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A STUDY ON CLINICAL PROFILE AND SHORT TERM OUTCOME OF NEONATES WITH SUSPECTED IEM IN NICU IN A TERTIARY CARE HOSPITAL IN SOUTH INDIA

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ABSTRACT

Background: Neonates with inborn errors of metabolism (IEM) can present with non-specific symptoms and lead to high morbidity and mortality if not detected early. Hence it is inevitable to screen suspected IEM neonates, diagnose and treat early.

AIM: To study about the clinical profile and short term outcome of neonates with suspected IEM admitted in NICU.

Materials and methods: A cross sectional study was conducted in a tertiary hospital in Karnataka, India for a period of two years. 37 sick neonates who were admitted to NICU were taken for study and TMS was done for all using blood and urine samples. Arterial blood gas analysis, ammonia and lactate levels, serum electrolytes and other routine blood investigations were done.

Results: In our study, out of 37 sick neonates ,11 were TMS positive. We found 10 different types of IEM. Metabolic acidosis was the most common presentation followed by hypoglycemia and hyperammonemia. Past history of abortion was present in 24% cases and history of sibling death in 11% cases.

Conclusion: IEM represent a high percent (30%) of neonates who had sepsis like symptoms admitted in NICU. IEM should be considered in differential diagnosis of the sick neonates, and investigations, and management should be started rapidly to decrease morbidity and mortality.

KEYWORDS : Sick neonate, inborn error of metabolism, tandem mass spectroscopy

INTRODUCTION

Inborn errors of metabolism (IEM) are a highly heterogeneous group of disorders, which occurs due to mutation(s) in different genes involved in the metabolic pathways/networks. Manifestations of IEM occurs in neonates usually 24–48 h after birth and comprise ~5% of the total births occurring annually in India and getting admitted in sick newborn care units[1]. IEM is an important cause of morbidity and mortality in early childhood since it can lead to mental retardation, disabilities and death if left undiagnosed and untreated[2].

The incidence of IEM is estimated to be nearly 1 in 800 live births[3]. Many of the inborn errors of metabolism are not detected early due to delay in early identification of common characteristics. Since there are no specific symptoms to point out in these metabolic diseases, we are mainly dependent on biochemical tests for the diagnosis. The early diagnosis of IEM by laboratory-based screening tools can be helpful in preventing the complications due to the illness. Ideally, mass screening of neonates is an effective tool in the early detection of IEM cases presenting with non-specific symptoms. Tandem mass spectrometry (TMS) is a robust as well as effective diagnostic technique which can be utilized for the purpose of screening of suspected IEM cases. Its main advantages are good accuracy, sensitivity and specificity compared to other tools, and is feasible for cost effective mass screening of multi disease IEM[4].

MATERIALS AND METHODS

This was a cross sectional study conducted to study the clinical profile and outcome of neonates with suspected IEM admitted in the neonatal department of a tertiary care hospital in north Karnataka. It was conducted for a period of two years from July 2018 to august 2020.A total of 37 sick newborns clinically suspected for inborn metabolic disorders were enrolled consecutively.

INCLUSION CRITERIA :

Lethargy, poor feeding, vomiting, irritability, altered sensorium, convulsions, apnea, severe hypotonia, hypoglycemia, failure to thrive, difficulty in respiration, jaundice, liver dysfunction, , abnormal body odor, bleeding diathesis and also parameters like electrolyte imbalance, hypocalcaemia, hypoglycemia, abnormal ammonia and lactate level, metabolic and respiratory acidosis/alkalosis which could not be explained by other causes were also included. Exclusion criteria:neonates with clinically and laboratory proven sepsis ,birth asphyxia ,congenital heart diseases and radiological proven pneumonia.

Demographic characteristics, age at diagnosis, clinical and family history and parental consanguinity were recorded. The blood samples for TMS analysis were collected by heel prick method. A pinprick puncture in one heel of the newborn was done and blood was soaked into pre-printed collection cards or Guthrie cards. Urine samples were collected by soaking freshly voided urine on filter paper and were sent to the laboratory, where the screening for the disorders of amino acids, organic acids and fatty acid metabolism were done by Tandem Mass Spectrometer.

STATISTICAL ANALYSIS

With 95% confidence interval and margin of error of $\pm$ 15%, a sample size of 37 subjects will allow the study to determine the clinical profile of suspected sick neonates with suspected IEM in NICU in a tertiary care hospital in south India with finite population correction. For continuous variables, the summary statistics of Mean$\pm$SD were used. For categorical data, the number and percentage were used in the data summaries and diagrammatic presentation. Data were analyzed using SPSS software v.23 and Microsoft office 2007.

RESULTS

Out of 37 clinically suspected sick newborns, 21 (56.8%)

presented during the first week of life and 7(18.9%) presented during the 2nd week of life. four (11%) presented during 3rd week and 5(13%) during 4th week. (Table 1).22 neonates were males (59.5%) and 15 were females(40.5%). 10 neonates (27%) were preterm and 27 (73%) were full term. History of consanguinity was present in 17 (46%) cases. As per antenatal data, among 21 (57%) cases there was antenatal problem. Diabetes mellitus (27%), Fever (8%), hyper-tension (19%) were the main antenatal problems.(table1).Data from obstetric history showed that there was history of sibling death in 11% cases, history of abortion in 24% cases. Past history of intrauterine death was present in 16% cases (Table 1).Analyzing the sickness pattern, Twenty eight (75%) newborns presented with dull activity followed by 24 neonates(64%) who had hurried breathing and 16 neonates(43%) had poor feeding issues and 13(35%) had seizures, while 15 (40%) neonates had sepsis like features(Table 1).Lactic acidosis was the predominant biochemical abnormality (54%)(table 2). Next common abnormalities were hypoglycemia (48%) and hyperammonemia (27%).Urine ketone bodies were positive in 21 (56%) cases.(Table1).Considering the pattern of metabolic disorders, Out of 37 cases ,TMS was positive for 11 cases. Fatty acid oxidation defect cases were 4 followed by tyrosinemia 2 cases, 2 organic acid disorders and one case each of non ketotic hyperglycinemia, biotinidase deficiency, and ornithine transcarbamoylase deficiency.

Table 1 showing demographics and clinical history of neonates

CHIEF COMPLAINTS	N	%
Dull Activity	28	75.7
Seizures	13	35.1
Hurried Breathing	24	64.9
Poor Feeding	16	43.2
Vomiting	3	8.1
Irritability	5	13.5
Jaundice	3	8.1
AGE OF BABY IN ADMISSION		
1st week	21	56.8
2nd week	7	18.9
3rd week	4	10.8
4th week	5	13.5
SEX		
Male	22	59.5
Female	15	40.5
GESTATION AGE IN WEEKS		
Preterm	10	27
Term	27	73
BIRTH WEIGHT		
Normal	25	67.6
LBW	12	32.4
CONSANGUINITY		
Yes	17	45.9
No	20	54.1
BAD OBSTETRIC HISTORY		
Nil	20	54.1
Abortion	9	24.3
IUD	6	16.2
ANTENATAL HISTORY		
NIL	16	43.2
GDM	10	27.0
HTN	7	18.9
APH	2	5.4
Hypothyroid	2	5.4
Fever	3	8.1
PERINATAL PROBLEM		
Nil	23	62.2
PROM	5	13.5
Fever	3	8.1

Table 2 showing laboratory data of neonates

LABORATORY DATA	N	%
Sepsis	15	40.5
Hypoglycemia	18	48.6
SODIUM		
Normal	26	70.3
Low	7	18.9
High	4	10.8
POTASSIUM		
Normal	22	59.5
Low	11	29.7
High	4	10.8
AMMONIA		
Normal	27	73
High	10	27
CALCIUM		
Normal	30	81.1
Low	7	18.9
PH		
Normal	27	73
Acidosis	7	18.9
Alkalosis	3	8.1
LACTATE		
Normal	17	45.9
High	20	54.1
Urine ketone bodies +	21	56.8
TMS +ve	11	29.7

Table 3 showing pattern of metabolic disorders

IEM	NO	FREQUENCY
TYROSINEMIA	2	18%
CARNITINE PALMYTOYL TRANSFERASE 1A DEFICIENCY	1	9%
MULTIPLE ACYL COA DEHYDROGENASE DEFICIENCY	1	9%
ORNITHINE TRANSCARBAMOYLASE DEFICIENCY	1	9%
GLUTARIC ACIDEMIA	1	9%
3 HYROXY 3 METHYL GLUTARYL COA LYASE DEFICIENCY	1	9%
NON KETOTIC HYPERGLYCINEMIA	1	9%
BIOTINIDASE DEFICIENCY	1	9%
SHORT CHAIN ACYL COA DEHYDROGENASE DEFICIENCY	1	9%
PROPIONIC ACIDEMIA	1	9%

OUTCOME

Out of 11 proved cases,2 cases died during the course of treatment in NICU. Two cases went against medical advice and further follow up was not done. Rest 7 cases improved clinically with treatment and discharged. Statistically there was little difference between diagnosed IEM cases and undiagnosed cases when comparing sex of the patient, age of onset of symptoms, and type of the presenting symptom. There was statistically proven difference between IEM cases and undiagnosed cases with regard to family history of sibling death ($p=0.02$),consanguinity($p=0.04$) and plasma ammonia level ($p=0.012$).

DISCUSSION

This study included 37 neonates with suspected diagnosis of IEM. Investigations including ammonia and lactate in blood were done according to the suspected diagnosis. Screening for IEM was done by TMS. IEM was proved in 11 patients (30%).

IEM which manifests clinically in the neonatal period are usually severe and often mortality can be high if proper therapy is not initiated soon. Clinical findings are usually non-specific and can masquerade many other illnesses like neonatal sepsis. An inborn error of metabolism should be

always considered in the differential diagnosis of a critically ill neonate with metabolic abnormalities and should be investigated for it if there is high index of suspicion. It has been proven that for some disorders, if detected in the early neonatal period, dietary restriction can be done and special diet can be advised and thus preventing further complications in future[5].

The maximum amount of sick newborn presented at 1st week, 21 (57%) in number in this study. MH Hampe, et al. had found in their study that that most of the cases presented between 15 days to 2 months of age[6]. There was a slight male predominance (54%) which is also seen in other studies due to the occurrence of IEM with X-linked recessive inheritance[7]. In our study, out of 11 patients who had IEM, 7 patients (63%) had consanguineous parents. This might be due to high consanguineous marriage rate prevalent in India, but also because most IEM diagnosed in the patients are autosomal recessive which can run in families due to consanguineous marriage because family members share abnormal genes which are inherited. Hence during the initial evaluation of a sick neonate, history of consanguineous marriage and/or unexplained sibling deaths should be asked for and if present, IEM should be strongly considered[8,9]. There was history of sibling death in 11% cases, history of abortion in 24% cases. Past history of intrauterine death was in 16% cases. But work up for IEM was not done in none of these cases. This issue reflects the need for postmortem work up of every unusual mortality. The important clinical findings that caused the suspicion of IEM were dull activity (75%), hurried breathing (65%), poor feeding (43%), seizures (35%) and irritability (14%).

With respect to varying clinical presentations in IEM, it was shown that in a study done in India the clinical features were poor feeding (4.3%), lethargy (6.4%), failure to thrive (4%), seizures (10.6%), (6%), irritability (2.8%), metabolic acidosis (7.2%)[10]. Thus IEM is highly suspected in cases with sudden deterioration in neurological function like dull activity with hypotonia, poor feeding and irritability. In the studies of Sanseverino, et al. the sudden neurological changes lead to the metabolic investigation of 47.8% of the patients and were present in all those who had a definite diagnosis of an IEM[7,11].

Most common disorder in neonatal period are organic acid disorders that present with ketoacidosis and urea cycle defects characterized by hyperammonemia[12]. Our commonest findings were lactic acidosis (54%) and hypoglycemia (48%). These findings are similar to a study done by Mehmet, et al. where 29.4% neonates presented with hypoglycemia and 25.5% had lactic acidosis [13]. However, our other findings were hyponatremia, hypocalcemia, hypokalemia, hyperkalemia, acidosis and alkalosis.

Out of 37 sick neonates, 30% (11 cases) had abnormal TMS. We got 10 types of IEM cases in our study. We had 4 patients with fatty acid oxidation disorders (36%) followed by 2 patients who had organic acid disorders in which one had propionic academia and the other had glutaric academia type 1.among amino acid disorders we had two cases of tyrosinemia (18%) and one case of non ketotic hyperglycinemia .Among urea cycle disorders we had one case of ornithine transcarbamoylase deficiency. We also had one patient with biotinidase deficiency (table 3). Some cases may have gone unidentified as we had only done TMS and we did not perform GCMS and other genetic studies.

Limitations of study

Apart from TMS, other tests like GCMS, comprehensive analysis of mitochondrial genome with next generation sequencing, enzymatic studies were not done. MRI of brain was not done in all cases because of financial constraints .Study period as well as the samples studied were not large enough to precisely detect the clinical profile of IEM among suspected neonates.

CONCLUSION

From this study we concluded that IEM can present with non-specific symptoms among sick neonates in NICU and it can simulate many other illnesses like neonatal sepsis which can lead to misdiagnosis .IEM should be considered in the differential diagnosis of any sick neonate getting admitted in NICU and TMS sample should be sent for all suspected high risk neonates as it will help in early detection of the disease and will improve survival and decrease mortality and morbidity of patients. This study also emphasizes the need for implementation of neonatal screening for IEM for all newborns at birth.

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