Severe Respiratory Acidosis in Status Epilepticus as a Possible Etiology of Sudden Death in Lesch–Nyhan Disease: A Case Report and Review of the Literature

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Abstract *Introduction:* Lesch–Nyhan disease (LND) is an X-linked disorder of purine metabolism, associated with self-mutilation, dystonia, and chorea. Seizures are uncommon in LND. Patients with LND are at risk for sudden and unexpected death. The etiology of this is unknown, but appears to occur from a respiratory process. We propose that respiratory failure secondary to subclinical seizure may lead to sudden death in these patients.

Case: We report a case of an 11-year-old boy with LND who had two episodes of nocturnal gasping. The second event was immediately followed by a 10 min generalized seizure. Upon arrival at the hospital, an arterial blood gas test revealed a severe respiratory acidosis. Following aggressive treatment of his seizures, this patient did well, and was discharged home on oxcarbazepine with rectal diazepam. No further seizures have been noted in 1 year of follow-up.

Conclusions: In this case report and review, we hypothesize that sudden death from respiratory failure in Lesch–Nyhan disease may in some cases be due to seizure-induced respiratory failure, akin to sudden unexpected death in epilepsy (SUDEP). We suggest screening for paroxysmal respiratory events; consideration of electroencephalography for patients with LND presenting in respira-

tory distress or failure; and consideration of more aggressive treatment of seizures in these patients.

Brief Summary:

We present an 11-year-old boy with Lesch–Nyhan disease (LND) who developed respiratory failure and severe respiratory acidosis from his first known seizure, which evolved to subclinical status epilepticus. We propose that patients with LND have a predisposition to respiratory failure and sudden death, which in some cases may be provoked by seizure (sudden unexpected death in epilepsy, or SUDEP).

Introduction

Lesch–Nyhan disease (LND) is an X-linked recessive disorder resulting from a deficiency in hypoxanthine–guanine phosphoribosyl transferase (HPRT). This disorder of purine metabolism leads to overproduction of hypoxanthine and uric acid. Patients develop nephrolithiasis, gouty arthritis, and neurological manifestations including dystonia, choreoathetosis, ballismus, and a behavioral disease that includes disinhibited behavior and severe, stereotyped self-injury. Epilepsy may occur in LND, with estimates ranging from 2–3% (Jinnah et al. 2006; Jinnah et al. 2010); however, other studies have found a risk of seizure up to 30%, although this may be due to misinterpretation of abnormal movements as seizure (de Gemmis et al. 2010; Markowski-Leeman and Jinnah 2013). Seizures in LND usually begin in childhood, and are typically classified as generalized tonic-clonic (Jinnah et al. 2006).

Historically, many patients with LND died early of aspiration pneumonia, renal failure or urosepsis, though some patients with LND have been noted to die suddenly.

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Table 1 Case studies of sudden death in Lesch Nyhan syndrome

Case	Author	Heralding events	Known seizures	Circumstances of death	Age of death (years)	Autopsy	Cause of death
1	Hoefnagel et al. (1965)	None	N	After an attack of acute abdominal pain	13	N	Unknown
2	Hoefnagel et al. (1965)	Two prior generalized seizures	Y	Died after generalized seizure and vomiting	8	N	Unknown
3	Basserman et al. (1979)	None	N	Sudden death in sleep after a few days with fevers to 38°C and poor intake	7	Y	Cardiac dilation: assumed to be caused by cardiac failure as a result of viral infection
4	Watts et al. (1982)	Recurrent episodes of flaccid tetraparesis	N	Sudden death in sleep, found “twisted,” with emesis	18	Y	Brain and spinal cord with non-specific signs of anoxia
5	Mizuno (1986)	Intermittent abdominal pain	N	Died suddenly while writing a letter	19	N	Unknown
6	Mizuno (1986)	None	N	Sudden death in sleep	7	Y	No cause identified
7	Neychev and Jinnah (2006)	Four episodes of respiratory arrest with coma after emesis	N	Sudden death in sleep	15	N	Unknown
8	Neychev and Jinnah (2006)	One episode of unexplained respiratory arrest	N	Sudden death	45	N	Unknown
9	Neychev and Jinnah (2006)	None	N	Sudden death	41	Y	No cause identified
10	Neychev and Jinnah (2006)	One episode of unexplained apnea and arrest	N	Sudden death	34	Y	No cause identified
11	Neychev and Jinnah (2006)	None	N	Respiratory arrest and coma; remained comatose until death	21	N	Unknown

N none, Y yes

Case studies of sudden death in LND (Table 1) have posited a variety of putative respiratory mechanisms, including aspiration, laryngospasm, and central apnea (Neychev and Jinnah 2006). Though the frequency of this phenomenon is uncertain, one report of ten patients with LND, followed for 3–19 years, reported two sudden deaths (Mizuno 1986). Sleep-related respiratory abnormalities, including sleep apnea, are not common in this disease, although a decrease in slow wave and REM sleep with abnormal sleep-associated body movements has been described (Saito et al. 1998). The underlying etiology of sudden death in LND is unknown.

We present an 11-year-old boy with LND who presented in subclinical status epilepticus with severe respiratory failure as a “near-miss” of sudden death in LND. We hypothesize that patients with LND may be at increased risk of respiratory failure, which in some cases may be provoked by seizure.

Case Presentation

In the early morning on the day of presentation, the 11-year-old boy’s parents heard “hiccupping” or gasping from his room. He was found pale and unresponsive and was given a rescue breath. When emergency personnel arrived, he was alert with normal oxygen saturations. He was brought to the emergency department where aspiration was suspected but chest X-ray was negative. He was discharged home.

Later that morning, he had another episode of gasping, followed by a convulsive seizure. The seizure stopped after 10 min without intervention, but afterwards the patient was unresponsive and apneic. He was taken back to the emergency department, where providers saw no respiratory effort, and decided to intubate. He seized again and was loaded with 15 mg PE (phenytoin equivalent)/kg fosphenytoin. Venous blood gas revealed significant respiratory

acidosis (pH 6.9, $p\text{CO}_2 > 110$ mmHg, HCO_3^- 27 mmol/L), with a lactate of 3.3 mmol/L. He had a white blood cell count of 32 Kcu/mm, normal electrolytes and liver function, and a mild elevation in creatinine (0.74 mg/dl). Due to concern for meningitis in the setting of new-onset seizures, he was started on antibiotics. His cerebrospinal fluid was unremarkable, and antibiotics were stopped when cultures returned negative.

After transfer to the pediatric intensive care unit, he was placed on continuous electroencephalographic (EEG) monitoring which revealed subclinical status epilepticus with alternating unilateral frontotemporal seizures (Fig. 1). The interictal background showed moderate generalized slowing. His seizures were treated with benzodiazepines, fosphenytoin (5 mg PE/kg/day), and valproate (5 mg/kg every 6 h). Seizures decreased in frequency and stopped approximately 18 h after admission. EEG monitoring was continued for another two days, with no recurrence of electrographic seizures.

Magnetic resonance imaging (MRI) of his brain, done with and without contrast, was notable for T2 diffusion-restriction and increased T2 fluid attenuation inversion recovery (FLAIR) signal in the bilateral hippocampi (Fig. 2). No other acute abnormalities or underlying structural abnormalities were identified on his MRI of the brain. An MRI C-spine was included given his respiratory failure and hyperreflexia on exam, and a reported association of LND with atlantoaxial instability (Shewell and Thompson 1996), but this was normal. His urine purines showed a hypoxanthine level of 403.3 mmol/mol creatinine (normal range 0–38.6).

After extubation he remained in the hospital for two days, with no further respiratory concerns or clinical seizures. He returned to his baseline level of function prior to discharge. He was discharged on oxcarbazepine and has had no further seizures on this medication for the last year.

During a sleep study performed 10 months after discharge, the patient had normal oxygen saturation during sleep with no obstructive apneas, central apneas, or hypopneas recorded. Sleep efficiency was reduced (69%; normal 75–85%). There was an increase in deep or N3 sleep (51%; normal 15–25%).

Past Medical History

The patient was initially diagnosed with cerebral palsy, but by age 3, he developed self-mutilatory behaviors, including finger-biting and lip-biting. He was diagnosed with LND initially by HPRT assay. Genetic testing revealed a large deletion in the HPRT1 gene, involving exons 7 through 9. He was maintained on allopurinol. He had a normal routine

EEG at 22 months of age which was performed for staring spells which were ultimately not felt to be seizure.

His family history is significant for a paternal familial facial myokymia that was reportedly studied at Shriner's Children's Hospital. His mother had seizures in childhood and was briefly on medication.

Discussion

We report the case of an 11-year-old boy with LND who presented with what appeared to be a primary respiratory event, which was ultimately found to be seizure-related. There are elements of this case that are atypical for LND. He has an unusual family history of maternal childhood seizures and paternal myokymia. Our patient's sleep study showed increased time spent in deep sleep, in contrast to previously described adult patients with LND who had diminished deep sleep (Saito et al. 1998), but did not show any central or obstructive apnea that could theoretically trigger a seizure. Convulsive seizures are uncommon in LND; however, the respiratory arrest and apnea that has been described preceding sudden death in LND (Table 1) sounds consistent with the semiology of this patient's subclinical seizures.

This raises the possibility that sudden death in LND could be a seizure-related phenomenon, akin to sudden death in epilepsy (SUDEP). SUDEP is a rare but known complication of epilepsy defined as a sudden, unexpected, witnessed or unwitnessed, non-traumatic, and non-drowning death that occurs in benign circumstances in an individual with epilepsy, with or without evidence for a seizure, and excludes documented status epilepticus, in which post-mortem examination does not reveal a cause of death (Nashef et al. 2012). SUDEP typically presents in patients with poorly controlled generalized convulsions, though seizures are hypothesized to contribute to sudden death in other situations such as sudden infant death syndrome (SIDS) or sudden unexplained death in childhood (SUDC) (Hesdorffer et al. 2015). Subclinical seizures can create profound post-ictal hypoxia and could theoretically lead to death (Maglajlija et al. 2012), particularly in a metabolically abnormal brain. Metabolic abnormalities can affect cardiorespiratory function, autonomic nervous responses, or neurotransmitter release, all posited to increase the risk of SUDEP (Devinsky et al. 2016).

Individuals with LND are at risk for sudden death, and our case suggests that seizure-related respiratory failure may be a possible mechanism. One prior case has been reported associated with known epilepsy (Hoefnagel et al.), though other cases had features which may have been suggestive of seizure (Watts et al.), and some were associated with prior unexplained episodes of respiratory

Fig. 1 Electroencephalogram demonstrating status epilepticus in a patient with Lesch–Nyhan disease with alternating unilateral frontotemporal electrographic seizures (**a**, left-sided seizure; **b**, right-sided). Background showed moderate generalized slowing, consistent with encephalopathy

Fig. 2 MRI from the date of presentation showing increased T2 FLAIR signal (a) and T2 diffusion restriction (b) in the bilateral hippocampi, most likely secondary to seizure

arrest, as in our case (Neychev and Jinnah 2006) (Table 1). In our patient, heralding episodes of respiratory symptoms were felt likely to be an ictal or post-ictal phenomenon. Our case raises the possibility that individuals with LND may present with seizures with atypical semiology, and that respiratory failure in the setting of seizure may be one etiology of sudden death in LND. We suggest routinely asking LND patients about apnea and other respiratory symptoms, with consideration of an EEG for patients with these symptoms. In LND patients with clinical events suggestive of seizure, or a history of paroxysmal respiratory events and an abnormal EEG, a possible increased risk of sudden death should play a role in the discussion of initiating anti-epileptic medication. While earlier treatment (e.g., after suspected seizure or abnormal EEG) could be considered, medications could impact respiratory function of individuals with LND and may be risky in these patients. These decisions should be made carefully on a case-by-case basis. Further research is needed to understand the mechanism of sudden death in LND.

Conclusion

The severity of the acidosis in this patient presenting in subclinical status epilepticus after a first recognized seizure suggests that the sudden death from respiratory failure seen in LND could result from an unrecognized or first seizure. We suggest screening LND patients for paroxysmal respiratory symptoms, and considering seizure as a possible etiology.

Contributions of Individual Authors

Alison Christy prepared the article. Jenny Wilson and William Nyhan provided guidance and editing.

Guarantor for the Article

Alison Christy.

Compliance with Ethics Guidelines

Competing Interests

Alison Christy, William Nyhan and Jenny Wilson declare they have no competing interests.

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Ethics

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