Inborn Error of Metabolism [IEM] Screening in Neonates
Preeti Sharma*, Pradeep Kumar**, Shivani Gupta***, PS Dhot****, Rachna Sharma*****, TK Mahapatra******

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 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. 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. 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 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.

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. 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 newborn 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 expenses.

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. In maple syrup urine disease, 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 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 haemoglobin metabolism.
Table: 1 Various IEM disorders

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<th>IEM Disorders</th>
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<td>Hemoglobinopathies</td>
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<td>Carbamoyl Phosphate Synthetase - 1 Deficiency</td>
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Amino Acid Disorders

Amino Acid Disorders

Endocrinology

Endocrinology

G6PD Deficiency

TEST DONE ON URINE SAMPLES

Amino Acid Disorders

Phenyl ketonuria

Defect in Bioterin Cofactor Biosynthesis

Defect in Bioterin Cofactor Regeneration

GTP Cyclohydrolase (GTPCH) Deficiency

Dihydropteridine Reductase Deficiency

Benign Hyperphenylalaninemia(H-PHE)

Tyrosinemia Type I

Tyrosinemia Type II

Tyrosinemia Type III

Trasient Tyrosinemia in Infancy

Tyrosinemia caused by liver dysfunctions

Maple Syrup Urine Disease (MSUD)

Carbamoyl Phosphate Synthetase - 1 Deficiency

Adenosine Deaminase Deficiency

Lesch Nyhan Syndrome

Partial Deficiency ofHypoxanthine Adenine Phosphoribosyl Transferase

Adenine Phosphoribosyl Transferase Deficiency

Xanthinuria

Orotic Aciduria

Thymine uraciliuria

Dihydropyrimidase Deficiency
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 newborn 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 2.122 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 IEM24 but their final confirmation needs either enzymatic analysis or genetic studies. A study done on 125 thousand newborn, showed the prevalence of homocysteinaemia, 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. 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 Homocysteinemia, 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.31 In various countries, the IEM screening has expanded quite well. A pilot study was done by Rabah M. Shawky29 and his co-workers in 2015 which included around 40 neonates with various reasons of abnormal behavior like poor sucking, 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. al32 on 11060 neonates, out of which only 62 were diagnosed as IEM. The symptomatic neonates were presented with metabolic acidosis, jaundice, hepatosplenomegaly, recurrent vomiting, hyperglycemia, convulsions and unconsciousness. In a German study33, 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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