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Paediatrics

SCREENING OF INBORN ERRORS OF METABOLISM IN CHILDREN AT TERTIARY CARE HOSPITAL OF SOUTH RAJASTHAN

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ABSTRACT **Background: -**Genetic metabolic disorders result from the deficiency of an enzyme, its cofactors or biochemical transporters that lead to the deficiency of a required metabolite, the build-up of a toxic compound or a combination of both processes. Optimal outcomes for children with inborn errors of metabolism (IEM) depend upon recognition of sign and symptoms of metabolic disease and prompt evaluation and referral to a centre for their management. Delay in diagnosis may result in progressive neurological disease, injury or death.

Objective: -To study the spectrum of Inborn errors of metabolism (IEM) in children admitted in department of Pediatrics, RNT Medical College, Udaipur.

Material & Methods: The present study was conducted in Department of paediatrics, RNT Medical College, Udaipur (Rajasthan). It was a hospital based study**,** conducted from September 2018 to December 2020.Children from birth to 18 years of age having clinical suspicion and whose parents consenting for study were enrolled.During the study period, 104 children fulfilling inclusion criteria were investigated.

Results&Conclusion: Out of total 104 clinically suspected patients, 18 (17.3%) came positive for various IEMs. Out of these 18 patients the diagnosis of LSDs was confirmed in 7 (38.9%) patients with 5 patients diagnosed as gaucher disease (27.8%) & 2 as mucopolysaccharidoses (11.1%). Other 11 IEM detected were aminoacidopathies-5 (27.8%) (Homocystinuria-3, phenylketonuria-1 and tyrosinaemia-1), biotinidase deficiency-2 (11.1%) and one patient each of organic acidemia, Galactosemiaand fatty acid oxidation defect.

KEYWORDS :

INTRODUCTION

Inborn errors of metabolism (IEM)result from the deficiency of an enzyme, its cofactors or biochemical transporters that lead to the deficiency of a required metabolite, the build-up of a toxic compound or a combination of both [1]. Normally, the intermediate products of metabolism are further changed or removed from the body in order to prevent their accumulation. Any block in the metabolic pathway can result in accumulation of these intermediates or can get converted to toxic products that can give rise to clinical manifestations of disease [2].IEM individually are rare but collectively are not so uncommon. In India, 24 million newborns are born each year; 340,000 with G6PD, 20,800 with metabolic disorder and 10,400 with congenital hypothyroidism, the overall prevalence of IEM in India is one in 2497 newborn [3].Indian council of Medical Research (ICMR) performed multicenter study and concluded the incidence of congenital hypothyroidism and congenital adrenal hyperplasia to be 1 in 1130 and 1 in 5762 newborns, respectively. The occurrence of IEM is high in regions with greater incidence of consanguineous marriages [1].

Presentation of IEM is usually in the neonatal period or infancy but can occur at any time, even in adulthood. In newborns, IEM may present with poor feeding, dullness, lethargy, convulsion, vomiting, hypoglycemia, difficulty in breathing which may develop as early as few hours after birththat can mimic like sepsis or birth asphyxia.In Older age, inborn errors of metabolism may present with paroxysmal stupor, lethargy, emesis, failure to thrive, dehydration, bleeding diathesis, jaundiceor organomegaly. Neurologic findings of neurometabolic disorders are acquired macrocephaly or microcephaly (CNS storage, demyelinationand atrophy), hypotonia, hypertonia/ spasticity, seizures, or other movement disorders. General non-neurologic manifestations of neurometabolic disorders include skeletal abnormalities and coarse facial features (e.g., with mucopolysaccharidoses), macular or retinal changes (e.g., with leukodystrophies, poliodystrophies, mitochondrial disorders), corneal clouding (e.g., with Hurler's syndrome), skin changes (e.g., Fabry's disease, PKU,CAH), or hepatosplenomegaly (with various storage diseases)[4].

Newborn screening is the principal population-based public health screening program which is being practiced at present across the globe. It has dramatically changed clinical practice for care of children with inborn errors of metabolism. For those conditions that are identified by new-born screening, management has moved from a reactive response to one that permits active, early intervention [5]. Therefore, we performed newborn screening to early identification of IEM in children at tertiary care hospital of southern Rajasthan which could provide a more accurate estimate of the impact of treatment or risk factors for disease. The aim of this study was to evaluate the spectrum of IEM in southern rajasthan.

MATERIALS AND METHOD

The present study was a hospital based prospective study conducted from September 2018 to December 2020with the approval of institutional ethical committee of RNT Medical College, Udaipur (approval no. RNT/Stat./IEC/2019/1275)in Balchikitsalaya of MBGH, RNT Medical College, Udaipur (Rajasthan). Children up to 18 years of age fulfilling inclusion criteria &consenting for study were enrolled. Clinical features& Investigations suggestive ofIEM i.e. Lethargy, poor feeding, vomiting, irritability, altered sensorium, convulsions, unconsciousness, apnoea, severe hypotonia, dysmorphism, delayed milestones, intellectual disability, heart failure, failure to thrive,electrolyte imbalance, hypocalcemia, hypercalcemia, hypoglycemia, hyperglycenemia, abnormal ammonia and lactate level, metabolic and respiratory acidosis/alkalosis which could not be explained by other causes were included.Childrenwhose parents not consenting for study,financial constraints and the condition of patient was explained by any known condition/syndromes as well septicemia, meningitis and underlying systemic disorders were excluded from the study. Biochemical screening tests for inborn errors of metabolism such as blood glucose, electrolytes, lactate, arterial blood gases, ammonia and urine ketones were performed.

Children with positive results on screening were subjected to tandem mass spectrometry (TMS) by dried blood spot or Gas chromatography - mass spectrometry (GC - MS) by taking urine sample by capillary

action on filter paperand further sent to laboratories for analysis.Patients those who have features of LSDs like coarse facies, hepatosplenomegaly, bony deformity etc were screened for treatable five diseases (Gaucher's disease, Pompe disease, Fabry disease, Hurler syndrome, Niemann Pick B disease) whereas those having features of aminoacid, carbohydrate& lipid metabolism defects and 6 conditions (Congenital Hypothyroidism by serum TSH, Congenital Adrenal Hyperplasia by elevated levels of 17-hydroxyprogesterone, Glucose-6-phosphate-dehydrogenase deficiency by G6PD enzyme level, Galactosemia by total galactose level, Cystic Fibrosis by human immunoreactive trypsinogen level & Biotinidase deficiency by low biotinidase level) were screened by TMS/GCMS and immuno chemiluminometric assay respectively. Based on the results of these tests supportive (dietary and symptomatic) and definitive management according to standard protocols was initiated.LSDs screening was done by DBS provided by Sanofi Genzyme and tests were also done free of cost.

Statistical analyses were performed using SPSS version 17.0 (IBM Co. Chicago, IL, USA). Demographic data and initial clinical signs and symptoms were analyzed using Chi square test. Statistical significance was determined as $p < 0.05$.

RESULTS

A total of 104 children fulfilling inclusion and exclusion criteria were recruited in this study. The percentage of male patients (57.7%) was higher than females (42.3%). These patients belonged to five age groups: Group 1 (<30 days), Group 2 (30 days – 1 year), Group 3 (1 year – 5 years), Group 4 (5 years – 10 years) and Group 5 (>10 years). The proportional of both male and female patients is higher in age group 30 days to 1 year. Demographic data are shown in Table 1.

TABLES

Table1 Age and gender Wise Distribution of patients in the study

Age Group	Female	Male	Total
<30 Days	11(10.6)	15(14.4)	26(25)
30 Days- 1 Year	22(21.2)	25(24.1)	47(45.3)
1 Year - 5 Year	4(3.8)	12(11.6)	16(15.4)
5 Year- 10Year	4(3.8)	4(3.8)	8(7.6)
>10 Year	3(2.9)	4(3.8)	7(6.7)
Total	44(42.3)	60(57.7)	104(100)

In suspected IEM patients, various complaints were noted shown in Table 2.

Table2 Presenting complaints of the patients on admission

Clinical features	No. of patients (Suspected) Total (104)	No. of patients Positive Total (18)	P value
Dull and Lethargic/Altered Sensorium	75(72.1)	11(61.1)	0.344
Poor Feeding/Refusal to Feed	71(68.3)	7(38.9)	0.016
RefractorySeizure	13(12.5)	2(11.1)	0.868
Rapid breathing	46(44.2)	6(33.3)	0.388
Persistent vomiting	21(20.2)	6(33.3)	0.214
Hepatosplenomegaly	42(40.4)	8(44.4)	0.746
Yellowish discoloration of skin	19(18.3)	5(27.8)	0.348
Failure to gain weight	25(24)	5(27.8)	0.733
Abnormal facial features	13(12.5)	3(16.7)	0.628
Delayed Milestones	38(36.5)	11(61.1)	0.049
Short stature	19(18.3)	7(38.9)	0.048
Abnormal genitalia	4(3.8)	1(5.6)	0.735
Limpness of the body	4(3.8)	1(5.6)	0.735
Persistent hypoglycaemia	6(5.7)	0(0)	0.295

Overall, the most common complaints were poor feeding (p-0.016), delayed milestones (p-0.049) and short stature (p-0.048) which were significantly higher than other complaints such as persistent vomiting, dull and lethargic/altered sensorium, yellowish discoloration of skin and rapid breathing.

A total of 18 patients were confirmed for IEM, among these 7 (38.9%) were males and 11 (61.1%) females with Male: Female Ratio of 1:1.6. Out of 18 IEM patients, 7 were died (38.9%) whereas 9 were under follow up. Distribution of patients diagnosed as IEM and their outcome are shown in Table 3 and Table 4.

Table3 Distribution of patients diagnosed as IEM

Name of IEM	No. of patients			Percentage (%)
	Male (7)	Female (11)	Total (18)	
Gaucher's Disease	2	3	5	27.8
Aminoacidopathies (5) • Homocysteinuria • Phenylketonuria • Tyrosinaemia	1 0 0	2 1 1	3 1 1	27.8
Mucopolysaccharidosis type1	2	0	2	11.1
Biotinidase deficiency	1	1	2	11.1
Galactosemia	0	1	1	5.6
Organic aciduria	0	1	1	5.6
Fatty acid oxidation defect	0	1	1	5.6
Congenital adrenal hyperplasia	1	0	1	5.6

Table4 Outcome of IEM Patients

Outcome	No. of IEM Patients (18)	Percentage
Death	7	38.9
Under follow up	9	50
Lost to follow up	2	11.1

I. DISCUSSION

ii. Clinical presentation of suspected IEM patients were altered sensorium(72.1%) followed by refusal to feed (68.3%), rapid breathing (44.2%), hepatosplenomegaly (40.4%), delayed milestones (36.5%), failure to gain weight (24.0%), persistent vomiting (20.2%), yellowish discoloration of skin (18.3%), short stature (18.3%), refractory seizures (12.5%), persistent hypoglycaemia (5.7%), abnormal genitalia(3.8%) and limpness of the body (3.8%) on admission. Shawky et al (2015)reported that out of 40 suspected IEM patients, 26.5% presented with poor feeding, 15% convulsions and lethargy and persistent vomiting was presented in 2.5%[6].Whereas IEM positive patients presented with altered sensorium (61.1%), delayed milestones (61.1),hepatosplenomegaly (44.4%), short stature (38.9%), refusalto feed (38.9%), rapid breathing (33.3%), persistent vomiting (33.3%) and yellowish discoloration of skin (27.8%). Bhojwani et al (2020)found that out of 62 IEM positive cases, 54.83% had lethargy/coma followed by poor sucking (45.16%), hypotonia (43.54%), failure to thrive (37.09%),respiratory distress (35.48%), seizures (37.09%), hepatosplenomegaly and icterus (32.25%) [7].

In our study, most common age group in suspected IEM patients was 30 days to 1 year. Kadali etal (2014)found in their retrospective study that infantile followed by juvenile groups were most common age groups of presentation of LSDs whereas Verma et al (2012)found 4.5 years mean age of LSDs presentation in their study[8, 9].In our study, out of 18 confirmed IEM patients, 7 (38.9%) were males and 11 (61.1%) were females with Male: Female Ratio of 1:1.6. Bhojwani et al (2020)found that incidence of IEM was slightly more common in males with Male: Female ratio of 1.17:1 [7].Shawky et al. (2015)found in their study that out of 13 IEM patients, 12 (92.3%) were males and one (7.7%) female with Male: Female ratio 12:1[6].

In suspected IEM patients, 10 patient's parents (9.6%) had history of consanguinity. Bhojwani et al (2020)found in their study that out of 157 patients of suspected IEMs, consanguinity was present in 33.87% of families whereas 51.47% parental consanguinity was estimated in study performed by Waters et al (2018)[7, 10].Clinically suspected were investigated for possible IEMs. Out of total 104 patients, 18 were found positive for various IEMs. Forty were screened for lysosomal storage disorders based on their clinical features. The diagnosis of LSDs was confirmed in 7 (38.9%) patients out of which 5 were diagnosed with gaucher disease (27.8%) followed by mucopoly saccharidoses (2). Remaining 64 patients were screened for other IEMs out of which 11were positive for various IEMs including 5 (27.8%) of aminoacidopathies followed by biotinidase deficiency (11.1%) and 5.6% each of organic aciduria, carbohydrate metabolism disorder and fatty acid oxidation defects. Agarwal et al (2015)reported that out of 5858 suspected LSD patients, 119 were confirmed of LSDs of which gaucher disease (31.93 %) followed by mucopolys accharidoses (20.16 %)[11].Sharma etal (2018)found 2.9% prevalence (of the total 70,590 samples analysed, 2053 cases were found positive) of IEM [12]. Among those, the highest prevalent disorder was found to be G6PD deficiency, with 1.3% (923 positive of 70,590) cases reported

followed by haemoglobinopathies, 0.5% (360 positive of 70,590) and congenital hyperplasia with 0.34% (239 positive of 70,590) cases.

III. CONCLUSION

In our study of small number of patients (104) with clinical suspicion of IEM, 18 (17.3%) patients were diagnosed to have various IEM, this shows that the burden of disease in the society is not so less.Keeping this in mind enzyme replacement therapy (ERT) is available for many IEM, early diagnosis by newborn screening may help in preventing disability or death.

REFERENCES

1. Mishra OP, Prabhu S,Singh S, Nelson Essentionals of paediatrics first south Asia edition section 10. Metabolic disorders. 2016; 170.
2. Garrod AE. Inborn Errors of Metabolism: The Croonian Lectures delivered before the Royal College of Physicians of London, in June, 1908.London: Oxford University Press;1909.
3. Latheef SA. A database for inborn errors of metabolism in the Indian state of Andhra Pradesh. Bioinformation. 2010; 4 (7):276-277.
4. Beaudet AL, Scriver CR, Sly WS, ValleD. Molecularbases of variant human phenotypes.In:Scriver CR,ed. The Metabolicand Molecular BasesofInherited Disease. 8 thed. NewYork:McGraw-Hill; 2001:3-51.
5. www.indianpediatrics.net/dec2013/dec-1155-1156.htm
6. Shawky RM, Abd-Elkhalek HS, Elkhalek SE. Selective screening in neonates suspected to haveinborn errors of metabolism. Egypt. J. Med. Hum. Genet. 2015; 16: 165–171.
7. Bhojwani KL, &Gohil JR. Inborn Error of Metabolism (IEM) in Bhavnagar, Gujarat: a prospective study from 0-2 years by Tandem Mass Spectroscopy. 2020; https://doi.org/10.31237/osf.io/anb25.
8. Kadali S, Kolusu A, Gummadi MR, Undamatla J. The relative frequency of lysosomal storage disorders: A medical genetics referral laboratory's experience from India. J. Child Neurol. 2014; 29(10): 1377-1382.
9. Verma P, Ranganath P, Dalal A, Phadke S. Spectrum of lysosomalstorage disorders at a medical genetics centre in northern India.IndianPediatr. 2012;49:799–804.
10. Waters D, Adeloye D, Woolham D, Wastnedge E, Patel S, Rudan I.Global birth prevalence and mortality from inborn errors of metabolism: a systematic analysis of the evidence.J Glob Health. 2018; 8(2): 021102.
11. Agarwal S, Lahiri K, Muranjan M, Solanki N. The Face of Lysosomal Storage Disorders in India: A Needfor Early Diagnosis. Indian J Pediatr. 2015; 82(6): 525-9.
12. Sharma P, Kumar P, Tyagi M, Sharma R, Dhot PS. Prevalence of Inborn Errors of Metabolism in Neonates. J. Clin. Diagnostic Res. 2018; 12(5):07-13.