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Vitamin-dependent genetic disorders of childhood: A comprehensive review

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Abstract
Vitamin-dependent genetic disorders are inherited conditions that arise due to defects in the metabolism or utilization of specific vitamins, leading to various health problems, often presenting in childhood. These disorders result from mutations in genes encoding enzymes or transport proteins involved in vitamin pathways. This review explores the pathophysiology, clinical manifestations, diagnostic strategies, and therapeutic approaches for major vitamin-dependent genetic disorders, emphasizing the importance of early detection and intervention. Vitamin-responsive conditions may arise from acquired deficiency states or inherited defects in the metabolic pathways that lead to vitamin dependence. It is critical that pediatricians in practice have a comprehensive understanding of these potentially treatable conditions.

Keywords: Vitamin, disorders, childhood, review, therapy, supplementation

Introduction

Vitamins are essential micronutrients necessary for numerous physiological functions, including enzyme cofactor roles, antioxidant activity, and cellular metabolism. Genetic mutations affecting vitamin metabolism can lead to a spectrum of disorders with significant clinical implications, particularly in pediatric populations. This review focuses on disorders related to vitamins B6 (Pyridoxine), B12 (Cobalamin), B7 (Biotin), D, and E, providing a comprehensive overview of their pathophysiology, clinical presentation, diagnostic approaches, and management strategies. Vitamin-dependent genetic disorders are uncommon yet significant contributors to acute metabolism decompensations and predominantly symptoms of neurological disorders. Supplemental vitamin intake can avoid or alleviate symptoms, as well as enhance outcomes. The following discussion of vitamin-dependent genetic diseases presents medical professionals with a pragmatic description of the most prevalent signs, diagnostic monitoring, and medical care with the goal to increase their awareness and comprehension of these potentially curable illnesses. Vitamins are organic dietary substances that, in minute amounts, are necessary for the correct functionality of the human body. They function as cofactors for numerous enzymatic reactions the majority of the time. Vitamin-responsive conditions may arise from acquired deficiency states or inherited defects in the metabolic pathways that lead to vitamin dependence. As one of the most metabolically active systems in the body, the nervous system manifests vitamin-responsive conditions earlier and more severely. A concise overview of the diverse vitamin-responsive conditions in pediatric neurology will be provided in this review. An extensive variety of inherited and acquired disorders respond to vitamins and cofactors; for further information, the reader is directed to a selection of recent, high-quality articles [1].

In many countries, where malnutrition is pervasive and vegetarianism is predominant, vitamin deficiency is extremely prevalent; therefore, early detection is critical. Prompt treatment of inherited defects has been associated with decreased morbidity and mortality rates, as well as enhanced long-term neurocognitive outcomes. In this review, numerous vitamin-responsive conditions in pediatric neurology will be discussed. Thiamine deficiency manifests as beriberi in infants and causes Wernicke's encephalopathy and Korsakoff psychosis in adults. Biotin thiamine-responsive basal ganglia disease is characterized by neuroregression and distinctive neuroimaging features of basal ganglia involvement. It is caused by a deficiency in thiamine transporter [2]. Extensive administration of biotin and thiamine induces this condition.

Riboflavin, an enzyme that participates in the synthesis of mitochondrial energy, is supplemented in a number of mitochondrial metabolic conditions. Progressive pontobulbar palsy is Brown-Vialetto-Van Laere syndrome, which is brought on by a deficiency in riboflavin transporters that are sensitive to high concentrations of riboflavin. Pyridoxine responsive epilepsy is characterized by pharmacoresistant seizures in neonates and early infants. Biotinidase deficiency causes pharmacoresistant seizures in the same manner, but in addition to the typical cutaneous symptoms of rash and seborrheic dermatitis [3, 4]. Both are epileptic encephalopathies, and pyridoxine, biotin, and folinic acid must be tried in infants presenting with epilepsy who do not respond to conventional AEDs. Vitamin B12-responsive conditions may encompass deficiency states, inherited disorders of homocysteine and cobalamin metabolism, and peripheral neuropathy, all of which manifest as the syndrome of infantile tremor syndrome (Comprising megaloblastic anemia, tremors, and developmental delay or regression). The distinction between these disorders is established according to laboratory parameters such as serum methylmalonic acid levels, homocysteine levels, and clinical phenotype. Megadoses of multivitamins and vitamin B12 induce a profound improvement in infantile tremor syndrome [5]. A deficiency in vitamin E results in ataxia; additional vitamins that may induce neurological symptoms are vitamin K (Central nervous system bleeding) and vitamin C (pseudoparalysis).

Classification and Pathophysiology
Vitamin B6 (Pyridoxine)
Pathophysiology
Vitamin B6 is crucial for amino acid metabolism, neurotransmitter synthesis, and the function of glycogen phosphorylase. Pyridoxine-dependent epilepsy (PDE) is caused by mutations in the ALDH7A1 gene, which encodes antiquitin. Antiquitin deficiency leads to the accumulation of α-aminoadipic semialdehyde, a neurotoxic intermediate, resulting in seizures [6].

Clinical Presentation
PDE typically manifests within the first few days of life with intractable seizures that are unresponsive to standard antiepileptic drugs but respond dramatically to pyridoxine administration. Other symptoms may include developmental delays, intellectual disability, and irritability.

Diagnosis and Treatment
Diagnosis is primarily based on the clinical response to pyridoxine and confirmed by genetic testing. Biochemical tests may show elevated levels of α-aminoadipic semialdehyde in urine or plasma. Treatment involves lifelong pyridoxine supplementation, which can significantly reduce seizure frequency and improve developmental outcomes.

Vitamin B12 (Cobalamin)
Pathophysiology
Vitamin B12 is essential for DNA synthesis, myelin formation, and red blood cell production. Disorders of cobalamin metabolism, such as methylmalonic acidemia (MMA) and homocystinuria, often result from mutations in genes like MMUT, MMAA, MMAB, and MTRR. These mutations impair the conversion of methylmalonyl-CoA to succinyl-CoA or homocysteine to methionine, leading to the accumulation of toxic metabolites [7].

Clinical Presentation
Children with cobalamin disorders may present with failure to thrive, developmental delays, hypotonia, metabolic acidosis, megaloblastic anemia, and neurological abnormalities, including seizures and cognitive impairment.

Diagnosis and Treatment
Elevated methylmalonic acid and homocysteine levels in blood and urine, along with low cobalamin levels, suggest a cobalamin disorder. Genetic testing confirms the diagnosis. Treatment involves vitamin B12 injections or high-dose oral supplementation, dietary restrictions (low-protein diet), and management of metabolic crises. Early treatment is crucial to prevent irreversible neurological damage.

Biotin (Vitamin B7)
Pathophysiology
Biotin is a cofactor for carboxylase enzymes involved in gluconeogenesis, fatty acid synthesis, and amino acid catabolism. Biotinidase deficiency, caused by mutations in the BTD gene, impairs the body's ability to recycle biotin from biocytin, leading to multiple carboxylase deficiencies [8].

Clinical Presentation
Symptoms typically appear in infancy or early childhood and include alopecia, skin rash, developmental delays, hypotonia, seizures, ataxia, and metabolic acidosis. If untreated, the condition can be fatal.

Diagnosis and Treatment
Newborn screening programs can detect biotinidase deficiency early. Diagnosis is confirmed by measuring biotinidase enzyme activity in serum and genetic testing. Lifelong biotin supplementation is highly effective, preventing symptoms and normalizing metabolic functions.

Vitamin D
Pathophysiology
Vitamin D regulates calcium and phosphate homeostasis, essential for bone mineralization. Hereditary vitamin D-resistant rickets (HVDRR) results from mutations in the VDR gene, leading to resistance to the biological effects of vitamin D, despite normal or elevated levels of the hormone.

Clinical Presentation
HVDRR typically presents in early childhood with growth retardation, bone pain, muscle weakness, hypocalcemia, and skeletal deformities such as bowed legs (Rickets).

Diagnosis and Treatment
Diagnosis involves clinical evaluation, biochemical tests showing hypocalcemia, elevated parathyroid hormone levels, and high-normal or elevated 1, 25-dihydroxyvitamin D levels, along with genetic testing for VDR mutations. Treatment includes high doses of calcitriol (active vitamin D) and calcium supplementation to manage symptoms and promote normal bone development.

Vitamin E

Pathophysiology

Vitamin E acts as a potent antioxidant, protecting cell membranes from oxidative damage. Ataxia with vitamin E deficiency (AVED) is caused by mutations in the TTPA gene, which encodes α-tocopherol transfer protein, essential for the incorporation of vitamin E into lipoproteins

Clinical Presentation

AVED presents in late childhood or adolescence with progressive ataxia, peripheral neuropathy, muscle weakness, and retinitis pigmentosa. Without treatment, it leads to severe neurological disability.

Diagnosis and Treatment

Diagnosis is based on clinical symptoms, low serum vitamin E levels, and genetic testing for TTPA mutations. High-dose vitamin E supplementation can halt disease progression and improve neurological symptoms.

Diagnostic Approaches

Accurate diagnosis of vitamin-dependent genetic disorders relies on a combination of clinical assessment, biochemical tests, and genetic analysis. Early detection through newborn screening programs is essential for conditions like biotinidase deficiency and certain forms of MMA, enabling prompt intervention.

Biochemical Tests

Biochemical tests are critical for detecting abnormalities in vitamin levels and related metabolites:

- **Blood and Urine Analysis:** Measuring specific metabolites such as methylmalonic acid, homocysteine, and α-aminoadipic semialdehyde can indicate disruptions in vitamin metabolism.
- **Enzyme Activity Assays:** Assessing enzyme activity, such as biotinidase activity in biotinidase deficiency, can confirm the diagnosis.
- **Vitamin Levels:** Measuring serum vitamin levels, such as vitamin E in AVED, helps identify deficiencies.

Genetic Testing

Genetic testing plays a crucial role in confirming the diagnosis and identifying specific mutations:

- **Targeted Gene Panels:** These panels test for known mutations associated with specific disorders.
- **Whole Exome Sequencing:** This approach can identify novel mutations and provide comprehensive genetic insights, particularly in cases where clinical and biochemical findings are inconclusive.

Therapeutic Strategies

The cornerstone of treatment for vitamin-dependent genetic disorders is vitamin supplementation, tailored to the specific deficiency. Additional strategies include dietary modifications, metabolic crisis management, and emerging therapies like gene therapy and enzyme replacement therapy.

Vitamin Supplementation

- **Pyridoxine (Vitamin B6):** Lifelong pyridoxine supplementation is essential for managing PDE, reducing seizure frequency and improving development.
- **Cobalamin (Vitamin B12):** Regular vitamin B12 injections or high-dose oral supplementation, combined with dietary management, are crucial for treating cobalamin disorders.
- **Biotin:** Lifelong biotin supplementation effectively prevents symptoms and normalizes metabolic functions in biotinidase deficiency.
- **Calcitriol (Active Vitamin D):** High doses of calcitriol and calcium supplementation manage HVDRR, promoting normal bone development and preventing skeletal deformities [9].
- **Vitamin E:** High-dose vitamin E supplementation halts disease progression and improves neurological symptoms in AVED.

Dietary Modifications

Dietary modifications are necessary to manage metabolic stress and prevent complications in certain disorders:

- **Low-Protein Diet:** For cobalamin disorders like MMA, a low-protein diet reduces the load on defective metabolic pathways, minimizing toxic metabolite accumulation.
- **Specialized Formulas:** In some cases, specialized formulas free of problematic metabolites are used to manage dietary intake effectively.

Management of Metabolic Crises

Immediate medical intervention is required to manage acute metabolic crises, particularly in disorders like MMA:

- **Intravenous Fluids and Electrolytes:** These stabilize metabolic imbalances.
- **Emergency Medications:** Medications such as carnitine and antibiotics may be used to manage specific crises.

Emerging Therapies

Research into novel therapies offers hope for improved management of these disorders:

- **Gene Therapy:** Experimental gene therapy aims to correct underlying genetic defects, potentially providing a permanent cure.
- **Enzyme Replacement Therapy:** This approach involves supplementing missing or deficient enzymes to restore normal metabolic functions.

Long-term Management

Effective long-term management of vitamin-dependent genetic disorders involves regular monitoring, adherence to treatment, and comprehensive care:

- **Regular Monitoring:** Periodic assessments of vitamin levels, metabolic markers, and clinical symptoms are essential to adjust treatment plans.
- **Multidisciplinary Care:** A team of specialists, including geneticists, neurologists, dietitians, and primary care providers, ensures holistic management of the child's health.
- **Patient and Family Education:** Educating families about the disorder, treatment adherence, and recognizing early signs of metabolic crises is crucial for optimal care [10, 11].

Conclusion

Vitamin-dependent genetic disorders, though rare, present significant challenges due to their potential severity and early onset. Advances in genetic testing and newborn screening have greatly improved early detection and treatment outcomes. Continued research into the underlying mechanisms and novel therapies holds promise for further improving the quality of life for affected individuals. Early diagnosis, appropriate supplementation, and comprehensive care are essential for managing these complex conditions and enabling affected children to lead healthier lives.

Conflict of interest

The author declares no conflict of interest

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