Review Article

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Disorders in Amino Acid Metabolism Associated with Seizures

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ABSTRACT

Seizures are a common presenting manifestation in children with amino acid metabolism disorders such as maple syrup urine disease (MSUD), nonketotic hyperglycinemia, sulfite oxidase deficiency, serine deficiency, and GABA-related disorders. In monoamine biosynthesis disorders, seizures are rare, but paroxysmal dystonia is often misdiagnosed as seizures. Metabolic changes, including amino acid turnover, have been noted during epileptogenesis and chronic epilepsy. Autophagy, a catabolic pathway crucial for maintaining tissue and organism homeostasis, is influenced by amino acids and plays a role in brain physiology and pathology, including epileptic disorders. Amino acid synthesis defects can cause neurological symptoms such as early-onset seizures, mental disability, and skin disorders. Besides neurological symptoms, amino acid metabolism disorders can impact other organ systems, resulting in various clinical manifestations. Early recognition and proper management of these disorders are vital for preventing long-term complications and enhancing patient outcomes. Ongoing research into the complex relationship between amino acid metabolism and neurological function may offer new insights into the pathogenesis of seizures and other neurological disorders.

Introduction

Amino acid metabolism deficiencies are inherited metabolic disorders caused by gene mutations, leading to reduced protein or enzyme production. These deficiencies disrupt various metabolic pathways due to enzyme deficiency. Defects in amino acid synthesis can cause seizures, microcephaly, and mental disability, along with skin and brain abnormalities. These disorders can trigger seizures due to metabolic dysfunctions affecting amino acids, energy metabolism, cofactors, purine and pyrimidine metabolism, glycosylation disorders, and lysosomal and peroxisomal disorders.[1] Inborn errors of amino acid metabolism can present as seizures in newborns and infants, emphasizing the need for early detection and intervention.[2] Amino acid treatment has shown positive effects on patient well-being, behavior, and seizure frequency.[3] These disorders impact crucial metabolic pathways for amino acids, carbohydrates, fatty acids, mitochondrial oxidative phosphorylation, purine/pyrimidine, and metal metabolism, as well as organic acid disorders affecting amino acid metabolism by influencing deaminated products.[4] Grey and white matter involvement in various brain regions contributes to a range of neurological symptoms in individuals with amino and organic acid metabolism disorders, including developmental delay and motor dysfunction.[5] Phenylketonuria, a common congenital disorder of amino acid metabolism, can lead to seizures, intellectual disability, behavioral issues, and mental disorders.[6] Amino acidopathies and organic acidemias, arising from amino or fatty acid catabolism disorders, can cause seizures and cognitive impairments due to toxic intermediary buildup or structural damage.[7] Disorders like homocystinuria, characterized by homocysteine-induced seizures, highlight the role of amino acid metabolism in neurological manifestations.[8]

Some common amino acid metabolism deficiencies include phenylketonuria (PKU), maple syrup urine disease (MSUD), homocystinuria, tyrosinemia type II, citrullinemia, argininosuccinic aciduria, carbamoyl phosphate synthetase I (CPS) deficiency, argininemia, hyperornithinemia-hyperammonemia-homocitrullinuria (HHH) syndrome, N-acetylglutamate synthase (NAGS) deficiency, ornithine transcarbamylase (OTC) deficiency, and pyruvate dehydrogenase (PDH) complex deficiency.[9] Disorders of amino acid metabolism, such as nonketotic hyperglycinemia, urea cycle defects, and maple syrup urine disease, can have severe neurological consequences if not recognized and treated promptly.[10]

Branched-chain amino acid (BCAA) supplementation has shown promise in treating refractory epilepsy, although the effects of BCAAs on seizures can vary depending on the specific mechanisms involved.[11] These deficiencies can be detected through analytical techniques such as chromatography and mass spectrometry for amino acid level changes and genetic assays for mutation detection. Early diagnosis is crucial for the treatment of these disorders, as some of them are potentially treatable if detected at an earlier stage.[9] The incidence of amino acid metabolism deficiencies is estimated to be 1:800 collectively for all metabolic inherited disorders.[12] Aminoacidopathies, a class of treatable inborn errors of metabolism, account for thirteen out of the 91 potentially treatable disorders.[9] The number of disorders affecting amino acid synthesis has been rapidly increasing, with associated clinical phenotypes expanding due to advances in next-generation sequencing diagnostics.[3]

Abnormal amino acid metabolism has been linked to epilepsy.[13] Inherited metabolic abnormalities, like high levels of certain amino acids, are known to play a role in the development of drug-resistant epilepsy.[14,15] Studies indicate that abnormal plasma levels of amino acids like glutamate, glycine, and GABA are elevated in patients with drug-resistant epilepsy (PRE).[16] Conditions such as

maple syrup urine disease (MSUD), nonketotic hyperglycinemia, and GABA-related disorders have also been associated with seizures.[17] Changes in amino acid metabolism have been observed during epileptogenesis and in chronic epilepsy, suggesting that amino acid turnover could be a valuable biomarker and target for treatment in epileptogenesis.[18] In this informative article, we thoroughly explored the different disorders related to amino acid metabolism that present with seizure symptoms.

Succinate semialdehyde dehydrogenase (SSADH) deficiency

Succinic semialdehyde dehydrogenase (SSADH) deficiency is a rare neurometabolic disorder characterized by defective degradation of gamma-aminobutyric acid (GABA), leading to a wide range of symptoms including motor and mental delay, intractable seizures, speech disturbances, and ataxia. The pathophysiology of SSADH deficiency involves the accumulation of 4-hydroxybutyric acid (4HBA), which down-regulates GABA receptors and likely contributes to epileptogenesis.[19,20] The absence of SSADH, which is encoded by the ALDH5A1 gene, leads to the accumulation of GABA and GHB.[19] SSADH plays a crucial role in the final step of GABA breakdown, facilitating the conversion of succinic semialdehyde (SSA) into succinic acid (SA).[21] In the absence of SSADH, SSA is transformed into GHB and other similar metabolites through alpha or beta-oxidation mechanisms.[22] Clinical manifestations of SSADH deficiency often lack specificity and encompass developmental delays, intellectual disabilities, hypotonia, ataxia, and epilepsy.[19,23] In severe cases, the condition manifests as progressive neurodegeneration and intractable epilepsy during infancy. Additionally, the neonatal period is characterized by low expression of GABA receptors and GABA glutamate decarboxylase. In the immature brain, the activation of GABA receptors may induce heightened excitability due to elevated intracellular chloride ion concentrations. Disruptions in GABA signaling pathways can contribute to the development of epilepsy, which in turn, further disrupts GABA signaling.[23] Next-generation metabolic screening (NGMS) has revealed elevated levels of aspartic acid, glutaric acid, glycolic acid, 4-guanidinobutanoic acid, 2-hydroxyglutaric acid, gamma-hydroxybutyric acid (GHB), and 4,5-dihydroxyhexanoic acid (4,5-DHHA) in SSADH patients.[24] A clinical severity scoring (CSS) system has been developed to assess the severity of SSADH and can be used for counseling, genotype-phenotype correlations, biomarker development, clinical trials, and describing the natural history of the disease.[25] Early diagnosis of SSADH deficiency can be facilitated by analyzing urinary organic acids and confirming the diagnosis through DNA analysis. Wang Pingping and colleagues recently documented four Chinese patients afflicted with SSADH deficiency. All of these patients exhibited a history of developmental delay, two experienced convulsions, and three displayed reduced attention and sleep disturbances. By employing exome sequencing and analyzing flanking mutations within the intronic region of the ALDH5A1 gene, the researchers identified mutations at five distinct sites. Within this cohort, two individuals possessed homozygous mutations, specifically c.1529C>T and c.800 T>G, whereas the remaining two exhibited compound heterozygous mutations: c.527G>A/c.691G>A and c.1344 -2delA/c.1529C>T. Notably, the homozygous mutation c.800T>G within the ALDH5A1 gene represents a novel finding. This variant may be intimately tied to the onset of intractable epilepsy in this disorder and its subsequent severity.[22]

Methylenetetrahydrofolate reductase (MTHFR) deficiency

Methylenetetrahydrofolate reductase (MTHFR) deficiency is a rare metabolic disease that can lead to neurological disorders

and premature vascular disease. MTHFR deficiency is characterized biochemically by the accumulation of homocysteine in the blood and bodily fluids.[26,27] MTHFR, a methyl donor, facilitates the conversion of homocysteine to methionine. If there is a decrease or absence of MTHFR enzyme activity, it results in elevated levels of homocysteine in the plasma.[28] The presence of high homocysteine stimulates the NMDA receptors, leading to excitotoxicity and the generation of free radicals.[29] Furthermore, metabolites resembling homocysteine can interact with glutamate receptors and also exhibit excitotoxicity.[29,30] The T allele of the MTHFR gene is notably linked to the susceptibility to developing epilepsy.[31] Early diagnosis through genetic testing is crucial for timely treatment and improved outcomes. MTHFR deficiency has been associated with complex psychiatric mental health illnesses, and supplementation with folate has shown benefits in conjunction with psychotropic medications.[30] Homocystinuria due to MTHFR deficiency is an autosomal recessive disorder that can cause cerebral atrophy and dysplasia.[32] Maternal MTHFR gene polymorphisms have been linked to adverse clinical outcomes in neonates, such as intrauterine growth restriction, sepsis, anomalies, and mortality.[33] Screening for MTHFR gene mutations in mothers during the antenatal period can serve as a predictive marker for these adverse outcomes, allowing for proper clinical management.[33]

Hyperammonemia

Hyperammonemia is a condition characterized by excessive accumulation of ammonia in the blood.[34] It can occur in multiple myeloma patients without hepatic involvement. Valproic acid (VPA) use can also lead to hyperammonemia[35], with prevalence rates varying from 0.7% to 73% for asymptomatic cases and 0.7% to 22.2% for symptomatic cases. Several risk factors for VPA-induced hyperammonemia have been pinpointed, including concurrent medications, liver damage, and deficiencies in carnitine metabolism. Furthermore, hyperammonemia can manifest as a symptom of ornithine transcarbamylase (OTC) deficiency, a rare X-linked recessive urea cycle disorder. In neonates and infants, hyperammonemia can be caused by inherited metabolic diseases or acquired disorders such as liver failure or infections with urea-metabolizing organisms.[36] Malfunctioning urea synthesis leads to hyperammonemia. Elevated levels of ammonia in the brain foster heightened glutamine synthesis, disrupt the aquaporin system, augment astrocyte glutamine synthesis, trigger cerebral edema, intensify intracranial pressure, and ultimately cause brain dysfunction and epileptic seizures.[34] Timely identification and treatment are crucial for transient hyperammonemia of the newborn (THAN)[34], a well-defined condition that can present with coma and seizures.

Cerebral folate deficiency (CFD)

Folate metabolism is vital for nucleotide synthesis, methylation, amino acid metabolism, and mitochondrial translation.[37] Cerebral folate deficiency (CFD) is a rare neurological condition characterized by low 5-methyltetrahydrofolate (5-MTHF) levels in the cerebrospinal fluid, despite normal blood folate levels.[1,38] Genetic factors, like mutations in the folate receptor alpha (FOLR1) gene or variants in histone lysine demethylase 6B (KDM6B), are associated with CFD. It can manifest with neurological symptoms such as hypotonia, microcephaly, seizures, and spastic quadriplegia. Typically, symptoms appear around 4 to 6 months of age and may include delayed development, hypotonia, ataxia, dyskinesias, spasticity, speech difficulties, and epilepsy.[1,39] This is due to folate receptor antibodies binding to folate receptors in the choroid plexus, hindering folate transport and reducing 5-MTHF transfer across the blood-brain barrier into the cerebrospinal fluid.[40,41] While systemic folate deficiency is well-known, the depletion of 5-MTHF, the primary folate form

in the body, specifically occurs in the central nervous system, leading to CFD. Though the exact causal mechanism is unclear, research suggests impaired folate transport across the blood-brain barrier in folate-deficient central nervous systems, while peripheral tissues are relatively unaffected.[42] The lack of 5-MTHF in the cerebrospinal fluid is thought to result from reduced transport across the blood-brain barrier, possibly due to folate receptor antibodies binding to choroid plexus folate receptors. Some cases have shown autoantibodies against the folate receptor-alpha (FRα). Treatment with folinic acid has significantly improved clinical symptoms and normalized cerebrospinal fluid 5-MTHF levels.[1,43] Screening the cerebrospinal fluid of patients with unknown neurological disorders could be beneficial. Secondary CFD forms may arise from prolonged use of specific drugs or in conjunction with conditions like Rett syndrome and Aicardi-Goutieres syndrome.[41] Studies indicate a high prevalence of FRα autoantibodies in individuals with CFD and autism spectrum disorders (ASD), suggesting a potential link between CFD and ASD. Further research is needed to deepen our understanding of CFD causes and treatment approaches.

Glycine encephalopathy

Glycine encephalopathy, also known as non-ketotic hyperglycinemia (NKH), is a rare autosomal recessive metabolic disorder characterized by the accumulation of glycine in body fluids due to a defect in the glycine cleavage system (GCS). This condition is caused by mutations in the glycine decarboxylase (GLDC) and aminomethyltransferase (AMT) genes, which encode proteins within the glycine cleavage complex.[44,45] The disease manifests with various symptoms depending on the type, such as neurological symptoms in the neonatal type, seizures and psychomotor delay in the infantile type, and abnormal behaviors and movement disorders in the late-onset type.[46] Diagnosis of glycine encephalopathy can be complex and often necessitates invasive liver biopsy or comprehensive mutational screening of the GLDC, AMT, and GCSH genes. Nonetheless, new laboratory tests like the [1-(13)C]glycine breath test and multiplex ligation-dependent probe amplification (MLPA) have been developed to aid in diagnosis.[47-49] In its typical form, NKH often leads to a state of coma and mortality during the early neonatal period.[46] Survivors, on the other hand, exhibit severe neurological dysfunction and intractable epilepsy. Diagnosis of glycine encephalopathy can be challenging and often requires invasive liver biopsy or mutational screening of the GCS genes.[47] The disease has a grim prognosis, with many patients succumbing within the first year of life. Treatment options for glycine encephalopathy are limited, and most therapies aim to reduce glycine levels and manage seizures.[48] The disease has a high mortality rate, with many patients dying within the first year of life.[50]

Discussion

Seizures are a frequent initial indication in children with amino acid metabolism disorders. In classical maple syrup urine disease (MSUD), seizures often manifest in the neonatal period, while in intermittent or intermediate MSUD, seizures may emerge later or be infrequent. Nonketotic hyperglycinemia typically exhibits early myoclonic encephalopathy in infancy, although seizures may be uncommon in individuals with atypical forms.[17] Other conditions like sulfite oxidase deficiency, serine deficiency, and GABA-related disorders may also display various seizure types. Seizures are uncommon in monoamine biosynthesis disorders, yet paroxysmal dystonia is often misdiagnosed as seizures. Prompt diagnosis and early intervention are vital for enhancing the outlook of these disorders. Early identification and treatment are essential for managing these disorders and averting long-term complications.[17] Healthcare providers should consider amino

acid metabolism disorders in children with seizures, particularly if there is a family history of these conditions. Testing for specific amino acid levels and genetic mutations can confirm a diagnosis and guide appropriate treatment. Further research is necessary to comprehend fully the metabolic changes linked to epilepsy development and its chronic form, potentially identifying new therapeutic targets for this intricate neurological condition.[1] Autophagy, a critical catabolic pathway for maintaining tissue and organismal equilibrium, is influenced by amino acids and contributes to brain functions, including epileptic disorders. Neurological symptoms like early-onset seizures, cognitive impairments, and skin issues can stem from amino acid synthesis defects. Moreover, irregular amino acid levels can disrupt autophagy, leading to an accumulation of damaged proteins and organelles in the brain, potentially fostering neurodegenerative conditions like Alzheimer's and Parkinson's.[51] Understanding the intricate connection between amino acids, autophagy, and brain function is crucial for developing precise therapies for various neurological disorders.[51] Apart from neurological symptoms, amino acid metabolism disorders can impact other organs, resulting in a variety of clinical manifestations. Examples include liver dysfunction in conditions such as maple syrup urine disease, kidney issues in cystinuria, and muscle weakness in disorders affecting branched-chain amino acid metabolism.[52] These systemic repercussions underscore the significance of early detection and management of amino acid metabolism disorders to avert potentially severe consequences.

Conclusion

Early detection and appropriate management of these conditions are essential for preventing long-term complications and improving patient outcomes. Continued research on the complex connection between amino acid metabolism and neurological function may provide fresh perspectives on the onset of seizures and other neurological disorders. Comprehending the fundamental mechanisms of these conditions can result in more precise treatment choices and enhanced quality of life for patients. By exploring further the correlation between amino acids and neurological well-being, scientists might discover innovative therapeutic strategies that have the potential to transform the field of neurology. Keep an eye out for exciting progress in this research area.

Conflict of Interest

The authors declare no conflicts of interest.

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Ethical Considerations

None.

Author's Contribution

Study concept and design: M. GT, K.A., Data analysis and interpretation: M.B., A.M., S.A.D, K.A. Drafting of the manuscript: M.A., A.S., M.B. Critical review of the manuscript: H.N., M.A., A.S. All authors read and approved the final manuscript.

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