In the past few years, there has been a veritable explosion in the discovery of “new” inborn errors of metabolism. These new conditions are involved in complex pathways of intermediary metabolism affecting processes heretofore unknown. The phenotypes of these new conditions are in many ways milder than the classically described metabolic disorders. Several of these conditions present as nonsyndromic neurodevelopmental and/or neurobehavioral disorders. As such, these conditions should be considered in the differential diagnosis of conditions such as mental retardation, autism spectrum disorders, movement disorders, and cerebral palsy. This article reviews several of these recently described conditions including the clinical presentation, the biochemical profile, the diagnostic approach, and therapeutic options.

Much has been said about the increased incidence of autistic spectrum disorders seen in children today. The genetic and neurogenetic workup for affected individuals has been discussed at length in previous articles in this journal. It is known that inborn errors of metabolism are the cause for a subset of developmental disabilities and autism and that routine metabolic screening studies are recommended on a case-by-case basis and based on clinical features. This article reviews in more detail several inborn errors of metabolism that may present with or include features of autism and/or neurodevelopmental delay. These conditions included disorders of creatine biosynthesis, gamma-aminobutyric acid catabolism, purine and pyrimidine metabolism, and glucose transport across the blood-brain barrier.

**Guanidinoacetate Methyltransferase Deficiency**

Guanidinoacetate methyltransferase (GAMT) deficiency (Online Mendelian Inheritance in Man [OMIM] + 601240) is an autosomal recessive inborn error of creatine biosynthesis. GAMT deficiency is characterized by developmental arrest or delay in the first few months of life with epilepsy and extrapyramidal movement disorders as common features.1 Neurologic signs and symptoms are variable, and autistic spectrum disorders are sometimes seen in older affected individuals. The diagnosis of GAMT deficiency is based on excessive amounts of guanidinoacetate in body fluids and decreased levels of creatine/phosphocreatine in the brain.2 Very low creatinine concentrations in plasma and urine may also aid in the diagnosis. The guanidinoacetate methyltransferase (GAMT) gene is located on chromosome 19p13.3, and the guanidinoacetate methyltransferase enzyme (GAMT, EC 2.1.1.2) catalyzes the second step of creatine biosynthesis. Treatment of GAMT deficiency includes oral supplementation with creatine and has variable clinical efficacy.

The index case for GAMT deficiency was reported by Stockler1 in 1994. Stockler’s case involved a 22-month-old male with muscular hypotonia and progressive extrapyramidal movement disorder. There was also an extremely low excretion of creatine. The clinical phenotype seen in affected individuals includes progressive encephalopathy during the first months of life. This encephalopathy is characterized by muscular hypotonia, dyskinetic movements, developmental arrest, and occasionally regression. Loss of speech with autistic and self-injurious behaviors was present in 3 of 4 affected individuals first described.3 Dysmorphic features are not a part of GAMT deficiency.

The diagnosis of GAMT deficiency should be suspected based on clinical features and decreased creatinine concentrations in plasma, cerebrospinal fluid (CSF), and urine. The more prominent and better diagnostic analyte is guanidinoacetate. Guanidinoacetate is elevated in urine (2,224–3,987 μmol/L, normal 63–429 μmol/L), plasma (12.9–20.7 μmol/L,
normal 0.52-1.14 μmol/L, and CSF (10.6-12.7 μmol/L, normal 0.032-0.087 μmol/L) of affected individuals. Magnetic resonance spectroscopy shows increased guanidinoacetate and absent creatine and phosphocreatine in the brains of all affected individuals.4,3

Creatine is synthesized from glycine, arginine, and methionine. The first reaction forms guanidinoacetate and ornithine and is catalyzed by arginine-glycine aminidinotransferase (AT, EC 2.1.4.1). The second reaction is catalyzed by GAMT. During this step, guanidinoacetate receives a methyl group from S-adenosylmethionine forming creatine. Phosphocreatine and creatine are nonenzymatically degraded to creatinine. The GAMT gene located at 19p13.35 is composed of 4.5 kb of genomic DNA. The product is a 236 amino acid cytosolic protein. Five disease-causing alleles have been identified to date by sequencing GAMT in clinically diagnosed individuals.7-9

Pathophysiology of GAMT deficiency is thought to be caused by deficiencies of creatine and phosphocreatine pools and increased concentrations of guanidinoacetate. Excess guanidinoacetate may lead to the formation of other potentially toxic guanidino compounds. The treatment for GAMT deficiency is aimed at replacing creatine. Systemic creatine deficiency is treatable with oral supplementation of creatine monohydrate. Creatine monohydrate is nontoxic and tolerable at very high doses. Variable improvements have been noted in affected individuals treated with creatine monohydrate; however, none of the affected individuals has had a complete resolution of features.1,2,11-13

**Succinic Semialdehyde Dehydrogenase Deficiency**

Succinic semialdehyde dehydrogenase (SSADH) deficiency (OMIM #271980), also known as 4-hydroxybutyric aciduria (4-HBA), is an autosomal recessive inborn error of metabolism first described by Jakobs et al in 1981.14 Since then, over 150 cases have been identified. Clinical features include mild to severe impairment of motor skills, language, speech, and intellect. Many affected individuals also presented with hypertonia and a nonprogressive form of truncal and appendicular ataxia. The causative gene is aldehyde dehydrogenase 5 (ALD5A1) located at 6p22.15 SSADH (EC 1.2.1.24) is deficient in affected individuals impairing the formation of succinic acid from succinic semialdehyde and leading to the increased production of 4-HBA. Treatment is limited to vigabatrin, a GABA-transaminase inhibitor, and efficacy over the long-term is questionable. 4-HBA receptor antagonists or certain GABA receptor antagonists appear to have promise as therapeutics; however, clinical trial data are lacking.17

**Adenylosuccinate Lyase Deficiency**

Adenylosuccinate lyase (ADSL) deficiency (OMIM #103050) is an autosomal recessive disorder of purine metabolism. Characteristic neurologic features include psychomotor delay, autism, and seizures.19 The associated gene is adenylosuccinate lyase (ADSL). This enzyme deficiency is characterized by increased amounts of succinyl adenosine (S-Ado) and succinyl aminomimidazole carboxamide ribotide (SAICAR) in CSF, urine, and plasma. Treatment has been aimed at replenishing purine nucleotides. The prognosis for individuals with ADSL deficiency is variable, but poor.

ADSL deficiency is the first purine synthesis enzyme deficiency from the de novo pathway reported in man. First described in 1984, the features of ADSL deficiency comprise a variable spectrum presenting with profound psychomotor retardation, autistic features, epilepsy, hypotonia, peripheral hypertonia, and failure to thrive.20 Two female patients presented with mild psychomotor retardation and delayed motor development with muscle hypotonia, respectively. Dysmorphic features are not a part of the condition. To date, around 40 patients have been reported, and this is thought to be an underrecognized condition. The clinical heterogeneity
Phosphoribosylpyrophosphate Synthetase Superactivity

Phosphoribosylpyrophosphate synthetase (PRPS1) superactivity (OMIM #300661) is an X-linked inborn error of purine metabolism with features of gout and hyperuricemia. Some individuals affected with PRPS1 superactivity also have neurodevelopmental abnormalities, including sensorineural deafness. The associated gene is phosphoribosylpyrophosphate synthetase (PRPS1). PRPS1 superactivity should be suspected in individuals with hyperuricemia, gout, mental retardation, and sensorineural deafness. PRPS1 superactivity, an X-linked trait, has 2 common phenotypes. In families with more severe phenotype, affected males present in early childhood with hyperuricemia and associated gout. These affected males also have neurodevelopmental impairment with frequent sensorineural deafness. Heterozygous females in the early-onset families have also presented with gout, and several affected females were deaf. The late-onset juvenile or early adult-onset presentation is only known to affect males. Features of late-onset PRPS1 superactivity are restricted to hyperuricemia, and affected males have gout and uric acid urolithiasis but no neurodevelopmental impairment. There are 2 disorders allelic to PRPS1 superactivity. In the first condition, X-linked recessive Charcot-Marie-Tooth disease-5 (OMIM #311070), affected individuals have neurologic symptoms, including sensorineural deafness. The phenotype of the second allelic disorder, Arts syndrome (OMIM #301835), includes mental retardation, early-onset hypotonia, and susceptibility to infections. However, both of these conditions are caused by PRPS1 deficiency.

Dihydropyrimidine Dehydrogenase Deficiency

Dihydropyrimidine dehydrogenase (DPYS) deficiency (OMIM + 274270) is an autosomal recessive disorder of pyrimidine catabolism known also as uraciluria thyminuria. DPYS deficiency is also known as an inborn error of β-amino acid metabolism. Excess amounts of uracil, thymine, and 5-hydroxymethyluracil accumulate in the urine of affected individuals. The causative gene is dihydropyrimidine dehydrogenase (DPYS) located on chromosome 1 at 1p22. There is much phenotypic variation with DPYS deficiency. Neurologic features are prominent and include convulsions and mental retardation. Enzyme-deficient asymptomatic relatives of affected probands have been described.

DPYS deficiency has 2 clinical forms. Thirty-three individuals have been reported with the clinically heterogeneous early-onset form. Neurologic features appear prominent and include seizures and mental retardation. Other features present may include microcephaly, hypertonia, autistic features, and hyperreflexia. The second form is the pharmaco-
genetic form of DPYS deficiency and is followed by exposure to 5-fluorouracil. Features for 17 reported patients included gastrointestinal effects, neurologic toxicity, cutaneous, and gastrointestinal effects. With unexplained severe diarrhea in individuals undergoing chemotherapy, DPYS deficiency should be considered. 

Dihydropyrimidine dehydrogenase (EC 1.3.1.2) catalyzes the rate limiting and first step in uracil and thymidine catabolism. Pyrimidine catabolism is also the only way to produce β-alanine in mammals. Dihydropyrimidines do not accumulate in either form of DPYS deficiency. However, testing urine for excess pyrimidine metabolites by gas chromatography/mass spectroscopy is an adequate screening method. The preferred technique for accurate quantification of pyrimidine metabolites is HPLC.

Clinical findings that warrant screening for disorders of purine and pyrimidine metabolism were summarized by Duran et al. Possible clinical findings that may suggest abnormal purine/pyrimidine metabolism include gouty arthritis, mental retardation with neurologic deficits, immune deficiency of unknown origin, failure to thrive, unexplained hemolytic anemia, hyper- or hypotonia, self-mutilation, muscle weakness, and dysmorphic features.

**Glucose Transport Defect, Blood-Brain Barrier**

Glucose transport defect of the blood-brain barrier (GLUT1 deficiency syndrome, OMIM #606777) is an autosomal dominant inborn error of glucose transport across the blood-brain barrier. Affected individuals present with mental retardation and learning disabilities; also common are ataxia, dystonia, seizures, and acquired microcephaly. The responsible gene is solute carrier member 2, family 1 (SLC2A1) located on chromosome 1 at 1p35 to 31.3. SLC2A1 encodes a facilitated glucose transporter responsible for transporting glucose across the blood-brain barrier. The ketogenic diet has had good success at reducing or eliminating seizures in affected individuals.

In 1991, De Vivo et al described 2 patients who had seizures, acquired microcephaly, and developmental delay. These 2 patients had normal blood sugar and normal CSF lactate but consistently low CSF glucose suggesting a defect in transport of glucose across the blood-brain barrier. In 2005, Wang et al used 16 patients with confirmed molecular diagnosis to identify 3 main clinical phenotypes. The most common phenotype, identified in 13 of 16 patients, was a developmental encephalopathy with infantile seizures, acquired microcephaly, and spasticity. Seizures were unresponsive to typical anticonvulsant medication, but response was rapid with initiation of a ketogenic diet. The second and third phenotypes were notable for an absence of seizures. Cognitive impairment of all affected individuals ranged from mild to moderate learning disabilities to severe mental retardation. Biochemical analysis showed that all patients had decreased glucose uptake into erythrocytes and decreased CSF glucose levels when compared with controls.

SLC2A1, located at 1p35 to 31.3, is a 33-kb gene that encodes for a 492 amino acid cellular membrane protein located in red blood cells and at the blood-brain barrier. The pathogenesis of GLUT1 deficiency is caused by a persistent decrease in glucose in the developing brain, and it is hypothesized that glucose serves a dual role in the developing brain, acting as a fuel and as a signaling molecule.

The ketogenic diet has been used to treat patients with seizures and low CSF glucose. Four patients with GLUT1 deficiency were started on a ketogenic diet at 6 to 28 weeks of age. Ketosis developed within 24 hours. 3-Hydroxybutyrate concentrations available at the bedside correlated inversely with the base excess. At glucose levels of 40 mg/dL or less, patients remained asymptomatic in the presence of ketones. The ketogenic formula was tolerated well, parental compliance was good, and all patients remained seizure free on the diet.

**References**