EDITORIAL

METABOLOMICS: IMPACT ON DIAGNOSIS AND MONITORING OF 'INBORN' / 'ACQUIRED' METABOLIC DISORDERS

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The successful completion of Human Genome Project (HGP) and illustration of the 'blue print' of genetic information during the year 2003 (1) was rightly acclaimed as 'an inward voyage of discovery' to understand the mystery of human life. However, with all the excitements associated with HGP and the consequent emergence of an era of 'genomics' followed by 'transcriptomics' and 'proteomics', it was realized that the deservedly much acclaimed accomplishment at its best only enabled us to 'read' the blue print of genetic information but 'not necessarily to understand' the dynamics of 'life process' per se. Realizing the fact that life process, an outcome of complex biochemical reactions driven by the physiochemical properties of the biomolecules, is the summation effect of interaction between 'genetic' and 'epigenetic' factors; emerges yet another 'omics' namely the 'metabolomics', the science of 'metabolome'. The term metabolome, derived from word metabolism, was first coined by Oliver et al (1998) to describe the metabolic basis of phenotype expression (2). Nevertheless, although not referred to as metabolome, the very concept appear to have begun as early as 1970's by the core idea conceived by Robinson (3), that information-rich data on the quantitative and qualitative pattern of metabolites in body fluids would reflect the functional status of a complex biological system. Thus, the human metabolome, by analogy to human genome, the set of all the metabolites in a human system, is defined as 'quantitative measurement of the dynamic parametric metabolic response of living systems to pathophysiological stimuli or genetic modification' with a potential to improve disease identification, prognosis and monitoring; provide insight into drug metabolism and toxicology, which incidentally encompasses the major components of clinical biochemistry.

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The first report of Human Metabolome Project (HMP), released on 23rd Jan 2007, comprises 2,500 metabolites, described as the 'canaries of the genome' by David Wishart the project leader (4), also includes 1200 drugs and 3500 food components and the list will certainly grow further. Unlike the insignificant difference between the inter-individual and even interspecies genomics (1), the significant differences in metabolomics of different species underscore the uniqueness of chemical make up across the species. Similarly, the metabolomics of disease state of an individual differs from that of his healthy condition, hence the significance of metabolomics in the diagnosis and monitoring of metabolic disorders. The recent trend in employing higher end analytical armamentarium such as HPLC, GC/MS, MS/MS and NMR spectroscopy enables to evaluate the metabolome(s) of wide spectrum and high complexity. Such a complex information data on intermediate metabolite's profile, in conjunction with software driven bioinformatics, would be of immense use in diagnosis and monitoring varieties of metabolic disorders in general, IMDs in particular.

METABOLOMICS AND CLINICAL CHEMISTRY

The relevance of metabolome in clinical biochemistry, as a metabolic reflection of genomics is linked to the activity of enzyme(s), the work horses of metabolism; implying that defective gene of any given enzyme is likely to alter the metabolome. However, though the enzyme per se, the gene product, apart from being under the genomic control; the 'up' and 'down' regulation of enzyme activities are subjected to alterations by a host of extraneous factors that are of 'epigenetic' in nature. Thus it implies that the overall metabolism, considered as the reflection of 'life process', is not merely the exclusive product of gene(s) per se; instead the outcome of intricate interaction between the gene products and extraneous factors. Hence, any change in the metabolome of a living system, including human being, would suggest the dysregulation of specific metabolic step(s) driven by a given enzyme, either because of altered gene expression

due to underlying genetic defect or as a consequence of epigenetic factors affecting the enzyme function leading to the onset of '*metabolic disorder(s)*' that are of 'inborn' or 'acquired' in nature.

The inborn metabolic disorder(s) (IMDs), also referred to as 'Inborn Errors of Metabolism' (IEM), comprises a heterogeneous group of ~ 500 diseases (5) affecting primarily intermediate metabolic pathways resulting in malfunctioning of almost all the organs including the central nervous system (CNS). IMDs causing adverse effect on CNS function are often referred to as neurometabolic disorders. On the other hand, the list of '*acquired*' metabolic disorders including the '*metabolic syndrome*'(6,7) continue to increase. While the IMDs are attributed to underlying genetic defect and perpetuated by consanguineous marriages, the acquired metabolic disorders are largely due to fall out of modern life, i.e., reckless usage of pesticides, pharma preparations and irresponsible handling of industrial effluents and unhealthy food habits. There are also reports of chronic infectious diseases such as HIV infection affecting the adrenocortical metabolic pathways pertaining to neuroendocrine function (8,9). Further, the emergence of newer metabolic disorders as a consequence of medication and/or following organ transplantation is around the corner.

Metabolome, simply defined as a profile of intermediate metabolites, reflects the functionality of proteome which in turn is subjected to regulation by genetic (genome) and epigenetic factors. The concept of metabolome is not new to clinical biochemistry. The practice of quantifying intermediate metabolites, such as lactate/pyruvate (10), glucose, lipids etc., in biological fluids, the integral components of what is now referred to as metabolome, has been the accepted practice for the diagnosis and monitoring of disease. In fact, the evaluation of multi parametric metabolites; such as amino acids, ammonia and organic acids profile in IMDs (11,12) is probably the most unsung practice of metabolomics in clinical biochemistry. Thus the emergence of metabolomics can be viewed as reemergence of a particular component of clinical biochemistry to its full potential and is all set to change the scenario of evidence based laboratory medicine. In this changing scenario, the clinical biochemists have a greater role in interpreting the findings of metabolome and relate to clinical state.

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The diagnostic dilemma of IMDs stems from the rarity of the

disorders confounded with overlapping clinical symptoms (13). Add to this, many of the IMDs with same underlying biochemical defect have several forms with respect to their age of onset, clinical severity and natural history of the disease progression. This is where the clinical biochemist is called upon to solve the diagnostic puzzle and help in identifying or other wise to rule out the suspected metabolic disorder. The underlying inborn metabolic defect can be investigated at three different levels, viz., the metabolite level (metabolome), the enzyme level (functionality of gene product; proteomics) and in a limited but growing number of disorders, the DNA based diagnostics (genomics). Thus, the altered metabolome in IMDs, with excess of certain metabolites above their physiological level, proves to be neurotoxic during the neonatal period in particular. Unless detected ahead of clinical manifestation, the increase in metabolites beyond certain concentrations would cause irreparable damage to CNS leading to high morbidity and even death during the infancy. The laboratory based diagnosis of IMDs, which ranges from simple screening tests of qualitative in nature to quantification of metabolites in biological fluids such as urine, blood, cerebrospinal fluid (CSF). Some of the more familiar IMDs, broadly classified as under amino acidopathies, lipidoses, and mucopolysachharidoses, organic acidemia/acidurea and those affecting purine and pyrimidine metabolism are characterized by having altered metabolite's profile that are specific to disease.

Neurometabolic disorders, adversely affecting the growing nervous system during postnatal period (14), makes it mandatory that the screening for IMDs are carried out during the early neonatal period to initiate preventive therapeutic intervention. In the event of a neonate/child presenting with IMD, laboratory diagnosis would help in instituting appropriate detoxification followed by, depending on the case, dietary manipulation and / or vitamin supplement to check the further progression of the disease.

In Indian scenario, infant care is probably the most negelected particularly in rural settings. Causative factors responsible for high incidence of mortality and morbidity among infants are often attributed to infection without any definitive diagnosis to support, where one is likely to miss the metabolic cause. Hence, it is no surprise that clinicians would consider that IMDs as of rare disorders. Screening for IMDs, based on simple and cost effective methods, would pave the way for preventive measures to protect the growing brain well in advance before the onset of clinical presentations such as delay in mile stones or regression of psychomotor functions. Unlike, in many of the developed and even in developing countries, New Born

Screening (NBS) for metabolic disorders is not mandatory in India. The reason for not having any national policy on the need to have mandatory screening for IMDs is largely due to the ignorance and the apathy towards this aspect of health burden, compounded by the unfounded fear about the cost involved and the pessimism of not being able to treat those disorders. Further, there is no data base on the incidence of IMDs among the different ethnic groups and region wise. This is where the health planners need to apply their mind and come out with a systematic epidemiological study based on screening for different metabolic disorders in our population. Considering the vastness of our population, to make the screening program for IMDs a success story, it needs to be simple and cost effective. The fact that some of the simple, cost effective screening methods, in spite of their being non specific, do help in excluding the large population of unaffected would reduce the cost of metabolic screening to a realistic bare minimum. Hence, it is prudent to employ simple chemical tests to start with, that are cost effective, followed by confirmatory tests for those who were found to be positive for screening tests. A well planned metabolic screening program for IMDs would generate a wealth of information for clinicians on the incidence of these so called rare disorders, which in effect are not so rare, for suspecting and investigating for a given type of IMDs among selected community and region wise. Such an information would also help in ushering an era of NBS as a part of predictive medicine, which in turn would contribute in great measure to practice preventive medicine.

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