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2,8-Dihydroxyadenine Lithiasis in a Japanese Patient Heterozygous at the Adenine Phosphoribosyltransferase Locus

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Summary

All reported cases of 2,8-dihydroxyadenine (DHA) lithiasis have been due to functional homozygous deficiency of adenine phosphoribosyltransferase (APRT). Here we describe the first case of DHA lithiasis in a patient who has functional APRT activity in cultured lymphoblasts. The patient is heterozygous for Japanese-type (type II) APRT deficiency as demonstrated by starch-gel electrophoresis and DNA sequence analysis. We also demonstrate the use of starch-gel electrophoresis for differentiation between the type II mutant enzyme and the wild-type enzyme.

Introduction

Adenine phosphoribosyltransferase (APRT) catalyzes the synthesis of AMP from adenine and 5-phosphoribosyl-1-pyrophosphate (PRPP). In the absence of functional APRT activity, adenine is oxidized by xanthine oxidase to 2,8-dihydroxyadenine (DHA). This compound is extremely insoluble, and its accumulation often leads to crystalluria and to the formation of kidney stones (Simmonds et al. 1989).

Two types of APRT deficiency leading to DHA lithiasis have been identified (Simmonds et al. 1989). Type I patients have undetectable or extremely low levels of enzyme activity in cell extracts or in intact cells. These patients are homozygous or compound heterozygous for null alleles designated *APRT*Q0* (Fujimori et al. 1985; Hidaka et al. 1987). Type II patients, described only in Japan, have variable APRT activity in cell extracts, but they have extremely low or undetectable activity in intact cells or in vivo (Kamatani et al. 1987).

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These patients carry a mutant form of the enzyme that has an increased apparent K_m for the cosubstrate PRPP (Fujimori et al. 1986). Type II patients are considered to be homozygous for the mutant allele *APRT*J* (Fujimori et al. 1985; Hidaka et al. 1988), but we have recently identified a patient who is compound heterozygous for the *APRT*J* and an *APRT*Q0* allele (Sahota et al. 1990). Both types of APRT deficiency are found in Japan, but type II deficiency is the main cause (about 80%) of DHA stone formation in this population (Kamatani et al. 1987).

All heterozygotes for type I APRT deficiency (genotype *APRT*1/APRT*Q0,* where *APRT*1* is the wild-type allele) that have been examined so far have shown no evidence for any clinical or biochemical abnormality (Fox et al. 1977; Dean et al. 1978; Simmonds et al. 1989). Type II heterozygotes with the genotype *APRT*1/APRT*J* also appear to be clinically and biochemically normal (Fujimori et al. 1985; Kamatani et al. 1987). In the present report we describe a Japanese patient with DHA lithiasis who has functional APRT activity in cultured lymphoblasts. The patient is heterozygous for type II deficiency (genotype *APRT*1/APRT*J*), as demonstrated by starch-gel electrophoresis and DNA sequence analysis. To our knowledge, this is the first case of an APRT heterozygote presenting with DHA stones. Because

of the unusual nature of this patient, all results were confirmed in a blood sample obtained 3½ years after the first one. Details of the starch-gel procedure for differentiating between the type II mutant enzyme and the wild-type enzyme are also presented.

Patient and Methods

Patient

A 27-year-old Japanese male was admitted in August 1986 for further investigation of urolithiasis. He had previously passed two brownish stones (December 1983 and June 1984). Abdominal X-rays showed no stone shadow, but computed tomography of the kidneys revealed the presence of stones. During hospitalization, he passed a small stone that had an infrared spectrum identical to that of DHA. A blood sample was obtained in December 1986, and, to confirm all findings, a second sample was obtained in July 1990. Hemolysate APRT activity was 5.8 nmol/h/mg protein on the first occasion and 4.7 nmol/h/mg on the second. These values are 24% and 19%, respectively, of our control mean (mean $\pm$ SD = 24.5 $\pm$ 4.8 nmol/h/mg; N = 46). Family members were not available for investigation. The patient is referred to as TAK3 in the present report.

Lymphoblast Transformation

Patient blood collected in sodium heparin–containing vacutainers was shipped by air from Japan. B-lymphoblast transformations were initiated within 3 d of blood collection. Lymphocytes were separated on a Histopaque (Sigma) gradient and were transformed by Epstein-Barr virus according to a method described elsewhere (Neitzel 1986). Cultures were maintained in an atmosphere of 5% CO_2/5% O_2/90% N_2 in 15% calf serum (Hyclone Laboratories) in RPMI 1640 containing penicillin and streptomycin. Lymphoblast growth appears to be more favorable at lower oxygen concentrations (Mizrahi et al. 1972).

Preparation of Cell Extracts

Ten-milliliter lymphoblast cultures (5–8 × 10^5 cells/ml) were centrifuged at 1,000 g for 10 min, were washed twice with PBS, and were suspended in 300 µl of APRT extraction buffer (50 mM Tris-HCl, pH 7.4; 5 mM $MgCl_2$). The samples were sonicated and then were centrifuged at 88,000 g for 30 min at 4°C in the Beckman TL-100 bench top ultracentrifuge. Two to five microliters of the supernatant was used for protein determination by using the BioRad protein assay kit.

APRT Assay

APRT was assayed in cell extracts according to a method described elsewhere (Hochstadt 1978), with minor modifications. The final concentration of [U-^{14}C]-adenine (Amersham) was 0.2 mM, and that of PRPP (Na salt) was 1 mM. About 5 µg protein was used per assay, and the incubation time was 15 min. The reaction was terminated with perchloric acid, followed by neutralization with KOH. The substrate and products were separated on cellulose TLC sheets (Kodak) in 5% NaH_2PO_4. Radioactivity was determined with an AMBIS radioanalytic image analyzer. Specific enzyme activity was expressed as nanomoles adenine nucleotides formed per hour per milligram protein. For the determination of kinetic constants, the assay conditions were varied as described in Results.

Adenine Incorporation into Nucleotides

The conversion of adenine into AMP in intact lymphoblasts was studied by using a slight modification of a published procedure (Witney and Taylor 1978). Ten-milliliter cultures were centrifuged as above and were washed once with 10 ml serum-free RPMI, and the pellets were suspended in 2 ml serum-free medium. Cell viability was >80% as judged by trypan blue staining. Aliquots containing 1 × 10^6 cells in duplicate were made to total 475 µl with medium, were gassed for 30 s with 5% CO_2/95% air, and were incubated for 1 h at 37°C in a shaking incubator. Twenty-five microliters [U-^{14}C]-adenine (1.25 µCi) was added, giving a final concentration of approximately 8.8 µM. The cultures were regassed, and incubations continued for 3 h. Fifty microliters perchloric acid was added, and the samples were neutralized with 50 µl KOH according to the method described above. Ten to twenty microliters of the supernatant was processed for TLC and radioactivity analysis as described for APRT assay.

Growth in Selective Media

Cell samples (1–2 × 10^5) in duplicate were exposed to RPMI containing either 2,6-diaminopurine (DAP; 60 µg/ml) or alanosine-azaserine-adenine (AAA) (4 µg alanosine/ml, 4 µg azaserine/ml, 50 µM adenine), and cell counts were done every other day for 8 d. For further analysis of DAP sensitivity, cells were grown at variable DAP concentrations for 5 d, and the growth was compared with cells grown in drug-free RPMI.

Starch-Gel Electrophoresis

Starch gels were prepared and run according to a

method described elsewhere (Tischfield et al. 1973; Nichols and Ruddle 1974), with minor modifications. Twenty to thirty micrograms protein was loaded per lane, and the gel was run for 16–20 h. The gel was sliced into three layers, and the middle layer (the other two layers were discarded) was incubated for 60 min at 37°C in 20 ml of buffer containing 10 mM Tris-HCl (pH 7.4), 5 mM $MgCl_2$, 4.5 μM [8-^{14}C]-adenine (5 μCi), and 250 μM PRPP. The dried gel was either subjected to conventional autoradiography or analyzed on the AMBIS analyzer.

SphI and TaqI Digestions

For RFLP analysis, genomic DNA was digested with *Sph*I and *Taq*I. PCR-amplified DNA (see below) was also digested with *Taq*I. The *Sph*I sites lie outside the amplified fragment, but the polymorphic *Taq*I site is located within intron 2 (Stambrook et al. 1984). The genomic digests were run on agarose gels, were transferred to GeneScreen Plus membranes, and were probed with a random primer–labeled 2.2-kb *Bam*HI fragment of the human APRT gene (Stambrook et al. 1984). Prehybridization and hybridization conditions were as described in the GeneScreen instruction manual. The *Taq*I digests from amplified DNA were run on agarose gels and were stained with ethidium bromide.

PCR Amplification and Sequence Analysis

DNA was isolated from transformed lymphoblasts, and a 2.4-kb fragment spanning both the entire coding region and the flanking sequences of the *APRT* gene was amplified by using the Perkin Elmer—Cetus thermal cycler and the GeneAmp kit. The PCR product was purified and then was ligated into *Hinc*II-digested M13mp18. Single- and double-stranded DNA was sequenced by using the Sequenase version 2.0 kit from United States Biochemicals. Full details of these procedures have been described elsewhere (Chen et al., in press).

Results

APRT Activity in Cell Extracts

On the first occasion, APRT activity in lymphoblast extracts from TAK3 was 397 nmol/h/mg protein. Enzyme activity in a cell line established from the second blood sample (obtained 3½ years after the first one) was 298 nmol/h/mg. These values are 65% and 49%, respectively, of our control mean (mean ± SD = 614 ± 26 nmol/h/mg; $N = 6$). For comparison, enzyme activity in four type II homozygotes was 51%–75% of that in controls. Activity in eight type I homozygotes was less than 0.5% of that in controls.

Kinetic Properties of the Mutant Enzyme

For the determination of apparent K_m values, the concentration of one substrate was varied at a fixed concentration of the other. Both the amount of protein in the assay and the incubation time were adjusted to keep the conversion of substrate into product under 30%. The K_m values for PRPP from two control cell lines were 3.6 and 5.3 μM, respectively, but the K_m for TAK3 was increased to 12.5 μM. The K_m values for PRPP for two type II homozygotes were 10.4 and 12.0 μM. The kinetic plot for TAK3 appeared to be biphasic, suggesting the presence of at least two different enzymes. The K_m for adenine for TAK3 (0.9 μM) was similar to that for a control cell line (1.2 μM).

Adenine Incorporation into Nucleotides

Lymphoblasts from TAK3 incorporated the same proportion of adenine into nucleotides (16%–18%) as did lymphoblasts from a normal Japanese subject. This corresponded to 0.29 nmol nucleotides/h/10^6 cells, under the assumption that the rate was linear over the 3-h incubation period. Of the total radioactivity, 1.5%–2.0% was present in the adenosine band. No incorporation into nucleotides or adenosine was detected in lymphoblasts from two Japanese patients homozygous for type II APRT deficiency.

Growth in Selective Medium

Growth of TAK3 lymphoblasts in AAA medium was comparable to that in RPMI alone, but there was little or no growth in DAP medium (fig. 1). By contrast, cells from a Japanese patient homozygous for type II deficiency (NOR1) did not grow in AAA medium, but their growth in DAP medium was similar to that in RPMI alone (fig. 1). Growth of a variety of lymphoblast lines at variable DAP concentrations, expressed relative to growth in RPMI, is shown in figure 2. The ID_{50} (DAP concentration required to reduce the cell number by 50%) for a normal cell line (Nj3) was 5–6 μg/ml, whereas it was 11–12 μg/ml for TAK3. Three other cell lines (TAK2, HIR1, and 904) were completely resistant to growth inhibition by DAP at concentrations up to 60 μg/ml. TAK2 is a type II compound heterozygote (Sahota et al. 1990); HIR1

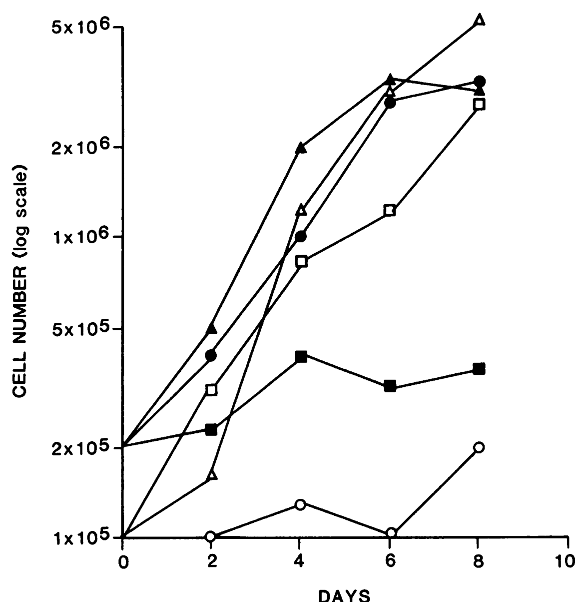

Figure 1 Growth of TAK3 (type II heterozygote) and NOR1 (type II homozygote) cell lines in selective (DAP or AAA) and nonselective (RPMI) medium. ▲ and △ = RPMI; ● and ○ = AAA; ■ and □ = DAP. Blackened symbols denote TAK3, and unblackened symbols denote NOR1.

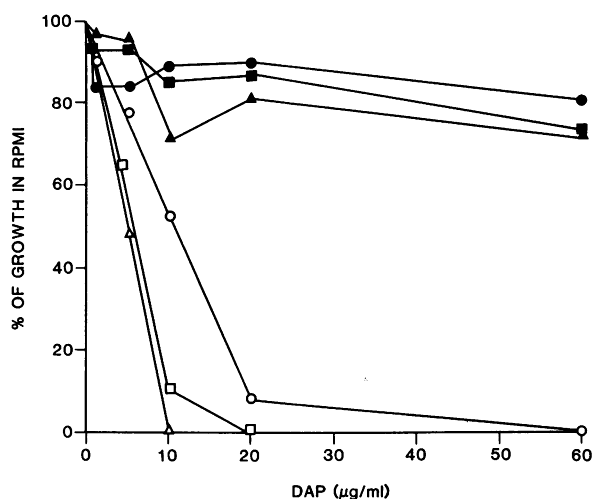

Figure 2 Effect of DAP concentration on lymphoblast growth relative to drug-free RPMI. Cell counts were done 5 d after drug exposure. ■ = TAK2 (type II compound heterozygote); ○ = TAK3 (type II heterozygote); △ = Nj3 (control); ▲ = HIR1 (type II homozygote); □ = ASA3 (type I heterozygote); ● = 904 (type I homozygote).

and 904 are homozygous for type II and type I deficiency, respectively.

Starch-Gel Electrophoresis

Lymphoblast extracts from patients with type II APRT deficiency exhibited a single band on starch gels (fig. 3). The migration of the enzyme from these patients was more anodal than that of the normal enzyme but was identical to that of the Chinese hamster enzyme (not shown). Cell extracts from TAK3, however, gave three bands (normal, hybrid, and Japanese type), demonstrating that this patient is heterozygous for type II deficiency. The three-band pattern is consistent with the fact that APRT is a dimer of identical subunits (Wilson et al. 1986). A similar electrophoretic pattern has been previously observed in the Nigerian population (Mowbray et al. 1972). The heterozygosity of TAK3 was confirmed by electrophoresis of an extract from a cell line established from the second blood sample.

RFLP Analysis

*Taq*I digestion of PCR-amplified DNA showed that patient TAK3 is homozygous for the *Taq*I RFLP (1.9-kb fragment). This fragment is equivalent to the 2.8-kb fragment seen in genomic digests (Stambrook et al. 1984). This RFLP pattern has been found in all patients homozygous for type II APRT deficiency (Hidaka et al. 1988; Kamatani et al. 1989) but has not been found in a patient who is a compound heterozygote for type II deficiency (Sahota et al. 1990). TAK3 was heterozygous for the *Sph*I RFLP (8- and 12-kb fragments) (fig. 4), whereas four type II homozygotes tested were homozygous for the 8-kb fragment. The restriction-digest patterns for TAK3 were confirmed in a DNA sample isolated from the second blood sample. As reported elsewhere, a northern blot from patient TAK3 showed an mRNA of normal size (about 1 kb) (Behzadian et al. 1986).

Nucleotide Sequence

To eliminate sequence artifacts due to PCR amplification, five independent clones from TAK3 were analyzed. Both alleles were sequenced, and differences between the alleles were confirmed by sequencing double-stranded DNA. The following numbering system is based on our revised *APRT* sequence (Chen et al., in press), where the A of the ATG start codon is designated base 1. The exon sequences of both alleles were identical to those of the wild-type gene, with the exception of the T-to-C transition at position 2066 in the *APRT*J* allele. This mutation is responsible for the ATG-to-ACG substitution at codon 136 (exon 5) in type II deficiency (Hidaka et al. 1988). A C-to-G at

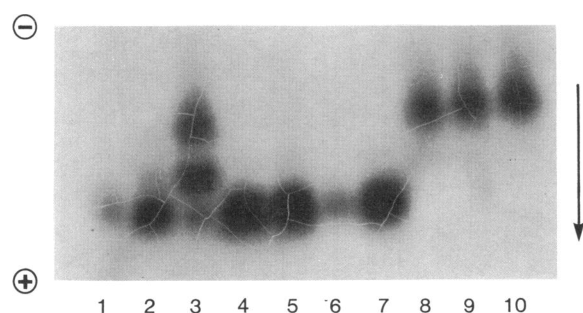

Figure 3 APRT starch-gel electrophoresis of cell extracts. Lane 1, NOR1. Lane 2, TAK3-DAP. Lane 3, TAK3. Lane 4, OSA1. Lane 5, SF. Lane 6, AZ. Lane 7, HIR1. Lanes 8–10, Control cell lines. Lanes 1 and 4–7 are type II homozygotes; lane 3 is a type II heterozygote (TAK3); lane 2 is TAK3 after long-term culture in DAP medium to select for cells expressing only the drug-resistant enzyme.

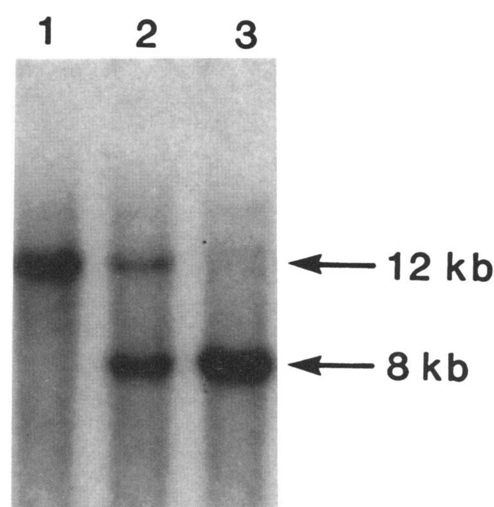

Figure 4 Southern blot of genomic DNA digested with *Sph*I and probed with the 2.2-kb *Bam*HI APRT fragment. Lane 1, Nj3 (normal Japanese subject). Lane 2, TAK3. Lane 3, OSA1 (type II homozygote).

position 995 in both alleles confirmed the lack of the *Taq*I site in intron 2. Both alleles of TAK3, like the wild-type gene, contained an A at position 854 (intron two), whereas the sequence reported, by Hidaka et al. (1988), from a type II patient had a C at this position in one allele. Three other polymorphisms were identified in the TAK3 sequence; these were a G-to-C transversion in intron 2 (position 710) and a G-to-A transition in intron 3 (position 1651) in both alleles and a G-to-C transversion in intron 3 (position 1642) in the normal allele. The base change at position 1651 has been observed in all the Japanese and non-Japanese patients we have sequenced, suggesting that our wild-type sequence (Chen et al., in press) is a rare variant at this position. The sequence of both alleles was confirmed in a DNA sample isolated from the second blood sample.

Discussion

DHA lithiasis due to APRT deficiency is an autosomal recessive disorder. Previous family studies in both types of enzyme deficiency have not shown any evidence for DHA stone formation, or any other disturbance in purine metabolism, in obligate heterozygotes. In the present paper we describe the first case of DHA lithiasis in a patient (TAK3) who has reduced APRT activity both in hemolysates and in lymphoblast extracts. The patient is heterozygous for type II APRT deficiency (genotype *APRT*1/APRT*J*), as demonstrated by starch-gel electrophoresis and DNA sequence analysis. Further evidence that one of the alleles is of the wild type comes from the ability of cultured lymphoblasts to (1) incorporate adenine into nucleotides, (2) grow in AAA medium, and (3) be inhibited by DAP.

In countries where adenine is used as a blood preservative, heavy transfusions with adenine-containing blood have resulted in DHA stone formation in some patients with normal APRT activity (Falk et al. 1972). This possibility has been excluded in the case of TAK3. The possibility that the DHA excreted by this patient may be derived from dietary adenine also appears highly unlikely, since detailed studies of the effects of dietary purine restriction in APRT deficiency have not demonstrated any significant reduction in total oxypurine excretion (Simmonds et al. 1989).

Mouse teratocarcinoma cell lines that are DAP resistant and APRT deficient are reported to have the ability to salvage adenine to nucleotides under conditions where purine biosynthesis de novo is inhibited but not under nonselective conditions (Turker and Martin 1985; Turker et al. 1985). It has been proposed that somehow the inhibition of de novo AMP synthesis induces salvage in these cell lines (Turker and Martin 1985). Our data indicate that the adenine salvage observed in transformed lymphoblasts from patient TAK3 is unlikely to be due to such an induction phenomenon. The possibility of sample mix-up or of cross-contamination of cell lines can be dismissed, since we have obtained identical enzymatic, electrophoretic, and DNA sequence results on two samples

received 3½ years apart. To explain the presence of functional APRT activity in cultured lymphoblasts, it may be postulated that the patient is a germ-line mosaic, but this has not been tested. It is possible that this is a case of autosomal dominant inheritance, but no family history is available to verify this. The TAK3 karyotype was that of a normal male.

The polyamine pathway appears to be the major source of endogenous adenine in man (Kamatani et al. 1984; Williams-Ashman et al. 1982). In this pathway, 5′-methylthioadenosine is produced in stoichiometric amounts with the polyamines but is rapidly degraded to adenine by methylthioadenosine phosphorylase (Sahota et al. 1983; Kamatani et al. 1984). The level of adenine metabolites excreted in APRT deficiency is consistent with the normal operation of this pathway (Kamatani et al. 1984). It remains to be established whether increased polyamine synthesis can lead to increased adenine production—and hence to DHA lithiasis—in an APRT heterozygote.

It is reported that there is no difference in the isoelectric point between normal APRT and the type II mutant enzyme (Hidaka et al. 1988). The two can, however, be separated by starch-gel electrophoresis, as described in the present report. The migration of the mutant enzyme is more anodal than that of the normal enzyme. Since the wild-type and type II mutant enzymes are of the same molecular weight, it is likely that small differences in charge are responsible for the starch-gel separation. This technique can be used for rapid differentiation between the type II mutant enzyme and the normal enzyme, as well as for demonstrating the heterozygous nature of APRT in some Japanese patients.

Acknowledgments

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