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Letter to the Editor

Rare treatable cause for global developmental delay with metabolic encephalopathy: Methylmalonic aciduria, cblA type

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Dear Sir,

Methylmalonic aciduria (MMA) represents a group of disorders that result from disturbed conversion from methyl malonyl CoA to succinyl CoA: This reaction is dependent on enzymes Methyl malonyl-CoA-epimerase (MCEE) and Methyl malonyl-CoA-mutase (MMUT) of mitochondrial localisation with cofactor 5 deoxyadenosine cobalamine (AdoCbl).[1] MMA cblA (OMIM#251100) is a recessive disorder caused by mutations in the *MMAA*gene.[2]

A 15-month-old boy born to consanguineous marriage presented with global developmental delay and altered sensorium for 2 days. The child has maintained neck control with poor eye-to-eye contact but has not yet attained rolling over and voluntary palmar grasp. On examination, the child has microcephaly (<3 World Health Organization Z Score), failure to thrive with hypotonia in all limbs with brisk deep tendon reflexes. The complete hemogram, Vitamin B12, and homocysteine were normal. There was metabolic acidosis and hyperammonaemia (Ammonia: 873 mcg/dL). Serum lactate was increased-35 mg/dL (3.6–18) and urine ketones were positive. Tandem mass spectrometry showed elevated Propionyl carnitine (C3): 7.13 (Normal: 0.30–5.81). Urinary organic acids showed elevated methyl-malonic acid. MRI brain showed mild cerebral atrophy. Whole exome sequencing revealed pathogenic non-sense homozygous variant c.433C>T: p.Arg145* in the *MMAA* gene. The variant on Sanger sequencing showed segregation with the disorder in the family. Following peritoneal dialysis, serum ammonia and acidosis were normalized. The child is on twice weekly injections of Vitamin B12 and noted significant improvement in the development. During the last follow-up at 36 months of age, the child attained sitting, crawling, good eye contact, follows one-step commands, pincer grasp, and started speaking 5–6 meaningful words.

The causes of isolated MMA without elevated homocysteine can be mutations in genes coding for enzymes *MMUT* (OMIM#251000), *MCEE* (OMIM#251120) or AdoCbl synthesis defects like CblA (*MMAA*), CblB (*MMAB*) and CblD2 (*MMADHC*).[3,4] Treatment involves parenteral Vitamin B12. The elevated ammonia can be due to either primary urea cycle disorder or secondary to organic academia. Metabolic acidosis with elevated lactate and ketosis favours the latter. One should consider this treatable condition in children with developmental delay, encephalopathy, metabolic acidosis and hyperammonemia, despite normal Vitamin B12, and homocysteine levels.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

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