Abstract: Background: Guillain-Barré syndrome is an autoimmune peripheral neuropathy characterized by progressive symmetrical and ascending weakness and areflexia. Non-polio enterovirus (coxsackievirus type A and B, ECHO virus and enteroviruses) infections are seen in infants and children ranging from asymptomatic infection to life-threatening serious clinical conditions. Paralysis has been reported to be associated with coxsackievirus B2-6, enterovirus 71 and echovirus type 3, 4, 6, 9, 11, 19 and 22. Epstein-Barr virus is frequently involved in the etiology of aseptic meningitis, encephalitis, and Guillain-Barré syndrome. Methods: A 22-month-old male patient with a diagnosis of Guillain-Barré syndrome is presented due to an interesting and severe clinical course. Results: Despite serious illness condition and prolonged intensive care treatment, the patient who was diagnosed with Guillain-Barré syndrome with dual infectious etiology fully recovered with repeated intravenous immunoglobulin treatment. Conclusion: In the light of a case with concurrent detection of both etiological agents, we sought to draw attention on the presence of co-infection and non-polio enterovirus, albeit not reported, in GBS patients presenting rapid progression of clinical course with prolonged plateau phase and delayed clinical response.

Keywords: Guillain-Barré syndrome, Coxsackievirus, Epstein-Barr virus, co-infection, children
Cover Letter

Dear Editor,

On behalf of my co-authors, I would like to submit the enclosed manuscript entitled “GUILLAIN-BARRÈ SYNDROME; EPSTEIN-BARR VIRUS AND COXSACKIE VIRUSES TYPE B CO-INFECTION” for publication in Cukurova Medical Journal. It has not been submitted for publication nor has it been published in whole or in part elsewhere. It will not be published elsewhere without permission of the Editors. The language of the manuscript was edited by a native speaker. I attest to the fact that all authors listed on the title page have read the manuscript, attest to the validity and legitimacy of the data and its interpretation, and agree to its submission. Each author have participated sufficiently in the work and take public responsibility for the content.

I kindly look forward for the result of review of manuscript.

Kindest regards,

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Introduction

Guillain- Barré syndrome (GBS) is a disorder characterized by progressive, symmetrical and ascendant weakness and areflexia. As well as sensory and autonomic involvement, it is accompanied by brain stem anomalies. GBS is the most common paralytic disease in countries with vaccination programs. According to the data obtained from community surveys, the incidence of GBS in children under the age of sixteen is 0.25-1.5/100,000 and both sexes are affected equally.

Non-polio enterovirus (NPEV) infections may mimic bacterial sepsis which cause nonspecific specific febrile illness in infants and children and involve coxsackievirus type A and B, ECHO virus and enterovirus. They are known to cause specific disease such as aseptic meningitis, encephalitis, paralysis in the central nervous system. While enterovirus 71 causes polio-like paralysis and brain stem encephalitis, coxsackievirus type B1 -B5 may lead to pleurodynia and myopericarditis. In the etiology of acute flaccid paralysis, the frequency of NPEV in India is reported to be 20-54 % and there have been an emphasis on the frequency of NPEV in flaccid paralysis cases after vaccination in the United States. Paralysis is particularly associated with coxsackievirus B2 - B6, enterovirus type 71 and echovirus 3, 4, 6, 9, 11, 19 and 22.

Epstein-Barr virus (EBV) is a DNA containing B- lymphotropic herpes virus and it presents a clinical course ranging from asymptomatic form to fatal infection. Central nervous system (CNS) complications include aseptic meningitis, encephalitis, cranial neuropathy affecting the facial nerve, isolated cerebellar disease, transverse myelitis and GBS.

This paper aims to put emphasis on NPEV probability and the presence of co-infection in an atypical GBS case with progressive clinical course, concurrent EBV and coxsackievirus type B and having delayed clinical response and longer follow-up period in intensive care unit.
Case summary

A 22-month-old male patient who had high temperature two weeks ago and not able to walk for two days was referred to the hospital for the complaints of not to walk and sit. The patient who had no medical history was born mature via vaginal delivery after a full-term pregnancy and vaccinated in the postnatal period. In the physical examination of the patient with normal neuromotor development, the patient was conscious and had a moderate general state and respiratory distress. In the neurological examination of the patient with tachypnea, tachycardia, hypertension and cranial nerves intact, the patient was not able to sit without support, tendon reflexes were absent in lower extremities and hypoactive in upper extremities. Muscle strength was 2/5 and 1/5 in upper and lower extremities respectively. The patient who felt restless was mewling but was able to breastfeed and gag reflex was bilateral. The patient experiencing infiltration in lower zones of both hemithorax on Chest radiography was initiated antibiotic treatment due to pneumonia diagnosis. On the second day of follow-up, the patient who had elevated respiratory distress and developed respiratory acidosis in blood gas was taken to the intensive care unit and intubated. The patient who received intravenous immunoglobulin (IVIG) therapy (0.4 g / kg / day, for five days, a total of 2 g / kg) underwent lumbar puncture in the third week of follow up. Protein 33 mg / dl, glucose 91 mg / dl (simultaneous plasma glucose 102 mg / dl) were detected in the cerebrospinal fluid (CSF). Electromyography (EMG) revealed findings compatible with acute motor axonal neuropathy (AMAN). Since clinical improvement was not achieved, IVIG was repeated on the 33rd day of follow up. Viral capsid antigen (VCA) of the EBV, IgG and IgM positivity was detected in the etiological examination. Coxsackievirus type B was detected in nonpoliovirus typing which was detected in fecal samples taken for the evaluation of acute flaccid paralysis. In the CSF examination repeated in the sixth week of follow-up, protein was 34 mg / dl and glucose
was 56 mg / dl (simultaneous plasma glucose was 70 mg / dl). In addition, coxsackie virus type B was detected in viral serology from CSF samples. In the repeated EMG of the patient who had normal cranial and spinal magnetic resonance imaging results which were performed for the differential diagnosis, the findings of AMAN remained stable. The patient intubated was followed for 54 days in the intensive care unit. Clinical improvement was achieved on the 40th day of follow-up with head movements and struggle for moving shoulder and upper extremities. On the 60th day of hospitalization, the patient was discharged from the hospital (was able to sit with a support) and on the control after three months he could walk for five-meters with help. On the six months control, the patient could walk independently and deep tendon reflexes were hypoactive.
Discussion

The disease was defined by Guillain, Barre and Strohl in 1916 as an ascending progressive motor weakness, areflexia, paresthesia and mild sensory loss and increased protein in CSF and absence of inflammatory cells. Although GBS affects both sexes equally and may be seen at any age, most of the cases are between the ages of four and nine and 1/3 are under three years of age. Fifty to 70% of the patients experience acute gastroenteritis, respiratory tract infection or weakness of the lower extremities after vaccination. Although it can be seen throughout the year, its frequency tends to increase in summer and early autumn months. The case presented here was under three years old and had a history of non-specific fever two weeks before and was diagnosed in the early autumn. In the initial examination, significant weakness in lower extremities and loss of reflex were accompanied by hyporeflexia in upper extremities. The patient with ascending progression of weakness findings was diagnosed with GBS.

In order to establish the diagnosis of GBS, the presence of progressive motor weakness in more than one limb and areflexia is required. Rapid progression, relative symmetry, autonomic dysfunction, mild sensory symptoms, cranial nerve involvement, not having fever at the beginning of neurological symptoms and recovery after two or four weeks are the clinical findings that strongly support the diagnosis. In addition, the presence of albuminocytologic dissociation in CSF and deceleration or blocks in nerve conduction velocity in electromyography study is sought. In our case, clinical features necessary for the diagnosis and findings which strongly support the diagnosis were present but no increase in CSF protein was detected. Since increased CSF protein is an indication that supports the diagnosis of the disease but not a gold standard for the diagnosis and increased CSF protein can be seen in 1/3 cases, the diagnosis of GBS was not excluded.
Differential diagnosis of disease involves bilateral cerebral stroke, acute cerebellar ataxia, posterior fossa tumors, anterior spinal cord syndrome, spinal cord compression, critical illness neuropathy, tick paralysis, porphyria, toxins or drug-induced neuropathy, botulism, myasthenia gravis, acute viral - inflammatory or metabolic myopathies. In the case presented, although the diagnosis of GBS was established with patient’s history and physical examination, laboratory and imaging studies were performed because of serious and long-term clinical table and these pathologies were excluded.

Guillain-Barre syndrome is considered to be an immune-mediated organ-specific disease. The role of cellular and humoral mechanisms, particularly the humoral immunity mechanism is shown in the pathogenesis. It was determined that infectious agents triggering the onset of the immune event bear resemblance to the tissue antigens of epitopes and CD4-helpers are at the forefront at the onset of the disease and lead to breakdown of blood / nerve barrier as a result of T- cell activation and to contact antibodies (Ab) against infectious agent to peripheral nerve antigens and demyelination and axonal damage. Antibodies against GM1, GD1a and GD1b in the serum of the patients and that against GQ1b gangliosides in Miller Fisher syndrome have been shown. As well as immune properties of infectious agent, immune response of the host is thought to be an important factor. Antibody production is triggered by infectious agents such as cytomegalovirus, EBV, mycoplasma pneumonia and campylobacter jejuni or vaccination, trauma, surgical procedures and axonal damage occurs as a result of immune-mediated damage. In the case presented, the presence of an acute infection supporting immune-mediated etiology is shown.

Different clinical variants of Guillain-Barré syndrome have been identified including acute inflammatory demyelinating polyneuropathy, acute motor axonal neuropathy, acute motor - sensory axonal neuropathy, Miller Fisher syndrome, cranial polynuiritis, Faringo-cervical- brachial syndrome and childhood acute sensory neuropathy and acute
Physiopathological process is different in AMAN and Ab production against axosolemma antigen directly cause damage to the nodes of Ranvier and form a transmission block and lead to further injury in distal peripheral nerve. Cranial nerve and sensory involvement was not detected in our case. Electrophysiological evaluation results were consistent with AMAN. Although synchronous occurrence of AMAN and Compylobacter jejuni gastroenteritis is more frequent in comparison to other forms, this was not observed in our case.

Epstein-Barr virus is a B-lymphotropic virus and complications of CNS include aseptic meningitis, encephalitis, and GBS. Replication of EBV in B lymphocytes and resulting lymphoproliferation is inhibited via T-cell response in which CD8-suppressors are prominent and natural killer. Those pathogens activate the T-cell response, an important mediator of the disease. Molecular similarity of the specific endogenous antigens with myelin P-2, ganglioside GQ1b, GM1 and GT1a cause separation of myelin and axons in the nodes of Ranvier of the peripheral nerve through T-lymphocytes and macrophages. VCA IgM, detected in the diseases, only shows acute infection and can be detected in serum within the first 4-8th weeks after contacted with the agent. In the case presented, serological findings consistent with acute EBV infection were observed and IgM and IgG positivity against viral capsid antigen was present.

Enteroviruses may lead to wide range of clinical tables from minor febrile illness to severe and fatal conditions (aseptic meningitis, encephalitis, paralysis, myocarditis and neonatal enteroviral sepsis) and the development of some chronic diseases (diabetes mellitus type 1, dilated cardiomyopathy). Enteroviruses can be isolated from pharyngeal swap, CSF, spinal cord, brain, heart, blood, conjunctiva and debris in the skin or mucous membranes. However, for retrospective evaluation, stool samples are used for the diagnosis. In a study conducted by Saeed et al. 1775 cases of acute flaccid paralysis were examined and NEPV was
detected in 474 (26%) cases. In studies of typing GBS, coxsackievirus type B in 63 cases (13%) and coxsackievirus type A in 181 cases (38%) were isolated. Saeed et al. determined that non-polio enterovirus are more common in men, maximum loss of strength occurs within four days, there is a negative correlation between age and severity of the disease, the fatality rate was 12% and residual paralysis remained at the end of the 60-day follow-up with a rate of 39% \(^{19}\). In our case, coxsackievirus type B was isolated from fecal and CSF samples. The patient was intubated and monitored in the intensive care unit due to the respiratory failure developed on the second day of hospital referral. Clinical improvement was achieved after prescribed period but the patient did not develop residual paralysis.

In the treatment of childhood GBS, trying to cease the autoimmune process which leads to destruction of the myelin sheath with early immunomodulatory therapy and providing an appropriate life support due to respiratory failure affect morbidity and mortality. Prevention of secondary complications and the importance of the physical rehabilitation are emphasized. Today, mortality rates decreased to 10% from 50% by the utilization of intensive care units. Immunomodulatory therapy shortens the duration of the disease but does not affect mortality significantly. It is recommended that the patients with rapid clinical progression, loss of ability to walk, significant bulbar involvement or respiratory failure should be treated \(^{20}\). The case presented here was treated with IVIG due to the rapid clinical course and respiratory failure. Plasmapheresis could not be implemented due to the low body weight and possible complications.

Children with GBS have shorter duration of disease and exhibit full recovery than that of adults. More than 90% of the children recover completely. On the other hand, mild weakness affecting ankle dorsiflexion but not allowing them to walk independently has been reported \(^{10}\). In the case presented, the patient was able to walk independently at the three and six months of control despite longer plateau period and severe clinical table.
In conclusion, dual infection may play a role in atypical cases of GBS and administration of repeated IVIG can be useful in patients without clinical response within three or six weeks.
List of abbreviations
GBS: Guillain-Barré syndrome
NPEV: Non-polio enterovirus
EBV: Epstein-Barr virus
CNS: Central nervous system
IVIG: Intravenous immunoglobulin
CSF: Cerebrospinal fluid
EMG: Electromyography
AMAN: acute motor axonal neuropathy
VCA: Viral capsid antigen
Ab: Antibodies

Declaration of Conflicting Interests
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Ethical Approval
This work was deemed exempt from formal review by the institutional review board of Ondokuz Mayis University, Faculty of Medicine. Informed consent was obtained from the parents.
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