National Journal of Physiology, Pharmacy and Pharmacology

REVIEW ARTICLE

Inborn error of metabolism screening in neonates

Preeti Sharma[1], Shivani Gupta[2], Pradeep Kumar[1], Rachna Sharma[3], Mahapatra T K[1], Gaurav Gupta[4]

[1]Department of Biochemistry, Santosh Medical College and Hospital, Ghaziabad, Uttar Pradesh, India, [2]MBBS Student, TSM Medical College and Hospital, Lucknow, Uttar Pradesh, India, [3]Department of Biochemistry, TSM Medical College and Hospital, Lucknow, Uttar Pradesh, India, [4]Department of Biochemistry, Government Medical College, Badaun, Uttar Pradesh, India

Correspondence to: Preeti Sharma, E-mail: prcdri2003@yahoo.co.in

Received: December 14, 2018; **Accepted:** January 08, 2019

ABSTRACT

Inborn errors of metabolism belong to heterogeneous group of disorders which cause a number of morbidities and mortality in pediatric population and come under the class of genetic rare diseases. With the advent of newer molecular tools and techniques, so for several hundreds of disorders have been defined after the first description by Garrod in the 20th century. Early and timely diagnosis of the disease may prevent the life of a patient, but there are many reasons persist, restricting the timely diagnosis of the disease.

KEY WORDS: Metabolic Disorders; Neonatal Disorders; Metabolic Errors

INTRODUCTION

Inborn errors of metabolism (IEM) form a large class of genetic disorders which occur as a result of gene defects. The majority of them are due to defects of single genes coding for enzymes.[1-3] Newborn screening of inborn error of metabolism refers to the coordinated and comprehensive way of detecting disorders which includes knowledge, awareness, screening, follow-up of abnormal test results, confirmatory testing, diagnosis, treatment and evaluation of periodic outcome, and efficiency, for example, early detection of phenylketonuria and various other disorders helps in significant decrease in morbidity and helps in prevention from mental retardation.[4-7] Screening refers to the various biochemical and clinical tests done on asymptomatic neonates for the sake of decrease in morbidity and mortality rates and improving the efficiency outcome of better and healthy living of neonates. The identification of IEM as a disorder in neonates was described in the early 20th century. First of all, the disease known as alkaptonuria was discovered by Archibald Garrod, in 1908[8,9] followed by a research in 1917 regarding the advice of less intake of the milk by the galactosemic infants, but the treatment of various disorders of IEM changed in the 1950s with phenylketonuria.[10]

Access this article online	
Website: www.njppp.com	Quick Response code
DOI: 10.5455/njppp.2019.9.1237608012019	

Successful treatment outcome depends on early and rapid diagnosis and early therapeutic implementation in IEM disorders of neonates. Neonate suffering from IEM disorder is suspected as a result of acute clinical symptoms.[11] Sometimes, non-specific clues also exist, like previous unexplained death of neonate in few families showing the risk of IEM disorders in the baby. These disorders are detected through newborn screening programme though in India awareness of the program and lethal consequences of IEM disorders are not paid proper attention which may be due to lack of knowledge about the disease spectrum among the population and lack of funds to meet the screening expenses.

MECHANISTIC BIOCHEMISTRY AND ENZYME DEFECTS

Errors in amino acid metabolism conclude some correlations between biochemical and pathological conditions, for example, alkaptonuria, an inherited metabolic disorder is

caused by the absence of enzyme homogentisate oxidase due to which accumulation of homogentisate occurs and is excreted in urine, which turns dark black on standing due to oxidation.[12-14] In maple syrup urine disease (MSUD), the oxidative decarboxylation of α-keto acids derived from valine, leucine, and isoleucine gets blocked, leading to mental and physical retardation. Phenylketonuria, another disorder of IEM, is caused by an absence of the deficiency of phenylalanine hydroxylase, leading to accumulation of phenylalanine as it cannot be converted into tyrosine. Following is the list of various IEM disorders of protein, fat, carbohydrate, nucleic acid, and hemoglobin metabolism [Table 1].[4]

CURRENT STATUS IN INDIA

It is nearly 60 years gone for newborn screening for IEM. In course of this long span of time, our country faced many challenges with regard to its startup, including awareness among masses and its implementation in the form of pilot projects for few of the metabolic disorders. Various studies have been done in India at different times which concluded the importance of screening of IEM in neonates. In India, the prevalence of IEM is quite high. Distinct religions, communities, ethnic groups, etc., are responsible for wide variation and prevalence of IEM in these groups.[15] Hence, there is a need to do research in variation of IEM among different groups and look forward for the risk or aggravating factors of IEM in particular groups.[16,17] Many foreign countries recommend newborn screening mandatory because as per their guidelines delay in detection of few of these disorders such as metabolic errors, endocrinological disorders, and hearing loss will all lead to significant morbidity and mortality.[18,19] Andhra Pradesh is the fifth largest state of India with infant mortality rate of 66.[20] A study was done in Andhra Pradesh regarding IEM and a database was generated for 43 IEM observed in newborns.[21] Furthermore, in India, the incidence of congenital hypothyroidism (CH) is 2.1[22] and the rate of glucose 6 phosphate deficiency is 2-7.8%.[23] In a study which was undergone over a period of 4 years in West Bengal using gas chromatography in the urine and tandem mass spectrometry for the detection of aminoacidurias concluded 15% newborns positive of IEM,[24] but their final confirmation needs either enzymatic analysis or genetic studies. A study done on 98,256 newborn showed the prevalence of homocysteinemia, hyperglycemia, MSUD, phenylketonuria, hypothyroidism, and G6PD deficiency. Another expanded study started in 2000 in Hyderabad for amino acid disorders, CH, congenital adrenal hyperplasia (CAH), G6PD deficiency, biotinidase deficiency, galactosemia, and cystic fibrosis, revealed high prevalence of CH followed by CAH and G6PD deficiency.[25] The prevalence was noticed 1 in every 1000. A Newborn Screening Pilot project concluded disorders such as homocysteinemia, hyperglycemia, MSUD, phenylketonuria, hypothyroidism, and glucose-6-phosphate dehydrogenase deficiency were found to be the common errors in the neonates.[26] Another pilot study in Hyderabad revealed high prevalence of disorders such as congenital adrenal hyperplasia, G-6-PD deficiency, and aminoacidopathies as the cause of IEM.[27]

IMPORTANCE OF IEM AMONG NEONATES

IEM are the most important cause of the neonatal illness and many of these disorders are treatable if diagnosed in early phase; therefore, there is a need of IEM screening in newborns.[11,28] In other various countries, IEM screening

Table 1: Various IEM disorders

IEM disorders		40	Iminoglycinuria	85	Lactose intolerance
S. No.	Hemoglobinopathies	41	2-Ketoadipic aciduria	Fatty acid oxidation disorders	
1	Beta-thalassemia	42	Sacchropenuria	86	SCAD
2	Sickle cell anemia (HB SS)	43	Hydroxylysinuria	87	MCAD
3	Sickle cell disease (Hb S/C)	44	Cystathionuria	88	LCAD
4	Variant hemoglobinopathies (C, D, H, Bart band), including HbE	45	Hyperprolinemia	89	VLCAD
Endocrinology		46	Hyperprolinemia type II	90	Short/medium-chain 3-hydroxy-CoA dehydrogenase deficiency
5	Congenital hypothyroidism	47	Hyperhydroxyprolinemia	91	Long-chain 3-hydroxy-CoA dehydrogenase deficiency
6	Congenital adrenal hyperplasia	48	5-Oxoprolinuria	92	Mitochondrial trifunctional protein deficiency
Endocrinology		50	Hypersarcosinemia	93	Carnitine transport defect
7	Cystic fibrosis	51	Imidazole aminoaciduria	94	Multiple CoA dehydrogenase deficiency
8	G6PD deficiency	52	Formiminoglutamic aciduria	95	Medium-chain ketoacyl-CoA dehydrogenase deficiency

(Contd...)

Table 1: *(Continnued)*

Test done on urine samples		53	Serum carnosinase deficiency	Peroxisomal disorders	
Amino acid disorders		54	Glutathionuria	96	Zellweger syndrome
9	Phenyl ketonuria	55	Hyperpipecolatemia	97	Neonatal adrenoleukodystrophy
10	Defect in biopterin cofactor biosynthesis	56	3-Aminobutyric aciduria	98	Infantile Refsum's disease
11	Defects in biopterin cofactor regeneration	57	Histidinemia	99	Zellweger-like syndrome
12	GTPCH deficiency	Organic acid disorders		100	Primary hyperoxaluria
13	Dihydropteridine reductase deficiency	58	Propionic academia	Disorders of purine pyrimidine metabolism	
14	Benign H-PHE	59	Multiple carboxylase deficiency	101	Adenosine deaminase deficiency
15	Tyrosinemia type I	60	Methylmalonic acidemia	102	Lesch–Nyhan syndrome
16	Tyrosinemia type II	61	Methylmalonyl-CoA mutase deficiency	103	Partial deficiency of hypoxanthine adenine phosphoribosyltransferase
17	Tyrosinemia type III	62	Methylmalonic aciduria	104	Adenine phosphoribosyltransferase deficiency
18	Transient tyrosinemia in infancy	63	Malonic acidemia	105	Xanthinuria
19	Tyrosinemia caused by liver dysfunctions	64	Biobutyryl-CoA dehydrogenase deficiency	106	Orotic aciduria
20	MSUD	65	Methylbutyryl-CoA dehydrogenase deficiency	107	Thymine-uraciluria
21	Carbamoyl phosphate synthetase-1 deficiency	66	Methylmalonic semialdehyde dehydrogenase deficiency	108	Dihydropyrimidinase deficiency
22	OTC deficiency	67	B-Ketothiolase deficiency	109	Hyperuric acidemia
23	Citrullinemia	68	Isovaleric acidemia	Lactic acidemia, hyperpyruvic acidemia	
24	Citrullinemia type II	69	3-Methylcrotonyl-CoA carboxylase deficiency	110	Pyruvate dehydrogenase deficiency
25	Argininosuccinic aciduria	70	3-Methylglutaconic aciduria	111	Pyruvate dehydrogenase phosphatase deficiency
26	Argininemia	71	3-Hydroxy-3-methylglutaric aciduria	112	Pyruvate carboxylase deficiency
27	Hypermethioninemia	72	Glutaric aciduria type-II	113	Pyruvate decarboxylase deficiency
28	Homocystinuria	73	Glutaric aciduria type-l	114	Leigh syndrome
29	Alkaptonuria	74	Mevalonic acidemia		Other IEM
30	Tryptophanuria with dwarform	75	3-Methyl-3-hydroxybutyric aciduria	115	Biotinidase deficiency
31	Xanthurenic aciduria	76	4-Hydroxybutyric aciduria	116	Canavan deficiency
32	Valinemia	Carbohydrate disorders		117	Fumarate hydrolase deficiency
33	Hyperleucinemia	77	Galactosemia	118	HHH syndrome
34	Dihydroptoyl dehydrogenase deficiency	78	Galactokinase deficiency		Miscellaneous genetic condition
35	3-Hydroxylbutyryl-CoA deacylase deficiency	79	Galactose epimerase deficiency	119	Neuroblastoma
36	Histidinuria	80	Transient galactosemia		
37	Hartnup disease	81	Fructosuria		
38	Lysinuric protein intolerance	82	D-glyceric aciduria		
39	Familial renal iminoglycinuria	83	Fructose-1, 6-diphosphatase deficiency		
		84	Endogenous sucrosuria		

MSUD: Maple syrup urine disease, H-PHE: Hyperphenylalaninemia, SCAD: Short-chain CoA dehydrogenase deficiency, MCAD: Medium-chain CoA dehydrogenase efficiency, LCAD: Long-chain CoA dehydrogenase deficiency, VLCAD: Very long-chain CoA dehydrogenase deficiency, HHH: Hyperornithinemia-hyperammonemia-hyperhomocitrullinemia, GTPCH: GTP cyclohydrolase, OTC: Ornithine transcarbamylase, IEM: Inborn errors of metabolism

has expanded quite well. A pilot study was done by Shawky *et al.*,[29] in 2015, which included around 40 neonates with various reasons of abnormal behavior such as poor suckling, poor crying, and convulsions and was suspected to have IEM and concluded that around 32.5% of selected neonates for the case study were diagnosed with IEM who have sepsis-like symptoms. Another study was done by Shawky *et al.*[30] in which the screening of mentally retarded children was done by paper chromatography and various other tests such as ferric chloride test and nitroprusside test resulting in 11.3% of neonates with confirmed diagnosis of IEM. In Brazil, a study was conducted on 101 hypoglycemic neonates having metabolic acidosis, jaundice, diarrhea, vomiting, hepatomegaly or splenomegaly, cataract, apnea, and convulsions. Around 63.3% of 101 were diagnosed as IEM.[31] In China, a study was conducted by Huang *et al.*[32] on 11,060 neonates, of which only 62 were diagnosed as IEM. The symptomatic neonates were presented with metabolic acidosis, jaundice, hepatosplenomegaly, recurrent vomiting, hypoglycemia, convulsions, and unconsciousness. In German study,[33] 106 neonates were diagnosed as IEM out of 250,000 neonates. In Taiwan, the newborn screening at the national level revealed phenylalanine metabolism defect as the most common defect of IEM followed by MSUD.[34-36] IEM screening should be done for the betterment of any country's health and wealth, but it is still lacking due to various hurdles coming in its way like financial constraints as it is quite expensive, so every individual person or country cannot afford it and also there is a lack of education and awareness among the citizens of one's country regarding the importance of IEM or its role in the well-being of the child in near future.

CONCLUSION

Individually rare kind of disorders, IEM manifest due to partial and full enzymatic defects leads to the accumulation of toxic metabolites in the body. To manage its morbid and mortal effects, early and timely diagnosis and management is essential. The newborn screening program one of the important ways to provide early and pre-symptomatic diagnosis. The approach is proved to be a boon for innocent infants suffering from IEM disorders who can live a normal life if properly managed.

ACKNOWLEDGMENT

The authors thankfully acknowledge the management of Santosh Medical College and Hospital, for supporting the work.

REFERENCES

1. Sharma P, Kumar P, Sharma R, Dhot PS. Inborn errors of metabolism screening and scope of GC-MS. Asian J Pharm Clin 2015;8:34-6.
2. Inborn Errors of Metabolism. Available from: http://www.authorstream.com/Presentation/somashekharc-432381-inborn-error-metabolism-iem-education-ppt-powerpoint. [Last accessed on 2018 Nov 12].
3. Yudkoff M. Inborn Errors of Metabolism. Available from: https://www.britannica.com/science/inborn-error-of-metabolism. [Last accessed on 2018 Nov 12].
4. Sharma P, Kumar P, Dhot PS, Sharma R. Prevalence of IEM in neonates. J Clinc Diagn Res 2018;12:BC07-13.
5. Das SK. Inborn errors of metabolism: Challenges and management. Indian J Clin Biochem 2013;28:311-3.
6. Ozben T. Expanded newborn screening and confirmatory follow-up testing for inborn errors of metabolism detected by tandem mass spectrometry. Clin Chem Lab Med 2013;51:157-76.
7. Yang CJ, Wei N, Li M, Xie K, Li JQ, Huang CG, *et al.* Diagnosis and therapeutic monitoring of inborn errors of metabolism in 100,077 newborns from Jining city in China. BMC Pediatr 2018;18:110.
8. Galton D, Garrod AE. The founding father of biochemical genetics. In: Pioneers of Medicine without a Noble Prize. London: Imperial College Press; 2014. p. 1-21.
9. KNOX WE. Sir Archibald Garrod's inborn errors of metabolism. II. Alkaptonuria. Am J Hum Genet 1958;10:95-124.
10. Timothy BJ, Omar HA, Merrick J. Adults with Childhood Illnesses. Considerations for Practice. Berlin, Boston: De Gruyter; 2011. Available from: https://www.degruyter.com/view/product/129350. [Last accessed on 2018 Nov 13].
11. Chakrapani A, Cleary MA, Wraith JE. Detection of inborn errors of metabolism in the newborn. Arch Dis Child Fetal Neonatal Ed 2001;84:F205-10.
12. Berg JM, Tymoczko JL, Stryer L. Biochemistry. 5th ed. New York: W H Freeman; 2002. Section 23.6, Inborn Errors of Metabolism Can Disrupt Amino Acid Degradation. Available from: https://www.ncbi.nlm.nih.gov/books/NBK22493. [Last accessed on 2018 Nov 14].
13. Mistry JB, Bukhari M, Taylor AM. Alkaptonuria. Rare Dis 2013;1:e27475.
14. Alkaptonuria, US National Library of Medicine, Medicine Plus. Available from: https://www.medlineplus.gov/ency/article/001200.html. [Last accessed on 2018 Nov 14].
15. Shetty KT. Metabolomics: Impact on diagnosis and monitoring of 'inborn'/'acquired' metabolic disorders. Indian J Clin Biochem 2007;22:3-5.
16. Indian Genome Variation Consortium. Genetic landscape of the people of India: A canvas for disease gene exploration. J Genet 2008;87:3-20.
17. Morris AAM. Neonatal screening for Inborn Errors of Metabolism. Indian Pediatr 2000;37:1303.
18. Rose NC, Dolan SM. Newborn screening and the obstetrician. Obstet Gynecol 2012;120:908-17.
19. Health Quality Ontario. Neonatal screening of inborn errors of metabolism using tandem mass spectrometry: An evidence-based analysis. Ont Health Technol Assess Ser 2003;3:1-36.
20. Available from: http://www.aponline.gov.in. [Last accessed on Nov 2018 14].
21. Latheef SA. A database for inborn errors of metabolism in the Indian state of Andhra Pradesh. Bioinformation 2010;4:276-7.
22. Sanghvi U, Diwarkar KK. Universal screening programme for congenital hypothyroidism. Indian Pediatr 2008;45:331-2.
23. Padilla CD, Therrell BL. Newborn screening in the Asia pacific

region. J Inherit Metab Dis 2007;30:490-506.
24. Lodh M, Kerketta A. Inborn errors of metabolism in a tertiary care hospital of eastern India. Indian Pediatr 2013;50:1155-6.
25. Kapoor S, Kabra M. Newborn screening in India: Current perspectives. Indian Pediatr 2010;47:219-24.
26. Rao NA, Devi AR, Savithri HS, Rao SV, Bittles AH. Neonatal screening for amino acidaemias in Karnataka, South India. Clin Genet 1988;34:60-3.
27. Rama Devi AR, Naushad SM. Newborn screening in India. Indian J Pediatr 2004;71:157-60.
28. Mak CM, Lee HC, Chan AY, Lam CW. Inborn errors of metabolism and expanded newborn screening: Review and update. Crit Rev Clin Lab Sci 2013;50:142-62.
29. Shawky RM, Abd-Elkhalek HS, Elakhdar SE. Selective screening in neonates suspected to have inborn errors of metabolism. Egypt J Med Hum Genet 2015;16:165-71.
30. Shawky RM, El-Din Riad MS, Osman HM, Bahaa NM. Screening for some inborn errors of amino acid metabolism which impair mental function. Egypt J Med Hum Genet 2001;2:71-91.
31. Chiaratti de Oliveira A, dos Santos AM, Martins AM, D'Almeida V. Screening for inborn errors of metabolism among newborns with metabolic disturbance and/or neurological manifestations without determined cause. Sao Paulo Med J 2001;119:160-4.
32. Huang X, Yang L, Tong F, Yang R, Zhao Z. Screening for inborn errors of metabolism in high-risk children: A 3-year pilot study in Zhejiang Province, China. BMC Pediatr 2012;12:18.
33. Schulze A, Lindner M, Kohlmüller D, Olgemöller K, Mayatepek E, Hoffmann GF, *et al.* Expanded newborn screening for inborn errors of metabolism by electrospray ionization-tandem mass spectrometry: Results, outcome, and implications. Pediatrics 2003;111:1399-406.
34. Frazier DM, Millington DS, McCandless SE, Koeberl DD, Weavil SD, Chiang SH, *et al.* The tendem mass spectrometry newborn screening experience in North Carolina: 1997-2005. J Inherit Metab Dis 2006;29:76-85.
35. Nongalleima K, Ajungla T, Singh CB. GCMS based metabolic profiling of essential oil of *Citrus macroptera* Montruz, leaves and peel, assessment of *in vitro* antioxidant and antiinflammatory activity. Int J Pharm Pharm Sci 2017;9:107-14.
36. Zerrouki K, Djebli N, Ozkan EE, Ozsoy N, Gul O, Mat A. *Hypericum perforatum* improve memory and learning in Alzheimer's model: Experimental study in Mice. Int J Pharm Pharm Sci 2016;8:49-57.

How to cite this article: Sharma P, Gupta S, Kumar P, Sharma R, Mahapatra TK, Gupta G. Inborn error of metabolism screening in neonates. Natl J Physiol Pharm Pharmacol 2019;9(3):196-200.

Source of Support: Nil, **Conflict of Interest:** None declared.