Original Article

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Expanded Screening of Inherited Metabolic Disorders by Tandem Mass Spectrometry: A Hospital-based Cross-sectional Study from a Single Paediatric Centre in Southern India

Biochemistry Section

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ABSTRACT

Introduction: Inborn Errors of Metabolism (IEMs) are a heterogeneous group of genetic disorders that often present in infancy and early childhood. Expanded screening using Tandem Mass Spectrometry (TMS) enables simultaneous detection of multiple metabolic disorders and facilitates early diagnosis and intervention.

Aim: To determine the spectrum and pattern of Inherited Metabolic Disorders (IMD) identified through expanded screening using TMS in a hospital-based paediatric population.

Materials and Methods: The present hospital-based cross-sectional study was conducted at the Institute of Child Health and Hospital for Children, Chennai, Tamil Nadu, India, from July 2021 to June 2024 and included 3,817 paediatric patients aged two days to 12 years who were clinically suspected of having IMD. Screening was performed using TMS on dried blood spot samples. Descriptive statistical analysis was carried out, and results were expressed as numbers and percentages using Microsoft Excel 2010.

Results: Out of 3,817 screened children, 93 cases (2.44%) were diagnosed with IMD, comprising 22 distinct conditions. The most frequently detected disorders were Glutaric Acidaemia Type I (12 cases; 12.90%), Propionic/Methylmalonic Acidaemia (MMA) (11 cases; 11.83%), and Maple Syrup Urine Disease (MSUD) (7 cases; 7.52%). Approximately, 75.27% (70/93) of affected children were diagnosed within the first year of life.

Conclusion: Expanded screening using TMS is an effective diagnostic approach for identifying a wide spectrum of IMDs in clinically suspected paediatric patients and highlights the need for wider implementation in tertiary care settings.

Keywords: Aminoacidopathy, Glutaric Acidaemia, Inborn errors of metabolism, Newborn screening

INTRODUCTION

IEMs are due to impaired activity of enzymes, transporters, or co-factors and result in the accumulation of abnormal metabolites (substrates) proximal to the metabolic block or decreased formation of essential products [1]. IEM typically present in the newborn period or in infancy, affecting the ability to convert nutrients or to use them for energy production [1]. The biochemical diagnosis of IEM and treatment monitoring involve analysis of metabolites, enzymatic activity, and/or molecular structure [2,3]. The most important achievement in expanded Newborn Screening (NBS) has been the use of TMS (MS/MS) as a tool for the detection of IEM [2,3]. In a single dried blood spot, TMS (MS/MS) is capable of measuring multiple analytes like amino acids, acylcarnitines, nucleosides, succinylacetone, and lysophosphatidylcholines, which enables the screening of IMDs [2,3]. The Expanded Screening for IEM is done for aminoacidopathies, fatty acid oxidation disorders, and organic acid disorders [4].

In aminoacidopathies, enzymes necessary for the metabolism of certain amino acids are unavailable or have reduced activity. As a result, the concentration of the affected amino acids and alternative metabolites (e.g., succinylacetone in Tyrosinaemia Type I) increases in the infant's body, which will have severe deleterious effects on the infant's health, including death [5,6]. Maple Syrup Urine Disease (MSUD) is caused by a disorder of branched-chain amino acid metabolism, resulting in elevated levels of Leucine (Leu), Isoleucine (Ile), and Valine (Val) in the blood. If untreated, lethargy progressing to coma, developmental delay, and convulsions will develop [7].

Urea cycle disorders are caused by a deficiency in one of the enzymes in the urea cycle. Severe hyperammonaemia results in accumulation of ammonia and its precursor metabolites in the body and can potentially lead to coma, seizures, and eventual death. In Argininosuccinate Lyase Deficiency, the enzyme responsible for the cleavage of Argininosuccinic acid (ASA) to arginine and fumaric acid is deficient and therefore leads to an elevated level of ASA in blood [8,9].

Free carnitine and acylcarnitines are markers for fatty acid oxidation disorders or organic acidurias. In fatty acid oxidation disorders {e.g., Carnitine Uptake Defect (CUD) and Medium-Chain Acyl-Coa Dehydrogenase (MCAD) deficiency}, enzymes necessary for fatty acid breakdown are unavailable or have reduced activity. Failure to diagnose fatty acid oxidation disorders may result in excessive fat build-up in the liver, heart, and kidneys. This build-up can cause a variety of symptoms, ranging from hepatic failure, encephalopathy, heart and eye complications to general problems with muscle development [10]. The metabolic pathways of organic acids are disrupted in organic acid disorders (e.g., Isovaleric Acidaemia and Glutaric Acidaemia), leading to accumulation of the acids in blood and urine. The accumulation of organic acids in blood alters the acid-base balance, resulting in clinical symptoms, including metabolic acidosis, ketosis, hyperammonaemia, failure to thrive, sepsis, or coma [11].

The prevalence of IEMs differs between countries because of the different IEM screening methods used and different IEM classifications. The birth prevalence of IEM in the Eastern Mediterranean region is about 76/100,000 live births [12]. In India, the prevalence of IEM is one in 2,497 newborns [13]. There are no global estimates of the burden of morbidity or mortality associated with IEM. Due to improvements in healthcare and laboratory testing facilities in India, metabolic disorders are increasingly being recognised. Expanded NBS is not a universal public health program in our country as compared to most developed countries, like the United States, many European countries, or Australia. The expanded

screening for IEM of high-risk babies is of great importance because early treatment in positive cases may prevent irreversible clinical consequences like mental retardation, motor deficit, developmental regression, or death. The study was conducted in a government paediatric tertiary care hospital in Southern India that had clinical or familial suspicion of IEM, as there is limited available data on large-scale studies of IEMs in Southern India. The detection of IEM was carried out by analysis of amino acids, acylcarnitines, nucleosides, succinylacetone, and lysophosphatidylcholines by TMS (MS/MS). The objective of the present study is to determine the detection rate and characterise the spectrum of IMDs detected through expanded screening using TMS among paediatric patients at a single tertiary care centre in Southern India.

MATERIALS AND METHODS

The present cross-sectional study was conducted at the Institute of Child Health and Hospital for Children, Chennai, Tamil Nadu, India. The data were collected from July 2021 to June 2024 and were analysed at a point in time during July 2024 for determining the detection rate and spectrum of aminoacidopathies, fatty acid oxidation disorders, and organic acid disorders in a single paediatric centre in Southern India. The study was approved by Institutional Ethics Committee, Madras Medical College, Chennai (IEC No. 06092024). Informed consent was obtained from all participants included in the study.

Inclusion criteria: Paediatric patients in the age group between two days to 12 years clinically suspected with symptoms suggestive of IEM, including seizures, developmental delay, hypoglycaemia, failure to thrive, metabolic acidosis and unexplained encephalopathy for whom an expanded screening for IEM was requested were included in the current study. The minimum age of two days was selected to ensure metabolic stabilisation following birth and to reduce the likelihood of false-negative results due to physiological metabolic transitions in the immediate neonatal period.

Exclusion criteria: Patients who had received a blood transfusion in the previous three months were excluded from the study.

Study Procedure

The expanded screening for IEM was carried out by TMS (LCMS-8040 coupled with Prominence HPLC system-Shimadzu) using dried blood spots. A total of 13 Amino acids, 33 acylcarnitines, two nucleosides, succinylacetone, and four lysophosphatidylcholines were considered for the interpretation of expanded screening of IEM. The measurement of amino acids, succinylacetone, free carnitine, acylcarnitines, nucleosides, and lysophospholipids involves extraction of analytes from dried blood spots with a solution containing labeled internal standards and analysis using a TMS (MS/MS) system in Multiple Reaction Monitoring (MRM) mode. The response of each analyte relative to its corresponding internal standard is proportional to the analyte concentration.

The MS/MS system consists of a sample delivery system, which is coupled to Electrospray Ionisation (ESI) and a triple quadrupole mass spectrometer. In the ESI, the sample is converted to a gaseous phase where the analytes acquire a positive or negative charge. The ions are further transferred into the mass spectrometer, which consists of two sets of quadrupoles (MS1 and MS2) and a collision cell (argon gas) between the quadrupoles. The mass spectrometer sorts and separates the ions according to their mass-to-charge ratio (m/z value) [14]. In the MRM acquisition mode, MS1 is set to select a particular precursor ion. After MS1 selection, the precursor ion is sent to the collision cell where Collision-Induced Dissociation (CID) takes place, and the precursor ion is fragmented into several product ions [10]. Thereafter, only a selected specific product ion is allowed to pass through MS2 to reach the detector and to record an analyte-specific precursor-product ion MRM-transition. Data acquisition and processing are performed by the software package included with the system.

STATISTICAL ANALYSIS

The statistical analysis was performed using Microsoft Excel 2010. The descriptive data were presented as numbers and percentages.

RESULTS

A total of 3,817 clinically suspected paediatric patients were screened using expanded TMS during the study period. Of these, 93 children were confirmed to have IMDs, resulting in a detection rate of 2.44% (93/3,817).

The spectrum and frequency of IMDs identified in the study are summarised in [Table/Fig-1]. A total of 22 distinct metabolic disorders were detected. Glutaric Acidaemia Type I was the most frequently diagnosed disorder (12 cases/93; 12.90%), followed by Propionic/MMA (11 cases/93; 11.83%) and MSUD (7 cases/93; 7.52%). Argininemia (ARG), Phenylketonuria (PKU), and CUD were each observed in six cases/93 (6.45%), while Multiple Carboxylase Deficiency (MCD) was detected in five cases/93 (5.37%). Several disorders, including Citrullinemia Type I, MCAD deficiency, Very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency, and Adenosine Deaminase (ADA) deficiency, were identified as single cases (1.07% each).

The age at diagnosis ranged from 11 days to nine years. A majority of affected children were diagnosed within the first year of life (70 cases/93; 75.27%). Organic acidaemias and aminoacidopathies were predominantly identified during infancy, whereas disorders such as Arginemia or Arginase Deficiency (ARG), hypermethioninaemia, and CUD were more commonly detected beyond infancy. The age-wise and gender-wise distribution of diagnosed disorders is shown in [Table/Fig-1].

S. No.	Disorder name	Total cases	Percentage	Age at diagnosis	Male	Female
1	Argininemia (ARG)	6	6.45%	9 years	3	3
2	Argininosuccinic aciduria (ASA)	3	3.22%	1 month	1	2
3	Glutaric Acidaemia Type I (GA I)	12	12.90%	6 months	7	5
4	Citrullinemia Type I	1	1.07%	9 months	1	0
5	Phenylketonuria (PKU)	6	6.45%	8 months	6	0
6	Maple Syrup Urine Disease (MSUD)	7	7.52%	2 months	2	5
7	Non-ketotic Hyperglycinemia	4	4.30%	11 days	2	2
8	Hyperprolinaemia Type I / II	4	4.30%	9 months	1	3
9	Hypertyrosinaemia	4	4.30%	1 year	3	1
10	Propionic / Methylmalonic Acidaemia (MMA)	11	11.83%	2 months	5	6
11	Isovaleric Acidaemia (IVA)	4	4.30%	15 days	2	2
12	3-Hydroxy-3-methylglutaric aciduria	2	2.15%	25 days	2	0
13	β-Ketothiolase Deficiency	2	2.15%	11 months	1	1

14	3-Methylcrotonyl-CoA Carboxylase Deficiency	2	2.15%	5 months	0	2
15	Multiple Carboxylase Deficiency (MCD)/ Biotinidase Deficiency	5	5.37%	6 months	2	3
16	Hypermethioninaemia	3	3.22%	4 years	3	0
17	MCAD Deficiency	1	1.07%	7 months	1	0
18	VLCAD Deficiency	1	1.07%	3 years	0	1
19	CPT-I Deficiency	4	4.30%	2.6 years	0	4
20	Carnitine Uptake Defect (CUD)	6	6.45%	3.4 years	3	3
21	ADA Deficiency (SCID)	1	1.07%	3 years	1	0
22	SCAD / IBD / Ethylmalonic Encephalopathy	4	4.30%	6 months	2	2
	Total	93	100%		48 (51.6%)	45 (48.4%)

[Table/Fig-1]: Distribution of Inherited Metabolic Disorders (IMD) by age, gender, and percentage.

Among the 93 diagnosed cases, 48 were males (51.61%) and 45 were females (48.39%), indicating an almost equal gender distribution. PKU and MCAD deficiency were detected exclusively in males, while 3-Methylcrotonyl-Coa Carboxylase (MCC) deficiency and Carnitine Palmitoyltransferase I (CPT-I) deficiency were observed only in females. No consistent gender predilection was observed for the remaining disorders.

The disease-specific primary and secondary biomarker cut-off values used for screening aminoacidopathies, fatty acid oxidation disorders, and organic acid disorders are summarised in [Table/Fig-2]. These cut-offs were established based on the percentile distribution of amino acids and acylcarnitines observed in affected subjects, with values exceeding the 99th percentile considered as upper cut-offs and values below the 1st percentile considered as lower cut-offs for the respective disorders.

S. No.	Disorder name	Primary marker	Secondary marker
1	Argininemia (ARG)	Arg=258.93	Arg/Orn=5.23
2	Glutaric acidaemia-Type I (GA I)	C^5DC=0.62	C^5DC/C^5OH=7.38, C^5DC/C^8=62, C^5DC/C^{16}=1.48
3	Citrullinemia Type 1 (CIT I)	Cit=1222.57	Cit/ Arg=129
4	Phenylketonuria (PKU)	Phe=1036.84	Phe/Tyr=32.86
5	Maple syrup urine disease (MSUD)	Leu + Ile=1961.91, Val=478.05	(Leu + Ile)/ Phe=45.3, Val/Phe=8.16, (Leu + Ile)/ Ala=28.86
6	NonketoticHyperglycinemia	Gly=1057.36	-
7	Hyperprolinaemia Type I/ Type II	Pro=771.05	-
8	Propionic Acidaemia (PA)/ Methylmalonicacidaemia (MMA) (PROP/MUT)	C^3=9.99	C^3/C^2=1.69, C^3/C^{16}=11.34
9	Isovalericacidaemia (IVA)	C^5=4.81	C^5/C^0=1.97, C^5/C^2=1.55
10	3-Hydroxy-3-methylglutaric aciduria (HMG)	C^5-OH=4.06	C^6-DC=1.12
11	ß-Ketothiolase deficiency (BKT)	C^5-OH=0.96	C^5:1=0.21
12	3-Methylcrotonyl-CoA carboxylase deficiency (3MCC)	C^5-OH=2.02	C^5-OH/C^8=12.7
13	Multiple Carboxylase Deficiency (MCD)/ Biotinidase deficiency	C^5-OH=5.66	Biotinidase enzyme assay=1.42 nmoles/ml/min
14	Hypermethioninemia	Met=282.24	Met/Phe=4.44, Met/Cit=14.35
15	Medium-Chain Acyl-Coa Dehydrogenase deficiency (MCAD)	C^8=3.64	C^6=1.17, C10:1=1.30, C^8/C^2=0.59, C^8/C^{10}=115.82
16	Carnitine Palmitoyltransferase-Type 1 deficiency (CPT I)	C^0=148.68	C^0/ (C^{16}+C^{18})=161.86
17	Carnitine Uptake Defect/ carnitine transport defect (CUD)	C^0=5.13	(C^0 + C^2 + C^3 + C^{16} + C^{18}:1 + C^{18})/ CIT=0.92
18	Severe combined immunodeficiency (ADA Deficiency)	dADO=1.26	ADO=2.50

[Table/Fig-2]: The cut-off values of primary and secondary markers for screening of metabolic disorders.

DISCUSSION

Expanded NBS using TMS (MS/MS) has significantly enhanced the early detection of IMDs. These disorders are genetic conditions that disrupt normal metabolic processes, leading to the accumulation of toxic substances or deficiencies in essential compounds. Early identification and treatment are crucial in preventing severe complications such as neurological impairment, organ damage, and early mortality. Specific prevalence data for IMDs in India are scarce, indicating a need for more comprehensive studies. A pilot study from Egypt reported an IMD prevalence of one in 1,944 newborns, highlighting a significant burden likely due to high consanguinity rates [15]. In Saudi Arabia, the incidence of IEM was found to be one in 1,381, one of the highest reported globally, also attributed to consanguineous marriages [16]. In China, studies have shown varying prevalence rates for IEM across different regions, with incidences ranging from one in 1,178 to one in 8,304, indicating regional genetic diversity [17]. The current study presents the detection rate and spectrum of IMDs in a single paediatric centre in Southern India and compares the findings with global studies to identify similarities and variations in disease prevalence, genetic influences, and screening efficiency.

Data from India, though limited, demonstrate comparable trends. A population-based NBS study from Andhra Pradesh using MS/MS reported an IMD prevalence of approximately one in 4,946 newborns, with MSUD, Propionic Acidaemia (PA), MMA, and Glutaric Acidaemia Type I (GA I) being among the most frequently identified disorders [18]. These findings align with the present study from Southern India, where GA I, PROP/MUT, and MSUD emerged as the most common disorders, suggesting a broadly similar disease spectrum within the region. The three most common disorders identified in this study were: Glutaric Acidaemia Type I (GA I)-12 cases (12.90%), Propionic/MMA (PROP/MUT)-11 cases (11.83%), and MSUD-seven cases (7.52%). Glutaric Acidaemia Type I (GA I) is a disorder caused by a deficiency of glutaryl-CoA dehydrogenase, resulting in the accumulation of glutaric acid and related metabolites, leading to progressive dystonia and neurodegeneration. GA I accounted for 12.90% of cases, with glutarylcarnitine (C5DC) as the primary marker and C5DC/C8 and C5DC/C16 ratios as secondary markers. Studies from China have reported a prevalence of one in 115,188 and one in 115,010 from Taiwan [19,20]. The observed average glutarylcarnitine (C5DC) in this study is 0.62 µmol/L, which is significantly higher than the published cut-off of >0.29 µmol/L, reinforcing the diagnosis of GlutaricAcidaemia Type I (Chace DH et al., 2002) [21]. Indian tertiary-care studies using MS/MS for screening and Gas Chromatography-Mass Spectrometry

(GC-MS) for confirmation have consistently reported GA I as one of the predominant organic acidaemias, particularly among clinically symptomatic infants [22]. The elevated C^5DC levels observed in the present study are comparable to these reports, supporting the robustness of MS/MS-based detection of GA I even beyond the neonatal period.

PA and MMA are metabolic disorders resulting from defects in the metabolism of propionic acid and methylmalonic acid, leading to metabolic acidosis, vomiting, lethargy, and developmental delay. The combined prevalence of PA and MMA in this study was 11.83%, with elevated propionylcarnitine (C_3) as the primary marker and C^3/C^2 and C_3/C_{16} ratios as secondary markers. In Suzhou, the combined prevalence of PA and MMA was 1 in 40,166, and in Taiwan, 13 cases of MMA among 1,495,132 newborns, indicating a prevalence of approximately 1 in 115,010 [23]. The observed average propionylcarnitine (C_3) is 9.99 µmol/L, surpassing the published cut-off of >6.88 µmol/L, suggesting metabolic dysfunction consistent with PA or MMA (Rinaldo P et al., 2008) [24].

MSUD is a disorder of branched-chain amino acid metabolism caused by a defect in the branched-chain alpha-ketoacid dehydrogenase complex, leading to the accumulation of leucine, isoleucine, and valine. Symptoms include feeding difficulties, developmental delay, seizures, and the characteristic maple syrup odour in urine. In this study, MSUD was detected in 7.52% of positive cases, identified by elevated leucine (Leu)/isoleucine (Ile), and valine (Val) levels. The Andhra Pradesh study identified 1 case of MSUD among 4,946 newborns, suggesting a prevalence of one in 4,946, whereas in Cyprus, MSUD was among the most common aminoacidopathies, following hyperphenylalaninemias [18,25]. The higher proportion of MSUD in the present study likely reflects delayed diagnosis and inclusion of symptomatic children rather than exclusive neonatal screening.

The other relatively frequent disorders identified in the present study include: ARG-six cases (6.45%), PKU-six cases (6.45%), CUD-six cases (6.45%), and MCD-five cases (5.37%). PKU is an autosomal recessive disorder caused by a deficiency in the enzyme phenylalanine hydroxylase, which leads to the accumulation of phenylalanine in the blood, causing intellectual disability and neurological damage if untreated. PKU accounted for 6.45% of positive cases in the current study, identified by elevated phenylalanine (Phe) levels and an increased Phe/Tyrosine (Tyr) ratio. The observed average value of phenylalanine in the present study is 1036.84 µmol/L, far exceeding the cut-off value of >85.45 µmol/L, indicating a strong presence of the disorder [26]. The MCAD deficiency is a disorder of fatty acid oxidation caused by mutations in the Acyl-CoA Dehydrogenase Medium Chain (ACADM) gene, leading to hypoglycaemia, lethargy, seizures, and sudden infant death if left untreated. In the present study, MCAD was detected in 1.07% of cases, with octanoylcarnitine (C_8) as the primary marker. The prevalence is lower than in Galicia, Spain (1 in 16,951) (Couce ML et al., 2017) [27].

The MCD accounted for 5.37% of positive cases in this study, identified by elevated C_5OH acylcarnitine levels and low biotinidase enzyme. The C_5OH acylcarnitine identified can be either 3-hydroxyisovalerylcarnitine or 2-methyl-3-hydroxybutyrylcarnitine. Since these two compounds are isomers and MS/MS analysis cannot differentiate the two compounds, the elevation of C_5OH could occur in one of the following organic acidaemias, namely MCD/HolocarboxylaseSynthetase Deficiency, Biotinidase Deficiency, 3-MCC deficiency (3MCC), 3-Hydroxy-3-Methylglutaric Aciduria (HMG), Beta-Ketothiolase Deficiency (BKT), 2-Methyl-3-Hydroxybutyric Aciduria (2M3HBA), and 3-Methylglutaconic Aciduria (3MGA). The observed average C_5OH acylcarnitine in this study is 4.06 µmol/L, surpassing the reference cut-off of >0.82 µmol/L, indicating potential defects in biotin metabolism and MCD (Therrell BL et al., 2015) [28]. Elevated C_5OH and tiglylcarnitine (C5:1) were reported in two cases in this study. The observed average tiglylcarnitine (C5:1) in this study is 0.21 µmol/L, which is above the reference threshold of >0.18 µmol/L, which may suggest β-ketothiolase deficiency (Yang Y et al., 2019) [29].

Some diseases, however, such as fatty acid oxidation defects or milder variants of classic metabolic disorders, may not be detected until adulthood. Despite the long asymptomatic period, their consequences can still be devastating and lead to death. Therefore, identification and treatment of these diseases before irreversible damage occurs is critical. In contrast to other more common diseases, the treatment of IEM is lifelong and requires frequent monitoring. Many Indian studies, including the present one, report delayed diagnosis beyond the neonatal period due to limited universal NBS coverage [30]. This delay contributes to higher metabolite concentrations at diagnosis and increased morbidity, underscoring the urgent need for nationwide implementation of expanded NBS programs in India.

Limitation(s)

As the present study was a hospital-based study involving clinically suspected children rather than a population-based NBS program, the findings may not reflect the true population prevalence and are subject to referral and selection bias. Genetic confirmation of the detected IMDs could not be performed due to resource and cost constraints that limited access to routine molecular diagnostic testing. Despite these limitations, the study provides valuable region-specific data on the spectrum and relative frequency of IMDs in Southern India and underscores the need for integrated biochemical, molecular, and longitudinal diagnostic approaches in future studies.

CONCLUSION(S)

Expanded screening for IEM using TMS (MS/MS) has significantly improved the early detection and diagnosis of IMDs. The three most common disorders identified in this study were: GlutaricAcidaemia Type I (GA I)-12 cases (12.90%), Propionic/MMA (PROP/MUT)-11 cases (11.83%), and MSUD-seven cases (7.52%). The use of both primary and secondary markers enhances diagnostic specificity and reliability, reinforcing the necessity of region-specific screening strategies to improve early detection and management of IMDs. The comparison of IMD prevalence across different populations highlights significant regional variations due to genetic, dietary, and environmental factors. Further studies, including whole-genome sequencing and long-term follow-ups, will be essential in refining screening strategies and improving early intervention outcomes.

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