Content available at: https://www.ipinnovative.com/open-access-journals

International Journal of Clinical Biochemistry and Research

Journal homepage: https://www.ijcbr.in/

Case Report

Methylmalonic acidemia (MMA) with homocystinuria cblD & cblF types - A rare disorder of vitamin B_{12} metabolism in the western region of India

Mukesh Udevir Singh [1,*], **Harshit Bhargava** [2]

[1] *Dept. of Biochemistry, Armed Forces Medical College, Pune, Maharashtra, India*
[2] *Dept. of Paediatrics, Armed Forces Medical College, Pune, Maharashtra, India*

ARTICLE INFO

Article history:
Received 25-09-2023
Accepted 13-10-2023
Available online 25-10-2023

Keywords:
Homocystinuria
Global developmental delay
Next generation sequencing
Sanger sequencing

ABSTRACT

Background: Methylmalonic acidemia (MMA) with homocystinuria cblD & cblF type, a very rare disorder of vitamin B12 metabolism, can result in severe neurological complications in a child. The incidence of combined MMA with homocystinuria cblD & cblF type is estimated as less than 1: 100,000. Mutation analysis by next-generation sequencing (NGS) and validation of the NGS variant by Sanger sequencing, is not only the gold standard in diagnosis of MMA but also, can help in the choice of treatment strategy as B12 responsive or unresponsive.

Case Description: We report a male child initially presented at 10 months of age with poor feeding, delayed growth and no head control (milestone, normally present at 3-4 months). The child on evaluation was diagnosed as a case of MMA with homocystinuria type cblD & cblF, based on investigations such as liquid chromatography-mass spectrometry (LC-MS) and mutation analysis done by next-generation sequencing (NGS) validation with Sanger sequencing. He was treated with vitamin B12 supplements and other supportive conservative therapy. Subsequently, he developed global developmental delay and severe neurological complications, within two years. The child was admitted to the pediatric ICU and he underwent percutaneous endoscopic gastrostomy (PEG) and placed on mechanical ventilation via tracheostomy in situ. Unfortunately, the child did not respond to treatment and succumbed to death, despite all resuscitative measures.

Conclusion: The aim of this case report is to create awareness about a clinical presentation associated with a very rare metabolic disorder, MMA with homocystinuria cblD & cblF types and the need for early diagnosis, also, to establish an outline for the treatment in these patients.

1. Introduction

Methylmalonic acidemia (MMA) is a biochemical hallmark of a genetically heterogeneous disorder of vitamin B_{12} metabolism. The incidence of MMA is estimated as 1/50,000.[1] According to phenotype, two main types have been identified, isolated MMA and combined MMA with homocystinuria. Isolated MMA is due to defects of methylmalonyl -CoA mutase (MCM) or the synthesis of adenosylcobalamin (AdoCbl), while combined MMA with homocystinuria, is characterized by raised plasma homocysteine and reduced levels of AdoCbl and methylcobalamin (MeCbl), which lead to decreased activity of the enzymes MCM and methyltetrahydrofolate–homocysteine methyltransferase, or methionine synthase respectively.[2]

Combined MMA and homocystinuria is a genetically heterogeneous disorder, instigated by inborn errors of cobalamin metabolism. Different types of the disorder have been classified, based on the gene involved: cblC, cblD,

* *Corresponding author*.
E-mail address: dr.mukeshsingh2512@gmail.com (M. U. Singh).

https://doi.org/10.18231/j.ijcbr.2023.043

cblF, cblX, cblJ and cblC being the most common subtype. Type CblC is caused by a mutation in the MMACHC gene on chromosome 1p34. Type cblD in which, the mutation in the MMADHC gene on chromosome 2q23, which has a role in directing cobalamin to the two cobalamin-dependent enzymes, MCM and Methionine synthase. Type cblF is caused by mutation in the LMBRD1 gene, located on chromosome 6q13. Type cblX is an X-linked recessive metabolic disorder, caused by mutation in the HCFC1 gene on chromosome Xq28, mutations of which inhibit its function in the transcriptional activation of MMACHC. Type cblJ is caused by a mutation in the ABCD4 gene on chromosome 14q24, which is tangled in the lysosomal release of cbl into the cytoplasm. Mutation analysis is not only the gold standard in the diagnosis of MMA but also helps in the choice of treatment strategy, B_{12} responsive or unresponsive.[2] Further, the incidence of combined MMA with homocystinuria cblD & cblF types is estimated as less than 1: 100,000.[3]

The clinical manifestations of combined MMA with homocystinuria vary, but classically include neurologic, developmental and hematologic abnormalities in children.[4]

The onset of manifestations of MMA, ranges from the neonatal period to adulthood. All phenotypes reveal, sporadic periods of relative health and metabolic decompensation, usually related to intercurrent infections and stress. In the neonatal period, the disease may present with lethargy, vomiting, hypotonia, hypothermia, respiratory distress, severe ketoacidosis, hyperammonaemia, neutropenia, and thrombocytopenia, and can lead to death at a very young age.[5] In adults, the presentation may be recurrent epileptic seizures, dizziness, schizophrenia and other mental disorders.[6]

2. Case Report

The child at the age of 10 months, presented with complaints of poor feeding, delayed growth and no neck holding/ head control (milestone normally present at 3-4 months) in paediatric OPD and was admitted at tertiary care centre *********. He was managed conservatively and evaluated for amino acid profile & acyl carnitine profile based on LC-MS. He had recurrent hospital visits for poor growth, global developmental delay and weakness in both lower limbs at the same hospital. He was on regular follow-up at Pediatric OPD and further evaluated for possible causes of metabolic disorder (NGS and Sanger sequencing) and diagnosed as a case of MMA with Homocystinuria. Subsequently, this child developed weakness in all four limbs along with respiratory failure and he was admitted to PICU at the tertiary care centre *****.

2.1. General examination at the time of admission

1. He had a global developmental delay
2. GCS score: E_4 V_T M_1
3. Temp. 100 ^{0}F, Pulse 118/min, regular
4. BP: 126/80 mm Hg, RR: 38/min
5. Pallor present, no cyanosis, no clubbing and no lymphadenopathy.

2.2. Systemic examination

1. Respiratory system: decreased air entry on both sides (Lt > Rt).
2. Cardiovascular system: heart sounds normal, no murmur.
3. Central nervous system: absent deep tendon reflexes, power grade 1 in all four limbs.
4. Abdomen: soft, non-tender, no hepatosplenomegaly.

2.3. Investigations

1. Hb: 9 gm/dL
2. TLC: 13,700 cells/mm^3 Neutrophils: 79.5 %, Lymphocytes: 13.6 %, Monocytes: 6.9 %
3. RDW: 18.4 %, MCV: 82.8 fL, MCH: 23.9 pg, Platelets: 4.3 lacs,
4. Vitamin B_{12}: 108 pg/mL (normal range: 190-950 pg/mL)
5. Sr Urea: 20 mg/dL, Sr. creatinine: 0.5 mg/dL, Sr electrolytes: Na-146 mEq/L,
6. K- 4.3 mEq/L, Total Bilirubin: 0.2 mg/dL, Direct Bilirubin: 0.1 mg/dL, Total protein: 7.9 g/dL, Albumin: 4.3 g/dL, Globulins:4.6 g/dL, ALT: 22 IU/L, AST: 23 IU/L,
7. Urine exam: normal.
8. ABG analysis: suggested compensatory respiratory acidosis.

Investigations were done to rule out metabolic disorders

1. LC-MS on DBS (dried blood spot):
   (a) Amino acid profile – within normal limits
   (b) Acyl carnitine profile - within normal limits
2. NGS and Sanger sequencing:
   Mutation analysis by next-generation sequencing (NGS), and validation by Sanger sequencing, revealed two novel variants on chromosome 2 and 6, mutations found as missense and frameshift respectively, which are responsible for MMA with homocystinuria cblD type and cblF type respectively. The detailed report is given in Table 1.

The child was managed with:

1. Low protein diet
2. IV antibiotics
3. Nebulization with 3% saline and levosalbutamol 4hrly
4. Syp carnitine 3.5 ml 12 hrly for 4 weeks then stopped

Table 1: Clinicalexome sequencing report analyzed by sanger sequencing

Gene	Chromosome /position	Observed nucleotide/ AA change	Zygosity	Inheritance	Mutation type	Exon No.	Associated disorder
MMADC	Chr.2 /15043225	c. T5278C/ p.Val193Ala	Heterozygous (carrier)	Autosomal Recessive	Missense	6	MMA with homocystinuria cblD type
LMBRD1	Chr.6 /70423676	c. 776delG/ p.Arg259His	Heterozygous (carrier)	Autosomal Recessive	Frameshift Deletion	9	MMA with homocystinuria cblF type

5. Tab. Thiamine 50 microgram once a day
6. Injection vitamin B_{12} (hydroxocobalamin) 50 microgram i.m. once in 04 weeks.

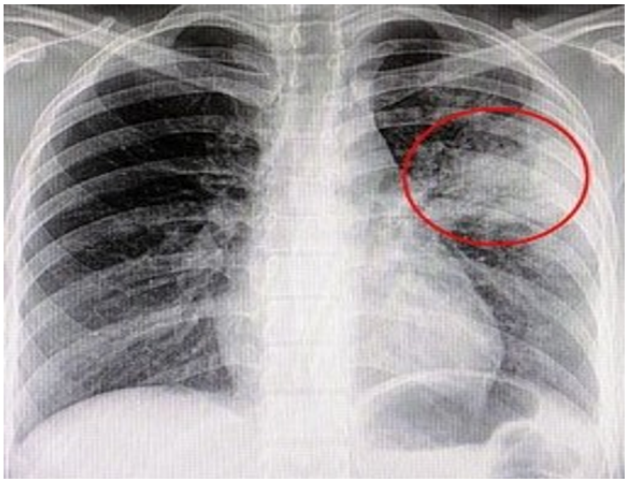

Fig. 1: X-ray chest PA view: s/o pneumonia

During hospitalization, he was placed on mechanical ventilation via endo-tracheal (ET) intubation and within 4 weeks, he had vocal cord paralysis and recurrent block of ET tube by copious mucus secretions, for which tracheostomy was done. He could not swallow (due to neuromuscular weakness) and hence, underwent percutaneous endoscopic gastrostomy (PEG) for enteral feeding (nutrition) as well as administration of medicine.

The child remained on supportive treatment with inj. Celecel (contain trace elements), Vitamin B12 and Syrup multivitamin, 150 mL feeds- 3 hrly through PEG and palliative care in PICU, kept on mechanical ventilation via tracheostomy in situ. Unfortunately, the child did not respond to treatment and succumbed to death, despite all resuscitative measures.

3. Discussion

Patients with MMA experience significant morbidity and mortality, and prognosis for long term survival is poor. There is a real challenge for a specialist, treating the case of a child with neurological manifestations and poor outcomes, despite the best medical care modalities. The children affected by MMA usually exhibit anorexia, failure to thrive, hypotonia, developmental delay, progressive renal failure, functional immune impairment, optic nerve atrophy, and hematologic abnormalities.[2]

However, the child developed global developmental delay with quadriparesis, which suggest predominant neurological manifestations, but these findings are very different from a study carried out by Jinrong Liu et al. which showed that the children predominantly present with late-onset diffuse lung disease and pulmonary arterial hypertension.[4] Hence, our study has categorized variable phenotypes of neurodevelopment in early-treated cblD and cblF patients diagnosed based on liquid chromatography- mass spectrometry (LC-MS) and Next Generation Sequencing (NGS) validation by Sanger sequencing. The long-term outcomes of cblD & cblF types of MMA with homocystinuria remain unsatisfactory and unresponsive to B12 supplements. The neurological manifestations and global developmental delay of variable severity may always be present, irrespective of age at diagnosis or treatment onset and the same, we had observed in this child. Moreover, all the patients suffering from MMA, often present with poor growth, feeding problems and seizures.[7]

4. Conclusion

This case report has categorised, variable phenotypes of MMA along with homocystinuria of cblD and cblF types in a child, which is a very rare metabolic disorder of cobalamin metabolism presented with neuro-developmental complications. The diagnosis is based on mutation analysis by next-generation sequencing (NGS), and validation by Sanger sequencing. The long-term outcomes of cblD & cblF MMA with homocystinuria remain unsatisfactory and have poor prognosis despite best-known treatment modalities. The apt diagnosis and adequate treatment at an early stage may improve the prognosis in responsive cases. It was observed that the child presented at 10 months of age, so it can be due to decreased B12 levels in mothers. Hence, maternal awareness as well as screening for Vitamin B12 deficiency during pregnancy is recommended and advised

to estimate Vitamin B12 levels in mothers. This report aims to create awareness about very rare clinical presentations associated with cblD & cblF types of combined MMA with homocystinuria and the need for early diagnosis, to establish an outline for the treatment in these patients.

5. Source of Funding

None.

6. Conflict of Interest

None.

References

1. Baumgartner MR, Hörster F, Dionisi-Vici C, Haliloglu G, Karall D, Chapman KA, et al. Proposed guidelines for the diagnosis and management of methylmalonic and propionic acidemia. *Orphanet J Rare Dis*. 2014;9(1):130. doi:10.1186/s13023-014-0130-8.
2. Zhou X, Cui Y, Han J. Methylmalonic acidemia: Current status and research priorities. *Intractable Rare Dis Res*. 2018;7(2):73–8.
3. Lopez J. Carl A. Burtis, Edward R. Ashwood and David E. Bruns (eds): Tietz Textbook of Clinical Chemistry and Molecular Diagnosis (5th edition). *Indian J Clin Biochem*. 2018;28(1):104–5.
4. Liu J, Peng Y, Zhou N, Liu X, Meng Q, Xu H, et al. Combined methylmalonic acidemia and homocysteinemia presenting predominantly with late-onset diffuse lung disease: a case series of four patients. *Orphanet J Rare Dis*. 2017;12(1):58. doi:10.1186/s13023-017-0610-8.
5. Keyfi F, Talebi S, Varasteh AR. Methylmalonic Acidemia Diagnosis by Laboratory Methods. *Rep Biochem Mol Biol*. 2016;5(1):1–14.
6. Zhou D, Wu W, Ding Y, Xunming J, Meng R. Methylmalonic Aciduria may be an Innegligible Etiology of Cerebral Venous Sinus Thrombosis. *Neuropsychiatry*. 2018;8(2):519–22.
7. Andersson HC, Marble M, Shapira E. Long-term outcome in treated combined methylmalonic acidemia and homocystinemia. *Genet Med*. 1999;1(4):146–50. doi:10.1097/00125817-199905000-00006.

Author biography

Mukesh Udevir Singh, Assistant Professor https://orcid.org/0000-0002-5296-9724

Harshit Bhargava, Assistant Professor

Cite this article: Singh MU, Bhargava H. Methylmalonic acidemia (MMA) with homocystinuria cblD & cblF types - A rare disorder of vitamin B_{12} metabolism in the western region of India. *Int J Clin Biochem Res* 2023;10(3):247-250.