Mild Lesch–Nyhan Disease in a Boy with a Null Mutation in *HPRT1*: An Exception to the Known Genotype–Phenotype Correlation

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Abstract Hypoxanthine–guanine phosphoribosyltransferase (HPRT) deficiency results in a continuous spectrum of clinical phenotypes though all include overproduction of uric acid with hyperuricaemia, urate nephrolithiasis and gout. *HPRT1* mutations that result in very low or no HPRT enzyme activities are generally associated with the classic Lesch–Nyhan disease (LND) phenotype with intellectual disability, motor handicap and self-injurious behaviour. Mutations that permit a higher residual HPRT activity are seen in some patients with the milder LND variant phenotypes with varying degrees of cognitive, motor handicap and maladaptive behaviour without recurrent self-injury. We present a boy with a LND variant phenotype due to a deletion of exon 5 of *HPRT1* predicted to fully abolish HPRT activity. Metabolic analysis confirms lack of significant residual enzyme activity. The boy, currently age 10, presented with hyperuricaemia, hypotonia, developmental delay and extrapyramidal and pyramidal involvement. He has never shown any signs of self-injurious or maladaptive behaviour. This boy is one of the rare cases with a suspected null mutation in *HPRT1* that associates with a milder than expected phenotype with lack of self-injurious behaviour.

Key Clinical Message *HPRT1* mutations that result in very low or no hypoxanthine–guanine phosphoribosyltransferase enzyme activities are generally associated with the classic Lesch–Nyhan disease. This report presents one of

the rare cases with a null mutation in the *HPRT1* gene that associates with a milder than expected phenotype with lack of self-injurious behaviour.

Introduction

Lesch–Nyhan disease (LND) is an X-linked monogenic disorder associated with development of gout due to marked overproduction of uric acid (Torres and Puig 2007). At one end of the clinical spectrum are patients with the classic LND phenotype associated with overproduction of uric acid, severe motor handicap resembling dystonic cerebral palsy, intellectual disability and recurrent self-injurious behaviour. At the other end of the spectrum, patients have an overproduction of uric acid without apparent neurological or behavioural deficits. Collectively, the attenuated phenotypes are classified as LND variants and are often distinguished from the classic LND by the lack of self-injurious behaviour although many exhibit maladaptive behaviour (Jinnah et al. 2010). In the vast majority of LND variants, patients have mutations in *HPRT1* that allow some residual activity of hypoxanthine–guanine phosphoribosyltransferase (HPRT), whereas complete loss of enzymatic activity is associated with classic LND (Jinnah et al. 2010; Fu et al. 2013).

Recognition of LND variants is important for understanding the pathogenesis and natural history as well as for diagnosis of all patients with HPRT deficiency. We present a boy hemizygous for a deletion of exon 5 in *HPRT1* resulting in almost complete absence of residual HPRT activity but with no signs of self-injurious or maladaptive behaviour.

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Case Report

A 10-year-old boy born to non-consanguineous parents was referred at age seven months due to hypotonia. The mother was diagnosed with phenylketonuria as a newborn and during her pregnancy, serum levels of phenylalanine were generally held below 360 $\mu\text{mol/L}$ as recommended during pregnancy. Family history was otherwise unremarkable. Brain magnetic resonance imaging showed no abnormalities. He had an elevated serum uric acid at 0.78 mmol/L (ref. 0.12–0.32 mmol/L) and the urine uric acid/creatinine ratio was at the upper normal limit (1,500 $\mu\text{mol/mmol}$ creatinine; ref. 260–1,540). Unfortunately, the genetic basis for possible Lesch–Nyhan disease was not investigated at this early age.

Dystonia with repetitive abnormal posturing of the limbs along with hypertonia emerged during the following year. Hyperreflexia limited to the legs, clonus limited to the ankles and a rate-dependent increase in limb tone with presence of catch in all four extremities indicated spasticity. Psychomotor delay became more evident during his second and third year, when it became clear that he was moderately mentally retarded. His gait worsened and by the age of five, he could hardly stand or walk by himself.

At the age of 10, a routine examination revealed elevated serum creatinine at 13.4 $\mu\text{mol/L}$ (1.1–6.4 $\mu\text{mol/L}$) and blood urea nitrogen at 86 mmol/L (29–56 mmol/L). Serum uric acid was elevated at 0.78 mmol/L (0.12–0.32 mmol/L). A renal ultrasound showed no signs of nephrolithiasis, but both kidneys were enlarged, hyperechogenic and without a clear border between the cortex and medulla. Analysis of purines and pyrimidines in urine revealed elevated excretion of uric acid (1,530 $\mu\text{mol/mmol}$ creatinine; ref. 100–660) and hypoxanthine (55 $\mu\text{mol/mmol}$ creatinine; ref. 2–19) suggestive of LND, which was confirmed by lack of HPRT activity in an erythrocyte lysate (<0.1% of normal control) determined essentially as described elsewhere (Shin-Buehring et al. 1980). We have previously found this level of HPRT activity in boys with classic LND and definite null mutations and consider such activity as assay background. Mutation analysis of *HPRT1* disclosed a 498 base pair deletion (c.385–51_402 + 430del) enclosing the entire exon 5, which encodes six centrally located amino acids. Segregation analysis revealed that the mutation was de novo.

The boy has had no signs of self-injurious behaviour, no impulsive act of aggression such as striking out or spitting and no use of foul or sexually charged language. No habitual fingernail biting, impulsivity, hyperactivity or any signs of an obsessive–compulsive disorder.

Discussion

LND is characterized by motor dysfunction resembling cerebral palsy, cognitive and behavioural disturbances and uric acid overproduction. The most common presenting features are hypotonia and developmental delay during the first year of life (Jinnah et al. 2006). Affected children have delayed milestones and may never walk. Within the first few years, extrapyramidal involvement (e.g. dystonia, choreoathetosis, opisthotonos) and pyramidal involvement (e.g. spasticity, hyperreflexia, extensor plantar reflexes) become evident (Jinnah et al. 2010). Cognitive impairment and behavioural disturbances emerge between ages two and four. Persistent self-injury (biting the fingers, hands, lips and cheeks; banging the head or limbs) is a hallmark of the classic LND. Self-injury typically presents before age four, and though it may be delayed until late teenage years (Jinnah et al. 2010), this is exceptional.

It is generally accepted that null mutations cause classic LND, whereas mutations resulting in some residual activity underlie the LND variant phenotype. Exceptions to this concept do exist. Fu et al. (Fu et al. 2013) summarized six cases with the LND variant phenotype and deletions affecting the coding region of *HPRT1*. These apparent exceptions could, however, be explained by either incomplete phenotypic evolution due to diagnosis at a very early age or due to unusual molecular mechanisms that permit residual enzyme activity (Fu et al. 2013). In addition, three HPRT deficient patients with apparent exon 5 exclusion, due to a splice site mutation, have been described. As a result of the splice defect, these patients were predicted to present an in-frame exon 5 deletion resulting in a protein deleted for six amino acids. Two of the patients were primarily described as LND (Jinnah et al. 2004; Mak et al. 2000) and one presented as a LND variant (Torres et al. 2010), but none of them presented typical self-injurious behaviour (Jinnah et al. 2010; Jinnah et al. 2006). Our patient has a full exonic deletion removing the same six centrally located amino acids which are predicted to be essential for correct function, and the mutation is anticipated to completely disrupt HPRT enzyme function. Confirming this, we found a very low residual activity of HPRT of less than 0.1% of normal mean value. Thus, it appears that both exon 5 deletion and exclusion may result in LND variant phenotype. To what extent this variant phenotype relies on an abnormal in-frame transcript remains unknown, as the exact consequence of the splice site mutations and the gross deletion on mRNA splicing is difficult to predict.

Absence of self-injurious and maladaptive behaviour at the age of 10 is highly unusual given the above

biochemical/molecular findings. Thus, this case represents an enigma as to why our patient presents clinically as a LND variant and not classic LND. In theory, accelerated de novo biosynthesis of inosine/guanosine monophosphate could compensate for the reduced purine recycling in our patient, leading to a milder phenotype than expected. This possibility remains speculative, however, as no studies have investigated whether the de novo pathway can influence the phenotype of LND patients (Fu et al. 2013). In summary, the present case represents one of the rare exceptions to the generally accepted genotype–phenotype correlation in the LND disease spectrum.

Contributors List

Dr. A. Bayat and F. Wibrand had the idea to write the article.

F. Wibrand and M. Christensen were responsible for performing the metabolic investigations.

M. Duno was responsible for the genetic investigations.

Dr. A. Bayat and Dr A. Lund were both responsible for collecting medical records, gathering relevant literature and together writing the first script. All authors were involved in the ongoing revision of the manuscript. All authors contributed to the revision of the final manuscript.

Conflict of Interest

Allan Bayat, Mette Christensen, Flemming Wibrand, Morten Dunø and Allan Lund declare that they have no conflict of interest.

Compliance with Ethics Guidelines

This article does not contain any studies with human or animal subjects performed by any of the authors.

References

- Fu R, Ceballos-Picot I, Torres RJ, Larovere LE, Yamada Y, Nguyen KV et al (2013) Genotype–phenotype correlations in neuro-genetics: Lesch–Nyhan disease as a model disorder. *Brain* 137:1282–1303
- Jinnah HA, Harris JC, Nyhan WL, O'Neill JP (2004) The spectrum of mutations causing HPRT deficiency: an update. *Nucleosides Nucleotides Nucleic Acids* 23(8–9):1153–1160
- Jinnah HA, Visser JE, Harris JC, Verdu A, Larovere L, Ceballos-Picot I et al (2006) Delineation of the motor disorder of Lesch–Nyhan disease. *Brain* 129(Pt 5):1201–1217
- Jinnah HA, Ceballos-Picot I, Torres RJ, Visser JE, Schretlen DJ, Verdu A et al (2010) Attenuated variants of Lesch–Nyhan disease. *Brain* 133(Pt 3):671–689
- Mak BS, Chi CS, Tsai CR, Lee WJ, Lin HY (2000) New mutations of the HPRT gene in Lesch–Nyhan syndrome. *Pediatr Neurol* 23(4):332–335
- Shin-Buehring YS, Osang M, Wirtz A, Haas B, Rahm P, Schaub J (1980) Prenatal diagnosis of Lesch–Nyhan syndrome and some characteristics of hypoxanthine-guanine phosphoribosyltransferase and adenine phosphoribosyltransferase in human tissues and cultivated cells. *Pediatr Res* 14(6):825–829
- Torres RJ, Puig JG (2007) Hypoxanthine-guanine phosphoribosyltransferase (HPRT) deficiency: Lesch–Nyhan syndrome. *Orphanet J Rare Dis* 2:48
- Torres RJ, Garcia MG, Puig JG (2010) Partial HPRT deficiency phenotype and incomplete splicing mutation. *Nucleosides Nucleotides Nucleic Acids* 29(4–6):295–300
- Torres RJ, Puig JG, Jinnah HA (2012) Update on the phenotypic spectrum of Lesch–Nyhan disease and its attenuated variants. *Curr Rheumatol Rep* 14(2):189–194