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EDITORIAL

Inborn Errors of Metabolism: Challenges and Management

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Introduction

The term 'inborn errors of metabolism' (IEM), which is also referred to as congenital metabolic diseases or inherited metabolic diseases was first coined by a British physician Archibald Garrod (1857–1936) to describe the hereditary deficiency or alteration in enzyme reactions in the early 20th century [1]. These result in substrate accumulation causes minor to severe clinical symptoms, mostly with neurological and psychiatric symptoms that often leads to death or life long disability. Although IEM have usually been considered pediatric diseases, they can present at any age [2]. The overall incidence of the IEM was estimated 1 in 1,400 births in British Columbia [3]; and about 1 in 4,000 in Hong Kong [4]. Using the Hardy–Weinberg formula IEM were estimated at 1/13,716 for maple syrup urine disease (MSUD), 1/14,804 for tyrosinemia type I, 1/16,144 for methylmalonic aciduria and 1/23,176 for propionic aciduria in Tunisia [5].

Classification

Traditionally the IEM are categorized as disorders of carbohydrate metabolism, amino acid metabolism, organic acid metabolism, or lysosomal storage diseases. However, diagnostically these metabolic disorders can be divided into five groups as: (a) energy metabolism disorders: disorders of respiratory chain, pyruvate dehydrogenase, GLUT1, fatty-acid β-oxidation, and key cofactors such as electron transfer flavoprotein, thiamine, biotin, riboflavin, vitamin E and coenzyme Q10; (b) intoxication syndromes: porphyrias, urea-cycle defects, homocystinurias, organic acidurias and amino acidopathies; (c) lipid-storage disorders: lysosomal storage disorders (Krabbe disease, metachromatic leukodystrophy, Niemann-Pick disease type C, Fabry disease and Gaucher's disease), peroxisomal disorders (adrenomyeloneuropathy, Refsum disease, disorders of pristanic acid metabolism, peroxisome biogenesis disorders), Tangier disease and cerebrotendinous xanthomatosis; (d) metal (such as iron, copper and manganese) storage diseases; and (e) neurotransmitter (serotonin, dopamine and glycine) metabolism defects [2].

Diagnosis

With 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, Cetavlon test, Cyanide nitroprusside test etc. However, the complete characterisation of the particular condition usually involves more specific studies, such as enzyme assays, DNA analysis and family studies.

Nowadays tandem mass (TM) spectrometry has become a key technology in the field of neonatal screening that allows detection of more than 20 inherited disorders of amino acid, fatty acid and organic acid metabolism from a single dried blood spot. It has replaced classic screening techniques of one-analysis, one-metabolite, one-disease with one analysis, many-metabolites, and many-diseases [6]. With the advancement of technology, traditional electrospray tandem mass spectrometry screening is now being extended to nanospray ionization and high resolution

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mass spectrometry, allowing the selective detection of more than 400 individual metabolic constituents of blood [7].

Treatment

Early diagnosis and subsequent nutritional modification management can reduce the morbidity and mortality. Dietary therapy is the mainstay of treatment in phenylketonuria (PKU), MSUD, homocystinuria, galactosemia and glycogen storage disease (Type I/III) [8]. These dietary modifications may involve substrate restriction, replacement of deficient products, removal of toxic metabolites or stimulation of residual enzymes. Substrate restriction includes not only a diet low in the substrate indicated by the disorder, but also strict calorie support in times of illness to avoid catabolism [9]. But, commercially available diets are very expensive. Therefore modification in routine Indian diet may be tried based on content of different nutrients, but the desirable fine control is not achieved [8]. However, many patients with -inborn errors, especially, those with storage or neurodegenerative disorders do not need any specific dietary therapy [9]. Newer therapies including bone marrow transplantation, enzyme replacement therapy, substrate inhibition therapy, pharmacological chaperones and many other approaches are transforming the lysosomal storage diseases into treatable conditions [10].

New Born Screening

Newborn screening (NBS) of IEM is a coordinated comprehensive system consisting of education, screening, follow-up of abnormal test results, confirmatory testing, diagnosis, treatment, and evaluation of periodic outcome and efficiency. The ultimate goal of NBS is to reduce morbidity and mortality from the disorders [6]. For example, early detection of PKU and early introduction of a diet low in phenylalanine results in a significant decrease in morbidity, prevent mental retardation and are associated with higher IQ scores [11]. The Universal NBS that started out using simple bacterial inhibition assays to screen PKU in the early 1960s [12] is a success story of preventive medicine. The nationwide NBS in Japan for PKU, MSUD, histidinemia, homocystinuria and galactosemia has been performed since 1977 and formulated the treatment guideline for the target diseases [13]. In Mainland China NBS began in 1981 to detect congenital hypothyroidism (CH) and PKU [14]; and in Denmark on February 1, 2002 as a national prospective pilot project [15]. However, in many countries including India, neonatal screening programs have been unable to expand and have been limited to a few diseases.

Indian Scenario

There are limited published studies on the newborn population screening from India. Homocysteneimia, hyperglycinemia, MSUD, PKU, hypothyroidism and G6PD deficiency were found to be the common errors in one NBS pilot project in Karnataka [16]. Another pilot program from Hyderabad revealed a high prevalence of CH (1 in 1,700) followed by congenital adrenal hyperplasia, G6PD deficiency and aminoacidopathies [17]. Though, a very high prevalence of IEM to the extent of 1 in every 1,000 newborns was observed in several single hospital based study [18, 19], but no study truly reflected the extent of the IEM in India.

Recommendations

Inherited metabolic disorders are individually rare but collectively numerous, causing substantial morbidity and mortality. These also result in psychosocial crises that challenge individual and familial modes of functioning across the life cycle [20]. Prenatal diagnosis and newborn screening help to reduce the societal burden as well as the morbidity due to IEM. However, the success of any screening programme requires the public participation. The most important is to get the government's policy and financial support for expanded screening.

In that context, a panel discussion on the "Challenges and management of on inborn errors of metabolism", organized by the Department of Biochemistry, College of Medicine & JNM Hospital, The West Bengal University of Health Sciences on the 7th March 2013, the panellists Dr. Robert Aquaron (France), Dr. Noah Weisleder (USA), Dr. Ashwin Dalal (CDFD, Hyderabad), Dr. Purnima Prabhu (P. D. Hinduja Hospital, Mumbai), Dr. Praveen Sharma and Dr. D.M. Vasudevan has brought out the following suggestions, for consideration by authorities:

- "Due to financial constraints, screening of all new born babies in India may be the long term aim; however, preliminary level screening with few low cost tests laboratories in all medical colleges and district hospitals can be established.
- Blood and/or urine from all new born babies are to be screened in these laboratories, and abnormal samples could be sent to tertiary centers for further analysis.
- About 10 tertiary laboratories in different regions of India should be set up, where advanced techniques such

as 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.

- At present, the dietary formulas are imported from abroad at a very high cost. Indian companies should be encouraged to make special diet formulas for such patients, so that treatment cost could be made affordable.
- Attempts should be made to raise funds from Indian and foreign granting agencies to launch/support these recommendations.
- Initiate awareness programmes throughout the country, so that medical personnel as well as general public are made aware of this grave public health problem, and the importance of the screening of all new born babies."

References

1. Garrod AE. The incidence of alkaptonuria: a study in chemical individuality. Lancet. 1902;13:1616–20.
2. Sedel F. Inborn errors of metabolism in adult neurology. Rev Neurol (Paris). 2013;169(Suppl 1):S63–9.
3. Applegarth DA, Toone JR, Lowry RB. Incidence of inborn errors of metabolism in British Columbia, 1969–1996. Pediatrics. 2000;105(1):e10.
4. Mak CM, Lam CW, Law CY, Siu WK, Kwong LL, Chan KL, Chan WT, Chow KM, Lee KW, Chan WP, Chan AY. Parental attitudes on expanded newborn screening in Hong Kong. Public Health. 2012;126(11):954–9.
5. Hadj-Taieb S, Nasrallah F, Hammami MB, Elasmi M, Sanhaji H, Moncef F, Kaabachi N. Aminoacidopathies and organic acidurias in Tunisia: a retrospective survey over 23 years. Tunis Med. 2012;90(3):258–61.
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(1):157–76.
7. Dénes J, Szabó E, Robinette SL, Szatmári I, Szőnyi L, Kreuder JG, Rauterberg EW, Takáts Z. Metabonomics of newborn screening dried blood spot samples: a novel approach in the screening and diagnostics of inborn errors of metabolism. Anal Chem. 2012;84(22):10113–20.
8. Kabra M. Dietary management of inborn errors of metabolism. Indian J Pediatr. 2002;69(5):421–6.
9. Wilcken B. An introduction to nutritional treatment in inborn errors of metabolism–different disorders, different approaches. Southeast Asian J Trop Med Public Health. 2003;34(Suppl 3):198–201.
10. Giugliani R. Newborn screening for lysosomal diseases: current status and potential interface with population medical genetics in Latin America. J Inherit Metab Dis. 2012;35(5):871–7.
11. Castro IP, Borges JM, Chagas HA, Tibúrcio J, Starling AL, Aguiar MJ. Relationships between phenylalanine levels, intelligence and socioeconomic status of patients with phenylketonuria. J Pediatr (Rio J). 2012;88(4):353–6.
12. Guthrie R, Susi A. A simple phenylalanine method for detecting phenylketonuria in large populations of newborn infants. Pediatrics. 1963;32:338–43.
13. Kitagawa T. Newborn screening for inborn errors of metabolism in Japan. A history of the development of newborn screening. Pediatr Endocrinol Rev. 2012;10(Suppl 1):8–25.
14. Shi XT, Cai J, Wang YY, Tu WJ, Wang WP, Gong LM, Wang DW, Ye YT, Fang SG, Jing PW. Newborn screening for inborn errors of metabolism in mainland china: 30 years of experience. JIMD Rep. 2012;6:79–83.
15. Simonsen H. Screening of newborns for inborn errors of metabolism by tandem mass spectrometry. Ugeskr Laeger. 2002;164(48):5607–12.
16. Devi AR, Rao NA, Bittles AH. Neonatal screening for amino acid disorders in Karnataka, South India. Clin Genet. 1988;34:60–3.
17. Devi AR, Naushad SM. Newborn screening in India. Indian J Pediatr. 2004;71:157–60.
18. Sahai I, Zytkowicz T, Rao Kotthuri S, Lakshmi Kotthuri A, Eaton RB, Akella RR. Neonatal screening for inborn errors of metabolism using tandem mass spectrometry: experience of the pilot study in Andhra Pradesh, India. Indian J Pediatr. 2011;78(8):953–60.
19. Kaur G, Srivastav J, Jain S, Chawla D, Chavan BS, Atwal R, Randhawa G, Kaur A, Prasad R. Preliminary report on neonatal screening for congenital hypothyroidism, congenital adrenal hyperplasia and glucose-6-phosphate dehydrogenase deficiency: a Chandigarh experience. Indian J Pediatr. 2010;77(9):969–73.
20. Weber SL, Segal S, Packman W. Inborn errors of metabolism: psychosocial challenges and proposed family systems model of intervention. Mol Genet Metab. 2012;105(4):537–41.