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Case Report

Genetic background of uric acid metabolism in a patient with severe chronic tophaceous gout

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ABSTRACT

Hyperuricemia depends on the balance of endogenous production and renal excretion of uric acid. Transporters for urate are located in the proximal tubule where uric acid is secreted and extensively reabsorbed: secretion is principally ensured by the highly variable *ABCG2* gene. Enzyme hypoxanthine–guanine phosphoribosyltransferase (HPRT) plays a central role in purine metabolism and its deficiency is an X-linked inherited metabolic disorder associated with clinical manifestations of purine overproduction. Here we report the case of a middle-aged man with severe chronic tophaceous gout with a poor response to allopurinol and requiring repeated surgical intervention. We identified the causal mutations in the *HPRT1* gene, variant c.481G>T (p.A161S), and in the crucial urate transporter *ABCG2*, a heterozygous variant c.421C>A (p.Q141K). This case shows the value of an analysis of the genetic background of serum uric acid.

1. Introduction

Uric acid (UA) is the end product of purine metabolism in humans. Urate homeostasis depends on a balance between production and the complex process of secretion and reabsorption in the renal proximal tubule and excretion in the intestine. The production is derived from *de novo* biosynthesis, dietary purine intake, and turnover of tissue nucleic acids. Hypoxanthine-guanine phosphoribosyltransferase deficiency (HPRTD) is one of the most common inborn errors of purine metabolism. This X-linked disorder (OMIM 308000) is classified into distinct forms. Partial HPRTD (#300323) is associated with a clinical manifestation of purine overproduction that results in increased UA synthesis – patients are at risk of gout and urate nephrolithiasis. However, some patients develop a variable spectrum of neurological manifestations, such as motor disability and intellectual impairment, (Lesch–Nyhan variants). Classical features of severe deficiency, Lesch–Nyhan syndrome (#300322), are characterized by neurological and behavioral abnormalities and the overproduction of uric acid. Neurologic and behavioral disabilities may include dystonia, choreoathetosis, ballismus, spasticity, hyperreflexia, mental retardation, and aggressive and impulsive behaviors. Patients often develop persistent and severe self-injurious behaviors [1].

HPRTD shows an X-linked inheritance pattern: female carriers have somatic cell mosaicism of HPRT activity and are usually asymptomatic, with enzyme activity in erythrocytes within normal limits. However, females with complete HPRTD have been described [2]. Female carriers with normal excretion of hypoxanthine and xanthine, and hyperuricemia and/or gout have also been reported [3]. It is noteworthy that heterozygotes for partial HPRT deficiency had significantly diminished HPRT activity in hemolysates compared with heterozygotes for Lesch-Nyhan syndrome. This suggests that selection against HPRT-deficient erythrocyte precursors is more intensive in Lesch-Nyhan syndrome carriers [4].

A diagnosis of HPRTD is determined according to the following scheme: (1) hyperuricemia and hyperuricosuria (a consequence of uric acid overproduction) with urinary hypoxanthine and xanthine elevation is present; (2) HPRTD is confirmed by low HPRT activity in erythrocytes; (3) results are confirmed by molecular genetics. Hyperuricemia can be treated with febuxostat or allopurinol. No sustained drug therapy

Abbreviations: HPRT, hypoxanthine-guanine phosphoribosyltransferase; UA, uric acid; HPRTD, hypoxanthine-guanine phosphoribosyltransferase deficiency; TG, tophaceous gout; PCR, polymerase chain reaction.

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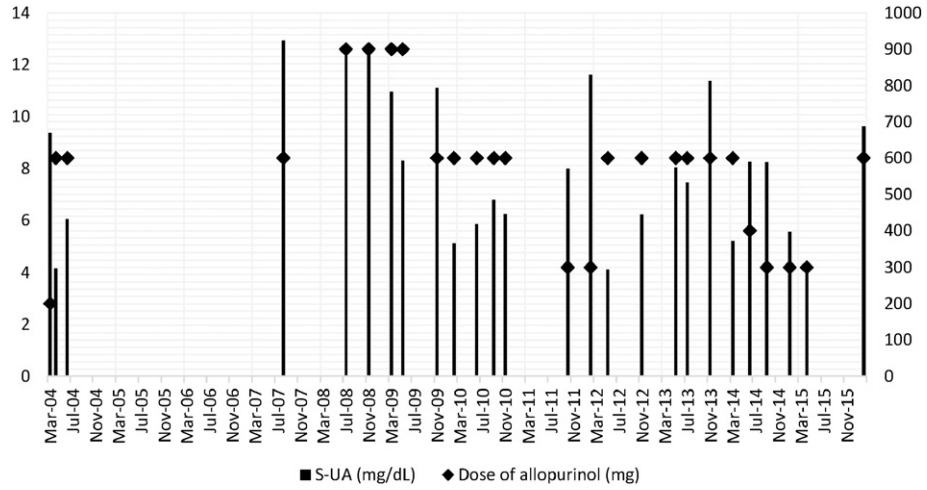

Fig. 1. Serum uric acid level (mg/dl, ref. ranges 3–7 mg/dl) and dosage of allopurinol (mg) in a patient with partial HPRT deficiency, years 2004–2016.

has proven uniformly effective for treatment of the neurological problems associated with Lesch-Nyhan syndrome. A reduction in self-injurious and aggressive behavior in children was reported after treatment with *S*-adenosylmethionine on five LND (Lesch–Nyhan disease) patients in an open-label clinical trial [4,5]. However, in an open-label, dose-escalation trial of the drug on 14 LND patients, the authors found that only four patients were able to tolerate the drug; however, when tolerated some beneficial effects were reported [6].

As we mentioned before, the balance between UA production and excretion influences serum UA concentrations. The renal excretion of UA is determined by glomerular filtration followed by secretion, and reabsorption in the proximal tubules. The secretion part of UA transport is principally ensured by the highly variable *ABCG2* gene. Common dysfunction of ABCG2 exporter has proved to be a significant genetic cause of hyperuricemia and gout [7,8].

This is the report on HPRT deficiency complicated by ABCG2 dysfunction allelic variant in patient with severe tophaceous gout.

2. Case report

Our patient was a 41-year-old Caucasian man, who suffered from severe chronic tophaceous gout (TG). He had the first episode of acute podagra at the age of 13. Since then he has had recurrent gout attacks with multiple joint affections. Nephrolithiasis developed at age 22. The

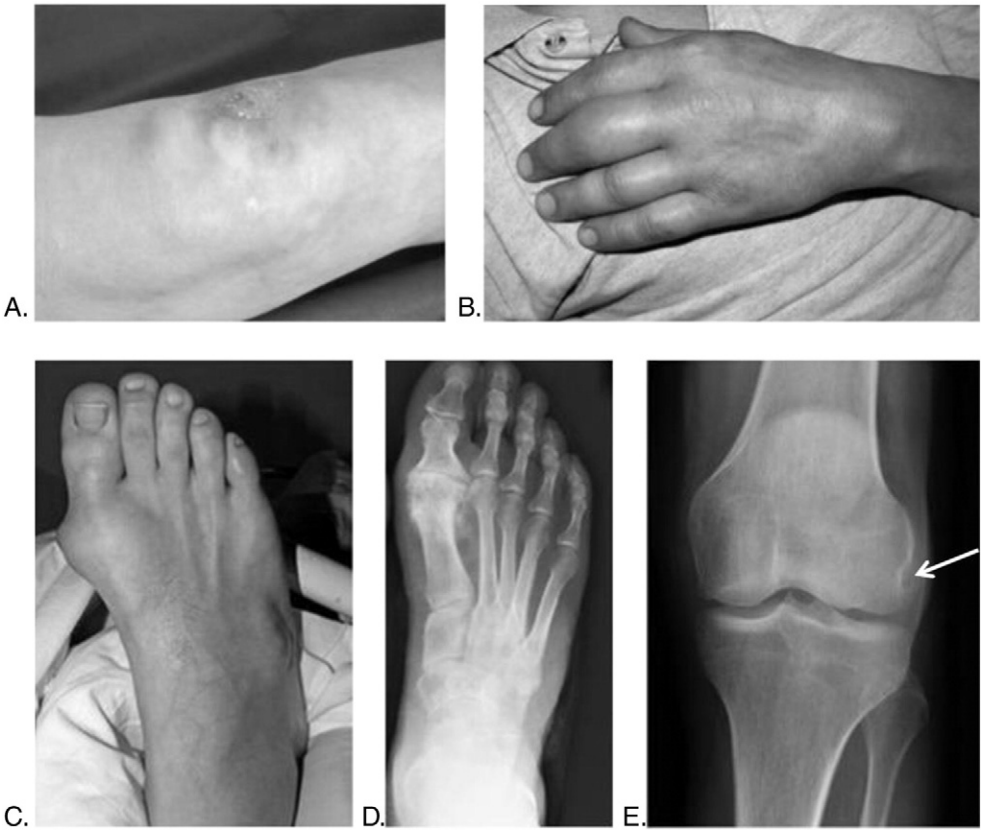

Fig. 2. Pictures of a 41-year-old patient with partial HPRT deficiency with chronic tophaceous gout. (A) Tophi on the left knee after spontaneous drainage (February 2016), (B) left hand during acute gouty attack (September 2009), (C) tophi on the right metatarsus (September 2009), (D) radiograph of the foot with the radiographic hallmark findings of chronic gout (February 2016), (E) radiograph of the left knee with a small round radiolucency on the lateral femoral condyle (suspected gouty tophus) (February 2016).