INTRODUCTION
EBV infection may result in hematological disorders, like thrombocytopenia and Acute Demyelinating Disease (ADEM) of the nervous system. An immuno-competent child rarely develops Acute Disseminated Encephalomyelitis and severe thrombocytopenia associated with Epstein-Barr Virus (EBV) infection.

The CNS complications usually occur 1 to 3 weeks after the onset of EBV infection but may occur at the outset of the disease. The pathogenesis of these complications has not been clarified. Studies suggest that some complications are due to direct viral infection, whereas others are due to autoimmune mechanisms. Neurologic complications are the most common cause of death in EBV.

Despite an extensive literature survey, the authors could not find any reported case of ADEM with thrombocytopenia following EBV infection. Hence this case is reported.

CASE REPORT
A 7 years previously healthy boy was admitted to local regional hospital with 2 days history of left sided weakness and headache. The patient’s condition had deteriorated over one week period and he developed irritability and agitation. MRI brain revealed multiple patchy asymmetrical lesions involving the subcortical and periventricular white matter, so there was strong suspicion of Acute Disseminated Encephalomyelitis (ADEM). The patient was started on methylprednisolone boluses and after he received three doses, he was transferred to our hospital at KFSH & RC. He was also treated at local hospital with intravenous vancomycin, ceftriaxone and acyclovir.

The patient was not known to have any medical or surgical problems prior to the admission when he developed leg pains and headache, for which he was treated with acetaminophen. There was no history of recent travel or vaccinations.

On admission to our hospital, the child was noted to have disturbed level of consciousness and mild hepatosplenomegaly without any lymphadenopathy. His neurological examination on the first evaluation showed impairment of consciousness, agitation, dystonic posturing of the left upper limb with increased tone and deep tendon reflexes of the same side, positive ankle clonus at the left ankle. There were no nuchal rigidity, and all accessible cranial nerves were intact. His abdominal reflexes were absent and plantar response was extensor bilaterally. His fundoscopic examination was also normal. The patient completed the courses of methylprednisolone in the hospital then he was kept on maintenance dose of oral prednisolone.

MRI brain was repeated on day 16th in the hospital. It showed multi-patchy hyperintense lesions involving the subcortical and periventricular white matter. His CSF routine examination and culture was normal. CSF examination for antibodies including anti-NMDA
antibody, potassium voltage channel antibodies and sodium voltage channel antibodies as well as the NADHM antibodies all were negative. CSF oligoclonal bands were absent in the CSF and immunoglobulin G index was normal. CSF lactate and ammonia, and serum lactate and ammonia were also normal.

High copy number of Ebstein-Barr virus determined 1000 copies/ml in serum and undetectable in CSF by PCR method. His routine blood complete examination was normal, no atypical lymphocytes were seen. Anti-nuclear and smooth muscle anti-bodies with complement 3, 4 and all were negative. CRP was normal and metabolic workup including tandem-MS, biotinidase, urine GC-MS, very long chain fatty acids, pristanic acid and phytanic acid all were within normal range. CT brain angiography result was also unremarkable.

During his hospitalization, the patient was also kept on clonazepam, chloral hydrate and haloperidol for agitation.

On the 20th day of his hospitalization, he developed severe thrombocytopenia and further deterioration of conscious level. The patient was admitted to the pediatric ICU, and intubated. CT of the brain at that time showed interval worsening of supratentorial and infratentorial hyper-attenuating foci, highly suspicious for hemorrhagic septic emboli or multifocal hemorrhage. Haematology team was consulted because of thrombocytopenia. Bone marrow aspiration was reported normal. He was initially treated with two doses of Intravenous (IV) Immunoglobulin (IG) and later on was started on IV methylprednisolone boluses. The thrombocytopenia was resistant to medical treatment including IVIG and pulse steroid. Rituximab was started, after two doses of Rituximab, patient showed dramatic improvement in his platelet count.

Two months later, the boy was well on follow-up and no further haematological or neurological anomalies were observed.

**DISCUSSION**

In this report, we described a patient with rare and severe neurological complications in association with EBV infection. ADEM is thought to be an autoimmune disease precipitated by infectious agents, which trigger an autoimmune reaction against neural constituents with cross-reactive molecular structures. Neurological manifestations are rarely seen during EBV infection, usually less than 1% among the diseased. The pathogenesis of EBV in the central nervous system is not well understood, beside direct viral invasion indirect immune effects are discussed as potential mechanism.

Severe thrombocytopenia is an extremely rare complication of acute Epstein-Barr Virus (EBV) infection. EBV infection usually causes haematological abnormalities, mainly atypical lymphocytosis, which is a feature of infectious mononucleosis, and uncomplicated cases often present with mild decreases in platelet counts. The clinical neurological manifestations usually occur 1 week to 3 weeks after the onset of infection but may occur at the outset of the disease.

This patient showed severe thrombocytopenia and various neurological manifestations including confusion, agitation, irritability, deterioration of conscious level, dystonia and spasticity, and left sided weakness and ended in severe quadriplegia but left side was more severely affected. These manifestations along with cerebrospinal fluid and serology, neuroimaging led to the clinical diagnosis of ADEM with severe thrombocytopenia.

The pathogenesis of these complications is still under debate. Studies suggest that some complications are due to direct viral infection, whereas others are due to autoimmune mechanisms. Acute disseminated encephalitis and postinfectious encephalomyelitis associated with Epstein-Barr Virus (EBV) are immune-mediated processes that result in multifocal demyelination of perivenous white matter. No standard therapy has been established for EBV associated central nervous disease, although dose of methylprednisolone pulse therapy seemed to be beneficial and IVIG might be beneficial. Antiviral agents could prevent active EBV viral replication, but did not affect the out clinical course of the disease. Thrombocytopenia in this patient did not show any response to steroids and IVIG, but showed a dramatic response to two doses of Rituximab.

When MRI findings suggest the diagnosis of acute disseminated encephalitis, associated with severe thrombocytopenia, the participation of Epstein-Bar virus...
in neurological and haematological complications should be taken into consideration.

Complications of primary EBV infection are not common but may be life-threatening if not treated. Clinicians should monitor such patients closely and give proper treatment to decrease possible morbidity or even mortality should complications occur.

REFERENCES