

Inherited Diseases Of Purine Metabolism

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Lesch–Nyhan syndrome (LNS, MIM 300322) is an X-linked recessive inherited disorder usually evident at 6–10 months of age with choreiform movements, compulsive self-mutilation, spasticity, mental retardation, hyperuricemia and gout. LNS is associated with many types of mutations in the gene for the purine salvage enzyme hypoxanthine-guanine phosphoribosyltransferase (HGPRT) (Nyhan, 1997; Jinnah et al., 2004). This enzyme normally catalyzes the recycling of purines from degraded DNA and RNA. There is an almost complete deficiency of this enzyme in patients with the full syndrome. However, individuals with a partial deficiency in HGPRT generally have hyperuricemia and gout but not the full neurologic manifestations (Puig et al., 2001). Treatment with allopurinol, which inhibits xanthine oxidase, reduces the levels of uric acid and the attendant symptoms of hyperuricemia but does not ameliorate the neurologic phenomena. Rasburicase, a urate oxidase enzyme, reduced urate to normal in one neonatal male (Roche et al., 2009). Positron emission tomography with [¹⁸F]-fluorodopa has demonstrated abnormally few dopaminergic nerve terminals and cell bodies in the basal ganglia and frontal cortex of LNS patients, suggesting pervasive developmental abnormalities in dopaminergic systems (Visser et al., 2000). A study of human neural stem cells from a fetal LNS brain demonstrated aberrant expression of several transcription factors and DA markers while HPRT-deficient DA neurons showed striking deficits in neurite outgrowth (Cristini et al., 2010). Developmental dopaminergic neuronal system abnormalities may be related to the genetic alteration that occur in the context of an aberrant multigene regulation pattern (Smith et al., 2000; Jinnah et al., 1999).

Mutations in the gene for adenylosuccinate lyase (ASL), inherited as an autosomal

recessive disorder in purine metabolism, are associated with severe mental retardation, seizures and autistic behavior, but apparently not self-mutilation (Stone et al., 1992; Sivendran et al., 2004). This homotetrameric enzyme catalyzes two distinct reactions in the *de novo* biosynthesis of purines: the cleavages of adenylosuccinate (S-Ado) and succinylaminoimidazole carboxamide ribotide (SAICAR), both of which accumulate in plasma, urine and cerebrospinal fluid of affected individuals. The accumulation of S-Ado in gray and white matter of patients can be detected as a specific signal by high-resolution proton MRS, which is a reliable noninvasive diagnostic tool (Henneke et al., 2010). Phenotypic severity may vary from neonatal fatality to severe or moderate childhood forms. Nineteen ADSL mutant proteins have been identified in 16 patients representing clinically distinct subgroups that could be correlated with biochemical properties of the mutant proteins (Zikanova et al., 2010). Mutations may involve the active site and/or cooperativity of subunit interactions that affect enzyme activity and stability (Ariyananda et al., 2009)

Deficiency of the muscle-specific myoadenylate deaminase (MADA1, MIM 102770) has been frequently associated with exercise-related weakness and has been believed a common cause of metabolic myopathy. MADA1 catalyzes the deamination of AMP to IMP in skeletal muscle and is critical in the purine nucleotide cycle. However, a more recent study has called into question the significance of the MADA1 deficiency, finding no difference in the mutation incidence between symptomatic and asymptomatic carriers (Hanisch et al., 2008).

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