Inborn Error of Metabolism [IEM] Screening in Neonates

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Abstract

Inborn errors of metabolism belong to heterogenous 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 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 eg. early detection of phenylketonuria and various other disorders help 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 early twentieth 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 milk by the galactosemic infants but the treatment of various disorders of IEM changed in 1950s with Phenylketonuria.[10]

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 nonspecific 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 nowborn screening programme though in India awareness of the programme 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 expanses.

Mechanistic Biochemistry And Enzyme Defects

Errors in Amino acid metabolism conclude some correlations between biochemical and pathological conditions eg. Alkaptonuria, an inherited metabolic disorder is caused by 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, the oxidative decarboxylation of á-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 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 heamoglobin metabolism[4].

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Table: 1 Various IEM disorders

S. No	IEM Disorders Hemoglobinopathies				
1	BetaThalassemia	40 41	Iminoglycinuria 2-Ketoadipic aciduria	85	Lactose Intolerance Fatty Acid Oxidation disorders
2	Sickle Cell Anemia (HB SS)	42	Sacchropenuria	86	Short Chain CoA Dehydrogenase deficiency (SCAD)
3	Sickle Cell Disease (Hb S/ C)	43	Hydroxylysinuria	87	Medium Chain CoA Dehydrogenase Deficiency (MCAD)
4	Variant Hemoglobinopathies (C, D, H, bart band), including HbE	44	Cystathionuria	88	Long Chain CoA Dehydrogenase Deficiency (LCAD)
	Endocrinology	45	Hyperprolinemia	89	Very Long Chain CoA Dehydrogenase Deficiency (VLCAD)
5	Congenital Hypothyroidism	46	Hyperprolinemia Type II	90	Short/Medium Chain 3- Hydroxy CoA Dehydrogenase Deficiency
6	Congenital adrenal Hyperplasia	47	Hyperhydroxyprolinemia	91	Long Chain 3- Hydroxy CoA Dehydrogenase Deficiency
	Endocrinology	48	5-Oxoprolinuria	92	Mitochondrial Trifunctional Protein Deficiency
7	Cystic Fibrosis	50	Hypersarcosinemia	93	Carnitine Transport Defect
8	G6PD Deficiency	51	Imidazole aminoaciduria	94	Multiple CoA Dehydrogensae Deficiency
	TEST DONE ON URINE SAMPLES	52	Formiminoglutamic aciduria	95	Medium Chain Ketoacyl CoA Dehydrogenase Deficiency
	Amino Acid Disorders	53	Serum carnosinase deficiency		Peroxisomal Disorders
9	Phenyl ketonuria	54	Glutathionuria	96	Zellweger Syndrome
10	Defect in Biopterin Cofactor Biosynthesis	55	Hyperpipecolatemia	97	Neonal Adenoleucodystrophy
11	Defects in Biopterin Cofactor Regeneration	56	3- Aminobutyric aciduria	98	Infantile Refsums Disease
12	GTP Cyclohydrolase (GTPCH) Deficiency	57	Histidinemia	99	Zellweger Like Syndrome
13	Dihydropteridine Reductase Deficiency		Organic acid Disorders	100	Primary Hyperoxaluria
14	Benign Hyperphenylalaninemia(H-PHE)	58	Propionic academia		Disorders of Purine Pyrimidine Metabolism
15	Tyrosinemia Type I	59	Multiple carboxylase deficiency	101	Adinosine Deaminase Deficiency
16	Tyrosinemia Type II	60	Methyl Malonic Acidemia	102	Lesch Nyhan Syndrome
17	Tyrosinemia Type III	61	Methyl Malonyl CoA Mutase Deficiency	103	Partial Deficiency ofHypoxanthine Adenine Phosphoribosyl Transferase
18	Trasient Tyrosinemia in Infancy	62	Methyl Malonic Aciduria	104	Adenine Phosphoribosyl Transferase Deficiency
19	Tyrosinemia caused by liver dysfunctions	63	Malonic Acidemia	105	Xanthinuria
20	Maple Syrup Urine Disease (MSUD)	64	Biobutyryl CoA Dehydrogenase Deficiency	106	Orotic Aciduria
21	Carbamoyl Phosphate Synthetase - 1 Deficiency	65	MethylButyryl CoA Dehydrogenase Deficiency	107	Thymine uraciluria
		66	Methyl Malonic Semialdehyde Dehydrogenase Deficiency	108	Dihydropyriminidase Deficiency

22	Ornithine Transcarbomylase (OTC) Deficiency	67	B- Ketothiolase Deficiency	109	Hyperuric Acidemia
23	Citrullinemia	68	Isovaleric aciedmia		Lactic Acidemia, Hyperpyruvic Acidemia
24	Citrullinemia Type II	69	3-MethylcrotonylCoA Carboxylase Deficiency	110	Pyruvate Dehydrogenase Deficiency
25	Argininosuccinic aciduria	70	3-Methyl Glutaconic aciduria	111	Pyruvate Dehydrogenase Phosphatase Deficiency
26	Argininemia	71	3-Hydroxy 3- methyl Glutaric Aciduria	112	Pyruvate carboxylase deficiency
27	Hypermethioninemia	72	Glutaric aciduria Type-ll	113	Pyruvate decarboxylase deficiency
28	Homocysteinuria	73	Glutaric aciduria Type-l	114	Leigh Syndrome
29	Alkaptonuria	74	Mevalonic Acidemia		Other IEM
30	Tryptophanuria with dwarform	75	3-Methyl 3-Hydroxy Butyric Aciduria	115	Biotinidase Deficiency
31	Xanthurenic Aciduria	76	4-Hydroxybutyric aciduria	116	Canavan Deficiency
32	Valinemia		Carbohydrate Disorders	117	Fumerate Hydrolase Deficiency
33	Hyperleucinemia	77	Galactosemia	118	Hyperornithinemia-Hyperammonemia-Hyperhomocitrullinemia(HHH) Syndrome
34	Dihydroptoyl Dehydrogenase deficiency	78	Galactokinase Deficiency		Miscellaneous genetic condition
35	3-Hydroxylbutyryl CoA Deacylase	79	Galactose Epimerase Deficiency Deficiency	119	Neuroblastoma
36	Histidinuria	80	Transient Galactosemia		
37	Hurtnup Disease	81	Fructosuria		
38	Lysinuric Protein Intolerance	82	D-Glyceric Aciduria		
39	Famillial Renal Iminoglycinuria	83	Fructose 1, 6 Diphosphatase Deficiency		
		84	Endogenous Sucrosuria		

Current Status In India

Its nearly 60 years gone for newborn screening foe inborn errors of metabolism. In course of this long span of time our country faced many challenges with regard to its start up, 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] So, 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 new born screening mandatory because as per their guidelines delay in detection of few of these disorders like metabolic errors, endocrinological disorders, 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] Also in India, the incidence of congenital Hypothyroidism is 2.1[22] and that of G6PD 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 125 thousand newborn, showed the prevalence of homocysteinemia, hyperglycemia, MSUD, phenylkeronuria, hypothyroidism and G6PD deficiency. Another expanded study started in 2000 in Hyderabad for amino acid disorders, congenital hypothyroidism(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 like Homocysteneimia, Hyperglycemia, Maple Syrup Urine disease; 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 like Congenital Adrenal

Hyperplasia, G-6-PD deficiency and aminoacidopathies as the cause of IEM.[27]

Importance Of Iem Among Neonates

The Inborn errors of metabolism 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, the IEM screening has expanded quite well. A pilot study was done by Rabah M. Shawky[29] and his co-workers in 2015 which included around 40 neonates with various reasons of abnormal behavior like poor suckling, poor crying, convulsions and were 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 [2001][30] in which the screening of mentally retarded children was done by paper chromatography and various other tests like ferric chloride test, nitroprusside test etc. resulting in 11.3% neonates with confirmed diagnosis of IEM. In Brazil, a study was conducted on 101 hypoglycemic neonates having metabolic acidosis, jaundice, diarrhoea, vomiting, hepatomegaly or splenomegaly, cataract, apnoea and convulsions. Around 63.3% of 101 were diagnosed as IEM.[31] In China, a study was conducted by Huang et. al[32] on 11060 neonates, out 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 a German study[33], 106 neonates were diagnosed as IEM out of 2,50,000 neonates. In Taiwan, the Newborn Screening at the National level revealed Phenylalanine Metabolism defect as the most common defect of IEM followed by Maple Syrup Urine Disease.[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 can't 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, Inborn errors of metabolism manifest due to partial and full enzymatic defects lead to accumulation of toxic metabolites in the body. In order 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 presymptomatic 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.

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Author's Contribution

Whole idea of manuscript was generated by Dr. Preeti Sharma and Dr. Pradeep Kumar flourished by writing by Ms. Shivani Gupta, Revised and corrected by Dr. PS Dhot, Dr. Rachna Sharma and Dr. TK Mahapatra.

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