Inborn Errors of Metabolism with Cognitive Impairment

Metabolism Defects of Phenylalanine, Homocysteine and Methionine, Purine and Pyrimidine, and Creatine

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KEYWORDS

• Phenylalanine • Homocysteine methionine • Purine pyrimidine
• Creatine metabolism defects

KEY POINTS

- Untreated classic phenylketonuria causes severe intellectual disability. Newborn screening was the logical and necessary consequence of development of a successful treatment.
- Untreated classic homocysteinuria affects the eyes, skeleton, vasculature, and brain. Affected individuals remain asymptomatic, but can later suffer severe thromboembolic episodes.
- Lesch-Nyhan syndrome is an X-linked recessive disorder caused by hypoxanthine-guanine phosphoribosyl transferase deficiency. The result is hypoxanthine accumulation and conversion into uric acid.
- Defects of creatine synthesis: guanidinoacetate methyltransferase deficiency, L-arginine:-glycine amidinotransferase deficiency, and creatine transporter defect, result in cerebral creatine deficiency.

INTRODUCTION

Intellectual disability (ID), according to the definition by the American Association of Intellectual and Developmental Disabilities, is a "disability characterized by significant limitations in both intellectual functioning and in adaptive behavior, which covers many everyday social and practical skills and originates before the age of 18."[1] It has a prevalence of 1% to 3% and it is estimated that the average lifetime cost to society per person is $1 million.[2] After a diagnosis of ID, it is important to try to identify a cause because, although uncommon, a metabolic disease amenable to treatment may be

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identified. Even if no treatment is available, establishing a diagnosis will help families to understand what to expect, discuss recurrence risks and may also help them to identify appropriate support groups and other resources.

Inborn errors of metabolism (IEMs) account for up to 5% of nonspecific ID.[3] Neurologic manifestations, other than ID, may be part of the IEMs phenotype and include seizures, ataxia, dystonia, spasticity, and psychomotor regression. Multisystem involvement such as hepatosplenomegaly, cardiomyopathy, hearing impairment, eye and skin manifestations, skeletal anomalies, coarse facial features, may indicate a potential metabolic etiology of ID.[3] Unusual body odors, specific food avoidance (eg, protein aversion), and self-injurious behaviors should make pediatricians consider IEMs. History of consanguinity and unexplained fetal or infantile deaths are additional clues toward the diagnosis of a metabolic disorder. Evaluating a child with ID takes a stepwise approach and should start with a detailed personal and family history along with a comprehensive physical examination focusing specifically on neurologic and behavioral findings. IEMs that cause ID include phenylketonuria (PKU), galactosemia, lysosomal storage disorders, urea cycle defects, homocystinuria, cholesterol biosynthesis defects, disorders of purine and pyrimidine metabolism, creatine deficiency syndromes, and congenital disorders of glycosylation. Van Karnebeek and colleagues[4] recommended first- and second-tier metabolic testing to identify individuals with suspected IEMs. A first-tier workup includes serum lactate, ammonia, copper, ceruloplasmin, total plasma homocysteine, plasma amino acids, acylcarnitine profile (whole blood or plasma), creatine metabolites in urine, urine purines and pyrimidines, urine organic acids, and urine oligosaccharides and glycosaminoglycans. Van Karnebeek and colleagues state that these tests can identify 60% of all IEM potentially amenable to treatment. The second tier incorporates specific testing, which is beyond the scope of this article because it requires molecular and invasive testing.

An early diagnosis of treatable metabolic conditions associated with ID can ameliorate if not prevent adverse disease outcomes and reduce the negative disease impact to affected individuals and their families. In this article, we present disorders of phenylalanine metabolism, disorders of homocysteine metabolism, inborn errors of purine and pyrimidine metabolism, and creatine deficiency syndromes that belong in this category.

DEFECTS OF PHENYLALANINE METABOLISM: PHENYLALANINE HYDROXYLASE DEFICIENCY (PHENYLKETONURIA), AND TETRAHYDROBIOPTERIN BIOSYNTHESIS AND REGENERATION DEFECTS

Presenting Symptoms

- Elevated phenylalanine level on newborn screen.
- Depending on the degree of elevation, the pediatrician will be asked to send a repeat newborn screening sample or refer child to a metabolic center immediately.

Clinical Presentation

A. The severe phenotype of PKU is unusual in the United States because successful screening allows early detection and prompt institution of treatment. However, individuals that are under strict dietary control, may still present with attention deficit hyperactivity disorder, anxiety, and academic difficulties.[5] If PKU is left untreated, affected individuals present with the following:
   - Profound ID.
   - Neuropsychiatric and behavioral manifestations: Hypertonia-spastic paraparesis, seizures, dementia, Parkinsonism, behavioral problems, autism, and microcephaly.