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Neuroimaging Highlight

Infant with Refractory Seizures and Characteristic Diffusion Restriction Pattern on Neuroimaging

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A 13-month-old girl, the third born to consanguineous parents of South Asian origin, presented at 2 months of age with clustering of multiple brief episodes of focal seizures (eye-blinking, staring and desaturation) and generalized seizures. She was treated with supportive measures and multiple antiseizure medications. Antenatal ultrasound revealed intrauterine growth retardation (IUGR). The baby was born full term via vaginal delivery (birth weight, 2420 g); the baby required hospitalization due to poor sucking, hypotonia and hypoglycemia.

Brain MRI at 9 weeks of age is shown (Figure 1A–H). Electroencephalography done at 2 months and 5 months of age showed multifocal epileptiform abnormalities, more frequent in the bilateral posterior head region and disorganized background. Screening for inborn error of metabolism was noncontributory. Subsequent trio genome sequencing[1] detected a homozygous pathogenic variant NM_033453.4:c.137del;p.(Gln46Argfs*43) in exon 3 of the inosine triphosphatase (*ITPA*) gene, confirming the diagnosis of developmental and epileptic encephalopathy 35 (DEE35). Both parents were heterozygous for this variant. There were no additional reportable genetic findings.

The child exhibited failure to thrive, profound developmental delay, microcephaly and refractory seizures. Poor visual fixation and following of light were observed. Axial hypotonia was more pronounced than appendicular hypotonia, and brisk deep tendon reflexes were observed. Atrial septal defect (ASD), bilateral talipes equinovarus and congenital right hip dysplasia were also detected. Follow-up brain MRI at 9 months of age (Figure 2A–H) revealed persistence of diffusion restriction and a lag in myelination. Echocardiography follow-up at 7 months of age revealed moderate secundum ASD (left to right shunt), deficient aortic rim and moderately dilated right ventricle. ASD was likely to be fenestrated. Seizure control was achieved with a combination of levetiracetam, phenobarbitone and topiramate starting at 10 months of age.

DEE35 is an autosomal recessive disorder caused by biallelic variants in the *ITPA* gene encoding inosine triphosphate pyrophosphohydrolase (ITPase). ITPase is one of the house-keeping enzymes that hydrolyzes noncanonical nucleotide triphosphates (toxic byproducts of cellular metabolism) and also plays a crucial role in the purine metabolic pathway.[2,3] ITPase deficiency results in the accumulation of noncanonical nucleotides and their deoxy forms, which not only leads to cellular toxicity and programmed cell death but also affects the enzymes utilizing adenosine triphosphate or guanosine triphosphate.[2,3] ITPA is widely expressed in the neurons and heart, and hence, altered G-protein signal transduction in ITPase deficiency influences the release of neurotransmitters, astrocyte glucose metabolism and neuronal plasticity in the central nervous system.[2,3]

Seven individuals with ITPA gene variants were first described by Kevelam et al. in 2015.[2] ITPase deficiency typically manifests in the early infantile period with developmental delay, microcephaly, epilepsy, cerebral visual impairment (CVI), axial hypotonia, spasticity and involuntary movements.[4] IUGR has also been reported in ITPase deficiency.[4] Our patient also had IUGR, profound developmental delay, microcephaly, refractory epilepsy, CVI and tone abnormalities.

Brain MRI in children with ITPase deficiency reveals diffusion restriction involving the cerebellar white matter, middle cerebellar peduncles, optic radiation, posterior limb of the internal capsule (PLIC), dentate nuclei, inferior colliculus, decussation of superior cerebellar peduncles and tegmental tracts.[5] Gray matter structures, such as globus pallidi and thalami, which have high myelin content, may also be involved. Diffusion restriction may be related to underlying active Wallerian degeneration.[5] Involvement of the anterior limb of the internal capsule, corpus callosum and cerebral white matter has been reported in older children with a variant in the *ITPA* gene. Cerebral atrophy, thinning of the corpus callosum

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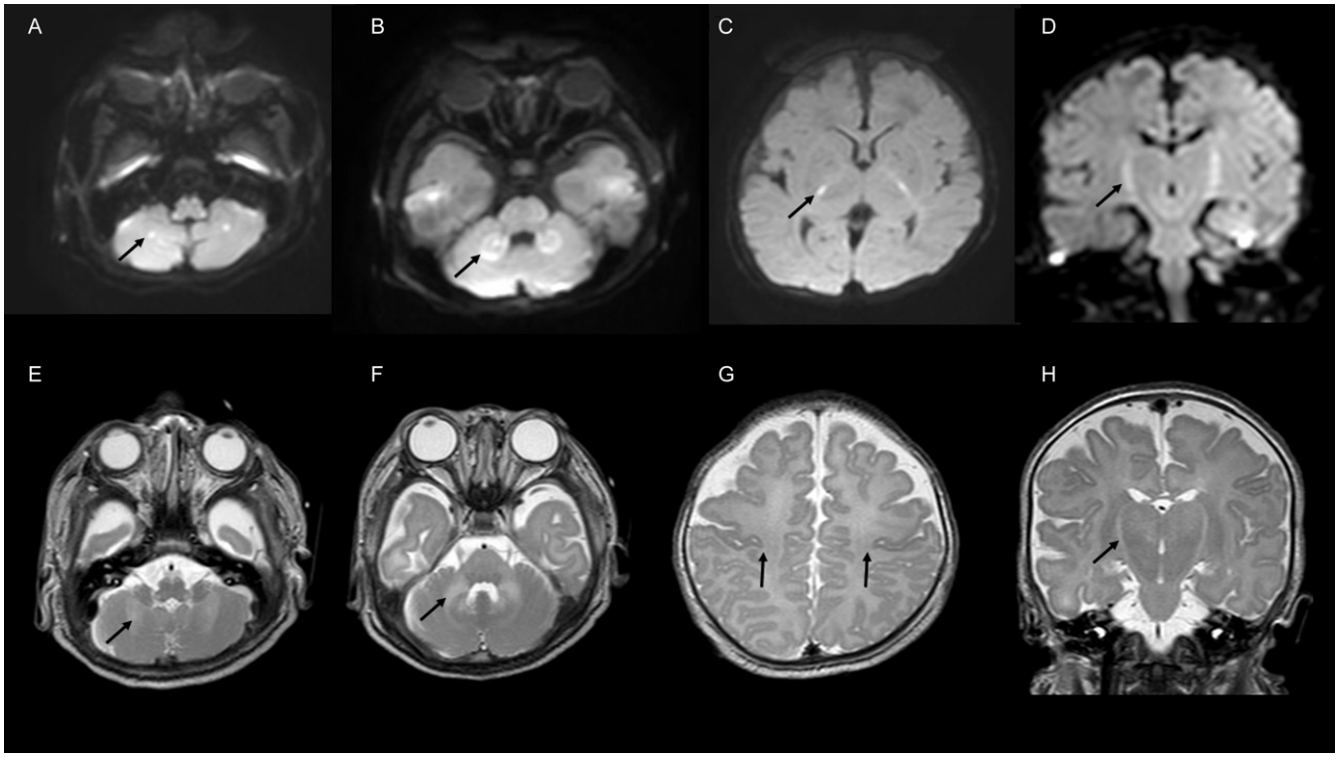


Figure 1. Brain MRI at 9 weeks of age. (A–C) Trace diffusion-weighted images (DWI) show diffusion restriction in the cerebellar white matter (black arrow), pyramids, dorsal medulla, dentate nuclei (black arrow) and posterior limb of the internal capsule (black arrow). (D) Trace DWI coronal images show diffusion restriction along the corticospinal tract (black arrow). The bright areas in trace DWI were dark on apparent diffusion coefficient (ADC) maps (not shown). (E–F) T2 axial images show hyperintensity in the cerebellar white matter (black arrow), pyramids, dorsal medulla, brachium pontis (black arrow) and dentate nuclei. (G) T2 axial images show a lag in myelination in the perirolandic white matter (black arrows). (H) T2 coronal images show hyperintensity along the bilateral corticospinal tract (black arrow).

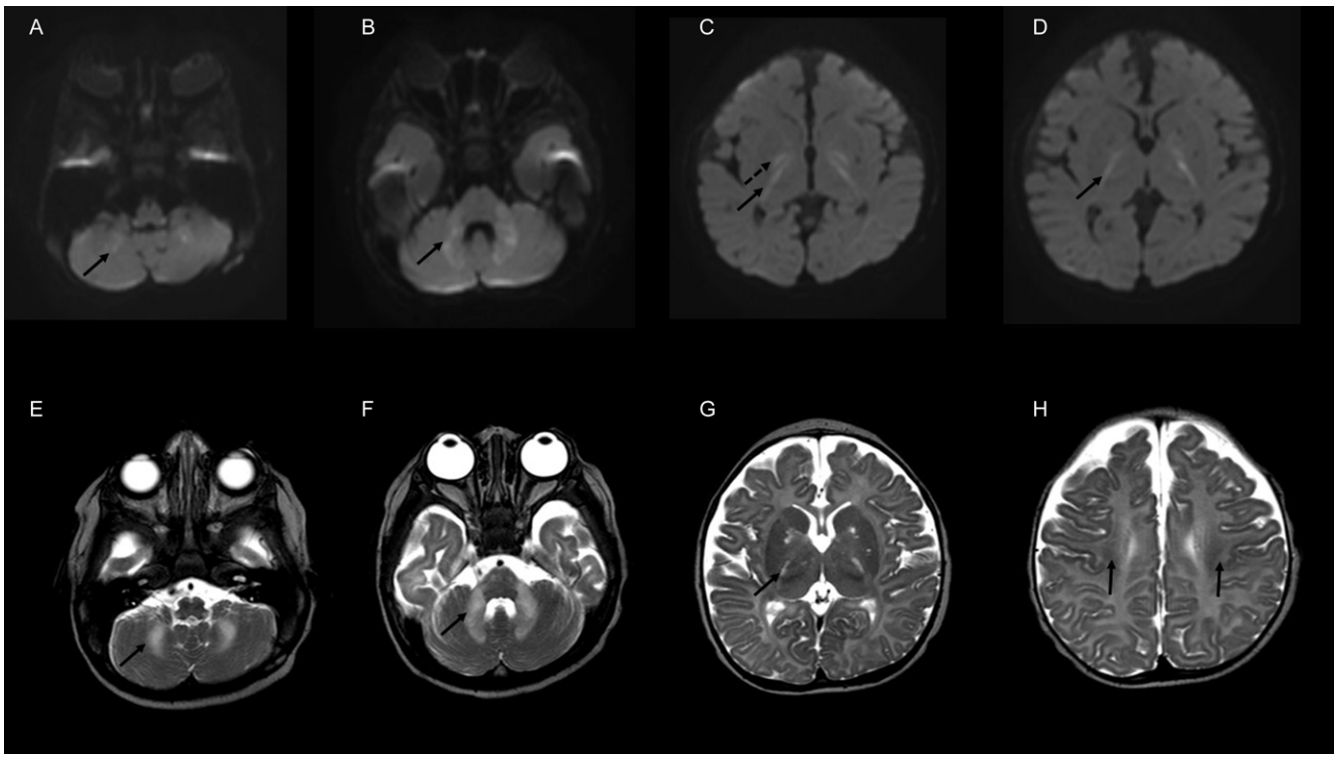


Figure 2. Brain MRI at 5 months of age. (A–D) Diffusion-weighted images (DWI) show persistent near-symmetrical diffusion restriction in the dorsal medulla, cerebellar white matter (black arrow), middle cerebellar peduncles (black arrow), globus pallidi (dashed arrow) and posterior limb of the internal capsule (black arrow). The bright areas in trace DWI were dark on ADC maps (not shown). (E–G) T2 axial images show hyperintense signal changes in the bilateral cerebellar white matter (black arrow), dorsal medulla, middle cerebellar peduncles (black arrow), posterior limb of the internal capsule (black arrow). (H) T2 axial images show a lag in myelination in the perirolandic white matter. Thinning of the corpus callosum was also noted (not shown).

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and delayed myelination are also observed in patients with a variant in the *ITPA* gene.[5] Our patient exhibited diffusion restriction in the cerebellar white matter, dentate nuclei, brainstem, PLIC and corticospinal tract and myelination lag at 9 weeks of age. A follow-up MRI at 5 months of age revealed persistence of diffusion restriction, thinning of the corpus callosum and myelination lag.

Non-ketotic hyperglycinemia is one of the closest imaging differentials associated with diffusion restriction in the PLIC.[4] Signal changes in the PLIC, cerebral white matter and hilus of the dentate nuclei are also observed in children with Krabbe disease, but diffusion restriction in the corticospinal tract is not observed.[2] Mitochondrial disorders can also mimic ITPA encephalopathy due to diffusion restriction and brainstem involvement.[2] ITPase deficiency should be considered in children with refractory seizures, microcephaly and diffusion restriction of early myelinating structures.

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