ICON Journal of Applied Medical Sciences
Volume 01 | Issue 02 | 2025
Journal homepage: https://iconpublishers.com/icon-j-app-med-sci/

DOI: 10.5281/zenodo.17174310

Research Article

Pathophysiology and Patterns of Inborn Errors of Metabolism

[1]Iwuamadi Ojiugo C., [1]Obasi Miriam O, [1]Oparaocha Divine Gift, [1]Okafor Onyeka, [1]Alozie Okezie and Johnkennedy Nnodim*

[1]Department of Medical Laboratory Science, Imo State University Owerri, Nigeria.

Corresponding author: Johnkennedy Nnodim
Department of Medical Laboratory Science, Imo State University, Owerri, Imo State, Nigeria.

Received Date : 10 Aug. 2025

Published Date: 22 Sept. 2025

Abstract

Rare genetic illnesses known as inborn errors of metabolism (IEMs) are brought on by abnormalities in enzymes or transporters that interfere with metabolic processes. With broad clinical ramifications, these disturbances may result in hazardous metabolite accumulation or critical product deficit. carried out a narrative assessment of peer-reviewed literature from 2010 to 2025, concentrating on the pathophysiological causes, metabolic routes, and clinical patterns of IEMs. Recent developments in tandem mass spectrometry, genomic diagnostics, and therapeutic interventions were highlighted in the databases that were searched, which included PMC and PubMed. With excellent sensitivity and specificity, tandem mass spectrometry (MS/MS) enables the simultaneous detection of more than 25 IEMs. Positive predictive value is increased through integration with next-generation sequencing (NGS). Critical information about the mutation spectrum, incidence, and neurodevelopmental impact of methylmalonic acidemia (MMA) has been uncovered by recent study. The accuracy of diagnosis is further enhanced by confirmatory biomarker-based tests. New approaches to treating IEM, such as RNA-based and AI-guided diagnostics, have the potential to revolutionize the field. Early detection and characterisation of IEMs have been significantly enhanced by developments in MS/MS and genomic/metabolomic platforms. Results are greatly improved by early intervention, particularly in circumstances like MMA. Future studies should focus on AI-driven diagnostics, tailored treatments, and the incorporation of genomes in screening.

Keywords: Genetic abnormalities, metabolic pathways, enzyme deficiencies, Inborn errors.

Introduction

Mutations that affect enzymes or transporters involved in particular metabolic pathways result in inherited genetic illnesses known as inborn errors of metabolism (IEMs). Although there are different forms of inheritance, these monogenic disorders usually follow an autosomal recessive inheritance pattern, which was first characterized by Sir Archibald Garrod in the early 20th century. Enzymatic malfunction that results causes a build-up of toxic substrates or a shortage of vital products, which ultimately damages cells and tissues [1]. Despite the rarity of each IEM alone, their combined incidence is substantial, ranging from 1 in 800 to 2,500 live births, depending on the demographic and screening methods used. IEMs can emerge clinically in a wide range of ways, from immediate newborn crises to late-onset or chronic illnesses that impact several organ systems [2]. The diversity of these conditions is a reflection of the intricacy of human metabolism, which includes interrelated processes including mitochondrial activity, fatty acid oxidation, amino acid metabolism, and glucose

metabolism. The development of targeted therapeutics, efficient care, and early diagnosis all depend on an understanding of the pathophysiological causes and categorization patterns of IEMs. This review offers a systematic methodology for classifying and analyzing IEMs by examining their metabolic foundation, phenotypic variability, and clinical implications [3].

Categorization and Trends of Inborn Metabolic Errors

Traditionally, IEMs are categorized according to the kind of metabolic pathway they impact, such as:

(a) Disorders of Carbohydrate Metabolism

These include disorders including inherited fructose intolerance, galactosemia, and glycogen storage diseases. Hepatomegaly, lactic acidosis, and hypoglycemia are caused by disruptions in glucose homeostasis caused by deficiencies in enzymes such as aldolase B or glucose-6-phosphatase.

(b) Disorders of Amino Acid Metabolism

Prominent examples include homocystinuria, phenylketonuria (PKU), and maple syrup urine disease (MSUD). PKU is caused by a lack of phenylalanine hydroxylase, which, if left untreated, can lead to a neurotoxic buildup of phenylalanine and intellectual impairment.

(c) Acidurias Organic

Characterized by the buildup of organic acids brought on by blockages in enzymes involved in the catabolism of amino acids. Examples include propionic acidemia and methylmalonic acidemia (MMA), which frequently manifest in neonates as severe metabolic acidosis [4].

(d) Disorders of Fatty Acid Oxidation (FAODs)

Energy deficiencies, particularly during fasting, are caused by defects in mitochondrial β-oxidation enzymes, such as medium-chain acyl-CoA dehydrogenase (MCAD). Clinical manifestations include abrupt death, lethargy, and hypoketotic hypoglycemia.

(e) Disorders of the Urea Cycle (UCDs)

These include hyperammonemia caused by deficiencies in ammonia detoxification. The most prevalent UCD, ornithine transcarbamylase deficiency, can result in neonatal encephalopathy.

Pathophysiological Mechanisms

The accumulation of upstream metabolites is the main pathogenic mechanism in many IEMs. For example, in PKU, too much phenylalanine overloads the big neutral amino acid transporters, which hinders the uptake of amino acids in the brain and the production of neurotransmitters [1].

Some IEMs cause essential chemicals to be synthesized insufficiently. For instance, reduced methionine and associated methylation products may result from homocystinuria, which could impact myelination and DNA synthesis. ATP generation is hampered by disorders like FAODs, especially when catabolic stress is present. This results in impaired heart and muscle function as well as heightened vulnerability to crises associated with fasting.

Pathologies That Are Secondary Organ dysfunction and structural alterations can be caused by a chronic metabolic imbalance. For example, lysosomal glycogen buildup results in myopathy and cardiomyopathy in glycogen storage disease type II (Pompe disease).

Diagnostic Hints and Clinical Patterns

IEMs can appear in people of all ages:

Neonatal Onset: Organic acidurias or urea cycle abnormalities are frequently indicated by rapidly progressing symptoms such as lethargy, vomiting, convulsions, and coma [4] Infancy and Childhood Onset: Manifestations include recurring metabolic decompensations, developmental delay, and failure to thrive. Adult or Late-Onset Forms: may show signs of cardiomyopathy, neuropsychiatric problems, or episodic weakness [5]. Syndromes in Clinical Practice arranged according to defining characteristics, like:

Neurological Syndromes: Manifested in lysosomal storage diseases and amino acidopathies.

Hepatic syndromes: tyrosinemia and galactosemia are common.

Cardiomyopathies: Often linked to storage disorders and FAODs.

Hypoglycemia or metabolic acidosis: These conditions are significant diagnostic triggers and warning signs for numerous IEMs.

Progress in Screening and Diagnosis

Screening for newborns (NBS) NBS has been transformed by the advent of tandem mass spectrometry (MS/MS), which makes it possible to identify several IEMs from a single blood spot early on [1, 2] The predictive value and diagnostic accuracy have been further improved by integration with next-generation sequencing (NGS) [5]. When diagnosing atypical or novel IEMs, whole-genome sequencing (WGS) and whole-exome sequencing (WES) have become essential techniques. In order to facilitate diagnostic and therapeutic monitoring, metabolomics provides a functional snapshot of the biochemical phenotype [3].

Strategies for Management

Dietary Adjustments mainstay for conditions such as galactosemia, MSUD, and PKU (low-phenylalanine diet). Normal development can be promoted and serious issues can be avoided with early nutritional changes. High cofactor dosages can correct certain enzyme abnormalities. For instance, biotin in multiple carboxylase insufficiency and vitamin B6 in homocystinuria [6] Treatment with Drugs includes gene or RNA-based therapeutic methods that are undergoing clinical assessment, enzyme replacement therapy (ERT) for lysosomal storage diseases, and nitrogen scavengers for UCDs [7]. 6.4. Emergency Management In order to eliminate hazardous metabolites from acute metabolic decompensations, quick action is needed using intravenous glucose, ammonia scavengers, and occasionally dialysis.

The knowledge of IEMs is growing as a result of ongoing investigations into the genetic and epigenetic control of metabolic pathways. There is new hope for targeted diagnosis and curative therapy thanks to machine learning technologies, gene editing, and personalized medicine [8].

Conclusion

A broad category of hereditary disorders with intricate pathophysiological pathways are known as inborn errors of metabolism. Effective management depends on early detection, which is made possible by molecular diagnostics and neonatal screening. Many IEMs are still difficult to treat because of their multisystem involvement and unpredictability. In order to enhance results and provide curative treatments, ongoing research is crucial.

References

1. Medical Advisory Secretariat. Newborn screening for inborn errors of metabolism: an evidence-based analysis. Ont Health Technol Assess Ser. 2011;11(2):1-116.
2. Burlina A, Margherita R, Sabrina M, Sara B, Carla C, Carlo D, et al. Expanded newborn screening in Italy using tandem mass spectrometry: two years of national experience. Int J Neonatal Screen. 2020;6(2):30.
3. Yang Y, Wang L, Wang B, Liu S, Yu B, Wang T. Application of next-generation sequencing following tandem mass spectrometry to expand newborn screening for inborn errors of metabolism: a multicenter study. Front Genet. 2019;10:86.
4. Zhou X, Cui Y, Han J. Methylmalonic acidemia: current status and research priorities. Intractable Rare Dis Res. 2018;7(2):73-8.
5. Chen T, Gao Y, Zhang S, Wang Y, Sui C, Yang L. Methylmalonic acidemia: neurodevelopment and neuroimaging. Front Genet. 2023;17:1110942.
6. Didehvar N, Ormazabal A, Del Toro M, García-Cazorla Á, Navarro-Sastre A, López RM. Second-tier testing in newborn screening for propionic and methylmalonic acidemias. Int J Neonatal Screen. 2022;8(1):5.
7. Berraondo P, Martini PGV, Avila MA, Fontanellas A. Messenger RNA therapy for rare genetic metabolic diseases. Gut. 2019;68(7):1323-30.
8. Iqbal MJ, Javed Z, Sadia H, Qureshi IA, Irshad A, Ahmed R, et al. Clinical applications of artificial intelligence and machine learning in cancer diagnosis: looking into the future. Cancer Cell Int. 2021;21(1):270.