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CASE REPORT

Lesch-Nyhan Syndrome in a Chinese Family with Mutation in the Hypoxanthine-Guanine Phosphoribosyltransferase Gene

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SUMMARY

Background: **Lesch-Nyhan syndrome (LNS) is a congenital X-linked recessive neurogenetic disorder caused by mutations in the hypoxanthine-guanine phosphoribosyltransferase (HPRT) gene. The main clinical manifestation includes hyperuricemia, juvenile-onset gouty arthritis, and neurological developmental disorders. Studies have reported more than 400 HPRT gene mutation sites, but the incidence of LNS in the Chinese population is extremely low.**

Methods: **Here we report a 16-year-old male patient who suffered neurological dysfunction at an early age and gouty arthritis in his youth.**

Results: **No activity of the HPRT enzyme was detected in the erythrocytes. Furthermore, we found a mutation on exon 3 of the HPRT gene in the patient and his mother (exon 3: c.143G>A), which resulted in arginine to histidine (p.R48H) substitution in the encoded protein. The same mutation was reported in several European families, but was found for the first time in a Chinese family.**

Conclusions: **Clinicians in China have poor experience in diagnosing LNS cases due to the low incidence in China. Therefore, LNS screening for infants or adolescents with hyperuricemia, gouty arthritis, and neurological dysfunction should be performed.**

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KEY WORDS

Lesch-Nyhan syndrome (LNS), hypoxanthine-guanine phosphoribosyltransferase (HPRT), hyperuricemia, mutation

INTRODUCTION

Lesch-Nyhan syndrome (LNS) is an X-linked recessive inherited disease caused by mutations in the hypoxanthine-guanine phosphoribosyltransferase (HPRT) gene [1]. Mutations in the HPRT gene decrease HPRT enzyme activity and block purine nucleotide synthesis, which promotes the conversion of hypoxanthine to uric acid (UA), leading to severe hyperuricemia [2]. The deficiency of HPRT enzymatic activity resulting from gene defects could also influence nervous system development [3,4]. Most of the affected patients are male

who suffer neuronal developmental disorders after birth resulting in a misdiagnosis of cerebral palsy. Hyperuricemia occurs in juvenile patients, and the long-term elevation of UA can cause gout and kidney damage [5]. The prevalence of LNS was 0.18/100,000 live births over the 20 years of study in the UK [6]. However, the incidence of LNS in China is extremely low and has been reported only in a few case reports and studies involving gene mutation analyses [7-9].

CASE REPORT

A 16-year-old male was admitted to Hangzhou First People's Hospital in January 2014 due to severe gouty arthritis. He had been diagnosed with cerebral palsy at 2 years of age at the local Children's Medical Center, presenting delayed development and difficulty in walking. By the age of 12 years, Achilles tendon lengthening was performed on both his legs due to gait dysfunction. The IQ of the patient was 90 without any self-harming tendency.

The patient had edema and pain in the right elbow, wrist and ankle joints. Furthermore, his serum uric acid level increased to 1086 μmol/L at 1 month before admission. Small tophi were found in the auricle and metacarpophalangeal and interphalangeal joints. Bilateral renal b-ultrasound showed strong medullary echoes, but the head MRI did not show any abnormalities. His parents were non-consanguineous and have no history of gout. Nervous system examination showed hyperreflexia of all four limbs, ankle clonus (+), and patella clonus (+). The patient was diagnosed with LNS based on the clear identification of gouty arthritis, high UA, and abnormal nervous system development. No activity of the enzyme HPRT was detected in the erythrocytes. Informed consent for gene analysis was provided by the patient as well as his family and the procedure was approved by the Ethics Committee of Hangzhu First People's Hospital. Sequencing was performed for the exons and splicing sites of the patient and his family. Genomic DNA was extracted from peripheral blood lymphocytes. The coding region and the intron-exon boundaries of HPRT gene were sequenced by standard methods. The exon 3: c.143G>A mutation was found in the patient, which resulted in an arginine to histidine (p.R48H) substitution in the encoded protein (Figure 1). The patient's mother was heterozygous with an A/G mutation, whereas the father and the healthy control only had a G at the specific locus (Figure 2, 3). The gene mutation was reported in China for the first time. The patient was treated with sodium bicarbonate to alkalize the urine and febuxostat for UA. Patient follow-up until Oct 2016 revealed that the frequency of gouty arthritis seizure dropped and the serum uric acid level was controlled at 500 - 600 μmol/L.

DISCUSSION

LNS, with a spectrum of disease, is a rare monogenic disorder associated with UA metabolism. It can be divided into 3 types according to the clinical symptoms. The classical type includes gout, neurological dysfunction, and self-harming tendencies. The mildest type includes only hyperuricemia. The intermediate type involves gout, and neurological dysfunction with self-harming tendencies [10]. Our patient has the third type of LNS. All three types of LNS are associated with the overproduction of uric acid. Hence, although hyperuricemia is a common disease, it deserves attention when it occurs in juvenile or adolescent patients because it may be related to metabolic deficiency.

The synthesis of purine nucleotides *in vivo* involves two pathways. In one, the purines are synthesized by utilizing ribose phosphate, amino acid, one carbon unit, and CO_2 in a series of enzymatic reactions, which is called de novo synthesis. The other called salvage synthesis involves synthesis of free purines or purine nucleosides *in vivo*, which are then used to synthesize purine nucleotides in a simple reaction. The former is the main synthesis pathway for purines. The latter is physiologically significant in that it can avoid the consumption of energy and amino acid in the de novo synthesis pathway. In brain tissues, purine nucleotides can only be synthesized by the salvage synthesis pathway as these tissues lack the enzymes required for the de novo synthesis. Therefore, a mutation in the gene encoding the HPRT enzyme can result in an increase in UA levels and affect nervous system development.

Some studies have reported there are more than 400 HPRT gene mutation sites [11]. The incidence of LNS in the Chinese population is extremely low. Mak et al. reported 4 cases of gene mutations (exon 3: c.222C>G, exon 8: c.569G>A) in 3 Taiwan families [12]. In 2014, Jian et al. found a new mutation (exon 3: c.245G>A) in a family from mainland China [8]. Exon 3 is thus a hot region of mutations in the HPRT gene [13]. Here we detected a mutation causing the substitution of guanine with adenine at position 143 in exon 3 (c.143G>A). This mutation was also reported in many European families. The relationship between the genotype and phenotype is a basic theoretical problem in genetics, and rare monogenic disorders provide a good model to study this relationship. Thus, LNS patients can serve as early study models. Our study demonstrated that the same mutation usually has a similar clinical manifestation. Sampat et al. summarized data on mutations in 10 patients from 8 families and studied some of the associated functions. The C.143G>A mutation is located in the CpG island region, which is a significant regulatory region for some genes. *In vitro* research has shown that mutations in this site can significantly reduce the thermostability of the enzyme and cause complete loss of enzyme activity [13].

Clinicians may have insufficient understanding of LNS due to the low incidence in China. However, as hyper-

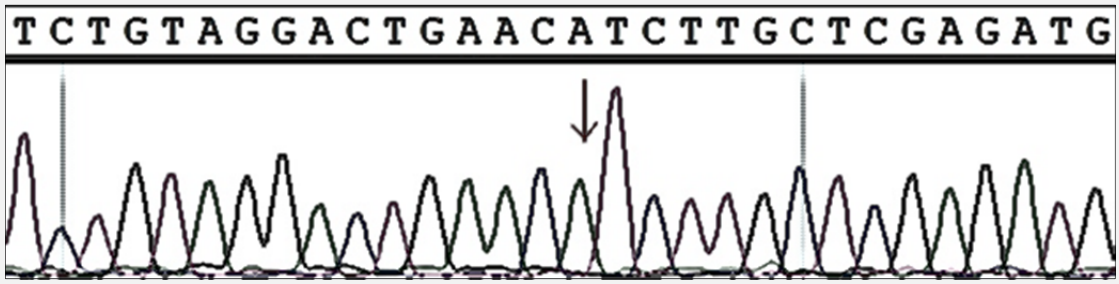

Figure 1. Homozygous A genotype in patient.

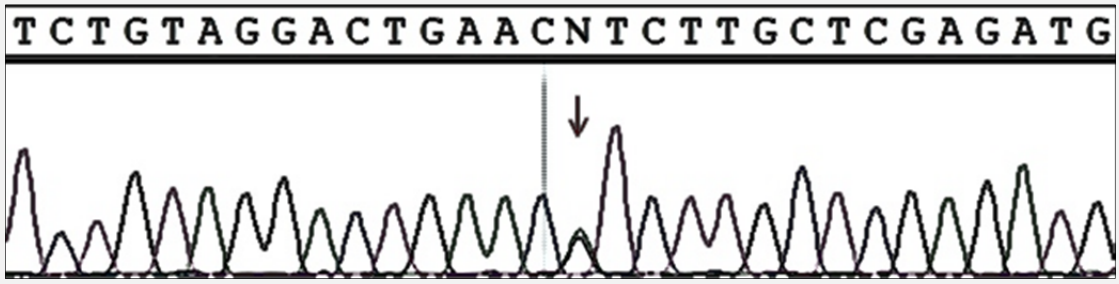

Figure 2. Heterozygous A/G genotype in patient's mother.

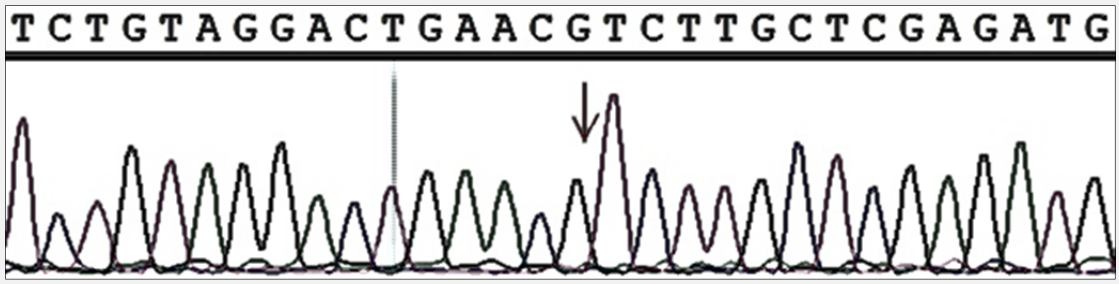

Figure 3. Homozygous G genotype in patient's father and healthy control.

uricemia is a common clinical phenomenon, the underlying causes may be ignored, leading to misdiagnosis or delay in the diagnosis. Therefore, it is necessary to perform LNS screening for patients with hyperuricemia during the infantile period and adolescence, especially for those with neurological dysfunction. Careful neurologic examination is warranted in juvenile and middle-aged patients with gout in order to detect mild symptoms that may lead to a diagnosis of HPRT deficiency.

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Declaration of Interest:
The authors declare that they have no conflict of interest.

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