

Case Report

Early infantile presentation of 3-methylcrotonyl CoA carboxylase deficiency: a case report

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ABSTRACT

3-methylcrotonyl CoA carboxylase (3-MCC) deficiency is an inborn error of leucine amino acid metabolism. An isolated enzyme deficiency should be differentiated from biotin metabolism disorder which has all of the four carboxylase deficiencies. With the advent of tandem mass spectrometry (TMS), high number of infants have been diagnosed with 3-MCC deficiency. Most neonates having 3-MCC deficiency appear normal, studies have shown an increased risk of developmental and metabolic abnormalities. Universal newborn screening is not routinely done in India. Many infants with 3-MCC deficiency may be missed at birth and may present with symptoms later in life. We reported a case of four and a half month old male infant with seizures due to 3-MCC deficiency. Very few data on 3-MCC deficiency is available in India and hence this case report.

Keywords: 3-methylcrotonyl CoA carboxylase, 3-MCC, Newborn screening, Inborn error of metabolism

INTRODUCTION

Screening newborn for metabolic disorders is a very important preventive health measure. More than 500 types of metabolic disorders are currently known to affect human beings and of these many are of amino acid metabolism.¹ The expanded newborn screening programs using TMS have enabled us to detect metabolic disorders before children develop symptoms. 3-MCC deficiency is a disorder of leucine amino acid metabolism which has a varied presentation ranging from asymptomatic to severe neurologic morbidity. With advanced screening methods, 3-MCC deficiency is one of the most commonly diagnosed disorders. Many children remain asymptomatic with no biochemical or developmental abnormalities. Several studies conducted have failed to show a promising correlation between the biochemical

parameters and clinical outcomes in children with 3-MCC deficiency.

The clinical presentation of 3-MCC is heterogenous. Many of the asymptomatic neonates and children present with hypoglycemia, vomiting, failure to thrive, seizures, metabolic acidosis and hyperammonemia.² These children need timely diagnosis and management as delay in management may result in severe neurologic morbidity and sometimes mortality. In countries including India where neonates are not screened for metabolic disorders routinely, children are diagnosed only when they present with symptoms. With limited studies on prevalence of metabolic disorders in Indian neonates, it is difficult to know the exact extent of these metabolic disorders in the population. Children with deficiency of 3-MCC should be followed up regularly to prevent the permanent neurologic damage or disability. We present a case of a

4.5 month old infant presenting with seizures during acute illness who was diagnosed with 3-MCC deficiency. Through this case report, we want to emphasize about high suspicion of metabolic disorders in infants and their timely diagnosis and management in order to reduce long term morbidities.

CASE REPORT

A 3 kgs full term male neonate with a normal Apgar score was delivered by normal vaginal delivery to a second para mother out of a non-consanguineous marriage. The antenatal period was uneventful. The child was exclusively breastfed for first 96 hours of life and was then shifted to a neonatal intensive care unit for generalised tonic convulsions. There was no lethargy or refusal to feed prior to this episode. The vitals were stable. There was no respiratory or circulatory insufficiency. Neurological and other systemic examinations were normal. The hematological and sepsis workup were unremarkable. Random blood sugar was 78 mg/dl, C-reactive protein was negative. Serum electrolytes and serum calcium were within the normal ranges. Blood culture was sterile and CSF analysis was suggestive of glucose 60 mg/dl, protein 28 gm/dl with no cells on microscopic examination. CSF culture was negative. Urine analysis was normal. Cranial ultrasound was normal. Blood gas analysis showed no abnormality. The newborn initially received empiric antibiotics-ampicillin and gentamycin in standard doses for 2 days which were discontinued after a sterile blood culture. Oral phenobarbitone (3 mg/kg/day) was started after a loading dose of 20 mg/kg. The newborn was asymptomatic and hence discharged on the 10 day of life on oral phenobarbitone. On follow up at 3 months, phenobarbitone was discontinued as neurologic examination was normal and the infant was asymptomatic. Electroencephalogram was also normal.

At 4.5 months of age, this infant presented with right lower lobe pneumonia and convulsions and was treated symptomatically with appropriate antibiotics. Developmental and neurological examinations were normal. Blood investigations showed a haemoglobin value of 9.6 gm/dl, haematocrit of 28% and TLC of 14,000 cells/ μ l with neutrophilia. Blood glucose levels and urine analysis were normal. Liver function test showed mild elevation of enzymes-alanine transaminase-80 IU/l, aspartate transaminase-88 IU/l with normal serum albumin and serum bilirubin levels. Magnetic resonance imaging of the brain was normal. As the child had repeated episodes of convulsions with marginally increased serum transaminases, metabolic cause was suspected. Serum ammonia and lactate were normal. Blood gas analysis was normal. TMS and gas chromatography mass spectrometry (GC-MS) was sent. TMS report showed elevated levels of 3-hydroxyisovalerylcarnitine and urine gas chromatography was positive for 3-hydroxyisovaleric acid and 3-methylcrotonylglycine. Therefore, the infant was

diagnosed to be suffering from 3-MCC deficiency. Genetic and molecular studies could not be done due to financial constraints. The infant was started on oral carnitine with low protein diet and had no further episodes of convulsions till the time of discharge. The mother too could not be investigated due to financial constraints. The child is under regular follow up and is asymptomatic now for the last 8 months. Phenobarbitone has been stopped. The child is now neurologically and developmentally normal.

DISCUSSION

3-MCC deficiency is an isolated deficiency of carboxylase enzyme required for the metabolism of leucine. Mutations in MCC1 and MCC2 genes encoding alpha and beta subunit of enzyme results in this deficiency.³ It is an autosomal recessive in inheritance. The exact prevalence of 3-MCC deficiency in India is not known but one study from Mumbai reported the prevalence of organic acidemia to be around 4%.⁴ The prevalence of 3-MCC deficiency in USA is reported to be around 1:2400 to 1:68000.⁵ With the advent of newer techniques like GC and TMS of blood and urine, this deficiency can now be detected early on. 3-MCC has a variable clinical manifestation ranging from asymptomatic in adults to developmental delay, seizures or metabolic acidosis.⁶

Many children remain asymptomatic but minor infections may precipitate symptoms. It is possible that 3-MCC deficiency creates a state of vulnerability, requiring a second event like fasting or infections to manifest an abnormal phenotype.⁷ Gibson et al also suggested that mothers of affected infants are not always asymptomatic and they reported fatigue and acute fatty liver during pregnancy.⁸

Shepard et al studied children with Specific symptoms of leucine toxicity such as hypoglycemia, acidosis and others and children with non-specific symptoms such as intellectual disability or seizures.⁹ The study found that cases with non-specific symptoms were more likely to have increased regions of homozygosity and that likely explained the patient's symptoms. The possibility remains that 3-MCC deficiency might constitute a predisposition to developmental disabilities in the presence of other stressors. Studies have shown that even a non-specific delay in at least one domain of development should raise the suspicion of 3-MCC deficiency in children.^{5,10}

In our case, the child presented to us in his neonatal period with convulsions without any metabolic acidosis. He was evaluated with blood investigations and radiological imaging, but no cause was found and so he was treated symptomatically with oral anticonvulsant. The child presented to us again at the age of 4.5 months with pneumonia and breakthrough seizures. We suspected a metabolic cause of seizures and hence metabolic panel was sent. TMS was positive for

isovalerylcarnitine and urine GC was positive for 3-hydroxyisovaleric acid and 3-methylcrotonylglycine. Propionic acidemia was ruled out as the TMS was negative for propionic acid metabolites propionylcarnitine, methylcitric acid and normal serum ammonia levels. A suspicion of multiple carboxylase deficiency was ruled out by normal serum biotin levels. Hence a diagnosis of 3-MCC deficiency was made.

The child was started on a low protein diet and oral carnitine (100 mg/day). He continued with oral phenobarbitone for 3 months and then discontinued as seizures were now controlled. Upon follow up, he is seizure free for 7 months. We continued oral carnitine and dietary restriction of proteins as before.

CONCLUSION

At present universal newborn screening for metabolic disorders is not done routinely in India. Metabolic evaluation is usually done in very sick neonates or children with metabolic acidosis with hyperammonaemia. Many cases are undetected and hence we report this case to stress the importance of newborn screening for metabolic disorders even in children with no specific symptoms of acidosis, hyperammonemia, hypoglycemia and developmental delay. Early diagnosis with preventive measures can prevent children from developmental and metabolic abnormalities. More prospective studies are required for the evaluation of 3-MCC deficiency and its effect on neurodevelopmental outcomes.

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