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Epilepsy in inborn errors of metabolism: two cases with unusual presentation

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ABSTRACT

Inherited metabolic disorders are a rare cause of epilepsy in children. We describe a case of Glutaric aciduria type 1 presenting with West syndrome and a case of intermittent Maple syrup urine disease presenting with epileptic encephalopathy. Early diagnosis and institution of appropriate therapy may be life saving and may improve the long term neuro-developmental outcome in children with inherited metabolic disorders.

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1. Introduction

Inherited metabolic disorders are a rare cause of epilepsy.¹ However, in many metabolic disorders, seizures are the predominant symptom especially in newborns and infants e.g. pyridoxine dependent seizures, biotinidase deficiency and glucose transporter defect. It is most important to look for those inborn errors of metabolism which are treatable with supplementation of vitamins and cofactors or special diets. We report two unusual cases of inherited metabolic disorders with associated epilepsy.

2. Case 1

A 10-month-old male infant presented with developmental delay and jerky movements of the head and limbs since 6 months of age. He was the second child of non-consanguineous parentage. The antenatal and perinatal periods were uneventful. He achieved social smile at 3 months and partial neck holding at 5 months. Since 6 months of age, parents noticed jerky movements with flexion of the head and upper limbs, suggestive of flexor spasms. These movements would occur in clusters whenever the child woke up from

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Fig. 2 – MRI of the brain of case 1: The axial T2W images show hyperintense signal changes involving the brainstem especially the dorsal tracts, the medial cerebellar hemispheres, bilateral basal ganglia (caudate and lentiform), thalami and cerebral white matter with fronto-temporal atrophy seen as prominent CSF spaces overlying the convexity and wide open sylvian fissures with CSF collections anterior to the temporal poles.

generalized polyspike wave discharges with electrodecrement. The blood ammonia, lactate, arterial blood gas analysis were normal and there was no urinary ketosis. The blood tandem mass spectrometry showed increased levels of leucine, isoleucine and valine. The urine gas chromatography mass spectrometry showed urine ketosis, and elevation of 3-hydroxy-butyrate and dicarboxylic aciduria. The findings were suggestive of maple syrup urine disease.

Parents were advised a low protein diet. The child also received thiamine, sodium valproate and oral prednisolone. His myoclonic jerks subsided within 3 days. He became more alert and started recognizing his parents by the time of discharge. At 3 months follow up, he has started sitting and vocalizing bisyllables. A repeat EEG obtained 3 months later was normal.

4. Discussion

We report describes two cases with neurometabolic disorder presenting with seizures. The inborn errors of metabolism are infrequent cause of epilepsy but their early recognition and appropriate management is pivotal.

Table 1 describes the metabolic disorders causing epilepsy. The underlying mechanisms may vary according to the metabolic disorder and includes deficiency of a vitamin or a cofactor, cerebral energy deficiency, chemical or physical disruption of neurotransmission, direct toxicity of the accumulating storage material or intermediates, associated hyperammonemia or hypoglycemia or electrolyte disturbances.¹

Fig. 3 – EEG of case 3 shows chaotic high voltage activity with intermixed spikes and sharp waves arising independently from bilateral leads.

Table 1 – Metabolic disorders causing epilepsy.

Treatable causes	Others
Multiple carboxylase deficiency	Molybdenum cofactor and sulfite oxidase deficiencies
Pyridoxine dependent epilepsy	Menkes disease
Pyridox(am)ine 5'-phosphate oxidase deficiency	Peroxisomal disorders
GLUT1 deficiency syndrome	Congenital disorders of glycosylation
Disorders of creatine metabolism	Mitochondrial disorders
Disorders of coenzyme Q ₁₀ biosynthesis	Organic acidemias
Disorders of serinebiosynthesis	Aminoacidopathies
	Urea cycle disorders
	Non-ketotic hyperglycinemia
	Purine metabolism defects
	GABA transaminase deficiency
	Storage disorders
	Progressive myoclonic epilepsies

Glutaric aciduria (GA) type 1 is caused by deficiency of glutaryl CoA dehydrogenase deficiency resulting in accumulation of glutarate, 3-hydroxyglutarate and glutaconate. Seizures are rarely seen in GA type 1 and usually occur during episodes of acute encephalopathy.^{2,3} Rather majority of the paroxysmal movements, which may be misdiagnosed as seizures, appear to be dystonic episodes.⁴ The accumulating glutarate has recognized excitotoxic effects via N-methyl-D-aspartate (NMDA) receptor⁵ and may thus be epileptogenic.

West syndrome has never been reported with GA type 1 previously although it has been rarely reported with other organic acidemias like propionic academia,^{6,7} methylmalonic academia,⁸ and D-glyceric aciduria.⁹ Thus, the case 1 further expands the phenotypic spectrum of GA type 1.

Maple syrup urine disease (MSUD) is caused by mitochondrial branched chain α -ketoacid dehydrogenase complex deficiency resulting in accumulation of branched chain amino acids and α -ketoacids. Five forms of MSUD have been described: classic, intermediate, intermittent, thiamine responsive and dihydrolipoyl dehydrogenase deficiency.

Case 2 had intermittent MSUD presenting with episodic encephalopathy, seizures and neuroregression with recovery. The patients with intermittent MSUD can have intractable seizures during an acute episode and the acute episodic deterioration can be fatal. However, with early diagnosis and treatment, the patients can have normal or near normal neurodevelopment. Seizures have also been described in other forms of MSUD.¹⁰ The neurotoxicity is predominantly mediated by leucine and its transamination product 2-ketoisocaproate.¹¹

Thus, inborn errors of metabolism should always be excluded in a child with unexplained seizures, especially if they are refractory to treatment. Table 2 shows the clinical cues that may help the neurologist to suspect an inborn error of metabolism in a child with epilepsy. This report describes the first case of GA type 1 presenting with West syndrome and a child with intermittent MSUD presenting with metabolic and epileptic encephalopathy.

Conflicts of interest

All authors have none to declare.

Table 2 – Pointers towards an inborn error of metabolism in children with epilepsy.¹²

Associated global developmental delay
Associated movement disorder – creatine deficiency, organic acidemia
Worsening of seizures before meals – GLUT1 deficiency
Vomiting – urea cycle disorders
Abnormal urine odor – maple syrup urine disease, phenylketonuria
Accelerated growth (macrosomia, tall stature) – GABA transaminase deficiency
Facial dysmorphism – Zellweger syndrome
Hair and skin abnormalities – Menkes disease, biotinidase deficiency
Albinism – phenylketonuria
Dislocated lens – sulphite oxidase deficiency
Inverted nipples, abnormal fat pads – congenital disorders of glycosylation
Organomegaly, coarse facies – storage disorders
Multi-system involvement – mitochondrial disorders, congenital disorders of glycosylation, peroxisomal disorders

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