

Adenine phosphoribosyltransferase deficiency

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Abstract

Adenine phosphoribosyltransferase (APRT) catalyzes the synthesis of AMP (adenosine monophosphate) from adenine and 5'-phosphoribosyl-1-pyrophosphate (PP-ribose-P) in the presence of magnesium (Mg²⁺). In APRT deficiency, adenine is oxidized, via 8-hydroxyadenine (8-HA), to 2,8-dihydroxyadenine (2,8-DHA), by xanthine dehydrogenase. Adenine is formed, as a by-product of polyamine synthesis, from 5'-methylthioadenosine by the action of 5'-methylthioadenosine phosphorylase (MTAP). This is probably the principal route of adenine formation in vivo. The defect is inherited as an autosomal recessive trait. The gene is located on chromosome 16q24. Two types of homozygotes have been found, based on APRT activity in erythrocyte lysates. Type I patients, predominantly Caucasian, have undetectable activity, Type II, found only in Japan, have 10-25% of normal activity due to a kinetic abnormality evident only under non-physiological conditions. No activity is demonstrable in either I or II in intact erythrocytes under physiological conditions. Heterozygosity for both defects is high (0.4 to 1.2 per hundred) which suggests homozygosity of the order of 1 in 250,000 to 1 in 33,000. Clinical symptoms - colic, hematuria, urinary tract infection and dysuria - are due to 2,8-DHA crystalluria or stones. Acute renal failure may be the presenting symptom and can be reversible, but undiagnosed homozygotes have progressed to chronic renal failure, dialysis and transplantation. In older subjects 2,8-DHA crystals have been detected first at renal biopsy following transplantation. Approximately 15% of homozygotes have been completely symptomless, but crystalluria is present in all homozygotes from birth. Allopurinol has prevented 2,8-DHA formation; lithotripsy has proved beneficial.

Key-words

APRT: adenine phosphoribosyltransferase; 2,8-DHA: 2,8-dihydroxyadenine; 8-HA: 8-hydroxyadenine; 2HA: 2-hydroxyadenine; HPLC/RPLC: high performance/reversed phase liquid chromatography, XDH: xanthine dehydrogenase (also termed xanthine oxidase).

Disease name and synonyms

- Adenosine phosphoribosyltransferase deficiency
- 2,8 dihydroxyadenine urolithiasis.

Definition

Adenine phosphoribosyltransferase (APRT: EC 2.4.2.7) normally catalyses the formation of 5'-AMP (adenylic acid) and pyrophosphate (PPi) from adenine and PP-ribose-P. Since AMP can also be formed by the *de novo* pathway APRT is generally considered a salvage enzyme and in Man and higher animals provides the only mechanism by which free adenine can be converted to the nucleotide [1]. The main source of endogenous adenine is the polyamine pathway of which adenine is a metabolic end-product. The inability to salvage adenine in APRT deficiency results in its alternative metabolism by xanthine dehydrogenase (XDH) via the 8-hydroxy intermediate to the extremely nephrotoxic end-product, 2,8-dihydroxyadenine (2,8-DHA). Deficiency of APRT is inherited as an autosomal recessive trait [1]. The gene is located on chromosome 16q24 [2].

Excluded diseases

2,8-DHA stones were previously mistaken for uric acid stones because of their identical chemical reactivity. Likewise, 2,8-DHA stones may be confused with xanthine stones. All three stone types are radiolucent and show up as a starry picture on ultrasonography. Consequently, diseases leading to excess excretion of xanthine or uric acid must be excluded as well by more reliable methods of stone analysis, coupled with erythrocyte enzyme assay and HPLC/RPLC as described below [1].

Diagnosis criteria

The chief clinical manifestation directly related to the defect is 2,8-DHA crystalluria or urolithiasis. This can lead to intratubular deposition/blockage and presentation of homozygotes in acute, or acute on chronic, renal failure, sometimes in coma, or following rejection of a transplanted kidney [1-3,4]. Varying ability to supersaturate the urine may explain the existence of affected and asymptomatic sibs in several families. The apparent lack of *in vivo* toxicity to tissues other than the kidney may relate to the high degree of protein binding and the fact that 2,8-DHA, like adenine, is secreted by the human kidney [1].

Differential diagnosis

Both symptomatic and asymptomatic homozygotes may be identified by the characteristic round brown 2,8-DHA crystals in

the urine, with a maltese cross birefringence by polarized light microscopy [1,5]. The diagnosis can be confirmed from the adenine and the 2,8-DHA excreted, together with the absence of functional APRT activity in intact erythrocytes [1]. The latter will be impossible to establish if recent transfusion has formed an essential part of the therapy [3]. Correct identification of 2,8-DHA stones requires ultraviolet (UV), infrared (IR), mass spectrometry (MS), x-ray crystallography, High-Performance or Reversed-Phase Liquid Chromatography (HPLC, RPLC), capillary electrophoresis or tandem MS. Three adenine derivatives are excreted; adenine, 8-hydroxyadenine (8-HA), and 2,8-DHA (approximate proportion 1.0:0.03:1.5) [1]. Total urinary purine end product (uric acid + precursor oxypurines + adenine derivatives) is normal (0.05 to 0.1 mM/kg/24h), with adenine metabolites comprising 30 percent of this total [1]. Homozygotes generally have normal levels of uric acid in plasma and urine and no other abnormal purines or pyrimidines are excreted. All other biochemical and hematological factors have been normal [1].

Prevalence

The frequency of heterozygosity for APRT deficiency in Caucasians is 0.4-1.1% , and 0.5% to 1.2% for the Japanese [1,7] which suggests homozygosity of the order of 1 in 250,000 to 1 in 33,000. This is similar to some of the more common autosomal recessive disorders, but the number of observed cases is lower than expected. Twenty-one patients have been reported from France - the largest number from any country in Europe. [4]. The potentially lethal nature of the defect when unrecognized, and the asymptomatic status in others, may be contributory. Death may also occur *in utero* [1]. Subjects with no detectable APRT lysate activity (type I defect) have been reported from 18 countries, excluding Japan [1-5]. Iceland, with 23 homozygotes from 16 families among a total population of 267,000 inhabitants, has the largest number on a per capita basis [5]. Among the 200 plus APRT deficient individuals in Japan, 45 have the type I defect [1,6,7]. The remainder have erythrocyte lysate APRT activity up to 25% of normal (type II defect) and have been found only in Japan [1,6,7]. Between 8 and 21% of individuals with either type of defect have been asymptomatic and approximately 60% of symptomatic subjects have been male in both instances [1]. Adults now comprise 60% of type I cases [1,4] while 75% of all Japanese patients are adults [6,7].

Molecular defect

The molecular basis of APRT deficiency has been determined. Fifteen different mutations have been found in type I patients. All Icelandic patients are homozygous for the same mutation (D65V) in the APRT gene, indicating a founder effect. Approximately 68% of type II patients are also homozygous for a missense mutation, Met 136-> Thr (M136T) in exon 5 which involves the PP-ribose-P binding site. At least 3 mutations appear to have common ancestral origins, some dating back to at least 3000 BC [1,5-7].

Clinical description

Clinical symptoms in APRT deficiency may vary from benign to life-threatening [1-7]. The majority of homozygotes present in acute, or acute on chronic, renal failure, sometimes in coma - symptoms related entirely to the insolubility of 2,8-DHA. However, 2,8-DHA crystalluria can occur without clinical symptoms [1]. The age of onset of symptoms has varied from birth to 74 years of age [1-7], the whole spectrum of symptoms associated with stone formation being reported: fever from urinary tract infection, macroscopic hematuria, dysuria, urinary retention, and abdominal colic. In 6 patients acute reversible anuric renal failure first drew attention to the defect [1]. In many instances it took from 20-50 years before the exact nature of the stone was recognized following the initial presentation with urolithiasis. More than 30 patients, over half of them Japanese, had already progressed to chronic renal failure and dialysis. Some had died [1-8]. A number subsequently had renal transplants, the majority of which have been successful, but only following recognition of the underlying defect and treatment with allopurinol [1,8].

Management including treatment

Allopurinol Therapy: 2,8-DHA formation has been controlled by allopurinol, but does not reduce the total sum of adenine compounds excreted, the proportion being rearranged so that adenine become the major urinary component [1]. Allopurinol at 10 mg/kg per day (child) or 300 mg per day (adult) has eliminated 2,8-DHA from the urine [1]. In subjects with acute or chronic renal failure, the dose must be reduced to 5 mg/kg per day in children and 100mg/day in adults, or the same reduced dose on alternate days or thrice weekly [3]. A high fluid intake is encouraged, and the use of allopurinol without alkali advised [1]. Allopurinol was discontinued after 14 years in the longest studied case [1], but recurrence of symptoms

several years later, required reinstatement of allopurinol.

Lithotripsy: As with other stones, therapy using extracorporeal shock wave lithotripsy with sonographic stone localization has proved beneficial, with one exception [9,10]. In the latter this was effective in only one of the two affected kidneys [1]. In Japan lithotripsy has also contributed to an increase in the number of patients diagnosed. In Europe, except in France, patients successfully treated for radiolucent or opaque stones are not investigated for the underlying cause and the family defect may go unrecognized. The significance of this is underlined by a recently identified case with a family history of 2 sibs with a long history of recurrent nephrolithiasis leading to dialysis in both.

Etiology

The potential nephrotoxicity of adenine, via its oxidation product 2,8-DHA, was first noted as early as 1898 during the feeding of adenine to animals and has been demonstrated in most mammalian species [1]. Renal pathology has shown acute intratubular crystal deposition to be the primary event. The first patient to be identified by 2,8-DHA crystals only after failed transplantation was reported in 1988 [1]. The necessity to improve clinical awareness and limit the morbidity in this treatable disorder is underlined by the fact that such cases are still being found [8 and unpublished observations]. Some transplanted homozygotes have sustained good renal function on allopurinol, 4 reverted to dialysis, two died [1]. Seventeen Japanese patients had hypoplastic kidneys indicating that hypoplastic kidneys, or developmental abnormalities, may be an early feature of the homozygous state. Follow-up in homozygotes presenting with severe renal damage and progressing to dialysis and transplantation [1,6,7], or those on long-term allopurinol therapy, has not shown evidence of any long-term toxicity due to adenine accumulation [1]. Several homozygotes identified in their 40's also have healthy children, indicating a lack of toxicity of adenine or its metabolites to the reproductive system.

Diagnostic methods

The presence of 2,8-DHA crystals or stones is highly suggestive of APRT deficiency which must be confirmed by measuring APRT activity in both lysed and intact erythrocytes. Type I deficiency homozygotes have low to undetectable APRT activity in erythrocyte

lysates, but the majority of heterozygotes have erythrocyte enzyme levels of about 25% of the normal mean [1]. Lymphocytes and fibroblasts from type I homozygotes also lack APRT activity, while heterozygotes have approximately 50% of normal activity. Intact erythrocytes from homozygotes show no conversion of radioactive adenine into nucleotides under any incubation conditions.

Patients with type II deficiency have been found only in Japan [6,7]. Homozygotes for the M136T mutation show up to 25% of normal APRT activity in hemolysates and about 50% of normal activity in T lymphocyte extracts. The remaining type II patients have approximately 10% and 25% of normal APRT activity in erythrocyte and lymphocyte extracts, respectively. However, intact erythrocytes from type II patients, just like type I patients, incorporate only minimal amounts of radioactive adenine [1]. Thus in type I patients enzyme activity in disrupted erythrocytes is almost absent, whereas in type II, owing to a kinetic abnormality, appreciable activity can be demonstrated under these non-physiological conditions, but not under physiological conditions in intact erythrocytes. These observations indicate that, although the enzyme from type II patients can be detected in cell extracts, it is not functional in intact cells or *in vivo*.

Antenatal diagnosis

Not appropriate, as this is a treatable disorder.

Unresolved questions

Erythrocytes from homozygotes for APRT deficiency have normal ATP and 5-phosphoribosyl-1-pyrophosphate (PP-ribose-P) levels [1]. The former observation confirms that the erythrocyte must maintain its ATP through the action of adenosine kinase. The latter, together with the normal PP-ribose-P synthetase activity and purine production [1] suggests that APRT, unlike hypoxanthine-guanine phosphoribosyltransferase (HPRT), is not vital for the overall regulation of purine metabolism in humans [1].

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