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The Curious Case Of "Lesch-Nyhan" Syndrome

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ABSTRACT

Lesch-Nyhan is a rare disorder related to X-linked recessive genes, which occurs exclusively in males. This happens due to mutation of Xq26 chromosome and deficiency of hypoxanthine guanine phosphoribosyl transferase (HGPRT) enzyme. LNS is characterised by classical triad of symptoms Hyperuricemia, Spectrum of neurological dysfunctions, cognitive and behavioural disturbances including self mutilation. The symptoms occurs due to increase accumulation of uric acid in the body fluids to dangerous levels. Here we present a case of 2-year old child admitted in department of paediatrics with self mutilation, increased uric acid levels, delayed milestones, renal failure. After investigations diagnosis of LNS was established through various examinations.

KEYWORDS

Lesch-Nyhan syndrome, Hyperuricemia, Self mutilation, Hypoxanthine

INTRODUCTION

Lesch-Nyhan Syndrome (LNS) was first described in 1964 at John Hopkins Hospital. The two brothers Micheal Lesch (a medical student) and William Nyhan (a paediatrician) presented with an very unusual symptoms that are severe retardation of motor development, dystonia, choreoathetosis, crystals in the urine and self mutilation. After the publication of the case study, other cases were also reported and recognized around the world, later it was described [1]. The Lesch-Nyhan Syndrome (LNS) is extremely rare X-linked recessive inborn error of purine metabolism. It happens due to mutation in Xq26. Also, there congenital absence of hypoxanthine guanine phosphoribosyl transferase (HGPRT) enzyme. HGPRT is an enzyme encoded in human by the HPRT1 gene. HGPRT is a transferase that catalyzes conversion of hypoxanthine to inosine monophosphate and guanine to guanosine monophosphate. This reaction transfers the 5-phosphoribosyl group from 5–phosphoribosyl 1-pyrophosphate (PRPP) to the purine. HGPRT plays a central role in the generation of purine nucleotides through the purine salvage pathway This deficiency causes excessive production of uric acid and consequent hypouricemia [2,3].

The HGPRT locus is a constitutively expressed housekeeping gene characterized by a notably higher level of expression in mammals. The HGPRT-encoding gene is situated in the long arm of X chromosome in the region q26-q27.2 and consists of 9 exons and 8 introns totalling 57 kb. This gene is transcribed to produce an m RNA of 1.6kb, which contains a protein –encoding region of 654 nucleotides, 657 comprising termination codon (UAA). The marked genetic heterogeneity of HPRT deficiency is well known and identification of mutations has been performed at the RNA and DNA level [4,5]. The gene in this incurable disease is only passed on to sons by the mother. However, females on the other hand, are carriers with increased risk for gouty arthritis or otherwise usually unaffected [6]. HGPRT deficiency leads to the classical traid of features: (i) Hyperuricemia, (ii) Spectrum of neurological dysfunctions (iii) cognitive and behavioural disturbances [5]. The first manifestation that is seldom recognized in early infancy is presence of urate crystals formation, due to abnormally increased levels of uric acid in urine. This increased uric acid leads to presence of orange colored deposits (commonly known as "orange sand") in the diapers of the babies [6].

The most common presenting features are developmental delay and decreased muscle tone (hypotonia), appears as early by three to six months of age, compulsion towards self mutilation or self harm usually reported at after 1 year of age. This self- mutilating behaviour typically begins as soon as the child's teeth appears and children try to eat themselves [7]. Although, there is no apparent neurologic dysfunction present at birth [8,9].

This behaviour continues with partial or total destruction of perioral tissue, especially the lower lip. Amputation of fingers, toes and tongue which may be partial or complete is very much common. The patients diagnosed with this syndrome may stab themselves in eyes with sharp objects [9].

The prognosis for LNS is very poor. Many patients die in their teens and those who reaches to twenties are often fragile. Most of the LNS sufferers are susceptible for infection and may die from kidney infections. According to the recent studies respiratory failures plays a major part with sudden death in certain cases. Although there are rare cases reported in India, but it is approximately 1 in 380,000 live births in Canada and 1:100000 to 1:300000 in world literature [10].

There are others diseases that involves self-mutilation like destructive behaviour pattern in cornelia de Lange Syndrome, tourette syndrome, Prader-Willi syndrome, Smith-Magenis syndrome, Fragile X syndrome, autonomic neuropathy type IV, can be confused with differential diagnosis [11].

The report presented below is of two- year old child diagnosed with Lesch- Nyhan Syndrome.

CASE REPORT

A two year old male child born 2nd degree consanguineously married couple was presented in Department of Paediatrics, for dysmorphism, self mutilating behaviour, delayed milestones, self engrossed and irritable behaviour. After recording the history from the parents, it was revealed that the child was born to the parents after normal vaginal delivery (37 weeks) induced due to preeclampsia and fever. The birth weight of the baby was 3.070 kgs with all the health parameters normal. There was no history of any metabolic or blood disorder. There is no known history of mental retardation, arthritis, asthma, atopy, psychiatric illness or any self- mutilating behaviour in the family.

The child was well during postnatal period with good muscle activities, good feeding, having bowel and bladder movements normal, other vitals were stable. On day 2nd of birth the baby was presented with yellowish discoloration of the eyes and face, a single surface phototherapy was given for one day and baby was discharged. There was an increase in Serum Bilirubin level 319 mg/dl, 232 mg/dl. After one week there was brief episode of shakiness for 2 seconds several times while changing the diaper of the baby with increase in Serum Creatinine which was 102 mg/dl (D1), 108 mg/dl (D2), 86 mg/dl (D3) and again 91 mg/dl (D4).

Abdominal ultrasound was ordered but it was unremarkable. Child was normal upto 3 months of age then started having regression of milestones. At 5 months old, he had weight 8 kg, height 69.8 cm and occipito-frontal circumference 39.5 cms. He was not appropriate for age and showed stereotyped behaviour. He was able to make eye contact, babble, follows objects, hypotonic movements of the limbs were present but the child was not interested in surroundings and restless. He has subtle dysmorphic features accompanied with fisting, decreased muscle tone including delayed motor milestones. He could not control his neck properly and not able to sit without support. However, his hearing and vision were normal, he could not respond to verbal commands effectively. Further the child has abnormality of renal medulla, brisk reflexes, central hyptonia, depressed nasal bridge, developmental regression, hyperuricosuria, macrotia, motor delay, nephrocalcinosis, and a history of prolonged neonatal jaundice.

Results of Whole Exome Sequencing (WES) done at 1 year showed that the child has a hemizygous likely pathogenic variant that was identified in the HGPRT1 gene and probable diagnosis of X-linked recessive Lesch-Nyhan Syndrome. At 2 year the child shows self injurious behaviour with self mutilation and hyperurimia. The level of AST (aspirate Transaminase) was 50 IU/L (ref. 3-37IU/L), Serum Uric Acid level 519 umol/L (ref. 113-321umol/L), Serum Creatinine level 38 umol/L (ref. 21-36 umol/L), Potassium level 4.90 mmol/L (ref. 3.3-4.6 mmol/L), Triglycerides level 1.24 mmol/L (ref. 0.1-0.8 mmol/L). Although, the complete blood count, Biochemical profile, Metabolic screening, Karyotype and Brain MRI results were normal.

On examination, there were wounds presented in the fingertips, perioral region. There were signs of tongue bite, lips bite, nail scratching around the nasal area.

Initially LNS was not considered as the differential diagnosis, as it is a very rare disease. Global developmental delay, cerebral hypotonia with suspected case of Genetic syndrome was put as a diagnosis. However, the Serum Uric Acid level was found out to be of 8.2 mg/dl with the striking features of mental, neurological and physical retardation and self mutilating behaviour helped in reaching for the correct diagnosis. After consultation with department of Genetics, a study was carried out and molecular diagnosis of Lesch-Nyhan Syndrome by Gene sequencing. The study confirmed the diagnosis of Lesch-Nyhan Syndrome due to mutation in the HPRT gene in the child and also revealed the carrier state of the mother.

Subsequently, the condition was controlled with oral allopurinol for increasing serum uric acid level. He was advised for occupational therapy and physiotherapy. For self mutilating behaviour mouth guard was decided and removal of teeths planned in case of severity. He is currently taking treatment for confirmed LNS which is followed by Departments of Rehabilitation, Genetics, Neurology, Medicine, Nephrology and Odontology.

DISCUSSION

The diagnosis of Lesch- Nyhan syndrome is based on HGPRT enzyme activity measured in live cells, psychomotor delay, molecular tests, clinical and biochemical findings. The MRI may not be efficient in diagnosis of LNS as most results are normal [12]. Torres and Puig have proposed a classification system into four groups depending upon clinical, biochemical, enzymatic and molecular analysis (Table 1) [13].

Table 1: Classification of HGPRT deficiency based on clinical, biochemical, enzymatic and molecular data.

	Partial Deficiency (Kelly-Seegmiller Syndrome)		Lesch-Nyhan Syndrome	
	Grade 1	Grade 2	Grade 3	Grade 4
HGPRT hemolysate	(+)	(-)	(-)	(-)
HGPRT erythrocyte	(+)	(+)	(-)	()
Size of protein altered	(-)	(-)	(-)	(±)
Self-mutilation	(-)	(-)	(-)	(+)

(+) Present or detectable, (-) absent or undetectable, (±) May be present or not, HGPRT: Hypoxanthine guanine phosphoribosyl transferase

Prenatal diagnosis of LNS can be performed with amniotic cells obtained by amniocentesis at about 15-18 weeks of gestation or chorionic villus biopsy obtained at about 10-12 weeks gestation [13,14].

The physicians should be careful while accepting the conclusion because most patients who have hyperuricemia (uric acid level, usually 9-12 mg/dl) suffers from LNS but sometimes it can be presented with only hyperuricosuria (uric acid excretion) and no hyperuricemia. Therefore, in a child with delayed development may be checked with uric acid in urine along with the serum. This may be sign of LNS. The sample may be collected by 24 hour or on spot urine to detect hyperuricosuria. However, there may be inaccuracies in the interpretation as the microorganisms present in the urine consumes purines, including uric acid in 24 hour urine sample. So, a spot urine sample may be more convenient to collect and analyze for correct uric acid/ creatinine ratio. The reference range in normal children is <1 mg as compared to 3-4 mg of creatinine in patients with LNS. In literature review, the finding of serum uric acid level >4-5 mg/dl and

uric acid /creatinine ration of 3-4 is highly suggestive of LNS [14].

Other signs and symptoms include dysarthria, apraxic discoordination of lip and tongue, dysfunction of ocular motor activity are sometimes seen. Self mutilating behaviour is integral to the disease but sometimes head banging with injuries to eyes and legs also appears [15].

The confirmatory test for diagnosis of LNS are:

i) Analysis of HPRT activity in erythrocytes

(ii) Analysis of mutation of HPRT1 gene

In analysis of HPRT activity in erythrocytes was first mentioned in the report by Seegmiller, et al, in 1967 which concluded that the enzyme activities approaches to zero in the patient suffering from LNS. Carrier detection may be a limitation in the simple testing of enzyme activity as in heterozygote it is normal. In analysis of mutation of the HPRT1 gene, it is located on the long arm of X chromosome (Xq26.1) and encodes human HPRT. It has strengths in being carrier and prenatal diagnosis [16].

There is no curative treatment for LNS but symptomatic treatments are possible. The management of the condition may be in steps. For increased uric acid level, the patient is prescribed Allopurinol, which is a oxidase inhibitor proved to be effective in reducing the uric acid concentration. For neurologic symptoms drugs and rehabilitation such as benzodiazepine and carbmazepine can be used. To manage self mutilating behaviour certain activities like physical restraints, flexible arm splints (to prevent finger biting) can be used. In certain cases teeths are removed to prevent perioral injuries. However, as per the studies S-Adenylmethioine and deep brain stimulation treatments has been reported as proven methods for self –mutilating behaviour [17].

CONCLUSION

LNS is rare disorder. Cases of LNS have rarely been reported in India. It may have slow progression, but symptoms can be seen relatively soon after birth. From appearance to orange crystals in infancy to self mutilating behaviour in later years, it is a journey of slow neurological progression. Although, the deficiency of HPRT activity plays an important role in diagnosis. The child requires constant love and attention. There may be no standard treatment but symptomatically it can be managed. Genetic counselling is highly recommended for parents who have children with LNS.

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