Fumaric Aciduria: A Rare Cause of Refractory Epilepsy

Sir,

Inborn errors of metabolism (IEM) are a heterogeneous group of inherited disorders that may result from enzyme deficiencies or cofactor defects, leading to a block in the biochemical pathway. The age at onset and clinical manifestations are often variable. Though metabolic disorders are rare causes of epilepsy, seizures are frequently encountered in children with IEM.[1] Here, we describe a child with polymorphic seizures who was diagnosed to have fumaric aciduria. A five-year-old girl, first born to a third-degree consanguineous couple was brought for evaluation of developmental delay and seizures noticed from 18 months of age. Fetal hypokinesia was documented in the last trimester. The child was born at full term by normal vaginal delivery with a birth weight of 3370 g and had delayed cry at birth. She was hospitalized in the neonatal intensive care unit for poor feeding and lethargy. The child developed myoclonic and generalized tonic seizures from 18 months of age, refractory to antiseizure medications. She had partial head control, reaching for toys, babbling, and waving bye-bye at 18 months of age. There was history of gradual regression of milestones after the onset of seizures. Progressive spasticity of limbs, deterioration of vision, and episodic worsening of neurological symptoms with intercurrent illnesses were reported by the parents.

The anthropometric assessment revealed a weight of 17 kg (25th to 50th centile), length of 105 cm (3rd to 10th centile), and head circumference of 45.5 cm (microcephaly). Poor eye contact and poor visual fixation to light were observed. Fundus examination was normal. Bilateral alternate divergent squint, spastic quadriparesis, exaggerated deep tendon reflexes, extensor plantar responses, and orofacial dyskinesias were observed.

Brain magnetic resonance imaging (MRI) showed diffuse cerebral and cerebellar atrophy, extensive white matter volume loss, thinning of corpus callosum, hyperintense signal changes in periventricular and deep white matter, ex-vacuo dilatation of ventricles, brainstem volume loss, and dark thalami on T2-weighted (T2W) and fluid-attenuated inversion recovery (FLAIR) images, and lactate peak on magnetic resonance spectroscopy [Figure 1a-c]. Possibilities of neuronal ceroid lipofuscinosis (NCL), myoclonic epilepsy with ragged red fibers (MERRF), GM2 gangliosidosis, and sialidosis were considered.

An electroencephalogram (EEG) showed multifocal epileptiform activity with poorly formed sleep markers. Cerebrospinal fluid (CSF) lactate level was 4.8 mmol/L (normal range: 0.3–1.3 mmol/L). However, CSF glucose (patient value: 69 mg/dL; concomitant blood glucose of 116 mg/dL) and protein (patient value: 30 mg/dL; normal: 15–45 mg/dL) levels were normal. Arterial blood lactate, acylcarnitine profile, isoelectric focusing for transferrin, blood hexosaminidase, palmitoyl protein thioesterase, and tripeptidyl peptidase I levels were normal. Nerve conduction parameters were normal. However, urine organic acid analysis by gas chromatography-mass spectrometry (GC-MS) revealed an approximately ten-fold increase in the excretion of fumaric acid.

Considering a presumed diagnosis of fumarate hydratase (FH) deficiency, our patient was managed with antiseizure medications, mitochondrial cocktail, and also physical therapies. Genetic testing revealed a homozygous missense variant c.1048C>T in exon 7 of *FH* gene, (p.Arg350Trp, rs755436052) [transcript ID- ENST00000366560 with genomic coordinate hg19- *GRCh37* chr1:241667402], classified as pathogenic by Intervar (https://wintervar.wglab.org/results.php). This variant, which has not been previously described in either Human Gene Mutation Database (HGMD) or 1000 Genomes database, is predicted to be damaging based on in silico analysis as it causes a change in a conserved residue. The allele frequency in both Exome Aggregation Consortium (ExAC) and the Genome Aggregation Database (genomAD) exomes is 0.00002. Both parents were found to be heterozygous for this variant.

Fumaric aciduria (FA) is a rare autosomal recessive disorder caused by the deficiency of fumarase or FH.[2] FH is an enzyme of the citric acid cycle responsible for

the conversion of fumarate to malate.[3] The citric acid cycle and the site of block in FH deficiency are depicted in Figure 2. Although FA was first described in siblings with predominant language delay, the first confirmed case of FH deficiency was documented in an infant with progressive encephalomyopathy.[2,4] The clinical presentation of FA has expanded to a variable phenotype that includes global developmental delay, microcephaly, macrocephaly, seizures, hypotonia, feeding difficulties, failure to thrive, vomiting, lethargy, and visual disturbances.[3] The phenotypic variability may be possibly due to the extent of residual enzyme activity present.[5] Other clinical features include hepatic involvement, encephalopathy, hypotonia, movement disorder, and symptoms of brainstem dysfunction.[3,6,7] Our patient had developmental delay, polymorphic seizures, and progressive neurological deterioration. Antenatal and neonatal abnormalities reported in FA are polyhydramnios, fetal hypokinesia, prematurity, intrauterine growth retardation, increased fetal weight, and neonatal polycythemia.[3,7] Fetal hypokinesia was observed in our case. Refractory seizures were the predominant feature in our patient; however, patients with FH deficiency may manifest with or without seizures.[3,8]

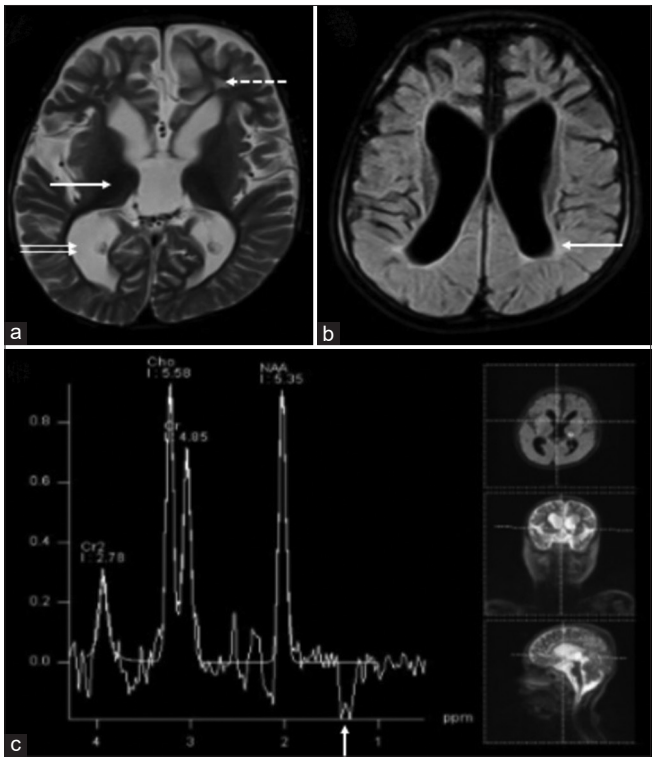

Figure 1: (a) MRI brain: T2 axial images show diffuse cortical atrophy, exvacuo dilatation of ventricles (white double arrows), dark thalami (white single arrow), white matter signal changes (white dotted line). (b) T2 FLAIR image show hyperintense signal changes in the periventricular white matter (white arrow). (c) MRS shows an inverted lactate peak at 1.3 ppm (white arrow)

Imaging findings in FA include underoperculization of sylvian fissure, prominent lateral ventricles, polymicrogyria, white matter volume loss, choroid plexus cyst, hypoplasia of corpus callosum, brainstem hypoplasia, hypomyelination, and heterotropia.[3,7] The proposed postulates for cortical malformations are energy depletion and toxic effects, resulting from increased fumaric acid during neurogenesis.[7] The constellation of imaging findings observed in our patient such as cerebral and cerebellar atrophy, dark thalami, and hyperintense signal changes in white matter have been described in children with lysosomal storage disorders such as neuronal ceroid lipofuscinosis, GM1 gangliosidosis, GM2 gangliosidosis, and Krabbe disease.[9]

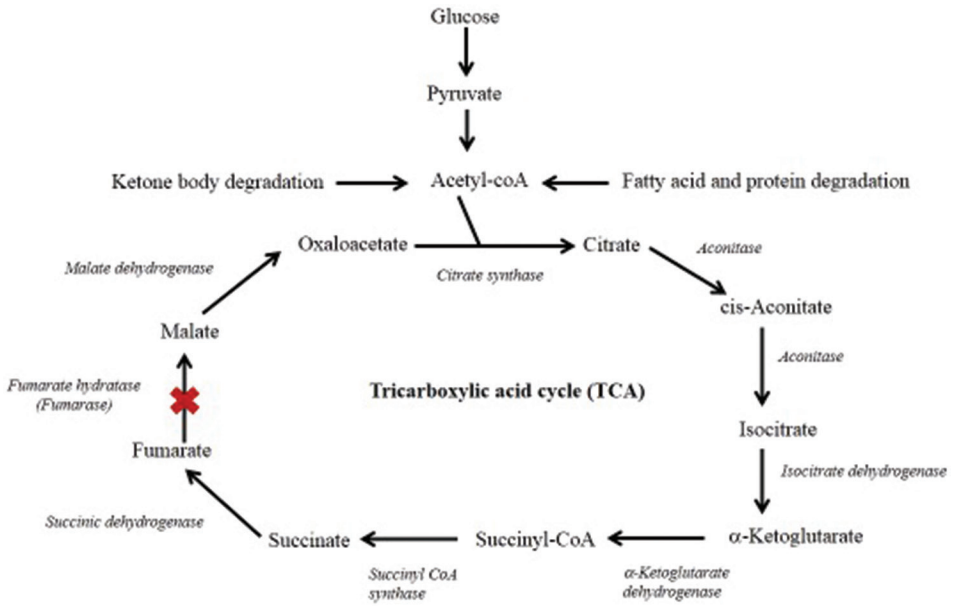

Figure 2: Citric acid cycle. The site of block in fumarase deficiency is depicted by red X

Elevated CSF lactate, lactate peak on magnetic resonance spectroscopy (MRS), urinary excretion of fumaric acid, and a likely pathogenic variant in the *FH* gene led us to a diagnosis of FA. While lactic acidemia is a consistent feature in defects involving other enzymes of the TCA cycle, a rise in blood lactate level is usually observed only in the terminal stage of FA.[10] Our patient had a normal blood lactate level at diagnosis, although the CSF lactate level was high. This suggests a possibility of an alternate metabolic pathway for fumarate metabolism in tissues other than the brain.[10] The cytosolic form of FH processes fumaric acid derived from argininosuccinate in the urea cycle and adenylosuccinate from purine and phenylalanine metabolism, whereas the mitochondrial form plays an integral role in the citric acid cycle, converting fumarate to malate.[3] A review of urine organic acid patterns in patients with FA revealed increased urinary excretion of fumaric acid with more modest increases of succinic acid and 2-ketoglutaric acid although some patients, including the case presented here, had isolated urinary fumaric acid excretion.[3]

All types of mutations in the FH gene (*FH*) have been identified in a patient with FH deficiency.[3,11] Our patient harbored a homozygous pathogenic missense variant in the exon 7. So far, no genotype-phenotype correlations have been established for this disorder. Management of FA is usually supportive, and seizures are usually difficult to control. Although most patients succumb in infancy or early childhood, those with a milder phenotype may survive.[6,7] FA is a rare IEM with variable clinical presentation. Children with FA may manifest with refractory seizures and hence, FA should be considered in the etiology list of metabolic epilepsies.

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Conflicts of interest

There are no conflicts of interest.

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