NARRATIVE REVIEW

Closing the gap: An urgent need for newborn screening of organic acid disorders in developing countries

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Abstract

Organic acid disorders are rare inherited metabolic disorders of key metabolic pathways. For the identification of specific organic acids, investigation of urinary metabolites and genetic testing are required through newborn screening programmes. Delayed diagnosis leads to complications, such as cardiac attacks, respiratory problems, neuro-developmental disorders, intellectual disability, and even premature death. The burden of such inherited disorders is quite high in developing countries of South Asia due to high rate of consanguinity in the region. Unfortunately, such disorders are left untreated due to the lack of screening facilities in such countries. The current narrative review was planned to highlight the urgent need for closing this gap and implementing effective newborn screening programmes for organic acid disorders in developing countries. The implementation of effective programmes is crucial for reducing morbidity and mortality, and for improving the quality of life for the affected children and of their families, thus promoting global health equity.

Keywords: Inborn errors of metabolism, Organic acidurias/acidemias, Newborn/neonatal screening.

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Inborn Errors of Metabolism

The term inborn errors of metabolism (IEM) was first coined in 1902, and defined a group of inherited metabolic disorders caused by a genetic defect in an enzyme, transport protein or cofactor. This results in the dysfunction of specific protein/enzyme involved in the synthesis or degradation of vital metabolites and macromolecules, such as proteins, carbohydrates and fats. Hence, it can significantly affect the critical steps in the metabolic pathways.[1] IEMs include aminoacidopathies, organic acid disorders (acidaemias/acidurias), fatty acid oxidation and carbohydrate metabolism defects, urea cycle defects, glycosylation defects, mitochondrial disorders, peroxisomal disorders, lysosomal storage diseases, purine and pyrimidine metabolism defects, neurotransmitter disorders, transport protein disorders, and lipid metabolism disorder. IEMs are individually rare, but collectively represent a significant portion of metabolic diseases that result in substantial mortality or long-term morbidity in the general population.[2]

As per Inborn Errors of Metabolism Knowledgebase database (IEMbase), until now there are a total of 1,893 reported metabolic diseases.[3] A study conducted in 2019 identified 1,126 IEMs. Among these, 1,015 IEMs are well characterised, while 111 IEMs still await molecular-level characterisation as these do not follow the strict criteria for the inclusion in the IEM nosology. This nosology has now been supplanted by the International Classification of Inherited Metabolic Disorders (ICIMD) that includes 1450 IEMs.[4,5] Furthermore, according to IEMbase,[3] the number of inborn errors is expanding with time due to their detection and characterisation by advanced analytical and confirmatory techniques like mass spectrometry, next generation sequencing (whole exome / whole genome sequencing).

Most of the IEMs have overlapping clinical presentations, which are usually nonspecific. However, some of the IEMs manifest a few specific signs and symptoms, such as metabolic decompensation, vomiting, dehydration, poor feeding, and seizures etc.

The genetic basis of all the IEMs is varied as they could be of different types of genetic variants, like insertions/deletions of one or several nucleotides (InDels), frameshift mutations, copy number repeats, and rearrangement of the genetic codes in a specific gene. Such genetic changes (polymorphisms/mutations) can occur randomly or inherited due to consanguinity. Most of the IEMs follow autosomal recessive pattern of inheritance, while a few are classified as dominant, mitochondrial and X-linked IEMs. The incidence rate of monogenic IEMs depends on a variety of factors, such as consanguinity, genetic diversity and the

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size of family that play a significant role in the prevalence of the disease. It was observed that high rates of consanguineous marriages have a vital role in genetic diseases, as it increases the incidence rate up to 50-fold in some parts of the world. Therefore, a few inborn errors are more common in specific regions/populations of the world.[6,7]

Classification of IEMs

Traditionally, IEMs have been classified as disorders of metabolic pathways of carbohydrates, amino acids, lipids, organic acids, lysosomal storage, mitochondrial, peroxisomal, purine and pyrimidine disorders.[8] However, a recently updated classification of IEMs proposes three broad categories based on the size of metabolic compounds. These categories include small and simple molecules, large and complex molecules, and have implications in energy metabolism (Figure 1-A).[9] In complex diseases, however, a whole network of metabolite fluxes subtly contributes to the overall phenotype of the disease. Whereas in small molecules, intoxication due to accumulation of tiny molecules (amino acids, organic acids etc.) or defective synthesis of metabolites leads to deficiency of specific compounds that is further classified into different groups based on the type of molecules (Figure 1-B).

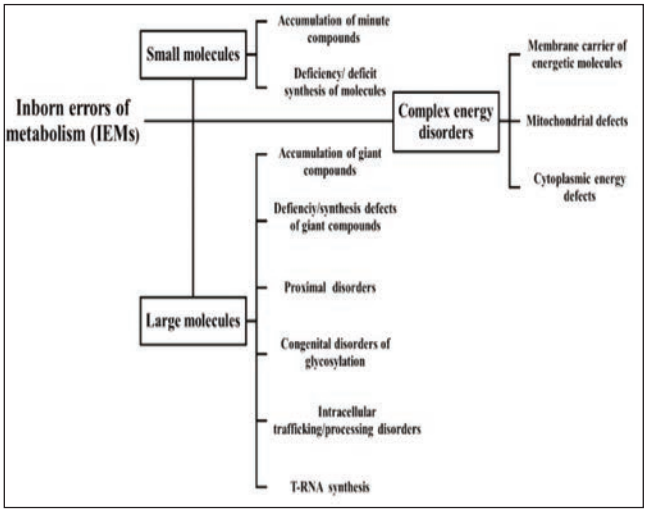

Figure-1 A: Recently updated classification of inborn errors of metabolism (IEMs).

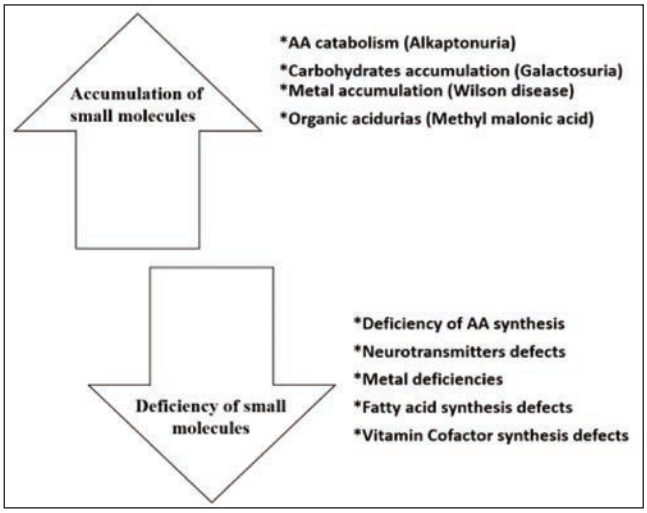

Figure-1 B: Inborn errors of metabolism (IEMs) classification based on the type of molecule.
AA: Amino acid

The current narrative review was planned to focus on OAs that are a group of treatable disorders among IEMs. In spite of advancements, the newborn screening programmes for OAs in most developing countries is not yet available for an accurate diagnosis and to initiate treatment for these progressive disorders.

Organic Acid Disorders

Organic acid disorders (OAs) are a subgroup of IEM characterised by small molecule defects. In OAs, a deficiency of enzymes leads to the accumulation of small organic compounds (methylmalonic acid, propionic acid, isovaleric acid etc.) in tissues and body fluids, especially in urine, which are usually present at a low concentration in normal healthy neonates. The incidence rate of OAs varies in different regions of the world and may vary from 1 out of 10,000 to 1 out of 1,000,000 live births.[10] These are rare and infrequently reported worldwide. The more prevalent OAs are glutaric aciduria (24.4%), propionic aciduria (9.6%), methylmalonic aciduria (17.1%) etc.[11] More than 65 specific OAs affecting metabolic pathways have been identified. The accumulation of metabolites significantly affects multi-organ system and leads to toxicity and complications if left untreated. OAs are further classified on the basis of their aetiology as primary (genetic) and secondary (non-genetic) (Figure 2). All the primary OAs are genetically characterised as autosomal recessive disorders, which can affect both

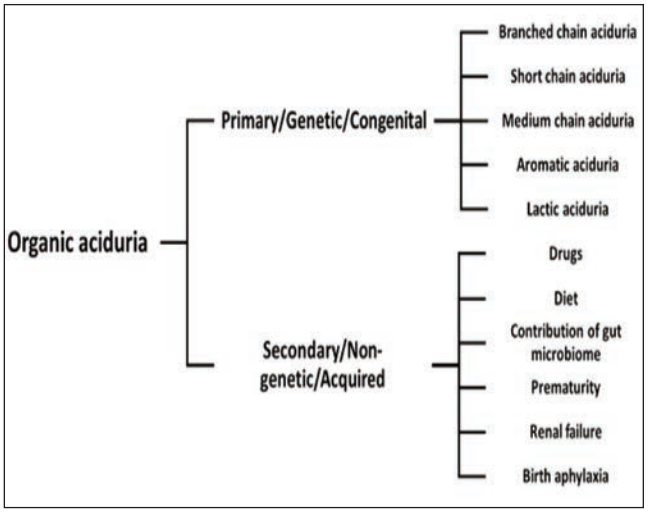

Figure-2: Types of organic acid disorders/acidurias (OAs).

males and females with equal frequency. The current review focuses on primary OAs that are part of IEMs, and need urgent treatment to overcome further life-threatening complications. Many of the OAs may present complications later in life with chronic and progressive multisystem (musculoskeletal, liver, kidneys, gastrointestinal tract, eyes, skin, or central nervous system) impairment and failure.[12]

Primary OAs are classified into 3 major types on the basis of their complications; Systemic OAs, Cerebral OAs, and Ketolytic / ketogenic OAs.[13] In these complications, the initial sign and symptoms appear with a gradual increase in anion gap along with other symptoms that resemble sepsis (i.e. lethargy, confusion, reduced intake, vomiting). Systemic OAs, like methylmalonic academia (MMA), progress to serious complications with age, such as hyperglycaemia, type 2 diabetes mellitus (T2DM), cardiomyopathy, cardiovascular diseases (CVDs) and kidney diseases, that alter the normal functioning of the body system.[14] The cerebral organic acidemias, like glutaric aciduria 1 (GA1) are present with or without systemic complications, but the organic acids are usually detected in urine which indicates the status of a functioning brain of the newborn. Ketolytic / ketogenic OAs, like 3-hydroxy-3-methylglutaryl-Coenzyme A lyase (HMG-CoA) deficiency, are the result of organic acids accumulation in body fluids that are identifiable in the urine and blood. However, hypoglycaemia is less common in this type of OAs due to abnormal ketone production.

Diagnosis of OAs

Earlier diagnosis of IEMs is difficult as the suspicion of an inherited disorder is mostly based on the parental history of the disease. After that, newborn screening is performed based on a panel of laboratory tests that are routinely available in most secondary care hospitals and diagnostic laboratories.[15] Furthermore, for the screening of particular IEMs, specialised testing includes hyperammonia, creatinine, lactate, pyruvate, metabolic acidosis, ketosis, and anion ion gap measurement.[16] If an OA is suspected, the anion gap is considered a basic diagnostic parameter, and mean value 12±4 is considered normal, whereas a value >16 is suggestive of an OA.[17]

With the development of advanced separation technologies, several analytical and high-throughput techniques are now available for the screening and diagnosis of IEMs, such as thin-layer chromatography (TLC), enzyme-linked immunosorbent assay (ELISA), high-performance liquid chromatography (HPLC), gas chromatography (GC), gas chromatography coupled with mass spectrometry (GC-MS), liquid chromatography

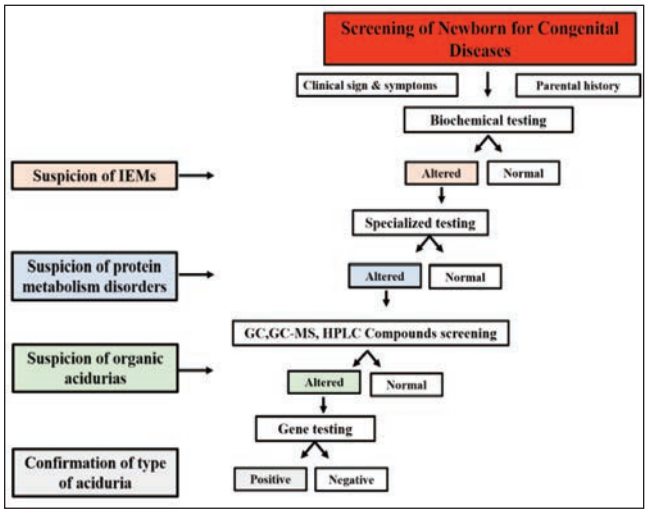

Figure-3: Diagnostic algorithm for organic acid disorders (OAs).
GC: Gas chromatography, GC-MS: Gas chromatography-mass spectrometry, HPLC: High-performance liquid chromatography.

coupled wirh mass spectrometry (LC-MS), tandem mass spectrometry (MS/MS) and nuclear magnetic resonance (NMR) spectroscopy.[18] GC-MS technique is still considered the ideal technique for the screening of organic acidemias due to its high sensitivity and reproducibility. Once a sample has been screened and found positive for OAs, this is then followed up by other confirmatory tests, such as enzyme-based assays, and deoxyribonucleic acid (DNA)-based mutation detection assays. For example, for propionic acidemia, DNA sequencing of propionyl-CoA carboxylase, Alpha subunit (PCCA) and propionyl-CoA carboxylase, Beta subunit (PCCB) is performed as a confirmatory test (Figure 3).[11,19]

To better diagnose, a two-tier approach is prescribed, which includes blood and urine metabolic pattern, as recommended by a panel of the American College of Medical Genetics (ACMG).[20] The simultaneous two-tier testing for the screening of IEMs, including OAs, is more comprehensive and cost-effective, delivering confirmatory results with significantly reduced turnaround time, which means reduced recall rate by eliminating false-positive (FP) results and prevention of unnecessary anxiety among parents. Upon confirmation of screened positive samples through follow-up testing, treatment decisions can be made.

Newborn Screening Programme in Asian countries, including Pakistan

Newborn screening (NBS) is a crucial public health programme that aims at detecting certain genetic, metabolic and congenital disorders, including IEMs, in infants shortly after birth. The benefits of an NBS programme are huge. Early detection and treatment of conditions identified through NBS can lead to better health

outcomes, reduced morbidity and mortality, and improved quality of life (QOA) for the affected infants.

Furthermore, early identification and treatment of conditions can lead to significant cost savings for health systems by avoiding more expensive treatments later in life and burden on hospitals. The challenges for implementing an NBS in developing countries, including Pakistan, are significant, including lack of funding, trained personnel, laboratory equipment and infrastructure. However, with the appropriate resources, partnerships and commitment, it is possible to establish and sustain a successful programme that may have a significant impact on the health and wellbeing of the affected infants, and may reduce stress on their families.

Presently, most high-income countries (HICs) have setups for NBS to screen most prevalent IEMs, including OAs, using high throughput analytical techniques. In Australia, Singapore and Japan, NBS programmes were initiated in 1965-67. In Japan, it further progressed into expanded NBS (ENBS) programme nationwide in 2014 on the basis of a pilot study performed between 1997 and 2012.[21] Currently, a few industrialised provinces screen >30 IEMs in Japan, including MMA, and propionic academia. While in other Asian countries, NBS programmes were initiated in the 1980s, mainly in Hong Kong, South Korea, Malaysia and Taiwan. The International Atomic Energy Agency (IAEA) provided a total of USD 6.7 million to develop policies/ schemes, national or regional research repositories and databases of IEMs, conducting epidemiological studies focussing only on congenital hypothyroidism (CH) in Asia-Pacific countries, including Bangladesh, China, India, Indonesia, Laos, Mongolia, Pakistan, Palau, Philippines, Sri Lanka and Vietnam, during a period from 1995 to 2007. However, the establishment of an NBS programme in low- and middle--income countries (LMICs) in Asia was not initiated. India has one-sixth of the world population, with the largest number of fresh births annually, but has no epidemiological data on IEMs due to limited research.[22] Similarly, in Pakistan, little data is available and the true prevalence data for such disorders is not known. The efforts of estimating the risk and screening of congenital hypothyroidism has been initiated at some big hospitals in Pakistan.[23,24] However, the congenital hypothyroidism screening programme at the national level is still lacking. The consanguinity rate is quite high (~70%) in Pakistan[25] and cousin marriages are routinely practised, so the incidence of various inherited genetic disorders is expected to be high. In the case of organic acidemias, such as MMA, propionic acidemia (PA) and isovaleric aciduria (IVA), it is reported that organic acidurias are more common in Asian countries compared to the West.[26] Therefore, due to limitation of the diagnosis of inherited diseases, including OAs, higher morbidity and mortality can be predicted in Asian LMICs, particularly in Pakistan.

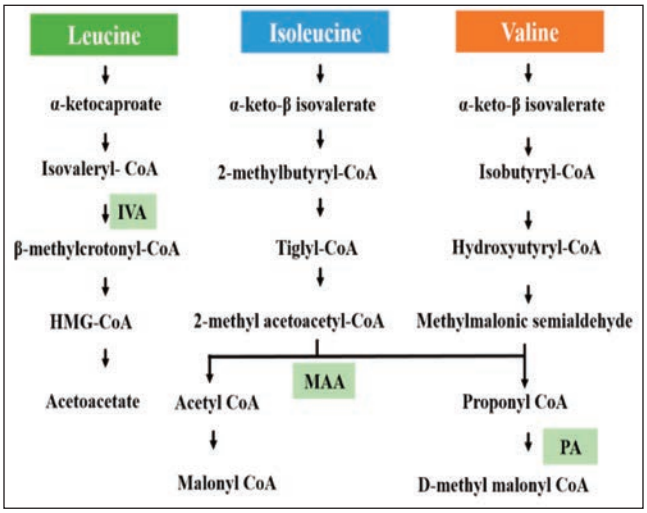

Figure-4: Common organic acid disorders (OAs) associated with protein metabolism.
IVA: Isovaleric aciduria, MMA: Methylmalonic acidemia, PA: Propionic acidemia, CoA: Coenzyme A.

Untreatable and Treatable Organic Acidurias

Small molecule defects, which include short-chain, branched-chain and propionic essential amino acid-related OAs (Figure 4), including PA, MMA, IVA, HMG-CoA lyase deficiency, beta-ketothiolase deficiency, glutaric aciduria type I, phenyl pyruvic aciduria, homogentisic aciduria etc., are classified as treatable disorders.[27] The diagnosis and management of small molecule defects is possible if these diseases are identified during early ages. Mostly complex/ large molecule defects are difficult to treat. This is because the accumulation of large molecules leads to severe difficulties in multi-organ system that gives diverse sign and symptoms, and altered routine laboratory profiling which makes the diagnosis difficult. Therefore, the diagnosis and management of defects involving complex molecules is a challenging task. Confirmatory testing is always required for a specific analysis of the relevant enzymes/metabolites in case of large molecule defects. Medium-chain dicarboxylic aciduria, including medium-chain acyl-CoA dehydrogenase (MCAD) deficiency, long-chain Acyl-CoA dehydrogenase (LCAD) deficiency, short-chain acyl-CoA dehydrogenase (SCAD) deficiency and 3-hydroxy dicarboxylic aciduria, are associated with fatty acid oxidation and are considered untreatable or difficult to treat organic acidurias having high morbidity and mortality.[28]

Treatment Options for Organic Acidurias

The available therapeutic options have limited success to treat OAs and no promising cure has been brought to the clinics yet to fully correct the underlying genetic defect of

these inherited diseases. The limited treatment options or preventative measures that are available for inherited metabolic disorders include nutritional support, supplementation of vitamins and trace elements, and pharmacological intervention etc. Management therapies, such as acute illness protocol or emergency protocol, are utilised according to the condition of the affected patient. Carefully addressing common childhood illnesses in patients with OAs can help avoid poor short- and long-term morbidity, disability and mortality outcomes.[29] However, treatment can be initiated only after confirmatory diagnosis of the disease.

Nutritional Therapies and Dietary Restriction of Non Metabolisable Compounds

The general nutritional preventive measures for all OAs include the frequent consumption of daily food supplements to avoid fasting conditions and to ensure the proper daily calorie requirements for all organs. In severe situations, continuous overnight feeding regimens through a gastrostomy or jejunostomy tubes are given to avoid fasting. The best available treatments for organic acidurias is to prevent the accumulation of the substrate and its downstream products that are causing intoxication. In most cases, high-calorie and low-protein diet is prescribed to amino aciduria patients to limit the consumption of the specific amino acids, such as branched-chain amino acids (BCAA) that cause toxicity.[13,30]

Use of Micronutrients as Supplements

In addition to the daily dietary plan, several micronutrients are prescribed to patients of OAs, as many enzymes require vitamins or micronutrients as a catalyst for their activities. The carboxylases (enzymes disrupted in PA and 3-methylcrotonyl-CoA carboxylase [3MCCC]) are biotin-requiring enzymes, as individuals may also require supplementation with biotin to regain the carboxylase function.[13]

Removal of the Toxins

There are two types of toxins found in the patients suffering from OAs. The first is the accumulated intermediate, formed due to the deficiency of enzyme. Scavenging the accumulated intermediates is accomplished by multiple pharmacological and conjugative agents. Most commonly used compounds are levocarnitine and glycine. The second is hyperammonia condition which is a result of the secondary inhibition of the urea cycle, presumably by accumulated metabolites that are predominately seen in the systemic and ketolytic/ketogenic OAs. Elevations in ammonia must be treated rapidly, and this can be done by using oral scavengers, such as sodium phenylbutyrate or carglumic acid, or intravenous scavengers, such as combination of sodium phenylacetate and sodium benzoate. In emergency conditions, it is performed through haemodialysis (HD), haemofiltration, or extracorporeal membrane oxidation (ECMO).[13]

Complications Associated with OAs

Multiple treatment and management strategies are available for the OAs, though these therapies are not curative and do not achieve a fully satisfactory outcome. Also, due to limited early diagnosis facilities for OAs, patients may suffer from high rate of acute to severe long-term complications that include metabolic decompensations, vomiting, dehydration, acidosis, ketoacidosis hyperammonemia, hypotonia, lethargy/coma, seizures, hypoketotic hypoglycaemia, pancytopenia with frequent neurological sequelae including mental retardation, epilepsy and spasticity, accompanied by insulin resistance (IR), gluconeogenesis in the context of catabolic situations.

Some OA patients show muscle-related symptoms, including weakness, fatigue and myalgia, along with metabolic acidosis, hepatomegaly, hypoglycaemia, hypotonia and cardiomyopathy. Methylglutaconic aciduria type I causes symptoms of acute encephalitis and dilated cardiomyopathy.[31] Moreover, several OAs present in the neonatal or infantile period with a wide anion gap, metabolic acidosis and hyperammonemia.[15] Of the 17 known OAs, around half are known to cause cardiac dysfunction (Organic Acidemia Association, 2020).[32,33] A study on 3-methylglutaconic aciduria (3-MGA) also revealed the progression of cardiomyopathy in OAs.[34] Furthermore, in MMA patients, major secondary complications include intellectual impairment, tubulointerstitial nephritis with progressive renal failure, metabolic stroke, which referes to acute and chronic basal ganglia injury, pancreatitis, growth failure, functional immune impairment, and optic nerve atrophy.[35] Late-onset forms of OAs are less frequent, and these are characterised by recurrent life-threatening episodes of metabolic crises characterised by encephalopathy, vomiting and dehydration. The occurrence of mental retardation is most likely multifactorial, like cerebral damage during decompensations with metabolic encephalopathy, cerebral accumulation of toxic metabolites, and presumably mitochondrial dysfunction.[11]

Mechanisms of Pathogenesis in OAs

OAs are complex disorders in which molecular pathways are significantly affected. Three main suggested mechanisms to disturb biochemical pathways are accumulation of the toxic substances in the organ, altering structural and normal functionality; disturbance of energy

metabolism leads to limited energy required for hormone synthesis and performing other vital processes; and emerging features of the molecular pathogenesis, including imbalance of antioxidant potential and mitochondrial dysfunction.[36,37]

Mitochondrial Dysfunction, Biogenesis, Oxidative Stress and Impaired Redox Signalling

It is well known that mitochondria have a crucial role in maintaining the cell physiology, particularly in tissues that require high energy, produce adenosine triphosphate (ATP) swiftly to fulfil energy demands. Accumulation of metabolites in OAs is a major contributor of the tissue damage and secondary cause of oxidative stress (OS) and impaired energy production due to altered mitochondrial functioning.[37] It was reported that OAs compromise bioenergetics by decreasing ATP synthesis, mitochondrial membrane potential, and causing imbalance to the contents and calcium retention capacity, besides inducing mitochondrial swelling, reactive oxygen and nitrogen species generation and apoptosis.[38] The accumulated toxic metabolites inhibit the functioning of mitochondrial enzymes, causing defects in complex I and IV of mitochondria which prevents the proton gradient from being maintained.[39] Furthermore, it is hypothesised that multiorgan failure is caused by mitochondrial dysfunctioning, and the common targetted organs are brain, heart, liver, bones and muscles etc. Reportedly, mitochondrial dysfunction occurs due to a relative lack of micronutrients and substrates, and it is implicated in the development of many chronic diseases, including neurological deterioration, pancreatitis, optic neuropathy, chronic liver disease and oncogenesis.[40]

Data on human and animal studies on lactic acidosis revealed that dysfunctioning of mitochondria causes decreased activities of respiratory chain complexes and alter OS parameters. Moreover, it up-regulates the mitophagy receptors, autophagy-related protein 32 (ATG32), B-cell lymphoma 2 (BCL2)-like 13 (BCL2-L-13) and FUN14 domain-containing protein 1 (FUNDC1), which as an activator of hypoxia-induced mitophagy, and it also activates other signalling pathways. The FUN14 is a functional domain 14, present in some small proteins families, called FUNDC1. All of these activities lead to insufficient gluconeogenesis and excessive lipid accumulation in different organs of the body, and cause severe complications.[41] Hence, there is a need to investigate such pathways in detail for understanding the diseases on individual basis.

Multi-Omic Techniques and the Diagnosis of OAs and Associated Complications

The diagnostic scenario of the OAs significantly changed in recent years due to the availability of advanced omics technologies. Currently, next-generation sequencing methods, which include whole genome and whole exome sequencing, made it possible to identify all the mutated genes, whose products (proteins/enzymes) are involved in controlling the metabolic pathways. Molecular testing panels are being increasingly used for the screening of specific mutations in the genes which control enzymes involved in these pathways. Molecular investigations identified several mutations in structural genes and major signalling pathway genes, such as Ras-MAPK (rat sarcoma-mitogen activated protein kinase) signalling pathway that is essential in the regulation of the cell cycle, differentiation, growth and cell senescence and comprising protein tyrosine phosphatase, non-receptor type 11 (PTPN11), serine/threonine-protein kinase (BRAF), harvey rat sarcoma viral oncogene homolog (HRAS), rapidly accelerated fibrosarcoma (1RAF1), son of sevenless 1 (SOS1), mitogen-activated protein kinase 1 and 2 (MEK1 and MEK2), which are perturbed in OAs and have a crucial role in regulation of cell cycle.[42] In addition, proteomics techniques could provide a better understanding of genotype–phenotype correlation and of the clinical spectrum of such diseases. For example, a comparative proteomic study of alkaptonuria patients revealed the differential expression of inflammation and OS proteins which may be associated with the aetiology of the disease in patients. These proteins can also be employed as potential biomarker candidates in the diagnosis and prognosis of disease related complications.[43]

The urinary organic acid profile is abnormal for any illness with decompensation, but in some disorders, diagnostic analytes may be present only in small or barely detectable level when the affected individual is not acutely ill. With the increasing advancements in technologies, such as GC-MS/LC-MS, scientists are using high-resolution metabolomic techniques to identify such low levels of metabolites for diagnosing and monitoring of OAs in urine and other samples.[44] Researchers are interested in conducting a deeper analysis of metabolites and their interactions, and due to rapid analysis and cost-effectiveness, metabolomic profiling will be added soon to ENBS.[45,46]

Over the last decade, a growing number of metabolomic studies focussed on IEMs, with a special interest on diseases displaying marked phenotypic and genotypic variability among affected patients, which are difficult to diagnose by NBSs.[44] Although the global scenario is going towards

advanced multi-Omic techniques for the early diagnosis of IEMs, integrated genomics, metabolic and proteomic approach could significantly contribute to achieve an accurate diagnosis for the individual patient, and discovering novel IEMs.[47] Unfortunately, developing countries, including Pakistan, lack basic health facilities and have no local or national NBS for any of the inherited metabolic disorder.

Strategies to Address the Challenge of NBS

The gap identified in literature cited above relates to the lack of NBS for OAs, primarily in developing countries, including South Asian countries. It has numerous consequences, including delayed diagnoses and the progression of severe health complications, placing a significant burden on affected individuals and their families. To tackle these issues, a comprehensive approach is required. First and foremost, awareness campaigns shall be initiated to emphasise the critical importance of NBS for OAs, targeting general public, healthcare professionals as well as policymakers. International collaboration with relevant organisations and governments can offer both financial support and technical expertise to healthcare professionals. Establishing infrastructure, procuring screening equipment, and ensuring access to reliable diagnostic tools are crucial. Research and data-collection on the prevalence of OAs can further support the case for NBS programmes. By implementing these strategies, the NBS gap for OAs can be addressed, which will ultimately reduce morbidity and mortality among newborns.

Conclusion

The need for NBS related to OAs in developing countries, including Pakistan, is acute as early detection and treatment of these rare inherited metabolic disorders is of critical value. Implementing a comprehensive NBS programme can help prevent serious health complications, reduce the burden of disease, and improve the QOL of affected infants and their families by reducing financial and emotional stress.

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