Question: 199

A 7-year-old boy who is new to your practice comes in for evaluation of developmental delay and poor school performance. He began speaking in sentences at age 4. He repeated kindergarten and is struggling in first grade. On physical examination, you note that he has fair hair and light skin compared with his brown-haired, olive-skinned younger brother and mother. He is wearing thick glasses, and his mother says that he was diagnosed as being near-sighted when he was 2 years old. He has a lanky build with long fingers, and on forward bending, there is a curve in the thoracolumbar spine.

Of the following, the condition that is MOST consistent with this presentation is

A. alkaptonuria
B. homocystinuria
C. nonketotic hyperglycinemia
D. oculocutaneous tyrosinemia
E. phenylketonuria
Inborn errors of amino acid metabolism (aminoacidopathies) result from the abnormal breakdown of amino acids in the cytosol. The symptoms associated with this group of disorders are due to the accumulation of toxic intermediates, such as phenylalanine, that cause organ damage. Disorders of amino acid metabolism are diagnosed with the aid of plasma and urine amino acid quantitation; sometimes, measuring urine organic acids also is helpful. The treatment of aminoacidopathies involves generally limiting protein intake, specifically limiting intake of the offending protein, and avoiding catabolic states. These conditions are typically autosomal recessive.

Individuals who have homocystinuria are deficient in the enzyme cystathionine synthase, which leads to increased methionine in the blood. There are two subtypes of homocystinuria: B6-responsive and B6-nonresponsive. Excess methionine may be associated with a noticeable, unpleasant odor. Affected individuals often have more lightly pigmented eyes, skin, and hair than their unaffected family members, as described for the boy in the vignette. Dislocation of the lens(es) of the eye(s) is usually apparent by 10 years of age, and the lenses typically sublux downward. Other eye anomalies include myopia, optic atrophy, cataracts, and retinal detachment. Skeletal abnormalities are a prominent feature of homocystinuria and overlap with those seen in Marfan syndrome; they include tall stature with thin body habitus, pectus excavatum or carinatum, narrow palatal contour, and scoliosis. Some individuals have arachnodactyly (long fingers), such as the boy in the vignette. Thromboembolism is the most common cause of morbidity and premature death. The average intelligence quotient (IQ) for individuals who have the B6-responsive form of the disease is 79, whereas the average IQ for those who have the B6-nonresponsive form is 57. It is important to identify those individuals who are B6-responsive to mitigate poor intellectual outcome. Newborn screening for homocystinuria is required by law in most states in the United States.

Individuals who have alkaptonuria are deficient in the enzyme homogentisate 1,2-dioxygenase, which is involved in the tyrosine degradation pathway. Affected persons are typically asymptomatic in childhood. With age, they develop dark gray or black pigmentation of the sclerae or ear cartilage. Sweat may be dark, and cerumen may be almost black. At all ages, the urine of an affected individual, when left to stand, turns dark. Arthritis starts to develop in early adult life and progresses to marked limitation of movement and ankylosis of the spine. Individuals who have alkaptonuria have a high incidence of heart disease, and myocardial infarction is a common cause of death. Intelligence is typically normal.

Nonketotic hyperglycinemia results from deficient activity of proteins in the glycine cleavage system. The classic form of the disease presents in the first few days after birth, coinciding with intake of protein-containing feedings. Affected children develop anorexia and lethargy, which progresses to coma. Most affected individuals die at this time. Those who survive the acute neonatal crisis subsequently develop spastic cerebral palsy, with no evidence of psychomotor development.

Oculocutaneous tyrosinemia (tyrosinemia type II) is caused by hepatic deficiency of the enzyme tyrosine aminotransferase in the cytosol. The most important clinical manifestations of this disorder involve the eye due to the accumulation of tyrosine. Corneal erosions, ulcers, and plaques can occur and ultimately lead to corneal clouding and visual impairment. Affected
children may present with tearing, photophobia, and eye redness and pain. Cutaneous manifestations include painful keratoses occurring most often on pressure-bearing regions, such as the palms and the soles. Treatment of oculocutaneous tyrosinemia includes the institution of a diet low in tyrosine and phenylalanine. It is not entirely clear whether oculocutaneous tyrosinemia is associated with an increased incidence of intellectual disability; a previously described positive association may be due to ascertainment bias.

Phenylketonuria (PKU) is caused by complete or near-complete deficiency of the enzyme phenylalanine hydroxylase, which converts phenylalanine to tyrosine. Sometimes, the only manifestation of untreated PKU is intellectual disability. However, vomiting can be an early symptom, and irritability, an eczematous rash, and an unusual odor (described as mousy, barny, woiflike, or musty) also may be present. More than 90% of affected individuals are light-eyed, fair-skinned, and light-haired compared with their unaffected family members. Developmental delays usually are apparent in untreated individuals within the first 6 postnatal months; if left untreated, affected individuals suffer severe-to-profound intellectual disability. Spasticity and seizures also may occur. PKU is treated with a diet that is low in phenylalanine in conjunction with tyrosine supplementation. Early treatment can prevent the symptoms and signs of disease. Every state in the United States has required neonatal screening for PKU.

References:


