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Hyperuricemia and gout due to deficiency of hypoxanthine–guanine phosphoribosyltransferase in female carriers: New insight to differential diagnosis

Eva Kostalova [a], Karel Pavelka [b], Hana Vlaskova [a], Blanka Stiburkova [a,b,*]

[a] Institute of Inherited Metabolic Disorders, First Faculty of Medicine, Charles University in Prague and General University Hospital in Prague, Prague, Czech Republic
[b] Institute of Rheumatology, Prague, Czech Republic

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ABSTRACT

Background: X-linked hypoxanthine–guanine phosphoribosyltransferase (HPRT) deficiency in an inherited disorder of purine metabolism is usually associated with the clinical manifestations of hyperuricemia. A variable spectrum of neurological involvement occurs predominantly in males. Females are usually asymptomatic. Carrier status cannot be confirmed by biochemical and enzymatic methods reliably.
Methods: We studied clinical, biochemical and molecular genetic characteristics of Czech families with hyperuricemia and HPRT deficiency. We analyzed age at diagnosis, clinical symptoms, uricemia, urinary hypoxanthine and xanthine, HPRT activity in erythrocytes, mutation in the *HPRT1* gene, X-inactivation, and major urate transporters.
Results: A mutation in the *HPRT1* gene in family A was confirmed in one boy and four females. Three females with hyperuricemia had normal excretion of purine. One female was normouricemic. An 8-month-old boy with neurological symptoms showed hyperuricemia, increased excretion of urinary hypoxanthine and xanthine and a very low HPRT activity in erythrocytes. We have found three other unrelated female carriers with hyperuricemia and normal excretion of hypoxanthine and xanthine among other families with HPRT deficiency.
Conclusions: HPRT deficiency needs to be considered in females with hyperuricemia with normal excretion of purine metabolites. Familiar hyperuricemia and/or nonfamiliar gout should always be further investigated, especially in children.

1. Introduction

Hypoxanthine–guanine phosphoribosyltransferase (HPRT) deficiency is an X-linked inherited metabolic disorder (OMIM 308000) classified into distinguished forms. Partial HPRT deficiency, also known as Kelley–Seegmiller syndrome (#300323), is usually associated with the clinical manifestations of purine overproduction which results in increased uric acid synthesis (hyperuricemia/gout, urolithiasis, nephrolithiasis and kidney stones); however, a variable spectrum of neurological manifestations, such as motor disability and intellectual impairment, is available (Lesch–Nyhan variants). Classical features of severe deficiency, Lesch–Nyhan syndrome (#300322), are moreover characterized by self-injurious behavior.

As a first step, the diagnosis of HPRT is determined by hyperuricemia and hyperuricosuria with urinary hypoxanthine and xanthine elevation. Secondly, HPRT deficiency is confirmed by low HPRT activity in erythrocytes. Finally, the results are confirmed by molecular genetics. Treatment controlling uric acid overproduction with allopurinol or febuxostat is available; however, allopurinol has not usually been considered to cause behavioral and neurological symptoms [1,2]. A recently reported treatment with S-adenosylmethionine in children with the Lesch–Nyhan syndrome showed a dramatic reduction of self-injurious and aggressive behavior, as well as a milder reduction of dystonia [3].

The human *HPRT1* gene is located on chromosome Xq26.1 and comprises 9 exons and 8 introns. The HGPRT enzyme (EC 2.4.2.8) has a central role in purine metabolism: catalysis of purine salvage and conversion of hypoxanthine to inosine monophosphate and guanine to guanosine monophosphate. At present, 410 mutations in the *HPRT1* gene causing variable disease phenotype (186 missense/nonsense, 59 splicing, 55 small deletions, 23 small insertions, 13 small indels, 65 gross deletions, 6 gross insertions/duplications, 3 complex rearrangements) have been described (HGMD® Professional 2014.2, June 2014).

Abbreviations: HPRT, hypoxanthine–guanine phosphoribosyltransferase; HUMARA, human androgen receptor gene; MRI, brain magnetic resonance imaging; PCR, polymerase chain reaction

* Corresponding author at: Institute of Rheumatology, Na Slupi 4, 128 50 Prague 2, Czech Republic. Tel.: +420 234075319; fax: +420 224914451.
E-mail address: stiburkova@revma.cz (B. Stiburkova).

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We report on a Czech family that X-linked HPRT deficiency may present as hyperuricemia and/or gout in both male and female carriers. They represent as a case on how unreliable the diagnostics of carriers are on biochemical and enzymatic levels only.

2. Materials and methods

2.1. Clinical and biochemical findings

The proband, a female A II/1 (Fig. 1), was brought to our laboratory at the same time as her nephew A III/4. The female A II/1 has been analyzed for hyperuricemia at the age of 19 years. She developed the first clinical gout attack at the age of 33 years in classical I. MTP joint localization. Since then, she had 8 gout attacks lasting usually for 1–2 weeks. She has been treated by 200 mg allopurinol daily and she has used colchicine during attacks. Without allopurinol treatment, she had hyperuricemia with normal purine excretion. Her 8-month-old nephew A III/4 was born after 34 weeks of uncomplicated pregnancy with Apgar score of 9–10–10. Abnormal development associated with hypotonia was noted at 3 months of age. His milestones were delayed. Intermittent action dystonia has developed. His mother (A II/2) observed orange crystals in the diaper once at the time when treatment with allopurinol began. Renal ultrasound at the age of 13 months was suspicious of incipient nephrocalcinosis without nephrolithiasis. Brain magnetic resonance imaging (MRI) showed normal results. At the age of 24 months, the patient sometimes bites buccal mucosa as compulsive self-injurious behavior characteristic for Lesch–Nyhan syndrome. Detailed purine metabolic investigations were performed as we reported previously [4,5].

2.2. Molecular genetic analysis

All tested individuals provided their informed consent (approved by the Ethics Committee of the authors' home institution) to participation in the analyses and the presentation of results. Genomic DNA and total RNA were extracted from peripheral white blood cells for sequencing. Genomic DNA was extracted also from urine and buccal swabs for X-inactivation analyses. Genomic DNA was isolated using QIAamp columns (Qiagen GmbH, Hilden, Germany) or NucleoSpin Blood (Macherey–Nagel GmbH, Düren, Germany). Total RNA was extracted by BiOstic Blood Total RNA Isolation Kit (MOBIO Laboratories, Inc., Carlsbad, CA). mRNA was reverse-transcribed using High Capacity RNA to cDNA Kit (Applied Biosystems, Carlsbad, CA) according to the manufacturer's instructions.

All coding exons of the *HPRT1* gene and selected exons of the *SLC2A9*, *SLC22A12*, *SLC17A3* and *ABCG2* genes have been amplified from genomic DNA. For transcript analyses, cDNA was used for PCR amplification in 2 RT-PCR products. Primer specification and reaction conditions are available upon request. PCR and RT-PCR products were purified using Wizard SV Gel and PCR Clean-Up System (Promega, Madison, WI) and directly sequenced on a capillary sequencer 3500xL Genetic Analyzer (Applied Biosystems, Carlsbad, CA).

The X-chromosome inactivation status was analyzed by studying the methylation of HpaII sites in the first exon of the human androgen receptor gene (HUMARA), which correlates with X-chromosome inactivation [6]. The novel STR polymorphic sites were used by Musalkova et al. [7].

3. Results

3.1. Biochemical analysis

The proband of family A II/1, her daughter A III/1 and her niece A III/3 had hyperuricemia with normal urinary excretion of hypoxanthine and xanthine. Her 8-month-old nephew III/4 demonstrated hyperuricemia, hyperuricosuria and increased urinary excretion of hypoxanthine and xanthine. The HPRT activity in erythrocytes was 5 nmol/h/mgHb and confirmed HPRT deficiency. One female (A II/2) was normouricemic. The patient A I/1 has been treated for hyperuricemia and gout since the age of 53 years. He does not have family mutation in the *HPRT1* gene. Pedigree and family data are shown in Fig. 1 and Table 1.

Subsequently, we analyzed biochemical and clinical data from other families with HPRT deficiency. We found three other unrelated heterozygous female carriers (a 12-year-old girl B, an infant C and an adult

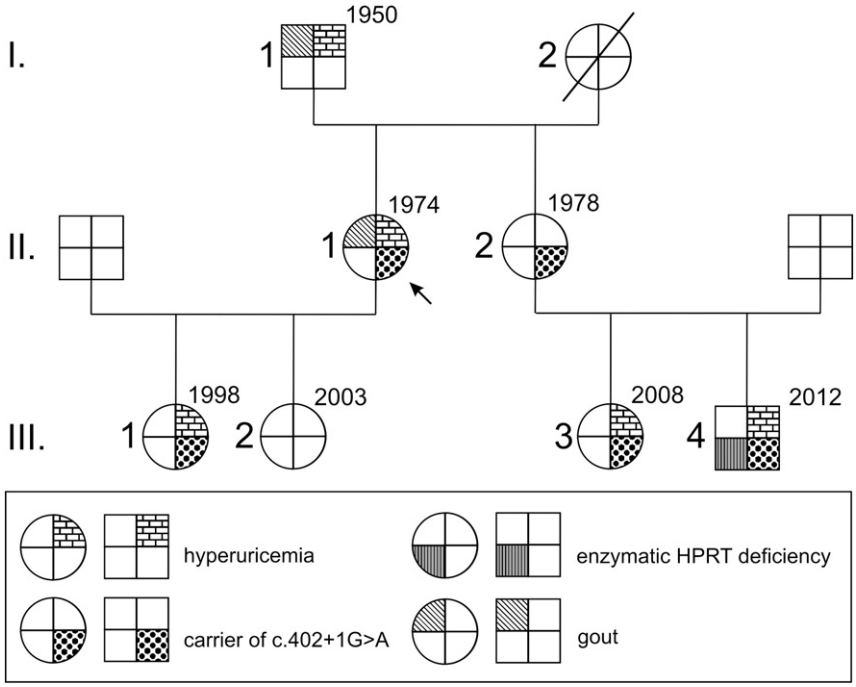

Fig. 1. Family A pedigree.