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Case Report

Congenital methemoglobinemia masquerading as spastic diplegic cerebral palsy

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ABSTRACT

Congenital methemoglobinemia is an autosomal recessive condition resulting from deficiency of methemoglobin reductase which is caused by homozygous or compound heterozygous mutation in the CYB5R3 gene on chromosome 22q13, manifesting clinically by decreased oxygen carrying capacity of the blood, with resultant cyanosis and hypoxia. The clinical features include microcephaly, developmental delay, spasticity and myelination defects, seizures, feeding difficulties. Methemoglobinemia is an abnormal increase of MetHb (>3%) of total haemoglobin which can be either hereditary and acquired. The acquired methemoglobinemia is mostly due to anaesthetic drugs and genetic one is due to deficiency of CYB5R3 or cytochrome B5 systems. The type I congenital methemoglobinemia is more common and less severe and is caused by CYB5R functional deficiency in red blood cells compared to type II which is more severe and less frequent and CYB5R deficiency is present in all cells. Sometimes it might mimic as static insult sequalae in the form of spastic diplegia. Here we reported an 8-month-old female with spastic diplegia with recurrent episodes of bluish discoloration later found to have autosomal recessive congenital methemoglobinemia.

Keywords: Congenital, Methemoglobinemia, Spastic, Cyanosis, Microcephaly

INTRODUCTION

Congenital methemoglobinemia is an autosomal recessive condition resulting from deficiency of methaemoglobin reductase which is caused by homozygous or compound heterozygous mutation in the CYB5R3 gene on chromosome 22q13, manifesting clinically by decreased oxygen carrying capacity of the blood, with resultant cyanosis and hypoxia.[1,2] Clinical phenotypes also include microcephaly, developmental delay, spasticity and myelination defects, seizures.[3] The activity of the NADH-cytochrome b5 reductase enzyme depends on the mutations in the CYB5R3 gene. The presence of NADH-cytochrome b5 reductase in an erythrocytic form as well as a membrane-bound form on mitochondrial and endoplasmic reticulum membranes plays important role in methaemoglobin reduction. There are two main forms of congenital methemoglobinemia (types I and II) depending on the type of mutation in the CYB5R3 gene and the resulting protein change. The localization of the NADH-cytochrome b5 reductase enzyme deficiency to red blood cells in type I leads to a less severe form characterized by cyanosis without neurologic impairment. This form can also be treated more easily than Type II. The neurological defects in cytochrome b5 reductase deficiency are mostly due to abnormalities with fatty acid metabolism.[4] The initial presentation can be confused with static insult sequalae

which the clinician has to be aware of especially in the setting of recurrent cyanotic episodes with no underlying pulmonary or cardiac disease.

CASE REPORT

An 8-month-old female infant born of non-consanguineous marriage presented with global developmental delay and recurrent bluish discoloration of palm and soles. She was born by normal vaginal delivery at term with birth weight of 3.2 kg and baby cried immediately after birth and there was no neonatal intensive care unit admission. The antenatal period was uneventful. The initial milestones were delayed (both motor and language); partial neck holding at 7 months, palmar grasp at 7 months, recognising mother at 5 months, cooing sound at 4 months. The developmental age was around 4-5 month. There was history of recurrent feed regurgitation. There was no significant family history in three generations. There was no unusual odour of urine, seizure, altered sensorium, excessive startle. The examination revealed weight of 6.7 kg (-0.47 SD), length of 60 cm (-2.18 SD) and head circumference of 38 cm (-2.9 SD). There was no dysmorphism or neuro cutaneous markers. There was episodic bluish discolouration of palm and sole (Figure 1 A and B). The child had acral cyanosis and microcephaly with pulse oximeter measurement showed an oxygen saturation of 86% at room air which did not increase on oxygen administration. The neurological examination revealed hypertonia and spasticity (lower limb more than upper limb) and brisk deep tendon reflexes. The development quotient was 25. Other systems were normal. The eye and hearing assessment were normal.

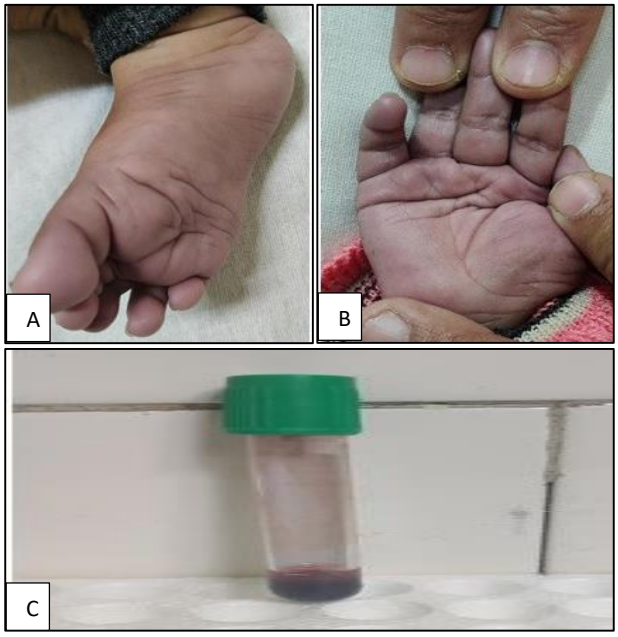

Figure 1 (A-C): Bluish discoloration of sole and palm; the vacutainer shows chocolate coloured blood on exposure to air.

The clinical challenge was to establish the aetiology of spastic diplegia especially in the absence of adverse perinatal event and recurrent episodes of cyanosis. The possibility of neurometabolic disorder especially ethyl malonic aciduria was considered and further investigations were planned. The tandem mass spectrometry (TMS), urine gas chromatography mass spectrometry (GCMS), serum ammonia and biotinidase were normal. The blood collected in a vacutainer turned chocolate coloured on exposure to air (Figure 1 C). The blood gas analysis was normal. The Hb electrophoresis was normal. The echocardiography was done twice which was normal. The brain MRI showed diffuse cerebral atrophy (Figure 2 A and B). The methaemoglobin level was 18.6% (reference normal range <1.5). In view of normal neuro metabolic screening and raised metHb level, the whole exome sequencing (WES) was sent which detected two heterozygous stop gained pathogenic variant at chr22:43019873G>A in exon 8 and chr22:43026976G>T in exon 4 of CYB5R3gene respectively confirming the diagnosis of congenital methemoglobinemia. The infant was started on vitamin C and riboflavin along with physiotherapy and neurodevelopmental stimulation therapy. The parental sanger validation for similar variant was planned.

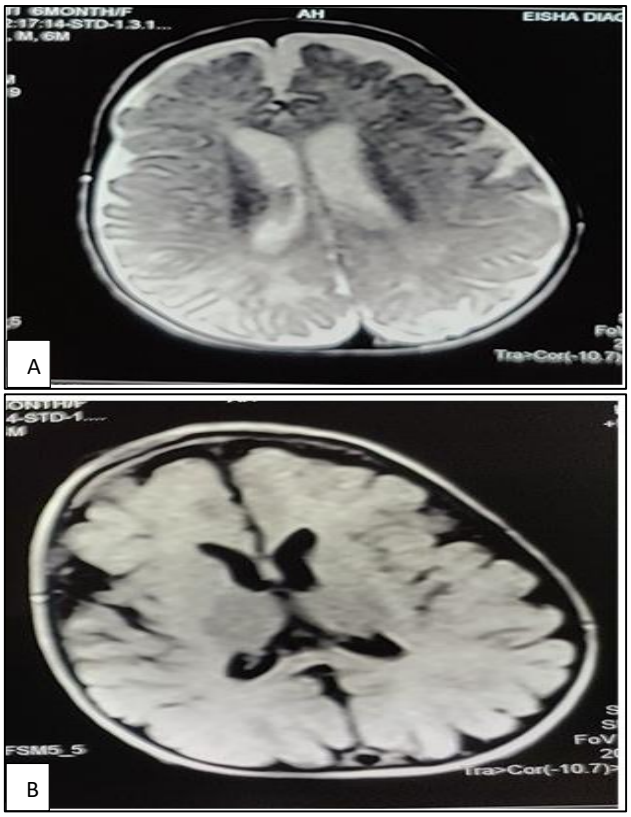

Figure 2 (A and B): T2/FLAIR weighted axial magnetic resonance (MR) image done at 6 month of age shows loss of volume of both cerebral hemisphere with widening of sulci and sylvian fissure on the both side with prominent lateral ventricle.

DISCUSSION

Congenital methemoglobinemia is a very rare autosomal recessive disorder resulting from deficiency of methaemoglobin reductase due homozygous or compound heterozygous mutation in the CYB5R3 gene located on chromosome 22q13. This is characterized clinically by decreased oxygen carrying capacity of the blood, with resultant cyanosis and hypoxia. The clinical phenotypes also include microcephaly, developmental delay, spasticity and myelination defects. Under normal condition MetHb levels are usually below 1% of the total haemoglobin. The type I congenital methemoglobinemia is more common and less severe and is caused by CYB5R functional deficiency in red blood cells compared to type II which is more severe and less frequent and CYB5R deficiency is present in all cells.[5,6] The acquired methemoglobinemia is mostly due to anaesthetic drugs.[7] The neurological manifestations include microcephaly, developmental delay, seizures, feeding difficulties, spasticity and usually manifesting at 4-9 months of life.[8] Most patients adapt to high methaemoglobin levels by compensatory polycythemia and have little to no symptoms unless exposed to oxidizing agents. The early neonatal presentation includes cyanosis, feeding difficulties in the absence of cardiac and pulmonary diseases. The differential diagnosis includes ethyl malonic aciduria characterised by relapsing petechiae, progressive neurodegeneration, acrocyanosis, and in some cases with chronic diarrhoea with markedly raised ethyl malonic acid in urine.[9] The diagnostic tests for congenital methemoglobinemia include blood gas analysis, blood levels of methaemoglobin, however definitive diagnosis is confirmed by genetic testing.[10] The acquired forms must be ruled out with relevant clinical history. The emergency treatment is only indicated if MetHb concentration rises above 10% and mainstay of therapy is intravenous methylene blue (0.5-2 mg/kg over 5 min) with or without hyperbaric oxygen.[11] For chronic cases vitamin C and riboflavin can be used. In our case, infant had spastic diplegia with global developmental delay and microcephaly with recurrent cyanotic episodes in the absence of congenital heart disease with raised levels of methmoglobin raising the suspicion of congenital methmoglobinemia which was later confirmed by whole exome sequencing.

CONCLUSION

This case report highlights the importance of keeping this condition as one of the differentials for spastic diplegia especially when there are no adverse perinatal event and is associated with recurrent episodes of cyanosis. It is very important to diagnose early so that therapeutic trial of vitamin C and riboflavin can be given and parents can be counselled accordingly.

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