CNS involvement and the diagnostic criteria of BBE, were described as a progressive, symmetric external ophthalmoplegia and ataxia. However, the presence of pseudobulbar affect, decreased consciousness and/or pyramidal signs do not exclude the diagnosis.[8] Furthermore, the diagnosis requires either hyperreflexia or a disruption in consciousness as we found in our case.[5]

In the publication of Horton et al, a 36-year-old man presented with two days' history of increasing unsteadiness on walking, motor and sensory examination revealed normal except for an upgoing Babinski. Cranial nerve examination showed ophthalmoplegia with bilateral sluggish pupillary response to light and limitation of eye movements in all directions. He had presented with ataxia of both upper and lower limbs with slurred speech. In addition, pseudobulbar effect was seen. Eight days prior to his admission, he had diarrhea. Eventually, the patient assessed positive for Campylobacter IgG serology with an equivocal result for Campylobacter IgA.[8] This adult picture resembles our case.

In our case, the GBS was preceded by an adenoviral upper respiratory tract infection. A recent paper highlighted two hypotheses regarding COVID-19 with selected adenoviral vector vaccines and the risk of GBS. They assumed that adenoviral selected vaccines could induce an autoimmune reaction to the peripheral nervous system in some cases and increase the risk of GBS after the vaccination. Another hypothesis provided is that the interaction of adenoviral particles with surface proteins e.g., CAR can infect neurons and provoke an immune response that can further lead to GBS.[9] The index child never had COVID 19 infection and was unvaccinated. His COVID antibody testing was negative.

Antiganglioside antibodies have been found to be linked to GBS subtypes and their variants. In our presented case, anti-GM2 IgM and IgG were found to be positive (Table 4). A published paper has found a correlation between positive anti-GM2 antibodies and their clinical features. Anti-GM2 antibodies including IgG and IgM are positive in GBS subtypes and variants. In this publication, the authors found that IgG-positive patients were presented with cranial predominant involvement, specifically with oculomotor and vestibular involvement, while IgM antibody positive cases had the heterogenous syndromes.[10]

Brain MRI findings in BBE have rarely been reported.[3] No significant brain abnormalities were seen in our patient. Our diagnosis was made based on the neurological presentation and the radiological finding of spinal nerve root enhancement (Figure 1 B). The nerve conduction studies were not performed due to some issues with the machine.

BBE may vary in presentation. A study reviewed nineteen patients with combined peripheral and CNS involvement that is expressed as BBE/GBS overlap. It showed that the prevalence was increased in males compared to females with a ratio of (3:1) and a median age of 8 years, 46% of participants reported to be positive for anti-GQ1b, NCS were abnormal in 64% of them and 25% of cases showed abnormal MRI findings of hyperintensity and/or contrast enhancement of the cauda equina, nerve roots and the conus medullaris were observed.[12] To highlight, the study recommended following a diagnostic approach with nerve conduction studies, electroencephalogram, brain, and spine MRI to all pediatric cases with overlapping BBE/GBS features.[12]

CONCLUSION

GBS diagnosis must be considered in any patient, presenting with acute neurological symptoms after an infectious disease with no other clear etiologies. That is because GBS can present with non-specific presentations due to its variants, thus a high index of suspicion should be applied while approaching those patients. It is critical to address the diagnosis since the clinical improvement following therapy is spectacular in some cases.

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