■ Clinical commentary

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Epileptic Disorders

ITPA-associated developmental and epileptic encephalopathy: characteristic neuroradiological features with novel clinical and biochemical findings

Meenal Garg[1], Jatinder Goraya[2], Gurpreet Kochar[3], Vivek Jain[4]

[1] Department of Paediatric Neurology, Surya Hospitals, Jaipur, India
[2] Pediatric Neurology, Department of Paediatrics, Dayanand Medical College and Hospital, Ludhiana, India
[3] Pediatric Neurology, Department of Paediatrics, SPS Apollo Hospitals, Ludhiana, India
[4] Pediatric Neurology, Department of Paediatrics, Santokba Durlabhji Memorial Hospital, Jaipur, India

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ABSTRACT

Developmental and epileptic encephalopathies (DEE) in children have an ever-expanding range of rare causes. Mutations in *ITPA* have been recently described as causative of DEE, but only a small number of patients have been reported so far. We describe two Indian children with novel variants in the *ITPA* gene. Both patients had characteristic, previously described, neuroradiological findings that helped us suspect this condition even before genetic evaluation. In addition, we present new and rarely reported clinical findings associated with this condition: migrating partial epilepsy, fever-triggered seizures, movement disorder including oculogyria and dystonic tremor. One of the patients also had high cerebrospinal fluid glycine levels. Both patients had drug-responsive epilepsy, in contrast to drug-resistant seizures in previously reported patients. These patients reiterate the utility of awareness of specific neuroradiological findings and subsequent genetic evaluation to help make a precise diagnosis. Our report also extends the clinical spectrum and provides insight into possible biochemical causes for the neuroimaging findings seen in this condition.

Key words: migrating partial epilepsy, movement disorder, hyperglycinaemia

VIDEO ONLINE

• **Correspondence:**
Vivek Jain
Paediatric Neurology,
Department of Paediatrics,
Santokba Durlabhji Memorial Hospital,
Jaipur, India
<vivek.jain@sdmh.in>
<vivekchildneuro@gmail.com>

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Developmental and epileptic encephalopathies (DEE) is a group of individually rare disorders characterized by early-onset severe epilepsy with developmental delay/decline [1]. DEE includes genetic disorders with varied clinical features, often creating a diagnostic challenge. Identification of aetiology, however, is important to determine optimum treatment and prognosis.

Mutations in the *ITPA* gene, encoding inosine triphosphate pyrophosphatase (ITPase), have been recently described to be causative of DEE [2]. Patients with this condition have specific neuroradiological changes, which can assist in early diagnosis. The likely cause of these changes, however, is unclear.

We here describe two patients with novel clinical features and biochemical changes to expand the phenotype and possibly explain the neuroradiological findings.

Patient 1

Patient 1 was the first child from a non-consanguineous relationship. From the early neonatal period, she was poorly

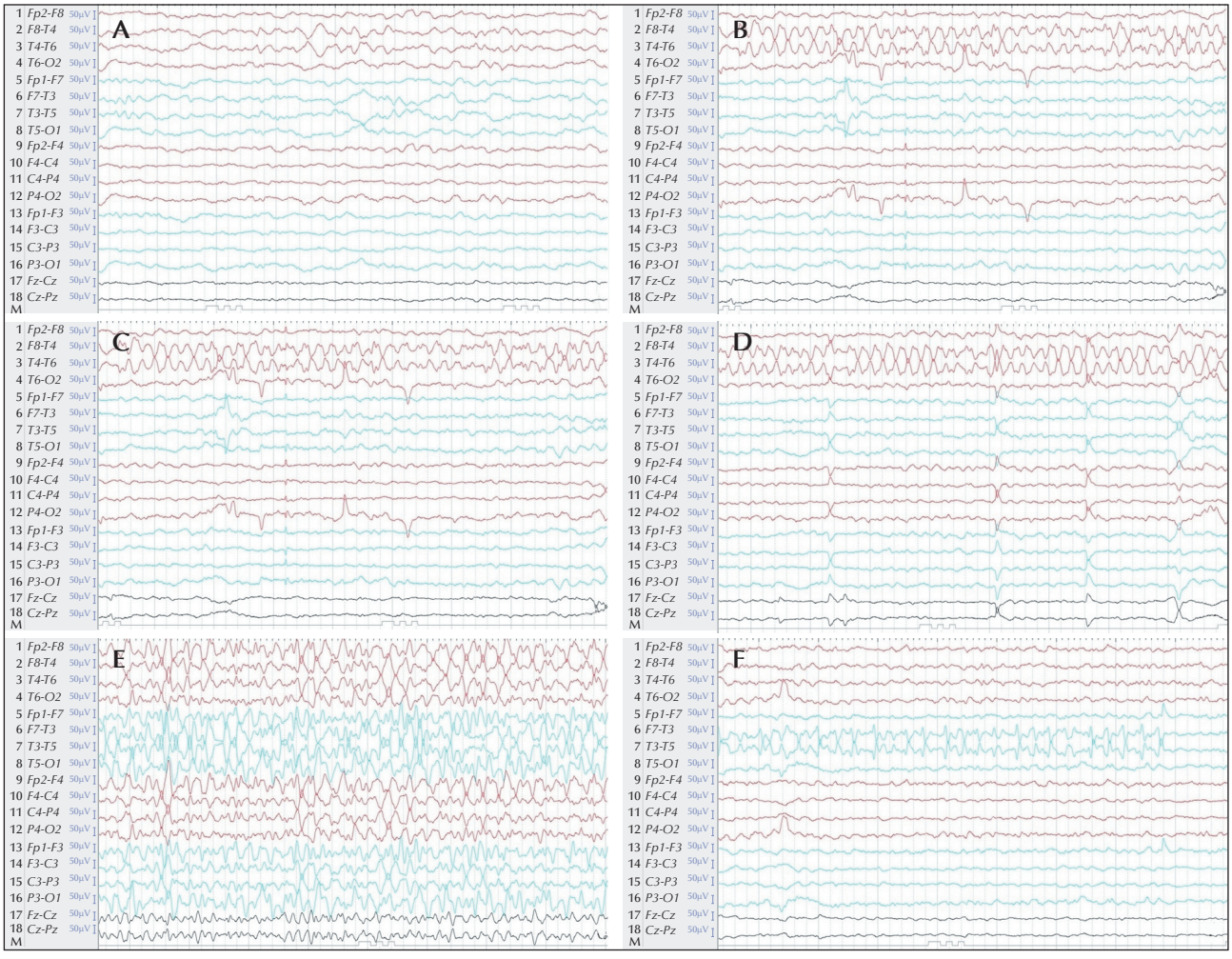
interactive and drowsy. She also had oculogyria episodes but without diurnal variation.

At four months of age, she had multiple episodes of afebrile tonic seizures, soon after her primary vaccination. Over the next month, she continued to have episodes of tonic seizures as well as oculogyric events.

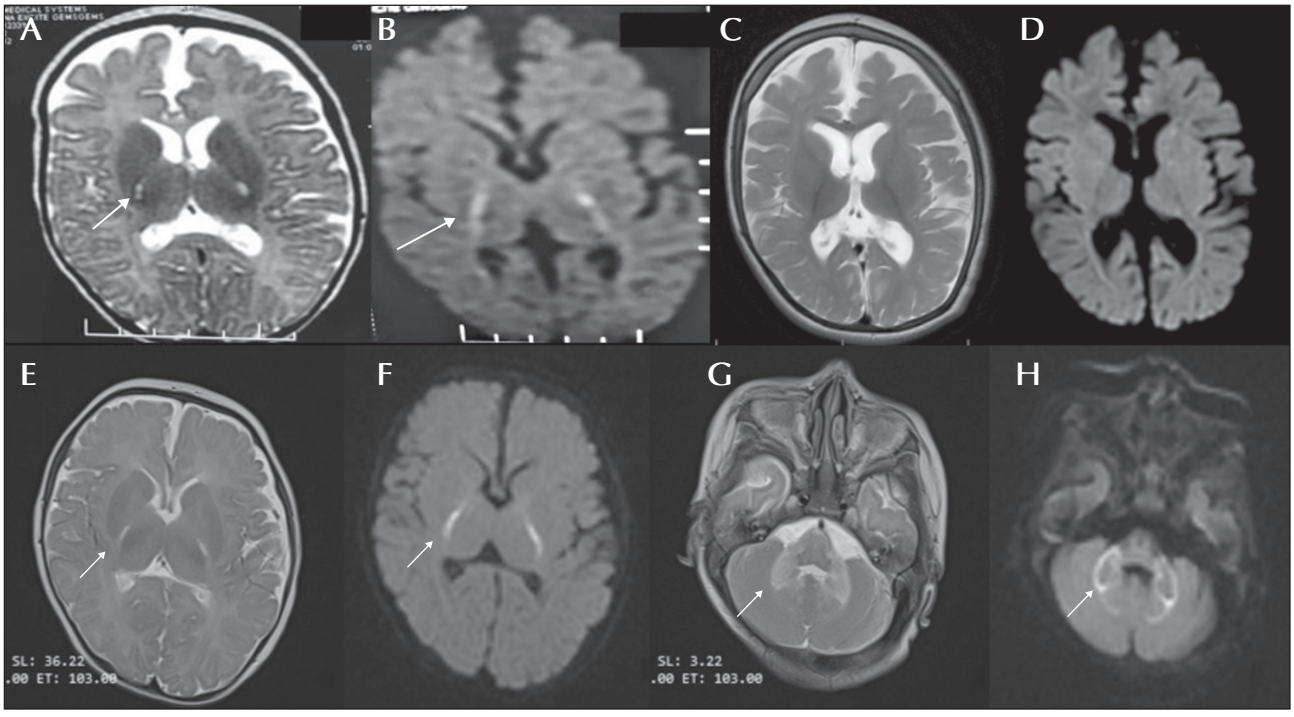
A month later, she started to have new types of seizures along with ongoing tonic events. In a single episode, these were brief focal motor convulsive seizures that could migrate to either side. She had many such events daily. In the interim, there had been no developmental progress.

At this time on her initial assessment, she had significant failure to thrive. She was difficult to arouse with poor visual and social interaction. She also had central hypotonia, limb dyskinesia and intermittent dystonic tremor.

Electroencephalography (EEG) showed a relatively well-preserved interictal background (*figure 1A*).



■ **Figure 1.** A prolonged EEG recording (sensitivity: 10 µV; low filter: 1 Hz; high filter: 70 Hz; paper speed: 30 mm/sec). (A) Normal awake interictal background with a mix of diffuse posterior 2-3-Hz high-amplitude delta activity with faster 4-5-Hz theta intermixed more anterior activity, with no persistent asymmetries. (B) Ictal onset from the right hemisphere associated with a change in background to rhythmic fast 4-4.5-Hz sharp-wave activity in the right mid-temporal region, which later slows down (C, D). (E) Ictal onset of a rhythmic sharp-wave activity at 4-5 Hz seen from the left hemisphere while slower activity is seen on the right hemisphere. (F) Slower sharp-wave activity at a frequency of 3-4 Hz seen in the left temporal region, which later resolves in the same epoch while the right hemisphere shows normal baseline activity.



■ **Figure 2.** (A-D) Patient 1: T2 axial and diffusion-weighted images showing T2 hyperintensity in the posterior limb of the internal capsule (arrow [A]) with diffusion-restriction (arrow [B]) of the same region. At 18 months of age, brain MRI in the same patient shows diffuse cortical atrophy on T2 axial image (C) and resolution of diffusion-restriction in the previously involved area (D). C-H) Patient 2: T2 axial and diffusion-weighted images showing T2 hyperintensity in the posterior limb of the internal capsule (E) and dentate nucleus (G) with diffusion-restriction in the same areas (F, H).

During a seizure, there was an ictal rhythm initially originating from the right hemisphere (*figure 1B-D*), clinically correlating with left side oromotor clonus, left arm posturing and bilateral eyelid blinking. Later, in the same event (*figure 1E*), there was a left-hemispheric-onset ictal activity. This was associated with a brief right side oro-motor clonus. The oculogyric episodes (*video sequence*) did not have any ictal correlate.

Migrating partial epilepsy of infancy, neurotransmitter disorders and sodium channelopathy associated epilepsy were considered as clinical differentials.

Metabolic investigation including blood lactate, ammonia and tandem mass spectrometry (TMS) was non-contributory. Cerebrospinal fluid (CSF) neurotransmitters could not be analysed, although serum prolactin was normal.

Magnetic resonance imaging (MRI) of the brain (*figure 2A, B*) showed T2 and fluid-attenuated inversion recovery (FLAIR) hyperintensities with diffusion restriction in the posterior limb of the internal capsule (PLIC) and red nucleus, suggestive of vacuolating myelinopathy.

Because of her poor interaction, neonatal-onset encephalopathy, severe epilepsy and suggestive MRI, a clinical possibility of non-ketotic hyperglycinaemia (NKH) was considered. Both CSF and plasma glycine were elevated (CSF glycine: 162 µmol/L [normal: 2-14 µmol/L]); plasma glycine: 651 µmol/L [normal: 166-330 µmol/L]) with a CSF:plasma glycine ratio >0.06. Treatment with oral sodium benzoate and dextromethorphan was instituted and trio whole-exome sequencing (WES) was requested.

The seizures were treated with phenobarbitone, topiramate, and later levetiracetam. Oculogyria responded to levodopa (1 mg/kg/day, escalated gradually to 4 mg/kg/day).

WES revealed a novel homozygous missense variation in exon 4 of the *ITPA* gene [(ENST00000380113.3: c.253G>A (p. Gly85Ser)]. The same variant was

detected in a heterozygous state in both the asymptomatic parents.
Ophthalmologic and cardiac evaluation, performed as part of the evaluation of *ITPA*-associated DEE, was normal.
At the last follow-up visit (24 months of age), she had significant global developmental delay, central hypotonia and dyskinesia, but improving visual and social interaction (*video sequence*). On follow-up MRI (*figure 2C, D*), there was resolution of vacuolar myelinopathy, although with diffuse cortical atrophy. The epileptic seizures were controlled on the same three anti-seizure medications, except for clusters of self-resolving breakthrough seizures during febrile illnesses at 15 and 18 months of age.

Patient 2

Patient 2 was the first child of a consanguineous relationship (first cousins). On Day 2 of life, he had a focal convulsive seizure which was attributed to mildly low serum calcium levels. Over the next three months, he had not acquired any developmental milestones and also had significant failure to thrive.
We saw him at four months of age following recurrence of his seizures. The onset of these brief seizures was associated with behavioural arrest followed by dystonic posturing of one arm and leg and then clonic jerking of the same side. On examination, he had microcephaly and failure to thrive with central hypotonia. He also had limited social and visual interaction.
Metabolic investigations including ionic calcium were normal. EEG showed a normal interictal background but with multi-regional spikes, especially in central and temporal regions from both hemispheres, seen independently. Ictal events could not be recorded on EEG. However, his seizures were easily controlled on a single medication (levetiracetam).
Brain MRI revealed symmetric T2 and FLAIR hyperintensities with diffusion restriction in the PLIC (*figure 2E, F*), similar to the first patient, also in the brainstem, cerebellar white matter and dentate nuclei (*figure 2G, H*). The similar imaging findings, as in our first patient, prompted us to consider *ITPA*-associated DEE in this child also.
WES revealed a likely pathogenic homozygous novel indel variant in exon 8 of the *ITPA* gene (ENST00000380113.3: c.517_519delinsGA [p. Asn173-GlufsTer51]). The parents were heterozygous asymptomatic carriers of the same mutation.
Eye examination and echocardiography were normal in this patient. At the last follow-up visit at seven months of age, he continued to have significant developmental delay, central hypotonia and microcephaly. However, there was no seizure recurrence on levetiracetam.

Discussion

For children presenting with DEE, there is a wide range of possible diagnoses. Owing to the wider availability of next-generation sequencing (NGS), new genetic causes, such as *ITPA* gene variants, are being increasingly identified [3]. Prior to this report, around 14 patients with biallelic *ITPA* mutations have been described [2, 4-7].
The *ITPA* gene encodes the ITPase enzyme, which plays an important role in purine metabolism [8, 9]. *ITPA* knockout mice show growth retardation, cardiac and neurologic abnormalities and early death [10].
A relatively consistent phenotype, as seen in our patients with *ITPA* variants, is early-onset developmental delay, failure to thrive, microcephaly, epilepsy and central hypotonia [2, 4-7]. However, our patients presented with some novel clinical features: oculogyric events and increased CSF glycine levels in one patient, and good seizure control in both with levetiracetam. Migrating epilepsy of infancy as a phenotypic presentation, reported in one of our patients, has also only been rarely reported [11].
One of our patients had post-vaccination onset of seizures. The post-vaccination onset of epilepsy with later fever-triggered seizures led us to consider *SCN1A*-related epilepsy, as a differential. Post-vaccination febrile seizures, followed later by afebrile seizures, have been previously reported in one case of *ITPA*-related DEE [5]. Thus, *ITPA*-associated DEE, among other genes with similar presentation, could be included alongside fever-triggered seizures as one of the considerations in patients with suspected genetic epilepsies [12].
In both our patients, the epilepsy was well controlled with ASMs. However, this was an unusual course compared to previously described patients, who have consistently been reported to have drug-resistant epilepsy [2, 7]. This can also help to counsel parents who otherwise are likely to be given a uniformly bad prognosis regarding seizure control.
As seen in our first patient, movement disorder, especially oculogyria and dystonic tremor, has not been previously reported. This phenomenon was so prominent that neurotransmitter disorders were also strongly considered in this patient. The oculogyric events responded well to levodopa, raising the possibility of a secondary neurotransmitter deficiency state for this condition.
None of our patients had ophthalmologic or cardiac abnormalities, reiterating that these are not essential clinical features in this condition.
Neuroradiological findings in *ITPA*-associated DEE are characteristic and have been extensively

reported before *(supplementary material)*. Kevalam *et al*. [2] explained these findings by hypothesizing that neuronal degeneration of early myelinating tracts leads to vacuolar myelinopathy. It is also possible that vacuolar myelinopathy might represent an ictal insult. However, the absence of similar changes in other DEEs goes against this hypothesis. Hence, there may be other underlying pathophysiological mechanisms.

One of our patients was surreptitiously shown to have significantly high CSF glycine. Interestingly, patients with NKH also have similar neuroradiological changes (vacuolar myelinopathy), as seen in *ITPA*-associated DEE [13]. This raises the possibility of the ITPase enzyme playing a role in the glycine degradation pathway, leading to elevated glycine levels and resultant vacuolar myelinopathy, in both these conditions. However, this finding will need further validation. As raised CSF glycine could just be a transient increase due to ongoing frequent seizures, this finding needs further validation. A follow-up CSF glycine level during the seizure-free period was unfortunately not available to confirm this possibility.

Another interesting aspect is the role of neuroradiology and NGS in confirming the correct diagnosis. Various differentials were considered based on clinical, MRI and biochemical findings. However, genetic evaluation confirmed the diagnosis in the first patient and helped us to consider the same possibility in the second patient, earlier.

In conclusion, our report adds two patients with novel clinical features, biochemical findings, and new mutations to the expanding pool of *ITPA*-associated DEE. Recognition of characteristic neuroradiological features can help early genetic testing, eliminating mimics, and facilitating appropriate genetic counselling for the family. ■

Supplementary material.
Supplementary data and summary slides accompanying the manuscript are available at www.epilepticdisorders.com.

Disclosures.
The authors declare no competing interests.

Consent.
Written informed consent was obtained from the parent(s) of the patients for publication of patient data and accompanying images and video. A copy of the written consent is available for review by the Editor of this journal.

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Legend for video sequence

The initial part of the video shows Patient 1 at five months of age with oculogyric episodes during prolonged video-EEG monitoring without ictal correlate. Dystonic tremors can also be seen in the video. In the later part of the video, at 24 months of age, she continues to have significant global delay, central hypotonia and dyskinesia but with improved visual and social interaction.

Key words for video research on www.epilepticdisorders.com

Phenomenology: dyskinesia (non-epileptic)
Localization: not applicable
Syndrome: not applicable
Aetiology: genetic disorders

TEST YOURSELF

(1) What are the characteristic clinical features of developmental and epileptic encephalopathies (DEE)?

A. Developmental regression and epilepsy
B. Autism spectrum disorder and refractory epilepsy
C. Early-onset developmental delay/decline with epilepsy

(2) What is the most helpful investigation to suspect *ITPA*-associated DEE?

A. Elevated CSF glycine
B. Characteristic neuroradiological findings
C. Migrating seizures on EEG

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com.