CASE REPORT

Late diagnosis of Lesch-Nyhan disease variant

Brian Percy Doucet, Dev Jegatheesan, John Burke

Department of Medicine, Mater
Misericordiae Health Services,
South Brisbane, Queensland,
Australia

Correspondence to

Dr Brian Percy Doucet,
brian.doucet@uqconnect.edu.au

SUMMARY

A 30-year-old man was referred for investigation and management of hyperuricaemia. History included recurrent nephrolithiasis and chronic gout with poor response to medical management. Hypoxanthine-guanine phosphoribosyltransferase (HGPRT) enzyme activity was investigated and found to be deficient confirming the diagnosis of Lesch-Nyhan disease. Hyperuricaemia was treated with allopurinol. To prevent nephrolithiasis, the patient was instructed to avoid dehydration and aim for a minimum urine output of 2 L/day. Urinary alkalinisation with potassium citrate was started. The patient was referred for genetic counselling. This case discusses the genetics, pathophysiology, clinical manifestations, diagnosis and management of HGPRT deficiency.

BACKGROUND

The diagnosis of hypoxanthine-guanine phosphoribosyltransferase (HGPRT) deficiency in adults is extremely rare. This case details an individual managed in a first-world medical system with recurrent renal calculi and chronic gout since the age of 16 years. Presumably, his uric acid levels were high throughout his life. Despite these clues, the diagnosis of HGPRT deficiency was not made until the age of 30 years. The patient had not received optimal medical management directed by the knowledge of his underlying genetic deficiency. The patient has lived a significant period of reproductive age with a genetic condition that he could have unknowingly passed to his offspring. This case report shows that HGPRT deficiency should be suspected in any patient with unexplained persistent hyperuricaemia not responding to typical allopurinol dosing.

CASE PRESENTATION

A 30-year-old Caucasian man was referred for further investigation and management of hyperuricaemia. The medical history included 14 years of chronic gout, recurrent nephrolithiasis, hypertension and psoriasis. There was no significant family history and no history of cognitive or neurobehavioural deficits. His management included allopurinol, but serum uric acid levels had been consistently measured above 0.8 mmol/L (reference range 0.15–0.50). His renal function was normal with creatinine 105 µmol/L, urea 7.3 mmol/L and estimated glomerular filtration rate 72 ml/min per 1.73 m².

On examination, there was no obvious posturing. A gouty tophus was palpated over the right olecranon and tophi were observed at the medial aspect of the first metatarsal-phalangeal joints (figure 1). Tophi and joint deformity were also observed in

Figure 1 A gouty tophus is seen over the right olecranon with a psoriatic plaque over the extensor surface.

the hands at the third proximal interphalangeal joints, the left second distal interphalangeal and the right fifth proximal and distal interphalangeal joints. Scaling plaques were noted on the extensor surfaces of the elbows and knees. Neurological examination revealed generalised hyperreflexia and weakness, power 4/5, in all muscle groups of the upper and lower limbs. There was no dystonia, clonus or spasticity.

INVESTIGATIONS

The history and examination findings were suspicious for Lesch-Nyhan disease (LND) variant. HGPRT activity was investigated with erythrocyte enzymology testing and the result of 0.1 U/g haemoglobin (reference range 3.0–6.7) confirmed the diagnosis of HGPRT deficiency. HPRT1 gene testing revealed a previously described hemizygous c.112C>T (p.Pro38Ser)¹ missense mutation consistent with LND variant.

DIFFERENTIAL DIAGNOSIS

Other causes of hyperuricaemia such as increased phosphoribosyl pyrophosphate activity and familial juvenile hyperuricaemia were considered.

TREATMENT

Hyperuricaemia was treated with allopurinol 900 mg daily and adherence was encouraged. To prevent nephrolithiasis, the patient was instructed to avoid dehydration and aim for a minimum urine output of 2 L/day. Urinary alkalinisation with potassium citrate 60 mEq/day was commenced.

OUTCOME AND FOLLOW-UP

The patient continues on the above treatment.

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DISCUSSION

HGPRT deficiency is an X-linked recessive disorder. Over 400 causative HPRT1 gene mutations have been described.² Prevalence has been estimated at between 1/235 000 and 1/380 000 live-births.³ The condition is almost exclusively diagnosed in the paediatric population though new diagnosis has been documented in adults.⁴

Many mutations allow residual HGPRT activity instead of complete enzyme inactivity. The enzyme activity <1.5% results in Lesch-Nyhan syndrome which includes hyperuricaemia, cognitive impairment, neurological dysfunction and behavioural deficits.⁴⁻⁵ Residual enzyme function between 1.5% and 8% results in LND variants. LND variants have hyperuricaemia with a spectrum of cognitive, neurological and behavioural deficits.²⁻⁵ Individuals with the least severe phenotypes have only hyperuricaemia with or without associated gout, nephrolithiasis and progression to end stage renal disease.²⁻⁴

HGPRT is a salvage enzyme that plays an essential role in recycling purines.⁶ When the HGPRT enzyme is deficient, all purine breakdown products are broken down into uric acid causing hyperuricaemia.⁶ Increased uric acid levels predispose gout, nephrolithiasis and eventual chronic kidney disease. Renal disease results from intratubular uric acid deposits and interstitial deposits of urate crystals.⁷ The mechanism of the cognitive and neurobehavioral deficits is not fully understood. Visser *et al*⁸ support the theory that the neurobehavioral deficits seen in LND may be related to basal ganglion dysfunction. Further study is required to identify if the neurobehavioral deficits seen in Lesch-Nyhan syndrome are due directly to the enzyme deficiency, to the resulting hyperuricaemia, or to some other cause.

Clinical suspicion of HGPRT deficiency increases with urine urate : creatinine ratio above 2.0 and increased 24 h urate excretion rate greater than 20 mg/kg.⁹ The diagnosis is confirmed by measuring the level of HGPRT enzyme activity in erythrocytes or cultured fibroblasts.⁹ HPRT1 gene sequencing has prognostic implications and can help with family gene screening.

The management of HGPRT deficiency is dictated by the patient's clinical features. All patients have an element of hyperuricaemia and should be managed with xanthine oxidase inhibitors. Allopurinol is used first line at doses up to 900 mg/day.¹⁰ Probenecid and other hyperuricosuric drugs are contraindicated as they increase the risk of uric acid nephrolithiasis.²⁻⁹ Patients with recurrent nephrolithiasis should avoid dehydration, aim for a minimum urine output of 2 L/day and may benefit from urinary alkalinisation with potassium citrate (60 mEq/day).¹⁰ In this case, the patients urinary pH was 5.75 and treatment with potassium citrate was commenced. Allopurinol treatment of hyperuricaemia from birth has not been proven to provide any benefit to neurological or behavioural symptoms.²⁻⁹⁻¹¹ Spasticity is treated with benzodiazepines or baclofen.⁹

Genetic counselling allows for further education on HGPRT deficiency. The X-linked recessive nature of the condition and the risk of the condition being passed to the patient's offspring can be explained by genetic counselling. Family gene screening may be performed to identify undiagnosed relatives and

carriers.⁹ Affected individuals with hyperuricaemia can be started on therapy to prevent chronic renal failure.

Learning points

- ▶ Hypoxanthine-guanine phosphoribosyltransferase (HGPRT) deficiency is an X-linked recessive disorder that gives rise to Lesch-Nyhan syndrome or Lesch-Nyhan disease variants.
- ▶ The enzyme activity <1.5% results in Lesch-Nyhan syndrome which includes hyperuricaemia, cognitive impairment, neurological dysfunction and behavioural disturbances. Residual enzyme function between 1.5% and 8% results in Lesch-Nyhan disease variants which include hyperuricaemia and a spectrum of cognitive and neurobehavioural deficits.
- ▶ HGPRT deficiency should be suspected in any patient with unexplained persistent hyperuricaemia not responding to typical allopurinol dosing.
- ▶ The diagnosis is confirmed by measuring the level of HGPRT enzyme activity in erythrocytes or cultured fibroblasts.

Contributors BPD preformed the literature review on the topic, and produced all written work on the report including all drafts leading to the final manuscript. DJ reviewed all drafts up to the final manuscript providing constructive input. JB reviewed all drafts up to the final manuscript providing constructive input. J B is a specialist nephrologist who is responsible for diagnosing the case and managing the patient and is the guarantor.

Competing interests None.

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