Disease and Diagnosis

➜ **Narrative Review**

An Overview of the Inborn Errors of Metabolism, Its Diagnosis, and Management

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Abstract
Biochemical anomalies impairing the body's normal metabolism are referred to as inborn errors of metabolism (IEM). Early diagnosis and management can avert the otherwise harmful situation that may occur due to inborn errors. Generally, their incidence can vary from one case in every 800 to 2500 cases. Thus, understanding the genetic defects behind the clinical presentation of the disease and their early management and treatment is the need of the hour. This review article gives an overall knowledge of the types of IEM, its pathophysiology, clinical presentation, diagnosis, and management of the disease.
Keywords: Inborn errors of metabolism, Genetic mutations, Enzyme, Metabolic defects, Targeted and untargeted metabolomics

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Introduction

Genetic disorders that impair normal metabolism with detectable biochemical anomalies arising from autosomal defects are referred to as inborn errors of metabolism (IEM). The term was first coined by a British scientist, Archibald Edward Garrod, and describes genetic deficiency or alteration in enzyme function. There are more than 500 types of inborn metabolic disorders in humans (Figure 1) of which 100 cases are related to amino acid metabolism (1). The figure itself can give an idea of how complex IEM can be, and how their diagnosis usually becomes difficult. Common metabolic defects are that of carbohydrates, lipids, fatty acid oxidation, amino acids, mucopolysaccharides, organic acids, urea cycle defects, lysosomal storage, and peroxisomal defects.

Mutations in the genes that encode the enzymes of metabolic pathways are the major cause of disorders. The metabolites are either absent or present in extremely small concentrations, leading to such defects (2,3). Patients with IEM are unable to synthesize or use amino acids, fatty acids, organic acids, and other macromolecules because of the defects in these enzymes of the metabolic pathways. The enzyme defects also lead to substrate accumulation in the body, leading to mild to severe symptoms. The disease symptoms may appear two to three days after the baby is born and started to feed or may get delayed and appear in adulthood. IEM is a serious cause of mortality and morbidity in neonates, and a delay in their diagnosis leads to several symptoms. The common symptoms in babies include mental retardation, hyperactivity, delay in speech, lethargy, dystonia, psychomotor delay, ataxia, seizures, encephalitis, and even coma. In addition to these neurological symptoms, other symptoms are skin rashes, organomegaly, vomiting, hypoglycemia, hyperammonemia, metabolic acidosis, lactic acidosis, and ketonuria. Blood and urine samples are generally collected for the detection of such disorders (Figure 2).

Methods

For the review, no particular structure was followed for searching research articles. The articles were mainly retrieved from PubMed and ScienceDirect databases, and the manual search of full-text papers was performed using words such as the inborn errors of metabolism, the prevalence of inborn error, genetic mutations, diagnosis of inborn error, classification of disease types, metabolomics approach toward inborn errors of metabolism, and et al.

Studies reporting the types of disease prevalence, diagnosis of the disease, and treatment of IEM were included in the study, and relevant information was summarized and integrated into this review. The review
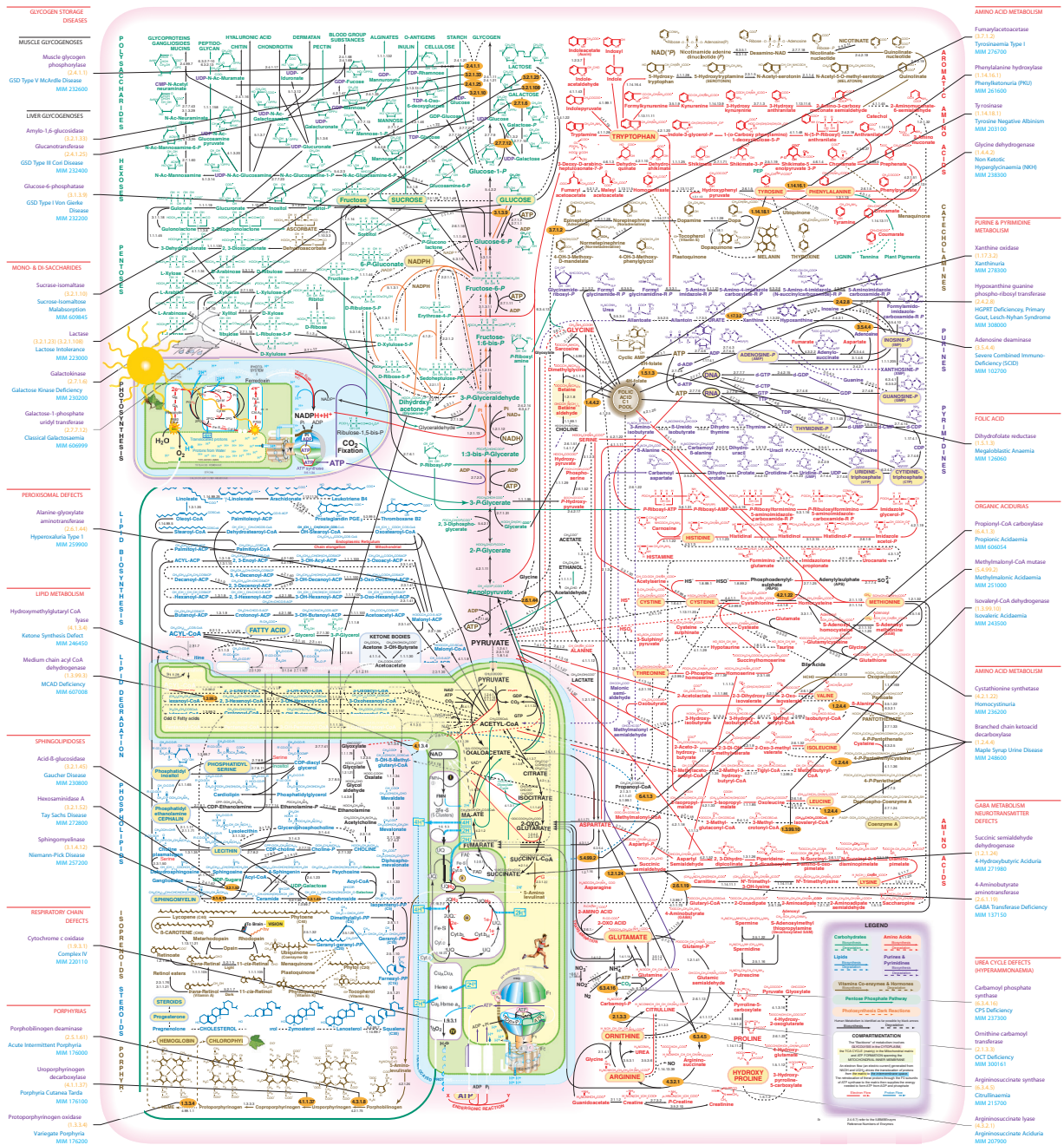
Figure 1. Pathways and Enzymes Leading to IEM. *Note*. IEM: Inborn errors of metabolism. The picture is designed by Donald E. Nicholson, The University of Leeds, England – and Sigma-Aldrich in collaboration with Mick Henderson, St. James' Hospital, Leeds – and the UK MetBioNet Training Group. Reproduced with permission from the International Union of Biochemistry and Molecular Biolog

included no exclusion criteria, and the literature search was not limited to any study design, time, region, or language.

Epidemiology and Etiology of the Disease

The prevalence of IEM differs according to geographical regions and among different ethnic groups. IEM is a rare disease with an incidence of less than 1 per 100 000 births when considered individually and can generally range from 1 in every 800-2500 cases (4,5). The overall percentage related to the prevalence of each of the

IEM categories, as demonstrated by Ferreira et al for generating a nosology of IEM, is shown in Figure 2 (6). Whatever the numbers, it should always be kept in mind that the number of IEM cases is always underestimated as many of them remain undiagnosed and not reported.

A systematic search of the published data (1980-2017) using databases such as EMBASE, Global Health, and Medline estimated the global birth prevalence of IEM to be 50.9 per 100 000 live births, and a pooled birth prevalence rate of eight classes of IEM was 64.6 per 100 000 live births. All global IEMs estimated 500 IEM cases for
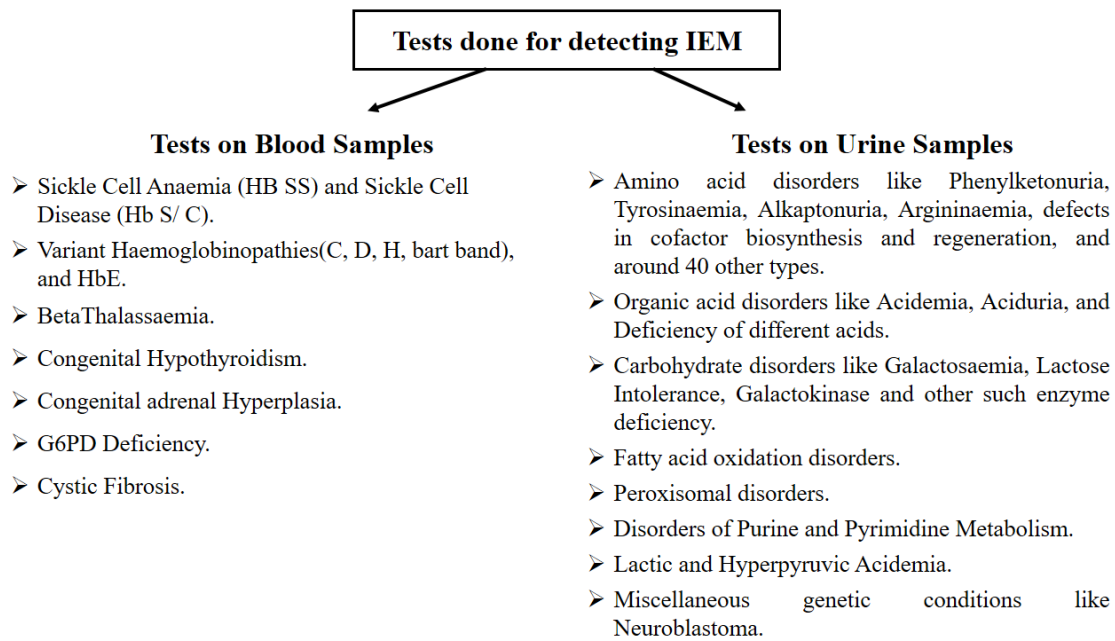
Tests done for detecting IEM

Tests on Blood Samples

➢ Sickle Cell Anaemia (HB SS) and Sickle Cell Disease (Hb S/ C).
➢ Variant Haemoglobinopathies(C, D, H, bart band), and HbE.
➢ BetaThalassaemia.
➢ Congenital Hypothyroidism.
➢ Congenital adrenal Hyperplasia.
➢ G6PD Deficiency.
➢ Cystic Fibrosis.

Tests on Urine Samples

➢ Amino acid disorders like Phenylketonuria, Tyrosinaemia, Alkaptonuria, Argininaemia, defects in cofactor biosynthesis and regeneration, and around 40 other types.
➢ Organic acid disorders like Acidemia, Aciduria, and Deficiency of different acids.
➢ Carbohydrate disorders like Galactosaemia, Lactose Intolerance, Galactokinase and other such enzyme deficiency.
➢ Fatty acid oxidation disorders.
➢ Peroxisomal disorders.
➢ Disorders of Purine and Pyrimidine Metabolism.
➢ Lactic and Hyperpyruvic Acidemia.
➢ Miscellaneous genetic conditions like Neuroblastoma.

Figure 2. Detection of IEM From Blood and Urine Samples. *Note*. IEM: Inborn errors of metabolism

every 1 million live births, giving a number of 70 587 new IEM cases per year projected from 2015 to 2020 (7). The study on the global prevalence was based on the 49 studies selected from 25036 records after the exclusion of duplicate entries and based on the selection criteria. The study provided details of various classes of IEMs (amino acids, organic acids, fatty acids, lysosomal, carbohydrate metabolism, urea cycle, peroxisomal, and mitochondrial disorders) such as the year of detection, location, setting, period of study, total live births, cases in the cohort, birth prevalence per 100 000 live births, and number of deaths in a birth cohort. The estimated global death rate due to all-cause IEM was 3.2 per 100 000 live births and 23 529 deaths per year (0.4% child death globally); although extensive early childhood death occurs due to IEM, it is not diagnosed as a factor of death (8).

In another study performed from October 2012 to November 2015, the prevalence of IEM in India was 2.9 % (2053 cases were found positive out of 70 590 screened cases) on the screening of 119 disorders, and G6PD deficiency (44 %) and hemoglobinopathies (17.5 %) were the most prevalent cases, respectively (9). The distribution of different types of IEM is illustrated in Figure 3.

Most of the IEMs are inherited disorders and autosomal recessive in nature (10,11). The phenotype only gets expressed if the offspring inherit the mutated allele from both of their parents. Such mutated homozygotes can occur from consanguineous marriages (12) or by random mutation in the parents' allele. The IEMs that are inherited as X-linked alleles have higher chances of prevalence in males and the random inactivation of X-chromosomes in females. The manifestations of X-linked IEMs vary from one female to another and from one tissue to another.
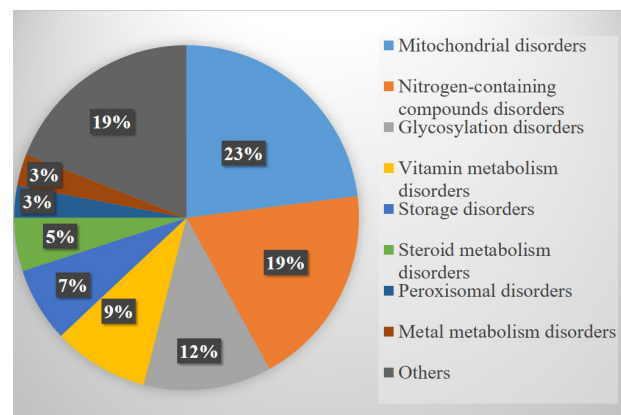

Figure 3. Prevalence of Different Types of the Inborn Error of Metabolism

Very few IEMs are autosomal dominant in nature and very few are linked to mitochondrial DNA (the maternal origin) (13,14). Most IEM disorders are due to a defect in an enzyme that leads to the accumulation of upstream metabolites that can have toxic effects and a reduction in essential downstream products (Figure 4).

Pathophysiology of the Disease

According to the pathophysiology of the disease, which is characterized by the alterations of multiple metabolic pathways, the pathophysiological classification of IEM can be group I diseases affecting a single function, gene, or organ, including the immune and endocrine system disorder, and group II diseases affecting biochemical pathways in different organs and systems. This condition can be further divided into three groups:

Group 1: Disorders of intermediary metabolism: This is a vast group involving different mechanisms. This

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group includes the IEMs that occur due to acute or progressive intoxication from compounds accumulated in the steps before the metabolic blockage. This group consists of the inborn errors of amino acid catabolism and synthesis, urea cycle defects, organic acidurias, metal disorders from intoxication due to accumulation and deficiencies, and errors in neurotransmitter catabolism, synthesis, and transport. The clinical expression is late in onset and intermittent. The diagnosis of this group is straightforward, and it is detected from plasma and urine samples by amino acid, acylcarnitine, and organic acid chromatography. The disorders are treatable with the immediate removal of toxins by drugs, special diets, and the like.

Group 2: IEMs that involve energy metabolism: The IEMs are due to deficiency in the production or the utilization of energy within the muscle, brain, liver, and myocardium. The mitochondrial defects are more severe, including the Kerbs cycle defects, disorders of mitochondrial respiratory chains, and the less severe cytoplasmic energy defects such as glycolysis and gluconeogenesis. The diagnosis of this group of disorders is complex and relies on the measurement of energetic molecules both in fasted and fed conditions in cycles, molecular analyses, and enzymatic analyses require biopsies and cell culture. Very few of these disorders are treatable.

Group 3: This group involves disorders due to the synthesis, catabolism, processing, and quality control of complex molecules. The organelles where these complex processes occur are the lysosomes, Golgi apparatus, mitochondria, peroxisomes, and endoplasmic reticulum. The symptoms of these disorders are permanent and sometimes progressive, not related to the diet, and not dependent on the intercurrent events.

Clinical Presentation of the Disease and its Outcomes

The clinical presentation of the disease varies with age and presents differently. The clinical presentation of the disease can occur in the mother's womb, at birth, or after delivery during the initial days which is presented as deterioration after normal birth and delivery (15). Most term IEM babies seem to be well at birth but deteriorate extremely fast, even if the babies received no oral feeds. The changes in catabolism occurring in the first days of life lead to the accumulation of toxic metabolites, causing this phenomenon. The rate at which the deterioration occurs depends on the type and extent of the disease, and the most affected organ. The most common clinical presentation of IEM is cardiomyopathy, sudden death, neurological symptoms, unexplained hypoglycemia, hepatic failure or deterioration, and acid-base disbalance (16,17). Apart from the metabolic disorders that are recognized from newborn screening, the clinical
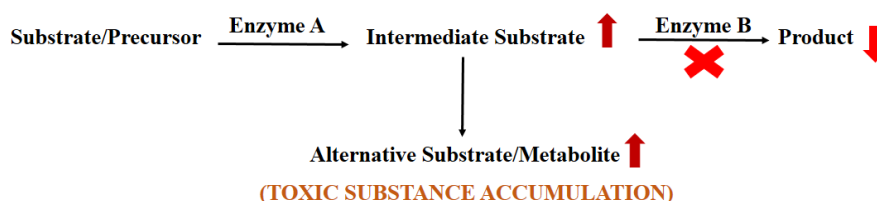

Figure 4. Mechanism of the Error. *Note.* Enzyme 'A' converts a substrate/precursor to an intermediate substrate at a normal rate, but an error in the production of enzyme 'B' leads to blockage in the conversion of the intermediate substrate to product, leading to the accumulation of an intermediate substrate or an alternative substrate/metabolite which can have a toxic effect on the body
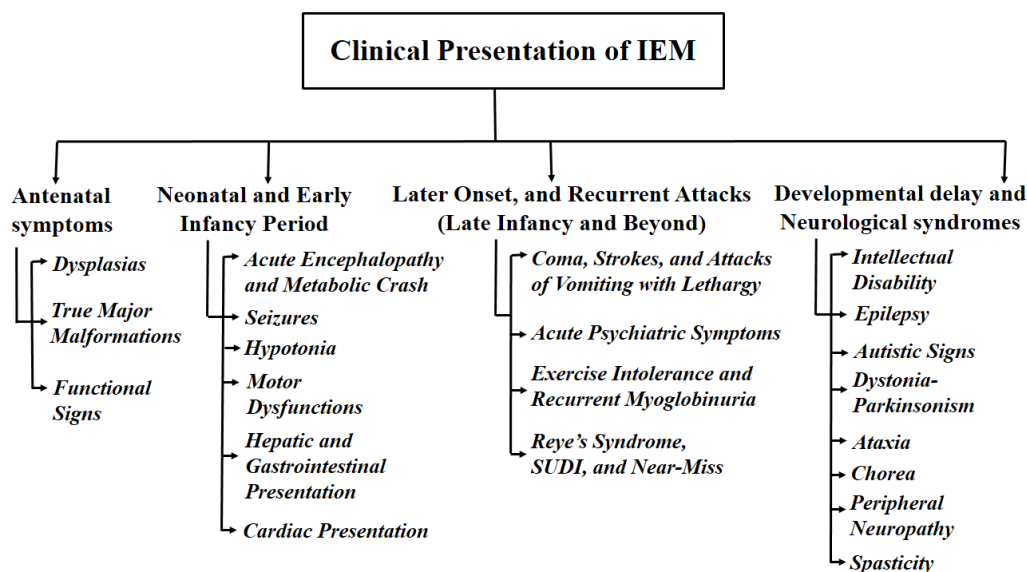

Figure 5. Classification of the Clinical Presentation of IEM. *Note.* IEM: Inborn errors of metabolism

presentation of the disorders can be broadly divided into four groups (Figure 5).

Some IEMs remain asymptomatic until late in infancy and present rapid and acute deterioration, including facial abnormalities such as a flattened nasal bridge, large fontanelle, epicanthal folds, and prominent forehead in the case of Zellweger syndrome (18). In addition, they present lipodystrophy, and inverted nipples in cases of congenital glycosylation disorders, genital abnormalities (19), flat nasal bridge, and cataracts in cases of Smith-Lemli-Opitz syndrome (20). Some IEMs also lead to abnormal odors such as sulfur in the case of cystinuria and tyrosinemia type I, maple syrup in the case of Maple syrup urine disease, mousy in the case of phenylketonuria, cat's urine in the case of multiple carboxylase deficiency, and the like (21).

Evaluation and Diagnosis

Clinical approaches for the diagnosis of IEM are highly difficult because of their overlapping manifestations, especially the rare variants of some diseases. The presentation of a clinical symptom can have various reasons. A universal clinical protocol for the diagnosis of all IEMs is therefore impossible. IEMs cannot be diagnosed based on clinical data, and rather laboratory data are the primary source of diagnosis (16,22). A study reported that out of 144 clinically diagnosed IEM infants, only 12 infants were confirmed of IEM using laboratory diagnosis (16).

The IEM is analyzed from blood and urine samples using one/more of the techniques such as enzyme-linked immunosorbent assay, tandem mass spectrometry, high-performance liquid chromatography (HPLC), gas chromatography-mass spectrometry (GC-MS), and enzyme assays (23,24). The diagnosis of IEM can be broadly divided into the following approaches:

Screening Tests

These tests are developed so that abnormal levels of metabolic biomarkers can be detected in the blood and urine sample before the manifestation of the disease. Thus, screening tests are important tools for the primary prevention of IEM. The diseases are detected in their latent asymptomatic stages, facilitating intervention and leading to improved outcomes (25). Medical intervention at an asymptomatic stage may lead to the slow progression of the disease (26) and prevent long-term or life-threatening consequences (27). Therefore, the screening tests of newborns should be made an absolute necessity with the same reliable and valid reports (28). Newborn screening programs have shown dramatic improvements in IEM outcomes. It has improved the mortality rates in cases of primary immune deficiencies (29), medium-chain acyl-CoA dehydrogenase deficiency (30), and cases of cystic fibrosis (31). The newborn screening sometimes gives wrong reports, especially in the cases of premature birth and babies who have a low birth weight (32,33).

Diagnostic Investigations

The biochemical diagnosis depends on identifying abnormally high levels of substrates or by-products arising from pathways upstream of the enzymatic blockage. The lower levels of products or the downstream metabolites of the enzymes can be detected as well (34). Proper diagnosis relies on the performed metabolic investigations that can lead to proper treatment of the disease (35,36). The severity and the symptomatic nature determine the applied diagnostic investigation. The investigations to detect IEM should include tests that detect the level and type of toxic substances, and the degree and nature of the affected system. This is generally decided by targeted mass spectrometry (MS)-based metabolite assays (34,37,38).

Metabolomics Approach for the Diagnosis of IEMs

The metabolomics approach reflects the biochemical status and thus the current phenotype of living organisms (39,40). The diagnosed compounds are catabolic and anabolic pathway metabolites, environmental factors, small molecules that act as regulators, microbial metabolites, and epimetabolites (41-43). Every change in a genetic level (e.g., mutations, single nucleotide polymorphism, and changes in gene expressions) is reflected in metabolism, and the true cellular phenotype is reflected accordingly. Metabolomics thus gives a clear picture of the insights of diseases and identifies novel biomarkers and the impact of the metabolism of drugs and its effects in vivo (44,45).

Metabolomics is mainly analyzed using MS and nuclear magnetic resonance (NMR) spectroscopy (45). Screening by mass spectroscopy is performed either by direct sample injection to the ionization source of the mass spectrometer or by gas chromatography (GC) or liquid chromatography (LC) before MS. The prior application of GC or LC reduces the complexity of the mixtures before MS (46). GC-MS and LC-MS are well suited to separate isomers, and detect and quantify the compounds compared to NMR or direct MS (47). Chromatographic separation helps in the identification of the compounds and yields additional information about the metabolites. The most common method is LC-MS, which is used for both polar and non-polar compounds. GC-MS is employed for the analysis of volatile metabolites. The analytical sensitivity and sample throughput of the metabolites are further improved by the introduction of tandem MS (MS/MS) and ultrahigh-performance LC. High-resolution MS (HRMS) has a mass sensitivity and accuracy of less than ng/L (48). Samples such as dried blood spots can be generated as thousands of detected metabolic signals in HRMS. In metabolomics, MS/MS is the principle approach of IEM screening because of its low sample volume requirement, high sensitivity and

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specificity, and rapid turnover. The magnetic property of the atomic nuclei is measured by NMR spectroscopy. NMR measures far few metabolites per sample than MS, is less sensitive than MS, and is less widely used accordingly. However, NMR is non-invasive in nature, fast, and reproducible. The structural and stereochemical insights of the isolated compounds can be obtained from NMR (49).

The analyses of metabolomics are divided based on two approaches (targeted and untargeted metabolomics). Targeted metabolomics looks at specific groups of compounds and analyzes them using internal standards for the reference value, while untargeted metabolomics deals with all known and unknown compounds and analyzes as many samples as possible (50-52). Considering a specific disease, targeted metabolomics detects the compounds that are directly linked to the disrupted enzyme, whereas untargeted metabolomics detects all the possible metabolites that are altered directly or in some other pathways due to the disrupted enzyme (53,54).

In specific targeted metabolomics, 10-100 metabolites are selected as targets in LC-MS/MS or direct MS/MS for the diagnosis of a specific disease. The fragment ions of the metabolites are detected and quantified using internal standards. GC-MS is employed in single-ion monitoring, and LC-triple quadrupole MS and LC-quadrupole linear ion trap MS are utilized in multi-reaction monitoring. The disadvantages of targeted metabolomics are as follows:

- The cost of internal standards increases with targeted metabolomics.
- Complexity in the analysis of data increases with targeted metabolomics.
- The risk of overlooking metabolic responses in other pathways is increased.
- The selective isolation of a group of metabolites may itself be wrong.
- Lack of specificity to classify the IEM varieties.

On the other hand, the advantages of targeted metabolomics are:
- Targeted metabolomics with pre-specified mass spectrometer conditions and internal standards helps in better quantification.
- The baseline levels of metabolites for defining healthy versus altered states can be established, and interlaboratory comparison becomes easier.
- Metabolites are identified from the applied internal standards and the specificity of MS/MS.

In untargeted metabolomics, all the ions within a certain mass range are detected in LC-MS/MS, and all possible metabolites are identified as well. The disease phenotypes are characterized based on the signal intensities of both known and unknown metabolites. The internal standards, normalizations, and quality controls help in the quantification of the metabolites. GC-MS (full scan),

LC-orbital ion trap MS, and LC-quadrupole time-of-flight MS are used for quantification. The disadvantages of untargeted metabolomics include:
- The definition of "normal metabolite levels" does not stand at the level of a population as the absolute quantification of the metabolites could not be performed.
- The normalized signal intensities are not robust enough.
- Comparison can only be performed based on different groups within the study.
- There is no fixed and valid data processing parameter and keeps changing with different software taken into consideration.
- There is no standard protocol or parameter for the identification of compounds.

On the other hand, the advantages of diagnosis using untargeted metabolomics are as follows:
- Novel metabolites can be discovered from the broader provided coverage.
- All metabolites in the samples detectable using the analytical techniques are covered.
- Signals for more than 1000 metabolites can be obtained.
- The overall genomic and environmental interaction leading to particular phenotypes can be identified.
- Cost does not increase with the increase in the number of metabolites.

Several studies have compared targeted and untargeted metabolomics approaches. Compounds such as 3-mesulfateamine sulfate, dopamine 3-O-sulfate, and vanillyl mandelate are not detected in the targeted approach, while the untargeted approach can detect and analyze differences between the deficiencies of aromatic amino acid decarboxylase from the elevation of drug-induced metabolites (55). Targeted metabolomics often provides uncertain results in cases of borderline disease categories (56). The targeted approach also gives much more false positives due to the low cut-off values kept in the screening to avoid missing cases (57-59). The untargeted metabolomics approach identified novel compounds that are altered in urea cycle disorders (UCD). The compounds are responsible for X-linked UCD and ornithine transcarbamylase deficiency in females. Thus, the untargeted approach helped in identifying metabolites that are responsible for long-term UCD complications in addition to known UCD biomarkers. The specificity was also extremely high as many metabolites were not detected in normal cases but in diseased conditions (60). However, a study on urine and cerebrospinal fluid IEM demonstrated a good correlation of amino acid measurement between targeted and untargeted metabolomics approaches, and the only difference was tryptophan degraded in the targeted assay while quantified accurately in the untargeted assay (61).

The untargeted metabolomics approaches could reveal 7 novel isoforms of urinary lyso-Gb3 in patients with Fabry disease using globotriaosylceramide (Gb3) and globotriaosylsphingosine (lyso-Gb3) as target biomarkers in the urine and plasma of Fabry. These isoforms were not detected in healthy individuals. The untargeted metabolomics represented 100 % specificity, and no false positive cases were identified (62-65). Moreover, targeted metabolite screening sometimes leads to false diagnostic reports and thus inappropriate treatment, as in the case of arginase deficiency (66). The untargeted approach revealed that more than 30 pathways are altered due to arginase deficiency which is linked to guanidino compounds (67).

Treatment and Management of the Disease

DDIEM is a drug database for IEM. This database contains a complete list of treatment options against each of the IEMs with the mode of action of the drugs, the phenotypes being corrected, along with evidence type and references for the same (68). The drugs used for specific cases of IEM and their potential can be easily studied from the database in cases of further research and advancement toward treating a particular case of IEM.

Patients with IEM may appear normal but can deteriorate to life-threatening conditions. Specific therapies and illness protocols need to be followed for the patients' disease management. The primary protocols to be followed for the management of IEM are as follows:

Hydration Maintenance

Keeping hemodynamic stability is highly important for neonates, infants, or children with IEM. Patients are treated with the administration of intravenous fluid containing 10% dextrose solution with 75 mmol/L of sodium. In addition, +/- 20 mmol/L of potassium can be started to reduce exposure to toxic nutrients or the catabolic state. Cardiac overflow is avoided by the careful monitoring of fluid replacement for the first 48 hours.

Electrolyte imbalance, metabolic acidosis, and anabolic state promotion also need to be performed gradually based on the therapeutic requirements of the disease condition of IEM.

Nutrition

The nutritional management of the patient is extremely vital in the cases of IEM. Patients who are in sepsis or are hemodynamically unstable cannot be fed by mouth in the initial one or two days to avoid further exposure to toxic metabolites. Total parenteral nutrition is preferred due to intestinal intolerance (69). The use of invasive techniques or high glucose/energy is required for immediate detoxification. On being stable, oral food intake is preferred, and the diet should be high-glucose, low-protein, carbohydrate-restricted, and with/without lipid restriction.

Removal of Toxin

Patients with acute metabolic toxins circulating in their bloodstream, including UCD or branched chain organic acidurias, may require to remove the toxin by extracorporeal measures. The procedures for toxin removal are venovenous hemodiafiltration or hemodialysis and peritoneal dialysis.

Enzyme Therapy

Enzyme-focused treatment to treat IEMs that occur due to the deficiency of enzymes has been practiced for decades for the management of IEM. The two strategies of enzyme-based treatment are enzyme replacement therapy and enzyme substitution therapy. In replacement therapy, the deficiency is directly replaced to improve the metabolic process of the body. In substitution therapy, a new enzyme is introduced so that the physiological defect is bypassed, and the accumulated substrate is converted to a harmless product using an alternative process of metabolization (70,71).

Table 1 lists enzymes that are used for enzyme replacement therapy, the year of approval, their generic

Table 1. Approved Enzymes for Enzyme Replacement Therapy

Enzyme	Year	Generic Name	Disease	Reference
Adenosine deaminase	2000	Pegademase	ADA deficiency	(72)
Alpha-Galactosidase A	2003	Agalsidase beta	Fabry	(73)
α-L-iduronidase	2003	Laronidase	Hurler and MPS I	(74)
N-acetylgalactosamine-4 sulfatase	2005	Galsulfase	Maroteaux-Lamy and MPS VI	(75)
Iduronate-2-sulfatase	2006	Idursulfase	Hunter and MPS II	(76)
Alpha1-antitrypsin	2009-2010	Alpha1-Proteinase inhibitor	A1AT deficiency	(77)
β-glucocerebrosidase	2010	Velaglucerase alfa	Gaucher	(78)
Acid alpha-glucosidase	2010	Alglucosidase alfa	Pompe	(79)
N-acetylgalactosamine-6 sulfatase	2014	Elosulfase alfa	Morquio syndrome A and MPS IVA	(80)
Lysosomal acid lipase	2015	Sebelipase alfa	Wolman and LAL deficiency	(81)

names, and the IEM for which they have been approved in the last two decades.

Substrate Reduction and Product Supplementation Therapy

Substrate reduction therapy (uses a small molecule as a drug that can decrease the accumulation of toxic substances that generally occur due to defects in substrate degradation. Substrate reduction therapy targets the pathway upstream of the IEM defect. It helps in maintaining the balance between the production and degradation of specific substrates in a metabolic pathway (82). Some other pathogenesis of IEM also occurs due to insufficient production or insufficiency in the recycling of essential substances. Thus, in such cases, the supplementation of the products is essential to avoid the deficiency of the compound. One of the most common examples is phenylketonuria where tyrosine cannot be synthesized from phenylalanine due to a deficiency of phenylalanine hydroxylase. The supplementation of tyrosine is recommended in such a case (83).

Gene Therapy

As IEMs are single-gene disorders, gene therapy for the replacement of mutated genes should reverse the pathogenesis of IEM. However, gene therapy has its disadvantages of cellular toxicity, affected immune response, and oncogenesis. Extensive clinical development has been performed in gene replacement therapies, of which the most successful has been the CRISPR/Cas9 system of editing, which is the most potent method of gene therapy (84).

Chaperone Therapy

Chaperones are small molecules that bind to the misfolded proteins to stabilize them. Chaperone proteins also help in the proper trafficking of the misfolded protein from the endoplasmic reticulum to the lysosome where the accumulated toxic substrates are metabolized. The chaperones used in the management of IEM have some advantages. They are non-immunogenic and their small size helps in easier diffusion and more bioavailability. In addition, oral medication instead of intravenous infusion and larger tissue penetration are possible in this therapy (85).

Cell or Organ Transplantation

The principal target of the therapeutic strategy of IEM is liver transplantation; as it is the main site of intermediary metabolism (86), hematopoietic stem cell, and bone marrow; as it allows healthy cells to colonize the bone marrow where the enzyme is deficient and helps enzyme replenishment (87).

Conclusion

The understanding of the pathophysiology of IEM has increased in the last decade, making the early detection and treatment of IEM highly easier than imagined. Screening helps in the treatment of patients before disease manifestation, improving the outcomes. Combination therapy can further improve IEM disease management. More multi-centered clinical trials are necessary for the development of evidence-based treatment strategies.

Competing Interests
The authors declared that there is no conflict of interests.

Ethical Approval
Not applicable.

Informed Consent
The study was a review and thus required no informed consent from the participants.

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