Lesch-Nyhan Syndrome

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Lesch-Nyhan syndrome (LNS) is an X-linked disorder of purine metabolism first described by Lesch and Nyhan in 1964(1). The disorder is clinically characterized by physical and mental retardation, choreoathetosis, spasticity, and a bizarre compulsion for self mutilation by biting fingers and lips(2,3). The primary biochemical defect is the absence of hypoxanthine-guanine phosphoribosyl transferase (HPRT) activity leading to over production of uric acid(4).

This disorder is rare and the course is tragic. There are only two earlier reports of LNS in the Indian literature(5). This disease has gained a lot of importance in recent years because of the possibility of potential cure by gene therapy. We report two cases of LNS from a single sibship.

Case Reports

Case 1: A 11-month-old boy first born to a consanguineously married couple (uncle-niece) was brought to us with developmental delay and a peculiar habit of biting his tongue and right thumb of one

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month duration. The child was apparently normal at birth. His developmental milestones were grossly delayed. At 11 months of age he was still unable to hold his head erect. He smiled at 6 months, recognized his mother at 9 months and cooed at 6 months of age. No further developmental achievements were noticed.

The child’s weight was 6.78 kg, height 68 cm, head circumference 41 cm, and chest circumference 43 cm, all well below 5th percentile of NCHS standard. The anterior half of the tongue was split with a deep ulcer underneath, covered with unhealthy slough (Fig. 1). He had erupted 6

Fig. 1. Bitten tongue — cuts and ulcer.

teeth. His right thumb was swollen with a deep ulcer measuring 1 x 0.25 cm and many other small ulcers and the surrounding skin was pigmented (Fig. 2). Both tongue ulcers and ulcer over thumb resulted from the child’s peculiar habit of biting.

Neurological examination revealed hypertonia in all the four limbs, more so in the upper limbs. All deep tendon reflexes were brisk and plantar reflexes were extensor on either side. Ocular fundii were normal. All other systems were normal on clinical examination.
Discussion

The classical clinical presentation with mental retardation, spasticity, bizarre habit of compulsive self mutilation leading to injury and amputation of tongue, lips and fingers, elevated uric acid levels in both cases, coupled with involvement of two male members on the maternal side (X-linked recessive inheritance) were indisputable features for the diagnosis of LNS in our two cases.

All patients with LNS described have been mentally retarded. Aggressive self mutilating behavior which may be as early as eruption of teeth is probably the most striking aspect of this syndrome. Most persons bite their lips and fingers destructively. Since, sensation is intact in these children, they scream in pain when they bite themselves. Self mutilation often increases dramatically when patients are placed in an unfamiliar environment. If they are shifted to an environment where they feel secure, mutilation often stops, but will start again with change of environment(6). This behavioral change is due to a biochemical error and in fact, LNS is the first instance in which a stereotyped pattern of human behavior has been associated with a distinct biochemical abnormality(1).

The motor defect is of much greater severity than their defect in intelligence. Involuntary movements of both choreic and athetoid type are prominent. Initially the patients may be hypotonic or hypertonic, later they are all hypertonic. Deep tendon reflexes are uniformly increased with positive Babinski sign in many of them. Athetoid dysphagia is a problem which leads to frequent aspiration, pneumonia and some times death.

Though patients will have hyper-
uricemia from neonatal period, clinical manifestations due to it develop only after 10-12 years that include hematuria, crystalluria, tophi, urinary tract stones and renal failure(1).

The HPRT, which is defective in LNS is an enzyme in the salvage pathway for recycling purine nucleotides. The enzyme activity is virtually absent in LNS and the most prominent consequence of the defect is an enormous overproduction of purine which leads to accumulation of large amounts of uric acid in the body. The structural gene that codes for HPRT resides in the distal part of the long arm of X-chromosome at a position between the genes for PP ribose- P synthetase and glucose-6-phosphate dehydrogenase, and has a length of 34 kilobases(6).

Although molecular genetics of this disease is well understood, the pathophysiology process by which a lack of HPRT produces neurological dysfunction remains unclear. The neurological symptoms develop when HPRT activity is below 1% of normal(2). In normal persons HPRT activity is present in all tissues of the body and is highest in the brain(6). In the brain it is 5 times higher in basal ganglia than other cells(2). The absence of this enzyme in LNS results in selective dysfunction of neurotransmitter system in basal ganglia(4). Dopaminergic functions are markedly depressed, presumably from decreased terminal arborization of dopamine neurons. There is also an apparent dysfunction or depletion of cholinergic interneurones in caudate and putamen. In contrast, GABAergic and those neurons which use glutamate as neurotransmitter remain unimpaired. This results in a disruption of balance between the functions of various neurons in basal ganglion(4). Along with these functional changes superimposed compensatory changes in other pathways, that can occur in a developing nervous system, may also be contributing to neurological symptoms in LNS(6). The brain is morphologically and neuroanatomically normal in these individuals.

In patients, a definitive diagnosis of the disease is made by measuring HPRT activity in erythrocytes(1). Since there is a well defined risk to the male offsprings efforts have to be made to identify the heterozygous carriers. As the gene encoding for HPRT is on the X-chromosome, heterozygous females will show mosaicism of normal and cells deficient in HPRT. Enzyme assay in blood cells is not helpful in identification of heterozygous carriers as there is an apparent selection against HPRT deficient cells in bone marrow and only normal cells appear in blood(3). The mosaicism can be demonstrated in skin fibroblasts grown in culture or by cloning(1). The assay of the enzyme in a single hair root is a simple and rapid method for detection of heterozygotes(3).

For couples at risk, a prenatal diagnosis of this inherited disorder is of prime importance. Considerable progress has been made in this direction. In first or second trimester of pregnancy affected fetus can be identified from fetal cells sampled by chorionic villous biopsy or amniocentesis(7). In fact LNS was one of the first in which amniocentesis was used successfully to diagnose an inborn error of metabolism in utero(6). Now it is possible to make a diagnosis even before the implantation of embryo occurs and so eliminating the trauma of repeated termination of pregnancies.

There is so far no drug that proved helpful in modifying the behavior of patients with Lesch-Nyhan syndrome. But those aspects of the disease due to in-
creased uric acid levels can be effectively managed by allopurinol. These patients appear to be more sensitive to the uric acid lowering action of allopurinol (6). Despite the effectiveness on uric acid metabolism this drug has no discernible effect on the CNS problems of the disease (6).

Some of the neurological manifestations of Gille-de la Tourette's syndrome appear to be similar to those of Lesch-Nyhan syndrome. Clonidine seems to work in some of these cases of Gille-de la Tourette's syndrome. So, it is proposed to use this drug in Lesch-Nyhan syndrome (6).

Now gene therapy — a new therapeutic approach to Lesch-Nyhan syndrome has become more feasible with the successful cloning of human HPRT gene. DNA cloned from HPRT genes has been transferred and expressed in HPRT deficient cells in vitro (6). Despite its potential risks, it may be appropriate to consider choosing this syndrome for early attempts to use gene therapy in human beings.

REFERENCES


