Case Report

Catastrophic Neurologic Manifestations of a Common Immunodeficiency Syndrome

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ABSTRACT
A high index of suspicion is needed in pediatric patients with neurological symptoms being the sole presenting manifestation, to diagnose infection with the Human Immunodeficiency Virus (HIV). This is a write up of two such cases who were admitted to the pediatric intensive care unit with neurological manifestations.

A 6 year old previously healthy child, who initially presented with intermittent drowsiness and fluctuation in blood pressure, later during hospital stay, developed progressive motor, cognitive, visual and language difficulties. Investigations revealed the child to be HIV positive and magnetic resonance imaging (MRI) findings were consistent with progressive multifocal leukoencephalopathy.

A 12 yr old child had stroke initially (for which extensive work up had been done) and later, after 8 months presented with the same complaints along with severe pneumonia. He succumbed to severe opportunistic infections. That he was HIV positive, had not been detected during the first admission as left sided weakness was the only presenting manifestation.

Keywords- HIV, Children, Leukoencephalopathy, neurological manifestations, progressive

Case Report

Case -1
A 6 Yr old previously healthy boy, born of second degree consanguinous marriage had been admitted with complaints of headache, non bilious vomiting and lethargy for 6 days. There had been no history of fever, weight loss, cough or loose stools. Child had a past history of urinary tract infection (klebsella) 20 days ago. On examination he was drowsy (responding to verbal commands) with neck stiffness and intermittent hypertension. He had been started on antibiotics and acyclovir, pending cerebro-spinal fluid (CSF) reports. Initial computerized tomography (CT) brain was normal. CSF, blood and urine screening for infection were negative. Blood investigations revealed hyponatremia, hypokalemia and a high anion gap metabolic acidosis. As he continued to have intermittent drowsiness and hypertension, a magnetic resonance imaging (MRI) was done which revealed symmetrical foci of restricted diffusion and subtle flair hyperintensity in bilateral globi pallidi. Considering the metabolic abnormalities and the MRI findings, organic academia (methylmalonic academia) was suspected but work up for organic academia (tandem mass spectrometry and urine for organic acids) was negative. During further hospital stay child had weight loss, rigidity, choreoathetoid movements, worsening cognition and aphasia. Further work up done for wilson disease (24 hr urine copper) was negative. HIV ELISA was done due to weight loss (in the 10 days of hospital stay) and new onset loose stools. It was positive and confirmation was done by Western blot analysis. Both parents were also found to be HIV positive. Repeat MRI revealed multifocal bilateral fairly symmetrical white matter hyper intensities in frontal, parietal, occipital lobes and cerebellar hemispheres along with lesions in bilateral globi pallidi. Diagnosis of

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possible progressive multifocal leucoencephalopathy (PML) was made based on clinical and neuroimaging evidence. He was shifted to another hospital with a dedicated anti retroviral therapy (ART) center for further treatment, as per parents request. He expired after a month’s time.

**Case -2**

A 12 yr boy weighing 28 kg was referred for complaints of fever, cough, worsening tachypnea with left hemiparesis for the last two weeks. There was a past history of left upper limb monoparesis 8 months ago. MRI done for the same then, had revealed an ischemic infarct involving the right parieto-occipital, semiovale and frontal regions. Extensive work up had been done during that episode and he had been discharged home on physiotherapy. This time he had to be intubated and ventilated for respiratory failure (pneumonia with acute respiratory distress syndrome). Investigations revealed child to be HIV positive with total leucocyte count 6520/mm3 CD4 count 0.52% with CD4/CD8 ratio 0.01, viral load of HIV-1 ribonucleic acid (RNA) polymerase chain reaction (PCR) 2,14,895 copies/milliliter. Chest skiagram and computerized tomography (CT) thorax were suggestive of Pneumocystis carini/cytomegalovirus (CMV) infection. A bronchoalveolar lavage was done which was positive for CMV PCR. Child also had evidence of CMV retinitis. Child was treated with antibiotics for opportunistic bacterial infections, gancyclovir along with anti retroviral therapy. He succumbed to sepsis and multiorgan failure after a month of pediatric intensive care unit stay. As parents denied consent for their HIV test it was not done.

**Discussion**

The neurological manifestations of Acquired Immunodeficiency Syndrome (AIDS) may result from direct neuronal infection, cytokine mediated effects of virus and/or immune dysregulation.1 Incidence of central nervous system (CNS) involvement is 3 times more in children than in adults. Neurological involvement has been reported in 50-60% of children with HIV and is the initial manifestation in up to 18% of children.2 In developing countries where majority of affected children are not on proper anti retroviral therapy, progressive HIV-1 encephalopathy is the main CNS manifestation.3 A presentation with stroke or progressive multifocal leukoencephalopathy in otherwise undiagnosed HIV children is limited to case reports.

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease of the CNS cause by ubiquitous John Cunningham (JC) virus. PML is an AIDS defining illness and HIV associated cases account for up to 85% of all cases of PML.4 It has been documented in persons having CD4 count >200 as well, suggesting the diagnosis as an immune reconstitution inflammatory syndrome.5

The gold standard for diagnosis of PML requires typical histopathologic triad (demyelination, bizarre astrocytes, and enlarged oligodendroglial nuclei) coupled with demonstration of presence of JC virus.6 However with facility constraints, a clinical finding with brain imaging can be diagnostic for possible PML. MRI brain is notably superior to other imaging modalities. Similar MRI findings may be seen in multiple sclerosis and AIDS associated dementia. However, dementia or multiple sclerosis is rare in children.

The area showing involvements are frontal and parieto-occipital lobe in majority although other brain areas have been described as well.6,7 On MRI, the affected regions are hypointense on T1-weighted images and hyperintense on T2-weighted and fluid-attenuated inversion recovery (FLAIR). There is no definitive treatment for PML. Various trials of cytotoxic, immunomodulatory and antiviral agents have not shown promising benefits.8 An initial benefit of mefloquine has been noted, but later on refuted by larger trial9,10 During pre-highly active antiretroviral therapy (HAART) era, survival was extremely poor in adults and children with PML. Survival among adults has improved during HAART era from 10% to 50% and mean time of survival from time of diagnosis of PML has increased from 0.4% to 1.8 yrs.11,12 No comparable data exists for children. Stroke is most common cause of focal neurological deficit in children with HIV-1. The prevalence varies from 1-5%.13,14 HIV infection is believed to cause stroke by predisposing to opportunistic infections,
by increasing cardio embolic stroke due to direct cardiac involvement, by interfering with blood coagulation through antiphospholipid antibodies or reduced protein S or by causing arteriopathy. Pre ART era had an equal proportion of ischemic and hemorrhagic stroke, however post ART era has witnessed increased ischemic infarcts. Index case number 2 presented with cerebral ischemic infarct as a presenting manifestation. The treatment for stroke is symptomatic with secondary preventive strategies should be started after initial management. The role of thrombolysis is uncertain with absence of randomized trial.

A high index of suspicion is needed to diagnose Acquired Immunodeficiency Syndrome in children presenting only with neurologic manifestations.

Legend

Image 1: Axial FLAIR MRI
Brain showing hyperintensities bilateral globus pallidi and parieto-occipital subcortical white matter.

Image 2: Axial T2 WI showing hyperintensities bilateral globus pallidi and parieto-occipital subcortical white matter.

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References