CASE REPORT

PAEDIATRIC CASE OF 3-METHYLCROTONYLGLYCINURIA WITH ENCEPHALOPATHY: A CASE REPORT FROM PAKISTAN

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3-Methylcrotonylglycinuria is a common inborn error of metabolism (IEM) resulting from the deficiency of 3-Methylcrotonyl-CoA carboxylase (3-MCC) and its prevalence ranges from 1:2400 to 1:6800. The disease may be asymptomatic or may present with signs of "metabolic crisis". In our four and a half months old male patient, the disease manifested as fever, fits and an altered level of consciousness, along with signs and symptoms of metabolic crisis. The purpose of this case report is to highlight a clinical presentation of 3-MCG, as seen in this patient to ensure timely diagnosis and treatment.

Keywords: Amino acid metabolism; Inborn errors; Inborn errors metabolism; Multiple carboxylase deficiencies; Metabolic acidosis

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INTRODUCTION

3-Methylcrotonylglycinuria is a common inborn error of metabolism resulting from the deficiency of 3-Methylcrotonyl-CoA carboxylase (3-MCC) and its prevalence ranges from 1:2400 to 1:6800.[1] It results from the deficiency of 3-methylcrotonyl-CoA carboxylase (3-MCC) which is a biotin-dependent enzyme.[1] 3-MCC deficiency is an autosomal recessive disease involving the genes MCCC-1 and MCCC-2.[2] Clinical manifestation can range from being asymptomatic to mild to severe signs and symptoms of metabolic crisis and neurologic involvement.[3] Diagnosis of 3-MCC deficiency is complex so it can be misdiagnosed. For patients landing in metabolic stress, correction of acidosis, and IV glucose administration is required. Research has proven the benefits of both carnitine and glycine supplementation.[3] A diet high in caloric intake and low in protein intake (especially leucine) is also regulated.[4]

CASE REPORT

A four-and-a-half-month-old, vaccinated male presented with complaints of fever and fits for the last 15 days and an altered level of consciousness for seven days. The patient developed a fever, which was acute in onset, intermittent, 101 F and was not relieved by oral antipyretics. The fever was associated with generalized fits involving both the upper and lower limbs. Fits lasted for around two to three minutes, with eyes rolling back, frothing saliva, and faecal incontinence. His parents rushed him to a nearby hospital, where doctors performed a Lumbar Puncture (LP) and initial care. Lumbar Puncture was unremarkable, and they admitted the patient for around 20 days. During his stay in the hospital, the patient aspirated while he was being fed, suffered severe respiratory distress and lost consciousness. Their parents brought him to a tertiary care hospital in Karachi, where the patient was intubated and kept on ventilator support. Due to financial constraints, they left against medical advice on the same day. Consequently, the parents brought the child to the National Institute of Child Health (NICH) Karachi, Pakistan, a tertiary care public hospital.

His past medical history and birth history was unremarkable. He was BCG vaccinated, had been breastfed exclusively since birth, and had been developmentally appropriate for his age. He was the first child of consanguineously married parents of Sindhi origin. Two maternal cousins passed away due to the same disease at the ages of ten months and three years. The presenting complaints in both cases were fits.

On arrival, the patient was an intubated male infant who landed in the emergency with a blood pressure of 93/51 mmHg, heart rate of 110 bpm, respiratory rate of 30 breaths/min, maintaining the saturation of oxygen 98%. His weight was five kg (less than the third centile), length was 58 cm (less than the third centile), and frontal-occipital circumference was 38 cm (less than the third centile). His CNS examination revealed increased tone in all four limbs, reflexes brisk in lower limbs, and planters bilaterally upgoing. GCS was 5T and pupils BERL. Anterior fontanel was full and open 1.5x1.5 cm. The rest of the examination was unremarkable.

Lab results showed elevated ALP levels, plasma lactic acids levels and plasma ammonia levels.

His ABGs showed severe metabolic acidosis indicated by a pH of 6.94, decreased pCo2, elevated pO2, decreased HCO3 and an elevated anion gap. His blood glucose, serum calcium levels, ALT levels and SaO2 levels were within normal ranges. Complete blood count and renal function tests were unremarkable.

A CT scan brain without contrast (Figure 1–3) showed prominent extra-axial subarachnoid spaces. It was suggestive of benign enlargement of subarachnoid spaces of infancy (BESSI), in bilateral frontal and temporal regions, with usual grey and white matter differentiation.

Plasma amino acids testing conducted by Cation-Exchange HPLC (Biochrom 30+)
Showed decreased serine, asparagine, glutamine, alanine, citrulline, cysteine, methionine, ornithine, histidine, and arginine. Urine for organic acids showed marked excretion of 3-methyl-crotonyl glycine, three hydroxy isovaleric acids, 3-hydroxybutyric acid, and moderate excretion of lactic acid. The report was suggestive of a double peak of acetoacetic acid, a moderate rise of 2-hydroxybutyric acid, and a small peak of 3 hydroxy valeric acids. The profile was typical of 3-methylcrotonylglycinuria due to a deficiency of 3-methylcrotonyl-CoA carboxylase.

The patient was intubated in the paediatric ICU and kept on ventilator support. We added IV antibiotics, and sodium bicarbonate bolus to correct severe metabolic acidosis and ensured neuroprotective measures according to the guidelines for the management of severe traumatic brain injury. Later, composition fluid (90 ml 10% DW/10ml of sodium bicarbonate) with 1.5 times maintenance was given. We successfully extubated the patient after seven days. Workup was found suggestive of 3-MCC deficiency; hence, we took a metabolic disease consultant on board, and she started syrup, L-carnitine and biotin supplements. After that, dried blood spot biotinidase levels were checked, which were found to be normal. The family was advised by the treating physician to send for a genetic workup for the 3-BMCCD gene. The parents were counselled about future pregnancies and the importance of early screening and management in the subsequent offspring. Initially, financial constraints were an obstacle. Later, the patient was lost to follow-up.

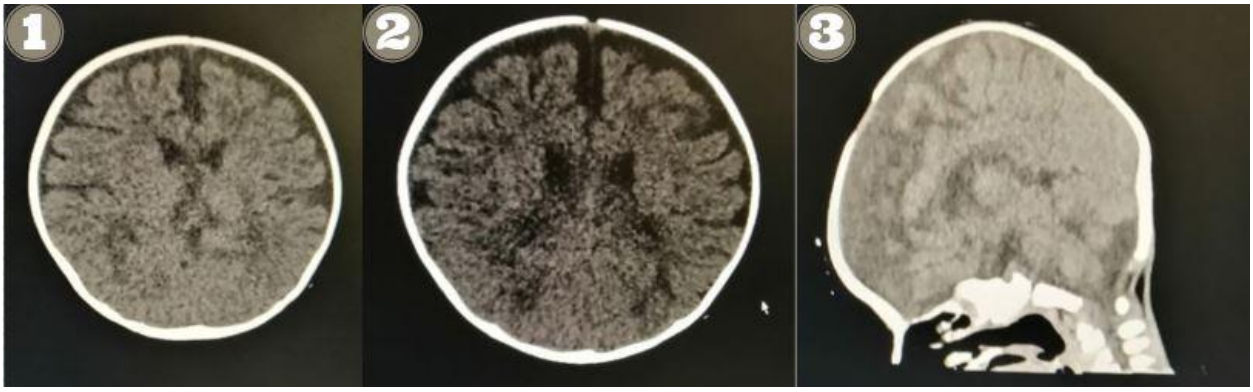

Figure-1: Axial section of CT scan brain showing benign enlargement of subarachnoid spaces of infancy

Figure-2: Axial section of CT brain showing frontal and parietal prominence of subarachnoid spaces

Figure-3: Mid-sagittal section CT brain

DISCUSSION

3-Methylcrotonyl glycinuria is an inborn error of metabolism which occurs due to the deficiency of 3-MCC.[2]. 3-MCC deficiency is an autosomal recessive disease involving MCCC 1 and MCCC2 genes which encode for MCCC-α and MCCC β - together constituting the MCC protein.[1] There is a high phenotypic variability of 3-MCC deficiency symptoms, with some patients presenting with symptoms during the first few months of infancy, but they can also appear later. At times, patients remain asymptomatic.[1]

Around 2.6% of the 38 children born with inborn errors of metabolism among ethnic minorities including Pakistan were reported to have 3-MCC deficiency.[5]

Similar to other metabolic disorders, triggers such as an illness, exercise or prolonged fasting may precipitate the disease.[6] Patients can give history suggestive of failure to thrive or developmental delay; others can remain asymptomatic. Symptomatic patients land with catabolic stress leading to vomiting, lethargy, apnoea, hypotonia, hyperreflexia, and seizures. They can have profound hypoglycaemia, mild to severe metabolic acidosis, hyperammonaemia, elevated liver transaminases, and ketonuria.[1,3] They have decreased plasma-free carnitine levels.[7] Similarly, our patient came to our setup with fever,

neurologic symptoms of fits, an altered state of consciousness, hyperreflexia and later developed respiratory distress. His CT scan brain indicated benign enlargement of subarachnoid spaces of infancy (BESSI) explaining the neurologic symptoms seen in 3-MCC deficiency.

His labs indicated metabolic acidosis, lactic acidosis and hyperammonaemia, as is seen in 3-MCC deficiency.

Infants can trans-placentally receive 3-MCC metabolites through their asymptomatic mothers.[8] Though they don't develop the disease, newborn screening detects elevated 3-MCC by tandem mass spectrometry.[9] Diagnosis in newborns using tandem mass spectrometry reveals an elevation of C5-hydroxy acylcarnitine (C5-OH) from the dried blood spot of an affected patient.[9,10] Further testing is needed to confirm the diagnosis.

Urine organic acid analysis shows elevated levels of 3-hydroxyisovaleric acid and 3-methyl-crotonyl glycine.[11] 3-MCC deficiency is differentiated from multiple carboxylase deficiency by assessing C3 acylcarnitine levels. If it remains high, the disorder is multiple carboxylase deficiency. Following carnitine supplementation, 3-hydroxy Iso valeryl carnitine is elevated in an acylcarnitine profile using tandem mass spectrometry. Similarly, our patient showed marked excretion of 3-methyl-crotonyl glycine, three hydroxy isovaleric acids, 3-hydroxybutyric acid, and moderate excretion of lactic acid. The report showed a double peak of acetoacetic acid, a moderate rise of 2-hydroxybutyric acid, and a small peak of 3 hydroxy valeric acids. The profile suggested 3-methylcrotonylglycinuria due to a deficiency of 3-methylcrotonyl-CoA carboxylase.

Antenatally, chorionic villus sampling and maternal acylcarnitine profile is done to determine whether they have 3-MCC deficiency rather than their infant.[12]1esearchers should also include other family members in the study.

For patients landing in catabolic stress, correction of acidosis, and IV glucose administration are needed. Research has proven the benefits of both carnitine and glycine supplementation.[3] Reducing dietary leucine consumption, implementing a protein-restricted diet, and employing a special leucine-depleted formula are the first steps in treating 3-MCC deficiency.[13] If defects with biotin metabolism are suspected rather than isolated 3-MCC deficiency, an early trial of biotin supplementation should be given.[14]

Failure to conform to the dietary restrictions and timely consumption of the prescribed supplements can lead to developmental delay[4], neurological abnormalities and seizures[12].

In one study of multiple carboxylase deficiency, which includes 3-MCC deficiency, a 2-month-old infant from Rawalpindi, Pakistan, presented with a metabolic crisis and seizures.[15] The child was a product of a consanguineous marriage, and the diagnosis was made based on laboratory findings, clinical presentation and CT brain findings. The patient's sibling died due to similar manifestations.[14] Our patient was also a product of a consanguineous marriage. The maternal cousins of our patient passed away after exhibiting a similar disease presentation but not receive prompt diagnosis and treatment. This may imply a connection between consanguineous marriage and the disease's hereditary component. This also highlights the use of clinical diagnosis in classifying 3-MCC as a differential in the setting of low resources.

Our case report highlights the importance of keeping inborn errors of metabolism as a differential in both asymptomatic and symptomatic patients landing in the emergency department with metabolic crises.

It is advisable to manage patients with a paediatric metabolic disease specialist on board because diagnosis and therapy of 3-MCC deficiency can be complex.

CONCLUSION

In low and middle-income countries, widespread accessibility of genetic panel testing and the newborn screening programme to the general public is yet to be made. This may create an obstacle in avoiding misdiagnosis and in prompt diagnosis and treatment of inborn errors of metabolism.

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