

Case Report

Lesch-Nyhan syndrome: case brief of a rare disease

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ABSTRACT

Lesch-Nyhan Syndrome is a rare X-linked disease due to absence of HPRT enzyme. It leads to hyperuricemia, gout, renal failure, neurological and behavioural disorders, including compulsive self-mutilation. Management includes drugs against hyperuricemia, measures to prevent self-mutilation and behavioural therapy. This case is that of an eight months old child coming for respiratory symptoms and self-mutilation, who was ultimately diagnosed with Lesch-Nyhan syndrome.

Keywords: HPRT deficiency, Hyperuricemia, Lesch-Nyhan Syndrome, Transverse sinus

INTRODUCTION

Purines, along with pyrimidines are molecules involved in formation of energy compounds and metabolism of nucleic acids. Various cycles like biosynthetic, catabolic and salvage pathways are involved in their metabolism.¹ Lesch-Nyhan syndrome (LNS) is a rare metabolic disorder involving purine metabolism. Its incidence ranges between 1:100000 to 1:300000 in world literature. It is an X-linked recessive disorder caused by deficiency of Hypoxanthine-guanine phosphoribosyl transferase (HPRT) enzyme, which is involved in the salvage pathway of purine metabolism, i.e. recycling of purines from degraded DNA and RNA.² Significance of the salvage pathway lies in the fact that it requires far less energy than the de novo synthesis of purines.³ Absence of HPRT enzyme leads to overproduction of uric acid in the body.

The condition usually manifests in infancy, between 6 and 10 months of age. The clinical features include hyperuricemia, intellectual disabilities, hypotonia initially leading to dystonic movements later on and compulsive self-mutilation. Self-mutilation may be seen in and around the oral cavity and fingers. Manifestations of

hyperuricemia like gout and renal failure necessitate medical management with uric acid lowering agents (like allopurinol, rasburicase and febuxostat). Renal failure is the usual cause of death in these patients. Some of the neurological manifestations may stem from reduced levels of dopamine concentrations in basal ganglia and cerebrospinal fluid.

Other diseases involving self-mutilation like hereditary sensory and autonomic neuropathy type IV, destructive behaviour patterns in Cornelia de Lange syndrome, Tourette syndrome, mental retardation etc. constitute the primary differential diagnoses.

Hereby a unique case of an eight months old male child presenting to the Dept of Pediatrics, MKCG Medical College, Berhampur with complaints of respiratory tract infection and self-mutilation leading to amputation of fingers and ulcers on the heels, and subsequently diagnosed with Lesch-Nyhan syndrome is being reported.

CASE REPORT

An eight months old male child (Figure 1) was admitted to the Department of Pediatrics, MKCG Medical College

for fever, cough and cold for 12 days and biting his own fingers leading to ulcerations of finger tips and self-hitting of his heels causing chronic ulcers, more on the left side.



Figure 1: Overall profile of the child.

Past history revealed that he had suffered from bronchiolitis once and wheeze associated lower respiratory tract infections thrice since 3 months of age, leading to hospitalisation on three occasions.



Figure 2: Mutilation of the left index finger with bifid thumb and right heel.



Figure 3: Ulcer on the heel of right leg.

He had been prescribed inhalational corticosteroids to prevent further episodes of wheezy LRTIs and anti

tubercular therapy as well by different doctors for recurring episodes of fever and cough within 2 months of this hospitalisation.

His birth history was uneventful. The patient was immunized as per his age according to NIS. The child was able to roll over but was unable to sit in tripod posture. Unidextrous reach and monosyllable speech was absent. He was able to recognize his mother, nevertheless.

There was no history of consanguinity, contact with active cases of TB, mental retardation, psychiatric illnesses, kidney failure, arthritis, asthma, atopy or similar type of self-mutilation behaviour in the family.

On examination, the child had tachypnea. Other vitals were stable. Upper and lower central incisors had erupted. Wounds were present on the fingertips of bilateral hands; the left hand being involved more than the right. Bifid thumb was present on left side (Figure 2). Ulcers on left and right heel were there (Figure 3). Rest of the general examination was normal.

Systemic examination revealed bilateral coarse rales and wheezes. Hypotonia was present. Deep tendon reflexes were sluggish, possibly due to hypotonia. Cranial nerves were intact. All other systems were normal.

In view of the self-mutilation behaviour, differential diagnoses of LNS, Hereditary sensory and autonomic neuropathy type IV (congenital insensitivity to pain with anhidrosis), Cornelia de Lange syndrome, Tourette syndrome and other non-specific intellectual disability were considered. Due to intact pain sensation and sweating, HSAN Type IV was ruled out. Absence of facial dysmorphism excluded Cornelia de Lange syndrome. Early age of presentation excluded Tourette syndrome. Hence, investigations for Lesch-Nyhan syndrome, namely serum uric acid and urine uric acid: creatinine ratio were sent. Other routine tests and chest x ray were also done.

Serum uric acid was 6.2 mg/dl. Urine uric acid: Creatinine ratio was 15:1. Hence, both the tests were in favour of Lesch-Nyhan syndrome. Financial constraints prevented HPRT assay, which is the confirmatory test for the disease, from being performed.

But clinical symptoms, age of onset, male gender, mild developmental delay, hypotonia and positive screening tests made the diagnosis of LNS a certainty. The patient was started on tab allopurinol. Antibiotics and other supportive care for wheezy LRTI led to rapid improvement of respiratory complaints. To prevent further mutilation, the patient's parents were advised to use gloves and socks with paddings. The possible need of tooth extraction and use of restraints in future was explained. The patient was discharged with the advice to follow up regularly.

DISCUSSION

Lesch-Nyhan syndrome as a distinct clinical entity was first reported by Michael Lesch, a medical student and his teacher, William Nyhan, a paediatrician in John Hopkins University, Baltimore.⁴ They described the condition as a familial disorder of uric acid metabolism and central nervous system disorder.

It is an X linked recessive disorder, caused by mutation of the HPRT gene, whose loci is Xq26- q 27. HPRT enzyme plays a central role in the salvage pathway of purine metabolism. It catalyzes the formation of GMP from guanine and phosphoribosyl pyrophosphate (PRPP) and IMP from hypoxanthine and PRPP. As a result of the mutation, hypoxanthine is either excreted as such or is converted to xanthine and uric acid. The uric acid, so produced is responsible for arthropathy and renal stones and gives the disease the name Juvenile gout.

MRI has suggested loss of basal ganglia volume. Though cell loss has not been documented, defective arborization of dendrites has been recognized. Due to HPRT deficiency, ultimate loss of adenosine and dopamine occurs. This gives rise to the neurological manifestations of LNS.

Clinical spectrum of physical, behavioural and neurological symptoms in LNS may vary from very mild cognitive deficits to severe intellectual disability and self-mutilation, depending upon the functional levels of HPRT enzyme. HPRT levels with more than 8% activity manifest with only hyperuricemia, between 2%-8% manifest hyperuricemia and neurological symptoms and those having HPRT activity below 2% manifest self-mutilation behaviour, with neurological and cognitive symptoms.

A condition with partial deficiency of HPRT enzyme too has been described and is known as Kelly - Seegmiller syndrome.⁵ Some workers believe that Kelly- Seegmiller syndrome and Lesch-Nyhan syndrome form a continuum of the same condition, the clinical manifestations depending upon the functional levels of HPRT enzyme.

Symptoms usually begin in the infancy. Normal developmental milestones are achieved till 3- 6 months of age. Developmental delays, recurrent vomiting and difficulty in managing secretions are the usual initial manifestations, followed by hypotonia. Hypotonia is transitional, as hypertonia and other extrapyramidal symptoms set in. Aggressiveness and self-mutilation follow. Self-mutilation is usually around the mouth and lips and occurs inspite of normal sensory pathways. Severe mutilation of lips, oral mucosa and amputation of fingers may occur as a result of intense and compulsive biting. While young children need to be physically restrained to prevent bodily damage, older patients may themselves ask for restraints. Dyarthritic speech leads to handicaps in social communication. Life span is

shortened due to kidney failure and respiratory compromise.

Definite diagnosis lies in detecting mutations by DNA analysis and HPRT enzyme assay in skin fibroblasts.^{6,7}

In the case discussed above, hyperuricemia was present (normal being 4-5 mg/dl). The uric acid: creatinine ratio was also elevated (normal being 3-4:1). Hence the screening tests for Lesch-Nyhan syndrome were positive. Financial constraints and lack of adequate resources prevented us from performing HPRT enzyme activity levels and genetic studies.

But, taking the age of onset symptoms, sex, the clinical symptoms and the positive screening tests into consideration in toto and excluding the other differential diagnoses, Lesch-Nyhan syndrome was the most probable diagnosis.

Appropriate and timely intervention, as in this case, may prevent further self-mutilation, arthropathy and kidney failure in these patients. Chugahara et al, Kale et al, Chen et al, have in their respective reports described the self-mutilation in and around the mouth and the need of using dental braces, splints or teeth extraction to prevent damage.⁸⁻¹⁰ Apart from this, cognitive behavioural therapy may be instituted. Fluphenazine has been shown to decrease self-mutilation.⁶ Recent research in this disease focuses on deep brain stimulation to treat the behavioural and cognitive issues.

CONCLUSION

Lesch-Nyhan syndrome though rare, can manifest in various forms, depending upon the activity levels of HPRT enzyme. Even though self-mutilation behaviour is the most common lead point for diagnosing LNS, clinicians should keep this condition in the differential diagnoses for male infants with hypotonia/ hypertonia with arthropathy and kidney stones. As uric acid lowering agents can prevent/ delay uric acid nephropathy and joint deformities, it is imperative to arrive at a correct diagnosis in a timely manner. This case is being reported to raise awareness about this disease.

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