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Epileptic Disorders

CLINICAL VIGNETTE

Recurrent status epilepticus and severe bifrontal hypometabolism in PGAP1-related neurodevelopmental disorder

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Glycophosphatidylinositol (GPI) plays an anchoring role, linking cell membranes to proteins.[1] GPI biosynthesis involves >20 proteins, including phosphatidylinositol glycans (PIGs) and post-GPI attachment to proteins (PGAPs).[1] Pathogenic variants in genes encoding PIGs and PGAPs are associated with global developmental impairment and congenital malformations.[1] *PGAP1* encodes an enzyme involved in GPI biosynthesis through the catalysis of GPI inositol deacylation.[2] Eight patients with PGAP1-related disorders have been described from five families, all with biallelic apparent loss-of-function variants.[3–7] The clinical phenotype involves severe to profound developmental impairment, with spastic quadriparesis, feeding problems, microcephaly, cerebral visual impairment, dyskinesia, and brain atrophy variably reported. Seizures were only reported in 2/8.[4,5] We present two brothers with PGAP1-related disorder, including the proband with recurrent status epilepticus and severe bifrontal positron emission tomography (PET) hypometabolism.

A Pakistani male was born at term via caesarean section following a pregnancy complicated by gestational diabetes, preeclampsia, polyhydramnios, and antenatal diagnosis of congenital diaphragmatic hernia (CDH; Figure 1D). CDH repair was done at 72 h of life and was uncomplicated.

At age 6 months, recurrent status epilepticus developed with seizures involving unresponsiveness, writhing, and unusual eye movements, lasting >60 min and requiring emergency medication to stop. In adolescence, seizure semiology changed to involve tachycardia, unilateral head and eye deviation, and eventually bilateral tonic–clonic convulsions. These events lasted ~2 min but occurred in clusters that almost always required emergency medications, such as diazepam, midazolam, or phenytoin, to stop. This pattern continued for many years despite the sequential addition of clonazepam, clobazam, lamotrigine, and levetiracetam. The family used rectal diazepam 20 mg as initial status epilepticus treatment before calling an ambulance. Seizure severity improved in late adolescence on lamotrigine 200 mg bid, levetiracetam 1500 mg bid, clobazam 10 mg morning, 35 mg evening, and clonazepam 1.5 mg morning, 2.5 mg evening. When last seen at age 19 years, he had ~1 seizure/month but no longer had clusters or required rescue medication.

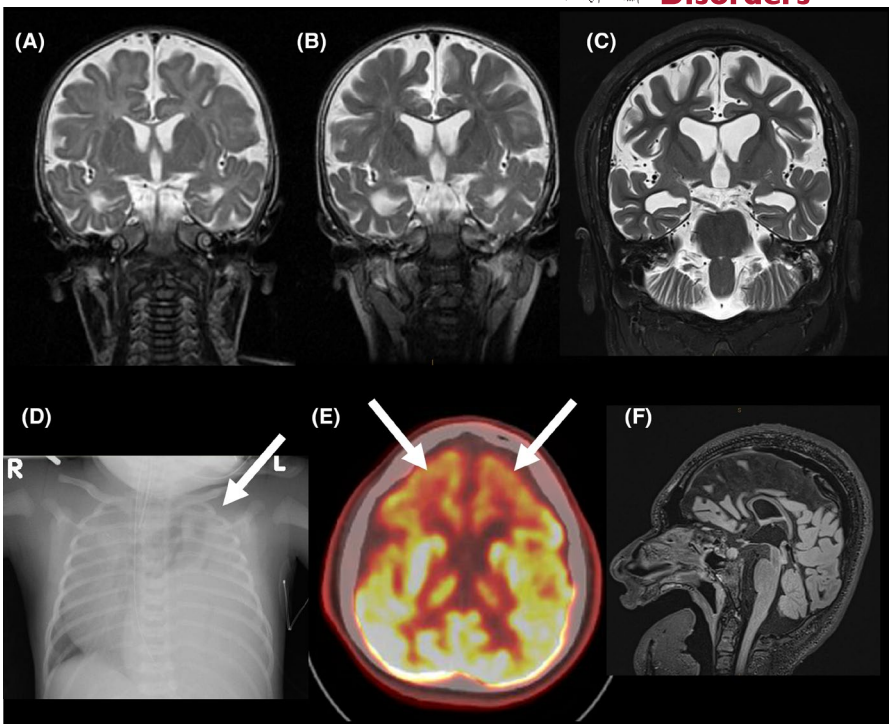

FIGURE 1 Brain atrophy in the proband is demonstrated with coronal T2 brain MRI showing progressive brain volume loss in images taken at (A) 5 months, (B) 18 months, and (C) 15 years of age. In (D), a chest x-ray taken at ~24 h of life shows a left congenital diaphragmatic hernia. Gas-containing bowel loops can be seen in the left hemithorax (arrow). The left lung is not seen, and the right lung is compressed by the left diaphragmatic hernia. In (E), brain PET at age 15 years shows severe hypometabolism in the frontal regions (arrows). The cerebellum was relatively unaffected by atrophy, as shown in the sagittal FLAIR sequence at age 15 years (F).

Past medical history was notable for sialorrhea, constipation, scoliosis, right orchidopexy, and dysphagia requiring gastrostomy tube insertion. He had obstructive sleep apnea requiring tonsillectomy/adenoidectomy but still required bilevel positive airway pressure treatment. He had cortical visual impairment and profound global developmental impairment with spastic quadriparesis. He never walked, could not hold objects, was nonverbal, and did not show a clear capacity to understand words or gestures.

His parents were first cousins from Pakistan and had two other sons, one healthy with normal intelligence and a second with a phenotype very similar to the proband, including profound intellectual disability (ID), epilepsy, and microcephaly (but not CDH).

On examination, the proband had deep-set eyes and a high-arched palate. Appendicular tone was increased, and deep tendon reflexes were diffusely brisk. Brain MRI showed progressive volume loss (Figure 1A–C). Brain PET showed severe bifrontal hypometabolism (Figure 1E). EEG typically showed mildly slow background with multifocal spikes and sharp waves. During prolonged video EEG at age 15 years, focal seizures were recorded, originating independently from either hemisphere. A clinical gene panel (Blueprint Genetics) identified a novel homozygous intragenic *PGAP1* deletion, c.(1861+1_1862+2)_(1952+1_1953-1)del, estimated to cover the region chr2:197712564–197712864, affecting exon 21; however, exact breakpoints could not be determined. Both parents were heterozygous for the deletion, and the proband's brother with profound ID was also homozygous. The deletion is classified as pathogenic by ACMG criteria due to absence from control databases (PM2), predicted null variant with loss of function effect (PVS1), and familial segregation (PP1).[8]

This report clarifies the epilepsy phenotype that may arise with *PGAP1* pathogenic variants and demonstrates that severe frontal hypometabolism can occur. While this finding indicates severe bilateral frontal lobe dysfunction, the underlying cause is unclear. The findings may also extend the phenotypic spectrum for PGAP1-related disorders to include CDH. The latter is unlikely to be coincidental, given that CDH is rare (1 in 3000 live births).[9,10] CDH involves incomplete diaphragm development with consequent herniation of abdominal viscera into the chest cavity. It requires urgent medical intervention at birth, as the consequent respiratory distress is life-threatening. Both genetic and environmental factors are believed to play a role in CDH. In addition to copy number variants, CDH has been associated with at least 16 genes,[11] including some in the GPI-anchoring pathway including *PIGA, PIGW, PIGL*, *PIGV*, and *PIGN*.[12–17]

AUTHOR CONTRIBUTIONS

Samia Benabess: Data collection, writing – original draft. Kenneth A. Myers: Conceptualization, data collection, preparation of figures, writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

SB has no relevant disclosures. KAM is a site principal investigator for studies sponsored by Ultragenyx and LivaNova, and is a member of advisory boards for Jazz Pharmaceuticals and AS^{2}Bio.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

PATIENT CONSENT STATEMENT

Written consent for publication was obtained from the patients' parents.

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