Mild Lesch-Nyhan disease in a boy with a null-mutation in *HPRT1*: an exception to the known genotype-phenotype correlation: three-year follow-up.

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Abstract

Lesch-Nyhan disease and its attenuated variants are caused by deficiency of the purine salvage enzyme, hypoxanthine-guanine phosphoribosyltransferase (HPRT). HPRT deficiency results in a continuous spectrum of clinical phenotypes though all include overproduction of uric acid with nephrolithiasis, renal failure, gouty arthritis and tophi. *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 have previously presented a 10-year-old boy with a LND variant phenotype due to a deletion of exon 5 of *HPRT1* predicted to fully abolish HPRT activity. Metabolic analysis confirmed lack of significant residual enzyme activity. He presented with hyperuricemia, hypotonia, developmental delay, extrapyramidal and pyramidal involvement. 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. He is currently 13-years-old and has yet to show any signs of self-injurious or maladaptive behaviour. In addition, an experience of oral baclofen on this patient is presented.

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.

Keywords: Lesch-Nyhan, Hypoxanthine-guanine phosphoribosyltransferase, HPRT1, genotype-phenotype correlation

Abbreviations: HPRT, hypoxanthine-guanine phosphoribosyltransferase; LND, Lesch-Nyhan disease.

1. Introduction

Lesch-Nyhan disease (LND) (OMIM 300322) is an x-linked monogenic disorder associated with development of gout due to marked overproduction of uric acid (Torres & 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). The vast majority of LND variants patients have mutations in *HPRT1* that allow some residual activity of hypoxanthine-guanine phosphoribosyl-transferase (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 have previously presented a boy at age 10 years with a hemizygous 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 (Bayat, Christensen, Wibrand, Duno, & Lund, 2015). This is a follow-up article on the same boy who is currently 13-years-old and has yet to show any signs of self-injurious or maladaptive behaviour. In addition, an experience of oral baclofen on this patient is presented.

2. 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 μmol/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 (1500 µmol /mmol creatinine, ref. 260-1540). 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 µmol/l (1.1-6.4 µmol/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 cortex and medulla. Analysis of purines and pyrimidines in urine revealed elevated excretion of uric acid (1530 µmol /mmol creatinine, ref. 100-660) and hypoxanthine (55 µmol /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). Mutation analysis of *HPRT1* disclosed a 498 basepair deletion (c.385-51_402+430del) enclosing the entire exon 5. Segregation analysis revealed that the mutation was *de novo*.

The boy is currently 13-years-old and has still no signs of self-injurious behaviour, no impulsive acts of aggression such as striking out or spitting, and no use of foul or sexually habitual charged language, no fingernail biting, impulsivity, hyperactivity or any signs of an obsessive-compulsive disorder. He was social and interactive at home and at school. Following the diagnosis of LND he had his

first kidney stone and started treatment with allopurinol (4 mg/kg daily). Urinary alkalinisation with potassium citrate was also started. Overproduction of uric acid was controlled with oral allopurinol and the dose of allopurinol was adjusted to maintain the uric acid within normal limits. Currently there are no signs of active podagra or progressive renal dysfunction. Glomerular filtration rate during the past three years has been stable around 56ml/min/1.73m^2. Currently serum creatinine is still elevated but stable at 15.3 μmol/l (1.1-6.4 μmol/l) and blood urea nitrogen at 91 mmol/l (29-56 mmol/l). A recently performed renal ultrasound showed no visible nephrolithiasis but both kidneys were still enlarged, hyperechogenic and without a clear border between cortex and medulla.

Results of a recent neuropsycho-logical examination revealed reading and spelling skills at a kindergarten level, mathematic skills at a first class level, and borderline intellectual functioning (his estimated Wechsler Adult Intellectual Scale, Third edition, fullscale IQ was 74).

On physical examination, dystonia with repetitive abnormal posturing of the limbs along with hypertonia and catch in all four extremities and hyperreflexia limited to the legs is still found. He also experiences severe dysarthria limiting his ability to speak. Using his hands he was able to maneuver an electric wheelchair, to open doors in his path and to play computer with a joystick. The boy is still primarily bound to a wheelchair and can hardly stand or walk by himself; however, treatment with oral baclofen has made his speech more understandable and has enabled him able to walk a few meters alone. He started with 0.5 mg/kg/day and was gradually increased in dosage to 1.5 mg/kg/day. Treatment with baclofen could however not prevent bilateral chronically hip dislocation resulting in a bilateral valgus subtrochanteric femoral osteotomy. The patient has been offered treatment with intrathecal baclofen and the parents are currently considering this treatment option.

3. 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; Torres, Puig, & Jinnah, 2012). 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) becomes 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 and among these are three HPRT deficient patients with exon 5 exclusion, due to a splice mutation. As a result of the splice defect, these patients presented also an in-frame exon 5 deletion and a predicted six amino acids excluded protein, while the rest of the sequence was normal. Two of them were primarily described as LND (Jinnah, Harris, Nyhan, & O'Neill, 2004; Mak, Chi, Tsai, Lee, & Lin, 2000) and one of them presented as a LND variant (Torres, Garcia, & Puig, 2010), but none of them presented typical self-injurious behavior (Jinnah et al., 2010; Jinnah et al., 2006). 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). Our patient has a full exonic deletion removing 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. We have previously found this level of activity in boys with classic LND and definite null mutations, and consider such activity as assay background.

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 (3). In summary, the present case still represents one of the rare exceptions to the generally accepted genotype-phenotype correlation in the LND disease spectrum. Current therapies for LND are off-label and experimental, often leading to inconsistent outcomes. Although LND is a severely disabling disease, no therapeutic standard can yet be indicated and treatment proceeds on the basis of isolated observations. Many therapies for LND, both pharmacological (antispastic drugs, anti-parkinsonian drugs, antipsychotics, dietary supplements) and cellular (enzyme replacement and stem cell therapies), are currently experimented, with inconsistent results (McCarthy et al., 2011). The use of oral and intrathecal baclofen for LND patients is not uncommon; a population study reported on ten users of oral baclofen and one of intrathecal baclofen, although it did not discuss therapeutic efficacy (McCarthy et al., 2011). In our patient, although oral treatment with baclofen did improve speech and comfort and reduced the degree of spasticity, it however didn´t significantly improve his ability to stand or walk. A few studies have been published regarding treatment with intrathecal baclofen (Jinnah et al., 2006; Pozzi et al., 2014) and have shown an improvement

regarding both dystonia and pathological behaviours. Baclofen is potentially useful as a therapy for LND, but additional studies should be conducted, in order to properly assess its efficacy. Both intrathecal and oral administration routes should be investigated, with systematic measurements and long follow-up periods. Another promising treatment option in patients with LND dystonia symptoms and self-injurious behavior is deep brain stimulation (Abel et al., 2014; Deon, Kalichman, Booth, Slavin, & Gaebler-Spira, 2012; Piedimonte et al., 2015) but since this treatment is based on single-case-stories, larger and more systematic studies are needed to evaluate the effect of deep brain stimulation.

4. Conflict of Interest:

Allan Bayat and Annika Wollenberg Juul declare that they have no conflict of interest.

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