Silence After The Storm; A Case of Bickerstaff's Brainstem Encephalitis

Fırtına Sonrası Sessizlik; Bickerstaff Beyin Sapı Ensefalitli Bir Olgu

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ABSTRACT

A pediatric case with Bickerstaff's brainstem encephalitis (BBE), which is a very rare monophasic post-infectious condition characterized by central nervous system involvement, unconsciousness, ophthalmoplegia and ataxia, is presented.

Twelve years old patient was brought with difficulty in eye movements and ataxia. On the second day, she became agitated and lethargic, and then bulbar palsy and whole body paralysis developed. Upper motor neuron involvement was evident. Routine biochemical parameters and serologic tests, cranial magnetic resonance imaging, lumbar puncture, autoimmune, paraneoplastic, and electrophysiological studies were evaluated. All were normal except for the encephalopathic first electroencephalography (EEG) and the EEG repeated on the 25th day was reported to be normal. Anti-ganglioside antibody, anti-GQ1b was found positive. Intravenous immunoglobulin (IVIG) started on the fourth day. A very rapid improvement was seen in the first week of IVIG treatment. She was able to walk in the second week. She was completely normal in 3 months. Although seven years passed, our patient has not had any relapse or neurological deficit.

We presented a case diagnosed as BBE treated successfully with single dose intravenous Immunoglobulin. We wanted to emphasize that BBE has a good prognosis even though it is an acutely developing severe condition.

Key Words: Ataxia, Brainstem, Encephalitis, Intravenous immunoglobulin

ÖZ

Oldukça nadir görülen, merkezi sinir sistemi tutulumu, bilinç bozukluğu, oftalmopleji ve ataksi ile karakterize monofazik bir post enfeksiyöz durum olan Bickerstaff beyinsapı ensefaliti tanılı pediatrik olgu sunulmuştur.

Oniki yaşında hasta göz hareketlerinde güçlük ve ataksi nedeniyle getirildi. İkinci gün ajitasyonu gelişti, letarjik oldu, sonrasında bulbar palsi ve tüm vücut paralizisi gelişti. Üst motor nöron tutulumu belirgindi. Rutin biyokimyasal parametreler ve serolojik testler, kraniyal manyetik rezonans görüntüleme, lomber ponksiyon, otoimmün, paraneoplastik ve elektrofizyolojik çalışmalar değerlendirildi. Ensefalopatik ilk elektroensefalografi (EEG) haricinde hepsi normaldi, 25. günde tekrarlanan EEG de normal raporlandı. Anti gangliosid antikor anti-GQ1b pozitif bulundu. Dördüncü gün intravenöz immunoglobulin (IVIG) başladı. IVIG tedavisinin ilk haftasında çok hızlı bir iyileşme görüldü. İkinci hafta yürüyebiliyordu, 3. ayda tamamen normale dönmüştü. Hastamızın aradan yedi yıl geçmiş olmasına rağmen herhangi bir nüksü veya nörolojik defisiti olmamıştır.

Tek doz intravenöz İmmünoglobulin (IVIG) ile başarıyla tedavi edilen BBE tanılı bir olguyu sunduk. Akut gelişen ciddi bir tablo olmasına karşın iyi prognozlu olduğunu vurgulamak istedik.

Anahtar Kelimeler: Ataksi, Bickerstaff beyin sapı, Ensefaliti, İntravenous immunoglobulin

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INTRODUCTION

Bickerstaff's Brainstem encephalitis (BBE) is characterized by altered state of consciousness, ophtalmoplegia and ataxia. It has been first defined by Bickerstaff and Cloake, and then by Fisher (1-3). Because of the anti-ganglioside antibodies -especially anti GQ1b- detected in the sera of these patients, BBE is known as a variant of Guillain-Barré syndrome (GBS) or a part of the anti-ganglioside antibody spectrum disorders (4-6).

We are presenting a case of BBE, who was admitted with ataxia and double vision, and then developed bulbar and whole body paralysis. Quick and complete recovery occurred after single dose of intravenous Immunoglobulin (IVIG). Different from the literature, our case is kind of unique in a way our patient did not need recurrent immunotherapy and achieved complete resolution.

Management of BBE in children may be difficult because there is no consensus on this topic. Thus, we want to share our case diagnosed as BBE which is rarely seen.

CASE REPORT

A twelve-year old girl was brought to child neurology outpatient clinic with the complaints of double vision, pain with the vertical and horizontal movements of the eye, numbling in the hands and feet, weakness and gait unsteadiness. Most recent history did not reveal any trauma, vaccination or infection. Her body temperature was 36.7 ˚C, blood pressure was 100/60 mm/Hg. She was conscious, along with normal cooperation and orientation. Her pupils were mydriatic. Fundoscopic examination and pupillary light reflexes were normal. Lateral gaze was limited due to third and sixth cranial nerve palsy. Muscle strength was 4/5 at the upper and lower extremities. Deep tendon reflexes (DTR) were brisk on the left side especially. Bilateral Achilles clonus was positive. Plantar reflex was bilaterally extensor (Babinski sign positive). Neck stiffness was not detected. Next day she was in delirium state, she was awake but seriously agitated, restless and crying continuously. She could not speak, and orofacial dyskinesia became permanent on the same day. She could not even swallow and close her chin so nasogastric tube was put for feeding. She was not able to sit or walk as well. Brain magnetic resonance imaging on day two was normal. Hemogram, biochemical parameters (blood glucose, electrolytes, and liver and kidney function tests, lipids) were normal. Erythrocyte sedimentation rate was 10 mm/h, C-reactive protein was negative. Cerebrospinal fluid (CSF) evaluation revealed no cells, CSF pressure: 7 cm H20, protein: 21 mg/dl, glucose: 68 mg/dl, chlorine: 102 mmol/l which all were normal. Oligoclonal bands were negative and IgG index analysis was normal. Viral and bacteriological serological markers (antibodies for Hepatitis A, B, C, Human Immune deficiency virus (HIV), Cytomegalovirus (CMV), Epstein-Barr virus (EBV), Herpes simplex virus (HSV), Rubella, Toxoplasma, Brucella) were found negative except HSV 1, EBV and Rubella IgG. Thyroid function tests, thyroid autoantibodies and biomarkers for autoimmune diseases (antinuclear antibody (ANA), anti-ds DNA, anti-smooth muscle antibody (ASMA), anti Jo 1, anti-mitochondrial antibody, anti Scl 70, anti sm/RNP, anti beta 2 glycoprotein 1, anti-gliadin, anticardiyolipin, anti SS-a, anti SS-b, tissue transglutaminase, endomysial antibodies (EMA), liver kidney microsomal antibody, p-ANCA, c-ANCA, rheumatoid factor) were evaluated and found negative except ANA and ASMA. Both immunoglobulins and complements were normal. Abdominal and pelvic ultrasonography were normal. Blood and CSF samples were sent to neuro immunology laboratory for limbic encephalopathy (anti NMDA-R, anti AMPA-1, anti AMPA-2, Anti CASPR-2(VGKC), anti LGI-1(VGKC), anti GABAR B1), paraneoplastic syndrome (anti-Hu, anti-Yo, anti-Ri, anti PNMA2/Ta, anti CV2.1, anti-amphiphysin) and anti-ganglioside antibodies (anti GM1 IgM, IgG, anti asialo GM1 IgM, IgG, anti GM2 IgM, IgG , anti GD1aIgM, IgG, anti GD1b IgM, IgG, anti Q1b IgM, IgG). Limbic encephalopathy and paraneoplastic panel resulted negative but anti GD1a, anti GD1b found positive, and anti GQ1b was found potently positive.

Bilateral flash visual evoked potential (VEP) reported bilateral long latency and small amplitude and bizarre configuration on left. First EEG was consistent with encephalopathy (background activity at rest 4-6 Hz theta with frontal 2-4 Hz delta slow waves). Electromyography (EMG) was normal. On the third day of hospitalization, IVIG 0.4 gr/kg/day for five days, totally 2 gr/kg started. Significant recovery was observed in succeeding days. On the third day of IVIG she started to swallow and syllable. By the first week she could sit in the bed for a short time, move her neck easily. She started to speak and was fed orally. On the tenth day after IVIG had started, her feeding and speech were totally normal, mydriasis resolved and she could sit and walk with help. Brisk DTR and clonus were still exist in neurological examination. She was discharged. After 3 weeks, she came to outpatient clinic by walking alone without any help. Neurological examination was normal except the external ophtalmoplegia, which was diminished evidently. Repeated EEG on the 25th day showed normal rhythm at rest as 8-9 Hz alpha. In the first month lateral gaze of right eye was limited but left eye was normal. Motor system evaluation was normal. In the 3rd month she was totally normal. She was diagnosed as BBE and treated without any sequela with only single dose of IVIG. She came to the outpatient clinic for yearly controls. This year, 2020, since she has become an adult, she called for the last control, and no recurrence or any neurologic deficit was not found.

DISCUSSION

Bickerstaff's Brainstem encephalitis (BBE) is a rare medical condition so only case reports are found in the literature. Case

series with large numbers also include the adults. There are similarities between the childhood BBE and adult BBE but also difficulties in diagnosing and managing the child with BBE because besides the three major characteristics -disturbance in consciousness, ataxia and ophtalmoplegia - the clinical spectrum may differ from patient to patient. Combination of clinical findings, neuroimaging (magnetic resonance imaging-MRI), electrophysiological studies (encephalography-EEG, electromyography-EMG), and anti-ganglioside antibody titers may help the physician at that point. Exclusion of the vascular disease involving the brainstem, Wernicke's encephalopathy, botulism, myasthenia gravis (MG), brainstem tumor, pituitary apoplexy, acute disseminated encephalomyelitis, multiple sclerosis, neuro-Behcet disease, vasculitis, lymphoma, Hashimoto encephalopathy are also needed (7-9).

Our patient's weakness in the extremities, confusion, agitation and first motor neuron findings after ophthalmoparesis that developed acutely within days, reminded us of BBE. Cranial imaging at the patient's arrival kept us away from vascular events such as stroke and hemorrhage affecting the brainstem. Pons glioma or MG was not considered because the signs and symptoms of the patient developed in few days. Evaluation of CSF was not found to be compatible with viral, bacterial meningitis and encephalitis. Wernicke's encephalopathy, which can be considered in differential diagnosis, was not considered because the patient had no feeding problem and the signs developed acutely. Due to clinical course and response to IVIG treatment, botulism was eliminated. Hashimoto encephalitis was not considered because the thyroid function tests and thyroid antibodies were normal, and also ophthalmologic findings-uveitis, papilledema, oral genital aphthae were not described in terms of neuro Behçet's.

Koga et al. (9) defined BBE as definite and probable and determined criteria for diagnosis. According to this criterion, acute progression of the ataxia, opthalmoplegia and alteration in consciousness in 4 weeks and remission in 12 weeks, positive anti GQ1b antibody and the exclusion of the above written diseases made sure that our patient's diagnosis is a definite BBE.

Odaka et al. (7) reported data of 62 patients, both children and adults, with the first symptoms such as diplopia in half and gait disturbance in one third of the patients in addition to alteration in consciousness and ataxia. Our patient also came with the same complaints. Neurological examination of their patients revealed mostly absent or decreased DTR, but also normal and brisk DTR. Babinski's sign was present in 40% of the patients. Our patient had positive extensor plantar reflex and brisk DTR. İto et al .(10) reported 53 BBE cases aged between 0-78 and found similar findings.

Neuroimaging findings reported by Odaka showed that 16 (30%) of the 54 patients who had MRI had high-intensity abnormalities on T2-weighted images of the brainstem, thalamus, cerebellum or white matter of the cerebrum (7). But only in five of 47 (11%) of the patients reported by İto had abnormal MRI findings (10). Neuroimaging is not good enough as a diagnostic helper for BBE. Electrophysiological studies were more satisfactory. Twentyfour patients out of 33 (73%) who had EEG recording showed teta or delta activity at rest and 15 of 34 (44%) had abnormal motor nerve conduction study (7). Abnormal findings of EEG was found in 17/30 (57%) of İto's cases (10). Our patient's first EEG was compatible with encephalopathy, but EMG was normal. İto's cases all were detected for antiganglioside antibodies and serum IgG anti-GQ1b antibodies were found in 36/53 (68%) as positive (10).

Prognosis is quite good in BBE; 37 (66%) of the 56 patients showed complete remission with no residual symptoms six months after disease onset. Treatment given were steroids, plasmapheresis, IVIG in combinations or alone. Even no specific immunotherapy was given to 11% of patients (7). According to Cochrane database, BBE requires treatment with IVIG or plasma exchange. Appropriate outcome measures are defined as complete resolution of ataxia and ophthalmoplegia in one and three months respectively (11). Our patient also achieved complete resolution in the 3rd month.

These large series were involved both child and adult. Santoro et al. (12) reported 47 paediatric BBE cases from the literature and also described five new cases. The phenotype of the patients was similar to previously published in the literature. They gave supportive treatment or antibiotics, acyclovir, steroids, IVIG and plasmapheresis alone or in combinations. They reported that immune treatment demonstrated shorter median time to resolution of symptoms compared to supportive treatment (12). We only gave single course of IVIG, and due to rapid recovery of patient another treatment was not needed.

Another retrospective study reported 19 children with BBE. Different from the other articles in the literature, anti-GQ1b IgG antibody was present only in 2 patients (13). All of the patients received 1 to 2 courses of IVIG therapy, 15 of them received steroid therapy and 2 cases also received plasma exchange (13). Clinical, neuroradiological, electrophysiological findings and treatment approaches were similar to other studies except the low detection of the anti-ganglioside antibodies. Since the clinical presentation differs from each other, we could not comment on the need for repetition or combinations of the immune therapies given to the patients. We preferred to wait for a while after the first IVIG, and our patient recovery made second dose or another therapy unnecessary.

CONCLUSION

Patients may come with different clinical findings. BBE diagnostic criteria may provide convenience. Intravenous immunoglobulin, steroid and plasmapheresis can be used alone or in combinations, and seems to be beneficial, but it

may be appropriate to decide on patient basis for recurrent immunotherapy applications and wait up to 3 months if there is improvement. Our patient is a fortunate example for the good prognosis of BBE, with full recovery after a single dose of IVIG without any attacks or residues at the end of the seven years. This case is reported to emphasize that BBE is an acutely developing severe condition but also has a good prognosis.

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