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Review article

Disorders of amino acid metabolism associated with epilepsy

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Abstract

Seizures are a common presenting manifestation in children with disorders of amino acid metabolism. However, seizures may be very common in some specific diseases, but are rare in other diseases. In patients with classical maple syrup urine disease (MSUD), seizures commonly occur in the neonatal stage. But in intermittent or intermediate MSUD, seizures may develop in a later stage, or are uncommon. Patients with nonketotic hyperglycinemia often present with early myoclonic encephalopathy in the first weeks of life. However, in patients with atypical variants, seizures may be rare. In addition, patients with sulfite oxidase deficiency, serine deficiency, or GABA-related disorders may also present with different types of seizures. In monoamine biosynthesis disorders, seizures are rare, but paroxysmal dystonia is frequently misdiagnosed as seizures. Therefore, the incidence of seizures in disorders of amino acid metabolism is variable. Timely diagnosis and early treatment may improve the prognosis of these disorders.

Keywords: Amino acids; Epilepsy; Neurometabolic diseases; Infant

1. Introduction

Disorders of amino acid metabolism are among the most common inborn errors of metabolism in humans [1,2], and have been recognized for years. As amino acids are important molecules involved in a variety of complex metabolic pathways, including neurotransmission, disorders of amino acid metabolism may affect important neurological functions in humans.

The clinical phenotypes in these disorders are variable, and frequently include different kinds of neurological symptoms, such as seizures [1,2]. Patients affected by these disorders may present either as an acute encephalopathy, like in nonketotic hyperglycinemia (NKH) [3], or develop progressive mental retardation, as in the natural history of patients with untreated phenylketonuria (PKU) [4].

The disorders of amino acid metabolism may affect sulfur-containing amino acids, branched-chain amino acids, and aromatic amino acids (Table 1). The present review discusses the clinical presentations, the diagnosis, and the treatment with emphasis on epileptic presentations.

2. Clinical manifestations and pathogenetic mechanisms

2.1. Common neurological manifestations

The neurological manifestations in disorders of amino acid metabolism are in general variable [1,2]. Some may present with insidious and slow course without major metabolic decompensation. However, without suitable treatment, many disorders may show acute decompensation with extensive neurological deterioration like in patients with NKH or maple syrup urine disease (MSUD). In contrast, some disorders may present with progressive mental deterioration like in untreated PKU.

The most common neurological symptoms in disorders of amino acid metabolism when untreated include psychomotor retardation of variable degree, episodic consciousness changes (up to coma), ataxia, and

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Table 1
Disorders of amino acid metabolism associated with infantile seizures.

Disorders of sulfur amino acid metabolism
Hypermethioninemia
Homocystinuria
Sulfite oxidase deficiency
Disorder of branched-chain amino acid metabolism: maple syrup urine disease
Classic form
Intermittent or intermediate form
Thiamine-responsive form
Nonketotic hyperglycinemia
Classic form
Atypical vs. late-onset form
Disorders in monoamine biosynthesis pathway
Phenylketonuria: classic
BH4 deficiency
Sepiapterin reductase deficiency
Tyrosine hydroxylase deficiency
Aromatic L-amino acid decarboxylase deficiency
Disorders related to GABA metabolism
Pyridoxine-dependent epilepsy
4-Hydroxybutyric aciduria (SSADH deficiency)
GABA transaminase deficiency

BH4: tetrahydrobiopterin; SSADH: succinic semialdehyde dehydrogenase; GABA: Gamma-aminobutyric acid.

seizures. Seizures can be either generalized tonic–clonic or focal seizures, and occasionally myoclonic or absence seizures.

2.2. Possible pathogenetic mechanisms

The pathogenetic mechanisms leading to the clinical presentations in disorders of amino acid metabolism are variable (Table 2) [3–8]. They may arise from the accumulation of specific amino acids, which may be toxic to the neurons and can lead to neuronal death. In patients with NKH, the clinical manifestations may arise from the accumulation of excessive glycine in brain, which is the major cause of neuronal damage [3,5,9]. The interaction of glycine with inhibitory glycine receptors in brainstem can result in respiratory difficulties in neonates with NKH. In addition, high brain glycine levels may also interact with excitatory *N*-methyl-D-aspartate (NMDA) glutamate receptors in cerebral cortex, leading to neuronal damage and clinical seizures [3,5,9]. Patients with NKH may also have dysgenesis of the corpus callosum, and dysmyelination of the brain, indicating that high glycine levels may affect the synthesis of myelin. Patients with MSUD have an accumulation of branched-chain amino acids, like leucine, isoleucine, and valine [6]. The pathogenetic mechanism of MSUD is caused primarily by the accumulation and neurotoxicity of leucine and/or its transamination product 2-ketoisocaproate, while isoleucine or valine may be less important [6,10,11]. High leucine levels have been shown to impair the regulation of cell volume, leading to severe subcortical gray matter edema in patients with MSUD. Recent animal studies also showed that the accumulation of leucine in brain may inhibit the transport of other essential amino acids like threonine, tryptophan and tyrosine using the same transporter as leucine. This may lead to subsequent impairment of proteins and neurotransmitter synthesis. The accumulation of branched-chain ketoacids in MSUD may also result in energy deprivation by inhibiting Krebs cycle activity in mitochondria of both neurons and glial cells. Because energy failure results in the loss of Na+/K+ ATPase function, it can further contribute to cell swelling and cerebral edema seen in MSUD [10–12].

In homocystinuria, homocysteine can activate NMDA receptors and induce oxidative stress, thereby increasing the vulnerability of neurons to excitotoxicity

Table 2
Possible pathogenetic mechanisms in disorders of amino acid metabolism.

Accumulation of specific amino acids
Nonketotic hyperglycinemia: glycine
Maple syrup urine disease (MSUD): branched-chain amino acids
Homocystinuria: homocysteine
Phenylketonuria: phenylalanine
Deficiency of amino acids
Serine deficiency
Defects in the biosynthesis of compounds derived from amino acids
Gamma-aminobutyric acid (GABA)
Monoamines: serotonin, dopamine, adrenaline, and noradrenaline
Defects in the degradation of metabolites of amino acids
Sulfite oxidase deficiency: sulfur-containing amino acids and sulfite

and oxidative injury [8,13]. Recent animal studies showed that homocysteine can inhibit Na+/K+ ATPase activity in hippocampus, leading to brain dysfunction and seizures in patients with homocystinuria [8,14].

Elevated phenylalanine in patients with phenylketonuria may increase oxidative stress, affect cerebral energy metabolism, impair the synthesis of myelin, and decrease the expression of brain-derived neurotrophic factor, which is closely related to neuronal survival and differentiation [15–17].

Another possible pathogenetic mechanism in disorders of amino acid metabolism is related to defects in biosynthesis of specific amino acids. In serine deficiency, the defects in the synthesis of serine may affect several important biological functions of humans, leading to severe psychomotor retardation and congenital microcephaly [18]. Occasionally, the neurological symptoms may arise from the deficiency of specific compounds derived from amino acids. Patients with defects in the synthesis of GABA from glutamate may present with developmental delay and seizures [19,20]. Defects in the synthesis of monoamines like dopamine, serotonin, adrenaline, and noradrenaline from phenylalanine and tryptophan may also result in psychomotor retardation and generalized hypotonia [20].

Other possible mechanisms leading to the clinical presentations are defects in degradation of metabolites of specific amino acids. For example, in sulfite oxidase deficiency or molybdenum cofactor deficiency, the defects in degradation of sulfite, the metabolites of sulfur containing amino acids lead to the accumulation of sulfite and subsequent neuronal death [21].

3. Disorders of amino acid metabolism and infantile epilepsy

Although seizures are common in some disorders of amino acid metabolism, they are uncommon or rare in other disorders. The incidence and onset age of seizures may also be different in the same disorder because of atypical presentations (Table 3). For example, seizures may be very common in patients with MSUD, NKH, sulfite oxidase deficiency, molybdenum cofactor deficiency, or serine-deficiency disorders, but will not happen or are very unusual in patients with hypermethioninemia or cystathioninuria. Although seizures are reported in 21% of patients with homocystinuria secondary to cystathionine β-synthase deficiency, they rarely develop in neonatal period or early infancy [8]. However, patients with homocystinuria due to methylene-tetrahydrofolate reductase deficiency may present in neonatal and early infancy with acute neurological deterioration, and seizures are much more common [22,23]. For patients with disorders of monoamine biosynthesis, although seizures are very uncommon, the patients frequently have paroxysmal dystonia or involuntary movements, which may be misdiagnosed as seizures [20,24].

Table 3
The disorders of amino acid metabolism associated with infantile epilepsy.

Seizures are very common symptoms
MSUD
Nonketotic hyperglycinemia
Pyridoxine-dependent epilepsy
Sulfite oxidase deficiency
Serine-deficiency disorders
4-Hydroxybutyric aciduria (SSADH deficiency)
BH4 deficiency
Seizures are uncommon symptoms
Homocystinuria
Phenylketonuria (if early treated)
Seizures are very rare or absent
Hypermethioninemia
Cystathioninuria
Seizures are very rare or absent, but presence of movement disorders that can be misdiagnosed as seizures
GTP cyclohydrolase I deficiency
Sepiapterin reductase deficiency
Tyrosine hydroxylase deficiency
Aromatic L-amino acid decarboxylase deficiency

In fact, disorders of amino acid metabolism are uncommon etiologies for infantile epilepsy or epilepsy syndromes. In infantile spasms, most infants are secondary to perinatal insults or CNS malformations, and disorders of amino acid metabolism are an uncommon etiology [25,26]. On the contrary, in some epilepsy syndromes, defects in amino acid metabolism may be an important cause of seizures. The best example will be early myoclonic encephalopathy (EME) [27,28]. EME is an early epileptic encephalopathy with suppression bursts in EEG [27,28]. The infants with EME usually have very early onset of symptoms (mainly neonatal period), severe psychomotor retardation, generalized hypotonia, erratic myoclonus, and intractable seizures. The interictal EEG reveals suppression-burst pattern activated in sleep, which is different from that in infants with early infantile epileptic encephalopathy, in whom the suppression-burst pattern appears in both waking and sleep states [28]. Although infants with EME may be secondary to several kinds of metabolic diseases, including propionic aciduria, methylmalonic acidemia, D-glyceric acidemia, sulfite oxidase deficiency, Menkes disease, and Zellweger syndrome, the most common etiology of EME may be NKH [3,28], which will be discussed in the next section.

The treatment of seizures in disorders of amino acid metabolism depends on correct and early diagnosis. Limiting the offending amino acids in the diet or supplement of deficient amino acids may improve the prognosis of seizures. The principles of anti-epileptic drug treatment in these disorders are similar to those in

children with epilepsy. However, there are some points needing special attention. Valproic acid, which can elevate the glycine levels in blood, is not suitable for the treatment in patients with NKH. Although vigabatrin is used in the treatment of succinic semialdehyde dehydrogenase (SSADH) deficiency, it can sometimes induce absence seizures in patients.

4. The clinical manifestations in nonketotic hyperglycinemia

Classical NKH is an autosomal recessive disorder of glycine metabolism caused by a defect in the glycine cleavage system (GCS) [3,5], a multienzyme complex located in the inner mitochondrial membrane of brain, liver, kidney, and placenta. GCS includes four individual proteins, P-protein, H-protein, T-protein, and L-protein, and are encoded by GLDC, GCSH, AMT, and GCSL genes, respectively. The majority of classical NKH patients presents within hours or days of birth with severe symptoms, like intractable seizures, and usually in the form of EME. Although classical NKH usually presents in neonatal period, there are several types of atypical NKH [29–31], and the clinical manifestations are usually heterogeneous, in sharp contrast to the uniform severe neurological manifestations in classical NKH. Three major forms of atypical NKH have been recognized. They may present in neonatal or infantile periods with milder clinical symptoms. The neurological presentations in the neonatal form of atypical NKH are similar to those of the classical one, but seizures are less severe, and the subsequent psychomotor development is usually better [30,31]. The infantile form is the most common one in atypical NKH [29]. Infants usually present with a mild to moderate developmental delay, and the seizures are less common, and can be of any type, including infantile spasms, focal or generalized seizures. In contrast, patients with late-onset NKH may present with spastic paraparesis, ataxia or choreoathetoid movements [29,30]. The psychomotor development is usually normal or only mildly delayed, and seizures are very uncommon. However, behavioral abnormalities are prevalent in both infantile and late-onset forms although the phenotype in late-onset NKH is more heterogeneous [29]. The genetic defects in patients with neonatal and infantile forms of atypical NKH had also been shown to involve GCS, indicating that the milder presentations in these patients may be related to the residual GCS activity in specific mutations [29]. In contrast, the late-onset NKH may represent a different entity with mutations unrelated to GCS, and further studies are needed to clarify the cause of hyperglycinemia in these patients.

Treatment of patients with NKH includes agents to decrease plasma glycine level, and NMDA receptor antagonists [32]. Treatments such as low protein diet, sodium benzoate, dextromethorphan, strychnine, and ketamine have been tried alone or in combination with variable effect. Imipramine and sodium benzoate had also been used in late-onset NKH with good response [33].

5. Maple syrup urine disease: a disorder of branched-chain amino acids

Maple syrup urine disease (MSUD) is an inherited neurometabolic disorder secondary to the deficiency of the branched-chain 2-keto acid dehydrogenase (BCKD) complex activity [6]. The mammalian BCKD complex consists of three catalytic components: E1, E2, and E3, and two regulatory enzymes. Mutations in these regions lead to the accumulation of three branched-chain amino acids, leucine, valine and isoleucine [6].

Most patients with MSUD suffer from severe classic form with neonatal onset [6,34]. They usually develop a catastrophic encephalopathy in the second week of life, with poor feeding, vomiting, lethargy, hypertonia or hypotonia, ketoacidosis, and intractable seizures, followed by death if untreated. The seizures can be of different types, with occasionally presenting with status epilepticus [35], and early treatment may improve the prognosis. Some patients with MSUD may have milder phenotypes, which are usually classified into intermediate, intermittent or thiamine-responsive MSUD, depending on the clinical presentations and their response to thiamine treatment [6,36,37]. Patients with intermediate form of MSUD may present with psychomotor retardation, failure to thrive, and mild ketoacidosis. The clinical symptoms can vary from mild manifestations to nearly classic form. In milder variants, patients may have only mild mental retardation without significant seizures. However, for those with severe variants of intermediate MSUD, they may have frequent seizures of different types, and may need a strict MSUD diet therapy from neonatal period to reach nearly normal neurological development.

Patients with intermittent MSUD usually presents with episodic ataxia, semicoma, or ketoacidosis precipitated by infection or stress [36]. The seizures can be intractable in acute encephalopathy, and the acute episodic deterioration can be fatal. However, patients can also have normal development or only mild psychomotor retardation if early diagnosis and treatment can be done, and seizures may be not common in mild variant.

A number of thiamine-responsive patients have also been reported. These patients usually do not have acute neonatal illness, and the early symptoms may be similar to intermediate or intermittent MSUD [36,37]. Most of these patients have mutations in E2 component of BCKD, which are different from those in classic MSUD. The biochemical mechanisms for thiamine-responsive MSUD remain unclear. However, the therapeutic effect of high-dose thiamine in these patients with mutations in E2 component may be related to enhanced E1 activity by high-dose thiamine treatment [6,38].

6. Disorders of sulfur-containing amino acids

Sulfite oxidase deficiency is a rare inherited autosomal recessive neurometabolic disease [39–41]. It can result from isolated enzyme defect or molybdenum cofactor deficiency, which leads to combined defects in xanthine dehydrogenase and sulfite oxidase. Sulfite oxidase deficiency can lead to the accumulation of toxic sulfites, resulting in the lethal neurological manifestations. Both isolated form of sulfite oxidase deficiency and the more common molybdenum cofactor deficiency may have similar clinical features, like intractable neonatal or infantile seizures, hypotonia or hypertonia, feeding difficulties, profound developmental delay, and dislocated lens. The seizures in isolated sulfite oxidase deficiency may even begin prenatally, and are much more severe compared with those in molybdenum cofactor deficiency. Neuroimaging studies in isolated sulfite oxidase deficiency usually reveal early multicystic white matter damage with profound cerebral atrophy mimicking those in hypoxic-ischemic encephalopathy [41]. However, milder phenotypes with later onset have also been reported [39,42], and molybdenum cofactor deficiency usually causes much less striking clinical changes.

The diagnosis of isolated sulfite oxidase deficiency can be made based on the findings of clinical presentations and a high sulfite level in urine. In molybdenum cofactor deficiency, the level of blood uric acid is also reduced, which can differentiate the two disorders.

The treatment for sulfite oxidase deficiency is disappointing. Although diet therapy was reported to have some benefits in mild form of sulfite oxidase deficiency [43], both therapeutic trial with thio-containing drugs to bind sulfites and decreased intake of sulfur-containing amino acids failed. Recently, substitution therapy with purified cyclic pyranopterin monophosphate, which is deficient in about two-thirds of the patients with molybdenum cofactor deficiency, was found to have effect in restoration of molybdenum cofactor-dependent enzyme activities, and stop neurodegeneraiton [44]. Therefore, it may become a potential therapeutic drug for molybdenum cofactor deficiency in the future.

7. Serine-deficiency syndrome

Serine-deficiency syndrome is a very rare infantile-onset neurometabolic disorder. There are two serine-deficiency syndromes: 3-phosphoglycerate dehydrogenase (3-PGDH) deficiency and 3-phosphoserine phosphatase (3-PSP) deficiency [9,45,46]. 3-PGDH deficiency is more common than 3-PSP deficiency [18].

As L-serine is a precursor of important metabolites such as nucleotides, phospholipids and the neurotransmitters glycine and D-serine, patients with serine deficiency usually present with congenital microcephaly, severe psychomotor retardation, and seizures. Severe psychomotor retardation followed by different patterns of clinical seizures is observed in the first weeks of life. Seizures can be generalized tonic–clonic, myoclonic, or epileptic spasms. Absence or atonic seizures can also be observed in older children.

The diagnosis of serine deficiency is based on the analysis of amino acids in plasma and CSF showing very low concentrations of serine and glycine. Oral supplementation of L-serine is proved to be very effective in the treatment of seizures [46]. Control of seizures can be reached even in patients suffering from intractable seizures for years, but not all of the patients can remain free of seizures. The clinical response of the seizures to treatment can be seen within 1–2 weeks after treatment. If clinical seizures can't be controlled by L-serine alone, glycine can be added. Early treatment can improve the prognosis, including seizure control and psychomotor development.

8. Disorders related to GABA metabolism

The disorders related to GABA metabolism include pyridoxine-dependent epilepsy, GABA-transaminase deficiency, and SSADH deficiency (4-hydroxybutyric aciduria) [19,47–49].

Pyridoxine-dependent epilepsy is a rare autosomal recessive disorder. In the majority of patients, the disorder is caused by deficient enzyme activity of α-aminoadipic semialdehyde dehydrogenase, and was recently shown to be due to mutations in ALDH7A1 gene, which encodes antiquitin [50]. In patients with pyridoxine-dependent epilepsy, they usually have intractable seizures of prenatal or neonatal onset, and seizures can be of any types with generalized tonic–clonic seizures being most common. Infants with this disease may also have severe psychomotor retardation without proper treatment. In typical cases of pyridoxine-dependent epilepsy, neonatal seizures can be controlled by 50–100 mg of pyridoxine, with continuing seizure control on pyridoxine 10 mg/kg/day. However, seizures may recur when pyridoxine is stopped, and can be controlled again when treatment is restarted. In atypical cases, seizures are usually of later onset (up to 2 years), and the patients may only respond to repeated administration of pyridoxine [51].

GABA-transaminase deficiency is also a very rare autosomal recessive disorder, characterized by severe psychomotor retardation, poor feeding, high-pitched crying, and intractable seizures of different types. You can only make the diagnosis based on the findings of high levels of GABA in serum and CSF [19,49].

SSADH deficiency is a relatively common autosomal recessive neurotransmitter disease, involving GABA degradation [19,48]. Clinical manifestations in SSADH deficiency are varied, and may range from very mild mental retardation, behavioral problems, to severe

psychomotor retardation with intractable seizures. The seizures can be generalized or partial, and sometimes absence and myoclonic seizures can occur. However, the pathogenetic mechanisms of neurological symptoms remain controversial, and may be related to the toxicity of 4-hydroxybutyrate. The diagnosis of SSADH deficiency is difficult, but the MRI abnormalities in globus pallidus may provide some clues for the diagnosis [48]. Treatment with vigabatrin, an inhibitor of GABA transaminase, can be of some help, but the results have been disappointing and the response is variable.

9. Disorders related to monoamine biosynthesis pathway

9.1. Classic phenylketonuria and tetrahydrobiopterin deficiency

Phenylketonuria (PKU) is the most common disease of amino acid metabolism [4,7,52]. The incidence of PKU is varied in different countries, with an incidence of 1 in 40,000 in Taiwan. In classic PKU, the less harmful condition of hyperphenylketonuria, the patients usually suffer from phenylalanine hydroxylase (PAH) deficiency [7]. PKU may occasionally result from defects in the metabolism of tetrahydrobiopterin (BH4) [53], the obligate cofactor of PAH. Of these, the most common defect is 6-pyruvoyltetrahydropterin synthase (PTPS) deficiency [53]. Both classic PKU and BH4 deficiency will lead to the accumulation of phenylalanine, which is the major toxic substance in the disease [7].

The symptoms of untreated PKU are diverse, and range from mild cognitive impairment to severe mental retardation, accompanied with motor impairment and seizures. The incidence of seizures in untreated PKU or BH4 deficiency patients is high [53,54]. Different seizure types, including infantile spasms, have been reported [55]. However, with early diagnosis and treatment, the incidence of seizures in classic PKU may be decreased [54,55].

The most important treatment for classic PKU includes low phenylalanine diet immediately after the diagnosis is made. For patients with seizures, they can become seizure-free with only diet therapy or combined anti-epileptic drug treatment. In contrast, in BH4 deficiency, in addition to low phenylalanine diet, supplement with L-dopa and 5-hydroxytryptophan is very important for psychomotor development.

9.2. Other disorders of monoamine biosynthesis

Several enzymes play important roles in biosynthesis of dopamine and serotonin, including GTP cyclohydrolase I, tyrosine hydroxylase, aromatic L-amino acid decarboxylase (AADC), and sepiapterin reductase [20,24]. Except for patients with GTP cyclohydrolase I deficiency, most patients with disorders of monoamine biosynthesis begin to have neurological symptoms since neonates or early infancy. The most common presenting symptoms and signs include developmental delay, microcephaly, generalized hypotonia, oculogyric crisis, excessive sweating and feeding difficulty. Seizures are very uncommon. Only occasional focal seizures or myoclonic jerks have been reported [56,57]. However, paroxysmal dystonia in these patients are frequently misdiagnosed as seizures. Patients with GTP cyclohydrolase I deficiency or Segawa disease usually have symptom onset in childhood around 6 years. Children may present with postural dystonia of a lower extremity, mostly with talipes equinovarus, or may begin with dystonic posture of one upper extremity at a later age. However, no seizure has ever been reported.

The response to L-dopa treatment in disorders of monoamine biosynthesis is variable. Patients with GTP cyclohydrolase I deficiency have very good response to L-dopa treatment. However, patients with tyrosine hydroxylase deficiency or sepiapterin reductase deficiency usually have mild to severe psychomotor retardation even with L-dopa treatment. In contrast, the response to dopamine agonists is usually very poor in patients with AADC deficiency. They can be treated with dopamine agonists and monoamine oxidase inhibitors [57].

10. Conclusions

The incidence of seizures in disorders of amino acid metabolism is variable, and sometimes age-dependent in atypical variants. For those disorders with a high incidence of intractable seizures, early diagnosis and treatment may improve the neurological outcome, including epilepsy, of the patients. Correct diagnosis may also reduce unnecessary antiepileptic drug treatment in some disorders of amino acid metabolism.

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