Case Report

Anti-N-methyl-D-aspartate-receptor Encephalitis as a Harbinger of Pediatric HIV Infection

Divya Nagabushana, Thavasimuthu Nishamol, Kajari Bhattacharya, Jitender Saini, Ravindranadh Chowdary, Anita Mahadevan, Kiran Polavarapu, Nalini Atchayaram

Department of Neurology, 1Neuroimaging and Interventional Neuroradiology, 2Neuropathology, National Institute of Mental Health and Neurosciences, Bengaluru, India

Anti-N-methyl-D-aspartate-receptor (A-NMDAR) encephalitis is the most common type of autoimmune encephalitis in the pediatric age group. It is known to be triggered by viral infections such as herpes simplex infections. However, A-NMDAR encephalitis with HIV infection is a very rare event, with cases reported mostly in adults. The current report is of a previously healthy child who presented with recurrent vomiting, irritability, visual impairment, and new onset complex partial seizures and right somatosensory seizures with generalization occurring in clusters. Over a period of 3 weeks, he developed rapidly progressive bilateral painless visual loss, visual hallucinations, and behavioral changes. Brain magnetic resonance imaging (MRI) showed predominantly cortical symmetrical T2/FLAIR hyperintense signal change in parieto-occipito-temporal regions. The serum and cerebrospinal fluid were strongly positive for anti-NMDAR antibodies, and he also tested positive for HIV-1 antibodies acquired by vertical transmission. The patient and mother tested positive for HIV antibodies for the first time. Repeat MRI revealed gliosis in the parieto-occipito-temporal regions, and hippocampi showed volume loss and T2/FLAIR hyperintense signal change in the posterior thalami with patchy hyperintensities in the right putamen. The seizures subsided with immunomodulation along with anti-epileptic drugs, but he had residual cortical visual impairment on follow-up. This is the first report of A-NMDAR encephalitis presenting as a harbinger of HIV infection in a child. This calls for testing for A-NMDAR antibodies in children with HIV infection presenting with neurological or neuropsychiatric manifestations.

KEYWORDS: Anti-NMDAR encephalitis, autoimmune, HIV, infection, pediatric, seizures

INTRODUCTION

Anti-N-methyl-D-aspartate receptor (A-NMDAR)-related autoimmune encephalitis (AE) is one of the most common forms of AE and affects predominantly young females with an ovarian teratoma.[1] AE occurring with HIV infection is very rare. HIV infection can present with autoimmune diseases in either the initial phase when the immune system is intact or when the individual is on antiretroviral therapy.[2] In this report, we describe the youngest reported case of a child presenting with A-NMDAR encephalitis and HIV infection simultaneously.

CASE REPORT

An 8-year-old boy presented with symptoms of vomiting followed by recurrent complex partial seizures.

Address for correspondence: Dr Nalini Atchayaram, Department of Neurology, Neuroscience Faculty Block, National Institute of Mental Health and Neurosciences, Bengaluru 560 029, India. E-mail: atchayaramnalini@yahoo.co.in

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seizures and right motor seizures with generalization for 3 days. He had occasional symptom of visual hallucinations. He had been in good health prior to this illness. Oral levetiracetam had been started but he continued to have recurrent seizures. Examination revealed a conscious dull child with visual impairment and no other focal deficits. Bilateral optic fundi were normal, and an initial computed tomography scan of brain was normal. Magnetic resonance imaging (MRI) brain showed bilateral symmetrical T2/FLAIR hyperintense signal change in parieto-occipito-temporal regions, predominantly involving the cortices with gyriral swelling and sulcal effacement. Subtle T2/FLAIR hyperintensity was noted in hippocampi and posterior part of the thalami (involving the pulvinar). Diffusion-weighted imaging (DWI) showed diffusion restriction in the subcortices of the involved regions with no abnormal post contrast enhancement [Figure 1]. Electroencephalogram (EEG) showed bilateral occipital and centro-temporal rhythmic slowing with infrequent superimposed fast beta-activity suggestive of extreme delta brush [Figure 2]. Bilateral visual-evoked potentials showed absent waveforms. Antibody against HIV-1 by the enzyme-linked immunosorbent assay method was positive. His CD4 count was 701/mm$^3$ and CD3 was 1866/mm$^3$. Serum viral load was 348,006 copies/mL. On testing, mother was also found to have retroviral disease with a CD4 count of 488/mm$^3$ and CD3 count of 1591/mm$^3$. Extensive workup for ruling out infectious, metabolic, and inflammatory etiology was conducted. Blood counts, serum electrolytes, renal, liver functions, serum ammonia, and thyroid function tests were normal. Vitamin B12 was low (123 pg/mL), and urine was negative for abnormal metabolites. Serum and cerebrospinal fluid (CSF) were negative for herpes simplex virus, enterovirus, Japanese encephalitis virus, JC virus antibodies, toxoplasma, treponema pallidum, cryptococcal antigen, anti-tubercular antibodies (IgG and IgM), and culture for acid-fast bacilli. Serum and CSF lactate were 14.6 and 13.9 mg/dL, respectively. CSF examination showed five lymphocytes, protein of 40 mg/dL, and glucose of 73 mg/dL. Serum and CSF testing by indirect immunofluorescence assay on transfected cell lines were strongly positive for NMDAR antibody.

**Figure 1:** A. FLAIR axial image shows asymmetrical hyperintense signal in the hippocampi (left > right). B. FLAIR image shows asymmetrical hyperintense signals in posterior temporal cortices with visible swelling of the cortical gyri and sulcal effacement. C–F. Axial DWI and apparent diffusion coefficient (ADC) maps at consecutive levels show hyperintense signal in the parieto-temporal cortices in DWI, with hypointensity predominantly seen in the subcortical white matter in these regions in corresponding ADC maps suggestive of diffusion restriction.
Figure 2: EEG demonstrates background slowing in bilateral occipital and centrotemporal regions with beta-activity superimposed on delta waves suggestive of extreme delta brush. Sensitivity: 20 μV/mm, high frequency filter: 70 Hz, low frequency filter: 0.5 Hz, paper speed: 3 cm/s, sampling rate: 256 Hz, bipolar longitudinal montage

Figure 3: A and B. T2W images show gyral hyperintensity in temporal lobes at presentation and gliosis in temporo-occipital regions at 1-month follow-up, respectively. C. FLAIR image shows subtle hyperintense signals in temporo-occipital regions and hippocampi at presentation. D. FLAIR section at the same level shows temporo-occipital gliosis with atrophy of hippocampi at 1-month follow-up. E. FLAIR image at the basal ganglia level shows subtle hyperintensity in pulvinar nuclei of thalami at presentation. F. FLAIR image at the same level at 1-month follow-up shows persisting mild hyperintensity in pulvinar. There is gliosis in temporo-occipital regions, with dilatation of the occipital horns
He was treated with intravenous steroids and small volume plasmapheresis. A search occult neoplasia was negative. At 15 days follow-up, the child had developed total visual loss, intermittent hallucinations, and abnormal behavior with delusions and disturbed sleep. He was treated with intravenous immunoglobulin following which he had improvement of behavior. Ophthalmological examination was done to rule out opportunistic infections such as CMV retinitis or HIV retinopathy and was found to be normal. MRI repeated at 4 weeks revealed gyral hyperintensity in temporal lobes and gliosis in temporo-occipital regions in T2W sequences. FLAIR image showed subtle hyperintense signal change in the temporo-occipital regions and hippocampi suggestive of gliosis with atrophy and subtle hyperintensity pulvinar nuclei of thalami [Figure 3]. Repeat CSF was normal, and EEG showed diffuse slowing. Further immunomodulation was withheld in view of clinical improvement and high viral load, and antiretroviral therapy considered. At 6 months follow-up, he had cortical visual impairment and infrequent seizures on antiepileptic medications. MRI repeated at 6 months showed gliosis in bilateral occipital regions with hippocampal atrophy.

**DISCUSSION**

A-NMDAR encephalitis is a rare, recently recognized condition and classically described in association with ovarian teratoma, occurring as a paraneoplastic phenomenon. Greater than 80% of the cases are young females. Among the pediatric patients, clinical features noted are altered level of consciousness, confusion, disturbed sleep, movement disorders, and seizures. Behavioral changes, such as repetitive or stereotypical behaviors, irritability, hyperactivity, hypersexuality, insomnia, and anger outbursts, may also be seen. Neoplasia may be found in only 5% of the cases among males. Association of HIV and A-NMDAR encephalitis is exceedingly rare. There have been a few reports of A-NMDAR encephalitis in adults and recently in an adolescent boy with retroviral disease. However, our patient presented with A-NMDAR encephalitis as a harbinger of HIV infection. Certain infections can trigger encephalitis and epilepsy in children either through directly causing primary encephalitis or inducing a secondary AE. The association and increased risk of other autoimmune diseases in HIV infection are possibly due to antigen-driven immune response and molecular mimicry. HIV can cause activation of B lymphocytes with production of autoantibodies and NMDAR hyperactivation, and it has also been demonstrated that HIV-tat protein can penetrate CSF and induce apoptosis in human primary neurons by binding to NMDAR. These may be some of the mechanisms involved in the development of A-NMDAR encephalitis in HIV infection.

A-NMDAR encephalitis-related cortical blindness is uncommon and has so far been reported in a 73-year-old lady with ovarian teratoma. Our patient had rapidly progressive visual loss suggestive of cortical blindness, and this was further supported by the MRI findings. MRI findings in AE are neither sensitive nor specific. In children, FLAIR or T2 hyperintensities in medial temporal lobes, brainstem or subcortical regions, and cerebellum are seen in less than half of the patients, including cortical and/or subcortical, basal ganglia, and infratentorial T2 hyperintensities with or without transient meningeal enhancement. MRI done at the time of first evaluation showed T2/FLAIR cortical hyperintense signal change in parieto-occipito-temporal regions, along with changes in hippocampi and thalami. The possible imaging differentials considered were post-ictal changes or status epilepticus, infectious cause, or AE. However, our patient did not have status epilepticus, and CSF findings were not suggestive of any neuro-infection. The follow-up images revealed gliosis and correlated with clinical picture of remission. EEG typically demonstrates focal or diffuse slowing and/or epileptiform discharges. An EEG pattern known as extreme delta brush has been described in anti-NMDAR encephalitis. EEG findings in our child also showed similar findings which support the diagnosis.

Treatment in children presenting with AE with HIV infection is difficult as use of immunosuppressive medications and steroids may worsen the immunodeficient state and cause flaring of infections. In our patient, an initial course of steroids with plasmapheresis did not lead to complete clinical improvement, thus requiring a course of intravenous immunoglobulin. Initiation of antiretroviral therapy in evidence of high viral load further stabilized the course. Close monitoring is important as relapses are common with AE and long-term immunosuppression is fraught with issues such as new opportunistic infections and malignancies in this group of patients.

In conclusion, this case highlighted two rare events: A-NMDAR encephalitis preceding HIV infection and the striking presentation of cortical blindness and occipital seizures in A-NMDAR encephalitis. A-NMDAR encephalitis should be considered as differential diagnosis in children with HIV infection presenting with acute neuropsychiatric disturbances. Presence of extreme delta brush in EEG and
neuroimaging can provide important diagnostic clues. Management requires antiretroviral therapy and immunotherapy with careful monitoring for complications.

**Patient Consent**
The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published, and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**
There are no conflicts of interest.

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