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Olgu Sunumu

Fisher-Bickerstaff syndrome with negative anti-ganglioside antibody test results associated with *mycoplasma pneumoniae* infection

Mycoplasma pneumoniae infeksiyonu ile ilişkili, anti-gangliyosit antikorların negatif olduğu Fisher-Bickerstaff sendromu

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ABSTRACT

Miller-Fisher syndrome and Bickerstaff brainstem encephalitis are two conditions that have probably a common autoimmune etiology. Anti-ganglioside antibodies are present in most of the patients with these clinical conditions. The symptoms of these disorders variably involve peripheral or central nervous systems. There is an unclassified group of patients who have symptoms of both Miller-Fisher syndrome and Bickerstaff brainstem encephalitis and a new eponymic terminology "Fisher-Bickerstaff syndrome" is suggested for these patients. *Mycoplasma pneumoniae* as a cause of Fisher-Bickerstaff syndrome has not been reported before. Clinical and radiologic features of a nine-year-old boy with "Fisher-Bickerstaff syndrome" associated with *Mycoplasma pneumoniae* infection are presented. A nine-year-old boy was presented with ptosis, diplopia, drowsiness, areflexia. He had a history of recent upper respiratory tract infection and laboratory evidence of *Mycoplasma pneumonia* infection. Brain magnetic resonance imaging revealed hyperintense lesions in the brainstem and electromyography revealed absent H reflex and reduced F wave responses in median nerves. Anti-ganglioside antibodies were not found. The patient dramatically responded to intravenous immunoglobulin treatment. *Mycoplasma pneumoniae* may cause Fisher-Bickerstaff syndrome without a rise in anti-ganglioside antibodies. Intravenous immunoglubulin treatment seems a good therapeutic option for these cases.

Key words: *Mycoplasma pneumoniae*, Fischer-Bickerstaff syndrome, intravenous immunoglobulin

ÖZET

Miller-Fisher sendromu ve Bickerstaff beyin sapı ensefaliti ortak otoimmün etiyolojisi olduğu düşünülen iki durumdur. Anti-gangliosid antikorları olguların çoğunda her iki durumda da pozitif saptanır. Semptomlar periferik ve santral sinir sistemi ile ilişkili olabilir. Hem Miller Fisher Sendromuna hem de Bickerstaff beyin sapı ensefalitine ait semptomların birlikte görüldüğü bir grup hasta için ise "Fisher-Bickerstaff sendromu" tanımı kullanılmaktadır. *Mycoplasma pneumoniae* daha önce Fisher-Bickerstaff sendromu etkeni olarak tanımlanmamıştır. Burada *Mycoplasma pneumoniae* infeksiyonu ile ilişkili Fisher-Birkerstaff sendromu olan dokuz yaşındaki erkek olgunun klinik ve radyolojik özellikleri sunulmuştur. Dokuz yaşında erkek olgu pitosis, diplopi, uykuya meyil ve arefleksi ile başvurdu. Geçirilmiş bir üst solunum yolu infeksiyonu öyküsü vardı ve laboratuvarında *Mycoplasma pneumoniae* infeksiyonu kanıtlandı. Beyin manyetik rezonans görüntülemede beyin sapında hiperintens lezyonlar saptandı. Elektromyografide H refleksi alınamadı ve median sinirde F dalgası yanıtları azalmıştı. Olgu intravenöz immunoglobulin tedavisine dramatik yanıt verdi. *Mycoplasma pneumoniae* infeksiyonu ile ilişkili olarak anti-gangliosid antikorları pozitif olmadan Fisher-Bickerstaff sendromu görülebilir. Bu olgularda intravenöz verilmesi iyi bir tedavi seçeneği olabilir.

Anahtar kelimeler: *Mycoplasma pneumoniae*, Fischer-Bickerstaff sendromu, intravenöz immunoglobulin

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INTRODUCTION

Miller-Fisher syndrome (MFS) is characterized by acute onset of external ophtalmoplegia, ataxia and weakness accompanied by the loss of deep tendon reflexes [1]. Patients who show drowsiness, ophtalmoplegia, ataxia, brisk reflexes, extensor plantar responses and hemisensory disturbance are considered to have Bickerstaff brainstem encephalitis (BBE) rather than MFS [2]. The finding that both conditions share common clinical findings and have autoantibodies in common suggested that the autoimmune mechanism is the same in both. A new eponymic terminology "Fisher-Bickerstaff Syndrome" is suggested for the nosology [3]. *Mycoplasma pneumoniae* is an important pathogen which causes nervous disorders during or after the course of a respiratory tract infection [4]. Central nervous system involvement occurs in 0.1% of all *M. pneumonia* infections. *Mycoplasma pneumoniae* is a rare cause of MFS and BBS [5-8].

CASE REPORT

A seven-year-old previously healthy boy was admitted to the Pediatric Neurology Department of Dokuz Eylül University School of Medicine, İzmir, Turkey with a three day history of drowsiness, weakness, headache, ptosis and diplopia. He also had a two weeks history of rhinorrhea and cough. He received no treatment or medical care for these symptoms. At admission, he was afebrile with normal vital signs. His consciousness was normal but he had periods of marked drowsiness. His sleep- wake cycle was severely disturbed and he was sleeping 20 hours a day. Muscle power in upper and lower extremities was 4/5 symmetrically. Deep tendon reflexes were absent. Upward gaze was limited with ptosis but light reflex was normal. He did not have ataxia. He had a postnasal purulent discharge and the remainder of physical and neurologic examination was normal. Some hematological test results were as follows: hemoglobin (Hgb), 12.7 g/dL; white blood cell count, (WBC) 13.1x103 μL; platelet count (plt), 297x103 μL, and erythrocyte sedimentation rate/ESR), 49 mm/hr. Chest radiography and computed tomography of the brain were normal. A lumbar puncture was performed revealing a pleocytosis with $60x10^3/\mu$/L WBC, 29 mg/dL protein, and 62 mg/dL glucose (simultaneous blood glucose 80 mg/dL). Cerebrospinal fluid lactic acid and IgG index were normal. He was started on cefotaxime and acyclovir therapy.

Electromyography of the patient revealed absent H reflexes with reduced F wave responses of median nerves with normal latency. Amplitudes and nerve conduction velocities of bilateral median, ulnar, tibial and peroneal nerves were normal. Repetitive stimulation of the right ulnar nerve also elicited normal responses. Brain magnetic resonance imaging was obtained because of excessive drowsiness and revealed brain stem, bilateral thalamic and multiple cerebral cortical lesions (Fig. 1). Electroencephalogram was normal.

No bacteria grew in cerebrospinal fluid and PCR test for Herpes virus, varicella, adenovirus and enterovirus yielded negative results. Serologic tests for toxoplasma, Epstein Barr virus, cytomegalovirus,

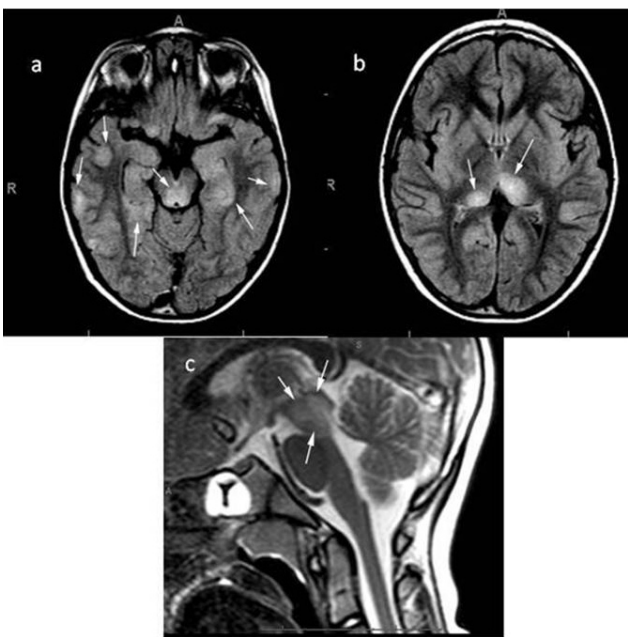

Figure 1. Initial cranial MRI transverse FLAIR (Fluid attenuated IR) images (a,b) show brain stem, multiple cerebral cortex and thalami lesions. Sagittal T2 weighted image (c) shows prominent mesencephalon involvement (arrows).

rubella gave negative results, but *Mycoplasma pneumoniae* IgM and IgG (26 RU/mL) were positive.

A presumptive diagnosis of Fisher-Bickerstaff syndrome was made and intravenous immunoglobulin was started at a dose of 2 gr/kg. Anti-ganglioside antibodies including anti-GM1 IgG, GD1a IgG, GQ1b IgG, GD1b IgG, GT1b IgG, GM2 IgG and GM3 IgG were negative. There was marked improvement in his clinical status with resolving of ptosis, and drowsiness. The sleep-wake cycle normalized.He was hospitalized for one week and one month after his discharge neurologic examination was normal and brain magnetic resonance imaging revealed almost complete regression of the lesions (Fig. 2). Repeated serology for *Mycoplasma pneumoniae* revealed increased titers of IgG (78 RU/mL), while IgM was still positive.

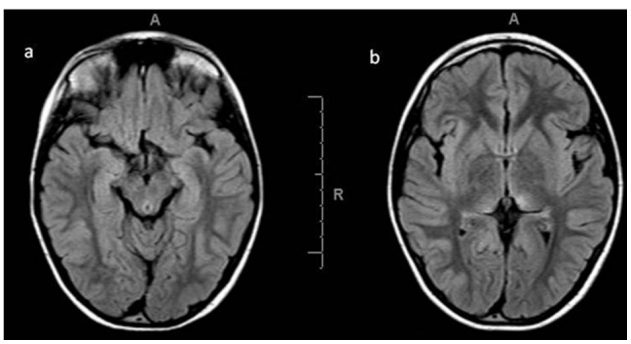

Figure 2. Control cranial MRI transverse FLAIR (Fluid attenuated IR) images (a,b) show almost complete resolution of the brain stem and brain lesions.

DISCUSSION

Miller Fischer syndrome is characterized by the classical triad of ophthalmoplegia, ataxia and areflexia. Ophthalmoparesis without ataxia, and areflexia, or with neither have been attributed as atypical forms of MFS. The clinical findings of ptosis, weakness with absent deep tendon reflexes with electrophysiologic features (absent H reflexes and reduced F responses of ulnar and median nerves without ataxia) suggested diagnosis of atypical MFS syndrome. However, central nervous system signs including excessive drowsiness, again ptosis and brain magnetic resonance imaging findings favoured BBE. In the original description of Fisher's, one of three patients had drowsiness and Bickerstaff described four cases of BBE with absent deep tendon reflexes [1-9]. Because of the similarities in the clinical presentations of MFS and BBE, there is controversy whether the lesions responsible for symptoms are primarily central or peripheral. The most common antibody implicated in the pathophsiology of these disorders is anti-GQ1b IgG ganglioside antibodies [3]. Anti-GQ1b IgG antibodies are positive in 68% of the patients with BBE and 83% of the cases with MFS. Most patients also have anti-GT1a IgG antibodies [3]. These antibodies especially anti-GQ1b IgG antibodies expressed at the neuromuscular junctions of oculomotor nerves, muscle spindles, Ranvier nodes of peripheral nerves and possibly in the brainstem are responsible for ophtalmoplegia, ataxia, areflexia, weakness and drowsiness [3]. Antibodies may exert some of their effects directly and they also bind targets, activate complements and induce nerve injury. Extensive search for antiganglioside antibodies in the cerebrospinal fluid and serum of the patient resulted in negative results. This finding suggests that there may be antibodies other than antiganglioside antibodies responsible for the disease. Absence of H reflex in our patient also suggests that these patients have a dysfunctional proprioceptive afferent system and muscle spindles which are an integral part of γ reflex loop are also affected.

Most of the patients with BBE and MFS have a history of antecedent infections. Most of the patients have serological evidence of recent Campylobacter jejuni and Haemophilus influenzae infections [3]. *Mycoplasma pneumoniae* which is known to cause atypical pneumonia is an important infectious pathogen in pediatric population. Extrapulmonary manifestations of *M. pneumoniae* are of major clinical significance and central nervous system is the most affected organ during or after the course of *M. pneumoniae* infections. Cytokine production or a direct type, immune mediated or indirect type and a vascular occlusion type mechanisms are three hypotheses to explain central nervous system involvement [10]. Central nervous system complications include encep-

halitis, acute disseminated encephalomyelitis, transverse myelitis, cranial nerve palsies, stroke, acute and chronic inflammatory polyneuropathies, ocular myasthenia gravis and cerebellitis [4]. *Mycoplasma pneumoniae* infection is also a rare cause of BBS and MFS [12-15]. The reported two patients with BBS associated with *Mycoplasma pneumoniae* also had elevated anti-GQ1b antibodies suggesting an immune-mediated process [7,8]. Regarding our patient, a vascular occlusion type mechanism does not seem probable because there was no diffusion restriction in the lesions. We suggest an immune mediated mechanism because some parts of the central and peripheral nervous system were involved. In cytokine production, one could wait more diffuse involvement of the central and peripheral nervous system. On the other hand, rapid clinical recovery of the patient after intravenous immunglobulin administration suggests an immune-mediated mechanism.

There are no randomized controlled trials evaluating the efficacy of intravenous immnuoglobuline and plasma exchange in Fisher-Bickerstaff syndrome. Our patient responded clinically to intravenous immunoglobulin with resolution of drowsiness, ptosis and weakness. There are also reports of *Mycoplasma pneumoniae* encephalopathy cases who recovered immediately after intravenous immunoglobulin administration [11,12]. The mechanism of action of intravenous immunoglobulin may be related to its effects of immunomodulatory actions or direct eradication of *Mycoplasma pneumoniae* [13,14]. Macrolides and tetracyclines are considered to be effective for respiratory tract infections, but their effectiveness in central nervous system involvement is unclear. Clarithromycin reaches levels in excess of its in vitro minimum inhibitory concentrations for the organism in the cerebrospinal fluid [15]. Macrolides also have suppressive functions for several cytokines that were frequently expressed in central nervous system disorders associated with *Mycoplasma pneumoniae* infections [16]. These facts may merit the use of macrolides for the treatment of central nervous system involvement.

In conclusion, *Mycoplasma pneumoniae* may cause Fisher-Bickerstaff syndrome without a rise in titers of anti-GQ1b antibodies. Treatment with intravenous immunoglobulin plus macrolides seems beneficial in the treatment of *Mycoplasma pneumoniae* associated Fisher-Bickerstaff syndrome.

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