Lesch-Nyhan Syndrome

In 1964, Lesch and Nyhan provided the first detailed clinical description of Lesch-Nyhan syndrome with a report of two brothers with hyperuricemia and a characteristic neurobehavioral syndrome that included motor dysfunction and self-injurious behavior. The prevalence of the syndrome is estimated to be approximately 1:380,000.

GENETICS/BASIC DEFECTS
1. Inheritance: X-linked recessive
2. Enzymatic defect: caused by deficiency of the enzyme hypoxanthine-guanine phosphoribosyltransferase (HPRT), which catalyzes the conversion of hypoxanthine to inosine monophosphate and guanine to guanine monophosphate in the presence of phosphoribosylpyrophosphate
3. Hypoxanthine-guanine phosphoribosyltransferase gene (HPRT1)
   a. Mapped to chromosome Xq26-q27.2
   b. The only gene known to be associated with Lesch-Nyhan syndrome
   c. Heterogeneous mutations
      i. Single base substitutions
      ii. Deletions
      iii. Insertion
      iv. Substitutions
4. Pathogenesis
   a. Metabolic basis of overproduction of uric acid: results from changes in the regulation of purine synthesis and degradation
   b. Pathogenesis of neurologic and behavioral features remains incompletely understood. Growing evidence suggests that these features result from dysfunction of the dopamine transmitter systems of the basal ganglia

CLINICAL FEATURES
1. Normal prenatal and perinatal course
2. Early developmental milestones
   a. Hypotonia and developmental delay: most common presenting features evident by 3–6 months of age
   b. Failure to reach normal motor milestones, such as delayed in crawling, sitting, and walking
3. Within the first few years
   a. Extrapyramidal involvement
      i. Dystonia
      ii. Choreaathetosis
      iii. Opisthotonus
      iv. Ballismus
   b. Pyramidal involvement
      i. Spasticity
      ii. Hyperreflexia
      iii. Extensor plantar reflexes
      iv. Ankle clonus
      v. Scissoring of the legs
4. Between 2 to 3 years
   a. Impaired cognition
      i. Moderate to severe mental retardation in most patients
      ii. Varying degree of impairment
      iii. Difficult to obtain adequate assessments of cognitive abilities
   b. Compulsive behavioral disturbances
      i. Aggressiveness
      ii. Vomiting
      iii. Spitting
      iv. Coprolalia
      v. Copropraxis
      vi. Manipulative behavior
   c. Persistent self-injurious behavior: a hallmark of the disease
      i. Biting the fingers, hands, lips, and buccal mucosa
      ii. Banging the head or limbs
5. Overproduction of uric acid
   a. Uric acid crystalluria noted as orange crystals in the diaper during the first weeks of life
   b. Deposition of uric acid crystals or calculi in the kidneys, ureters, or bladder
   c. Leading to nephrolithiasis, obstructive uropathy, and azotemia, if untreated
   d. Gouty arthritis develops later in the course of the disease
6. Other features
   a. Delayed growth and puberty
   b. Testicular atrophy in most affected males
   c. Associated orthopedic problems
      i. Hip subluxation or dislocation
      ii. Fractures
      iii. Autoamputation
      iv. Infections
      v. Minor scoliosis
      vi. Contractures
7. Life expectancy
   a. Most surviving into the second or third decade of life if properly managed
   b. No evidence suggesting disease progression over time
   c. Complications
      i. Aspiration pneumonia
      ii. Chronic nephrolithiasis
      iii. Renal failure
      iv. Sudden unexpected death
8. Lesch-Nyhan syndrome in females
   a. Extremely rare
   b. Female carriers
      i. Generally considered to be asymptomatic
      ii. Have increased uric acid excretion
      iii. Develop symptoms of hyperuricemia in later years
c. Affected females
   i. Affected carrier females: considered to have non-random X-chromosome inactivation or skewed inactivation of the normal HPRT1 allele
   ii. The first female case reported was caused by a microdeletion of the maternally derived HPRT gene and nonrandom inactivation of the paternally derived X chromosome
   iii. Two additional cases were caused by a point mutation in one allele and markedly reduced mRNA expression from the other allele

DIAGNOSTIC INVESTIGATIONS

1. EEG: nonspecific changes of slowing or disorganization
2. CT and MRI of the brain: nonspecific changes of atrophy of the basal ganglia or cerebrum
3. Positron emission tomography to demonstrate a selective decrease of 50–70% in dopamine transporters in the caudate and putamen
4. Hyperuricuria or hyperuricemia (serum uric acid concentration >8mg/dL): often present but not sensitive or specific enough for diagnosis
5. 24 Hour uric acid excretion (>20 mg/kg): characteristic but not diagnostic
6. Uric acid to creatinine ratio >2.0: characteristic for patients under 10 years of age
7. Hypoxanthine-guanine phosphoribosyltransferase enzyme activity <1.5% of normal enzyme activity in cells from any tissue (blood, cultured fibroblasts, or lymphoblasts): establishes the diagnosis
8. Molecular genetic testing of the HPRT1 gene
   a. Purposes
      i. To define the mutation in the affected males
      ii. To determine carrier status in at-risk females
   b. Sequence analysis to detect HPRT1 mutations in males affected with Lesch-Nyhan syndrome: available on clinical basis
   c. Direct DNA analysis using RT-PCR, multiplex genomic PCR, and sequence analysis performed on research basis

GENETIC COUNSELING

1. Recurrence risk
   a. Patient’s sib
      i. When the mother is not a carrier: not increased unless the mother has germline mosaicism in which case there is an undetermined, but real, risk of having future affected sons or carrier daughters
      ii. When the mother is a carrier
         a) A 25% risk of having an affected male
         b) A 25% risk of having a carrier female
         c) A 50% risk of having an unaffected male or female
   b. Patient’s offspring
      i. Severely affected males: not surviving to reproductive age
      ii. Less severely affected males: all of his daughters are obligatory carriers and none of his sons affected

2. Prenatal diagnosis available to at-risk pregnancies
   a. Fetal sex determination by amniocentesis or CVS
   b. Confirmation of a previously known HPRT1 disease-causing mutation in a male fetus
      i. Perform HPRT enzyme activity
      ii. Perform molecular genetic testing
   c. Assay of HPRT enzyme activity in cultured amniocytes or chorionic villus cells: the method of choice if the HPRT1 mutation has not been identified in the family
   d. Preimplantation genetic diagnosis possible for a previously characterized disease-causing mutation

3. Management
   a. Hyperuricemia
      i. Control hyperuricemia to reduce the risk of nephropathy, nephrolithiasis, and gouty arthritis
      ii. Allopurinol
         a) To block the conversion of oxypurines into uric acid
         b) To prevent uric acid accumulation and subsequent arthritic tophi, renal stones, and nephropathy
   b. Neurologic dysfunction
      i. No medication known to be consistently effective in controlling the extrapyramidal motor features
      ii. Baclofen or benzodiazepine for spasticity
   c. Neurobehavioral symptoms
      i. No effective intervention available
      ii. Use behavioral modification techniques
      iii. Control self-injurious behavior
         a) Require physical restraints
         b) Removal of teeth
         c) A noninvasive approach with a special appliance fabricated for the prevention of damage to oral and perioral soft tissues
   d. Surgery for orthopedic problems
      e. Bone marrow transplantation or red blood cell transfusions not significantly ameliorate the neurologic disorder

REFERENCES


Fig. 1. Two boys with Lesch-Nyhan syndrome showing severe mental retardation and self-mutilation of the lips and tongue.