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Profile of inborn errors of metabolism among the neonates admitted in special newborn care unit of a tertiary care hospital

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ABSTRACT

Background: Inborn errors of metabolism (IEM) refer to a group of hereditary disorders that occur due to the disruption of normal biochemical processes in the body. Although the incidence of IEM is rare, together their incidence is more than 1:1000.[1] IEM usually presents with non-specific symptoms, which could only be ruled out by the presence of a high level of suspicion of the disease. This study shares our experiences of different presentations and incidences of metabolic disorders by doing tandem mass spectrometry and highlights the importance of metabolic screening as a part of routine newborn screening. **Aims and Objectives:** To study the profile of inborn errors of metabolism among the sick neonates admitted in the special newborn care unit (SNCU). **Materials and Methods:** This is a hospital-based cross-sectional study done at SNCU of a tertiary care hospital. A total of 100 consecutive newborns with suspicion of IEM were taken as study participants and underwent IEM screening. **Results:** Out of 100 newborns, the majority were male. Twenty-three newborns were diagnosed with IEM. The most common IEM noted is G6PD deficiency with an overall incidence of 34%, followed by amino acid disorder. Consanguinity shows a significant association with IEM, with an incidence of 72% with a $P<0.001$. Hypoglycemia ($P=0.04$) and feed intolerance ($P=0.03$) also show a significant association with IEM. **Conclusion:** The incidence of IEM has gradually increased with the advent of metabolic screening. Early diagnosis is crucial with respect to both management and genetic counseling. The higher degree of suspicion can only bring out the actual incidence and improve its outcome.

Key words: Inborn errors of metabolism; Consanguinity; G-6PD deficiency; Recurrent hypoglycemia; Feed intolerance

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INTRODUCTION

Inborn errors of metabolism (IEM) refer to the group of hereditary disorders that occur due to the disruption of normal biochemical processes in the body. It occurs either due to a deficiency of a single enzyme or multiple enzyme activities or alteration in protein structure and function in the body, having various consequences. Although the incidence of IEM is rare, together their incidence is more than 1:1000.[1] Recent studies have revealed that the incidence is much higher, especially with the advent of newborn screening programs in various countries. The occurrence of IEM is high in regions with a greater incidence of consanguineous marriages.[2] Among the newborns, especially in the rural parts of our country, sudden death in many newborns is very hard to explain. The majority of them have multiple signs and symptoms that could not fit a specific diagnosis. Screening for inborn errors of metabolism (IEM) has played a crucial role in elucidating these conditions, provided a better understanding of their underlying causes and clinical manifestations. It not only helps to redefine and justify the diagnosis, but also helps in

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curing some of them, and helps in counseling the parents for their future pregnancies.

The presentation of IEM lacks specificity. Most of these presented as non-specific symptoms, which could only be ruled out by the presence of a high level of suspicion of the disease. Moreover, not all IEMs are present during neonatal life. Some of them are present during infancy or even later. The battery of tests, including blood gas, blood ammonia, lactate, both urinary and blood levels of ketone, amino acid, and acyl-carnitine levels in blood, is required to diagnose the disease. Tandem mass spectrometry (TMS) appears as a breakthrough in the diagnosis of IEM and is gaining worldwide support in the diagnosis of IEM. Although following screening, confirmation is done by blood level of specific amino acids or acyl-carnitine or from urine gas chromatography-mass spectrometry for organic acids.

Treatment of IEM is difficult, with only a handful of them available. Most of them are very expensive, and some of them are not easily available. However, early initiation of treatment can limit the morbidity and have a better outcome. However, it requires lifelong therapy that imposes a substantial burden of cost on the family. For those where therapy is not available, diagnosis is useful for genetic and prenatal counseling. In some cases, where IEM presents in late childhood, it usually has irreversible neurological sequelae. For this reason, IEM screening is a widely accepted method for newborn screening in developed countries. In developing countries, it still requires a lot of data to understand its importance and to include IEM screening in newborn screening (NBS) programs.

There are fewer studies from this northern part of West Bengal. This study shares our experiences of different presentations of metabolic disorders and the incidence of the same in this part of Bengal by doing a simple screening test of IEM, and it also depicts the importance of metabolic screening as a part of routine NBS.

Aims and objectives

The aim of this study is to determine the profile of inborn errors of metabolism among sick neonates admitted in Special Newborn Care Unit (SNCU), to identify specific metabolic pathway defects, and to assess the clinical outcomes associated with these conditions.

MATERIALS AND METHODS

It is a hospital-based, cross-sectional study done in the special newborn care unit of Malda Medical College and Hospital. The study period is 1 year (From December 2022 to November 2023). The study was started after getting permission from the Institutional Ethics Committee (IEC) under the letter number (P/MLD-MC/IEC22/41). The study population is taken by convenience sampling from the first 100 newborns with suspicion of IEM.

Inclusion criteria

Include all newborns with suspicion of IEM, such as recurrent hypoglycemia, hepato-splenomegaly, persisting jaundice, intractable seizures, and recurrent apnea in term newborns.

Exclusion criteria

Include those parents who are not willing to enroll in the study.

After taking written informed consent for the study from parents, history was taken from parents, including antenatal complications, consanguinity, sibling death, and maternal medications. After taking history, five hanging drops of blood were taken by the heel prick method on a filter paper specially designed for TMS and sent to the laboratory as soon as possible for screening. At the same time, ABG and other blood investigations were taken for reference. All the data are kept confidential and sequentially entered into Microsoft Excel.

Data analysis

Data were analyzed using the Statistical Package for the Social Sciences version 26.0. To find the association between two categorical variables, the Pearson Chi-square test for independence of attributes/Fisher's exact test, as appropriate, was used. The means of the two variables were compared using a paired t-test. To measure the difference between two continuous variables, "z" test was used. Results were expressed in frequencies, percentages, mean, and standard deviation. A $P<0.05$ was considered statistically significant.

RESULT

Out of 100 newborns included in the study, 60 were male, 36 were female, and four had ambiguous genitalia. Mean gestational age, birth weight, age at pregnancy, and clinical presentations were listed in Table 1. Results of TMS show – out of 100 newborns, 23 had IEM (Figure 1). The most common IEM noted among study participants is G-6 PD deficiency, out of which four are male, three are female, and one of them had ambiguous genitalia. Six amino acid disorders include – one argininemia (urea cycle defect), one phenylketonuria (PKU), one hypermethioninemia, one maple syrup urine disease, and two hyperglycinemia.

Out of 23 neonates diagnosed with inborn errors of metabolism (IEM), two had fatty acid oxidation defects—Carnitine Palmitoyltransferase II (CPT II) deficiency and

Table 1: Demographic table of study participants

Variables	Parameters
Gender (n=100)	
Male	60
Female	36
Ambiguous	4
Antenatal parameters	
Mean gestational age	36.48±3.78 weeks
Mean birth weight	2.2±0.6 kg
Mean age of pregnancy	24±6 years
H/o consanguinity	11 (n=100)
H/o sibling death	20 (n=100)
Clinical presentations (n=100)	
Feed intolerance	66
Hypoglycemia	32
Jaundice	43
Recurrent apnea (term)	21
Hepato-splenomegaly	24
Recurrent seizure	19
TMS panel (n=100)	
G6PD deficiency	8
Congenital adrenal hyperplasia	4
Amino acid disorders	6
Fatty acid disorders	2
Organic acidemias	3

G6PD: Glucose 6-phosphate dehydrogenase, TMS: Tandem mass spectrometry

Table 2: Analysis of Gender, consanguinity, and outcome with IEM

Variables	IEM present	IEM absent	P-value
Gender (n=100)			
Male	13 (21.7)	47 (78.3)	0.0007
Female	6 (16.7)	30 (83.3)	
Ambiguous	4 (100)	0	
Consanguinity (n=100)			
Present	8 (72.7)	3 (27.3)	<0.001
Absent	15 (16.9)	74 (83.1)	
Outcome (n=100)			
Discharge	17 (19.8)	69 (80.2)	0.064
Death	6 (42.9)	8 (57.1)	

IEM: Inborn errors of metabolism. P<0.05 is considered significant

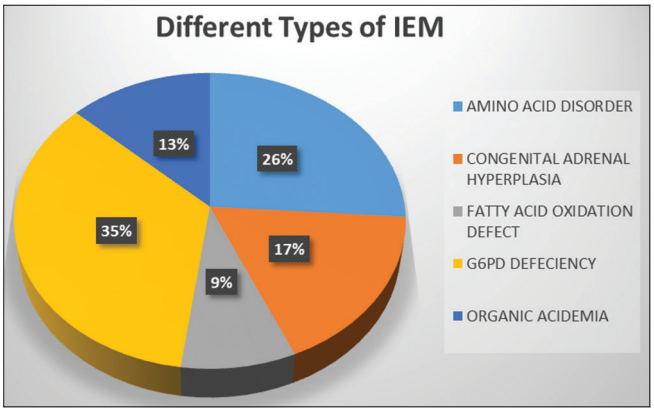

Figure 1: Pie chart shows the distribution of different inborn errors of metabolism

Isobutyryl-CoA Dehydrogenase Deficiency. Three patients were diagnosed with organic acidemias, including Glutaric Acidemia Type II, Methylmalonic Acyl-CoA Dehydrogenase Deficiency, and Isovaleric Acidemia. Analysis shows a significant association between consanguinity and IEM (P<0.001) (Table 2). When the gender of the infants was compared with IEM (Table 2), out of 23 patients with screen positive for IEM, 13 were male, six were female, and four had ambiguous genitalia, which turns out to be statistically significant (P=0.0007). Among the different forms of presentations, feed intolerance is significantly associated (P=0.03) with different types of IEM, followed by hypoglycemia (P=0.04) and hepatosplenomegaly (P=0.035) (Table 3). The outcome was noted as discharge-86 and death-14. Death is more noted among infants with amino acid disorders, three out of six, which is statistically significant (P=0.034), and had a standardized ratio of 2.1 compared to death from other IEM.

DISCUSSION

The study shows that males were more affected by IEM than females. All the babies with ambiguous genitalia were having IEM. Statistical association shows a positive correlation between gender and IEM. These results were consistent with a study done by Lodh and Kerketta.[3]

Gestational maturity also plays an important role in the incidence of IEM. The mean gestational age associated with IEM noted is 36.48±3.78 weeks. Our study is consistent with a study done by Epstein Weiss et al.,[4] which shows that the mean gestational age of a baby born with IEM is 38.1±1.89 weeks. The mean maternal age associated with IEM noted is 24.83±6.35 years, which is way less than the study done by Epstein Weiss et al.,[4] where they got a mean gestational age of 27.55±5.55 years. Hence, the association of IEM with an earlier age of pregnancy may be a significant finding, though more study is required, further on larger population to justify its validity.

Consanguinity always had a great impact on the incidence of IEM since most of the X-linked recessive diseases surfaced as a result of consanguinity. Our study was also not different from that. The literature had already reviewed the validity of the association between consanguinity and IEM. Singer et al.,[5] did a study that also shows that consanguinity is associated with IEM. Our study had a similar picture to a study done by Jayashree et al.,[6] which shows that consanguinity is more associated with IEM. In her study, 85% were born to consanguineous marriage parents, which, on analysis, is significant (P=0.016). Shawky et al.,[7] in their study, showed that, out of 13 patients who had IEM, 7 patients (53.8%) had consanguineous parents. They explain it as Egypt having a high consanguinity rate with other countries.[8] The findings of our study are

Table 3: Analysis of clinical presentation with different types of inborn errors of metabolism

Clinical presentation	FAOD	G6PD	OA	AA	CAH	P-value
Hypoglycemia						
Present	1	2	3	0	0	0.04
Absent	1	6	0	6	4	
Feed Intolerance						
Present	1	2	3	5	1	0.033
Absent	1	6	0	1	3	
Hepatosplenomegaly						
Present	1	1	2	4	0	0.35
Absent	1	7	1	2	4	

FAOD: Fatty acid oxidation disorder, G 6PD: Glucose 6-phosphate deficiency, OA: Organic aciduria, AA: Amino acid disorders, CAH: Congenital adrenal hyperplasia. P<0.05 is considered significant

similar to a study done by Lodh and Kerketta[3] where they found 29 cases of IEM born to parents with a history of consanguinity. Al-Thihli et al.[9] done a study that shows the prevalence of consanguinity among the study subjects is 95%. In their study, out of 285 patients, 229 were born of consanguineous marriage, which is significant. Keyfi et al.,[10] also proved that 707 out of 1118 infants with metabolic diseases (63.24%) were children of consanguineous parents. Rahman et al.,[11] in their study, also showed 34% consanguinity among the parents.

In neonates, non-specific symptoms such as hypoglycemia, feed intolerance, persistent jaundice, hepato-splenomegaly, and recurrent seizures are common accounts of neonatal sepsis. However, many times sepsis screens were negative, and even with proper antibiotics, they would not respond. IEM may be an important cause, and most of the time it remains undiagnosed. Our study shows hypoglycemia and feed intolerance had a significant association with IEM. A significant association was found between hypoglycemia and organic acidemia. This strong association was further supported by a standardized ratio of 2.1 in hypoglycemic patients with amino acid disorders. These findings, combined with a reported P=0.03 for hypoglycemia with different types of IEM, emphasize the robust nature of this relationship in our study. This warrants careful monitoring and management of the blood glucose level in this patient. Shawky et al.,[7] in 2015, done a study on 40 neonates with various symptoms such as poor suckling, poor crying, and convulsion, with suspicion of IEM, concluding that 32.5% of neonates had IEM, who had sepsis-like symptoms. A similar study done in Brazil on 101 neonates with hypoglycemia, metabolic acidosis, jaundice, vomiting, cataract, hepatomegaly, and splenomegaly showed that 63.3% had IEM.[12] A similar study done by Huang et al.,[13] also concludes similar findings with non-specific symptoms such as hypoglycemia, convulsion, and jaundice.

The most common IEM noted in our study was G-6PD deficiency 34.7%, followed by congenital adrenal hyperplasia, amino acid disorder, organic aciduria (OA), and fatty acid oxidation defect. One possible reason may be that the majority of the study participants were male, though we also found one female. Since G-6PD deficiency is an X-linked recessive disorder and our study shows an important association with consanguinity, this is probably one of the reasons for this incidence. A large sample size is required to validate these findings. This study shows similar findings to a study done by Keyfi et al.,[10] where they found that the most frequent disorders among their patients were G-6PD deficiency (14.04%), followed by OAs (methylmalonic and propionic acidurias) (9.12%), PKU (8%), and IVA (6.98%). Lee et al.,[14] done a study found 30 cases (69%) of amino acidemias (predominantly citrin deficiency, hyperphenylalaninemia due to 6-pyruvoyl-tetrahydropterin synthase deficiency, and tyrosinemia type I), 5 cases (12%) of organic acidemias (predominantly holocarboxylase Synthetase deficiency), and 8 cases (19%) of fatty acid oxidation defects (predominantly carnitine-acyl carnitine translocase deficiency).

The limitation of our study is less study participants. Since IEM is a rare disorder, it requires more samples to show the actual incidence of the disease. However, in this part of Bengal, the incidence of IEM is much more than in the rest of Bengal. Consanguinity may stand as an important contributing factor; still, it is difficult to comment on it. It requires more study over a larger population to root out the actual incidence of it.

CONCLUSION

This study concludes the importance of IEM screening as a part of NBS. Males were more commonly associated with IEM, with an overall incidence of 23%. The most prevalent IEM noted in this region is G-6PD deficiency. Significant associations were observed between IEM and factors such as consanguinity, feed intolerance, hypoglycemia, and hepato-splenomegaly. This is probably the first study from the northern part of Bengal. This study suggests that these findings may only represent a small portion of the broader

picture, indicating the need for further research to have a better understanding of IEM and the implementation of it in routine NBS in India.

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Authors' Contributions:
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