

A Suspected Case of MEHMO – Rare X-linked Mitochondrial Disorder

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ABSTRACT

Introduction: MEHMO (Mental retardation, epileptic seizures, hypogonadism and hypogenitalism, microcephaly and obesity) is a rare and complex X-linked disorder which characterized by profound intellectual disability, epileptic seizures, hypogonadism and hypogenitalism, microcephaly and obesity. By genetic haplotype and linkage analysis, disease locus has been assigned to Xp21.1 - Xp22.13.

Case report: The patient was born to non-consanguineous parents near the term of delivery and clinically was very similar to the syndromal description of MEHMO. Family history of deaths of 2 maternal uncles below the age of 2 years suggests X-linked inheritance.

Conclusion: The findings of index case warrant clinicians to be more vigilant while assessing such cases and calls for thorough clinical examination, family history, detailed lab work up and molecular genetics whenever possible to support and contribute towards literature in future.

Keywords: MEHMO, X-linked Mitochondrial Disorder, Microcephaly, Seizure

INTRODUCTION

MEHMO (Mental retardation, epileptic seizures, hypogonadism and hypogenitalism, microcephaly and obesity) is a rare and complex X-linked disorder which characterised by profound intellectual disability, epileptic seizures, hypogonadism and hypogenitalism, microcephaly and obesity was first described by Delozier Blanchet and named by Steinmuller.^{1,2} By genetic haplotype and linkage analysis, disease locus has been assigned to Xp21.1 - Xp22.13.² Newer researches show that mutations in EIF2S3 encoding the translation initiation factor eIF2 γ are associated with MEHMO.³ This syndrome characterise by the morphological abnormalities as well as decrease activity of mitochondrial DNA (mtDNA) encoded respiratory chain enzymes e.g. complex I, III and IV.⁴ Thus defect in the energy production house lead to the insufficient protein and energy production consequently premature damage of multiple systems of body.

Here we are reporting a case which clinically is very similar to the syndromal description of MEHMO, because of limited resources and early death of the index case we could not able to do molecular and genetic study. Typical index case findings and death of mother's mother two sons in their early years of life give strong indication towards MEHMO.

CASE REPORT

The patient was born to non-consanguineous parents near the term of delivery; baby was healthy at birth no early neonatal

complication reported by the family members. When child presented to us he was one and half year old he came for the complaints of respiratory difficulties, which later diagnosed as Pneumonia. His weight was 13.8 kgs and forehead was sloppy circumferences of head was 43 cm, microcephaly was first noted when he was admitted for seizures, somewhere else in private clinic. During seizure child would have sudden, symmetric, tonic muscle contraction producing flexion of the trunk and extremities. EEG revealed hypsrrhythmia and brain MRI was suggestive of mild cerebral atrophy. His seizures were poorly controlled, he was tried on multiple medications including: Valproate, ACTH, Vigabatrin, Prednisolone and Pyridoxine at different period of time in adequate dose range. In his metabolic assessment, blood lactate level was found to be raised (Blood lactate level-26 mg/dl) although blood sugar level was in the normal range. General Physical Examination finding show child was obese, sloping forehead, left foot post axial polydactyly, long eyelashes, micro-penis and undescended testis (Figure 1). Neurological examination showed hypotonic baby who did not fix/follow, drooling of saliva, neither head control nor any spontaneous movements, Babinski was up going no other reflexes could be elicited, pupillary reflex was normal and power in both upper and lower limb was 1/5. His total Glasgow Coma Scale (GCS) score was 7 (GCS: Eye response-4, Verbal response-1, Motor response-2). Later in follow up patient died at the age of 22 months, due to limited financial support by the family members genetic and molecular study could not be done.

Family history of deaths of 2 maternal uncles below the age of 2 years suggests X-linked inheritance. As the primary informant in the index case was only paternal aunt, so exact finding of these two cases could not be corroborated (Figure 2).

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Figure-1: Patient at the age of one and a half year. • Note hypogenitalia, obesity and microcephaly

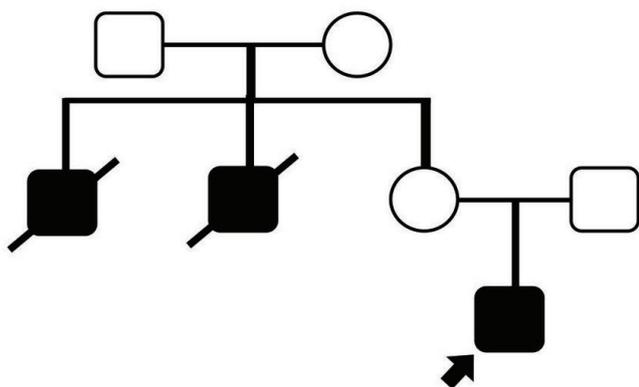


Figure-2: Showing pedigree of the family of the index case. • Shaded symbols indicate affected individuals • Affected male family members are shown as filled square symbols • Arrow indicates index case

DISCUSSION

Firstly, the clinical picture of the index case summarised by combination of symptoms which include severe developmental delay, microcephaly, epileptic seizures, hypogenitalism and obesity, was very similar as described by Steinmuller in his case of MEHMO.² Secondly, in index case study of family pedigree tree suggested X-linked recessive inheritance as only male children were affected and both males died in early years of life. Above described clinical findings and family history are very much similar and suggestive of MEHMO syndrome as described in literature.² Although we are not much sure about diagnosis of two cases in the family who died before two years of age. In the same line because of limited financial resources and logistic reasons, we were not able to do linkage analysis to prove whether inheritance in the family was X-linked. As patient was living in a small village of North India, father died in road traffic accident after which mother left child with his paternal aunt who was taking care of child. Because of the poor family support, poor financial support and logistics no genetic and molecular study could be done. We tried to rule out all the possible related syndromes and final provisional diagnosis was made on the basis of clinical scenario, lab findings and family history of the case.

The underlying genetic loci which have been identified till now in the MEHMO syndrome are Xp21.1 - Xp22.13 and mutations in EIF2S3, it encodes translation initiation factor eIF2 γ , more severe mutations in EIF2S3 cause full MEHMO phenotype.^{2,3} Consequently, basic defect in this syndrome appears to result from abnormal mitochondrial function. Despite above two genetic loci, precise underlying defect and genetic mutation need more evidences in favour of MEHMO syndrome. Molecular and genetic study in such rare syndrome need more number of cases to locate candidate genes to the critical region. The role of pedigree analysis and familial genetics in such cases cannot be neglected as it will help in mutation analysis in patients.

CONCLUSION

The findings of index case warrant clinicians to be more vigilant while assessing such cases and calls for thorough clinical examination, family history, detailed lab work up and molecular genetics whenever possible to support and contribute towards literature in future.

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