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Review Article

Screening of Inborn Errors of Metabolism - Use of Current and Future Technology in Indian Scenario

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ABSTRACT

IEM screening is a vital process that identifies apparently healthy infants with serious inherited disorders, generally metabolic in origin, that are usually correctable by dietary or drug interventions before they suffer significant morbidity or mortality. IEM is autosomal recessive, the defective gene is present in both parents, and these can be passed on from generation to generation. The incidence of IEM varies in different geographical regions and different ethnic groups. Approach to metabolomics is important for detection of IEM because their basic pathophysiology is very much related to metabolism. Dried blood (and other biofluids) spots samples (DBS) have also been investigated. The most advanced and now a day's used technologies includes nuclear magnetic resonance (NMR) spectroscopy], and mass spectrometry (MS), either combined or not to a gas phase or liquid phase separation method. Early recognition of IEM by screening tests in combination with strong clinical suspicion will help the clinicians to initiate prompt early treatment to prevent lethal neurological complications and developmental delay. The future of IEM diagnosis may be found in the developing area of metabolomics by doing simultaneous quantitative metabolic profiling of many metabolites in biological fluids.

Key words: IEM screening, Inborn errors of metabolism.

INTRODUCTION

Olivier et al. first coined the term "metabolome" in 1998. [1] It refers to the comprehensive complement of all metabolites present in a given biological system, fluid, cell, or tissue. [2] Metabolism is a process, in which an organism is able to convert substrate into product, which is necessary for its growth and development by maintaining the balance between energy and nutrient intake, consumption and storage. Presently most of the metabolic diseases are not curable and most of them have fatal consequences. [3] IEM are disorders in which the defective enzyme blocks the normal metabolic pathway resulting in accumulation of toxic intermediate substrate, accumulation of precursors, deficiency of product, redirection of substrate into alternative pathways or secondary metabolic consequences. [4] For instance, in IEM of amino acids, plasma concentrations of amino acids may provide important information about metabolic processes in the body. [5] If there is increase in amount of one or more amino acids in urine, it is considered to be aminoaciduria. [6] Aminoaciduria is the most common cause of preventable mental retardation after congenital hypothyroidism. [7]

Study from Qatar and Saudi Arabia have confirmed that some IEM are more prevalent in the Arab world like homocystinuria, organic aciduria and maple syrup urine disease. [8] Disorders of amino acid metabolism are caused by enzyme deficiencies resulting in the accumulation of metabolites to levels which cause organ damage. The brain, liver and kidneys are the most frequently affected organs. [9] Symptoms may be acutely present or become apparent weeks or months after birth as a result of the cumulative effect of damage. Treatment consists of dietary restriction of offending amino acid(s) along with disease-specific medical formula that provides adequate protein for growth and development. With strict dietary adherence, outcome is generally good.

IEM screening is a vital process that identifies apparently healthy infants with serious inherited disorders, generally metabolic in origin, that are usually correctable by dietary or drug interventions before they suffer significant morbidity or mortality. [10] New born screening (NBS) represents one of the major child health advances of this past century". [11] In expanded NBS, a single test allows for early detection and treatment of a large number of disorders and it can potentially prevent serious consequences. [12] Morbidity and mortality vary considerably. Some are relatively harmless (e.g. cystinuria and pentosuria), but some IEMs cause severe handicap (e.g. Phenylketonuria and Maple syrup urine disease). [13] IEM can affect any organ at various stages of life, from newborn to adulthood depending on significant accumulation of toxic metabolites or on the deficiency. Most of the IEMs manifest with neurobehavioral manifestations and association of about 5.75% has been reported between mental retardation (MR) and IEMs. [14,15] Earlier recognition of these inborn errors of metabolism has the potential to reduce morbidity and mortality rates in infants. [16]

INHERITANCE

IEM is autosomal recessive, the defective gene is present in both parents, and these can be passed on from generation to generation. [17] They can also be inherited as autosomal dominant or X-linked recessive or as mitochondrial inheritance. The male to female ratio is 1:1 for all patterns of inheritance. [18]

INCIDENCE

The incidence of IEM varies in different geographical regions and different ethnic groups. The occurrence of IEM is high in regions with greater incidence of consanguineous marriages. [19] In United Kingdom, the incidence of IEM was reported 1 in 784 live births, [20] in the US, the collectively incidence, is estimated to be between 1 in 1400 to 1 in 5000 live births. In British Columbia, Canada, approximately 24 children per 100 000 births (~60% of the total disease groups surveyed) have a disease involving amino acids (including PKU), organic acids, primary lactic acidosis, galactosemia, or a urea cycle disease. Approximately 2.3 children per 100000 births (~5%) have some form of glycogen storage disease. Approximately 8 per 100000 births (20%) have a lysosomal storage disease; ~3 per 100000 births (7%-8%) have a respiratory chain-based, mitochondrial disease and ~3 to 4 per 100000 (7%-8%) of births have a peroxisomal disease. [21] The incidence of IEM in Thailand is yet unknown, however, by estimation it is generally accepted to be 1 in 5,000. [22] In an Australian cohort, the prevalence of inborn errors, excluding phenylketonuria, was 15.7 per 100,000 births. [23] In a South Korea study, screening of 79,179 newborns for organic, amino acid and fatty acid metabolism disorders, accounted for approximately 5.4% of annual births. [24]

In Saudi Arabia an incidence of 1 in 666 live births has been reported, [25] in Singapore its prevalence rate was reported to be 3.5%. [26] In an Italian cohort of 1,935 cases, the last 5 years showed an incidence

of 36.25/100, 000. [27] Another study from South Korea reported a prevalence of 1 in 2800 with a sensitivity of 97.6% and specificity of 99.2%. [24] Screening of IEM in an Australian cohort found the prevalence of 15.7 per one lakh births. [28] Sudan is one of the first Arab countries to document on existence of IEM, with phenylketonuria reported in 1964 and galactosemia in 1965, because of high incidence of consanguinity, IEM are widely spread among ethnic groups in Sudan. [29,30] Genetic diversity among Arabs, high rates of inbreeding and large family size are optimal for the manifestation of many autosomal recessive disorders including IEM. [31] The worldwide incidence of aminoaciduria ranges from 1:200 in Saudi Arabia to 1:6250 in Australia. [18]

In India the overall prevalence of IEM is one in 2497 newborns and another study reveal the prevalence of IEM in Andhra Pradesh. Twenty four million newborns are born each year; 780,000 are born with congenital malformation, 340,000 with G6PD, 20,800 with metabolic disorder, 21,000 with Down syndrome, 10,400 with congenital hypothyroidism, 9000 with thalassemia and 5200 with sickle cell anemia. In a hospital based study in India biochemical screening of 4400 cases of mental retardation revealed that 5.75 % (256 cases) were due to a metabolic disorder. [15]

A screen of 112,269 neonates for amino acid disorders in the south Indian state of Karnataka showed four disorders to be the most prevalent: tyrosinaemia, maple syrup urine disease and phenylketonuria (with a combined frequency of 1 per 2,495), and generalised amino aciduria, with a frequency of 1 per 1,605. [32,33]

No nation-wide study is available in India, though one more study from south India reports the incidence to be 1:3660. [34] While from North India, no incidence study is available.

APPROACH TO THE INVESTIGATION OF IEM

The "omic" approach provides new effective tools which is effective for screening, diagnosis, monitoring and treatment of these diseases as it involves biological information capture and data management. It helps to provide new innovative tools for rapid diagnosis of IEM. Approach to metabolomics is important for detection of IEM because their basic pathophysiology is very much related to metabolism. The various forms of IEM present with nonspecific clinical symptoms and appropriate laboratory testings plays an important role in diagnosis. Biofluids, cells or tissue extracts are primary sources for metabolomics. Dried blood (and other biofluids) spots samples (DBS) have also been investigated [35-38] and were shown to be an interesting alternative to conventional liquid samples for generating metabolite profiles. DBS has gained interest for IEM profiling because of its low volume requirement, low cost and handling convenience. [35,39-41] The most advanced and now a day's used technologies includes nuclear magnetic resonance (NMR) spectroscopy], [33,43] and mass spectrometry (MS), either combined or not to a gas phase or liquid phase separation method. [44] These technologies are suitable for metabolomics studies because they deliver global, unbiased, and comprehensive chemical information from complex mixtures. Recently, approaches using another gas phase separation, ion mobility spectrometry (IMS), [45] has been gaining interest in metabolomics. [46-48] coupled with high-resolution mass spectrometry and chromatography (LC-IM-MS), IMS provides additional analyte selectivity without significantly compromising the speed of MS-based measurements. Use of pharmacological chaperones helps to specifically bind to misfolded proteins, stabilizing their conformation, thereby preventing early degradation and allowing proper cellular trafficking and localization. This has been largely studied for Fabry's disease and other lysosomal diseases. [49, 50] Cell therapies have been introduced. Due lack of liver donor, hepatocyte transplantation have investigated for several

inherited metabolic disorders. The introduction of hepatocytes is less invasive than liver transplant. For these reasons, extra hepatic transplantation sites such as lymph nodes are currently being pursued for liver cell therapy. [51,52] Replacement of the defective gene provides a definitive cure for IEM as they are monogenic disorders. Hence both ex vivo and in vivo approaches are being applied. *Ex vivo* gene replacement of hepatocytes are desirable as an alternative to hepatic transplantation in inborn errors of metabolism because it would eliminate the need of life-long immune suppression. [53, 54] In the *in vivo* approaches, vector is directly injected into the organism by either systemic (intravenous, portal vein injections) or localized (intramuscular, intracerebral) injections. RNA targeting has the potential for therapy of several disorders including IEM. Here the molecules bind nucleic acids with high specificity and modulate mRNA metabolism. [55] Molecular techniques through gene editing are approaching very fast and they have already entered into clinical trials. The recently included gene therapy for IEM includes zinc finger nucleases (ZFN), transcription activator like effecter nucleases (TALEN) and clustered regularly interspaced short palindrome repeat (CRISPR) /Cas9. [56,57]

TREATMENT

Traditional therapies for metabolic diseases include dietary therapy such as protein restriction, avoidance of fasting, or cofactor supplements. Evolving therapies include organ transplantation and enzyme replacement. Efforts to provide treatment through somatic gene therapy are in early stages, but there is hope that this approach will provide additional therapeutic possibilities. Even when no effective therapy exists or when an infant dies from a metabolic disorder, the family still needs an accurate diagnosis for clarification, reassurance, genetic counseling, and potential prenatal screening.

CONCLUSION

Early recognition of IEM by screening tests in combination with strong clinical suspicion will help the clinicians to initiate prompt early treatment to prevent lethal neurological complications and developmental delay. Pre-symptomatic diagnosis of these disorders can minimize the irreversible complications and significantly improve the long-term prognosis, by early treatment. The commonest mistake made in the management of an IEM is delayed diagnosis or misdiagnosis. It is important for pediatricians and neonatologists to keep in mind IEM as a cause of illness in the neonatal period. In unexplained cases, the possibility of an IEM should be entertained, as early as possible, as many disorders are treatable and, in most cases, successful outcome is dependent on a rapid diagnosis and early instigation of therapy. The goal is early detection of children at increased risk for selected metabolic or genetic diseases so that medical treatment can be promptly initiated to avert metabolic crises and prevent irreversible neurological and developmental delay. It is important that the primary care physician maintain an active role in the care of a child with an IEM, providing well and sick child care. Their expertise in assessing the patient's clinical status and assistance with home monitoring assists the metabolic treatment center in providing optimum care. A cooperative effort will benefit all involved, and facilitate the best outcome for the patient.

Early clinical and laboratory diagnosis along with adequate treatment can provide these children a meaningful normal life. The future of IEM diagnosis may be found in the developing area of metabolomics by doing simultaneous quantitative metabolic profiling of many metabolites in biological fluids.

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