Highlighting the Importance of Newborn Screening in India by Comparative Analysis of Inborn Errors of Metabolism in High-Risk Babies with Methylmalonic Acidemia.

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Abstract

This is a comparative analysis of 7789 high-risk IEM cases, using the example of methylmalonic acidemia (MMA), a rare metabolic disorder to emphasize the critical role of newborn screening in early diagnosis and management. Case 1 involves a patient not diagnosed at birth through newborn screening, while Case 2 involves a patient diagnosed in the neonatal period due to symptom presentation. The differences in their clinical outcomes underline the importance of early detection through newborn screening programs. The MMA was the most common organic aciduria with an incidence of 1:26 diagnosed among 12 common IEMs causing developmental delay, disabilities, or death in high-risk neonates & children. These 12 IEMs (incidence 1: 26 to 409) with high incidence are strongly recommended as candidate disorders for newborn screening programs in India. This paper compares two cases of MMA to illustrate the significant impact of newborn screening.

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Keywords:
- Newborn screening
- IEMs
- High-risk babies
- MMA
- Prevention

Introduction:

Methylmalonic acidemia (MMA) is an inborn error of metabolism (IEM) inherited as an autosomal recessive metabolic disorder [(1)]. The prevalence of MMA is still unknown in Asian countries like India and China but in European countries, USA& Canada, it is around 1/29000 to 1/ 26000[(2)]. MMA is characterized as a genetically heterogeneous disorder of methyl malonate and cobalamin (cbl; vitamin B12) metabolism. MMA occurs due to a defect in mitochondrial enzyme methyl malonyl-CoA mutase (MCM) which converts methyl malonyl-coenzyme A (CoA) into succinyl-CoA, or a defect in the metabolism of 5'-deoxyadenosylcobalamin, the cofactor of MCM methyl malonic acid that leads to Methylmalonic acid in the blood [(3)]. It leads to various health issues which range from lethal to severe including developmental delays, feeding problems, metabolic crises, and death in severe cases. Early diagnosis and intervention are crucial in managing MMA and preventing severe complications.

Currently, universal newborn screening for metabolic disorders is neither a Government health policy nor is it routinely performed in India [(4)]. Diagnosing and managing Inborn Errors of Metabolism (IEM) in India and other developing countries is challenging, as most advanced comprehensive metabolic tests using mass spectrometry are not routinely available. Metabolic evaluation is typically done only in very sick neonates or children with high suspicion of symptoms

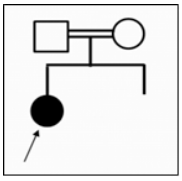
like lethargy, coma, metabolic acidosis, seizures, hyperammonemia, etc [5]. This paper compares two cases of MMA to illustrate the significant impact of newborn screening. The given case comparison underscores the importance of newborn screening programs in India in preventing severe childhood complications and enhancing the quality of life for patients with MMA and best clinical outcomes.

Case presentation:

Patient Details: In the present study, the two cases of MMA are clinically & metabolically compared as below-

Case 1: A female child born of a consanguineous marriage was referred by a pediatrician for Whole Exome Sequencing at 1 year of age due to a history of lethargy, vomiting respiratory distress since day 1 of life, and severe metabolic acidosis. The patient had not undergone newborn screening as it was not routinely available as a government health policy for newborn screening. Unfortunately, the child passed away by the time the exome report was available (Case 1-Pedigree) (Figure 1).

Figure 1: Case 1-Pedigree analysis



The Whole Exome Sequencing by NGS revealed a mutation in the MMAA gene, but no screening or metabolic workup had been performed initially (Table 1).

Table 1: The Whole Exome sequencing of Case 1 showing details about gene mutation

Gene (Transcript)	Location/ Variant	Zygosity	Disease (OMIM)	Inheritance/ Classification
MMAA (NM_172250.3)	Chr4:146575176 c.850G>T / p.Asp284Tyr)	Homozygous	Methylmalonic Aciduria, cblA Type (OMIM#251100)	Autosomal Recessive, Variant of Unknown Significance

Case 2: A 20-year-old boy has been following with us for the last 20 years with his parents (Figure 3). He had undergone newborn screening by urinary GCMS testing at 1 month of age during NICU. During the neonatal period, he presented with metabolic acidosis, refusal to feed, and failure to thrive. The mother noticed similar clinical symptoms in an earlier sibling who had died at the neonatal stage with severe metabolic acidosis and other similar symptoms (Figure 2) and hence became alert of the situation & informed the neonatologist.

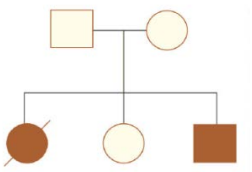


Figure 2: Pedigree analysis of Case 2

The metabolic workup was quickly undertaken and urinary GCMS analysis confirmed the diagnosis of MMA. The therapy management of the baby was quickly started with a high dose of cobalamine, folate &carnitol, etc. along with Sodium benzoate for acidosis over a long period and normal growth was achieved (Figure 3). He has been since then appropriately put on a low protein & high carbohydrate diet and periodic monitoring with urinary GCMS analysis every 6 months to monitor the abnormal biomarkers of MMA. The diet & dose adjustments were done if high abnormal markers of MMA were detected.

(A) **(B)**

Figure. 3: A) Neonate diagnosed with MMA; B) Same patient at the age of 20 years.

Investigation:

The urine samples of high-risk cases were sent to the laboratory along with detailed family, birth & clinical history. The pedigree charts were drawn as shown for Cases 1 & 2 (Figures 1 & 2). The routine metabolic tests for ammonia, lactate, ABG analysis, etc. were informed. The urine-soaked, air-dried filter paper was sent in the envelope for Gas Chromatography/Mass Spectrometry (GCMS) metabolic profiling which is a non-invasive method for simultaneous analysis of 140+ metabolic conditions (Figure 4). The urine sample was processed for GC/MS analysis & data was analyzed using the method of Matsumoto &Kuhara (1996) [6].

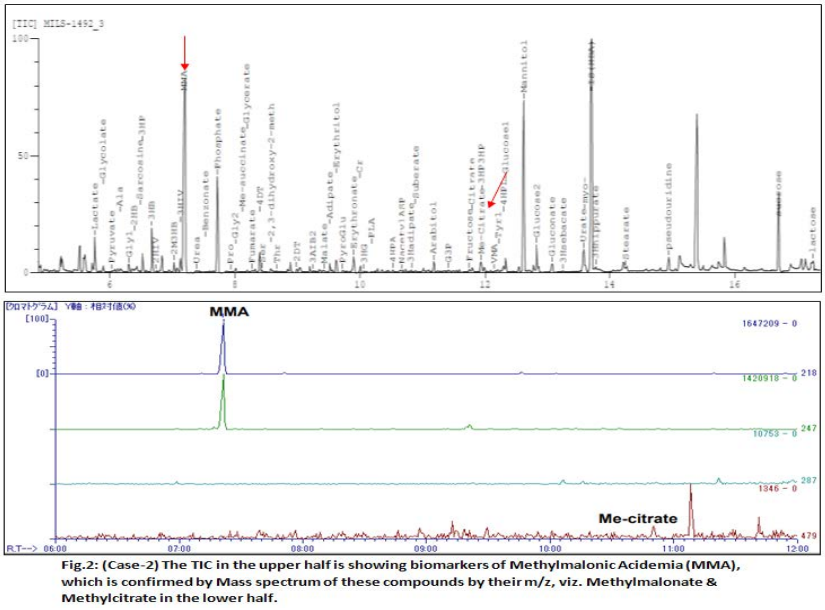


Fig.2: (Case-2) The TIC in the upper half is showing biomarkers of Methylmalonic Acidemia (MMA), which is confirmed by Mass spectrum of these compounds by their m/z, viz. Methylmalonate & Methylcitrate in the lower half.

Figure 4: The TIC in the upper half shows biomarkers of Methylmalonic Acidemia (MMA), which is confirmed by the Mass Spectrum of these compounds by their m/z, viz. Methylmalonate & Methylcitrate in the lower half.

Management & Outcome:

Later, at the age of 19, genetic counseling was done to the family members, emphasizing the identification of mutation for familial inherited condition which is significant for further prevention of the disease in the family. Next-Generation Sequencing (NGS) identified a mutation in the MMADHC gene (Table 2). This gene is involved with Combined MMA and homocystinuria cblD type (MAHCD) and or isolated homocystinuria, and isolated MMA of complementation group cblD. However, as per the phenotypes& mass spectrometry correlation patient was suffering from Combined MMA and homocystinuria cblD type (MAHCD).

Table 2: The Whole Exome sequencing showing details about gene mutation-Case2

Gene (Transcript)	Location/ Variant	Zygosity	Disease (OMIM)	Inheritance/ Classification
MMADHC ENST00000428879	Chr 1p34.1 Exon 3/ c.202C>T(p.Gln68Ter)	Homozygous	Combined MMA a and homocystinuriacblD type (MAHCD), isolated homocystinuria, and isolated MMA of complementation group cblD	Autosomal recessive, Pathogenic

Early detection and precise diagnosis at 3 months of age led to appropriate therapy with vitamin B12, carnitine, and biotin, along with periodic metabolic profiling. The patient's clinical status has shown improvement, and he is currently being monitored at the age of 20 years; going to college for finance studies indicating normal intellectual development.

Discussion:

The periodic data analysis revealed MMA as the most common organic aciduria in 7789 referral high-risk cases with an incidence of 1:26 among 12 IEMs which showed high incidence varying from 1in 26 to 1 in 409 (Table-3).

The results of this comparative analysis offered evidence of the profound impact of newborn screening on the outcomes for patients with MMA. In Case 1, the absence of newborn screening resulted in a delayed diagnosis, leading to severe metabolic acidosis and the eventual death of the patient (refer to Case 1 Pedigree – Figure 1). The lack of early intervention and metabolic workup significantly contributed to the poor outcome. The exome report, which came too late, confirmed a mutation in the MMAA gene which revealed VUS but strongly correlated with the clinical phenotypes. The case offered evidence that early detection and intervention could have potentially altered the clinical course.

Table 3: Recommendation of 12 NBS Disorders Based on Overall Incidence of IEMs in 20 Years

High- Risk Screening Data by GC/MS Comprehensive Test (2005-2024)

* Overall Incidence of 12 IEMs is 1: 26 to 1: 409 (2024 Analysis)

Total N = 7789; Normal = 5805 (75 %); IEM Abnormality = 942 (12 %)

Sr. No	Inborn Error Of Metabolism	2005 N= 2040 Abn = 176 - 8.6%	2015 N= 3341 Abn= 291- 8.7%	2020 N= 6510 Abn=681 – 10%	2024 N= 7789 Abn= 942-12%
1.	Methylmalonic Acidemia (MMA)	1: 55 (37)	1: 64 (52)	1: 30 (214)	1: 26 (291)
2.	Tyrosinemia / Hepatic Dys	1: 78 (26)	1: 88 (38)	1: 72 (55)	1: 90 (86)
3.	Hyperglycinemia	1: 146 (14)	1: 119 (28)	1: 171 (38)	1: 185 (42)
4.	Glutaric AciduriaType1	1: 102 (20)	1: 90 (38)	1: 90 (73)	1: 94(82)
5.	Galactosemia	1: 136 (15)	1: 176 (19)	1: 130 (50)	1: 86 (90)

6.	Maple Syrup Urine Disease(MSUD)	1: 156 (13)	1: 239 (14)	1: 99 (66)	1: 89 (87)
7.	Propionic Acidemia (PA)	1: 170 (12)	1: 176 (19)	1: 105 (62)	1: 101(77)
8.	Urea Cycle Disorder (UCD)	1: 170 (12)	1: 134 (25)	1: 186 (35)	1: 194 (40)
9.	Fructose-1,6-Diphosphatase Def. (FDPD)	1: 136 (15)	1: 134 (25)	1: 217 (30)	1: 149 (52)
10.	Multiple Carboxylase Def. (MCD)	1:510 (4)	1: 257 (13)	1: 260 (25)	1: 216(36)
11.	Isovaleric Acidemia (IVA)	1: 680 (3)	1: 835 (4)	1: 591 (11)	1: 409 (19)
12.	Beta-Ketothiolase deficiency	- -	1: 304 (11)	1: 383 (17)	1: 194(40)

In contrast, Case 2 benefited from newborn screening, which facilitated early diagnosis and prompt initiation of appropriate therapy. The newborn screening by GCMS at 1 month of age allowed for the identification of MMA, enabling timely treatment with vitamin B12, carnitine, and biotin and normal development. The patient's condition was closely monitored through periodic metabolic profiling, ensuring the absence of abnormal markers and preventing severe complications. The subsequent NGS at age 19 years provided further insights into the pathogenic mutation in MMADHC gene at Chr 1p34.1 Exon 3/c.202C>T (p. Gln68Ter) inherited as autosomal recessive responsible for the congenital metabolic disorder (Table 2). The patient has shown significant clinical improvement and continues to lead a better quality of life; at present studying for finance graduation and is well aware of his diet and regular medicine, highlighting the efficacy of early detection and ongoing management.

Conclusion:

The study highlights a dire need for comprehensive newborn screening programs for preventable IEMs using mass-spectrometry to ensure early detection and management of not only Methylmalonic Acidemia (MMA) but also 12 common preventable metabolic disorders. Early diagnosis through newborn screening facilitates timely and appropriate interventions, substantially improving patient outcomes and quality of life. The significant contrast in outcome between the two cases in this study emphasizes the life-saving potential of newborn screening in preventing severe complications associated with MMA. Thus, it is imperative to adopt widespread newborn screening practices to promptly identify and manage various preventable childhood congenital metabolic disorders like MMA. This proactive approach can prevent fatalities, reduce morbidity, and enhance the overall health and well-being of affected individuals.

Since the majority of the IEMs are also autosomal recessive genetic disorders, genetic counseling about the recurrence risk& nature of inheritance is essential for families who have/ had one affected child. Many cases are asymptomatic and undetected; hence, we report this case to underscore the importance of newborn screening programs, including MMA for early detection and intervention. Early screening, confirmed diagnosis, and preventive measures can improve survival rates, prevent childhood morbidity & mortality, and thereby subsequently reduce a national burden.

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