CASE REPORT

Normal Uricemia in Lesch–Nyhan Syndrome and the Association with Pulmonary Embolism in a Young Child—A Case Report and Literature Review

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Deficiency of hypoxanthine phosphoribosyltransferase activity is a rare inborn error of purine metabolism with subsequent uric acid overproduction and neurologic presentations. The diagnosis of Lesch–Nyhan syndrome (LNS) is frequently delayed until self-mutilation becomes evident. We report the case of a boy aged 1 year and 10 months who was diagnosed with profound global developmental delay, persistent chorea, and compulsive self-mutilation since the age of 1 year. Serial serum uric acid levels showed normal uric acid level, and the spot urine uric acid/creatinine ratio was >2. The hypoxanthine phosphoribosyltransferase cDNA showed the deletion of exon 6, and the boy was subsequently diagnosed to have LNS. He also had respiratory distress due to pulmonary embolism documented by chest computed tomography scan. This report highlights the need to determine the uric acid/creatinine ratio caused by increased renal clearance in LNS in young children. The presence of pulmonary embolism is unusual and may be the consequence of prolonged immobilization.

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Lesch-Nyhan syndrome (LNS) is a genetic disorder of purine salvage caused by a complete deficiency of hypoxanthine phosphoribosyltransferase (HPRT) activity resulting from a mutation in the corresponding gene on the long arm of the X chromosome. Affected individuals usually suffer from overproduction of uric acid that may lead to hyperuricemia or nephrolithiasis. High serum uric acid level is usually the biochemical finding that prompts special testing for the specific diagnosis. However, infants with LNS may have borderline serum uric acid levels because of an increased renal clearance of uric acid. Diagnosis can be made by clinical features and further confirmed by direct sequencing of all exons of the HPRT gene.

Pulmonary embolism is more commonly found in adults with underlying predisposing factors and conditions that interfere with normal venous blood flow. In children, pulmonary embolism is rare. The few reports about pediatric pulmonary embolism reflect its relative rarity and difficult evaluation. Imaging evaluation of pulmonary embolism is crucial for diagnosis. The use of a multidetector computed tomography (MDCT) shortens the time of the study and greatly improves its resolution.

2. Case Report

A boy aged 1 year and 10 months presented with developmental delay. He was born to nonconsanguineous healthy parents, and had been diagnosed with nephrolithiasis at the age of 5 months. When the patient was 6 months old, recurrent airway infection and respiratory distress complicated by laryngomalacia required repeated hospital admission and central catheterization during hospitalization. He was diagnosed with profound psychomotor retardation and was bed-ridden since 1 year of age. He also had chorea when awake, and compulsive self-destructive behavior such as biting fingers, lips, and buccal mucosa were noted for about 6 months.

Laboratory tests showed normal complete blood count, electrolytes, blood gas, ammonia, and lactate. Although serial serum uric acid level showed normal uric acid level (7.6 mg/dL), the spot urine uric acid/creatinine ratio was 116/50 or >2.0, which subsequently pointed to a diagnosis of LNS. There were no particular findings on brain magnetic resonance image and electroencephalography.

The patient and his family, as well as control individuals were analyzed using multiplex quantitative polymerase chain reaction (PCR) to amplify the FGFR2 gene, the KRIT1 gene, and the HPRT gene simultaneously. The HPRT cDNA, amplified from the total RNA of the patient’s peripheral blood by multiple specific primers for multiplex PCR, showed the deletion of exon 6. The family study revealed that the patient’s mother was a heterozygous carrier (Figure 1). He was put on allopurinol for his uric acid overproduction and nephrolithiasis.

Because of his persistent respiratory distress, the study of chest MDCT with intravenous contrast injection was performed. The images of chest MDCT showed pulmonary embolism with nonobstructive lobar and segmental arterial thrombi in the basal segments of the left lower lobe. This may explain the persistent respiratory distress of the patient (Figure 2).

Figure 1  The pedigree and sequence amplified cDNA of the HPRT gene in the patient (black). The patient’s mother is a heterozygous carrier.
3. Discussion

The diagnosis of LNS is frequently delayed until self-mutilation becomes evident.\(^8\) It is the most striking feature of LNS and is only present in patients with the complete enzyme defect, although some patients never show this type of behavior. The self-mutilation associated with LNS typically first appears with the emergence of teeth, and steadily worsens with increasing age.\(^9\) In the current patient, such behavior prompted the investigation of his uric acid under the suspicion of LNS. Patients with HPRT deficiency must be confirmed by clinical, biochemical, enzymatic, and molecular analyses. In this case, despite fulfilling the diagnosis criteria of LNS, the patient’s serial serum uric acid only showed normal uric acid. Thus, the uric acid/creatinine ratio was used to corroborate the clinical diagnosis. In young children, renal function is quite efficient in eliminating uric acid into the bladder, and hence, they may have borderline hyperuricemia due to increased renal clearance. As such, the urinary uric acid/creatinine ratio can be used as a screening test for inherited disorders of purine metabolism based on the age of the patient. Values for the urinary ratio should be \(<1.0\) after the age of 3 years.\(^{10}\)

The \textit{HPRT} gene is localized to the Xq26 region, and the complete amino acid sequence for HPRT is known to be 44 kb, which consists of nine exons with a coding for a 219-amino acid protein that converts hypoxanthine into inosinic acid and guanine into guanylic acid. To date, more than 300 disease-associated mutations in the \textit{HPRT} gene have been identified,\(^5\) but reports of LNS in Taiwan remains limited. Mak et al\(^ {11} \) reported a case series of four patients with LNS from three families. Three patients in two families were revealed to have novel missense mutation in exons 3 and 8, and in one patient, a splicing region of intron 4 of the HPRT encoding region was reported. Hou\(^ {12} \) reported a 9-year-old boy with LNS complicated with atlantoaxial subluxation, and the direct genomic DNA sequencing of the \textit{HPRT} gene revealed a single nucleotide substitution in intron 5. To the best of our knowledge, this is the first case report of LNS associated with pulmonary embolism, complicated by the patient’s long-term immobilization.

In conclusion, this report highlights the value of the uric acid/creatinine ratio as a screening test for young male children highly suspected to have LNS. To the best of our knowledge, this is the first case report of LNS with exon 6 deletion reported in Taiwan.

Treatment of LNS remains limited for self-mutilation and motor syndrome. However, allopurinol should be started as soon as the enzyme deficiency is diagnosed, although it has no reported effect on behavioral and neurological symptoms. It should be adjusted to reduce hyperuricemia and achieve a urinary uric acid/creatinine ratio lower than 1.0. Allopurinol is efficacious and generally safe as treatment for uric acid overproduction in patients with HPRT deficiency.\(^ {13} \)

Pediatric patients rarely present with conditions that place them at high risk for thrombus formation. When it occurs, pulmonary embolism has been shown to cause serious illness and even death. Traditional risk factors in adults may be a consequence of continuous immobilization,\(^ {14} \) because the pathophysiology of thrombus formation is blood flow stasis.\(^ {15} \) Nonetheless, there is no article on LNS that suggests the complication of pulmonary embolism, and as such, it can be considered a consequence of long-term immobilization stemming from his profound retardation and recurrent central catheterization.

In conclusion, this report highlights the value of the uric acid/creatinine ratio as a screening tool for young male children highly suspected to have LNS. To the best of our knowledge, this is the first case report of LNS associated with pulmonary embolism, complicated by the patient’s long-term immobilization.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

References