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CASE REPORT

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# The Role of Video-EEG Monitoring in Lesch-Nyhan Syndrome

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## ABSTRACT

***Introduction:*** *Lesch-Nyhan syndrome (LNS) is a rare genetic disease secondary to a HPRT1 mutation on chromosome X. It is characterized by dystonia, developmental delay, hyperuricemia and self-harming behaviours. The HPRT enzyme is implicated in the purine salvage pathway. The deficiency of HPRT results in accumulation of uric acid. There have been some cases associated with epilepsy, but it still remains a rare occurrence in LNS patients.*

***Case presentation:*** *We describe the case of a 20-month-old male patient with a heterozygous HPRT1 mutation c11_17del.p (Arg4Leufs*4) associated with LNS. The child associated epileptic seizures mistaken by his parents as non-epileptic sleep events associated with apnea. Seizures were discovered secondary to a polygraphic long-time sleep video-electroencephalography (EEG) monitoring. The dystonic movements and epileptic seizures responded to Levetiracetam, but the management of the behavioural disorder remained a challenge.*

***Conclusions:*** *Lesch-Nyhan syndrome is a rare inherited metabolic disease and its pathogenesis is not fully known, which makes the treatment management very difficult. Despite the fact that epilepsy is uncommon in LNS children, it should always be considered as part of the differential diagnosis in movement disorders. Therefore, long-term video-EEG monitoring is recommended as well as a detailed patient history to identify possible clinical/subclinical epileptic seizures that require treatment.*

**Keywords**: Lesch-Nyhan syndrome, HPRT1 mutation, dystonia, epilepsy, video-EEG.

## INTRODUCTION

Mutation of an enzyme called hypoxanthine-guanine phosphoribosyl transferase 1 (HPRT1) is an X-linked disorder which determines a deficiency in HPRT, leading to a rare inherited metabolic disorder known as Lesch-Nyhan syndrome (LNS) (1, 3, 5). The disease occurs in males who receive the defective X chromosome from the carrier mother, but it can also be a de novo mutation (2, 3, 6).

Hypoxanthine-guanine phosphoribosyl transferase is involved in the purine salvage pathway by converting hypoxanthine and guanine into inosine monophosphate (IMP) and guanosine monophosphate (GMP), respectively (3); HPRT deficiency

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results in the accumulation of guanine and hypoxanthine, which are converted into uric acid (3, 11).

The classic form of LNS is characterized by hyperuricemia, hyperuricosuria and its complications, neurological abnormalities such as global developmental delay, choreoathetosis, with the latter being followed by spasticity and dystonia and the hallmark of LNS self-injurious behaviour (1, 3, 8, 9, 11).

Patients with LNS are asymptomatic until 3-4 months of age, but soon develop hypotonia and developmental delay, followed by extrapyramidal signs between 8-12 months of age, with the most common sign being progressive dystonia to a point where children cannot attain crawling, walking and are non-ambulant (3, 11).

Self-harming behaviour starts with teeth eruption by the age of one, manifesting as biting of lips, fingers or cheeks causing disfiguration, although sensitivity including pain is intact. It is important to mention that the aggressive behaviour can also be directed towards others (3, 11).

Epilepsy is a rare occurrence in LNS patients, ranging from 2-3% of cases, with generalized tonic-clonic seizures, status epilepticus, epileptic spasms associated with a hysarrhythmic EEG pattern, or subclinical seizures, usually with a childhood onset (6, 9).

Magnetic resonance imaging (MRI) in patients with LNS showed reduction in intracranial volume, especially in the basal ganglia and frontotemporal and limbic regions and white matter reduction (2, 3). The classic form was associated with reduced volume in the ventral striatum and prefrontal areas (2, 7).

Patients with LNS have a short life span and rarely survive into their second or third decade (3). The main causes of death include renal failure, urosepsis, respiratory failure, infections like pneumonia, and sudden death (3, 9). ❑

## CASE PRESENTATION

A 20-month-old male child was addressed to our department with the diagnosis of global developmental delay and LNS, seeking proper therapy for dystonia and sleep apnea episodes.

He is the second child of non-consanguineous parents, with two healthy sisters. He had a proper prenatal and postnatal development until the age of four months, when his parents noticed a neuropsychomotor delay and sought medical advice for the first time. Initially he was diagnosed with central hypotonia and subsequent investigations, including cerebral ultrasound and brain MRI, showed no structural abnormalities. In 2018, the medical team decided to perform arrayCGH genetic testing and test for metabolic diseases, which provided negative results. As the child began to show involuntary movements (dystonia), he was further tested with a dystonia-oriented gene panel, with negative results.

At eight months, the child started physical therapy, slowly managing to attain head control at nine months of age.

In the first six months of life, the infant had involuntary movements of the left hemibody, so an EEG was performed that showed a mildly hypovolted EEG pattern over the left centro-parietal leads, with no antiepileptic therapy being initiated at the time.

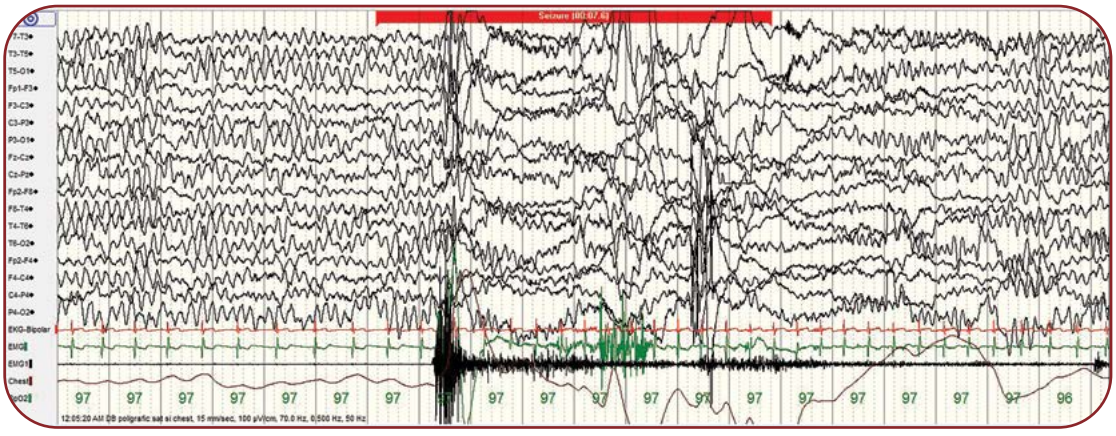

**FIGURE 1.** EEG trace showing large amplitude generalized SW complexes, followed by electrodecrement, with a classic corresponding "diamond-shape" EMG lead aspect and no apnea episodes (from "Dr. V. Gomoiu" Children's Hospital archives, Pediatric Neurology Department, Rare Disease Center of Expertise)

In 2019, the second brain MRI revealed a neuroglial cystic lesion in the left hippocampus and Nitrazepam was added for the movement disorder, but the medication provided no benefit and brought on inefficient clearance of upper airway secretions, so it was withdrawn.

A genetic evaluation was performed and a Whole Exome Sequencing (WES) testing was recommended, which revealed a heterozygous HPRT1 mutation c11_17del.p (Arg4Leufs*4) associated with LNS.

Upon admission in our pediatric neurology department, the child's physical examination revealed a low weight for his age and hyperpigmentation on his abdomen spreading bilaterally to the hips. Neurological examination revealed microcephaly, inconstant opisthotonus, dystonic movements mostly of his upper and lower limbs, severe developmental delay with axial hypotonia, limbs spasticity, hyperreflexia predominantly on the lower body, bilateral Babinski sign and a global developmental age of five months.

Psychological evaluation showed severe poor expressive language with a developmental quotient of 30 points. The child showed self-harming behaviour with injury to his thumbs and no alteration of his pain sensitivity; his mother said that he started to bite his right hand when he turned two and has also started being aggressive towards others.

Blood samples showed a slightly elevated uric acid level. Long-time monitoring polygraphic video-EEG was performed due to the fact that the mother reported episodes suggestive of sleep apnea besides the child's distonic movements. The video-EEG revealed the presence of epileptic seizures – asymmetrical epileptic spasms, but no apnea episodes. Antiepileptic therapy with Levetiracetam was initiated, with a favourable outcome of both the dystonia and epileptic seizures.

## DISCUSSION

We described the case of a 20-month-old male patient diagnosed with LNS, an extremely rare genetic disorder, with general dystonia, severe developmental delay, self-mutilation behaviour and biochemical abnormalities. What made the case interesting was the fact that the mother noticed sleep events suggestive for sleep-apnea, which prompted a polygraphic video-EEG evaluation. Epileptic seizures are uncommon in LNS, but apnea has been described as being associated to subclinical seizures in LNS, leading to respiratory arrest and sudden death (9). Given that seizures can be easily mistaken as dystonic movements it is paramount to establish a clear patient history and perform video-EEG recordings in order to identify clinical or subclinical seizures in children with LNS. In our case, the epilepsy suspicion was confirmed after a sleep EEG. As a therapeutical approach, despite the fact that the literature recommended benzodiazepines as being effective in both dystonia and epilepsy, we decided to initiate treatment with Levetiracem considering the child's medical history of inefficient upper airway secretion clearance when treated with Nitrazepam (9).

We managed to attain seizure control and attenuation of his dystonia with Levetiracetam.

In our case, the patient showed two of the four early signs described in LNS, but the mother could not recall whether her child had hyperuricemia at birth or traces suggesting urate crystals in his diapers.

The main challenge remains the management of self-injurious behaviour because the exact mechanisms of neurological and behavioural implications is still unknown (1-3, 10). Studies revealed that HPRT is highly expressed in the basal ganglia areas of the brain, so a HPRT deficit resulted in basal ganglia dysfunction (2-4, 10).

Our patient needs further nephrological investigations in order to decide the optimal moment of Allopurinol treatment initiation and regular follow-up by a multidisciplinary team comprising a child neurologist, nephrologist, physiotherapist, psychologist, psychiatrist, and even a dentist, because in many cases the pharmacological therapy cannot control the compulsive behaviour and sometimes theeth extraction is the last option (1-3, 7, 8, 10).

The family underwent genetic testing and a heterozygous mutation was identified in one of the patient's sisters. Prenatal genetic counseling is advised, since LNS can be diagnosed during pregnancy by chorionic villus biposy or amniocentesis in male infants (3, 6). ❑

## CONCLUSIONS

Lesch-Nyhan syndrome is a rare genetic disease characterized by dystonia, developmental delay, hyperuricemia and especially

self-harming behavioral disorder. An infant with LNS is asymptomatic at birth and a few key points could lead to an early diagnosis. An infant with severe hypotonia, hyperuricemia at birth, recurrent vomiting and possible orange crystals in his diaper should rise the suspicion of LNS (3, 11). The pathogenesis of LNS is not fully understood, which makes the treatment and overall management difficult as there is no curative treatment. What we currently know, however, is that HPRT deficiency mainly affects the basal ganglia and brain development, partially explaining the neurological and behavioral manifestations.

Our case showed that video-EEG made a difference in establishing the diagnosis of epilepsy versus dystonia or sleep apnea.

Although epilepsy is a rare condition in LNS children, it should always be considered as part of the differential diagnosis of movement disorders and we must not forget the risk of SUDEP in these patients. Nevertheless, it is mandatory to perform a video-EEG evaluation and take a detailed patient history in order to identify any possible clinical/subclinical epileptic seizures that can further negatively impact the neuropsychomotor development of an LNS child. Thus, we highlight the importance of long term video-EEG monitoring in LNS. Parents should also be trained to differentiate between seizures and dystonic episodes.

Because it is a disease with X-linked recessive transmission, genetic counseling is recommended for females with a family history of LNS, as the diagnosis can be established before birth by amniocentesis or chorionic villus biopsy prompting early diagnosis. ❑

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