Case Report

DOI: 10.5582/irdr.2016.01076

Lesch-Nyhan syndrome: The saga of metabolic abnormalities and self-injurious behavior

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Summary **Lesch-Nyhan syndrome (LNS) is an X-linked recessive disorder of purine metabolism caused by a mutation in Xq26.2-q26.3 (OMIM 308000.0004). The presence of the diagnostic triad, *i.e*. signs of self-injurious behavior (SIB) and results of pedigree analysis and novel molecular biology & genetic testing, confirms the diagnosis of LNS. With a level of hypoxanthine guanine phosphoribosyl-transferase 1 (HPRT1) enzyme activity < 2%, patients develop neurological, neurocognitive, and neuromotor symptoms along with SIB. Described here is a case of 4-year-old boy who was diagnosed with LNS. The boy displayed SIB, *i.e.* biting of the lips and fingers, and he had cerebral venous sinus thrombosis caused by LNS.**

Keywords: Lesch-Nyhan disease, self-injurious behavior, X-linked disorder

1. Introduction

Lesch-Nyhan syndrome (LNS) is an X-linked recessive disorder of purine metabolism with a prevalence of 1:100,000 to 1:380,000 (*1,2*). The primary cause of LNS is a mutation in Xq26.2-q26.3 (OMIM 308000.0004) that leads to a reduced or complete deficiency in the hypoxanthine guanine phosphoribosyl-transferase 1 (HPRT1) enzyme in affected individuals (*2,3*) .

The phenotype of LNS varies and it depends upon the level of HPRT activity. When the level of HPRT1 activity > 8%, only hyperuricemia manifests. A level of HPRT1 activity between 2% to 8% is referred to as an HPRT-related neurological dysfunction (HND) that is characterized by neurological, neurocognitive, and behavioral abnormalities. A level of HPRT activity < 2% is referred to as LNS, which involves significant neuromotor and cognitive defects and the display of self-inflicted injurious behavior (SIB) (*3*).

SIB has been reported to usually begin with eruption of the primary teeth at 12 months of age, however it may manifest at 4-5 years of age. SIB has been attributed to defective maturation of certain dopamine neuronal pathways in the brain (*1-3*). One of the distinct features of SIB seen in LNS is the presence of pain and the display of remorse after an episode. Patients display an inability to overcome a compulsive desire to hurt themselves – both in the form of physical injury and/or emotional distress. This can be extremely distressing to caregivers and it also puts these patients at risk (*4*). A rare case of LNS with complications and SIB has been presented here.

2. Case Report

A 4-year-old male child was admitted to the Pediatric Emergency Department with altered sensorium and poor oral intake for 20 days prior along with seizures for 5 days and a fever for 3 days. A history revealed that the boy was born from non-consanguineous parents and a normal full-term vaginal delivery. Neck holding was absent and self-mutilation by finger biting was described as starting at 10 months. At 3 years and 6 months of age, the boy's parents noted an intermittent tightening of the limbs and finger and lip biting with increasing severity. A family history revealed that his elder male sibling had succumbed to a similar illness, dying suddenly at the age

Released online in J-STAGE as advance publication December 21, 2016.

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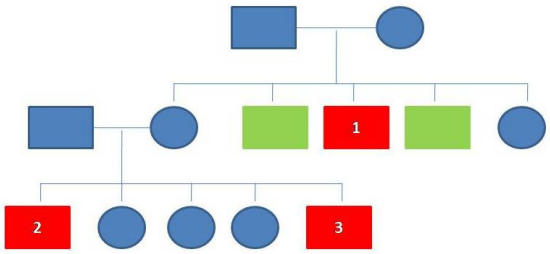

Figure 1. Pedigree chart showing survivors as blue boxes/ circles. Red boxes represent individuals with LNS who died at age 3 (1), age 7 (2), and age 4 years and 5 months (3); green boxes represent maternal uncles with renal failure who died at age 30 and age 32. LNS, Lesch-Nyhan syndrome.

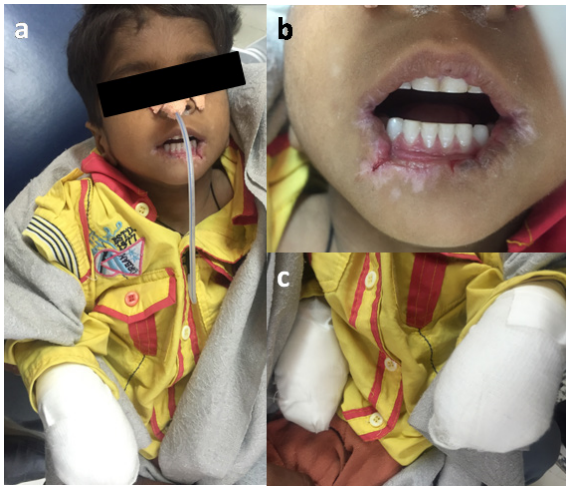

Figure 2. Ryle's tube is in place in a 4-year-old boy with LNS displaying altered sensorium (a), severe atrophy of the lower lip as a result of SIB (b), and bandaged upper limbs (c). LNS, Lesch-Nyhan syndrome; SIB, self-injurious behavior.

7. His three sisters were normal and were age 6, 8, and 12. One of his maternal uncles had died at the age of 3 and had SIB while two others had suffered from renal failure and had subsequently dies at age 30 and age 32 (Figure 1).

A physical examination upon admission revealed a generalized pallor and fresh wounds on the fingers of both hands and the lower lip. The parents had bandaged the hands and feet to prevent any further damage due to biting (Figure 2 a-c). His weight was 8 kg with no abnormalities in the CNS or abdomen. Neurological assessment revealed a GCS score of E2V2M3, pupils were 3 mm and reactive bilaterally, and all four extremities had reduced bulk and tone. Reflexes were absent on the right side and 1+ in the left upper extremity and 2+ in the left lower extremity. Blood results revealed a hemoglobin level of 5.9, a urea/creatinine ratio of 49/0.5, and a Na/K level of 148/4.2. Blood results suggested megaloblastic anemia. On oral examination, the lower lip had atrophied due to self-injury and there were traumatic ulcers with raw margins, although the upper lip appeared normal. The child also had fair oral hygiene and a normal complement of all primary teeth

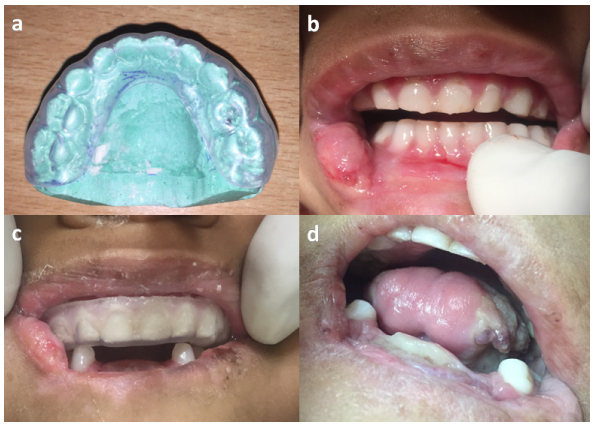

Figure 3. A soft resin mouthguard was created to prevent SIB. (a) Signs that lower lip wounds were healing after the mouthguard was affixed, (b) A substantial reduction in SIB and healing of lip wounds after extraction of the primary mandibular incisors, and (c) Recurrence of SIB in a different biting pattern leading to ulceration of the lateral borders and ventral surface of the tongue (d). SIB, self-injurious behavior.

(Figure 2b).

The level of HPRT1 enzyme activity was assessed and found to be 0.8%. Genetic testing revealed that the patient had a G580A substitution in the *HPRT1* gene. These features were pathognomic for LNS.

Magnetic resonance imaging revealed cerebral venous sinus thrombosis (CVST) and right cortical venous thrombosis (frontal and parietal veins) with thrombosis of the superior and left transverse sinus veins and a venous infarct in the right superior frontal gyrus (with cortical laminar necrosis). Cortical venous congestion was noted in the rest of the frontal and parietal cortices on the right. This was appropriately managed with a satisfactory course.

Pediatric consultants advised the extraction of all primary teeth, but a conservative approach was taken to manage self-injury. A maxillary impression was taken using a size 0 tray and alginate, and a soft resin mouthguard was made. This "bite guard" was affixed to the maxillary teeth using light-cured resin cement (Figure 3a). The frequency of self-biting initially decreased and epithelization of lip and finger wounds was visible (Figure 3b). However, SIB, *i.e.* tongue biting, soon started, warranting extraction of the primary mandibular incisors (Figure 3c).

Upon discharge, sensorium was normal and feeding was accomplished through Ryle's tube. Two subsequent follow-ups indicated a further reduction in SIB, but hypotonia and irritability persisted (Figure 3c). During the third follow-up, a new pattern of biting was noted, and this biting had resulted in ulcers on the lateral borders and ventral surface of the tongue (Figure 3d). All of the remaining primary mandibular teeth had to be extracted under local anesthesia in two visits. At the age of 4 years and 5 months, the patient died suddenly at night like his elder sibling.

3. Discussion

SIB is considered to be a characteristic feature of LNS (*1*). This behavior is secondary to a neuro-metabolic abnormality caused by a disorder in HPRT1-mediated purine metabolism (*3*). SIB has also been observed in congenital insensitivity to pain with anhidrosis, mental retardation, and syndromes as Cornelia de Lange syndrome, Munchausen syndrome, Moebius syndrome, Gilles de la Tourette syndrome, and Rett syndrome (*5*). Since the oral cavity is the earliest primary focus and the means of interaction with environment, it falls prey to any attempt at self-injury, with sharp teeth being the preferred tool (*5,6*). After the eruption of the primary teeth, SIB is displayed, as was noted in the current case. The presence of the diagnostic triad, *i.e.* signs of SIB and results of pedigree analysis and novel molecular biology & genetic testing, confirmed the diagnosis of LNS (Figure 4) (*2,3,7*).

When the level of HPRT activity is below 2%, the dopaminergic pathway in the brain is severely affected and neuro-cognitive, neurological, and motor dysfunction result (*2,3*). CVST was noted in the current case. CVST is a rare condition that is due to the hypercoagulability of blood. Patients with abnormal purine metabolism and hyperuricemia have been reported to be susceptible to thrombosis and infarction (*8*). This further aggravated the patient's condition.

SIB in LNS has been found to decrease when restraints are used, such as hand and feet bandages (*4*). However, oral injuries, and especially those of the lower lip and tongue, can still occur. Conservative modalities such as a mouthguard, bite guard, lip bumpers, or bite planes have been tried in the past but they have not been effective (*9-11*). Extraction of both primary and permanent teeth may be the ultimate solution in most cases (*2,5,6*). In the current case, the patient's pattern of self-biting changed after a bite guard was affixed and later when the primary mandibular incisors were extracted. Use of light-cured resin cement in the current case was found to be advantageous since it set immediately and was less likely to dislodge.

LNS has been associated with a shorter life expectancy, with death occurring in the second or third decade of life due to renal failure (*1,3*). Sudden death has also been reported in younger children due to a respiratory obstruction, aspiration of gastric fluids, laryngospasms, central apnea, cyanotic breath-holding, or high cervical spine damage (*12*). In the current case, the patient and his older male sibling both died suddenly.

4. Conclusion

LNS is a rare disorder but it can easily be diagnosed. The predominant feature of SIB, *i.e.* self-biting, requires a pediatric dentist to play a key role in the management team. Although the extraction of both primary and permanent teeth can completely eradicate the chances of injuries, a conservative modality should be attempted first.

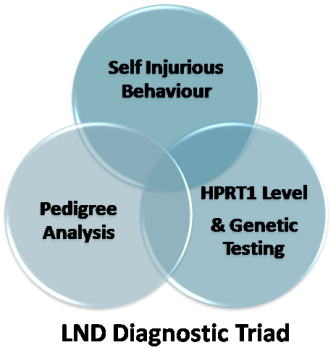

Figure 4. LNS diagnostic triad. LNS, Lesch-Nyhan syndrome.

Acknowledgements

The authors wish to thank the parents of the child in this case, Mr. Ram Kumar and Mrs. Gayatri Devi, for permission to use their child's medical records and photographs in this article.

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(Received September 28, 2016; Revised November 7, 2016; Accepted November 16, 2016)