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Short Communication

Inborn Errors of Metabolism: Indian Scenario

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Introduction

The term 'inborn errors of metabolism' (IEM), was first coined by a British scientist Archibald Garrod to describe the genetic deficiency or alteration in enzyme function [1]. The enzyme deficiency leads to substrate accumulation which causes minor to severe clinical symptoms, mostly with neurological and psychiatric symptoms that often leads to death or life long disability. Neurological symptoms of the patients included psychomotor delay, mental retardation, seizures, dystonia, ataxia, lethargy, coma, encephalitis, speech delay, hyperactivity etc. other symptoms were failure to thrive, organomegaly, vomiting, skin rashes, metabolic acidosis, hyperammonemia, hypoglycemia, lactic acidosis and ketonuria. If these patients are not diagnosed and treated early in life, they go on to have irreversible brain damage. Many body systems are affected, and the predominant damage will be to the central nervous system. The babies may develop permanent mental retardation, growth retardation etc. The overall incidence of the IEM was estimated 1 in 1,400 births in British Columbia [2]; and about 1 in 4,000 in Hong Kong [3]. Traditionally the IEM are categorized as disorders of carbohydrate metabolism, amino acid metabolism, organic acid metabolism and lysosomal storage diseases.

Inborn errors of metabolism consists a large group of more than 500 different genetic disorders. Mutations in genes encoding a single enzyme in metabolic pathways cause these disorders. Some of these disorders are very rare, whereas certain other disorders are more common. It is now known that along with amino acidurias, organic acid disorders (OAD) form the most important class of IEM in high-risk population and among severely-ill children [4]. Although individually rare, the conjunctive frequency of OAD in high-risk group may be up to 200 times higher than that identified in the general population [5]. There are considerable racial and ethnic differences in the incidence pattern of these disorders. Phenylketonuria (PKU) are common in the Western population; in Asian countries including India, organic acidurias like propionic acidurias, methyl malonic acidurias and maple syrup urine disease (MSUD) are more common [6]. Clinical presentation of IEM is wide-ranging and it affects different organ systems, including CNS.

Indeed CNS involvement is one of the most common presenting symptoms [7]. The diseases can appear two or three days after milk feeding starts; or sometimes it may be delayed, even appearing in adult life.

Diagnosis and treatment

As the identification of specific enzymes and metabolic pathways, metabolic diseases can be diagnosed in many cases with routine biochemical blood tests and metabolic screening of urine, such as ferric chloride test, DNPH test, Rothera's test, Cyanide nitroprusside test etc. High performance liquid chromatography (HPLC) can be used for analysis of amino acids, organic acids or other metabolites in blood [8]. However specific diagnosis requires enzyme assays, DNA analysis etc. Nowadays prenatal diagnostic techniques are also available [9]. RIA, ELISA, fluorescence-based assays and gas chromatography mass spectrometry (GCMS) are widely used for diagnosis of IEM. The methodology to be used for newborn screening programs should attempt to keep false negatives low and false positives manageable. Internal and external quality control is essential [10].

The introduction of tandem mass spectrometry was a turning point in the history of newborn screening (NBS) for metabolic dis-

eases. Tandem mass spectrometry (TM) employs a single assay for multiple disorders, has increased efficiency with low cost per sample, although the initial cost of the equipment is high. It also breaks the paradigm in NBS of one test one disorder [11]. It has replaced classic screening techniques of one-analysis, one-metabolite, and one-disease with one analysis, many-metabolites, and many-diseases. The incidence of congenital hypothyroidism (CH), congenital adrenal hyperplasia (CAH) and G6PD deficiency, haemoglobin disorders, organic acidurias and amino acidurias in India is high [12]. In India the annual birth rate is 21.76 births/1,000 population and in Delhi alone nearly 900 births take place every day; considering this figure there would be one or two babies born in Delhi alone with a metabolic defect each day [13]. Given the density of population, the rate of occurrence of IEM may be expected to be high and preventable complications can be attended to early and before the affected child is incapacitated by implementing nationwide newborn screening programmes [14]. Since dried blood spot remains stable for many years, the mode of collection should be capillary blood from the heel, impregnation of drops of blood into filter paper, drying of these blood spots and transport of the specimens to a central screening laboratory [15]. The ideal time of sampling for our set up, to take the sample after first 24 hours of life.

Early diagnosis, treatment and dietary management can reduce the morbidity and mortality. The combination of protein restriction and medical food is used for treatment in phenylketonuria, MSUD, homocystinuria, galactosemia, glycogen storage disease (Type I/III), organic acidurias and amino acidurias [16]. These dietary modifications may involve substrate restriction, replacement of deficient products, and removal of toxic metabolites or stimulation of residual enzymes [17].

Conclusion

Prenatal diagnosis and newborn screening help to reduce the social burden as well as the morbidity due to IEM. However, the success of any screening programme requires the public participation. Based on current evidence, all hospitals in urban areas in India should initiate NBS for congenital hypothyroidism (CH), congenital adrenal hyperplasia (CAH) and G6PD deficiency, haemoglobin disorders, organic acidurias and amino acidurias. Facilities for confirmation of diagnosis follow up and treatment should be established. Laboratories for preliminary level screening with few low cost tests can be established in all medical colleges and district hospitals. In tertiary laboratories advanced tests like High performance liquid chromatography (HPLC), Gas liquid chromatography (GLC), tandem mass spectrometry (TM), specific enzyme analysis, PCR based molecular biology tests, etc. are made available. Identified genetic centres should take up one disorder or a group of IEM, mutually exclusive of each other, to undertake the responsibility of molecular diagnosis.

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