

Inborn Errors of Intermediary Metabolism in Critically Ill Infants at a Tertiary Care Children Hospital

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ABSTRACT

Background:- Inborn errors of intermediary metabolism are complex genetic disorders with clinical heterogeneity. Infants with such disorders present with diverse clinical manifestations ranging from acute life threatening to chronic late onset forms with single or multiorgan involvement.

Objective:- To study the clinical characteristics, spectrum and outcome in critically ill infants, suspected of IEM at a tertiary care children hospital.

Methods:- We screened 136 critically ill infants who fulfilled the inclusion criteria, over a period of two years with ethical clearance from Ethical Clearance Committee of GMC (Ref No. 121/ETH/GMC/ICMR). The clinical characteristics of study group were recorded and investigations which included ABG, lactate, ammonia levels and TMS & GCMS (Tandem Mass Spectrometry & Gas Chromatography Mass Spectrometry) were done. Those patients who were confirmed by TMS & GCMS as having IEM were evaluated for their outcome.

Results:- 136 patients who fulfilled the inclusion criteria, 32 (23.5%) had IEM. Of these 32 patients 12 had organic acidemias, 8 had primary lactic acidosis, 6 had amino acid disorders with 50% as Maple syrup urine disease, 4 had urea cycle disorders (citrullinemia type-I), Acyl Co-A dehydrogenase deficiency 1 & 1 had biotinidase deficiency. These patients mostly presented with fast breathing, vomiting, seizures, refusal of feeds and encephalopathy followed by rapid circulatory & respiratory decompensation. This study found statistically significant association between IEM and, parental consanguinity, history of sib death and sudden clinical deterioration. Mortality rate in diagnosed IEM infants was 75%.

Conclusion:- Suspicion of IEM in critically ill infants is required when there is history of parental consanguinity, history of previous sib death or rapid clinical deterioration. We recommend a large study to determine the prevalence of different types of IEM.

Key words:- Inborn Errors of Metabolism (IEM), Organic Acidemias, MSUD, Urea Cycle Defects, TMS & GCMS.

GLOSSARY: ABG: Arterial Blood Gas, BSR: Blood Sugar Random, CBC: Complete Blood Count, CSF: Cerebro-Spinal Fluid, GCMS: Gas Chromatography Mass Spectrometry, GMC: Government Medical College, IEM: Inborn Errors of Metabolism, KFT: Kidney Function Tests, LFT: Liver Function Test, MSUD: Maple Syrup Urine Disease, NICU: Neonatal Intensive Care Unit, PICU: Paediatric Intensive Care Unit, RTA: Renal Tubular Acidosis, TMS: Tandem Mass Spectrometry

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INTRODUCTION

Inborn errors of metabolism are complex, heterogeneous group of genetic diseases. Individually, they are rare but as a group they remain an important entity in paediatric age group with diverse clinical manifestations ranging from acute life threatening manifestations to chronic late onset forms, with single or multiorgan involvement. Inborn errors of metabolism (IEM) represents a challenge to paediatricians as these disorders manifest in neonatal age and early infancy with limited variety of responses to illness. They also present clinically similar to more common

illnesses of infancy. So, prompt suspicion of these diseases in critically ill infants & the knowledge of initial diagnostic approaches can aid in the selection of appropriate biochemical tests like TMS & GCMS and emergency management measures to be taken. As mortality is high in these infants due to unavailability of specific therapy, an accurate diagnosis is crucial for genetic counselling.

Most neonates in developing countries are not screened for IEM, making prompt & accurate diagnosis critical as soon

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as the clinical manifestations appear. The objectives of the present study are to know the clinical manifestations, spectrum & the outcome of critically ill infants admitted in NICU & PICU who comprise the study group after ruling out other common causes with similar clinical presentation. "Life Cell Diagnostic Division, Keelakottaiyur, Chennai" is a reputed, fully equipped private metabolic laboratory of India where from samples for TMS & GCMS got analysed.

METHODS

This is a prospective observational study conducted in the postgraduate department of paediatrics from 2016 to 2019 after due clearance from the Ethical Clearance Committee of GMC Srinagar (RefNo. 121/ETH/GMC/ICMR).

STUDY GROUP:

INCLUSION CRITERIA

All critically ill infants who were admitted in NICU or PICU of GB Panth Hospital with clinical manifestations of lethargy, poor feeding, convulsions, fast breathing, encephalopathy, fever, developmental delay or unusual odour not explained by common causes (like meningitis or sepsis or seizure due to meningitis or underlying metabolic disorder (like hypoglycaemia, hypocalcemia), metabolic liver disease, pyloric stenosis, RTA, developmental delay due to known cause like cerebral palsy, post kernicterus sequelae, neurodegenerative disorders etc.

EXCLUSION CRITERIA

Patients admitted to NICU or PICU who presented with similar clinical manifestation but these manifestations were explained by common diseases as mentioned above

DATA COLLECTION

The enrolled patients underwent lab investigations like: CBC, ABG, Blood Sugar Random (BSR) LFT, KFT, Blood Culture, Urine Examination, CSF Examination. Other investigations included serum ammonia, serum lactate, urine for ketones and reducing substances. If through these investigations, common diseases like meningitis or sepsis or seizure due to meningitis or underlying metabolic disorder (like hypoglycaemia, hypocalcemia), metabolic liver disease, pyloric stenosis, RTA, developmental delay due to known cause like cerebral palsy, post kernicterus sequelae, neurodegenerative disorders etc. were diagnosed, they were excluded from study group and the rest of the

patients were subjected to TMS & GCMS to look for IEM. Among the study group those who were reported positive by TMS&GCMS were labelled as IEM group and those who were reported negative by TMS & GCMS were labelled as Non IEM group

Dried blood sample collection for TMS is relatively simple & is done by collecting few drops of blood "Heal prick blood" of about 3 mm in diameter on a specialized filter paper of size 15 mm diameter (4 each) provided by the laboratory.

Dried urine samples were collected on another sheet of filter paper size 10cm x 3cm by soaking the paper with freshly voided urine of patients. Samples were left dried for 3 hours. Dried blood samples and dried urine samples were couriered within 24 hours of their collection to the Metabolic Screening Lab "Life Cell Diagnostic Division, Keelakottaiyur, Chennai" for the analysis of TMS & GCMS.

We compared the various parameters/variables of these two groups and were spastically analysed

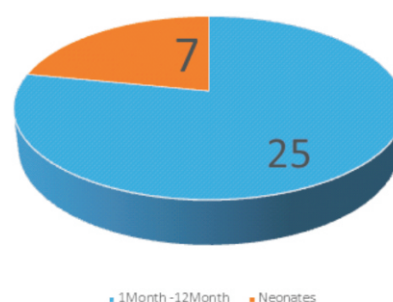
STATISTICAL ANALYSIS

The recorded data was compiled & entered in a spreadsheet Microsoft Excel & then exported to data editor of SPSS version of 25.0. Continuous variables were expressed as mean and categorical variables were summarized as frequencies and percentages. Graphically the data was presented by bar diagrams. Student's independent T-Test, Mann Whitney Test (whichever appropriate) was applied for comparing categorical variables. A P-value of <0.05 was considered statistically significant.

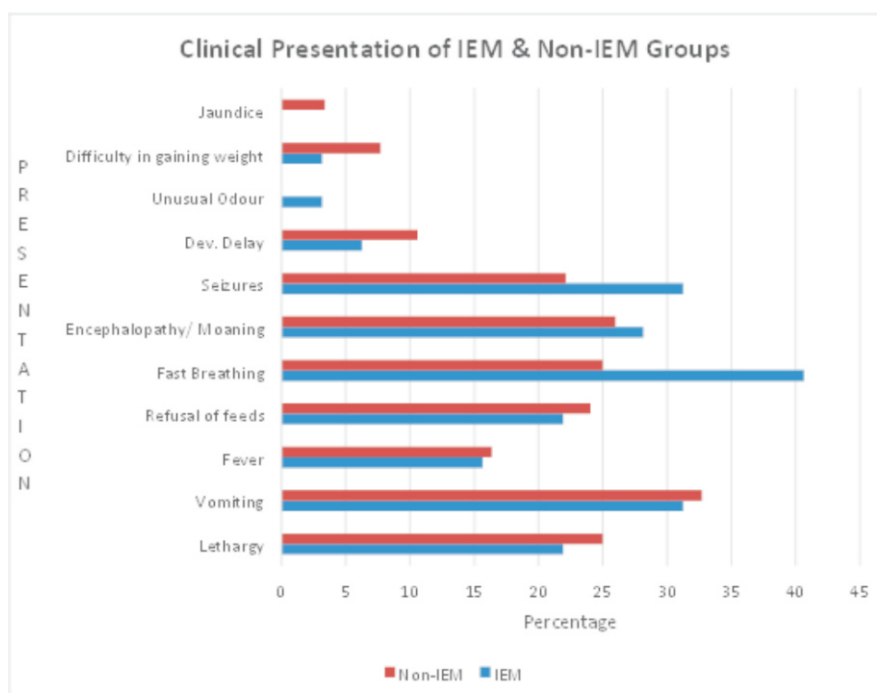
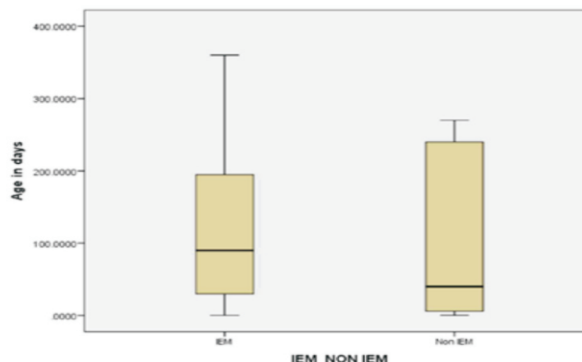
RESULTS

The observations and results that were obtained from the study group are shown in the various Statistical Tables below.

Fig.1: Age distribution of IEM positive patients



Age In days			p-value
IEM	Minimum	0.2	0.507
	Maximum	360.0	
	1st Quartile	30.0	
	Median	90.0	
	3rd Quartile	202.5	
Non-IEM	Minimum	0.2	
	Maximum	270.0	
	1st Quartile	6.0	
	Median	40.0	
	3rd Quartile	240.0	



In IEM group 17 had both history of sib death and consanguinity and 5 had all the three criteria

Distribution of significant variables between iem and non iem group

	Parental consanguinity	History of sib death	Sudden clinical deterioration
IEM group	27	18	5
NON-IEM group	33	24	29
Total	60	42	34

Findings on investigations in iem and non-iem group

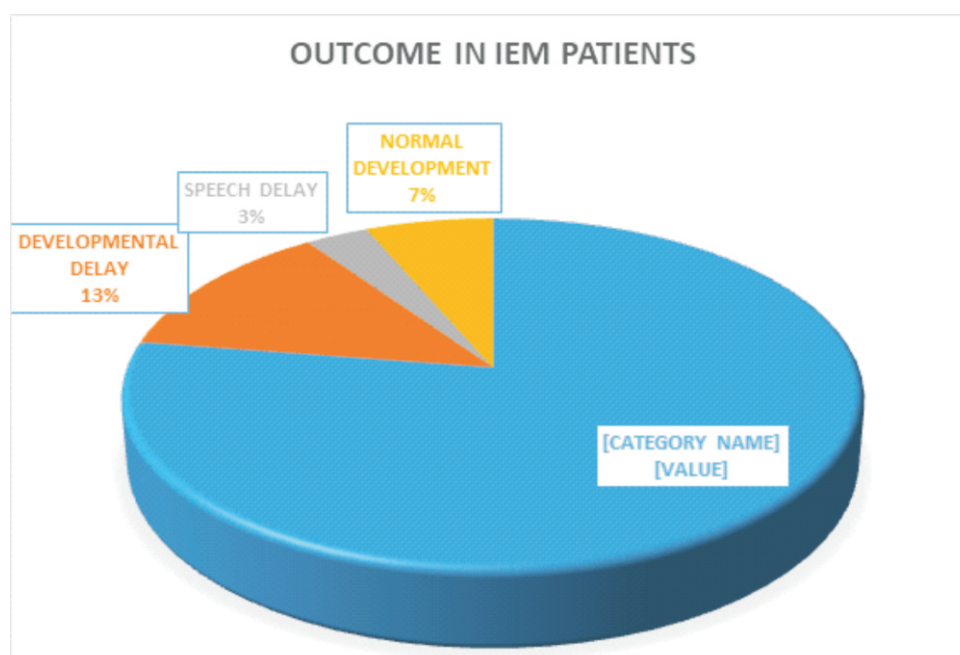
INVESTIGATIONS	IEM GROUP	NON-IEM GROUP	P-VALUE
ABG (Metabolic Acidosis)	27(84.38%)	52(50%)	<0.001
Serum Lactate Raised	11(34.38%)	12(11.54%)	<0.001
Serum Ammonia Raised	8(25%)	21(20.19%)	0.561
Hypoglycemia	5(15.63%)	11(10.58%)	0.438

Spectrum of disorders within iem group

	Frequency	Percentage Overall, In Group
Organic acid oxidation disorders	12	(37.5%)
MMA	6	(18.8%) (50%)
PPA	5	(15.62%) (41.67%)
Glutaric acidemia type 2	1	(3.1%) (8.33%)
Lactic academia	8	(25.0%)
Amino acid disorders	6	(18.75%)
MSUD	3	(9.4%) (50.00%)
Canavan's disease	2	(6.3%) (33.33%)
Non ketotic hyperglycemia	1	(3.1%) (16.66%)
Urea cycle disorders	4	(12.5%)
Citrullinemia type 1	4	(12.5%) (100%)
Fatty acid oxidation disorder	1	(3.1%)
Medium chain acyl Co -A dehydrogenase deficiency	1	(3.1%) (100%)
Biotinidase deficiency	1	(3.1%)
Total	32	(100.0%)

Age at Clinical Onset, Diagnosis, Hospital Stay & Outcome Of IEM Group

Diagnosis	Average age	Number of Patients	Hospital stay	Out come
Methyl Melonic academia	40 days -1 year	6	2-4 days	4 expired within 4 days of hospital admission , 2 survived & are on treatment.
Propionic academia	2 month -1 year	5	24 hrs to 5 days	4 expired within 4 -5 days one surviving with developmental delay & are on treatment
Glutaric acidemia type -II	One year	1	5 days	Developmental delay with seizures
Primary lactic acidosis	2 days -1 year	8	2-5days	7 expired one doing well on treatment
Maple syrup urine disease	1months -1 year	3	2-4days	All expired
Canavan's Disease	2-6 months	2	7 days	Surviving with developmental delay & seizures
Non ketotic hyperglycemia	2days	1	3 days	Expired
Urea cycle defect	2-15 days	4	4-5days	All expired
Medim chain acyl coA deficiency (FAO)	40 days	1	7days	Expired
Biotinidase deficiency	2 months	1	10	Doing well



Most of the babies who died were having an average age of 3 months and died averagely on 5th day of their admission in NICU/ PICU.

DISCUSSION

Discussion: Inborn errors of metabolism affect various biochemical pathways in the body. They usually present in neonatal period or early infancy but can present even in other childhood stages. Although frequency of IEMs in children with sickness has been studied by many, studies analysing its occurrence, specifically in critically ill infants are only few 3,18,29,33. These patients were treated as per the protocols of NICU/PICU of our hospital ranging from fluid resuscitation, electrolyte & pH correction to mechanical ventilation & any other specific intervention as per diagnosis.

Our study population comprised of 136 critically ill infants admitted to NICU/PICU who fulfilled inclusion criteria. The prevalence of IEM in this cohort was 23.5% which is comparable to 25.8% as reported by Satwani et al¹⁸, 32.5% by Rabah M et al³¹, 18.8% by Fateen E et al²⁰ and 23% by Joshi SN et al²¹

In our study population consanguinity was 85% which is comparable to above studies explaining statistically significant association ($p < 0.001$) between consanguinity and prevalence of IEMs. Consanguinity being practiced in the Muslim cultures throughout the world and our study

population being the same, thereby leading to higher prevalence of IEM in our study cohort. IEMs are autosomal recessive disorders and explains why there is significant association between IEM and consanguinity.

Further, our study shows statistically significant association between IEM group and history of previous sib death (56.25%), as comparable to 52.3%, 63.33%, 40% in studies conducted by Syeda Shireen Gul et al, Hanna Al Obaidy and Shehla Choudhry, Maood Khan et al respectively.

Overall mortality in IEM group was 75% with 100% mortality in urea cycle defect & MSUD as compared to overall mortality of 50% reported by Shela Choudhary, Masood khan et al and 28.6% by Jovet P, Touati G et al.^{16,29}. Most of these patients reporting to us in crisis stage and lack of proper resources for treatment in our setup explains the higher mortality

In our study, IEM group had statistically significant association with metabolic acidosis and raised serum ammonia levels, comparable with the studies^{16,37}

Since clinical features were similar with other illnesses like sepsis, CCF, intraventricular hemorrhage etc. so there was no differentiating clinical feature between the study and non study groups. However, fast breathing (acidotic breathing)

was seen more in IEM group.^{16,37}

Developmental delay, unusual odour, & poor weight gain were not the usual symptoms.

CONCLUSION

The critically ill infants with history of sib death, parental consanguinity, fast clinical deterioration and persistent metabolic acidosis with above specified nonspecific clinical features should prompt paediatrician for quick IEM work up as it is key to diagnosis & outcome, besides giving genetic counselling. Mortality remains high in absence of specific treatment despite efficient supportive therapy.

Limitations of the study:

Primary lactic acidosis is a presentation of number of inborn errors of metabolism but further sub types like mitochondrial disorders could not be diagnosed due to lack of resources.

A large study is recommended to determine the prevalence of different types of inborn errors of metabolism.

Conflict of Interest: None

Funding: None

Written informed consent: Taken

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