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Neuroimaging Highlight

Infant with Macrocephaly, Refractory Seizures, and a Leukodystrophy

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A previously healthy 3-month-old girl, born to a non-consanguineous couple (Italian/French ethnicity) with no adverse perinatal events, presented with macrocephaly and explosive-onset focal motor, generalized, and myoclonic seizures. Extensive metabolic investigations (including serum thiamine levels) were unremarkable. Serial regular - Electroencephalography (EEGs) showed ictal and inter-ictal findings from bilateral central and midline regions. Magnetic Resonance Imaging (MRI) brain (Fig. 1) at 4 months of age was suggestive of infantile Alexander disease (AD), later confirmed with genetic testing (c.230 A > G pathogenic variant in *GFAP* gene). Initial Cerebrospinal fluid (CSF) testing showed elevated proteins (0.88 g/L). Serum cytokine profile showed normal levels for Interleukin (IL)-1b, IL-6, IL-10, IL-18, and interferon-gamma and mildly elevated tumor necrosis factor-alpha (TNF-α). Her seizures were treated with multiple antiseizure medications. She was subsequently started on classical ketogenic diet at 5 months of age. This resulted in>50% reduction in her seizures; however, she continued to experience 5–10 seizures per day. She had global developmental delay, spasticity, and intermittent dystonia. She subsequently died at 1.5 years of age.

AD is an autosomal-dominant leukodystrophy caused by astrocyte dysfunction, which classically presents with seizures, macrocephaly, and frontal-predominant leukodystrophy. Seizures in leukodystrophy are often seen with astrocytopathies like AD, vanishing white matter disease and megalencephalic leukodystrophy with subcortical cysts.[1] Seizures tend to occur later in course of the disease but may occur at an early stage in AD or Krabbe's disease.

Seizures were drug-resistant in the reported case and required classical ketogenic diet (KD). KD has been tried in infantile AD. Hamada et al reported 3 cases of infantile AD treated with classical KD (age at initiation 7–14 months); all three showed marked reduction in their seizure frequency.[2]

A mouse model of AD has demonstrated that pathological astrocytes cause a pronounced immune response, which then mediates neuronal dysfunction and seizures.[3] Elevated CSF cytokines (IL-6, IL-8, and macrophage chemotactic protein 1) have been demonstrated in a single case with infantile AD and drug-resistant seizures; their fluctuation correlated with the clinical seizure control.[4] Limited serum cytokine profile in our reported case did not reveal any significant elevations at baseline; CSF levels could not be done.

On imaging, our patient had diffuse white matter involvement and signal changes in bilateral striatum, thalamus, optic chiasm, corpus callosum, midbrain, and dentate nuclei. Other features included periventricular rim of T1-hyperinstensity and characteristic

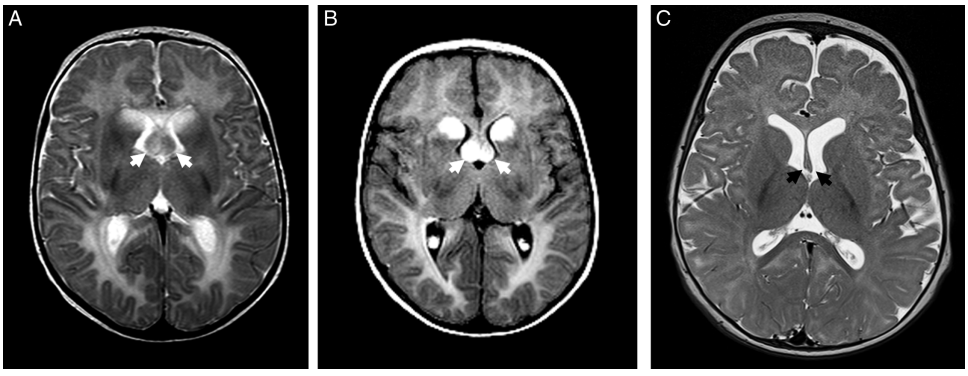

Figure 1: MRI-brain: axial-T2 (**a**) and post-gadolinium FLAIR (**b**) sequences demonstrate diffuse white matter hyperintensity with swollen caudate nuclei and anterior forniceal columns bilaterally (cherry-like appearance) and avid enhancement (white arrows). Other findings included periventricular T1-hyperintensity rim, T2-hyperintensities in thalami, midbrain, and dentate nuclei. Normal MRI (**c**) at similar age shows normal forniceal appearance (black arrows).

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contrast enhancement. Interestingly, there were markedly enlarged/enhancing bilateral forniceal columns. Comparable forniceal changes have also been described in Wernicke's encephalopathy and post-traumatic diffuse axonal injury.[5]

Similar imaging features along with macrocephaly can occur in children with Canavan disease. However, sparing of caudate and putamen and absence of contrast enhancement differentiates Canavan disease from AD.

Competing interests. None.

Ethical statement. Informed consent was obtained from the parents for publication of this report as per the hospital policies.

Statement of authorship. All authors contributed to the clinical care, data acquisition/interpretation, manuscript drafting, and final approval.

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