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GENETIC BASIS, CLINICAL MANIFESTATIONS, AND MODERN DIAGNOSTIC APPROACHES TO INHERITED METABOLIC DISEASES IN CHILDREN

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ABSTRACT: Inherited metabolic diseases (IMDs), also known as inborn errors of metabolism, comprise a heterogeneous group of genetic disorders caused by defects in enzymes, transport proteins, receptors, cofactors, or other components of cellular metabolic pathways. Although each individual condition is rare, collectively these diseases represent an important cause of neonatal and pediatric morbidity, neurodevelopmental impairment, recurrent metabolic decompensation, organ dysfunction, and preventable mortality. The clinical spectrum ranges from acute life-threatening neonatal encephalopathy to slowly progressive neurological, hepatic, cardiac, muscular, or multisystem disease. Early recognition is therefore essential because a considerable number of IMDs are treatable when therapy is initiated before irreversible tissue damage occurs. Modern diagnostic strategies combine careful clinical assessment with biochemical tests, tandem mass spectrometry, chromatography, enzymatic assays, targeted molecular testing, next-generation sequencing, whole-exome or whole-genome sequencing, and expanded newborn screening. This thesis summarizes the genetic basis of common pediatric IMDs, their major clinical manifestations, and contemporary diagnostic approaches, with emphasis on early detection and the integration of biochemical and molecular-genetic methods into pediatric practice [1-8].

Keywords: inherited metabolic diseases, inborn errors of metabolism, children, genetic mutations, newborn screening, tandem mass spectrometry, molecular diagnostics, next-generation sequencing.

INTRODUCTION

Inherited metabolic diseases are mainly monogenic disorders in which pathogenic variants alter the structure or function of proteins involved in metabolism. The classical concept focuses on enzyme deficiencies that cause accumulation of toxic substrates, deficiency of essential products, formation of abnormal metabolites, or impairment of cellular energy production. Contemporary classifications are broader and also include defects of intracellular trafficking, organelle biogenesis, cofactor metabolism, transport systems, and regulatory pathways [1,2,6]. Most IMDs are inherited in an autosomal recessive manner; however, autosomal dominant, X-linked, and mitochondrial inheritance patterns are also encountered. Consanguinity, founder effects, and population-specific variants can influence disease prevalence, making genetic counseling and family-based testing especially important in pediatric practice [1-3].

The major diagnostic difficulty is the nonspecific nature of early symptoms. Poor feeding, vomiting, lethargy, seizures, hypotonia, jaundice, developmental delay, hepatomegaly, hypoglycemia, acidosis, hyperammonemia, or unexplained deterioration during infection may initially resemble sepsis or common pediatric disorders. A high index of suspicion is therefore required. The rapid development of biochemical technologies and genomic sequencing has transformed the diagnostic pathway from

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prolonged sequential testing to integrated, often parallel, biochemical and molecular investigation [4,6-8].

MAIN PART

The genetic basis of IMDs is determined by pathogenic variants in genes encoding metabolic enzymes, transporters, structural proteins, cofactors, or proteins responsible for mitochondrial and lysosomal function. Phenylketonuria, for example, is most commonly caused by pathogenic variants in the PAH gene, leading to deficient phenylalanine hydroxylase activity and accumulation of phenylalanine. Untreated disease may result in severe intellectual disability, microcephaly, seizures, behavioral abnormalities, and hypopigmentation. Galactosemia is usually associated with GALT deficiency; exposure to galactose may provoke vomiting, jaundice, hepatocellular injury, hypoglycemia, cataracts, and sepsis-like deterioration during the neonatal period. Maple syrup urine disease is caused by defects in the branched-chain alpha-ketoacid dehydrogenase complex, resulting in accumulation of branched-chain amino acids and their ketoacids, with encephalopathy, abnormal tone, feeding difficulties, and characteristic odor in severe neonatal forms [1,2,6].

Organic acidemias such as methylmalonic and propionic acidemia are important causes of recurrent metabolic crises in infancy. Children may present with vomiting, dehydration, metabolic acidosis, ketosis, hyperammonemia, neutropenia, cardiomyopathy, or neurological dysfunction. Urea-cycle disorders differ because hyperammonemia may develop without prominent metabolic acidosis. In neonates, rapidly increasing ammonia concentrations can lead to respiratory alkalosis, cerebral edema, seizures, coma, and death. Fatty-acid oxidation disorders frequently become apparent during fasting or intercurrent infection and may cause hypoketotic hypoglycemia, liver dysfunction, rhabdomyolysis, cardiomyopathy, or sudden unexpected deterioration. Mitochondrial disorders are particularly heterogeneous and may affect the brain, skeletal muscle, heart, liver, vision, hearing, and endocrine organs [4,6].

Lysosomal storage diseases form another important group. Defects in lysosomal enzymes or associated proteins cause progressive accumulation of macromolecules within cells. Depending on the specific disorder, clinical manifestations may include hepatosplenomegaly, skeletal abnormalities, coarse facial features, developmental regression, cardiomyopathy, neuropathy, and visual or hearing impairment. Because several lysosomal diseases now have disease-modifying therapies, including enzyme replacement and substrate-reduction strategies, early diagnosis has direct therapeutic relevance [1,3,6].

Clinical assessment should begin with detailed history and physical examination. Important clues include parental consanguinity, unexplained sibling deaths, recurrent neonatal losses, similar symptoms in relatives, episodic deterioration triggered by fasting or infection, developmental regression, unusual odors, organomegaly, cataracts, cardiomyopathy, dysmorphic features, or a combination of neurological and visceral abnormalities. Initial laboratory evaluation in a critically ill child should include blood glucose, electrolytes, blood gas analysis, lactate, ammonia, liver function tests, creatine kinase, ketones, complete blood count, and urinalysis. The pattern of abnormalities may rapidly narrow the differential diagnosis [2,4,6].

Modern biochemical diagnostics are based on the measurement of disease-specific metabolites. Tandem mass spectrometry can simultaneously quantify multiple amino acids and acylcarnitines from a small dried-blood-spot sample and is therefore widely used in newborn screening. Gas chromatography-mass spectrometry is particularly valuable for urinary organic-acid analysis, while high-performance liquid chromatography and related platforms can be used for amino acids,

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carbohydrates, and other metabolites. Enzyme activity assays remain important for selected lysosomal, mitochondrial, and other metabolic diseases. In many cases, biochemical confirmation is essential even when a genetic variant has been identified, because it demonstrates functional consequences and helps distinguish pathogenic variants from incidental findings [5-8].

Newborn screening is one of the most effective approaches for preventing irreversible complications of selected IMDs. Screening programs are designed to identify affected infants before symptoms develop, enabling early dietary treatment, cofactor supplementation, avoidance of fasting, pharmacological therapy, or specialized follow-up. Classical examples include phenylketonuria and congenital disorders detected through biochemical markers. Expanded screening using tandem mass spectrometry can identify multiple aminoacidopathies, organic acidemias, and fatty-acid oxidation defects from a single blood specimen. The exact panel should be adapted to national epidemiology, available treatment, laboratory capacity, and health-system resources [1,4,6].

Molecular-genetic diagnostics has become a central component of contemporary practice. Targeted testing is appropriate when the biochemical phenotype strongly suggests a specific disorder. Gene panels are useful when multiple genes cause overlapping phenotypes, while whole-exome sequencing can identify coding variants across thousands of genes. Whole-genome sequencing additionally evaluates noncoding regions, structural variants, and some genomic rearrangements. Rapid genomic sequencing is increasingly applied in critically ill neonates and children with unexplained multisystem disease, where shortening the diagnostic interval may alter treatment, prognosis, and family counseling. Nevertheless, genomic data should be interpreted together with clinical and biochemical findings, because variants of uncertain significance and secondary findings can complicate interpretation [6-8].

A combined diagnostic model is therefore preferred. Biochemical profiling identifies the disturbed pathway; molecular testing defines the genetic defect; segregation analysis confirms inheritance within the family; and functional studies resolve uncertain variants when necessary. Once the diagnosis is established, genetic counseling should explain recurrence risk, carrier status, reproductive options, and the possibility of prenatal or preimplantation genetic testing. This family-centered approach is particularly important for autosomal recessive disorders, in which parents are usually asymptomatic carriers and the recurrence risk for each pregnancy is typically 25% [1-3].

CONCLUSION

Inherited metabolic diseases in children are genetically diverse conditions with highly variable clinical manifestations. Their early symptoms are often nonspecific, but certain combinations - especially unexplained neurological deterioration, recurrent vomiting, metabolic acidosis, hyperammonemia, hypoglycemia, hepatomegaly, cardiomyopathy, developmental regression, or crises precipitated by fasting and infection - should immediately raise suspicion of an IMD. Contemporary diagnosis requires integration of clinical assessment, routine biochemical tests, specialized metabolite analysis, enzyme assays, newborn screening, and molecular-genetic methods. Tandem mass spectrometry and next-generation sequencing have substantially increased diagnostic speed and accuracy, while rapid genomic testing is becoming increasingly important in critically ill children. Early detection is clinically significant because timely dietary, pharmacological, or disease-specific therapy may prevent irreversible neurological and systemic complications. Strengthening newborn screening, access to molecular diagnostics, and medical-genetic counseling can therefore improve outcomes for affected children and their families [1-8].

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