Original Research Article

Clinical spectrum of inborn errors of metabolism in children in a tertiary care hospital

Jayashree K. R.[1], Madhivanan S.[1]*, Kumarasamy K.[1], Karthick A. R.[2]

[1]Department of Paediatrics, [2]Department of Pediatric Intensive Care, Institute of Child Health and Hospital for Children, Madras Medical College, Chennai, Tamil Nadu, India

*Correspondence:
Dr. Madhivanan S.,
E-mail: dr.madhi67@gmail.com

ABSTRACT

Background: Inborn Errors of Metabolism (IEM) are a group of disorders occurring due to disruption of normal biochemical process. Prompt diagnosis is often only the beginning of a long medical journey for the affected children and their family. Pediatricians play a vital role in establishing the continuity of care, providing treatment when needed and referrals to specialists. Reported prevalence of IEM is 1 in 2497 newborn though, true pan India prevalence is still unknown. This study was carried to determine the clinical spectrum of inborn errors of metabolism in a tertiary care hospital in South India.
Methods: Records of all patients suspected and diagnosed to have inborn errors of metabolism in Institute of Child Health and Hospital for Children, Madras Medical College from April 2018 to October 2019 were sequentially included in the study. Details of clinical presentation, investigations and treatment were noted and analysed.
Results: In this study 65 children diagnosed to have inborn errors of metabolism were included in the study and of them 27(41.5%) had derangement in carbohydrate metabolism, 16(24.6%) in protein metabolism and 22(33.9%) in lipid metabolism. Mean age at presentation was 37 months with range of 2 months to 10 years of age. Most common clinical manifestation was poor feeding (67.7%) followed by fever (64.6%) and dyspnea (63.1%). Of these 65 children, mortality was observed in 10 cases (15%).
Conclusions: IEM contribute to a significant cause of global child morbidity and mortality. A high index of suspicion is most important in making the diagnosis. IEM should be considered in children with features mimicking sepsis and unexplained course. Screening programmes and prenatal diagnosis of IEM will go a long way in preventing these disorders and early diagnosis helps initiate prompt therapy which is very much essential to prevent lethal complications.

Keywords: Clinical profile, Inborn errors of metabolism, Outcome

INTRODUCTION

Inborn errors of metabolism are the group of hereditary diseases which occur due to disturbances in normal biochemical process. Although individually rare, they collectively cause significant morbidity and mortality in children. Their average incidence of 1 in 1,00,000. But due to huge number of enzymatic derangements, they are collectively common with overall incidence of 1 in 800 to 1 in 2500. They are one of the major contributors to chronic diseases in childhood.[1]

Due to IEMs there will be (a) Production of incomplete product as seen in Phenylketonuria - deficiency of tyrosine (b) There may be accumulation of substrates which may be harmful e.g. Urea cycle disorder - ammonia which is toxic to brain (c) Increased levels of alternative pathway products which might have toxic

effects or interfere with other metabolic products e.g. Formation of abnormal products in propionicaciduria because of accumulated Propionyl coA, participating in reactions normally using acetyl coA.[2]

Clinical manifestations depend on the concentrations of accumulated toxic metabolites. As a consequence of this, IEM may be exhibiting severe symptoms or may be asymptomatic. Frequently manifested symptoms which suggest that IEM may fall into several categories including hypoxia, seizures, lethargy, vomiting, poor feeding and other changes that may often cause death if not promptly intervened.[3]

Asymptomatic individuals become symptomatic following exposure to triggers such as fasting, diet, Fever, drugs, anaesthesia. Usually early symptoms of IEM are non-specific, which makes it difficult to diagnose as they overlap with sepsis, birth asphyxia, hepatitis, viral infections, arthritis. Prompt diagnosis is required even in asymptomatic individuals to prevent sequelae. Proper diagnosis requires the use of biochemical markers, and the diagnosed cases may require lifelong therapy, so it imposes a substantial burden on the patient's family which includes cost if diagnosis and treatment.[4]

One single test is not enough to identify the IEM. Different strategies are required to diagnose it. Accumulated biochemical substances can be estimated in blood or urine. Knowledge of analytical chemistry, enzymology and biochemistry helps to plan final work of IEM. To improve the establishment of diagnosis and management of long-term effects, Newborn Screening (NBS) Gas Chromatography Mass Spectrometry (GCMS) Tandem Mass Spectrometry (TMS), molecular analysis and enzyme assay has been developed. With the above diagnostic techniques, the number of patients diagnosed with IEM are at a rise. Some of them are responsive to therapy if treatment stated early.[5] In case where the therapy is unavailable, diagnostic methods will be useful for genetic and prenatal counselling. Asymptomatic newborn with IEM can later present with irreversible neurological damage, hence NBS is widely accepted in developed countries. In contrast, less information is available from developing countries.

METHODS

This prospective observational study was conducted in the Institute of Child Health and Hospital for Children, Madras Medical College, Chennai between April 2018 to October 2019. Our hospital has an average of 30,000 to 35,000 admissions per year.

Children between 1 month to 12 years admitted in the Pediatrics Department and found to have inborn errors in metabolism were included in the study. Children diagnosed with inborn errors and started on treatment before admission were excluded from the study.

After getting informed consent from the parents/ guardian, detailed history, clinical examination findings and laboratory parameters were collected. Relevant history included fever, vomiting, poor feeding, lethargy, seizure, developmental delay, abnormal posturing, regression of milestones, abnormal odour, dysmorphic facies, abdominal distention, dyspnoea. On clinical examination pallor, jaundice, extensive Mongolian spot, hepatomegaly, splenomegaly, ascites, cherry red spot, optic atrophy, corneal clouding, hypotonia, hypertonia, ataxia, joint stiffness, spasticity, cerebellar signs, abnormal startle reflex were looked for. All the children underwent initial investigations like complete blood count, blood sugar, renal function test, liver function test, thyroid function test, arterial blood gas analysis, serum ammonia, lactate, uric acid, chest x ray, ultrasound abdomen, peripheral smear, echocardiogram. Some children needed CT Brain or MRI brain with relevant clinical examination finding.

To confirm the diagnosis, Bone marrow examination, Enzyme assay, Tandem Mass Spectroscopy, Gas Chromatography, urine organic acid levels, liver biopsy were done depends up on clinical correlation and availability of diagnostic tools. In cases with Glycogen Storage Disorders (GSD), enzyme assay for Pompe's disease was only available here. Other types of GSD diagnosed only with liver biopsy. The liver biopsy suggestive of GSD cases without enzyme analysis group under GSD other than Pompe's disease. All the above data were entered in a pre-structured Proforma.

RESULTS

Out of the 65 children included in the study, 38(58.5%) were boys and 27(41.5%) were girls. Only 9(13.8%) children out of total 65 were born to non-consanguineous marriage parents. 23(35.4%) children and 33(50.8%) children were born to II- and III-degree consanguineous marriage parents respectively.

With regards to anthropometry, microcephaly was noted in 20(30.8%) children and macrocephaly in 11(16.9%) children. 25(38.5%) children were severely wasted (<-3SD). 11(16.9%) children had wasting (-2SD to -3SD). Nearly one third of the children (n=22, 33.8%) had severe stunting and one third had stunting (n=21, 32.3%) (Table 1).

42(64.6%) children presented with fever. 31(47.7%) had excessive vomiting. 38(58.5%) children had lethargy on admission. 41(63.1%) children had abdominal distension. Majority of the children (n=44, 67.7%) had history of poor feeding and nearly one fourth (n=18, 27.7%) had developmental delay. 40% (n=26) had at least one episode of seizures either before or during hospitalization. Regression of milestones was noted in 12 children (18.5%).

Nearly two-thirds of the children had hepatomegaly (n=63.1, 36.9%) and nearly half had splenomegaly (n=32,

49.2%). Cherry red spot was observed in 12 children (18.5%) and 7(10.8%) had optic atrophy. 9(13.8%) children had hypotonia whereas 19(29.2%) had hypertonia. Ataxia was noted in 2(3.1%) children. About one-fourth (n=15, 23.1%) had spasticity on examination. 11(16.9%) children exhibited abnormal startle reflex (Table 2).

Table 1: Profile of children with IEM.

Profile		Number(%)
Sex	Male	38(58.5%)
	Female	27(41.5%)
Weight	-1SD to -2SD	29(44.6%)
	-2SD TO -3SD	11(16.9%)
	<-3SD	25(38.5%)
Height	-1SD to -2SD	22(33.8%)
	-2SD to -3SD	21(32.3%)
	<-3SD	22(33.8%)
Head circumference	Normal	34(52.3%)
	Microcephaly	20(30.8%)
	Macrocephaly	11(16.9%)
Consanguinity (p=0.016)	Ii-degree	23(35.4%)
	III-Degree	33(50.8%)
	Non-consanguineous	9(13.8%)

Table 2: Profile of symptoms and signs.

Profile		Number (%)
Fever	Yes	42(64.6%)
	No	23(35.4%)
Excessive vomiting	Yes	31(47.7%)
	No	34(52.3%)
Lethargy	Yes	38(58.5%)
	No	27(41.5%)
Poor feeding	Yes	44(67.7%)
	No	21(32.3%)
Seizures	Yes	26(40%)
	No	39(60%)
Developmental delay	Yes	18(27.7%)
	No	47(72.3%)
Regression of milestones	Yes	12(18.5%)
	No	53(81.5%)
Hepatomegaly	Yes	41(63.1%)
	No	24(36.9%)
Splenomegaly	Yes	32(49.2%)
	No	33(50.8%)
Cherry red spot	Yes	12(18.5%)
	No	53(81.5%)
Optic atrophy	Yes	7(10.8%)
	No	58(89.2%)

20(30.8%) children experienced at least one episode of hypoglycemia. 29(44.6%) children had deranged liver functions but only 5(7.7%) children had alteration in renal parameters. 10(15.4%) children were found to be hypothyroid. 18(27.7%) children had elevated ammonia levels. Lactate was found to be elevated in 24(36.9%) children. Nearly half the children (n=27, 41.5%) had elevated uric acid levels.

10(15.4%) children succumbed to the disease and remaining 55(84.6%) children were discharged and were on regular follow-up.

27(41.5%) children had disturbance in the carbohydrate metabolism. Among them, 1 had galactosemia (1.5%), 6 had mucopolysaccharidosis (9.2%), 4 had Pompe's disease (6.1%) and remaining 16 children had other glycogen storage disorders (24.6%).

Protein metabolism was affected in 16 children (24.6%). 8 children had organic acidemia (12.3%), 3 had urea cycle defect (4.6%) and 5 had aminoacidurias (7.7%).

Lipid metabolism was deranged in the remaining 22 children (33.8%) and among them, 8 were diagnosed to have Niemann Pick disease (12.3%), 3 had Tay-Sachs disease (4.6%), 5 children had Gaucher's disease (7.7%), 3 children had Krabbe's disease (4.6%) and remaining 3 had GM1 gangliosidosis (4.6%) (Table 3) (Figure 1).

Table 3: The aetiologias of hereditary metabolic disorders.

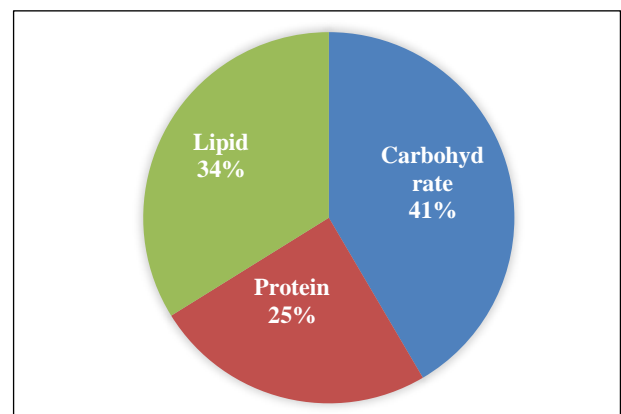| Inherited metabolic disorder	Number(%)
A - carbohydrate disorders	
Glycogen storage disorders	20(30.7%)
Galactosemia	1(1.5%)
Mucopolysaccharidosis	6(9.3%)
B - protein metabolism	
Urea cycle defect	3(4.6%)
Aminoacidurias	5(7.7%)
Organic acidurias	8(12.3%)
C - lipid metabolism	
Gaucher's disease	5(7.7%)
Tay sachs disease	3(4.6%)
Niemann pick disease	8(12.3%)
Krabbe's disease	3(4.6%)
GM1 gangliosidosis	3(4.6%)

Figure 1: Inherited Metabolic disorders - etiology.

DISCUSSION

This study was conducted with an aim to elaborate about clinical spectrum of inborn errors of metabolism in a tertiary care hospital. Totally 65 cases of IEM are taken for descriptive analysis.

Ramaswamy Ganesh et al, did a study in clinical profile and outcome of children with inborn errors of metabolism over a period of 1 year from June 2017 to May 2018. 31 newly diagnosed patients were studied for clinical, biochemical parameters and their diagnosis. 65% were born to consanguineous marriage parents. 51% had lysosomal storage disorders, 26% were disorders of amino aciduria, 6% of children had errors in carbohydrate and bile acid metabolism. In this study 85% were born to consanguineous marriage parents. Among them, 23 were II-degree consanguineous and 33 were III-degree consanguineous marriage parents. 41% had deranged carbohydrate metabolism, 34% had involvement of lipid metabolism and the remaining 25% had errors in protein metabolism.[6]

Majid Alfadhel et al, done a retrospective cohort study over 13 years. According to that study, the classification of IEM relied upon the accumulation of large and small molecules diseases. Their study showed higher prevalence of small molecule diseases than large molecules. But in this study large molecule diseases more common than small molecule. At the same time, in large molecular diseases, Lysosomal Storage Disorders (LSD) were more common, and sphingolipidosis were more common in LSD.[7] This study also reiterates the same findings.

Huma Arshad Cheema et al, conducted a study about various inherited metabolic disorders in children and found that disorders in carbohydrate metabolism was the most prevalent. This study also had similar picture with this study with higher prevalence of derangement in carbohydrate metabolism, followed by lipid storage disorders. 8.8% of children succumbed to the disease in their study and this study also had similar findings with mortality of 15.4%.[8]

Satwani et al, conducted a prevalence study in selected metabolic disorders. Their study showed higher incidence of IEM in boys compared to girls. This study also had similar findings, with higher incidence in boys (58.5%).[9] Excessive vomiting, poor feeding, fever and respiratory distress were the most common initial presentations in this study. Satani et al, also reported similar findings. Respiratory distress was the most common finding in their study.[10]

Selim et al, conducted a study of selected screening of inborn errors of metabolism and found that amino acid disorders were more commonly encountered than organic acidemias. Contrary to that, this study showed organic acidemias to be more common than aminoacidurias.[11] Clinical presentation with developmental delay and neurological damage were more common which is similar to this study.

Suvasini sharma et al, observed developmental delay, regression of milestones, behavioral impairments, seizure to be more common clinical presentation with IEM. This study supports the same with clinical manifestations similar to their study. Seizures were observed in 40% of children, developmental delay in 27%, regression of milestones in 18% of children in their study.[12] In this study the most common clinical presentation was poor feeding followed by abdominal distention, fever and seizure. This observation was supported by Verma et al, in which common presentation was failure to thrive, hepato-splenomegaly, short stature and neuro regression.[13]

Limitations of the study was included only 65 children due to availability of cases and time constraint. This is a hospital-based study which is not strictly representative of the background population. Except for Pompe's disease, enzymes assay for other glycogen storage disorders were not available and not done. So specific types could not be made out. For some disorders like mitochondrial disorders, fatty acid oxidation defects, mucolipidosis, pyruvate metabolism etc., enzyme assay or other diagnostic modalities are not available. Molecular genetic testing, next generation gene sequencing, mutation analysis is not done.

CONCLUSION

Though IEM may not appear as a large number, yet it is significant as many of them will present with critical illness and many of them will survive with lot of neurological damage. Screening programmes and prenatal diagnosis of IEM will go a long way in prevention and in genetic counselling. This would benefit the society as a whole in reducing and preventing psycho-social burden of the medical consequences due to IEM. The concept that "genetic disorders are very difficult to diagnose and if diagnosed, it is impossible to treat" no more stands.

ACKNOWLEDGEMENTS

REFERENCES

1. Alam S, Lal BB. Metabolic liver diseases presenting as acute liver failure in children. Ind Pediatr. 2016 Aug 1;53(8):695-701.

2. Burton BK. Inborn errors of metabolism in infancy: a guide to diagnosis. Pediatrics. 1998 Dec 1;102(6):e69.

3. Arnold GL. Inborn errors of metabolism in the 21st century: past to present. Ann Transl Med. 2018 Dec;6(24):467.

4. Chakrapani A, Cleary MA, Wraith JE. Detection of inborn errors of metabolism in the newborn. Archiv Dis Childhood-Fetal Neon Ed. 2001 May 1;84(3):F205-10.

5. Bittles AH. Consanguinity and its relevance to clinical genetics. Clin Gene. 2001 Aug;60(2):89-98.

6. Ganesh R, Abinesh R, Janakiraman L. Clinical spectrum of inherited disorders of metabolism. Ind J Pediatr. 2019 Oct 1;86(10):892-6.

7. Alfadhel M, Benmeakel M, Hossain MA, Al Mutairi F, Al Othaim A, Alfares AA, et al. Thirteen-year retrospective review of the spectrum of inborn errors of metabolism presenting in a tertiary center in Saudi Arabia. Orphanet J Rare Dis. 2016 Dec 1;11(1):126.

8. Cheema HA, Malik HS, Parkash A, Fayyaz Z. Spectrum of inherited metabolic disorders in Pakistani children presenting at a tertiary care centre. J Coll Physicians Surg Pak. 2016 Jun 1;26(6):498-502.

9. Satwani H, Raza J, Hanai J, Nomachi S. Prevalence of selected disorders of inborn errors of metabolism in suspected cases at a tertiary care hospital in Karachi. JPMA. 2009;59(12):815-9.

10. Mohamed S. Recognition and diagnostic approach to acute metabolic disorders in the neonatal period. Sudanese J Paediatr. 2011;11(1):20.

11. Nagaraja D, Mamatha SN, De T, Christopher R. Screening for inborn errors of metabolism using automated electrospray tandem mass spectrometry: study in high-risk Indian population. Clin Biochem. 2010 Apr 1;43(6):581-8.

12. Sharma S, Prasad AN. Inborn errors of metabolism and epilepsy: current understanding, diagnosis, and treatment approaches. Inter J Mole Sci. 2017 Jul;18(7):1384.

13. Verma IC, Bijarnia S. Inborn Errors of Metabolism in the Neonatal Period-Is it Time to Change our Practice?. Ind J Pediatr. 2012 Apr 1;79(4):528-9.