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### **REVIEW ARTICLE**

### Inborn metabolic disorders – An update

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**Abstract:** Inborn metabolic disorders (IMD) are a class of genetic diseases involving disorders of metabolism and are congenital. Majority of such disorders are due to defects of a single gene that code for enzymes that facilitate conversion of various substrates into products. IMDs are referred to as congenital metabolic diseases or inherited metabolic diseases. Recent innovations in medical technology have changed new-born screening programs. The early and specific diagnosis of inborn metabolic disorders and prompt initiation of appropriate therapy are still the best determinants of outcome for these patients. The topic of IMD is challenging for most physicians. The number of known metabolic disorders is probably as large as the number of presenting symptoms that may indicate metabolic disturbances. Advances in the diagnosis and treatment of IMDs have improved the outlook for many of these conditions so that early diagnosis, if possible in infancy, can be helpful. At present Laboratory testing for several metabolic disorders is done by new-born screening programs in all children in many hospitals to rule out IMD early. The content of this review articles will make awareness among the researchers on many clinical manifestations of IMD providing the basis for early diagnosis for initiating prompt treatment.

Key Words: IMD; GD; Genetic disorders; PKU; MSUD

### **INTRODUCTION**

Recent advances in the diagnosis and treatment of inborn metabolic disorder (IMD) have improved substantially the prognosis for many of these conditions. This makes it essential that the practicing pediatrician be familiar with the clinical presentation of these disorders. Therefore, appropriate laboratory testing for metabolic disorders should be performed in any infant who exhibits these findings. Although sepsis may be the initial consideration in a neonate with these symptoms, IMD should always be in the differential diagnosis, particularly in a full-term infant with no specific risk factors. Hypoglycemia may be the predominant finding in a number of IMDs, including glycogen storage disorders, defects in gluconeogenesis, and fatty acid oxidation defects. A subset of lysosomal storage disorders may present early with coarse facial features, verv organomegaly, or even hydrops fetalis. Specific patterns of dysmorphic features and congenital anomalies characterize yet another group of IMDs, such as Zellweger syndrome and the Smith-Lemli-Opitz syndrome [1].

IMDs are caused by mutations in genes coding for enzymes and other proteins involved in cell metabolism. Many IMDs can be treated effectively. Although IMDs have usually been considered paediatric diseases, they can present at any age, mostly with neurological and psychiatric symptoms, and therefore constitute an integral subspecialty of neurology. The five groups of IMDs may be classified as: (a) energy metabolism disorders such as respiratory chain disorders, pyruvate dehydrogenase deficiency, GLUT1 deficiency, fattyacid β-oxidation defects, and disorders involving key cofactors such as electron transfer flavo protein,

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**Dr. S. Swaminathan,** Senior Consultant & Head, Department of Biochemistry, Apollo Speciality Hospitals, Vanagaram, Chennai – 600 095, Tamil Nadu, India. thiamine, biotin, riboflavin, vitamin E and coenzyme Q10; (b) intoxication syndromes such as porphyrias, urea-cycle defects, homocystinurias, organic acidurias and amino acidopathies; (c) lipid-storage disorders such as 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 cerebro tendinous xanthomatosis; (d) metal-storage diseases such as iron, copper and manganese metabolic disorders; and (e) neurotransmitter metabolism defects, including defects of serotonin, dopamine and glycine metabolism [2].

#### PHENYLKETONURIA

With the introduction of new-born screening programs and with early dietary intervention, children born with Phenylketonuria (PKU) can now expect to lead relatively normal lives. A better understanding of the biochemistry, genetics and molecular basis of PKU, as well as the need for improved treatment options has led to the development of new therapeutic strategies [3]. Breast feeding has been recommended for the dietary treatment of infants with PKU, but studies documenting clinical experience in other IMDs are very few. Patients with maple syrup urine disease (MSUD) also experience such problems, both in metabolic control and in insufficiency of breast milk, resulting in termination of breast feeding. Breast feeding of infants with inborn errors of protein catabolism is feasible, but it needs close monitoring with attention to such clinical parameters as growth, development and biochemistry, including

amino acids, organic acids and ammonia [4]. The problems that have contributed to the paradox of identifying individuals with IMD through new-born screening but not guaranteeing that they receive optimal treatment and the nutritional treatment of PKU is recommend for IMD treatment [5]. Access to interpreter services, exploration of the sociocultural background and of family ecology, as well as bi-directional communication and medical decision making according to the "best interest of the child" principle, may improve outcomes in patients requiring complex treatment and care [6].

### Alkaptonuria

In an unexpected turn of events, several genes involved in human IMD, including the gene for Garrod's favorite disease, alkaptonuria, have been characterized by exploitation of the experimental advantages of another mold, Aspergillus nidulans, which shares with N. crassa the experimental advantages that prompted pioneers of biochemical genetics to use them: rapid growth, facile genetic manipulation, and an environment (the composition of the growth medium) that can be manipulated [7]. Garrod gave evidence for the dynamic nature of metabolism by showing involvement of normal metabolites in normal pathways made variant by Mendelian inheritance. His concepts and evidence were salient primarily among biochemists, controversial among geneticists because biometricians were dominant over Mendelists, and least salient among physicians who were not attracted to rare hereditary 'traits'. In 2008, at the centennial of Garrod's Croonian Lectures, each charter of IMD has acquired its own genomic locus, a cloned gene, a repertoire of annotated phenotype-modifying alleles, a gene product with known structure and function, and altered function in the Mendelian variant [8]. The diagnosis can be made in neonates when blackish stain is noticed in an unwashed diaper. Since the aggregate incidence of IMD is relatively high, a high degree of suspicion is essential to correctly diagnose an inborn error of amino acid metabolism [9,10]. Alkaptonuria is a rare disorder of metabolism characterized by deficiency of homogentisic acid oxidase. This leads to the characteristic features like darkening of urine, ochronosis and arthropathy. Darkening of urine is one of the first symptoms noticed by the parents of the child suffering from this disorder [11].

### HOMOCYSTINURIA

Disorders of intracellular cobalamin (vitamin B12) metabolism result from deficient synthesis of the coenzymes derived from vitamin B12: adenosylcobalamin and methylcobalamin. Disturbances of cobalamin-cofactor synthesis result in elevated levels of homocysteine and/or methylmalonic acid. Nine defects of intracellular cobalamin metabolism have been described [12]. Acute and chronic recurrent pancreatitis have been reported in patients with a variety of IMD. Among these are hyperlipidaemias, various disorders of

branched-chain amino acid degradation, homocystinuria, haemolytic disorders, acute intermittent porphyria and several amino acid transporter defects. Some of these disease entities are exceedingly rare [13]. Although cerebrovascular thrombosis is usually thought to be responsible for neurological dysfunction in homocystinuric patients, neuropathological studies and clinical and radiological evidence suggested that dystonia was not caused by brain infarction. Movement disorder associated with homocystinuria may result from the neurochemical changes in the basal ganglia related to the inherited defect in sulphur amino acid metabolism [14]. IMDs are individually rare but are an important cause of mortality and morbidity in infants and children. Dietary therapy is the mainstay of treatment for PKU, MSUD, homocystinuria, galactosemia and glycogen storage disease (Type I/III). Some disorders like urea cycle disorders and organic acidurias require dietary modification in addition to other modalities [15].

#### MAPLE SYRUP URINE DISEASE

MSUD is caused by a deficiency in the branchedchain alpha-ketoacid dehydrogenase complex. Accumulations of branched-chain amino acids (BCAAs) and branched-chain alpha-ketoacids (BCKAs) in patients with MSUD induce ketoacidosis, neurological disorders, and developmental disturbance. Damage to neuronal cells found in MSUD patients are presumably because of higher concentrations of both blood BCAAs and BCKAs, especially alpha-ketoisocapronic acids. These clinical data from MSUD patients provide a valuable basis on understanding leucine toxicity in normal subjects [16]. Liver transplantation appears to be quite beneficial for treatment of MSUD. However, there is a limited availability of donor livers worldwide and the first-year costs of liver transplants are quite high. Subcutaneous fat transplantation may have merit as an adjunct to dietary treatment of MSUD. Additional studies are needed to further refine this approach [17] Significant substrate removal can be achieved in some IMDs, either through stimulation of residual enzyme activity in defective enzyme systems or by activation of alternate metabolic pathways. Both possibilities almost certainly depend on gross elevation of substrate concentrations. By contrast, only minimal in vivo oxidation of leucine appears possible in MSUD [18]. The amino acids restricted are leucine, isoleucine, and valine in MSUD; leucine in HMG-CoA lyase deficiency; and isoleucine, methionine, threonine, and valine in propionic academia (PPA) and methylmalonic aciduria (MMA). Efficacy of the protein-modified diets (PMD) depends on accuracy in prediction of the restricted amino acid requirement and the willingness and ability of parents and patients to conform to its demands [19]. Certain IMDs manifest during the neonatal period by acute accumulation of neurotoxic metabolites leading to coma and death or irreversible neurological damage. Outcome critically depends on the immediate elimination of the accumulated neurotoxins. Recent technological progress provides improved tools to optimize the efficacy of neonatal dialysis [20].

### UREA CYCLE DISORDERS

Treatment of urea cycle disorders (UCD) and related metabolic diseases consists of nutritional restriction of proteins, administration of specific amino acids and use of alternative pathways for removing excess nitrogen. Although combinations of these treatments are extensively employed, the prognosis of severe cases remains unsatisfactory. Liver transplantation is one alternative for which a better prognosis is reported [21]. UCD are a group of IMDs, characterized by hyperammonemia, metabolic alkalosis and clinical features of encephalopathy. Various modalities of treatment have been recommended such as reducing ammonia level using sodium benzoate and sodium phenyl butyrate, neuroprotective strategies, low protein diet, liver transplantation and hepatocyte transplantation. Molecular diagnosis is important to identify the pathogenesis of these disorders as it helps in prognosis [22]. Therapeutic modality has a substantial impact in urea disorder patients on the metabolism of branched chain amino acids suggesting that better titration of protein restriction could be achieved with branched chain amino acid supplementation in patients with UCDs who are on alternative route therapy [23].

Neurological dysfunction is an important manifestation of IMD. Although these are more common in childhood, adult onset forms with a different clinical presentation are often encountered. Recent advances in the diagnosis and treatment of these conditions have substantially improved the outcome in many of these conditions. Establishing a specific diagnosis in these disorders will enable the clinician in offering a definitive longterm treatment, prognosis and genetic counselling [24]. Early suspicion of the diagnosis of a UCD, and prompt referral to a tertiary centre is vital. Drug treatment using chronic administration of sodium benzoate has been abandoned by some centers, but the acceptability of phenylbutyrate is an issue for many patients. Using citrulline chronically is not always successful in recommended doses, and may result in an arginine level too low for maximum control [25]. When the concentration of blood ammonia becomes < 180µmol/L (5 times normal), there was no severe neurological damage, but the level of blood ammonia exceeded 350µmol/L (10 times normal) at the first hyper ammonaemic attack, the patient may die or acquire severe neurological defects and hence it is important to have early diagnosis and aggressive treatment [26]. Diagnosis of UCD is based on clinical suspicion and determination of blood ammonia in suspected patients with neurological symptoms in the intensive care setting. Treatment is based on the removal of ammonia by dialysis or hemofiltration,

reduction of the catabolic state, abolishment of nitrogen administration and use of pharmacological nitrogen scavenging agents [27].

### GAUCHER DISEASE

Recent studies have highlighted T-cell dysfunction and modifier genes contributing to an increased cancer risk in Gaucher Diseases (GD). Macrophagetargeted enzyme replacement therapy (ERT) reverses systemic features of GD1; while cancer risk appears to be reduced in the era of ERT, it is not known whether this is a direct effect of therapy. Delineation of the mechanisms underlying the increased cancer risk in GD will provide additional novel insights into the role of lipids and macrophages in cancer pathogenesis and may have the potential to reveal novel therapeutic targets [28]. The elevated scores of the GD patients on Matrix Metholopeptidases (MMP) like hypochondranis, depression and hysteria scales are similar to those of the centre for reducing health disparities. The chronic pain patients also showed elevations on MMPI-2 scales Hs D and Hy, which were elevated in the GD patients and such elevations in the chronic pain patients were higher than those shown by the GD patients. Hence patients with GD exhibit moderate to severe psychological complications, similar to patients with other long-term chronic illnesses [29]. Adult patients with GD often have other medical problems unrelated to their primary diagnosis. The high incidence of neurological complaints in these patients may be attributable to concurrent medical problems and/or side-effects from concomitant medications. These issues may influence patients' assessment of their disease severity and/or response to treatment [30].

As a genetic disorder, the incidence of GD is variable on a global scale. Enzyme replacement is the therapy of choice and has demonstrated good efficacy in treating the visceral and skeletal symptoms of GD. A cost-effective plant-cell-derived human recombinant glucocerebrosidase, taliglucerase alfa, has been developed that demonstrated a promising safety and efficacy profile in phase I clinical trials and is currently in phase III and IV trials for the treatment of pediatric and adult patients with GD [31]. Recent research shows that the changes in the dental radiograph of patients with GD are very specific. Currently, this disorder and its associated molecular genetics are a prototype for research of new treatments such as allogenic bone marrow transplantation and molecularly engineered enzymes [32]. Therapies have revolutionized the care of patients with Type 1 GD reversing many of the pathological consequences of this disease and preventing further progression. Furthermore, they have served as a model for the treatment of other lysosomal storage diseases and many IMDs [33].

The use of a protocol for assessing the intensity of the deposit is mandatory to establish the indication for treatment, especially in rare diseases. At present, there are several options for treatment of GD: enzyme replacement therapy and substrate reduction therapy. Regular assessments are needed to establish the response and the degree of of the therapeutic achievement goals recommended through expert consensus [34]. At present, the inflated pharmaceutical niche of GD appears to be resilient, but if the remaining unmet needs of patients are to be convincingly addressed development and commercial sustained, courageous scientific investment and clinical experimentation will be needed [35].

### TAY-SACHS DISEASE

The success of Tay-Sachs disease (TSD) screening in the Ashkenazi Jewish population has made it the prototype for screening among the IMDs. The TSD example becomes increasingly relevant as heterozygote detection becomes possible for other genetic disorders that are increased in well-defined populations. Cystic fibrosis is such a disease in the Caucasian population [36]. Carriers of an inborn error of lysosomal catabolism can be recognized, as they have enzyme levels approximately half of those of normal individuals. Of the various tissues, readily available for assay, plasma and leukocytes and in some situations tears are preferred. mixed leukocytes Although have proved satisfactory in TSD screening programs, purified preparations of granulocytes or lymphocytes will allow better discrimination in most situations. Enzymes are assayed relative to some other reference parameters which must be a constant or highly correlated with test enzyme activity [37].

### FATTY ACID OXIDATION DISORDERS

Inborn errors of fatty acid oxidation (FAO) disorders represent a group of metabolic disorders that has brought forward many interesting developments as highlighted by the rapid pace of discovery of new defects and by the recognition of an ever-increasing spectrum of clinical phenotypes [38]. Therapeutic approaches are generally effective in preventing severe symptomatic episodes, including sudden death. New-born screening for fatty-acid oxidation disorders promises to identify many affected patients before the onset of symptoms [39]. The clinical phenotypes of FAO disorders include disease of one or more of these fatty acid-metabolizing tissues [40]. The collective role played by FAO and probably other metabolic disorders among the causes of Cyclic Vomiting Syndrome (CVS) is unknown. Guidelines for a diagnostic approach to FAO disorders at the biochemical level are extensively studied and have been documented. Hopefully, a better understanding and an awareness of FAO disorders could improve the diagnostic evaluation of patients with CVS [41]. To date, seven inborn errors of mitochondrial fatty acid oxidation have been identified. The diagnosis of these disorders is of prime importance because of the severity of the clinical symptoms. These can be prevented, in some cases, by an appropriate diet (a high carbohydrate, low fat diet, sometimes supplemented with L-carnitine). In other cases, genetic counselling can be offered [42]. Only by systematically evaluating developmental and neuropsychological outcomes using standardized methods will the true implications of new-born screening, laboratory results, and treatments for neurocognitive outcome in these disorders become clear [43].

Mutation analysis of metabolic disorders, such as the FAO defects, offers an additional and often superior tool for specific diagnosis compared to traditional enzymatic assays. With the advancement of the structural part of the Human Genome Project and the creation of mutation databases, procedures for convenient and reliable genetic analyses could be easily developed. The rapid development of mutation detection systems, such as the chip technologies, makes such profile analyses feasible. However, it remains to be seen to what extent mutation analysis will be used for diagnosis of FAO defects and other metabolic disorders [44]. Mitochondrial fatty acid beta-oxidation disorders (FAOD) are a group of clinically and biochemically heterogeneous inherited metabolic defects. The spectrum of phenotypes have expanded from hepatic encephalopathy to encompass myopathy, cardiomyopathy, peripheral neuropathy, sudden death and pregnancy complicated by foetal FAOD. Laboratory investigation commonly begins with a search for diagnostic metabolites in physiological fluids, followed by in vitro functional studies if the initial findings are inconclusive, and confirmation by enzymology and molecular analyses. Occasionally a stress test in vivo may be required. At other times, there may be no firm diagnosis achieved [45].

### GALACTOSEMIA

Long-term outcomes of classic galactosemia (GAL) remain disappointing. It is unclear if the complications result mainly from prenatal-neonatal toxicity or persistent glycoprotein and glycolipid synthesis abnormalities. Increased levels of agalactosylated and monogalactosylated structures and decreases in certain digalactosylated structures were identified in the patients. The persistent abnormal glycosylation of serum glycoproteins seen with the microarray data indicates persisting metabolic dyshomeostasis and gene dys-regulation in "treated" GAL. Strict restriction of dietary galactose is clearly lifesaving in the neonatal period; long-term severe galactose restriction may contribute to ongoing systemic abnormalities [46]. Classic galactosemia, an inborn error of human galactose metabolism, is characterized by a deficiency of the enzyme galactose-1-phosphate uridyltransferase (GALT). The current model for the pathophysiology of this disease ascribes most of its symptoms to the toxicity of intracellular galactose-1phosphate (Gal-1-P), one of the substrates of GALT which accumulates in the untreated disease state leading to imbalance in glycolipids. This novel biochemical abnormality observed in galactosemic patients is not addressed by dietary galactose-restriction therapy and could explain some of the chronic neurologic and other complications of galactosemia [47].

Increasing number of patients with IMD is now reaching adulthood and are in position to reproduce. Because of the rarity of individual disorders our knowledge of risks factors associated with pregnancy is limited. The management of labor and the postpartum period (for women and newborns) has to be carefully planned to avoid significant metabolic decompensation [48]. GAL leads to hepatic, ophthalmic, neural and renal derangements. The perioperative management of a new-born with galactosaemia operated for correction of transposition of great arteries should be explored further [49].

### **G**LYCOGEN STORAGE DISEASES

Liver transplantation has been performed in different types of Glycogen Storage Diseases (GSD). It should only be considered in high risk patients with substantial cirrhosis. Many countries have included classical GAL in their newborn screening programs. A lactose-free infant formula can be lifesaving in affected neonates whereas a strict fructose-restricted diet is indicated in hereditary fructose intolerance [50]. Mutations in genes that play fundamental roles in metabolic pathways have been found to play a role in tumor development and susceptibility to cancer. At the same time, significant progress has been made in the treatment of patients with IMD, resulting in increased longevity and the unmasking of cancer predisposition, associated frequently with hepatocellular carcinoma in these conditions [51]. In patients with GAL, hereditary fructose intolerance or tyrosinaemia type I, presentation is dominated by a liver failure requiring galactose and fructose exclusion along with a low-protein diet. Many patients with beta-oxidation defects may present with hypoglycaemia that is usually corrected easily. The precise diagnosis can be easily missed in those patients that do well in the following weeks but may develop cardiac failure, arrhythmia and/or liver failure. Patients presenting with intractable convulsions, vitamin responsiveness to biotin, pyridoxine and folate must be considered [52].

### MUCOPOLYSACCHARIDOSES

In a study, the effects of the administration of normal human plasma to patients affected by mucopolysaccharidoses I and II (Hurler's and Hunter's syndromes) during infusion was followed by a decreased urinary excretion of relatively large molecular weight glycosaminoglycans and by an increased excretion of their products of degradation. Among the latter, products of the degradation of dermatan sulfate and heparan sulfate could be demonstrated [53]. IMD has been anecdotally reported in the literature as presenting with features of cerebral palsy (CP) or misdiagnosed as 'atypical CP'. A significant proportion is amenable to treatment either directly targeting the underlying pathophysiology (often with improvement of symptoms) or with the potential to halt disease progression and prevent/minimize further damage. Limited by the rare nature of IMDs and incomplete information in the literature, a surprisingly large number of IMDs can present with CP symptoms, as 'CP mimics'. Although individually rare, a large proportion of these diseases are treatable such that neurological damage can either be reversed or prevented and clinician's awareness of treatable CP mimics is important for appropriate screening, diagnosis, early intervention and systematic studies are required to elucidate the collective frequency of treatable IMD s in CP [54].

#### LYSOMAL DISORDERS

Lysosomal disorders are among the few causes of nonimmune hydrops fetalis in which an accurate recurrence risk can be ascertained. With an early and accurate diagnosis, genetic counseling and family planning can be offered in these difficult cases [55]. Lysosomal storage diseases are IMDs, the hallmark of which is the accumulation, or storage of macromolecules in the late endocytic system. They are monogenic disorders that occur at a collective frequency of 1 in 5,000 live births and are caused by inherited defects in genes that mainly encode lysosomal proteins, most commonly lysosomal enzymes. A subgroup of these diseases involves the lysosomal storage of glycosphingolipids. Study of these disorders has led to significant progress in the development of therapies, several of which are now in routine clinical use. Emerging mechanistic links with more common diseases suggest to rethink on current concept of disease boundaries [56]. The lysosomal storage disorders comprise a heterogeneous group of IMDs characterized by tissue substrate deposits, most often caused by a deficiency of the enzyme normally responsible for catabolism of various by products of cellular turnover. At present, therapy of the CNS manifestations remains a major challenge because of the inability to deliver therapeutic agents across the intact blood brain barrier. With improved understanding of underlying disease mechanisms, additional therapeutic options may be developed, complemented by various strategies to deliver the therapeutic agent(s) to recalcitrant sites of pathology such as brain, bones and lungs [57].

### Porphyria

Erythropoietic protoporphyria (EPP) is an inherited inborn error of porphyrin metabolism caused by decreased activity of the enzyme ferrochelatase, the terminal enzyme of the haem biosynthetic pathway, which catalyses the insertion of iron into protoporphyrin to form haem. EPP is characterized clinically by photosensitivity to visible light commencing in childhood and biochemically by elevated red cell protoporphyrin levels. The basic enzymatic defect in EPP is at the level of the bone marrow stem cells, which are the target cells of choice in the development of retroviral-mediated gene transfer and definitive treatment of EPP by gene therapy is a distinct hope for the future [58]. Determination of porphyrins and their precursors in clinical materials is of pivotal importance in establishing the diagnosis of porphyrias. The methods of determination of porphyrins and their precursors in clinical materials and techniques employed needs further studies [59]. Possible underlying organic causes of psychiatric symptoms can be overlooked in the clinical setting. It is important to increase awareness amongst psychiatric and neurological professionals with regard to certain IMD as, in some cases, diseasespecific therapies are available that can, for instance, treat underlying metabolic causes. Alongside improved frameworks for additional multidisciplinary diagnostic work in patients with suspected organic disease, the development of convenient and affordable biochemical screening and/or diagnostic methods has enabled new ways to narrow down differential diagnoses [60]. Congenital erythropoietic porphyria is a rare autosomal recessive disorder that usually presents with marked skin photosensitivity, hypertrichosis, blistering, scarring, milia formation and dyspigmentation of the photo-exposed areas [61]. Congenital erythropoietic porphyria is an autosomal recessive inborn error of metabolism that results from the markedly deficient activity of uroporphyrinogen III synthase [62].

## **G**ENETIC DISORDERS

With early diagnosis and increasingly effective medical care, more women with genetic syndromes are undergoing pregnancy, often presenting challenges for providers [63]. In such cases IMDs are characterized by dysregulation of the metabolic networks that underlie development and homeostasis and constitute an important and expanding group of genetic disorders in humans. Diagnostic methods that are based on molecular genetic tools have a limited ability to correlate phenotypes with subtle changes in metabolic fluxes. The direct and dynamic measurement of metabolite flux will facilitate the integration of environmental, genetic and biochemical factors with phenotypic information. Ultimately, this integration will lead to new diagnostic and therapeutic approaches that are focused on the manipulation of these pathways [64]. Various mechanisms have been proposed to explain abnormal brain development in IMDs production of a toxic or energy-deficient intrauterine milieu, modification of the content and function of membranes, or disturbance of the normal expression of intrauterine genes responsible for

morphogenesis. The recognition of a metabolic disorder as the cause of the brain malformation has implications for both the care of the patient and for genetic counselling to prevent recurrence in subsequent pregnancies [65]. Genetic disorders were identified infrequently among children presenting with Reye's syndrome in the past. A standard investigation for IMD revealed that two patients had enzymatic defects of fatty acid oxidation, and the other two had partial deficiencies ornithine transcarbamoylase. None had of experienced a previous episode of Reye's syndrome, and three of the four had been entirely healthy in the past, suggesting that as the incidence of Reye's syndrome has decreased, patients with its clinical features are now more likely to have manageable IMD (eg, disorders of ureagenesis, ketogenesis, and branched-chain amino acids) [66]

### NIEMANN-PICK DISEASE

Niemann-Pick disease (NPD) type C is an IMD that affects lipid degradation and storage. Hepatosplenomegaly and progressive neurological symptoms are the main clinical features. Lipid storage disease should be suspected especially in younger patients with organomegaly and progressive signs of neurologic disease [67]. NPD type B is caused by a three-base deletion in chromosome 11. Chondrosarcoma and multiple exostoses occur due to loss of tumour suppressor EXT<sub>2</sub> from centromeric region on gene chromosome 11, though it is difficult to establish the link between the two, as the two together have not yet been reported in the literature. NPD may present diagnostic difficulties when it occurs with chondrosarcoma. The two diseases have not been reported together in the world literature and there is some evidence to show that chromosome 11 is central to both diseases. More research is needed to see if one leads to the other [68]. Renal involvement in lipid storage diseases is well recognized. Electron microscopy or chemical analysis of urinary sediment has been used for the diagnosis of these diseases. Urine cytology, supplemented by cytochemistry, polarization, and auto fluorescence may help in the diagnosis of NPD in an infant [69]. Progressive neurological deterioration is the ultimate cause of premature death in Niemann-Pick Type C disease (NPCD). Yet it remains unknown why a defect in basic cellular lipid homeostasis would lead to such profound neurological dysfunction and degeneration. The established belief that the central nervous system disorder of NPCD is secondary to lipid accumulation has led to a deficiency of research and information on the neurological manifestation of the disease. The independence of brain pathology from visceral complications in NPCD has implications for its treatment. Further studies of the neurological mechanisms underlying the disease will have a significant impact on future clinical diagnosis and management of patients. Diagnostic delay may occur in NPCD due to false positive testing for GD. Diagnosis of NPCD requires a high index of suspicion and should be considered in a patient with hepato splenomegaly even in the absence of neurodevelopmental signs. Prompt diagnosis will become increasingly important as effective therapies are developed for NPCD [70]. A notable proportion of adult-onset cases have been reported where NPCC has mistakenly been diagnosed and treated as a psychiatric condition usually based on patients' initial presentation with psychotic or schizophrenia-like symptoms. Underlying organic causes of psychiatric disorders such as psychosis should be considered among patients with atypical symptoms and/or resistance to standard therapy. Alongside improved frameworks for additional multidisciplinary diagnostic work in patients with suspected organic disease, the development of convenient and affordable biochemical screening and/or diagnostic methods has enabled new ways to narrow down differential diagnoses [71].

# **CONCLUSION**

This review article has highlighted the various research findings during the last three decades on IMDs. Among the IMDs extensively highlighted in this review article are disorders of carbohydrates, fats, proteins and haemoglobin metabolism and various disorders associated with genetic, energy metabolism, intoxication syndrome, lipids and metals storage and neurotransmitter metabolism disorders. The content of this review article will certainly help the researchers to further explore research in this field of IMDs as early diagnosis and treatment help in the new born screening. Screening tests must be timely and effective with a high predictive value. Current approaches to detecting IMDs revolve around laboratory screening for certain disorders in asymptomatic new-borns, follow-up and verification of abnormal laboratory results, prompt physician recognition of unscreened disorders in symptomatic persons and rapid implementation of appropriate therapies are the need of the hoses.

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