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■ Case report ■

A case of Bickerstaff's brainstem encephalitis in childhood

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= Abstract =

Bickerstaff's brainstem encephalitis (BBE) is a rare disease diagnosed by specific clinical features such as 'progressive, relatively symmetric external ophthalmoplegia and ataxia by 4 weeks' and 'disturbance of consciousness or hyperreflexia' after the exclusion of other diseases involving the brain stem. Anti-ganglioside antibodies (GM, GD and GQ) in the serum or cerebrospinal fluid (CSF) are sometimes informative for the diagnosis of BBE because of the rarity of positive findings in other diagnositic methods: brain magnetic resonance imaging (MRI), routine CSF examination, motor nerve conduction study, and needle electromyography. We report a rare case of childhood BBE with elevated anti-GM1 antibodies in the serum, who had specific clinical symptoms such as a cranial polyneuropathy presenting as ophthalmoplegia, dysarthria, dysphagia, and facial weakness; progressive motor weakness; altered mental status; and ataxia. However, the brain MRI, routine CSF examination, nerve conduction studies, electromyography, somatosensory evoked potentials, and brainstem auditory evoked potentials were normal. BBE was suspected and the patient was successfully treated with intravenous immunoglobulins. (Korean J Pediatr 2010;53:607-611)

Key Words : Encephalitis, Brain stem, Child

Introduction

Bickerstaff's brain stem encephalitis (BBE) is characterized by the acute onset of external ophthalmoplegia, ataxia, altered consciousness, and hyperreflexia after the exclusion for other diseases involving the brain stem[1-3]. In addition, the neurological signs that suggest this abnormality of the central nerves system presents with: abnormalities of the pupils, facial weakness, bulbar palsy, dysesthesia, limb weakness, positive Babinski sign, nystagmus, and blepharotosis[4].

Most cases have a history of a prior infection such as *Campylobacter jejuni* that can be diagnosed by serum IgM, IgG, and IgA antibody titers to C. *jejuni*[1-3], an autoimmune mechanism produced by microbial infection may trigger the pathogenesis of BBE[4]. The successful use of plasmapheresis, steroid treatment, intravenous immunoglobulins (IVIG) for the treatment of BBE suggests an autoimmune etiology[5, 6]. There have been several reports of BBE associated with antiganglioside antibodies. Anti-GQ1b antibodies are frequently detected in as much as among 66 % of patients with BBE[4, 7]. Other antibodies that may be positive in patients with BBE are: anti-GM1, anti GD1a, and anti-Ga1NAc-Gd1a[8]. We report a case of BBE with elevated anti-GM1 antibodies in the serum and CSF in addition to specific clinical symptoms: a cranial polyneuropathy presenting as ophthalmoplegia, dysarthria, dysphagia, and facial weakness; progressive motor weakness; altered mental status; and ataxia.

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Case report

A previously healthy girl, 9 years 6 months of age, presented to the Chonnam National University Hospital (CNUH) due to double vision, slurred speech and intermittent ataxia following a fever that was documented once three days before admission. There were no other associated symptoms such as diarrhea, cough, coryza or sore throat. On the day following admission her both eyelids became ptotic and the eyes were totally opthalmoplegic. Both pupils were dilated and fixed without light reflexes.

Hospital day	1st	2nd	3rd	5th	6th	7th	8th	10th	11th	12th	13th	19th	20th	23th	24th	25th	37th
Mental status	Alert	Drowsy/Stuporous →											Alert →				
Muscle strength Upper (R/L)	G5/G5	G5/G5	G3/G3 →			G2/G2 →				G3/G3	G4/G4 →				G5/G5 →		
Lower (R/L)	G5/G5	G3/G3 →				G2/G2 →			G3/G3	G4/G4 →					G5/G5 →		
Bulbar palsy	Dysarthria	Dysarthria, dysphagia, facial palsy, respiratory failure →													Mild facial palsy		
Ocular movement	Intact	Total ophthalmoplegia (external and internal) with ptosis →													Limited gaze (+)		
DTR (R/L)	++/++	+/+ →												++/++ →			
Treatment		IVIG →															
		MethylPRD															
				Ventilator care →													

Fig. 1. Patient hospital course. Abbreviations : R, right; L, left; DTR, deep tendon reflex; G, grade; IVIG, intravenous immunoglobulin; MethylPRD, methylprednisolone.

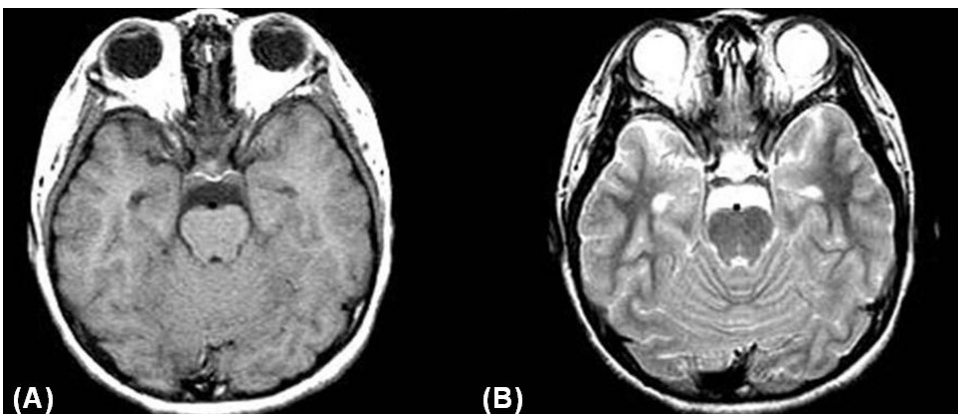

Fig. 2. Brain magnetic resonance imaging scan obtained on day 2 shows no abnormal intracranial findings in T1 (A) and T2 (B) weighted images.

The patient could not wrinkle her forehead or push her tongue out. In addition, she was unable to swallow. The finger-to-nose and heel-to-knee maneuvers were abnormal bilaterally. The muscle strength in the extremities was reduced in the lower to upper limbs and was grade 2-3 on the Medical Research Council Scale. Deep tendon reflexes were brisk but sensation was intact. The patient gradually became drowsy and stuporous. The patient rapidly deteriorated over the first two weeks and developed transient malignant hypertension with seizures on 7th day. However, by one month gradual improvement was noted (Fig. 1).

The routine tests on admission showed no abnormalities in the complete blood count, blood chemistry (including plasma glucose, ammonia, electrolytes, C-reactive protein, pH and bicarbonate), urine analysis and CSF examination. Additional studies revealed increased levels of IgM and IgG anti-GM1 antibodies, both in CSF and serum. IgM 3 EU/mL and IgG 3-6 EU/mL (normal, 0 EU/mL), respectively, in the CSF; and IgM 20.32 EU/mL and IgG 32.57 EU/mL (normal, <20 EU/mL), respectively, in the serum. In addition, there was transient elevation of antistreptolysin O (ASO) (845 IU/mL on admission and 438 IU on 11th day) in the serum and transient positive mycoplasma antibodies (1:80) associated with a positive cold agglutinin test (1:128) in the blood. No abnormal findings were revealed on repeat CSF examination on day 5: stain, culture, oligoclonal bands, myelin basic protein, IgG and albumin (including Ig G index), mycoplasma PCR and herpes simplex virus (HSV) PCR. The plasma renin activity (PRA,

10.5 ng/mL/hr) was transiently increased with the development of malignant hypertension. However, during follow-up, the PRA and aldosterone levels returned to normal (1.3 ng/mL/hr and <1.0 ng/dL, respectively). The brain magnetic resonance imaging (MRI) on admission showed no abnormalities (Fig. 2). The electroencephalogram was normal on admission but showed irregular high amplitude delta wave slow activity during deterioration of the patient's mental status. However, there were no epileptiform discharges postictally on day 7 when malignant hypertension was noted (Fig.3). The nerve conduction velocity, electromyography, somatosensory evoked potentials, brain stem auditory evoked potentials and visual evoked potentials evaluated during admission in 1 month showed no abnormal findings.

The patient was diagnosed with brainstem encephalitis with a bilateral cranial polyneuropathy including the cranial second, third, fourth, sixth, seventh, ninth, and twelfth nerves. We treated the patient with intravenous immunoglobulins (400 mg/kg for 5 days) and methylprednisolone (for the first 3 days). On day 5 she required the assisted ventilation until day 18 due to respiratory failure; however, by day 18 she could be weaned from this respiratory support. The extraocular nerve palsies, motor weakness and deep tendon reflexes gradually improved over the next three weeks. The deep tendon reflexes were weakly present in all four extremities. The patient was discharged after 37 days of admission and was followed in the outpatient clinic with mild limitation of the right lateral gaze and facial expression. However, all symptoms completely resolved by about three months after discharge.

Discussion

Bickerstaff and Cloake[1] reported three cases of drowsiness, ophthalmoplegia and ataxia in 1951, and proposed that the lesion responsible for these clinical signs was in the midbrain. Bickerstaff[9] reviewed this syndrome for the handbook of Clinical Neurology under the title of 'brainstem encephalitis. The diagnostic criteria for BBE include: (1) progressive, relatively symmetric ophthalmoplegia and ataxia by four weeks, (2) either altered consciousness (coma, semicoma or stupor) or pyramidal signs (hyperreflexia or pathological reflexes), and (3) limb strength of 5 or 4 on the Medical Research Council scale[10]. The clinical symptoms of BBE are similar to those of the Fisher syndrome (FS); the common features are ophthalmoplegia, ataxia and CSF albumin-cytological dissociation[10]. However, the diagnosis of BBE must include alteration of consciousness or pyramidal signs, which reflect a serious brainstem lesion; the FS does not include these characteristics[10].

The etiology of BBE remains unknown. However, one widely accepted hypothesis suggests an infectious agent triggers an immunological response[3, 11-15]. Bickerstaff and Cloake[1] speculated that the etiology of BBE is similar to

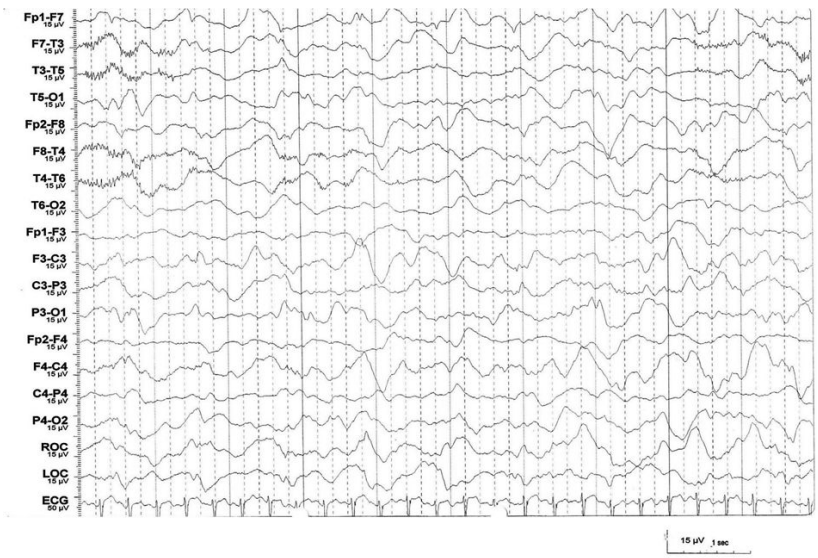

Fig. 3. The postictal electroencephalography on day 7 shows irregular high amplitude slow activity without epileptiform discharges.

that of the Guillain-Barre syndrome (GBS). However, the relationship between the BBE and the GBS has not yet been established[4, 6, 10, 16]. Various antecedent infections such as *Campylobacter jejuni*, cytomegalovirus, Epstein-Barr virus, *Mycoplasma pneumoniae* and HSV have been reported to be linked to GBS[17]. BBE also often follows a viral illness such as cytomegalovirus, varicella zoster virus, and Epstein-Barr virus[12-14]. In our case, the ASO and mycoplasma antibody titers were transiently elevated but no symptoms suggesting an infection were present. As not all the viruses previously reported to be associated with BBE were tested, it was impossible to conclude that this case was not associated with an antecedent triggering infection.

From an immunological perspective, anti-GQ1b IgG antibodies are frequently detected in the sera of patients with BBE, GBS and FS, and used to support the clinical diagnosis[6, 7]. Even though anti-GQ1b antibodies have been most frequently reported in patients with BBE[4, 7], other antibodies such as anti-GM1, anti GD1a, anti-Ga1NAc-Gd1a and anti-Campylobacter jejuni antibodies may also be positive, though less common[8]. Matsuo et al. reported that the IgM antibody titers of GM1b and GalNAc-GD1a were longitudinally correlated with clinical improvement[18]. Our patient had anti-GM1 IgM and IgG antibodies in the serum and CSF. However, other antibodies related to BBE including anti-GQ1b IgG antibodies were not tested because they were not commercially available. Therefore, the data was limited with regard to the other related antibodies in addition to anti-GM1 IgM and IgG antibodies.

Brain imaging is rarely useful for the diagnosis of BBE. Abnormal lesions (high-intensity areas on T2-weighted images of the brainstem, thalamus, cerebellum and cerebrum) on MRI have been reported to be present in only 11% of the patients with BBE[19]. During the first week of illness, CSF albumin-cytological dissociation was reported in 25% of patients with BBE[19]. The EEG showed mostly slow wave activity in the θ to δ range indicating CNS involvement, consistent with altered consciousness[4]. With regard to nerve conduction studies, most patients with BBE were normal[4].

Most patients with BBE are treated with immunotherapy, such as steroids, plasmapheresis and intravenous immunoglobulin (IVIG); the outcome for patients with BBE is generally good[16].

In conclusion, we report a rare childhood case of BBE with a good clinical outcome after successful treatment with IVIg and methylprednisolone. The diagnosis of BBE in our case was supported by the specific clinical symptoms (e.g. cranial polyneuropathy presented as ophthalmoplegia, dysarthria, dysphagia, and facial weakness; progressive motor weakness; disturbed mental status; and ataxia) and the presence of anti-GM1 antibodies in the serum and CSF.

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Bickerstaff 뇌간 뇌염은(BBE) 4주 이내의 진행성이며, 비교적 대칭성으로 오는 안근 마비와 실조증, 의식 장애 또는 심부건 반사 항진 등의 임상적 특징을 가지며, 뇌간을 침범하는 타 질환을 배제하였을 때 진단할 수 있는 드문 질환이다. 혈청 또는 뇌척수액의 항 Ganglioside 항체(GM, GD and GQ) 는 때로 BBE의 진단에 도움이 되기도 하며, 뇌 자기 공명 영상, 뇌 척수액 검사, 신경 전도 검사 및 근 전도 검사 등은 진단에 크게 도움이 되지 않는다. 저자들은 안근 마비, 실조증, 언어 운동 장애, 연하 장애, 점진적 사지 마비, 의식 저하 등의 증상을 보이며 혈청과 뇌척수액에서 anti-GM1 항체의 증가를 보여 BBE로 진단하고 면역 글로불린과 스테로이드 치료 후 완치되었던 9세의 여아의 증례를 경험하였기에 문헌 고찰과 함께 이를 보고하는 바이다.

References

1) Bickerstaff ER, Cloake PC. Mesencephalitis and rhombencephalitis. Br Med J 1951;14:77-81.
2) Fisher M. An unusual variant of acute idiopathic polyneuritis (syndrome of ophthalmoplegia, ataxia and areflexia). N Engl J Med 1956;255:57-65.
3) Al-Din AN, Anderson M, Bickerstaff ER, Harvey I. Brainstem encephalitis and the syndrome of Miller Fisher: a clinical study. Brain 1982;105:481-95.
4) Odaka M, Yuki N, Yamada M, Koga M, Takemi T, Hirata K, et al. Bickerstaff's brainstem encephalitis: clinical features of 62 cases and a subgroup associated with Guillain-Barr? syndrome. Brain 2003;126:2279-90.
5) Yuki N. Successful plasmapheresis in Bickerstaff's brainstem encephalitis associated with anti-GQ1b antibody. J Neurol Sci 1995;131:108-10.
6) Yuki N, Susuki K, Odaka M, Hirata K. Overlapping Guillain-Barré syndrome and Bickerstaff's brainstem encephalitis associated with anti-GQ1b antibody after herpes sim-

plex virus infection. Acta Neurol Scand 2001;104:57-60.
7) Williams MH. The spectrum of IgG GQ1(b) syndrome: an unusual cluster. J Clin Neurosci 2001;8:315-8.
8) Ozawa T, Onodera O, Inuzuka T, Soma Y, Tsuji S. Efficacy of early plasmapheresis in Bickerstaff's encephalitis. Intern Med 1998;37:986-9.
9) Bickerstaff ER. Brainstem encephalitis (Bickerstaff's encephalitis). In: Vinken PJ, Bruyn GW, editors. Handbook of Clinical Neurology, Vol. 34. Amsterdam: North-Holland; 1978:605-9.
10) Odaka M, Yuki N, Hirata K. Anti-GQ1b IgG antibody syndrome: clinical and immunological range. J Neurol Neurosurg Psychiatry 2001;70:50-5.
11) Yuki N, Sato S, Tsuji S, Hozumi I, Miyakate T. An immunologic abnormality common to Bicherstaff's brain stem encephalitis and Fisher's syndrome. J Neurol Sci 1993;118:83-7.
12) Tagawa Y, Yuki N. Bickerstaff's brainstem encephalitis associated with shingles. J Neurol 2000;247:218-9.
13) Kanzaki A, Yabuki S, Yuki N. Bickerstaff's brainstem encephalitis associated with cytomegalovirus infection. J Neurol Neurosurg Psychiatry 1995;58:260-1.
14) Kamasaki A, Kinoshita I, Koga M, Yamaguchi T, Yuki N. A case of brainstem encephalitis associated with Epstein-Barr virus infection: differentiation of acute disseminated encephalomyelitis and Bickerstaff's brainstem encephalitis. No To Shinkei 2001;53:951-5.
15) Wali GM. Bickerstaff's brainstem encephalitis associated with typhoid fever. Postgrad Med J 1991;67:1011-2.
16) Fox RJ, Kasner SE, Galetta SL, Chalela JA. Treatment of Bickerstaff's brainstem encephalitis with immune globulin. J Neurol Sci 2000;178:88-90.
17) Jacobs BC, Rothbarth PH, Van Der Mech? FG, Herbrink P, Schmitz P, de Klerk MA, et al. The spectrum of antecedent infections in Guillain-Barré syndrome: a case-control study. Neurology 1998;51:1110-5.
18) Matsuo M, Odaka M, Koga M, Tsuchiya K, Hamasak Y, Yuki N. Bickerstaff's brainstem encephalitis associated with IgM antibodies to GM1b and GalNAc-GD1a. J Neurol Sci 2004;217:225-8.
19) Ito M, Kuwabara S, Odaka M, Misawa S, Koga M, Hirata K, et al. Bickerstaff's brainstem encephalitis and Fisher syndrome form a continuous spectrum. J Neurol 2008;255:674-82.