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Bickerstaff's brainstem encephalitis in childhood: a literature overview

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Abstract. – OBJECTIVE: This is a review on clinical presentation, diagnosis, and treatment of reported cases of Bickerstaff brain encephalitis.

MATERIALS AND METHODS: Cases of pediatric Bickerstaff's brainstem encephalitis collected from PubMed, Cochrane Library and Scopus Web of Science databases were reviewed. The inclusion criteria of the cases were based on age ≤ 18 years and the clinical characteristics of the disorder.

RESULTS: Twenty-seven articles on Bickerstaff's brainstem encephalitis, including 236 children from a total of 42 from January 1990 to January 2020, were selected. The phenotype of the pediatric cases confirmed those described in the previously published articles. Almost half of the cases demonstrated the positivity of anti-GQ1b antibody titers, but the antibodies' presence was not linked to longer healing time. However, it was found that individuals with neuroimaging changes needed a longer time to recovery. Overall, patients treated with any type of immunotherapy (intravenous immunoglobulins, steroid or plasmapheresis) demonstrated faster resolution of symptoms than supportive care.

CONCLUSIONS: Bickerstaff's brainstem encephalitis is an uncommon disorder, the short-term and long-term prognoses depend on the clinical presentation of the disorder, co-morbidity, instrumental investigations, and precocity of treatment.

Key Words:
Guillain-Barré variant, Acute encephalitis, Inflammatory encephalitis, Acute encephalopathy.

Introduction

Bickerstaff brain encephalitis (BBE) is an uncommon type of inflammatory neuropathy that mainly affects the central nervous system. It was reported the first time in 1951[1]. The disorder shares some features with another post-inflammatory neuropathy, the Miller Fisher syndrome (MFS), and was then reported by some authors as a unique disorder, called Guillain-Barré polyneuropathy. Among the group of these disorders it is also included the Guillain-Barré syndrome (GBS), which is the most frequent and is mainly characterized by acute onset, rapidly progressive, symmetrical muscular weakness, gait unsteadiness, and hyporeflexia[1-8]. BBE is unique from these entities, since it presents marked alterations in cognitive state.

Many of the existing large-scale studies of BBE have been conducted in Japan where the annual incidence is estimated to be 8 per 100 million individuals, and children constitute a minority of reported cases[8].

Children with GBS show a shorter and more benign course comparing to cases of adult age[1]. The MFS and BBE are reported to be less frequent than GBS. The MFS is characterized by a triad of ophthalmoplegia, ataxia and areflessia[5], and BBE by central nervous system (CNS) involvement with alteration of consciousness or long tract signs beyond the classical ophthalmoplegia, and ataxia[4,6-8]. BEE occurs after a previous infection, mainly respiratory and gastro-enteric, in which after an apparent remission, the affected individuals start to show the main features of the syndrome: the loss of consciousness, ophthalmoplegia and ataxia. These pivotal symptoms may also occur in MFS; therefore, to get the diagnosis of BEE other specific features are necessary, such as hyperreflexia or drowsiness till coma[8].

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Despite the rapid onset and gravity of the picture, the course is usually benign and with a monophasic development with remission in around six months in most cases. The remission can be total or partial with several grades of nervous involvement, as reported in the literature. Standard treatment consists of intravenous administration of immunoglobulin or steroids, a single or combined strategy, and plasmapheresis in the most severe cases[9-11].

Materials and Methods

A literature review was performed on three electronic medical databases (PubMed, Cochrane Library and Scopus Web of Science) by three authors (M.S, M.L., M.M.), evaluating cases published in the period between January 1990 and January 2020. In the search bar we first introduced the MeSH term "Bickerstaff" and "child" or "pediatric", and a number of 42 manuscripts was collected. We selected articles by excluding those in which "Bickerstaff" was reported as a single case and choosing those in which the term "Bickerstaff" was included in the title or as the article's main content. Only, English articles were chosen thus obtaining a total of 27 items. Finally, a 10-year-old boy's personal experience with a complex type of BBE and a good response to treatment was reported.

Selection Criteria and Data Extraction

Eligible studies for the present review were searched in databases selecting with a screening of the titles and abstracts through the following inclusion criteria: publications within the last 30 years, written in English language, studies published in peer-reviewed journals reporting clinical or pre-clinical results. Exclusion criteria were articles in which adults were mainly enrolled, studies involving rehabilitation, studies with surgery as a primary outcome or systematic review involving a similar topic. Additionally, we excluded studies with no accessible data or without an available full-text. We also excluded all the remaining duplicates. The study selection and the data extraction were performed independently by two authors (S.M., L.M.), and the discrepancies were resolved by discussion among the authors. The senior investigator (M.B., P.P.) were consulted to revise the full process. We followed the rules of the Declaration of Helsinki and our study was approved by the board of our AOU Policlinico-San Marco, Catania (Ct. 138843). We also followed the Prisma flow diagram of the literature selection and review process checklist from Moher et al[12] (Figure 1).

Statistical Methods and Analysis

A descriptive summary was performed. It was not possible to perform a meta-analysis and a statistical analysis due to the different nature of the studies and the lack of controlled studies.

Results

Description of the Studies

Once the research was carried out, a total of 29 articles were identified. After removing the duplicates, 27 articles were screened from the titles and abstracts (Figure 1). The reviewers analyzed the 27 selected articles, and the eligibility of the study inclusion was assessed independently; in case of conflicting opinions, a consensus was reached after discussion between the authors. Twenty-seven papers based on clear fulfillment of the inclusion criteria were analyzed.

The 27 selected articles were analyzed according to Pathogenesis (4), Clinical (3), General (2), Cerebrospinal fluid (4), Review (4), Marginal role (1), Complications (3), Treatment (3), Diagnosis (3).

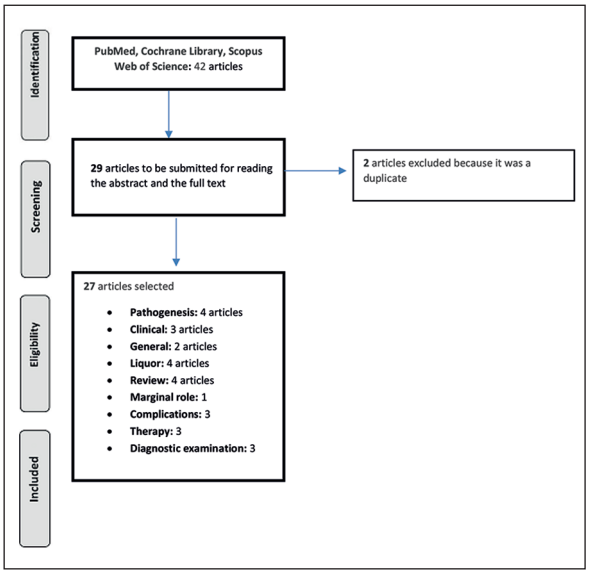

Figure 1. Flow diagram of literature selection and review process. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097.

Discussion

Despite specific data about incidence and prevalence not precisely specified, BBE seems to be quite uncommon and often under-diagnosed, especially in children[13].

It is a result of several types of common infections, which mainly affect the respiratory and digestive tracts, most frequently caused by *M. pneumoniae*, *H. influenzae*, *C. jejuni*, although other viral agents, such as Rubella, Measles, virus Chickenpox, Cytomegalovirus, Epstein Barr Virus (EBV) or HIV have been reported as trigger factors[14-17].

Several cases of BEE associated with *M. pneumoniae* infection have been reported[14]. To note, treatment with a combination of immunotherapy and antibiotics gave excellent results with a favourable course[14]. Another infection associated with BBE is the EBV. Rho et al[15] reported on a 2-year-old boy who had a diagnosis of GBS and BBE caused by EBV. Treatment with a combination of immunoglobulin and methylprednisolone, plus acyclovir, showed a complete recovery after 3 months.

The neurological manifestations occured after a period of apparent recovery, in a few weeks. This time after the infection and the onset of neurologic manifestation came out in favour of autoimmune pathogenesis. It has been suggested that the production of particular gangliosides from some bacterial agents (i.e., *C. jejuni*), strictly similar to those of myelin constituent, may induce a molecular mimicry phenomenon in which the production of specific antibodies (anti-GQ1b) may act either on microbial antigen or nervous system[16-22]. The disorder has usually a rapid and acute onset, characterized by a typical picture of ophthalmoplegia and cerebellar symptoms as ataxia. It usually begins with cranial nerve involvement progressing to various consciousness alterations, leading to coma in some rare cases[23-24]. Ocular disturbances start with diplopia and progressive ophthalmoplegia, usually symmetric followed by gait disturbance within 4 weeks from the previous infection. However, these two symptoms, ophthalmoplegia and cerebellar involvement, are common to BEE and MFS. The subsequent manifestations of hyperreflexia or consciousness disturbances, as drowsiness, sleepiness, or coma are more suggestive for central involvement, leading to a more probable clinical diagnosis of BEE. Several other symptoms or signs are commonly but not constantly reported, as weakness of the limbs (till real flaccid symmetrical tetraparesis), superficial or deep sensory disturbances, facial weakness or palsy and oculomotor impairment as blepharoptosis, internal ophthalmoplegia, bulbar palsy, nystagmus, mydriasis or abnormalities of pupils[8-9]. In the acute phase, BEE can be so severe to look like a picture of "brain-death" disease[23].

BBE has some similarities with MFS and diagnostic differences consist of the impaired consciousness in BBE, while in MFS the affected individuals show a flexion response and alert consciousness. However, these signs are often difficult to distinguish from one another. Brain MRI can help diagnose BBE when lesions are evident. Brain MRI documents in most of the cases abnormalities with hyperintensity in white matter, especially in thalami regions. However, a clinical case of a 3-year-old boy with BEE but with normal brain magnetic resonance was reported in which the evidence of cerebellar involvement was demonstrated by statistical analysis of parametric mapping by positron emission tomography (PET). Therefore, in the suspicion of BEE but with normal cerebral MRI, the possibility of performing functional imaging tools, such as PET, to document the involvement of the central nervous system should be considered[25]. The disorder mainly has a monophasic course; moreover, there are documented cases with a biphasic or relapsing course[26-27]. As reported by Ishii et al[26], recurrence appears to be more frequent in BBE or MFS than GBS and its probability should be higher in younger patients. Recently, Chamsi Basha et al[24] described a 3-year-old child who had the first episode of Bickerstaff encephalitis treated with immunoglobulins. The subsequent year, the child experienced progressive ataxia following an upper respiratory tract infection that led to a deterioration of the general clinical conditions within 12 hours of hospitalization and required cardiopulmonary resuscitation. Brain MRI showed signs of bilateral diffuse CNS involvement in the brain stem, thalamus and basal ganglia. Brain death was observed on the 11th day of hospitalization.

Diagnosis is founded upon clinical findings (useful the localization of symptoms on CNS to discriminate BEE), positive history for recent upper tract infections, as well as laboratory and instrumental studies. Anti-GQ1b IgG antibodies are positive in two-third of cases but their detection could be possible even in MFS; despite this, its high specificity and sensitivity usually allow a correct diagnosis[8]. A frequent (but not specific)

observation is a raised protein level in CSF with or without pleocytosis[28]. Nerve conduction velocity (NCV) studies[29] show a picture of axonal demyelination with decreasing of NCV, presence of blockages, and other suggestive signs. Fong et al[30] described a 7-month-old boy with ophthalmoplegia followed by rapidly increasing paralysis of all four limbs and consciousness disturbances. The initial hypothesis was BBE with overlapping GBS, supported by the results of the sequential nerve conduction study (NCS) compatible with an acute inflammatory demyelinating polyneuropathy (AIDP). The child had complete clinical recovery after 6 weeks of illness and improved NCV results following the administration of methylprednisolone, immunoglobulin and plasmapheresis. Therefore, this case shows the importance of sequential NCV in children with BBE and overlapping GBS to allow them to get a rapid and correct diagnosis and an electrophysiological prognosis, particularly if the first results of NCS are not clear[29].

EEG and other electrophysiological evaluation are of limited value on diagnosis, due to the unspecific and very common signs reported[29].

However, in the suspicion of BBE, it is necessary to consider the possibility of belonging to a more complex group of disorders, such as ophthalmoplegia, ataxia, and areflexia (SOAA). More than one confirmed case of transient coma has been reported following SOAA after previous type B flu infection in which an extensive brain stem injury, including reticular formation was found, as well as evidence of cerebrospinal CSF antibodies serum IgG anti-GQ1b in the acute phase[23].

In almost all the cases reported, the disorder follows its course without representing a danger for the child's life; however, it is necessary to remember the possible onset of complications, such as pneumonia, respiratory failure, autonomic system disorders up to the coma followed by *exitus*[24]. Excluding these severe cases, BEE has a good prognosis, with recovery usually within 4-6 weeks from the beginning of treatment[10-11,13].

As previously reported[31-36], BEE can be superimposed with GBS and/or MFS; healing will be longer and slower in these cases. Recently, we hospitalized a 10 years old boy who manifested as initial signs ataxia, ophthalmoplegia associated with diplopia, muscular weakness localized at limbs. Subsequently, the child developed respiratory muscle involvement, with breath failure in association with cognitive impairment and loss of consciousness. We administered IVIG and corticosteroids, with a recovery of muscular strength and consciousness within two weeks (unpublished data). No other recurrent episodes in the following two years were reported.

Conclusions

The present data collected by the literature showed that BBE in children is often superimposed on GBS and MFS. Besides, it is sometimes accompanied by demyelinating disease of the central nervous system. Antiganglioside antibodies are often undetectable. Immunoglobulin therapy generally achieves a good response. The prognosis for simple BBE is good in most of the cases. For BBE superimposed on GBS or other, recovery will be slower and, if untreated, can lead to *exitus*. We suggest a correct diagnosis of a clinical assessment that includes NCS, EEG, cerebral and spinal MRI for the affected children presenting with a clinical picture of BBE/GBS/MFS. The coexistence of GBS and BBE can give rise to various complications and severe responses to treatment compared to that observed in patients with BBE alone. Therefore, a consensus on the diagnostic criteria, treatment, and management of children with BBE/GBS/MFS should be indicated at the aim of having a common line in the assessment of the affected children on this complex and uncommon but not always benign disorders.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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References

1) Bickerstaff ER, Cloake PCP. Mesencephalitis and rhombencephalitis. Br Med J 1951: 4723: 77-81.
2) Hughes RA, Cornblath DR. Guillain-Barré syndrome. Lancet 2005; 366: 1653-1666.

3) Ryan MM. Guillain-Barré syndrome in childhood. J Paediatr Child Health 2005; 41: 237-241.

4) Steer AC, Starr M, Kornberg AJ. Bickerstaff brainstem encephalitis associated with Mycoplasma pneumonia infection. J Child Neurol 2006; 21: 533-534.

5) Overell JR, Willison HJ, Recent development in Miller-Fisher syndrome and related disorders. Curr Opin Neurol 2005; 18: 562-566.

6) Dong HQ; Liu Z, Tang Y, Lu Y, Wang Q, Jia JP. Recurrent Fisher-Bickerstaff syndrome: report of a Chinese case. Chin Med J 2011; 124: 2786-2788.

7) Pavone P, Pratico' AD, Ruggieri M; Verrotti A, Castellano-Chiodo D, Greco F, Falsaperla R, Pavone L. Acquired peripheral neuropathy: a report on 20 children. Int J Immunopathol Pharmacol 2012; 25: 513-517.

8) Ito M, Kuwabara S, Odaka M, Misawa S, Koga M, Hirata K, Yuki N. Bickerstaff 's brainstem encephalitis and Fisher syndrome form a continuous spectrum: clinical analysis of 581 cases. J Neurol 2008; 255: 674-682.

9) Odaka M, Yuki N, Yamada M, Koga M, Takemi T, Hirata K, Kuwabara S. Bickerstaff's brainstem encephalitis: clinical features of 62 cases and a subgroup associated with Guillain-Barré syndrome. Brain 2003; 126: 2279-2290.

10) Pavone P, Le Pira A, Greco F, Vitaliti G, Smilari PL, Parano E, Falsaperla R. Bickerstaff's brainstem encephalitis (BBE) in childhood: rapid resolution after intravenous immunoglobulins treatment. Eur Rev Med Pharmacol Sci 2014; 18: 2496-2499.

11) Sugiyama N, Hamano S, Koga M. [High-dose intravenous immunoglobulin therapy in a child case of Bickerstaff's brainstem encephalitis]. No To Hattatsu 2003; 35: 327-330.

12) Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009; 6:e1000097. doi: 10.1371/journal.pmed.1000097.

13) Koga M, Kusunoki S, Kaida K, Uehara R, Nakamura Y, Kohriyama T, Kanda T. Nationwide survey of patients in Japan with Bickerstaff brainstem encephalitis: epidemiological and clinical characteristics. J Neurol Neurosurg Psychiatry 2012; 83: 1210-1215.

14) Coriolani G, Ferranti S, Squarci G, Grosso S. A case of Bickerstaff encephalitis associated with Mycoplasma pneumonia infection. Neurol Sci 2020; 41: 1605-1606.

15) Rho YI. Overlapping Guillain-Barré syndrome and Bickerstaff's brainstem encephalitis associated with Epstein Barr virus. Korean J Pediatr 2014; 57: 457-460.

16) Kikuchi M, Tagawa Y, Iwamoto H, Hoshino H, Yuki N. Bickerstaff's brainstem encephalitis associated with IgG anti-GQ1b antibody subsequent to Mycoplasma pneumoniae infection: favorable response to immunoadsorption therapy. J Child Neurol 1997; 12: 403-405.

17) Meyer Sauteur PM, Roodbol J, Hackenberg A, de Wit MC, Vink C, Berger C, Jacobs E, van Rossum AM, Jacobs BC. Severe childhood Guillain-Barré syndrome associated with Mycoplasma pneumoniae infection: a case series. J Peripher Nerv Syst 2015; 20: 72-78.

18) Kundu GK, Rahman MM, Paul BK, Sarkar S. Bickerstaff's brainstem encephalitis - a case report. Mymensingh Med J 2015; 24: 628-630.

19) Yuki N, Shahrizaila N. How do we identify infectious agents that trigger Guillain-Barré syndrome, Fisher syndrome and Bickerstaff brainstem encephalitis?. J Neurol Sci 2011; 302: 1-5.

20) Shahrizaila N, Yuki N. Bickerstaff brainstem encephalitis and Fisher syndrome: anti-GQ1b antibody syndrome. J Neurol Neurosurg Psychiatry 2013; 84: 576-583.

21) Hacohen Y, Nishimoto Y, Fukami Y, Lang B, Waters P, Lim MJ, Yuki N, Vincent A. Paediatric brainstem encephalitis associated with glial and neuronal autoantibodies. Dev Med Child Neurol 2016; 58: 836-841.

22) Matsuo M, Odaka M, Koga M, Tsuchiya K, Hamasaki Y, Yuki N. Bickerstaff's brainstem encephalitis associated with IgM antibodies to GM1b and GalNAc-GD1a. J Neurol Sci 2004; 217: 225-228.

23) Matsumoto H, Kobayashi O, Tamura K, Ohkawa T, Sekine I. Miller Fisher syndrome with transient coma: comparison with Bickerstaff brainstem encephalitis. Brain Dev 2002; 24: 98-101.

24) Chamsi Basha A, Kolko N, Santoro JD, Alomani H. A probable case of recurrent Bickerstaff brainstem encephalitis with fulminant course in a pediatric patient. Neurologist 2020; 25: 14-16.

25) Park JY, Ko KO, Lim JW, Cheon EJ, Yoon JM, Kim HJ. A pediatric case of Bickerstaff's brainstem encephalitis. Korean J Pediatr 2014; 57: 542-545.

26) Ishii J, Yuki N, Kawamoto M, Yoshimura H, Kusunoki S, Kohara N. Recurrent Guillain-Barré syndrome, Miller Fisher syndrome and Bickerstaff brainstem encephalitis. J Neurol Sci 2016; 364: 59-64.

27) Santoro JD, Lazzareschi DV, Campen CJ, Van Haren KP. Pediatric Bickerstaff brainstem encephalitis: a systematic review of literature and case series. J Neurol 2018; 265: 141-150.

28) Illes Z, Blaabjerg M. Cerebrospinal fluid findings in Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathies. Handb Clin Neurol 2017; 146: 125-138.

29) Alberti MA, Povedano M, Montero J, Casasnovas C. Early electrophysiological findings in Fisher-Bickerstaff syndrome. Neurologia 2020; 35: 40-45.

30) Fong CY, Aung HWW, Khairani A, Gan CS, Shahrizaila N, Goh KJ. Bickerstaff's brainstem encephalitis with overlapping Guillain-Barré syndrome: usefulness of sequential nerve conduction studies. Brain Dev 2018; 40: 507-511.

31) Mondéjar RR, Santos JM, Villalba EF. MRI findings in a remitting-relapsing case of Bickerstaff encephalitis. Neuroradiology 2002; 44: 411-414.

32) Sekiguchi Y, Mori M, Misawa S, Sawai S, Yuki N, Beppu M, Kuwabara S. How often and when Fisher syndrome is overlapped by Guillain-Barré syndrome or Bickerstaff brainstem encephalitis? Eur J Neurol 2016; 23: 1058-1063.

33) Fargas i Busquets A, Roig Quilis M, Gratacòs Vinyola M, Macaya Ruiz A, del Toro Riera M, Fitó Costa A. [Ophthalmoplegia-ataxia-areflexia in pediatrics. Three new patients and review of the literature]. An Esp Pediatr 1998; 48: 483-488.

34) Santoro JD. Long-term sequelae of pediatric bickerstaff brainstem encephalitis includes autonomic and sleep dysregulation. J Child Neurol 2019; 34: 153-160.

35) Zhuo XW, Ding CH, Li JW, Zhang WH, Yang XY, Deng J, Tian XJ, Han TL, Fang F. [Clinical features of 19 children with Bickerstaff brainstem encephalitis]. Zhonghua Er Ke Za Zhi 2019; 57: 363-367.

36) Chae CS, Kwon KM, Lee JS, Kim YH. A case report of overlapping Miller Fisher syndrome, Guillain-Barré syndrome, and the Bickerstaff brainstem encephalitis. Neurologist 2018; 23: 128-130.