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Extensive Longitudinal Transverse Myelitis Associated With CSF Epstein-Barr Virus Infection: A Case Report

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Abstract

Background. Acute transverse myelitis (ATM) in children can be secondary to central nervous system infections. Several reports have associated ATM with Epstein-Barr virus (EBV) infection. **Case presentation.** We report a previously healthy 10-year-old boy with paraparesis that started 7 days before admission. Spinal T2W MRI revealed extensive hyperintense lesions. Cerebrospinal fluid WBC was 268/μL and PCR examination was positive for EBV. High dose methylprednisolone (1 g/kg) was given for 5 days, the child was symptom free 3 months after presentation. **Conclusion.** Epstein-Barr infection should be considered in ATM, particularly when CSF WBC count is high.

Keywords

acute transverse myelitis, case report, children, epstein-barr virus

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Background

Acute transverse myelitis (ATM) is a rare neuro-immune spinal cord disorder that can be a part of a continuum of neuro-inflammatory disorders. Most cases of ATM are idiopathic, but at times can be associated with infections such as Mycoplasma, Lyme disease, Herpes Simplex and other viruses.[1] A small number of case reports have associated Epstein-Barr virus (EBV) infection with ATM in children.[2–6] We report a case of an immunocompetent child with ATM affecting the entire length of the spinal cord with an atypically high CSF pleocytosis and positive polymerase chain reaction (PCR) for EBV.

Case Presentation

A previously healthy 10-year-old Indian boy developed acute onset of weakness and numbness of both lower limbs 7 days before admission. The weakness reached nadir over a period of approximately two days. On the fourth day of the illness, he developed a difficulty in micturition leading to urinary retention while bowel passage was normal. There was a history of fever, vomiting, and headache 2 weeks before admission.

General physical examination was unremarkable. On neurological examination, the child was fully alert, there were no cranial nerve palsies or meningeal signs. Biceps, triceps, and brachioradialis reflexes were normal while knee and ankle reflexes were brisk. Muscle tone was normal, muscle power (MRC scale) for both lower limbs was 1/5. Upper limbs were unaffected. Touch, position, temperature sensations were decreased more in the left lower limb compared to the right, but a clearly defined sensory level could not be identified.

An outside cerebrospinal fluid (CSF) report showed white blood cells (WBC) 258/μL, with lymphocyte 93.4%. A repeat CSF on the following day showed a WBC of 268/μL. CSF PCR for *Mycobacterium tuberculosis*, *Escherichia coli, Haemophilus influenzae, Listeria monocytogenes, Neisseria meningitidis, Streptococcus agalactiae, Streptococcus*

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pneumonia, cytomegalovirus, enterovirus, HSV 1 and 2, human herpesvirus 6, human parechovirus, varicella zoster virus, and *Cryptococcus neoformans/gatti* were negative. Cerebrospinal fluid PCR for EBV was positive, serum IgG for EBV capsid antigen was positive while IgM was negative. Cerebrospinal fungal stain and culture, oligoclonal bands, anti-aquaporin-4, and anti-MOG tests were negative. Whole spine contrast MRI showed a mild diffuse increase in cord bulk with an intramedullary hyperintense signal on T2 weight images involving the entire length of the spinal cord and conus medullaris, indicating a longitudinally extensive transverse myelitis (Figure 1). Contrast MRI of the brain revealed leptomeningeal enhancement involving the brain and pial surface of the spinal cord (Figure 2).

The patient was treated with a high dose (1 g/day) of intravenous methylprednisolone for 5 days, after which he began to show clinical improvement. It was then continued with oral prednisone (60 mg/day) for 4 weeks and then was tapered off. Ceftriaxone, clindamycin, and azithromycin were also given. He underwent physiotherapy that was continued after discharge. A follow-up CSF examination performed on the seventh day of admission showed a reduction of WBC count to 59/μL and negative EBV PCR.

At the time of discharge, muscle power improved to grade 4/5 on both lower limbs. He started walking a few steps without support. There was no numbness in the lower limbs, bowel passage and micturition were normal. Sensations of touch, position, temperature were normal. He was discharged on oral prednisolone and physiotherapy after nine days of hospitalization (16 days after initial onset). Two weeks after discharge patient regained almost complete mobility. Three months after discharge the child was completely normal and his spine and brain MRIs showed complete resolution of lesions and disappearance of contrast enhancement.

Discussion

Acute transverse myelitis (ATM) is a disorder of immune-mediated demyelination of the spinal cord. It is a rare condition with an estimated incidence of 1.7 cases per million children under the age of 16 years per year.[7] The Transverse Myelitis Consortium Working Group established diagnostic criteria for ATM which include acute bilateral sensory, motor, and autonomic dysfunction attributable to spinal cord with clearly defined sensory level, although the latter may not be evident in 40% of children.[1] Most cases are idiopathic and presumably occur as post-infectious complications resulting from an autoimmune process. However, occasionally ATM can be directly associated with infections such as enteroviruses, HIV, HTLV-1, Zika, tuberculosis, and Epstein-Barr virus.[8]

Epstein-Barr virus (EBV) is a very common herpes virus, with a seroprevalence rate of 85% among adults. Infectious mononucleosis (IM) is the primary illness associated with EBV, characterized by the classic triad of fever, pharyngitis, and cervical lymphadenopathy. Central nervous system (CNS) disease can occur in up to 5% of cases; mainly aseptic meningitis, meningoencephalitis, and encephalitis, with immunocompromised patients being at the highest risk.[9] Myelitis is a very rare CNS manifestation of EBV in healthy patients.[2,10]

Our patient had a distinct ATM involving the entire length of the spinal cord. This longitudinally extensive ATM has been previously reported in a few cases of EBV myelitis.[3,4] A CSF cell count of 268 cells/μL, seen in our case was rather high as compared to that typically seen in idiopathic ATM which usually ranges between normal and less than 100/μL.[11] One study, however, reported a higher CSF WBC of 136 ± 67 cells/μL in children.[12] The high cell count raised suspicion of a secondary infectious cause of ATM, and CSF PCR sent for EBV came positive. Previous case reports on EBV-associated ATM have shown CSF WBC ranging from normal to 316/μL,[2,4] but a cell count exceeding 1.000/μL has been reported in an immunocompromised adolescent.[5] History of headache and pial enhancement around the brain and spinal cord on MRI might suggest a resolving meningitis or meningoencephalitis, which is a more common CNS manifestation of EBV compared to myelitis.[9] There were no signs of meningeal irritation or increased intracranial pressure at admission and throughout hospitalization in our case, and there were no systemic signs

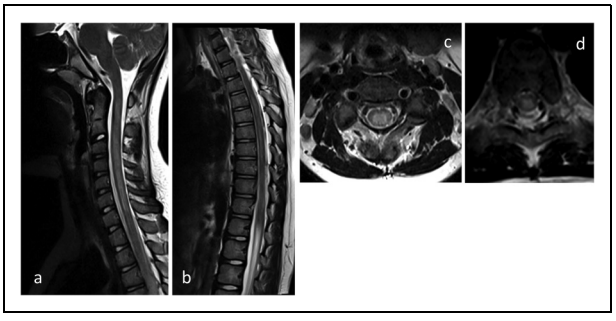

Figure 1. T2w sagittal images of the cervical and thoracic spine (a,b) along with axial images (c,d) reveal diffuse long segmental T2w hyper-intense signal in the spinal cord more in the central gray matter region along with mild cervical cord swelling.

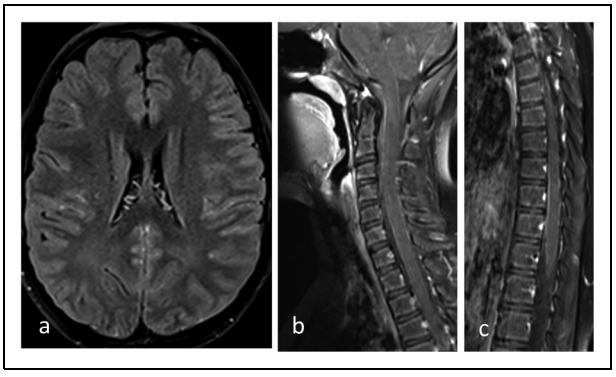

Figure 2. Flair contrast image of the brain (a) and T1w contrast (b,c) image of the cervical and thoracic spine shows mild smooth enhancement along the pial surface of spinal cord.

and symptoms suggestive of infectious mononucleosis. Epstein-Barr virus is not known to infect neurons, the negative result for IgM might indicate that the illness had already occurred for at least 4 weeks.[9] Because of this, a post-infectious immune response may be responsible for the mechanism of pathogenicity in this case, even though PCR result indicated the presence of the virus. Differentiating between primary infection and its immune response may be difficult in this case.[13]

A longitudinally extensive transverse myelitis might indicate neuromyelitis optica spectrum disorder (NMOSD). However, there were no symptoms of visual disorder or area postrema syndrome, and both NMOSD and MOG antibodies were negative. Although funduscopic examination or orbital MRI was not done, the possibility of NMOSD should be considered and future follow-up may include these examinations alongside anti aquaporin-4 and anti MOG antibodies, should symptoms reappear.

Methylprednisolone, given in a high dose (30 mg/kg/day, up to 1000 mg) for 3 to 5 days, is the first line treatment of choice for ATM, although this recommendation is currently not supported by any randomized controlled trials.[1,14] A recent quasi experimental study demonstrated full recovery in 41.2% and partial recovery in 58.8% of 34 children with longitudinally extensive ATM treated with methylprednisolone.[15] While several antiviral agents, particularly ganciclovir, can inhibit EBV replication in vitro, none was found to be effective in improving signs and symptoms of infectious mononucleosis caused by EBV based on a meta-analysis.[16] There is currently no consensus for antiviral treatment in CNS involvement of EBV. Several case reports have demonstrated the successful use of ganciclovir especially in immunocompromised patients where there is a risk of devastating outcomes,[5,6] and also in healthy patients.[2,4] We decided not to give ganciclovir because our patient showed marked improvement with methylprednisolone even prior to the identification of EBV PCR, and because ganciclovir can be associated with severe toxicity.[17]

Although weakness in ATM is usually severe, a high proportion of children will regain their mobility. A single center experience in India reported that 62% of children became ambulatory without support. Predictors for poor prognosis include respiratory weakness, the need for ventilation, muscle power of ≤ 1 on the medical research council (MRC) scale, spinal shock, delay of diagnosis, and treatment.[18] One of the main concerns about ATM is the potential progression to multiple sclerosis (MS) that can occur in 13% of cases.[19] Risk factors for progression into MS include the presence of brain lesion, discrete, shorter segmented spinal lesions on MRI, and oligoclonal bands,[11] none of which was found in our patient.

Conclusion

Although rare in immunocompetent individuals, longitudinally extensive ATM secondary to EBV should be considered, particularly in the presence of a high CSF cell count that is atypical for idiopathic ATM. As there is as yet no evidence based treatment for ATM secondary to EBV, the use of antiviral medication should be individualized.

Authors' Contribution

Pratibha Singhi was the physician in charge of patient management, provided the design and final approval of the manuscript. Rakchhya Gautam was the assistant physician in the patient management, involved in the data collection and writing of the manuscript. Jai Prakash Sharma was in charge of radiologic examination and review. Raden Muhammad Indra prepared the manuscript and literature review. Achmad Rafli collected and organized all of the data and contributed to the preparation of the manuscript.

Declaration of Conflicting Interests

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Ethical Approval

Not applicable, because this article does not contain any studies with human or animal subjects.

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