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CLINICAL BRIEF

ADSL Deficiency – The Lesser-Known Metabolic Epilepsy in Infancy

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Abstract
Adenylosuccinate lyase deficiency is a rare inherited disorder of purine metabolism causing severe neurological impairment ranging from early-onset neonatal epileptic encephalopathy to progressive psychomotor retardation and autism in later life. Diagnostic workup involves the measurement of toxic succinyl purines in body fluids and gene sequencing. The authors describe a 13-mo-old girl with compound heterozygous variants in the *ADSL* gene, presenting as early-onset seizures, severe neurological impairment, development delay, and hypotonia. Neuroimaging revealed cerebral atrophy, delayed myelination and diffusion restriction in bilateral basal ganglia, thalamus and periventricular white matter. The present case highlights ADSL deficiency as a rare cause of metabolic epilepsy that needs timely recognition and prevention of unnecessary investigations.

Keywords Adenylosuccinate lyase deficiency · Metabolic epilepsy · Encephalopathy · IEM · Epilepsy

Introduction

Adenylosuccinate lyase (ADSL) deficiency is a rare, autosomal-recessive defect of purine metabolism, causing metabolic epilepsy. Less than 100 cases have been described until now, and the prevalence is 1 in 1.25 million [1]. The authors describe a 13-mo-old girl with ADSL deficiency and characteristic neuroimaging findings.

Case Report

A 13-mo-old girl, born to non-consanguineous parents, presented with recurrent seizures from day 45 of life. The initial seizures were focal-onset, clonic type of motor seizures followed by generalized-onset, tonic-clonic type of motor seizures by 3–4 mo of age, and flexor type of epileptic spasms by 15 mo of age. She had developmental delay since infancy, and at 13 mo of age, she could hold her head partially, intermittently open hands, vocalize, and responded intermittently to her parents. The perinatal period was uneventful. Family history was not contributory. On examination, she had microcephaly (head circumference 41 cm, −3.6 Z score), developmental age corresponding to 3–4 mo, poor visual tracking, generalized hypotonia, and brisk muscle stretch reflexes. The rest of the systemic examination was unremarkable. A clinical diagnosis of early infantile-onset epileptic encephalopathy secondary to a structural or metabolic/genetic cause was considered.

Magnetic resonance imaging (MRI) of the brain showed generalized atrophy and hypomyelination. The diffusion-weighted image and apparent diffusion coefficient showed diffusion restriction in bilateral basal ganglia and periventricular white matter (Fig. 1). Magnetic resonance spectroscopy in the index patient at TE 144 showed the presence of raised choline and reduced N-acetyl aspartate (Fig. 2).

The electroencephalograph showed a modified hypsarrhythmia pattern. Arterial pH, lactate, acylcarnitines, and amino acids in the blood, urinary organic acids, and cerebrospinal fluid levels of glucose, glycine, lactate, and pipecolic acid were normal. Clinical exome testing followed by Sanger confirmation revealed a compound heterozygous, pathogenic variation (c.701 + 1G > G/A and c.926G > G/A) in introns 6 and 9 of the *ADSL* gene. Parents were carriers for one

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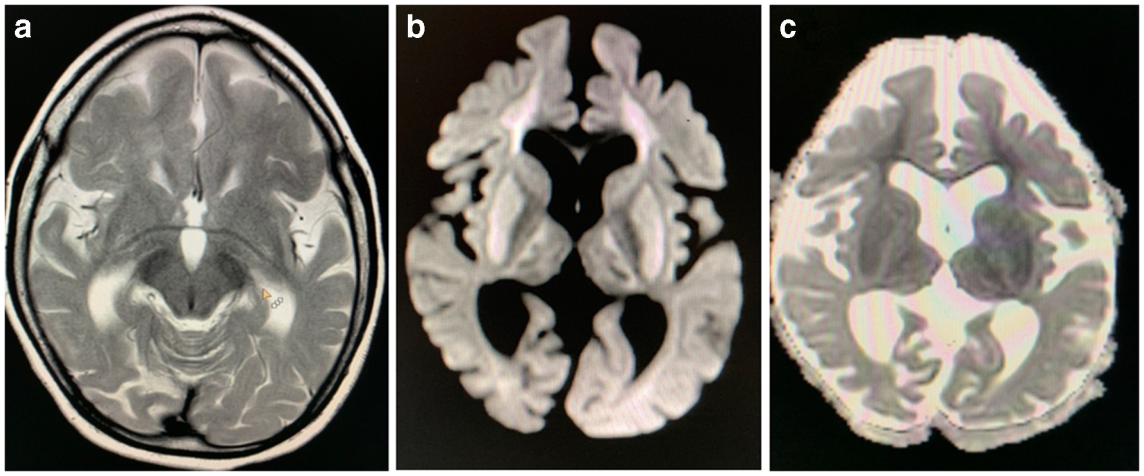

Fig. 1 Magnetic resonance imaging of the brain. **a** Axial T2-weighted section showing generalized atrophy and hypomyelination, **b** axial diffusion-weighted and **c** apparent diffusion coefficient showing diffusion restriction in bilateral basal ganglia and periventricular white matter

variation each. She was given supportive care. She is currently four years old. She has severe psychomotor retardation, microcephaly, brief intermittent seizures, secondary autistic features, and an abnormally exaggerated startle response.

Discussion

ADSL deficiency presents in three forms: (1) a fatal *'neonatal form'* with severe fetal hypokinesia, arthrogryposis, and respiratory failure, (2) an *'early-onset type 1'* form with recurrent polymorphic seizures, microcephaly, severe delay, and autistic features, and (3) a *'late-onset type 2'* form with mild to moderate intellectual impairment, language deficits and epilepsy [2]. Reported prenatal manifestations include reduced fetal movements, loss of fetal heart rate variability, microcephaly, and intrauterine growth retardation. Diffuse cortical atrophy and delayed myelination are the dominant neuroimaging findings. Additionally, there can be vermian cerebellar atrophy, corpus callosum agenesis, and lissencephaly [2, 3]. Interestingly, our case showed additional findings of extensive restricted diffusion in bilateral basal ganglia, thalami, and periventricular white matter. The diffusion restriction possibly signifies cytotoxic edema secondary to impaired energy metabolism or toxic effects of metabolic intermediates of the purine pathway [4]. MR spectroscopy in ADSL deficiency typically may show the presence of a succinyladenosine (S-Ado) signal at 8.3 ppm and succinyl amino-imidazole carboxamide riboside (SAICar) signal at 7.5 ppm [5]. Although the authors could not assess for the S-Ado and

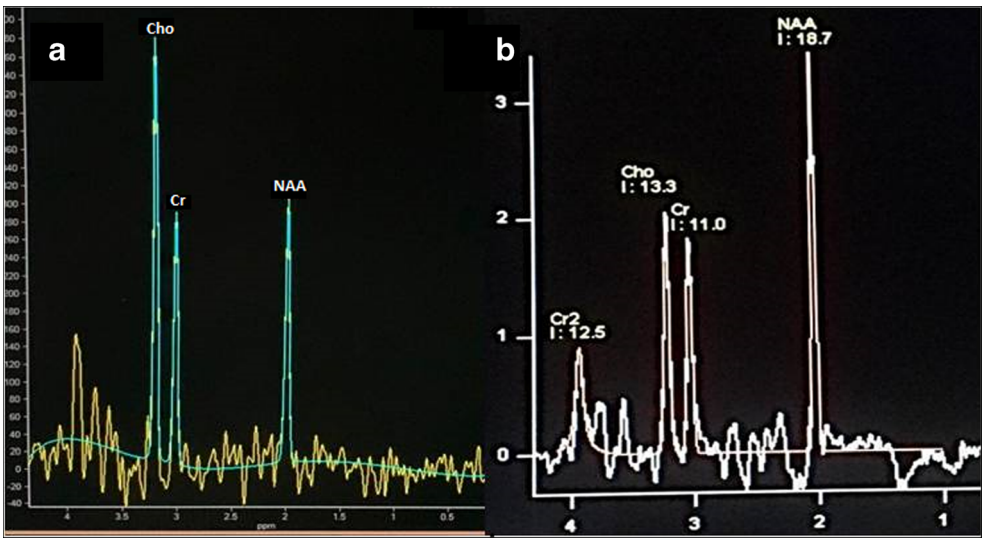

Fig. 2 Magnetic resonance spectroscopy of the brain. **a** Spectroscopy in the index patient at TE 144 shows the presence of raised choline and reduced N-acetyl aspartate. **b** A normal spectroscopy at 1.5 y of age for comparison

SAICar peaks in their case due to limited spectroscopy, the presence of dominant choline and reduced N-acetyl aspartate point towards an underlying purine metabolic defect. N-acetyl aspartate is present only in neurons, axons and dendrites [6]. It is a biomarker for neuronal integrity and its reduction reflects parenchymal or specifically, neuronal damage. Choline, on the other hand, is a component of cell membranes and neurotransmitters. A high choline reflects increased cellular proliferation, membrane turnover or inflammation [6].

The clinical features in ADSL deficiency are attributed to the toxic effects of succinylpurines [5]. Biochemical measurements of S-Ado and SAICar in body fluids corroborate the diagnosis but are not routinely available [5]. Hence, genetic analysis forms the basis of the diagnosis and prenatal counseling of such rare inborn errors of metabolism. D-ribose increases the availability of phosphoribosyl transferase (a substrate for purine biosynthesis) and has been occasionally tried [7]. Management is mainly supportive.

The basal ganglia are highly metabolically active and hence, often the target of toxic and metabolic insults. Bilateral symmetric, diffuse abnormalities commonly indicate a systemic or metabolic cause, whereas unilateral, asymmetric or focal abnormality indicates an infectious, vascular or neoplastic cause [8]. A prominent diffusion restriction in the basal ganglia is seen in acute metabolic insults such as hypoglycemia, osmotic myelinolysis or hyperammonemia in hepatic decompensation or urea cycle defect, toxicity of respiratory chain metabolic toxins such as carbon monoxide, methanol, and cyanide, inherited metabolic defects such as Wilson disease, thiamine deficiency, metabolic strokes in organic acidemias, Leigh disease, and severe hypoxic ischemic encephalopathy. ADSL deficiency adds to the list of these causes with intense basal ganglia diffusion restriction.

The common metabolic and genetic causes of epilepsy presenting from birth till one year of age include pyridoxine pathway defects [including pyridoxine dependent epilepsy, pyridox(am)ine-5′-phosphate oxidase deficiency, folinic acid-responsive seizures and defects in pyridoxal phosphate-binding proteins], biotin pathway defects (biotinidase and holocarboxylase synthetase deficiency), amino-acid pathway defects (including glycine encephalopathy, serine biosynthesis defects, molybdenum cofactor and sulfite oxidase deficiency, maple syrup urine disease), transportopathies (glucose transporter defects, Menkes, biotin thiamine responsive basal ganglia disease), organic acidemias, urea cycle defects, tetrahydrobiopterin deficiencies and the rare presentations of organelle-based disorders such as congenital form of neuronal ceroid lipofuscinosis. As a first step in the diagnostic evaluation of such cases, a magnetic resonance imaging is done to look for structural insults in the brain. The second step should include metabolic screening based on the results of first-tier tests such as glucose, pH, ammonia, lactate, and ketones. A cerebrospinal fluid level is needed to look for glycine and glucose levels. A trial of vitamins in adequate doses is warranted in all cases with drug-refractory epilepsy/epileptic encephalopathies at all ages, as the vitamin-responsive epilepsies are treatable. Genetic testing can do a final confirmation.

Authors' Contributions AB: Patient management, literature review and initial draft preparation; VB: Manuscript preparation and radiological data interpretation; GD: Manuscript preparation and interpretation of biochemical data; AKS: Patient management and manuscript preparation, AGS: Clinician in charge, critical review of the manuscript and final approval of the version to be published. AGS is the Guarantor for this paper.

Compliance with Ethical Standards

Conflict of Interest None.

Informed Consent Written informed consent obtained from parents.

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