Complete deficiency of adenine phosphoribosyltransferase

A third case presenting as renal stones in a young child

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SUMMARY We report a third case of 2, 8-dihydroxyadenine stones in a child with a complete lack of the adenine salvage enzyme—adenine phosphoribosyltransferase (APRT). The propositus, a 20-month-old girl of consanguineous Arab parents, presented with multiple urinary tract infections and supposed 'uric acid' stones in the right renal pelvis and left ureter. Both parents and one brother were heterozygotes for the defect, in keeping with an autosomal recessive mode of inheritance. In contrast with the other purine salvage enzyme disorder of childhood with true uric acid stones (the Lesch-Nyhan syndrome), uric acid excretion was normal in all family members. As in our previous case, treatment with allopurinol, without alkali, has eliminated the urinary excretion of 2, 8-dihydroxyadenine: the stones were removed surgically. 2, 8-Dihydroxyadenine should be considered in any child thought to have uric acid stones and tests made to distinguish the two compounds.

Many urinary stones or crystals identified in children result from the overexcretion of normally minor urinary constituents, compounds of limited solubility whose overexcretion may be the direct consequence of a block in an essential step in a metabolic pathway. Examples are found in hereditary oroticaciduria (Smith *et al.*, 1972), xanthinuria (Dent and Philpot, 1954), and the Lesch-Nyhan syndrome (Nyhan, 1973). In the Lesch-Nyhan syndrome, uric acid stones or gravel form because of gross overproduction of uric acid arising from a lack of the hypoxanthine salvage enzyme—hypoxanthine-guanine phosphoribosyltransferase (HGPRT: EC 2.4.2.8) (Fig. 1). These children also have bizarre neurological complications and other clinical manifestations (Nyhan, 1973).

APRT = adenine phosphoribosyltransferase; HGPRT = hypoxanthine guanine phosphoribosyltransferase; NP = nucleoside phosphorylase; XO = xanthine oxidase; AMP = adenosine monophosphate (adenylate); IMP = inosine monophosphate (inosinate).

Fig. 1 Metabolic pathways of purine degradation and salvage illustrating the origin of 2, 8-dihydroxyadenine. In the absence of APRT, adenine becomes available for oxidation by xanthine oxidase to hydroxy- then dihydroxyadenine, in a fashion analogous to the production of uric acid from hypoxanthine. In man, adenine cannot be converted to adenosine by nucleoside phosphorylase as hypoxanthine may be converted to inosine, so this route is not available for disposal of adenine. The only alternative pathway is oxidation.

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A complete lack of the other purine salvage enzyme—adenine phosphoribosyltransferase (APRT: EC 2.4.2.7)—was described in children of two separate families, one in France (Cartier and Hamet, 1974; Debray *et al.*, 1976) and the other from our own unit (Simmonds *et al.*, 1976a, b; Van Acker *et al.*, 1977). Children with this deficiency also present with urolithiasis, because of the excretion of 2, 8-dihydroxyadenine, an extremely insoluble analogue of uric acid (Fig. 1). The excretion of this compound follows the accumulation of adenine in the absence of the salvage enzyme, APRT, and its oxidation by xanthine oxidase via the 8-hydroxy intermediate (Fig. 1) (Bendich *et al.*, 1950).

We report studies in a third family with a complete lack of the APRT enzyme. Stones of 2, 8-dihydroxyadenine were present in the daughter. As in the two previous cases, the stones were first mistaken for uric acid because 2, 8-dihydroxyadenine and uric acid are indistinguishable in chemical tests used routinely for identifying uric acid stones (Simmonds *et al.*, 1978).

Clinical data

The patient was born in August 1975, the 3rd child of consanguineous Arab parents (Fig. 2). Birth was normal and she was well until aged one year, when she began to suffer repeated attacks of abdominal pain and fever. These were diagnosed as urinary tract infections and, in May 1977, she was referred, aged 21 months, for investigation of lithiasis. An IVU

showed a nonfunctioning left kidney, and a radio-lucent calculus in the pelvis of the right kidney (Fig. 3). She was 81 cm in height, 10.0 kg in weight, and had red hair. Neither kidney was tender or palpable, and neurological examination was normal. However, urine culture showed a growth of $>10^8$ *Klebsiella aerogenes*/ml, with numerous leucocytes, red cells, and debris. Hb was 11.6 g/dl, WBC 14 400/mm³ (14.4×10^9 /l). Plasma electrolytes were normal, with blood urea 4.5 and 3.4 mmol/l (27 and 20 mg/100 ml). Plasma creatinine was initially 40 μ mol/l (0.45 mg/100 ml), but later was 100 and 120 μ mol/l (1.13 and 1.36 mg/100 ml). Serum urate was 0.24 mmol/l (4 mg/100 ml) by a nonspecific colorimetric method. The differential diagnosis of uric acid, or 2, 8-dihydroxyadenine urolithiasis was considered.

At the 1st operation (May 1977) cystoscopy and ureteric catheterisation showed a block in the left ureter 2 cm from the bladder. This calculus was removed by ureterolithotomy, and the stone in the pelvis of the right kidney was removed later at the same operation. Both stones were friable and greyish in colour. The urinary infection was treated with cephalexin 125 mg four times a day.

Examination of the stones by thermogravimetric analysis (Rose and Woodfine, 1976) suggested uric acid, but further examination by wet chemistry (Westbury and Omenoger, 1970) and by other specific techniques (see Methods) showed them to be composed of almost pure 2, 8-dihydroxyadenine (Simmonds *et al.*, 1978). Studies of urinary purines

Fig. 2 The family of the proband. None of the other members of the family has dihydroxyadenine stones, but only the immediate family was tested for APRT activity (Table 2). Consanguinity is present, the father's grandparents and the mother's great-grandparents being the same.

Fig. 3 IVU taken in May 1977 when patient was aged 21 months. The left kidney does not function at all, and there is a large radiolucent stone (arrow) in the pelvis of the right kidney.

and purine enzyme activities showed complete lack of APRT (see Methods and Results).

The child was treated with allopurinol 10 mg/kg per 24 h and she returned home. Three months later, in August 1977, she returned for more extensive examination. In the interval she had had several more urinary tract infections, treated with cephalixin and nitrofurantoin. In two of these, *Kl. aerogenes* was again grown from the urine, and in the 3rd attack—*Escherichia coli*. Otherwise she was well and had grown 1.6 kg, and 4 cm in height. Examination of renal function showed a glomerular filtration rate of 90 ml/min per 1.73 m², with only 13% of renal function from the left kidney, as judged by scanning with DMSA. Plasma creatinine was 50, 46, and 56 µmol/l (0.56, 0.52, and 0.63 mg/100ml) and blood urea 3.0, 4.1, and 6.0 mmol/l (18, 24, 36 mg/100 ml). Urine cultures showed *Klebsiella*. IVU and micturating cystography showed a doubtful calculus in the right renal pelvis, and several stones in a grossly refluxing left ureter and pelvis (Fig. 4).

At the 2nd operation the left renal parenchyma appeared reasonably well preserved, and the stones were removed from the left by ureter pyelolithotomy and ureterolithotomy. A stricture at the site of the previous removal of stone from the left ureter was repaired. At a 3rd operation (September 1977), retrograde catheterisation of the right urinary tract showed 2 stones in the pelvis of the right kidney similar to those removed previously: these were extracted.

The *Klebsiella* infection was again treated with cephalixin, followed by co-trimoxazole, and the

allopurinol dosage increased to 20 mg/kg per 24 h; on this dose the urine became free of 2, 8-dihydroxy-adenine. Because of the risk of xanthine or oxipurinol calculi, this dosage was later reduced to 15 mg/kg per 24 h, and the child returned home on this treatment.

During the period of investigation of the propositus, her father suffered from an episode of renal colic, but the stone passed was subsequently identified as pure calcium oxalate.

Fig. 4 Micturating cystogram, August 1977, when patient was aged 24 months. There is reflux of contrast medium into the left urinary tract, and several stones are present in the pelvis and ureter. There is also a ureteric stricture at the site of previous stone removal.

Methods

Stone analysis was carried out by methods already reported (Simmonds *et al.*, 1976 a, b; Rose and Woodfine, 1976). Methods used in the identification and quantitation of urinary purine metabolites by chromatography and 2-dimensional high-voltage electrophoresis have also been reported previously (Simmonds, 1969). A new rapid and simple method, isotachopheresis of the urine, has also been investigated (Simmonds *et al.*, 1978; Sahota *et al.*, in preparation) and appears to have potential for screening for homozygotes for APRT deficiency.

APRT activity was estimated in both intact (Dean *et al.*, 1978) and lysed erythrocytes, as previously described (Cartier and Hamet, 1968; Van Acker *et al.*, 1977). Blood from the child, her parents, and from her two brothers (aged 12 and 9 years) was taken in the fasting state and centrifuged and separated immediately. 24-hour urine collections were made on a low-purine, caffeine-free diet with toluene as preservative. A 15-hour water deprivation test was performed.

Routine biochemistry was investigated using a Vickers multichannel automated analyser. Complement components C3 and C4 were assayed by radial

immunodiffusion using monospecific antisera; haemolytic complement by a plate assay incorporating EA, and serum lipid levels were also measured by standard automated procedures. Lymphocytes were obtained from our patient and her parents; transformation in response to stimulation with PHA, pokeweed and concanavalin A were studied using ³H-thymidine incorporation as indicator of response (Panayi and Corrigan, 1977).

Results

Urinary purine metabolites. Detailed results of the stone identification have been reported (Simmonds *et al.*, 1978).

Urinary purine levels on four separate occasions in our patient are given in Table 1. Total adenine metabolites in each varied between 34 and 28% of the total purine metabolites, the latter being normal when expressed as mmol/kg per 24 h. Plasma uric acid levels were normal in our patient (Table 2) and in her parents on a low purine diet. Urinary uric acid levels were normal in the child, but at the upper limit of normal for her parents. Plasma uric acid levels were also normal in the two brothers (Table 2). Ultraviolet scans obtained using separation of

Table 1 Purine and pyrazolophyrimidine excretion (mmol/24 h) in a homozygote for APRT deficiency

	12 May (mmol/l)*	Hypothetical mmol/24h based on pseudouridine excretion	16 August	21 September	19 October
Pseudouridine	0.758	0.15	0.12	0.13	0.13
Uric acid	1.023	0.205	0.21	0.37	0.37
Xanthine	0.046	0.009	0.09	0.09	0.17
Hypoxanthine	0.051	0.010	0.16	0.02	0.05
Adenine	0.19	0.035	0.11	0.12	0.20
8-OH adenine	0.09	0.018	Not detected	0.04	0.03
2, 8-diOH adenine	0.32	0.064	0.04	0.04	Negligible
Total		0.34	0.51	0.66	0.82
Dosage			0.73 (10 mg/kg)	0.73 (10 mg/kg)	1.47 (20 mg/kg)
Allopurinol			0.04	0.06	0.27
Oxipurinol			0.34	0.39	0.64
Oxipurinol riboside			0.06	Not detected	Not detected
Allopurinol riboside			0.09	0.04	0.18
Total			0.53	0.49	1.09
Dose excreted (%)			72	67	74

*Random sample—24-hour urine collection not possible.

Table 2 Purine salvage enzyme activity† (APRT and HGPRT) and uric acid levels in a family with APRT deficiency

Date (1977)		Patient	Father	Mother	Brother (12 years)	Brother (9 years)
16 August	APRT§	0.61	5.06	7.33	23.38	7.57
16 August	HGPRT§	122.22	124.25	126.15	109.58	96.43
12 May	Plasma uric acid	3.3 (0.20)†	5.0 (0.30)†	3.0 (0.18)†	Not tested	Not tested
16 August	mg/100 ml (mmol/l)	1.8 (0.11)‡	7.0 (0.42)	3.7 (0.22)	3.7 (0.22)	3.4 (0.20)
12 May	Urinary uric acid	36 (0.21)*	631 (3.75)	415 (2.47)	Not tested	Not tested
16 August	mg/24h (mmol/24h)	36 (0.21)‡				

*Estimated (see Table 1); †low purine, caffeine-free diet (all other results are on a normal diet); ‡on allopurinol.

§Nmol of base converted per mg Hb/h		APRT	HGPRT
	(Control child adult)	28.15 21.35	118.5 136.7

urinary purines by isotachopheresis (not shown) showed the presence of the abnormal and diagnostic metabolite adenine only in the case of the homozygote; the scan in her case, as in the previous homozygotes, being otherwise indistinguishable from that of a healthy control (Simmonds *et al.*, 1978).

Effect of allopurinol therapy. Total allopurinol metabolites are also given in Table 1; the percentage of the administered dose absorbed and excreted being relatively constant (67–74%) and similar to that in the previous case studied by us (Simmonds *et al.*, 1977; Van Acker *et al.*, 1977) and in healthy controls (Simmonds, 1969). At a dose of 10 mg/kg per 24 h the principal metabolite of allopurinol was oxipurinol. At the higher dose (20 mg/kg per 24 h) increased amounts of unchanged allopurinol and its riboside were detected in the urine, indicating effective inhibition of xanthine oxidase at this dosage. In agreement with this was the absence of detectable 2,8-dihydroxyadenine excretion at the higher dosage. This was accompanied by an increment in the urinary adenine levels, as anticipated, but without any reduction in total purine excretion, in contrast with the situation in a control child, both as noted in our previous case (Van Acker *et al.*, 1977).

Other investigations. Other biochemical investigations, including fasting serum cholesterol and triglyceride concentrations, were essentially normal. The results of the lymphocyte transformation studies were within the lower limit of the normal range for adults in the case of the heterozygotes, and apparently normal for a child of the age of our patient as were complement levels (C3, C4, and total haemolytic complement) in all family members.

Water deprivation tests showed a normal ability to concentrate the urine above 900 mmol/kg in the father and the two brothers. The mother's result was slightly lower, while the patient showed a complete inability to concentrate the urine, compatible with her urinary tract infection and stones. Renal function, as measured by creatinine clearance, was not reduced in other members of this family.

Discussion

This patient is the third in whom 2, 8-dihydroxyadenine stones have been identified as a result of a complete lack of the salvage enzyme—APRT. In all three patients the stones were initially confused with uric acid stones. A brother of the second patient was asymptomatic, although he, too, lacked the enzyme, suggesting that the defect was relatively benign in that it can occur without clinical manifestations. Studies in this third patient have confirmed this and

show that children with this defect are clinically normal, apart from having urolithiasis. Correction of their renal complication will allow them to lead a normal life, unlike children with the Lesch-Nyhan syndrome.

Partial APRT deficiency has been described in five separate families, but these cases were discovered during screening for HGPRT deficiency. The association between partial APRT deficiency, gout, and hyperuricaemia, described in some of these families, now appears fortuitous (Kelley *et al.*, 1968; Delbarre *et al.*, 1974; Emmerson *et al.*, 1974, 1975; Fox and Kelley, 1974). Two recent reports (Emmerson *et al.*, 1977; Fox, 1977), have put the incidence of heterozygosity for APRT deficiency at somewhere between 0.5 and 1%.

The discovery of another patient with complete lack of APRT so soon after our other one suggests that the condition may previously have been misdiagnosed, and is more common than its description suggests (Cartier and Hamet, 1974; Simmonds *et al.*, 1976a; Van Acker *et al.*, 1977). The urinary metabolites excreted by the child, as in the previous cases, are a direct consequence of the enzyme defect; in the absence of the APRT enzyme the only alternative metabolic route for adenine is oxidation by xanthine oxidase via the 8-hydroxy intermediate to the extremely insoluble 2, 8-dihydroxyadenine (Fig. 1). Because of its similar structure (Fig. 1) it reacts mole for mole as uric acid during routine chemical testing; hence its frequent misdiagnosis.

An interesting observation, previously noted in both the other affected children and now confirmed, is that total purine end-product including uric acid appears essentially normal. This is surprising in view of the fact that adenine nucleotides with guanine nucleotides have been considered to exert feedback inhibitory control of *de novo* purine production; and absence of the analogous enzyme, HGPRT, in the Lesch-Nyhan syndrome is associated with gross overproduction of uric acid. The normal results in APRT deficiency would suggest that endogenous adenine production is neither extensive nor critical for the overall control of purine production in man. This is in keeping with a dietary origin suggested for the adenine in this defect (Simmonds *et al.*, 1977; Van Acker *et al.*, 1977).

Correction of the urolithiasis in this defect will allow the children to lead a normal life, unlike children with the Lesch-Nyhan syndrome in whom treatment did not lead to an improvement in the mental or neurological parameters. Interestingly, the father of our patient, as did the father of our previous patient, suffered an episode of renal colic with the passage of oxalate stones. The urinary uric acid level in both men is in the upper limit of normal. Xanthine

oxidase inhibition will obviously prevent 2, 8-dihydroxyadenine formation (Fig. 1) and allopurinol, a xanthine oxidase inhibitor, will therefore be the drug of choice. The common practice of alkalinisation of the urine for uric acid stones (De Vries and Sperling, 1975) will be ineffective in 2, 8-dihydroxyadeninuria, as the solubility of this compound does not alter within the physiological pH range (Debray *et al.*, 1976). It may even be harmful, since allopurinol plus alkali was ineffective in controlling stone formation in our previous patient (Van Acker *et al.*, 1977), whereas allopurinol alone at a dose of 10 mg/kg per 24 h resulted in immediate cessation of stone formation and crystalluria. A higher dose, 20 mg/kg per 24 h, was necessary to produce the same effect in our present patient, but this may have been due to the presence of stones not removed at the initial operation, in the meantime she is being treated with an intermediate dose, 15 mg/kg per 24 h. As the excretion of adenine metabolites was much greater when our previous patient was on a high rather than a low purine diet we also suggest that a low purine diet be given together with appropriate allopurinol dosage. This may be important as free adenine is not normally present in man for any length of time. APRT-deficient children being treated with allopurinol are testing the *in vivo* toxicity of free adenine. They should therefore be watched carefully, and undergo frequent checks for alteration in any other clinical or biochemical parameters.

Enzyme studies in erythrocyte lysates have confirmed heterozygosity in the parents and the complete deficiency in the child. One brother is also heterozygous, which would be in keeping with the autosomal mode of inheritance suggested in previous studies (Emmerson *et al.*, 1977; Van Acker *et al.*, 1977).

Studies in intact erythrocytes have shown that at normal physiological concentrations of adenine, heterozygotes are indistinguishable from normal individuals; while at higher substrate concentration results comparable with those in erythrocyte lysates are obtained (Dean *et al.*, 1978). This would explain why heterozygotes are essentially normal, since they can cope with normal loads of dietary adenine.

The reason why 2, 8-dihydroxyadenine stones were confused with uric acid stones is the subject of a separate report (Simmonds *et al.*, 1978). Even if specialised techniques are not available, the following clues may help to distinguish children with the defect: uric acid stones are hard and yellow, while 2, 8-dihydroxyadenine stones are friable and greyish-blue on crushing. Uric acid levels in plasma and urine will also be normal in 2, 8-dihydroxyadeninuria. The children are otherwise clinically normal, and have no neurological symptoms or signs. We suggest

that any child who is thought to have uric acid stones should have stones and urine examined more closely. If possible, the stones should be submitted for specialised confirmatory studies.

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