Late Onset Multiple Acyl-CoA Dehydrogenase Deficiency: A Rare Treatable Neurometabolic Disorder

Sir,

Multiple acyl-CoA dehydrogenase deficiency (MADD) also called glutaric aciduria (GA) type II, is a rare inborn error of metabolism that affects the oxidation of fatty acids and catabolism of branched-chain amino acids namely lysine and tryptophan. MADD occurs due to a defect in electron-transfer flavoprotein (ETF) encoded by *ETFA* and *ETFB* genes or electron-transfer flavoprotein dehydrogenase (ETFDH) encoded by *ETFDH* gene. We describe an adolescent boy with recurrent vomiting, unprovoked seizures and progressive muscle weakness who was diagnosed with MADD.

A 12-year-old boy presented with progressive difficulty in squatting, rising from squatting position and climbing stairs for seven months. He had difficulty in rising from supine but no difficulty in rising arms or buttoning shirts. He had difficulty in swallowing, hypophonia, and jaw, neck, and leg pain with inability to walk for two days. He had lost his head control and had breathing difficulty at presentation. There was no history of visual or hearing disturbances, eyelids drooping, eye movement restriction, or deviation of angle of mouth. There were no sensory disturbances or involuntary movements. There were no antenatal risk factors; he was born at term by forceps delivery with birth weight of 2400 g with no neonatal concerns. His premorbid development was normal. Family history was non-contributory. He had recurrent vomiting from 7 years of age and unprovoked generalized seizures twice at 9 and 11 years of age. Investigations elsewhere at 9 years showed a normal Computed Tomography scan (CT) brain with an abnormal EEG, for which he was managed with valproate and clobazam. Anthropometry assessment was normal weight 35 kg (IAP z score -0.79), height 148 cm (IAP z score -0.6), and head circumference of 53.2 cm. He had acidotic breathing, stable vitals, and SaO2 of 97% in room air. His higher mental functions were normal. Cranial nerve examination revealed normal fundus, jaw weakness, bulbar weakness, and hypophonia. Generalized wasting and proximal > distal weakness of lower > upper limbs was observed. Hypotonia and hyporeflexia was noted. There were no cerebellar or extrapyramidal signs. Systemic examination did not reveal any organomegaly. Provisional diagnosis of metabolic myopathy was considered.

On evaluation, blood glucose level was low (patient value: 55 mg/dL) and urine ketones were 3+. Arterial blood gas analysis revealed pH of 7.26, bicarbonate of 10.3 mmol/L, and blood lactate of 5 mmol/l. Plasma ammonia was elevated (patient value: 227 µg/dL, normal range: 27-102 µg/dL). Serum creatine kinase (patient value: 58520 U/L, normal reference range: 46-171 U/L) and CKMB (patient value: > 300 ng/ml, normal range: 0-6.22 ng/ml) were elevated. Echocardiography was normal. Electromyography (EMG) was suggestive of myopathic process. Serum amino acid analysis revealed elevated proline. Urinary organic acid analysis by Gas Chromatography -mass spectometry (GCMS) revealed elevated lactic, ethylmalonic, 2-hydroxyglutaric, adipic, suberic, sebacic, and glutaric acids along with hexonylglycine. Acylcarnitine profile showed elevated levels of C4-DC, C6, C6-DC, C8, C10, C12, and C14. Awaiting the exome sequencing reports, child was managed with intravenous

dextrose fluids, bicarbonate, nasogastric high calorie feeds with protein and fat restriction, levetiracetem and supplementation of riboflavin, coenzyme Q, carnitine, and thiamine. He showed gradual improvement and in two weeks, was ambulant, off nasogastric feeds with normalization of serum creatine kinase. Exome sequencing revealed a homozygous missense variation c.587C>A in the exon 5 of *ETFDH* gene that results in amino acid substitution of histidine for proline at codon 196 (p.Pro196His). This p.Pro196His has not been reported in the 1000 genome and gnomAD databases. This variant was seen to be in the 4Fe-4S ferredoxin-type, iron-sulphur binding domain of the protein. *In silico* analysis showed the variant to be 'probably damaging' by PolyPhen-2 (HumDiv), 'damaging' by SIFT (Sorting Intolerant from Tolerant), LRT (Likely-hood Ratio test) and MutationTaster2 and CADD PHRED (Combined Annotation dependent depletion) score was 29.[1] The reference codon is conserved across all species. Due to lack of functional evidence this is classified as variant of uncertain origin using the American College of Medical Genetics guidelines. No variants in *ETFA* or *ETFB* were identified in the patient. Diagnosis of multiple acyl-CoA dehydrogenase deficiency was considered based on the biochemical and genetic testing findings. Both parents were noted to be heterozygous carriers for the same mutation. His younger brother (11-year-old) is well and screening for him and is also advised and awaited.

MADD is an autosomal recessive disorder with an estimated birth incidence of 1: 250,000.[2] This disorder is characterized by three distinct phenotypes, namely, neonatal form with or without congenital anomalies and late onset form with muscle weakness.[3] The phenotype among late-onset MADD ranges from acute severe metabolic decompensation in childhood to asymptomatic adults. Chronic muscle weakness, muscle pain, and exercise intolerance were the common symptoms reported in this sub-type while these patients may also manifest episodic vomiting, encephalopathy, and hypoglycaemia.[4] Respiratory insufficiency, cardiomyopathy and hepatopathy have also been described.[4] Urinary organic acid shows an elevated 2-hydroxyglutaric acid, glutaric, adipic, butyric, lactic, suberic, sebacic, ethylmalonic, and isovaleric acids. Acylcarnitine analysis shows an increase in short, medium, and long-chain acylcarnitines C4-C18.[3] Muscle biopsy demonstrates lipid storage myopathy. Diagnosis may be challenging as biochemical abnormalities are often mild or atypical. Genetic testing is often used to confirm diagnosis.[2]

In a cohort of 350 patients with late onset MADD, mean age at presentation was 19.6 y and chronic muscle weakness was twice as common as acute decompensation.[4] Majority had *ETFDH* mutations (93%) and were riboflavin responsive (98.4%). In a Chinese cohort of 13 patient's age at symptom onset varied from 26 to 57 years.[5] Interestingly, a few had masseter weakness similar to our patient. Dramatic riboflavin responsiveness was also documented in this cohort. To the best of our knowledge, only three patients with MADD have been published from India. The first report described bilateral symmetrical hyperintensity and diffusion restriction involving globus pallidi in an infant; the second, a young male with bipolar affective disorder with metabolic profile suggestive of GA type II and the third, a young male with myopathy.[6-8]

Patients with late onset MADD have good survival on treatment. Nevertheless, treating clinicians must be aware of the mortality risk (5%) during metabolic decompensation.[4] This highlights the need for a sick-day plan and awareness of the patient's family to seek emergent medical treatment during such metabolic crises. Our patient has done well at one year follow-up on appropriate diet, high dose riboflavin, carnitine, coenzyme Q, and sick-day management plan.

Late onset MADD should be considered among children and young adults presenting with episodic or chronic muscle weakness especially in clinical setting of recurrent unexplained episodes of vomiting and metabolic crisis. Riboflavin responsiveness has been well established in this disorder. Sick day plan is of utmost importance because of the mortality risk during acute metabolic crises. Neonatal screening can enable presymptomatic diagnosis and early treatment.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Submitted: 23-Apr-2022 **Revised:** 29-Jul-2022 **Accepted:** 05-Aug-2022
Published: 31-Oct-2022

DOI: 10.4103/aian.aian_370_22