

Kelley-Seegmiller syndrome in a patient with complete hypoxanthine-guanine phosphoribosyltransferase deficiency

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This paper is supported from a grant of Sassari University (ex 60%).

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Received on April 2, 2002; accepted in revised form on June 4, 2002.

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Key words: HPRT, Lesch-Nyhan syndrome, Kelley-Seegmiller syndrome, gout.

ABSTRACT

Different degrees of hypoxanthine guanine phosphoribosyltransferase (HPRT) deficiency are associated with hyperuricemia, uric acid nephrolithiasis and severe gout. Up to 25-30% of HPRT deficient patients, indicated as neurological variants or HPRT-related hyperuricemia with neurological dysfunction (HRND), may develop neurological manifestation, from mild to severe; the most serious ones manifesting in the devastating Lesch-Nyhan syndrome, characterized by choreoathetosis or self-mutilation. Here we present a 30 years old male patient suffering from gout and mild psycho-motor impairment without Lesch Nyhan disease despite severe HPRT deficiency residual activity 0.02% with hypoxanthine, no activity at all with guanine as a substrate. The Curtius's theory that neurologic impairment is dependent on V_{GPR}/V_{HPRT} ratio is not confirmed by our observations. The finding of such a severe HPRT deficiency in a non-Lesch-Nyhan patient needs further investigation. G6PD deficiency was also referred together with β -thalassemic trait. We have studied purine and pyridine nucleotide metabolism in the erythrocytes and discussed the literature. The bone marrow sample shows a megaloblastic aspect.

Introduction

Hypoxanthine-guanine phosphoribosyltransferase (HPRT, EC 2.4.2.8) is an ubiquitous, cytoplasmic, purine metabolism enzyme that catalyses the conversion of hypoxanthine and guanine, to their respective mononucleotides inosine 5'-monophosphate (IMP) and guanosine 5'-monophosphate (GMP). HPRT deficiency leads to two major forms of human disease. Major alterations resulting in complete loss of enzyme activity cause the Lesch-Nyhan syndrome, whilst mutations leaving some residual enzyme activity are typically associated with less severe clinical manifestations; hyperuricemia and gout are a common feature.

HPRT deficiency below 0.5% of normal value is usually associated with the devastating Lesch-Nyhan syndrome (1, 2), a rare X-linked recessively inherited

disorder of purine metabolism, manifested by hyperuricaemia, hyperuricaciduria with uric acid urinary stones, gout and severe progressive neurologic dysfunction which is characterized by moderate to mild mental retardation only occasionally severe, delayed motor development, spastic cerebral palsy, choreoathetosis and aggressive and compulsive self-mutilation with biting of fingers and lips, sometimes aggressive behaviour. Crystalluria and haematuria may be present in the first months of life. Gouty arthritis and tophi rarely develop before puberty, but both may develop early (3, 4). Urolithiasis is common, acute renal insufficiency may be present in all degrees of HPRT deficiency, even at presentation. Death due to infection or renal failure secondary to uric acid nephropathy is common by the third decade. The patients are often institutionalized for cerebral palsy and diagnosis may be delayed because sometimes the neurological abnormalities and the self mutilating behaviour become apparent in late infancy or early childhood or diagnosis is made when gout appears.

Partial HPRT deficiency, known as Kelley-Seegmiller syndrome in rheumatologic literature (5,6), results in the overproduction of uric acid leading to hyperuricemia, uric acid nephrolithiasis and severe gouty arthritis. The neurological variants present an intermediate picture in which there are motor and neurological abnormalities, but no abnormal behavior.

Major clinical manifestations are in the affected male with evidence of transmission through carrier females. Females with mutant HPRT alleles are heterozygous for the disease (7). They are generally healthy and present a somatic cell mosaicism even if the expression of mutant allele is less than expected (8). They may develop gout after menopause, but the syndrome has been reported even in girls (five cases all over the world) due to new mutation in the second allele or non-random X-inactivation (9-12). Furthermore heterozygotes for the Kelley-Seegmiller syndrome present a significantly lower HPRT activity in haemolysate than heterozygotes for the Lesch-Nyhan syn-

drome (7).

In this report we present the case of a virtually complete HPRT deficiency without Lesch-Nyhan syndrome and discuss the literature.

Case report

We describe P.G., a male patient aged 30 presenting with hyperuricemia and gout since the age of 16. The family history revealed that the mother was hyperuricemic, one maternal and one paternal uncle suffer of adult gout. G6PD deficiency was also referred together with α -thalassemic trait. At birth he showed neonatal jaundice, successively he experienced some hypotonia and mild dysarthria, motor development was delayed. He also presented a mild degree of spasticity, dystonia, hyperreflexia and incoordination at the right side with prevalent use of the left hand. At present he suffers from very mild mental retardation, is self-sufficient and works in a textile factory. He never developed choreoathetosis and compulsive self-mutilating behaviour. At the age of 16 he first developed left podagra. One year later, on the second episode of podagra he was hospitalized: uricemia was 14.1 mg/dl, uricuria 1330 mg in a 24-hour period. microscope examination of urine samples showed an outstanding content of uric acid crystals. Ultrasound abdominal examination revealed bilateral renal microlithiasis.

After starting allopurinol therapy he suffered from oral ulcers for six years; allopurinol withdrawal resolved ulcers, but raised uricemia up to 22.6 mg/dl. Physical examination revealed mild hepatosplenomegaly. Laboratory tests showed very low G6PD activity (0.08 U/M; normal value > 0.8), α -thalassemia trait, severe hypochromic microcytic anemia (Hb 7.3 mg/dl) with 8.4% reticulocyte, bilirubin 2.0 mg/dl, negative Coombs' test. Chest radiography and echocardiography were normal. Encephalic MRI did not show any visible lesions. Bone marrow examination is compatible with megaloblastic anemia.

We have studied purine and pyridine nucleotide metabolism in the patient's erythrocytes. The patient was on allopurinol treatment which was not discontinued.

Studies were conducted by HPLC-linked methods previously described (13, 14). HPRT activity in erythrocyte lysates was extremely low to undetectable (0.025 nmoles/h/mg Hb; control values 119 ± 12). GPRT activity was also virtually absent.

No conversion of [14 C] hypoxanthine into IMP occurred in intact erythrocytes, while [14 C] adenine conversion into nucleotides was increased several times compared to controls. In intact erythrocytes, GTP concentration was lower and NAD concentration was twice normal values; NADH was also increased, as already reported in HPRT-deficient erythrocytes. NADP concentration was almost doubled compared with normal values, while NADPH was undetectable, as expected in G6PD deficiency (15). The activities of the following enzymes measured in erythrocyte lysates were increased: adenine phosphoribosyl transferase, orotate phosphoribosyl transferase and orotidine monophosphate (OMP) decarboxylase [the latter two at least in part due to allopurinol treatment (16)], phosphoribosyl pyrophosphate synthetase, 5' nucleotidase in agreement with previous data (17), nicotinic acid phosphoribosyltransferase, nicotinic acid/nicotinamide mononucleotide adenylyl-transferase and NAD synthetase. The increased activity of the last three enzymes supported the hypothesis that increased synthesis may cause the raised NAD levels. The possibility of a younger mean red cell population in this patient combining α -thalassemia and G6PD deficiency should also be taken into account.

Discussion

In humans, mutations in the gene encoding the purine salvage enzyme hypoxanthine-guanine phosphoribosyltransferase (HPRT) are associated with a spectrum of disease that ranges from hyperuricemia alone to hyperuricemia with profound neurological and behavioral dysfunction.

Jinnah *et al.* (18) grouped the patients into three categories based on their clinical features. The first class was

designated HPRT-related hyperuricemia (HRH). The patients demonstrate only marked overproduction of uric acid, with hyperuricemia, nephrolithiasis and gout. The second class, designated HPRT-related hyperuricemia with neurological dysfunction (HRND) or Lesch-Nyhan variants, shows an intermediate severity. Uric acid overproduction coexists with varying degrees of neurological abnormalities without self-mutilation behaviour. The third is characterized by the full spectrum of disease known as Lesch Nyhan disease (LND).

HRT and HRND are even described with the eponym of Kelley-Seegmiller syndrome in honour of the authors who described the enzyme defect. In fact, Kelley first described the partial deficiency of HPRT in 5 male patients with juvenile gout and an increased incidence of urate renal stones in 1967 (5). Up to 25-30% of these patients may have minor neurological features, but do not self-mutilate as in Lesch Nyhan syndrome in which the enzyme deficiency is complete. The overproduction of uric acid found in partial and complete HPRT deficiency results from an accelerated rate of *de novo* purine biosynthesis and breakdown. Uric acid clearance is high before puberty, thus overproduction is not evident at first, but later on it presents with hyperuricaemia, nephrolithiasis and early gout. The purine *de novo* synthesis intermediates are raised in the HPRT deficiency, as in our patient. In partial deficiency, HPRT activity is sometimes absent in haemolysate, but still measurable in intact red cells whilst in complete deficiency HPRT activity is absent in both haemolysate and intact red cells. In our patient the HPRT activity is 0.025, the GPRT activity is zero in haemolysate, in particular no conversion of [14 C] hypoxanthine into IMP occurred in intact erythrocytes.

The clinical and biochemical features of HGPRT deficiency are not completely known. Several hypotheses have been proposed for the mechanisms relating HGPRT deficiency with neurological dysfunction although the real mechanism connecting cause and effect are unclear.

Curto and coworkers used a biomathematical analysis approach to the purine metabolism (19). The theory is that two reactions are catalyzed by HGPRT and only one of these might be responsible for symptom associated with HGPRT deficiency. They considered the ratio of $V_{\text{GPR}}^{\text{HPRT}}$ to V_{HPRT} as a risk factor for developing neurological disfunctions. According to these authors, the lower the ratio in erythrocytes lysate, the higher the risk of severe neurological symptoms, especially when the ratio is lower than 0.5. According to this theory the V_{HPRT} deficiency has a counteracting effect. There are a few clinical studies providing results about the enzyme activity in the two possible reactions. The results in our patient do not confirm this hypothesis.

In 1959 Catel and Schmidt (20) described a patient with Lesch Nyhan syndrome (first original description) with no abnormal behaviour; afterwards Bakay (21) showed some HPRT activity in incubated fibroblasts from this patient, but no activity in blood samples. Nyhan (22) reported five similar cases and also described a family in which HPRT and G6PD deficiency were segregating (23). G6PD locus is located in the terminal band (Xq28) of the long arm of the X chromosome distally and close to the HPRT locus (Xq26-27.2).

Lesch-Nyhan syndrome is characterized in some cases by macrocytic anemia (24). In our patient a severe anemia is present and bone marrow samples show a megaloblastic aspect. Studies on fibroblasts are needed for a better understanding of this patient's metabolic aberration.

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