6 Disorders of Leucine Metabolism

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6.1 Introduction

Of the disorders of leucine metabolism, only maple syrup urine disease (MSUD) is associated with elevated body fluid levels of the branched-chain amino acids (BCAA), namely leucine, isoleucine, and valine. Due to irreversible steps early in the metabolism of the BCAA, elevated levels of these amino acids do not occur in those disorders that result from blocks in the pathways distal to the site of MSUD. Rather, the disorders are associated with organic acidemias/acidurias.

Severe forms of the disorders of leucine metabolism present as acute, overwhelming metabolic illness in the neonatal period, often during the 1st week of life. Other milder or variant forms may be episodic and might not become symptomatic until late childhood or even adult life. Also, some patients are asymptomatic and identified only through family studies or by newborn screening.

Maple syrup urine disease results from deficient activity of the branched-chain α-ketoacid dehydrogenase complex (BCKDC). During episodes of metabolic decompensation, the BCAA and their corresponding branched-chain α-ketoacids (BCKA) accumulate. At such times, affected patients have the odor of maple syrup in body fluids and cerumen from 2-oxo-3-methylvalerate, after which the disorder is named. The BCKDC consists of three catalytic components (E1, E2, and E3) encoded by four different genetic loci. The E1 component is a thiamine pyrophosphate-dependent decarboxylase comprised of two subunits, α and β, which are encoded by two separate loci. The E2 component is a dihydrolipoyl acyltransferase and the E3 component a lipoamide dehydrogenase. A regulatory BCKDC-specific kinase and phosphatase are also involved but not yet fully characterized. Mutations in all four of the catalytic loci have been associated with clinical disease.

Five clinical forms of MSUD exist, which are differentiated by the amount of residual enzymatic activity, age and severity of onset, and responsiveness to thiamine, a cofactor for the BCKDC. Classic MSUD patients present with poor feeding, lethargy, abnormal movements, and a progressive encephalopathy during the 1st week of life. Most patients have less than 2% of normal BCKDC specific activity; they are not responsive to thiamine administration.
Intermediate MSUD has similar symptoms, but with a later, variable age of onset. Patients have between 3 and 30% of normal residual specific activity of the BCKDC and they are not responsive to thiamine. Intermittent MSUD is characterized by episodes of ataxia and ketoacidosis that are associated with intercurrent illnesses or increased protein intake. Affected patients have between 5 and 20% of normal residual specific activity of the BCKDC and are not responsive to thiamine. Patients with thiamine-responsive MSUD have between 2 and 40% of normal residual specific activity of the BCKDC and show varying degrees of correction of their metabolic abnormalities in response to pharmacologic doses of thiamine. Deficiency of the E3 component results in decreased activity of the BCKDC (0–25% of normal) along with reduced activity of the pyruvate dehydrogenase complex and the 2-oxoglutarate dehydrogenase complex, because the E3 component is common to all three mitochondrial complexes. These patients have a combination of symptoms and biochemical findings for all three of the individual deficiencies and present during infancy with acidosis and a progressive encephalopathy. Although all three BCAA are elevated in body fluids, the pathophysiology of all forms of MSUD is thought to be related to the elevated levels of leucine.

With advances in the molecular pathology of MSUD, a certain degree of molecular genotype-clinical phenotype correlation has emerged. Patients with E1α and E2 mutations have varying clinical presentations (classic, intermittent, intermediate), depending upon the specific mutation involved. To date, all reported patients with E1β mutations have had the severe, classic clinical form of the disorder. All reported thiamine-responsive patients have had E2 mutations. The most frequent mutation, the E1α mutation Y393N, is associated with a severe classic presentation and found not only in the Mennonites, among whom it is common, but also in the general population in North America. Another common E1α mutation, G241R, is associated with intermediate clinical disease in the Hispanic-Mexican population. In that specific mutations have been shown to be associated with a certain type of clinical disease, determining the exact mutation involved through mutational analysis will help guide clinical management for the individual patient, especially in regard to the need for thiamine supplementation and the degree of restriction of dietary natural protein necessary to control the disorder (Chuang and Shih 2001; Morton et al. 2002).

Classic isovaleric acidemia (IVA) results from deficient activity of isovaleryl-CoA dehydrogenase and patients present with acute, neonatal metabolic disease or with chronic, intermittent episodes during the 1st years of life. Affected patients have the odor of “sweaty feet.” In addition to marked ketoacidosis, they may have bone marrow suppression and significant secondary hyperammonemia. Reduced activity of isovaleryl-CoA dehydrogenase also occurs as part of multiple acyl-CoA dehydrogenase deficiency, which is discussed with the disorders of mitochondrial fatty acid oxidation (Sweetman and Williams 2001; Ogier de Baulny and Saudubray 2002).