Bickerstaff’s brainstem encephalitis (BBE) in childhood: rapid resolution after intravenous immunoglobulins treatment

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Abstract. – Three young patients with Bickerstaff’s brainstem encephalitis (BBE) are reported. Some weeks following an upper tract infection, the children after a short period of recovery, showed acute onset of symmetric weakness of the lower limbs with difficulty in standing by and walking. The distal muscle weakness had a rapid progression with involvement of the cranial nerve, and then with severe impairment of the consciousness till to coma in one of the three children. BBE is a rare and often undiagnosed affection in childhood. Common neuro-immune pathogenesis, overlap of clinical signs and strict correlation among BBE with Fisher syndrome and Guillain-Barrè syndrome lead to think that these affections represent an unique spectrum with different central and peripheral involvement.

In these children, treatment with intravenous immunoglobulins resulted in a progressive and rapid resolution of the clinical features.

Key Words: Guillain-Barrè syndrome, Encephalitis, Immunoglobulins treatment, Miller Fisher Syndrome.

Introduction

Guillain-Barrè syndrome (GBS), Fisher syndrome, and Bickerstaff’s brainstem encephalitis, share a common autoimmune pathogenetic mechanism and the disorders have been considered part of a clinical spectrum with variant central nervous system (CNS) and peripheral nervous system (PNS) involvement¹.⁴. Among these disorders, the GBS is the most frequent and is characterized by acute onset, rapidly progressive, symmetrical muscular weakness, instable deambulation and hyporeflexia¹.⁵.⁶. The incidence of GBS linearly increases with the age varying from 0.8/100,000 case/year under 15 years age until 4/100,000 cases/year at the age over 75 years. Children with GBS show a shorter and more benign course comparing to the adult age¹.

Fisher syndrome and Bickerstaff’s brainstem encephalitis are less frequent than GBS. The FS is characterized by a triad of ophthalmoplegia, ataxia and areflexia⁷ and BBE by CNS involvement with alteration of consciousness or long tract signs beyond the classical ophthalmoplegia, and ataxia⁴.⁸.⁹. In these disorders the treatment consist of the single use of steroids or intravenous immunoglobulins (IVIG) or a combination of the two.

BBE starts usually with peripheral nerve involvement and/or cranial nerve progressing rapidly to affect consciousness in different grade till coma. We report on three children 12, 8 and 9 year-old respectively with typical form of BBE who rapidly improved after cycles of intravenous immunoglobulins.

Case Reports

Case 1

FG is a 12-year-old boy. Family history is irrelevant. Mother denied to have taken drugs or to have had infectious diseases during the gestation. Both parents are healthy and non-consanguineous. The patient was born at term after a normal delivery. His birth weight was 3,200 g, height 50 cm and head circumference 35 cm. Psychomotor development was normal: he started to walk at the age of 14 months and he pronounced his first words at the age of 13 months.
His present scholastic performance is good. The patient was admitted to the Pediatric Department of the University of Catania, Italy since he had symmetrical weakness in the lower limbs, gait unsteadiness and external right strabismus. The parents referred that two weeks before, the child showed signs of a upper tract infection with fever and cough lasted three days treated with antibiotics. After a two weeks period of complete resolution, the child started to show new febrile episode with malaise, vague aches followed by difficulty in walking. He was admitted to a general Hospital in the province of Catania, where treatment with antibiotics and steroids was started, and then sent to our department after two days. At the admission, the child showed at neurological examination full consciousness, hypotonia of lower limbs, and ataxia. Strabismus was present in the right eye. Tendon reflexes were reduced. Remaining of physical examination was normal with no other cranial nerves involvement, except for the abducent. The neurological manifestation had a rapid and progressive worsening with difficulty to walk, ataxia, bilateral strabismus, and impairment of deglutition and speech. Two-three days later, although under upper mentioned treatment, he presented consciousness involvement until coma (Glasgow Coma Scale [GCS] E1V 2M 4). Serum antibodies showed the presence of antiCMV IgM. Serum antibodies anti-herpes simplex virus, varicella zoster virus, Epstein.Barr virus, Mycoplasma pneumoniae, Borriella burgdorfei, enterovirus, adenovirus and parvovirus B12 were negative. Cerebrospinal fluid exam yielded sterile cerebrospinal fluid and albuminocytological dissociation with 10-15 leukocytes, and increased protein (119 mg/dl) and decreased glucose concentration (29 mg/dl). Anti-ganglioside GQ1b IgM and IgG antibody in serum were present. Full serum and cerebrospinal fluid investigations were normal. The deep tendon reflexes, although difficult to elicit, were weakly present in all 4 extremities. The remaining of the physical examination was normal. The next day, he became lethargic. Hematological and cerebrospinal fluid investigations were normal. Brain and spinal MRI scan was normal. EEG showed slow wave activity. He was treated with IVIG at the dose of 2 g/kg body weight for 2 days with full recovery after 10 days to the onset of neurological sings.

Case 2

A 8-year-old boy had ataxic gait, diplopia and lethargy after two weeks an upper respiratory tract infection, treated with antibiotics. On admission, he showed muscle weakness of the lower legs, cerebellar ataxia, generalized areflexia, and ophthalmoplegia. Examination of remaining cranial nerves were normal. Brain and spinal cord MRI with and without gadolinium enhancement were negative for pathological lesions. EEG recording showed diffuse slow activity in the theta/delta range. Funduscopic findings were normal. The cerebrospinal fluid revealed albuminocytologic dissociation. IgG antibodies against GQ1b were negative. Immunoglobulin was administered intravenously at the dose of 2 g/kg body weight for two days and then his symptoms gradually diminished. After 7 days of treatment he had neither conscious disturbance nor limb weakness. There still were mild ophthalmoplegia and diminished deep tendon reflexes, but they disappeared by 15 days after the onset.

Case 3

A 9-year-old boy manifested fever 10 days before admission when he started to show cerebellar ataxia, drawness and diplopia. The neurologic examination confirmed the presence of ophthalmoplegia. Finger-to-nose and Rhomberg test were abnormal. The deep tendon reflexes, although difficult to elicit, were weakly present in all 4 extremities. The remaining of the physical examination was normal. The next day, he became lethargic. Hematological and cerebrospinal fluid investigations were normal. Titles of anti-GM1 immunoglobulin M antibodies were negative. Brain and spinal MRI scan was normal. EEG showed slow wave activity. He was treated with IVIG at the dose of 2 g/kg body weight for 2 days with full recovery after 10 days to the onset of neurological sings.
Discussion

BBE has first been reported by Bickerstaff and Cloake in 1951 and Bickerstaff in 1957. In its complete form this disorder affects the brain with severe consciousness and cranial and peripheral nerves involvement. Symmetrical lower limbs hypotonia, ophthalmoplegia, ataxia and consciousness disturbances with hypo/areflexia are the main clinical symptoms. In a large series of 581 patients reported by Ito only two patients under the age of 10 years old were reported indicating that this affection is really rare in childhood. In the Unit of Pediatrics and Pediatric Emergency, University Hospital of Catania, Italy, in the last ten years we have observed 26 patients with classical GBS, only three patients were affected by FS and three by BBE confirming the not high incidence of this affection.

It has been included as a variant in the group of Guillain-Barré syndrome and it has been postulated that molecular mimicry and a cross-reaction immune response play an important role in the pathogenesis of this affection. Its variants are hypnotized to represent unusual clinical response to different antibodies or, a different local response to the host.

Increased titres of anti-ganglioside GQ1b IgG antibodies have been frequently recorded in patients with MFS, GBS and BBE, and are used in support of the clinical diagnosis. However, a positive anti-GQ1b antibody is not essential for the diagnosis of BBE. Odaka et al in a group of 62 adult patients have found that serum anti-GQ1b IgG antibody was positive in 66% of the patients: in the present three patients we obtained positivity of the anti-GQ1b antibody only in patient 1. Brain-MRI lesions are usually not reported in patients with BBE and Odaka et al referred that MRI brain anomalies were observed only in 30% of their patients. In both patients of Yuki et al, as well as in our, no abnormal findings were detected on the brain-MRI despite the presence of altered consciousness.

The present patients showed clinical and laboratory features typical of BBE. They had fever some weeks before the clear neurological manifestations, and then they showed a progressive involvement of central nervous system with deficit of cranial nerve, progressive weakness, ataxia, and then after few days impairment of consciousness.

On the experience of a full recovery after treatment with IVIG in a child with polyneuritis cranialis (PC), we tried to perform the same treatment in the children with BBE. The patient 1 was previously treated with antibiotics and steroids and showed poor improvement of his symptomatology, and the affection continued to progress rapidly till coma. Treatment with IVIG was started and it was clearly evident the improvement of the clinical signs the days after the treatment was started till the complete recovery of the child. The remaining two children, in whom consciousness involvement was present but less severe, we started the treatment directly with IVIG since the onset of the symptoms. Also in these children the clinical improvement was progressively rapid. The treatment was started with cycles of IGIV at the total dosage of 2 g/kg. We wish to underline that the improvement had in all the patient a rapid and progressive improvement soon after the first cycle of therapy.

In the adult age, such as happen to the neuro-immune disorders, treatment with IVIG, steroids and plasmapheresis is still disputable. BBE in adult age is generally good, although cases of partial recovery or of exitus have been reported. Conversely to what happen in adult age, the prognosis in cases of GBS and related disorders is usually good in childhood.

The result obtained in the present children give a confirmation of the usefulness of the IVIG treatment in the cases of GBS and related disorders.

Conclusions

We think this case was worthwhile as the occurrence of BBE is rare in childhood and it could be not appreciated among the pediatricians within the events of coma in childhood. Therefore, the prognosis seems to be favorable and the treatment with IVIG valid and effective.

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Conflict of Interest

The Authors declare that there are no conflicts of interest.
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