

CASE REPORT

Lesch Nyhan Syndrome

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INTRODUCTION

Lesch-Nyhan syndrome (LNS) is a rare inherited disorder caused by a deficiency of the enzyme hypoxanthine-guanine phosphoribosyl transferase-1 (HGPRT-1), produced by mutations in the HPRT gene located on the X-chromosome. LNS affect about one in 380,000 live births. The disease process mainly affects the male child and females are asymptomatic carriers. HGPRT deficiency leads to the characteristic triad of features: Hyperuricemia, Spectrum of neurological dysfunctions, and Cognitive and behavioural disturbances¹.

Self-injuring behaviour (SIB), it is rarely a presenting feature but eventually develops in nearly all cases. Affected patients are cognitively impaired and have behavioural disturbances that emerge between two and three years of age². Overproduction of uric acid “orange sand” in the diapers - uric acid crystalluria is due to HGPRT deficiency that causes a build-up of uric acid in all body fluids. Increased synthesis and decreased utilization of purines leads to high levels of uric acid production. This results in both high levels of uric acid in the blood and urine, associated with severe gout and kidney problems such as renal failure or frank hematuria-nephrolithiasis^{3,4}. Clinical manifestations according to age: At birth- no apparent neurologic dysfunction. After several months developmental retardation and neurologic signs become apparent. Before 4 months-hypotonia, recurrent vomiting and by age of 8-12 months-extra pyramidal signs prominent. The age at onset of self-injury may be as early as 1 year and occasionally as late as the teens.^{5,6}

Physical examination may show: growth

retardation, cognitive dysfunction and average IQ=60, all patients are wheelchair bound, self-mutilation like partial amputations of the fingers, lips, tongue, or oral mucosa, scarring from repetitive self-abrasion or hitting, in addition due to high levels of uric acid gouty arthritis and arthritic tophi may be seen. Lab. Studies can show hyperuricemia, hyperuricosuria, macrocytic anaemia. The diagnosis of Lesch-Nyhan syndrome may be confirmed by a thorough clinical evaluation, including a detailed patient history and specialized blood tests. The absence of the HPRT enzyme in cells from any tissue confirms the diagnosis. Molecular genetic testing for the HPRT1 gene is available to determine the specific disease-causing mutation. Carrier testing for Lesch-Nyhan syndrome is possible using molecular genetic testing^{5,6}. Prenatal diagnosis and preimplantation genetic diagnosis are possible if the disease causing HPRT1 gene mutation has been identified in an affected family member. Prenatal diagnosis can also be done by enzyme analysis. We report a case of LNS in a 22months old child who presented with buccal mucosal ulcers secondary to self-bites.

CASE REPORT

A 22 months old boy presented to our institution with history of motor development delay, dystonia and excessive irritability since 4 months of age. Self biting of fingers since 2 months, buccal mucosal ulcers since 20 days. He was the third child of healthy nonconsanguineous parents. There was no history of similar illness in first- degree and second-degree family members. The prenatal and neonatal periods were uneventful. At admission his length, weight and head circumference were 83 cm (–1 SD), 9.2 kg (–2 SD), and

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48 cm (median) respectively. By 6 months of age, his head control was poor and he had abnormal dystonic movements and extensor spasms with marked hypotonia. Laboratory investigations including hemogram, thyroid function tests, liver function tests, computed tomography scan of cervical region were within normal limits, Brain magnetic resonance imaging (MRI) showed no signs of cortical atrophy or abnormal intensities except for arachnoid cyst, MR Spectroscopy was found to be normal. The patient developed hyperuricemia (uric acid [UA], 10.1 mg/dL) and increased urinary UA/creatinine ratio, 4.4 [control range 2.0]. EEG-Normal, Ammonia-24 micro mol/L (Control range-54, Lactate-13.0 mg/dl (Control range 4.5-19.8)

Child was treated with physiotherapy. He attained roll over at 14 months of age and started crying for his daily needs. But he started biting his own fingers at 19 months of age with developmental delay, we suspected the possibility of LNS. Laboratory investigations showed hyperuricemia, increased urine uric acid to creatinine ratio. Finally the diagnosis was confirmed by clinical exome sequencing. The report shows hemizygous nonsense variation in exon 7 of HPRT1 gene (ChrX:g.134498412134498412C>T;Depth:82x) that results in a stop codon premature truncation of protein at codon 170 (p.Arg170Ter;ENST00000298556.8) was detected. To know whether it's complete or incomplete HGPRT deficiency levels to be determined. No such facilities are available in India. Hence we are planning to send the sample to United Kingdom.

On follow-up child is showing remarkable improvement in self-injurious behavior. Rest of clinical picture remains same. Beside the pharmacotherapy child is also receiving physiotherapy. Child was referred to dentist and he prescribed him tooth guard for protection of tongue, gums and teeth.

DISCUSSION

LNS is a rare disorder but it can easily be diagnosed by investigations like serum uric acid and urine uric acid to creatinine ratios available at most of the diagnostic centres.

Diagnosis of LNS is based on HPRT enzyme activity, preferably measured in live cells such as cultured fibroblasts, and on molecular genetic techniques demonstrating the gene mutation. Results might provide predictive clues about ultimate disease severity in

addition clinical and biochemical (hyperuricemia and hyperuricosuria), together with psychomotor signs of HPRT deficiency. An orange crystal in the diapers of a newborn is one of the early clues of the disease that may be observed. Overproduction of uric acid may lead to the development of uric acid crystals or stones in the kidneys, ureters, or bladder. Such crystals deposited in joints later in the disease may produce gout-like arthritis, with swelling and tenderness.

Self-Injury Behaviour (SIB) in LNS can be differentiated from SIB associated with autism or developmental disabilities by its sudden and more severe onset. Allopurinol will lower uric acid levels to normal but does not affect the behavioral aspects of the disease. Treatment options for management of SIB are physical restraints, behavioral, and pharmacological treatment (benzodiazepines) but the success rate is limited⁷. Physical restraints have been the sole reliable resource for preventing SIB. Cloth body restraints, cloth mittens, and plastic arm splints have all been useful in reducing the frequency of injury. Drastic measures, such as removal of the teeth or provision of tooth guards, are often taken to prevent further tissue damage. However, in many cases even with physical restraints, self-injury continues. Our patient's self-injurious behavior controlled with both pharmacotherapy and physical restraints. The aggressive behaviour usually wanes in patients older than 10-12 years of age. Patients with LNS usually die in their late second or third decade. The cause of death is renal failure or infections that are a result of decrease in lymphocyte and immunoglobulin G levels. With optimal care, few patients live beyond 40 years and most are confined to a wheelchair⁸.

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