Amino Acid Disorders

MORE THAN 70 inherited disorders of amino acid metabolism are known, including many that cause neurological impairment. The diagnosis and management of these disorders often requires measurement of amino acid concentrations in body fluids.

CLINICAL AMINO ACID ANALYSIS

The development of automated amino acid analyzers has made measurements of amino acid concentrations in biological fluids relatively easy. These analyzers separate amino acids either by ion-exchange chromatography or by high-pressure liquid chromatography. The results are plotted as a graph (Fig. 1). The concentration of each amino acid can then be calculated from the size of the corresponding peak on the graph.

Most amino acid disorders can be diagnosed by measuring the concentrations of amino acids in blood plasma; however, some disorders of amino acid transport are more easily recognized through the analysis of urine amino acids. Therefore, screening for amino acid disorders is best done using both blood and urine specimens. Occasionally, analysis of cerebrospinal fluid (CSF) amino acids will provide a diagnostic finding. For example, patients with non-ketotic hyperglycinemia typically have an elevation of CSF glycine that exceeds the corresponding increase in plasma glycine.

DISORDERS OF AMINO ACID CATABOLISM

Most of the known disorders of amino acid metabolism are disorders of amino acid catabolism. When an enzyme deficiency interferes with one of these pathways, a specific amino acid or amino acid by-product may accumulate to toxic levels. Of course, a deficiency of downstream products may also be detrimental. Reflecting important differences in treatment strategies, the disorders of amino acid catabolism may be divided into three categories: urea cycle disorders, defects in the catabolism of specific essential amino acids, and defects in the catabolism of specific nonessential amino acids.
Urea Cycle Disorders

The catabolism of amino acids liberates unneeded nitrogen in the form of ammonia (NH₃). If ammonia accumulates to higher than normal levels, it becomes toxic, especially to the brain. In most lower organisms and marine creatures, excess NH₃ is eliminated by diffusion into the surrounding environment. However, human beings and other terrestrial vertebrates are unable to eliminate sufficient ammonia by this route. Instead, we have evolved a series of biochemical reactions, known as the urea cycle, that serve to convert ammonia to urea, which is then excreted in urine (Fig. 2). The complete urea cycle is functional only in the liver.

Eight inherited disorders of the urea cycle are known (Table 1). Their collective incidence is approximately 1 in 8000 live births. Except for ornithine aminotransferase (OAT) deficiency, all these disorders cause hyperammonemia and may result in mental retardation. OAT deficiency, also known as gyrate atrophy of the choroid and retina, causes visual loss due to retinal degeneration.

Overall, the clinical presentations of the hyperammonemic syndromes are similar. Severe enzyme defects tend to present in neonates with life-threatening episodes of hyperammonemia and cerebral edema. Typically, an affected child is well at birth but then develops lethargy, irritability, and/or vomiting at 1 or 2 days of age. Tachypnea and a transient respiratory alkalosis are frequent. Sepsis is usually considered a likely diagnosis. If the hyperammonemia is not detected and appropriate treatment is not begun promptly, the child’s disease is likely to progress to seizures, coma, and death. Less severe enzyme defects may present later in infancy with poor growth, hepatomegaly, developmental delay, spasticity, and/or other neurological symptoms. Older children or adults may present with

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Table 1: Urea Cycle Disorders

<table>
<thead>
<tr>
<th>Enzyme defect</th>
<th>Disorder</th>
<th>Suggestive plasma amino acid findings</th>
<th>Urine orotate</th>
<th>Other distinguishing features</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-acetylglutamate synthetase (NAGS)</td>
<td>NAGS deficiency</td>
<td>N/↑↑↑citrulline</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>Carbamoyl phosphate synthetase (CPS)</td>
<td>CPS deficiency</td>
<td>↓ citrulline</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>Ornithine transcarbamoylase (OTC)</td>
<td>OTC deficiency</td>
<td>↓ citrulline</td>
<td>↑↑↑</td>
<td>X-linked; random X-inactivation affects phenotype in females</td>
</tr>
<tr>
<td>Argininosuccinate synthetase</td>
<td>Citrullinemia</td>
<td>↑↑↑citrulline</td>
<td>↑</td>
<td>Hepatomegaly, cirrhosis, brittle hair</td>
</tr>
<tr>
<td>Argininosuccinate lyase</td>
<td>Argininosuccinic aciduria</td>
<td>↑↑↑citrulline</td>
<td>↑↑</td>
<td></td>
</tr>
<tr>
<td>Arginase</td>
<td>Argininemia</td>
<td>↑arginine</td>
<td>↑</td>
<td>Commonly presents with spastic diplegia</td>
</tr>
<tr>
<td>Mitochondrial ornithine transporter</td>
<td>HHHH syndrome</td>
<td>↑ornithine</td>
<td>↑↑</td>
<td>Homocitrullinuria</td>
</tr>
<tr>
<td>Ornithine aminotransferase (OAT)</td>
<td>OAT deficiency</td>
<td>↑ornithine</td>
<td>N</td>
<td>Normal ammonia levels; gyrate atrophy of choroid and retina</td>
</tr>
</tbody>
</table>

Abbreviations used: N, normal; ↑↑↑, increased; ↓, decreased; HHHH, hyperammonemia, hyperornithinemia, homocitrullinuria.
acute episodes of metabolic encephalopathy brought on by a physical stress or they may present with chronic symptoms, such as learning disorders, mental retardation, or seizures. Some have presented with stroke-like episodes. A dietary history may reveal an aversion to high-protein foods. Magnetic resonance imaging of the brain is often abnormal in both acute and chronic presentations.

The pathophysiology of urea cycle defects is incompletely understood. As with most metabolic defects, substrates upstream of the enzymatic block accumulate, and downstream products may become depleted. Glutamine and alanine levels generally increase together with the ammonia level. Evidence suggests that at least some of the cerebral edema is due to the osmotic force of accumulated intracellular glutamine.

When a urea cycle defect is present, the plasma amino acid pattern and urine orotic acid level often suggest the specific diagnosis (Table 1). Low citrulline levels characterize N-acetylglutamate synthetase deficiency, carbamoyl phosphate synthetase deficiency, and ornithine transcarbamoylase (OTC) deficiency. Among these, the urine orotic acid level is elevated only in OTC deficiency. Citrullinemia, argininosuccinic aciduria, argininemia, and the HHH syndrome can be distinguished by specific amino acid patterns. Enzyme assays or gene sequencing may be useful to confirm a suspected diagnosis or to provide a prenatal diagnosis in an at-risk pregnancy. A small fraction of patients with hyperammonemia and elevated plasma citrulline levels will have citrullinemia type II, a secondary disturbance of the urea cycle that is caused by mutations in the gene for citrin, a mitochondrial aspartate/glutamate transporter.

The acute treatment of hyperammonemic crises may require hemodialysis. The long-term treatment of urea cycle defects generally requires a protein-restricted diet, often including replacement of natural protein with preparations of essential amino acids. Treatment with extra arginine and citrulline to replace depleted urea cycle intermediates is beneficial. Administration of benzoate, phenylacetate, or phenylbutyrate increases the excretion of nitrogen by alternative routes. Treatment of seizures with valproic acid should be avoided because this drug may worsen hyperammonemia. Despite careful dietary and pharmacological treatment, the long-term prognosis for cognitive function in patients with severe urea cycle defects is poor. Liver transplantation is an option that is being used more frequently.

Defects in the Catabolism of Essential Amino Acids

Table 2 lists selected disorders of the catabolism of specific essential amino acids. Because these particular amino acids are not synthesized by human beings, many of these disorders may be effectively treated by reducing the dietary intake of the relevant amino acid(s). However, early treatment may be essential to prevent irreversible consequences, such as brain damage. Some patients may also benefit from treatment with specific enzyme cofactors. For example, thiamine, a cofactor required for the function of the branched-chain ketoacid dehydrogenase, helps some patients with maple syrup urine disease. Biotin can be used to treat multiple carboxylase deficiency due to either biotinidase deficiency or a partial loss of holocarboxylase synthetase activity.

Defects in the Catabolism of Nonessential Amino Acids

Table 3 lists selected disorders of the catabolism of nonessential amino acids. Because these amino acids are synthesized within the human body, restricting the dietary intake of the offending amino acid is usually not sufficient to prevent disease progression. Thus, these disorders tend to be more difficult to treat than those involving essential amino acids.

Disorders of tyrosine catabolism may be ameliorated to some extent by restricting the dietary intake of both tyrosine and its precursor phenylalanine. Recently, the medical treatment of tyrosinemia type I has been revolutionized by the use of 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexane dione, also known as NTBC or nitisinone. This compound prevents the accumulation of the toxic tyrosine metabolites fumarylacetoacetate, maleylacetoacetate, and succinylacetone by blocking the catabolism of tyrosine at an earlier step. NTBC is also being tried as a treatment for alkaptonuria. In the future, other metabolic disorders may be treated using the same general strategy of inhibiting an earlier step in the affected pathway.

DISORDERS OF AMINO ACID SYNTHESIS

Serine Deficiency

Very few disorders of amino acid biosynthesis are known. One such disorder, which is of significant neurological interest, is serine deficiency due to reduced activity of 3-phosphoglycerate dehydrogen-
These patients have congenital microcephaly and develop spastic quadriplegia, psychomotor retardation, and intractable seizures. The pathogenesis of these symptoms most likely involves not only a deficiency of serine in the brain but also deficiencies of various serine derivatives, such as glycine, serine phospholipids, sphingomyelins, or cerebrosides. In the proper clinical setting, this diagnosis is suggested by low levels of serine and glycine in the CSF and fasting plasma. Oral treatment with supplemental serine usually stops the seizures and ameliorates some of the other features of the disorder.

### Δ^1-Pyrroline-5-Carboxylate Synthase Deficiency

Δ^1-Pyrroline-5-carboxylate (P5C) synthase catalyzes the reduction of glutamate to P5C, a critical step in the biosynthesis of proline, ornithine, citrulline, and arginine. Baumgartner et al. reported homozygous mutations in P5C synthase in two siblings who suffer from progressive neurodegeneration, joint laxity, skin hyperelasticity, and bilateral subcapsular cataracts. Metabolic studies have shown these patients to have paradoxical preprandial episodes of hyperammonemia and low plasma levels of proline, ornithine,
citrulline, and arginine. The hyperammonemia apparently results from the decreased availability of ornithine, a urea cycle intermediate that is synthesized from P5C (Fig. 2). The connective tissue abnormalities might reasonably be attributed to the deficiency of proline, which is a major constituent of collagens. Confirmation and further delineation of this fascinating syndrome await the identification of additional patients.

**Homocystinuria**

The biochemical pathway that humans use to synthesize cysteine (Fig. 3) serves simultaneously as the catabolic pathway for methionine and as a source of the important methyl donor S-adenosylmethionine. Homocysteine, an intermediate in this pathway, accumulates in each of the several forms of homocystinuria. The most common form, homocystinuria type I (inherited as an autosomal recessive trait), is due to deficiency of cystathionine-β-synthase. Clinical features may include subluxations of the lenses of the eyes, mental retardation, psychiatric disorders, a tall and thin body habitus with long fingers and other skeletal abnormalities reminiscent of Marfan syndrome, a fair complexion, and a predisposition to thromboembolic events, especially in the brain. Laboratory abnormalities include the presence of homocystine in the urine and elevations of plasma methionine and homocysteine. Cystathionine-β-synthase uses pyridoxal 5'-phosphate (a derivative of pyridoxine) as a cofactor, and approximately 40% of patients with homocystinuria type I respond to treatment with high doses of pyridoxine (vitamin B6). Treatment should also include folate, cysteine, a low methionine diet, and, in some cases, betaine.

Homocystinuria type II may be caused by any of several recessive defects in vitamin B12 metabolism that interfere with production of methylcobalamin, a cofactor required by methionine synthase. Cell complementation studies have revealed the existence of at least five such defects, designated cblC–cblG. In addition to homocystinuria, these patients have megaloblastic anemia, poor growth, developmental delay, seizures, and other neurological abnormalities. Their plasma homocysteine levels are elevated; however, in contrast to homocystinuria type I, their methionine levels are decreased. Patients with cblC, cblD, and cblF also suffer from methylmalonic aciduria due to defective formation of adenosylcobalamin (a cofactor for methylmalonyl-CoA mutase). Treatment should include both vitamin B12 and betaine.
Homocystinuria type III, inherited as an autosomal recessive trait, is caused by deficiency of methylene tetrahydrofolate reductase. Patients with a complete absence of enzyme activity present with neonatal apneic episodes and myoclonic seizures, progressing to coma and death. Incomplete enzyme deficiencies can produce a range of phenotypes, including mental retardation, seizures, microcephaly, spasticity, psychiatric symptoms, peripheral neuropathy, and/or premature vascular disease. Megaloblastic anemia does not occur. Laboratory findings typically show moderate elevations of plasma homocysteine and low or low-normal levels of methionine. Treatment is difficult, and various combinations of agents have been recommended. Regimens that include betaine appear to be the most successful.

**DISORDERS OF AMINO ACID TRANSPORT**

A variety of specific transport mechanisms catalyze the movement of amino acids across biological membranes. Some such transporters operate on groups of structurally related amino acids, whereas others serve only one specific amino acid. Table 4 lists most of the known disorders of amino acid transport. These transport mechanisms may be specific to certain cell types and may even be localized to specific portions of the plasma membrane. For example, lysinuric protein intolerance is caused by deficiency of a dibasic amino acid transporter that in renal and intestinal epithelial cells is localized to the basolateral membrane. When this transporter is defective, intestinal absorption and renal tubular reabsorption of lysine, arginine, and ornithine are impaired. Therefore, urinary excretion of these amino acids is high, and their plasma levels are low. Patients with this disorder suffer from protein intolerance and episodes of hyperammonemia that result from having insufficient arginine and ornithine for proper functioning of the urea cycle. Other clinical features may include poor growth, osteoporosis, immune deficiencies, alveolar proteinosis, pulmonary fibrosis, or mental retardation. The occurrence of mental retardation is most likely related to the severity of the episodes of hyperammonemia. Treatment involves a moderate dietary protein restriction and replacement of urea cycle intermediates through oral citrulline administration.

Amino acid transport mechanisms may also be specific to certain subcellular organelles. For example, cystinosis is a lysosomal storage disease caused by mutations in a lysosomal membrane protein. These mutations result in decreased efflux of cystine from lysosomes. The major clinical manifestation of cystinosis is renal failure. The diagnosis of cystinosis can be made by demonstrating an increased cystine content in lymphocytes. Treatment with cysteamine helps remove cystine from lysosomes through the formation of mixed disulfides and slows progression of the disease, but kidney transplantation is often necessary. Later, extrarenal manifestations may occur, including ocular problems, hypothyroidism, diabetes, myopathy, or encephalopathy.

Hartnup’s disorder is inherited as an autosomal recessive trait with a prevalence of approximately 1 in 30,000 people. These patients have decreased...
Intestinal absorption and decreased renal tubular reabsorption of many neutral amino acids, including tryptophan. Symptoms of episodic ataxia and a "pellagra-like" rash are seen in some patients. Mental retardation has been reported in a few. However, population screening suggests that the vast majority of patients with Hartnup's disorder remain asymptomatic. Human cells require nicotinamide, which may be synthesized from either tryptophan or niacin. Niacin deficiency produces pellagra. Treatment with niacin has been reported to improve the symptoms of Hartnup’s disorder in some patients, and it is likely that sufficient dietary niacin intake is one of the factors that accounts for the lack of symptoms in most Hartnup patients.

**DISORDERS OF AMINO ACID DERIVATIVES**

**Neurotransmitter Disorders**

Many neurotransmitters, including serotonin, γ-aminobutyric acid, dopamine, epinephrine, and norepinephrine, are derived from amino acids. Defects in the metabolism of these compounds are discussed elsewhere in this encyclopedia.

**Creatine-Deficiency Syndromes**

Recently, three interesting disorders of the metabolism of creatine have been described. The incidence and the clinical variability of these disorders have not yet been determined. However, each of these defects has been associated with severe neurological symptoms in at least a few patients. Two of the three disorders appear to be treatable with oral creatine.

Creatine is formed from glycine, arginine, and S-adenosylmethionine (Fig. 4). Creatine synthesis occurs primarily in the liver, pancreas, and kidneys. Other organs, especially the brain and muscles, take up creatine from the blood. Inside cells, creatine is phosphorylated and serves as a reservoir of high-energy phosphate groups, allowing more rapid regeneration of adenosine triphosphate and thus supporting many energy-requiring reactions.

A deficiency of either arginine:glycine amidinotransferase or guanidinoacetate methyltransferase impairs the production of creatine. Patients with these autosomal recessive disorders have shown variable neurological symptoms, including mental retardation, seizures, hypotonia, and/or dystonia. Cerebral magnetic resonance spectroscopy (MRS) in affected individuals shows absence of the usual peaks corresponding to creatine and phosphocreatine. Treatment with oral creatine gradually restores brain creatine concentrations to nearly normal levels and results in some clinical improvement. Similar symptoms and MRS findings have also been described in patients with mutations in the X-linked gene encoding the transporter that allows creatine to enter brain.

**Table 4 SELECTED DISORDERS OF AMINO ACID TRANSPORT**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Amino acid(s)</th>
<th>Transporter</th>
<th>Major sites involved</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystinosis</td>
<td>Cystine</td>
<td>Cystine transporter</td>
<td>Lysosomal membranes</td>
<td>Renal failure; late endocrine, ocular, and neuromuscular manifestations</td>
</tr>
<tr>
<td>Cystinuria</td>
<td>Cystine, arginine, lysine, ornithine</td>
<td>Shared cystine and dibasic amino acid transporter</td>
<td>Renal tubules, intestinal mucosa</td>
<td>Cystine renal stones</td>
</tr>
<tr>
<td>Lysinuric protein intolerance</td>
<td>Arginine, lysine, ornithine</td>
<td>Dibasic amino acid transporter</td>
<td>Renal tubules, intestinal mucosa</td>
<td>PI, hyperammonemia, MR, poor growth, osteoporosis, hepatosplenomegaly</td>
</tr>
<tr>
<td>Dicarboxylic aminoaciduria</td>
<td>Aspartate, glutamate</td>
<td>Dicarboxylic amino acid transporter</td>
<td>Renal tubules, intestinal mucosa</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>Hartnup disorder</td>
<td>Most neutral amino acids</td>
<td>Neutral amino acid transporter</td>
<td>Renal tubules, intestinal mucosa</td>
<td>Most asymptomatic, intermittent ataxia and rash possible</td>
</tr>
<tr>
<td>Histidinuria</td>
<td>Histidine</td>
<td>Histidine transporter</td>
<td>Renal tubules, intestinal mucosa</td>
<td>Possible MR, possible seizures</td>
</tr>
<tr>
<td>Iminoglycinuria</td>
<td>Glycine, hydroxyproline, proline</td>
<td>Shared glycine and amino acid transporter</td>
<td>Renal tubules, intestinal mucosa</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>Methionine malabsorption</td>
<td>Methionine</td>
<td>Methionine transporter</td>
<td>Intestinal mucosa</td>
<td>MR, seizures, hyperpnea, white hair, α-hydroxy butyricaciduria</td>
</tr>
</tbody>
</table>

*Abbreviations used: PI, protein intolerance; MR, mental retardation.*
and muscle cells. As might be predicted, patients with such transporter defects have not responded to treatment with oral creatine.

—Edward G. Neilan and Vivian E. Shih

See also—Amino Acids

Further Reading


**Amino Acids**

Although it has been proposed that the first living things on Earth may have been self-replicating polymers of ribonucleic acids, amino acids are now equally indispensable to all known forms of life. The genetic code carried in nucleic acids is translated into proteins composed of linear polymers of amino acids. It is largely these proteins that carry out the work of the living cell. Thus, amino acids play a critical role in nature as the building blocks of proteins. In addition, amino acids serve living things as sources of metabolic energy, as neurotransmitters, and as required substrates for the biosyntheses of a variety of other important molecules.

**Structure of Amino Acids**

The term amino acid usually refers to an \( \alpha \)-amino carboxylic acid in which the \( \alpha \) carbon atom adjacent to a carboxylic acid moiety (\(-\text{COOH}\)) carries three other substituents: an amino group (\(-\text{NH}_2\)), a hydrogen atom (\(-\text{H}\)), and a variable side chain conventionally symbolized as “\(-\text{R}\)” (Fig. 1). These four substituents are arranged around the \( \alpha \) carbon in a tetrahedral fashion. Two nonoverlapping arrangements are possible. By convention, these optically active, mirror-image stereoisomers are designated the \( \text{L} \) and \( \text{D} \) forms. Except in the case of glycine, in which \( \text{R} \) is a second hydrogen atom, the four substituents are different, making the \( \alpha \) carbon a center of chirality.

Only the \( \text{L} \)-isomers of amino acids are commonly found in proteins. The biosynthetic pathways that

![Figure 1](image1.png)

**Figure 1**

The structure of amino acids. Most are optically active and exist as mirror-image \( \text{L} \)- or \( \text{D} \)-isomers.