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REVIEW

Adenine phosphoribosyltransferase deficiency: Leave no stone unturned

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Abstract

Adenine phosphoribosyltransferase (APRT) deficiency is a rare autosomal recessive disease leading to generation of large amounts of 2,8-dihydroxyadenine (DHA). DHA is excreted in urine, where it precipitates into crystals due to its low solubility. DHA crystals can aggregate into stones or cause injury to the renal parenchyma (DHA nephropathy). Recurrent urolithiasis and DHA nephropathy are the two clinical manifestations of APRT deficiency. Diagnosis of APRT deficiency can be made during childhood as well as adulthood. Diagnosis mainly relies on the recognition of DHA in stones or urine crystals. Measurement of APRT activity and genetic testing are useful for confirmation of diagnosis, for family screening and should be considered in difficult cases of urolithiasis or crystalline nephropathy. Allopurinol therapy is the cornerstone of treatment and is highly effective in preventing recurrence of stones and kidney disease. High fluid intake and dietary modifications are also recommended. Early diagnosis and treatment are of paramount importance to prevent renal damage. Unfortunately, diagnosis of APRT deficiency is often overlooked and irreversible renal failure still occurs in a substantial proportion of patients. Clinicians must be alert to the possibility of APRT deficiency and consider the appropriate diagnostic tests in certain cases. This review discusses the genetic and biochemical mechanisms of APRT deficiency, and the issues of diagnosis and management.

Key words: Adenine phosphoribosyltransferase; Dihydroxyadenine; Urolithiasis; Crystalline nephropathy; 2,8-dihydroxyadenine nephropathy

Core tip: Adenine phosphoribosyltransferase (APRT) deficiency is a rare but underrecognized genetic disease causing recurrent dihydroxyadenine urolithiasis and crystalline nephropathy. Clinical presentation is variable and diagnosis can be made at any age. Treatment with a xanthine dehydrogenase inhibitor is highly effective in preventing recurrence of stones and kidney disease. Unfortunately, diagnosis of APRT deficiency is often overlooked and irreversible renal failure still occurs in a substantial proportion of affected individuals. Early diagnosis is of paramount importance to prevent long term complications.

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INTRODUCTION

In 1968, Kelley *et al*[1] identified partial adenine phosphoribosyltransferase (APRT) deficiency of autosomal inheritance in otherwise healthy individuals and reported mutant forms of the enzyme. In 1974, Cartier *et al*[2] described one child with 2,8-dihydroxyadenine (DHA) urolithiasis secondary to complete APRT deficiency inherited in an autosomal recessive manner. In 1977, Van Acker *et al*[3] described one family with APRT deficiency. Later, most cases were reported in Japan, where the prevalence of DHA stones appeared to be especially important[4]. Clinical presentation of APRT deficiency is not restricted to urolithiasis. DHA can cause renal failure by precipitating in the renal tubules and interstitium[5-7]. We previously proposed the denomination "DHA nephropathy" for the kidney disease caused by the precipitation of DHA crystals into the renal parenchyma[8]. Unfortunately, APRT deficiency is often recognized late after recurrent stone episodes or once irreversible renal insufficiency has occurred[7,9-11]. Given that the disease is easily treatable, clinicians must be alert to the possibility of APRT deficiency and consider ordering the diagnostic tests in appropriate cases. This review discusses the genetic and biochemical mechanisms of APRT deficiency, and the issues of diagnosis and management. Unless otherwise indicated, the term "APRT deficiency" refers to complete APRT deficiency in this review.

MECHANISMS OF THE DISEASE

APRT is an ubiquitously expressed enzyme that catalyzes the reaction in which 5'-adenosine monophosphate and inorganic pyrophosphate are synthesized from adenine and phosphoribosyl pyrophosphate. APRT provides the only pathway for the metabolism of adenine[12]. As a result of APRT activity, adenine is present only at low levels in blood and urine[13]. In the absence of functional APRT, adenine is metabolized to 8-hydroxyadenine, which is then converted to 2,8-dihydroxyadenine (DHA) by the xanthine dehydrogenase enzyme (XDH)[14]. DHA is eliminated in urine through and tubular secretion[15]. APRT deficiency thereby leads to excretion of large amounts of DHA in urine[3]. Due to the very low solubility of DHA, this causes the formation of DHA crystals, which can aggregate into stones[3,16], or precipitate into tubular lumens, inside renal epithelial cells, and in the interstitium, thereby causing crystalline DHA nephropathy (Figure 1)[4,7,9,11,17-19].

Two types of APRT deficiency are recognized based on the level of enzyme activity in cell extracts[13]. APRT activity is null in type Ⅰ, whereas it is about 15% to 30% of the normal activity in type Ⅱ[4]. It has to be stressed that this classification has no relevance *in vivo* or in intact cells, where enzyme activity is less than 1% in types Ⅰ and Ⅱ[20,21]. The clinical presentation is similar in both types of deficiency[4,7,10,22]. However, it is still important for clinicians to be aware of this classification when it comes to interpreting the results of APRT activity measurement (see below Diagnostic tests). Type Ⅰ APRT deficiency has been mostly reported in Caucasian individuals, but also in diverse ethnic groups[7,10,23]. Type Ⅱ has been almost exclusively described in Japanese patients, where it accounts for 70% of cases of APRT deficiency[4].

PREVALENCE OF APRT DEFICIENCY

Although APRT deficiency is often viewed as a very rare condition, its prevalence worldwide remains unknown and the number of reported cases are increasing each year. The vast majority of cases and studies published came from Japan, France and Iceland[4,7,10]. One explanation to this may be that certain mutations are frequent in these countries (Met136Thr in Japan, c.400 + 2dup in France and Asp65Val in Iceland). However, the variability in number of cases identified and reported among different countries may also reflect variability in awareness of APRT deficiency and availability of diagnostic tests. In our series, several affected families originated from places outside Europe, including African countries, Turkey, Martinique, Lebanon and Canada[7]. This suggests that APRT deficiency is a ubiquitous disease. The increase in the number of identified cases in some countries, like France, probably reflects improved recognition and diagnosis of the disease[8].

The prevalence of complete APRT deficiency was estimated to be 1/27000 in the Japanese population, corresponding to a heterozygote frequency of 1.2%[4]. The heterozygote frequency in caucasian populations, estimated from measurements of enzyme activity in healthy subjects, ranges from 0.4% to 1.2%, suggesting that the prevalence of homozygosity is higher than 1/100000[24,25]. If this holds true, more than 60000-80000 individuals may be affected worldwide. The limited number of cases recorded in most countries suggests that many individuals with APRT deficiency are currently unrecognized[26]. APRT deficiency may be a seriously underestimated cause of urolithiasis and chronic kidney disease, progressing over time to end stage renal disease (ESRD) in a non-negligible proportion of cases when left untreated[7,10].

CLINICAL PRESENTATION AND NATURAL HISTORY

The age at diagnosis of APRT deficiency varies widely, ranging from infancy to more than 70 years of age[4,7,10,22]. In our series, diagnosis was made before the age of 16 in only 37% of patients[7]. In an Icelandic series, 47% of affected individuals were diagnosed before the age of 18[10]. In some instances, APRT deficiency is diagnosed late because some patients present with symptoms late in their adulthood, while in other instances, despite early onset symptoms, recurrent urolithiasis and kidney disease, diagnosis is often delayed due to low index of suspicion[7,8,10,22]. Urolithiasis is the most common manifestation of APRT deficiency in both children and adults[10,27]. The first urolithiasis episode may occur during infancy as

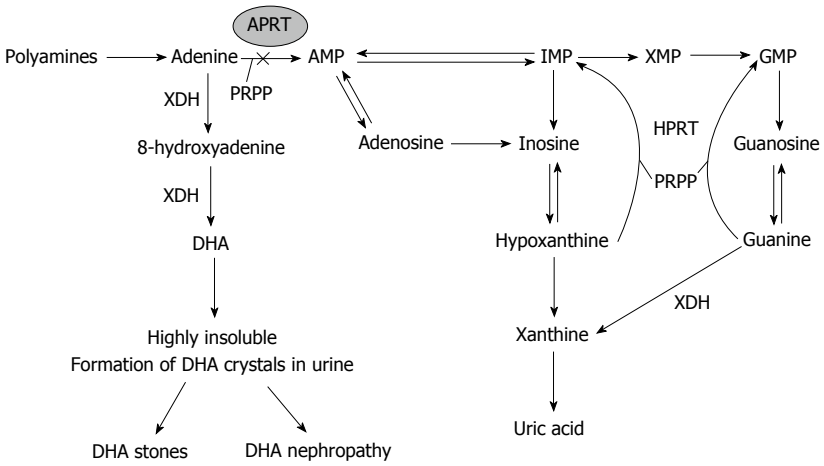

Figure 1 Biochemical pathway of purine metabolism and mechanisms of adenine phosphoribosyltransferase deficiency. DHA: 2,8-dihydroxyadenine; APRT: Adenine phosphoribosyltransferase; HPRT: Hypoxanthine phosphoribosyltransferase; PRPP: Phosphoribosyl-pyrophosphate; IMP: Inosine monophosphate; XDH: Xanthine dehydrogenase enzyme; AMP: Adenosine monophosphate; GMP: Guanosine monophosphate; XMP: Xanthosine monophosphate.

well as later than age 40[4,7,8,22]. In affected infants, reddish-brown diaper stains related to DHA crystalluria can be observed[10]. In some instances, bilateral DHA stones can cause urinary tract obstruction and acute renal failure, especially in children[10,28,29].

DHA stones are usually radiolucent and thus can be detected only by imaging techniques able to detect radiolucent stones, such as ultrasonograpy or computed tomography. However, DHA stones may sometimes appear as radiopaque when containing calcium salts[4,30]. Due to their radiolucent character, DHA stones are often mistaken for uric acid stones. Differential diagnosis for radiolucent stones also includes cystine and xanthine.

DHA nephropathy represents the second manifestation of APRT deficiency. It is commonly observed in adults but rarely in children[10,27]. DHA nephropathy typically occurs in patients who have remained undiagnosed and untreated despite a history of recurrent urolithiasis. However, it should be emphasized that DHA nephropathy can also occur in patients who experienced just a few episodes of stones or even in patients with no history of urolithiasis[31]. Imaging studies demonstrating the absence of stone do not definitively rule out the possibility of DHA nephropathy. DHA nephropathy usually develops insidiously and cause chronic kidney disease progressing over a period of years[31]. Less commonly, the presentation can be acute or subacute. Massive precipitation of DHA into the kidney can sometimes be triggered by urine concentration and supersaturation of DHA in the context of dehydration. In Japanese and European studies, nearly 30% of patients had decreased renal function and 10% had ESRD when APRT deficiency was diagnosed[4,7,10]. In our French cohort, among patients who were diagnosed and treated later than 40 years of age (n = 14), 6 patients (42.8%) had glomerular filtration rate (GFR) > 60 mL/min per 1.73 m^2, 3 patients (21.4%) had GFR of 30 to 60 mL/min per 1.73 m^2 and 5 patients (35.8%) had GFR < 15 mL/min per 1.73 m^2[7].

In some patients, APRT deficiency is not diagnosed until after kidney transplantation, which can have disastrous consequences. These patients are at high risk of losing their transplant in the absence of appropriate therapy. Several cases of DHA nephropathy recurring after kidney transplantation and rapidly leading to transplant failure have been reported[9,11,18,19,32,33]. In most tragic cases, several kidney transplantations failed before APRT deficiency was properly recognized and treated[19,32].

Nearly 15% of individuals with APRT deficiency may be asymptomatic[7,10], but are at risk of developing complications if left untreated. The factors underlying the variability of clinical presentation are unknown. There is no phenotype-genotype correlation, which is explained by the fact that biallelic mutations in *APRT* lead to null enzyme activity in all cases, whatever the mutations maybe. Inter-individual differences in water intake and consumption of foods high in purines may be involved in the variability of the clinical presentation. The potential influence of modifying genes has not been reported in humans. It is unknown whether osteopontin is a modifier of APRT deficiency severity in humans, as demonstrated in mice[34].

APRT deficiency is not known to cause extrarenal manifestation. Although clinical observations in some heterozygotes suggested that APRT deficiency may contribute to hyperuricemia and gout[35-37], patients with APRT deficiency usually show serum uric acid within the normal range. Rare cases of eye discomfort and corneal involvement were reported in APRT deficiency, but the significance of this association remains undetermined[38,39]. It is unknown whether long-term exposure to high systemic levels of DHA could have deleterious consequences. This issue may be of particular relevance for patients with APRT deficiency and ESRD, who might be subjected to constant DHA exposure due to the loss of renal clearance of DHA.

Heterozygotes are asymptomatic and usually have normal excretion of DHA and no DHA crystals in their urine, despite the fact that they have partial APRT defi-

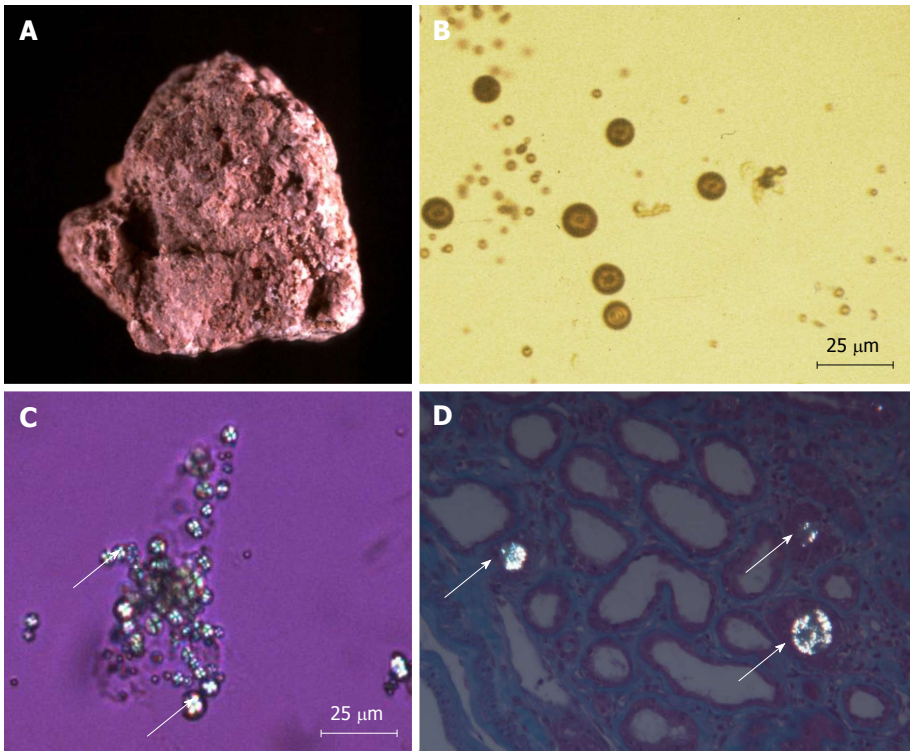

Figure 2 Stones and crystals of 2,8-dihydroxyadenine. A: Typical aspect of a 2,8-dihydroxyadenine (DHA) stone, showing a rough and humpy surface and a reddish-brown color that turns grey when drying. The stone is friable and sections show porosities and beige to brown color; B: Light microscopy aspect of DHA crystals in urine (non-polarized image), showing a round shape and a reddish-brown color; C: Urine DHA crystals in polarized light, showing typical central Maltese cross pattern (arrows); D: Periodic acid-Schiff of kidney biopsy under polarized light in a patient with adenine phosphoribosyltransferase deficiency, showing crystals within the renal tubules (arrows) (× 400). Fourier transform infrared microscopy study of the biopsy demonstrated that crystals were composed of DHA.

ciency[3,38]. However, one case of DHA urolithiasis was reported in an individual with a mutation (*APRT*J*) in only one of the two alleles[40]. To the best of our knowledge, no other case of symptomatic heterozygote has been reported to date and the mechanisms that might cause urolithiasis in some heterozygotes remain unknown.

GENETICS

APRT deficiency is caused by biallelic mutations (homozygous or compound heterozygous) in *APRT* gene, which is over 2.8 kb long. The gene contains five exons and encodes a 540 bp mRNA[5]. Over 40 mutations in the coding region of *APRT* gene have been identified in more than 300 affected individuals worldwide, with the majority arising from Japan[38]. Mutations causing type I APRT deficiency are referred to as *APRT*Q0*, which includes a wide variety of mutations in the coding region, including missense[5,41-43], non-sense[5-7], insertion and deletion[5,7,44,45], and splice-site mutations[5,7,44,46]. Type I deficiency is caused by homozygous or compound heterozygous *APRT*Q0* mutations. Certain mutations are more common in some populations. The c.400 + 2dup mutation (previously named IVS4 + 2insT)[44], appears to be the most frequent mutation in the European population[5,13,44,47,48]. and account for 40% of mutations in France[7]. Another mutation, Asp65Val , is highly prevalent in Iceland[10] and has been also reported in British and Spanish families[7,41,47].

Type Ⅱ APRT deficiency has been observed almost exclusively in Japan and is due to a missense mutation (*Met136Thr*) called APRT*J[4,42]. Patients with type Ⅱ deficiency have two APRT*J alleles, or less frequently one APRT*J and one APRT*Q0 allele[45]. The only known exception to this is a peculiar mutation (*V150F*) that was shown to cause type Ⅱ deficiency in a Polish patient[49].

DIAGNOSTIC TESTS

The identification of DHA in stone or urine is pathognomonic of APRT deficiency. Tests available for diagnosis of APRT deficiency include stone analysis, urine microscopy, renal biopsy, APRT activity and molecular genetic testing.

Stone analysis

Stone analysis should combine morphological examination by stereomicroscopy (Figure 2A) and analysis using infrared spectroscopy or X-ray crystallography, which will unambiguously demonstrate the DHA nature of the stone[50-52]. Standard biochemical methods to evaluate the composition of urinary stones can mistake DHA for uric acid and other purines, and are no longer recommended.

Urine microscopy

Urine examination by light and polarized microscopy can

detect DHA crystals, which have a characteristic appearance (Figure 2B and C)[50,51]. In general, the first morning urine specimen is particularly valuable for crystalluria study, because it is more concentrated. The amount of crystals is high in the urine of untreated affected individuals[7]. Infrared spectrophotometry (IRS) provides characterization of the composition of crystals and confirms diagnosis. In our experience, urine microscopy has an excellent sensitivity and DHA crystals can be detected in the urine of nearly all affected individuals. Rarely, false-negative may be observed[10].

Renal biopsy

Renal biopsy is, at least in theory, not necessary for diagnosis, given that DHA crystals can be identified in urine. In some instances where crystalline nephropathy was not expected, however, renal biopsy can demonstrate the presence of DHA crystals into the renal parenchyma and lead to diagnosis of APRT deficiency (Figure 2D). DHA crystals are mainly observed within tubules and in the renal interstitium. It must be emphasized that DHA crystals in renal biopsy often lack the characteristic morphology of crystals that can be observed in urine. We strongly recommend that crystals seen in renal biopsy specimen be fully characterized in order to avoid confusion with other crystalline deposits, especially uric acid and calcium oxalate. Whenever available, the combination of polarizing microscopy and Fourier transform infrared microscopy (FTIRM) is a reliable method for characterizing crystals in renal biopsy[53,54].

APRT activity

Measurement of enzyme activity in cell lysates is a useful tool for diagnosis of APRT deficiency[55,56]. Unfortunately, the availability of this test is limited in most countries. As discussed above, APRT activity is null in almost all non-Japanese patients with APRT deficiency (type I APRT deficiency). The only exception known to this is a patient of Polish origin with type Ⅱ deficiency related to a peculiar mutation[49]. Complex *in vivo* assays, such as uptake of adenine by intact cells, may rarely be used to assess the functional significance of such new mutations associated with residual activity in cell extracts. In type Ⅱ APRT deficiency, which is observed in patients of Japanese origin, APRT activity is usually less than 30% of normal level[4]. Therefore, a detectable APRT activity in cell extracts does not rule out the possibility of APRT deficiency, although this possibility is an exception in non-Japanese patients.

In heterozygous individuals with one APRT*Q0 and one non-mutated allele, APRT activity is decreased but still detectable (in our experience 5% to 60% of normal value)[8]. In heterozygotes carrying the APRT*J allele, the enzyme activity is usually higher than 50%, which tends to overlap with the values observed in normal individuals[21,22]. To put it in a nutshell, APRT activity assay demonstrates abnormal values in virtually all individuals with APRT deficiency (0% in type I and less than 30% in type Ⅱ) but is not a reliable technique to identify heterozygotes.

Molecular genetic testing

Mutation screening of the *APRT* gene can be relatively easily performed by sequencing of exons and flanking intronic sequences[5]. The diagnosis is confirmed if genetic testing shows functionally significant mutations in both alleles (see Genetics). In our experience, approximately 10% of mutations are not unidentified by *APRT* sequencing[7]. This may be due to large allelic deletions or mutations in promoter region.

Others

Measurement of purine metabolites in urine, as performed by certain laboratories, may reveal increased levels of adenine, suggesting a diagnosis of APRT deficiency. An assay for measurement of DHA would be more desirable but is not currently available. Developing a urinary DHA assay for screening and monitoring of treatment in clinical laboratories is one of the objectives of the APRT Deficiency Research Program, which is a part of the international Rare Kidney Stone Consortium (rarekidneystones.org)[38].

TESTING STRATEGY

Testing strategy may vary depending on the local availability of diagnostic tests. It may also depend on whether the aim is to establish diagnosis in a proband (individual without a family history of APRT deficiency) or to screen relatives of an affected individual. An algorithm for the diagnosis and treatment of APRT deficiency is provided in Figure 3. Key points are also summarized in Table 1.

Strategy for diagnosis in a proband

We recommend screening for APRT deficiency in all cases of urinary stones in children, recurrent urinary stones (especially if stones are radiolucent) and history of urinary stones associated with acute or chronic kidney disease of uncertain cause (including ESRD patients and renal transplant recipients).

Diagnosis primarily relies on the recognition of DHA in stones or crystals. Whenever a stone is available, it should be analyzed, even if it was passed a long time ago. Urine microscopy examination should be systematically done. IRS analysis of crystalluria is recommended when DHA is suspected or, more broadly, when crystals of uncertain composition are observed.

As discussed above, renal biopsy is not necessary for the diagnosis of DHA nephropathy, given that DHA crystals can be detected in urine in almost all affected individuals. Whenever histopathological findings consistent with crystalline nephropathy are observed, full characterization of the nature of crystals is mandatory. Such findings should prompt clinicians to search for crystals in urine. Crystals can be characterized in renal biopsy specimen using FTIRM. However, this technique is restricted to a few laboratories and crystalluria study is often an

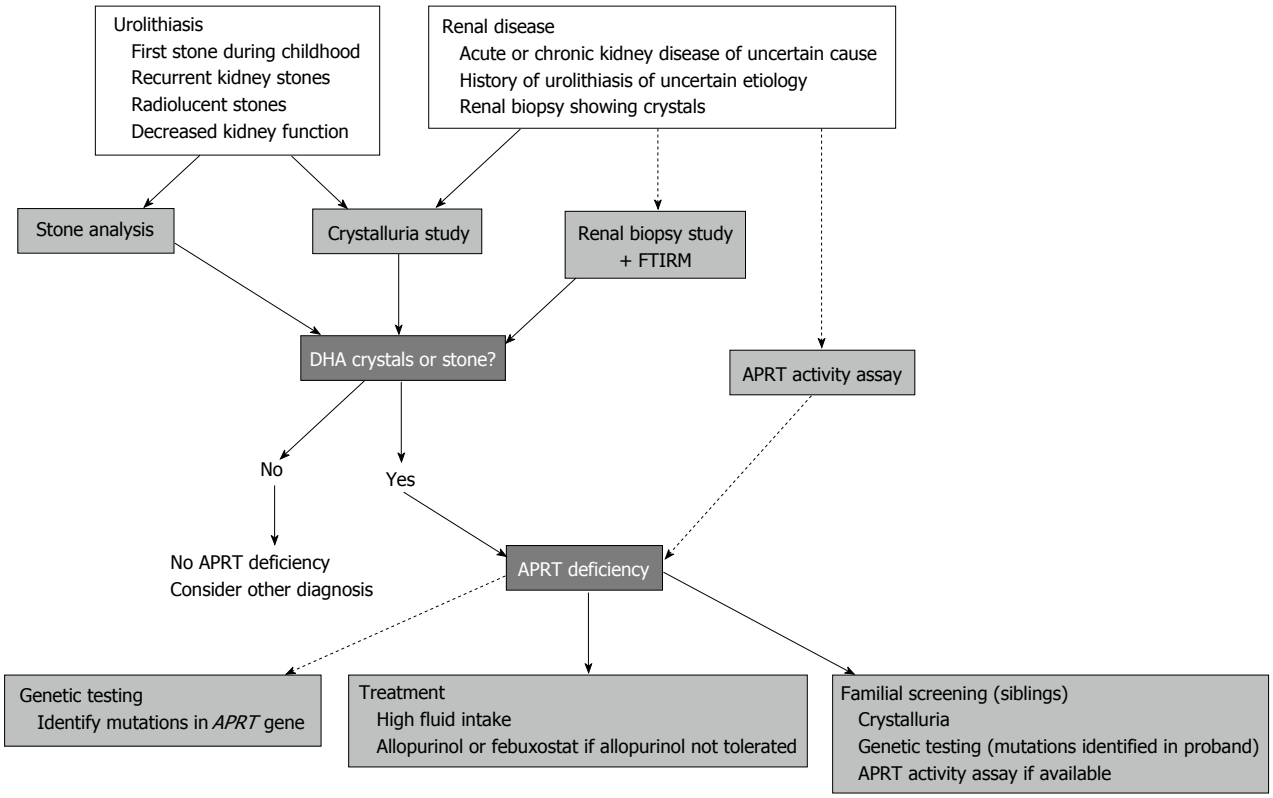

Figure 3 Algorithm for diagnosis and management of adenine phosphoribosyltransferase deficiency. This clinical algorithm summarizes situations where adenine phosphoribosyltransferase (APRT) deficiency should be suspected, testing strategies and management of the disease. FTIRM: Fourier transform infrared microscopy; DHA: 2,8-dihydroxyadenine.

Table 1 Key points about the diagnosis and treatment of adenine phosphoribosyltransferase deficiency

Key points
APRT deficiency is a rare but underrecognized genetic disease
Recurrent urolithiasis and DHA nephropathy are the two clinical manifestations of APRT deficiency and diagnosis can be made at any age
DHA nephropathy can relapse after renal transplantation
In most cases, urine microscopy and stone analysis will lead to diagnosis
APRT activity assay and genetic testing are useful for confirmation of diagnosis, for family screening and in difficult cases of urolithias or crystalline nephropathy
Allopurinol is the cornerstone of preventing recurrence of kidney stones and DHA nephropathy

APRT: Adenine phosphoribosyltransferase; DHA: 2,8-dihydroxyadenine.

easier way to identify DHA crystals.

If adequate stone and urine analysis exclude the presence of DHA, APRT deficiency is very unlikely and no other tests are usually needed. However, an exception can be made when the index of suspicion is high, especially in cases of crystalline nephropathy of uncertain cause.

Although the presence of DHA in crystals or stones is pathognomonic of APRT deficiency, APRT activity assessment and/or genetic testing are recommended to confirm diagnosis[38]. Measurement of enzyme activity is particularly helpful when stone or urine analysis is not feasible (*e.g.*, anuric patient). We strongly recommend APRT activity measurement in ESRD patients awaiting a kidney transplant who have a history of urolithiasis, when the cause of the kidney disease and the composition of the stones are uncertain.

Genetic testing is useful as a confirmatory test but is not intended as a primary screening procedure. Identifying the disease-causing mutations is of great relevance for familial screening once diagnosis has been confirmed in the proband.

Strategy for familial screening

Each sibling of a proband with APRT deficiency has a 25% chance of carrying two mutations and being affected. It is important to keep in mind that affected individuals may be asymptomatic but is still at risk for developing complications if the disease remains undiagnosed and untreated. All siblings, symptomatic or not, should therefore be investigated for APRT deficiency.

Once the mutations causing APRT deficiency have been identified in the proband, it is recommended that

the siblings undergo genetic testing. APRT activity measurement may also be useful, especially in the case where causative mutations could not be found in the proband. Urine microscopy examination should also be performed. Considering the risk, although very small, of false negative[10], urine microscopy should not be solely used to screen at-risk relatives. Further investigations, including assessment of renal function and imaging studies, are warranted in individuals with biallelic mutations, decreased APRT activity, or DHA crystals in urine. As discussed above, DHA crystals are usually absent in the urine of heterozygotes. APRT activity may be decreased but not null in heterozygotes.

TREATMENT AND SURVEILLANCE OF APRT DEFICIENCY

Treatment

No treatment is known to increase APRT activity. However, the disease can be efficiently treated with allopurinol, which inhibits XDH, thereby blocking the formation of DHA from adenine. Allopurinol is the cornerstone of treatment for APRT deficiency. Allopurinol therapy usually leads to a rapid reduction of DHA crystalluria and stone formation[7,27]. Allopurinol efficiently prevents the occurrence or progression of DHA nephropathy in most patients[7,10]. However, kidney disease can be irreversible, especially if tubulointerstitial lesions are advanced. The usual daily dose of allopurinol is 300 to 600 mg (maximum dose 800 mg) in adults and 5 to 10 mg/kg in children. In adults, we recommend initiating allopurinol therapy at a dose of 300 mg/d, which is sufficient to achieve good control of the disease in most patients. The dose should be increased in patients with persistent crystalluria and must be adapted when renal function is impaired. Allopurinol is well-tolerated by most patients, including children[27]. Febuxostat, a specific inhibitor of XDH[57], may be used in patients who do not tolerate allopurinol. However, the benefit and safety of febuxostat in APRT deficiency patients has not been evaluated. All patients with APRT deficiency, symptomatic or not, must receive life-long therapy with a XDH inhibitor. Patients and their families should be educated on the importance of life-long therapy and the risk of developing urolithiasis and DHA nephropathy if the treatment is stopped. Treatment with allopurinol is of paramount importance in patients undergoing kidney transplantation in order to prevent recurrence of DHA nephropathy, which can lead to transplant failure[9,11,18,19,32,33].

Whether patients with APRT deficiency on dialysis benefit from allopurinol is unknown. One may be concerned about the long-term impact of chronic exposure to high systemic levels of DHA. Although no deleterious effects have been reported to date, existing data on APRT deficiency patients undergoing chronic dialysis are very limited. In dialysis patients awaiting a kidney transplant, it seems preferable to initiate allopurinol therapy and achieve stable metabolic control prior to transplantation rather than initiate treatment only after a new kidney has been implanted.

Along with XDH-inhibiting drugs, high fluid intake achieving a urine volume of 2.5 liters daily (in adults) should be advised. It is usually recommended to avoid foods high in purines, although the impact of this diet on DHA excretion has not been established. Urinary alkalinization is not recommended, as DHA has very low solubility at pH values lower than 8.5[13].

Available data are limited regarding urological management of DHA stones. In our experience, patients can benefit from various procedures, including extracorporeal shock-wave lithotripsy, endoscopy and surgery, as for the treatment of other types of stones.

Surveillance

For the surveillance of patients with APRT deficiency, we recommend monitoring their renal function, performing quantitative analysis of crystalluria, and renal ultrasound every 6 to 12 mo in stable patients. The treatment usually leads to the disappearance or at least a drastic reduction of the number of DHA crystals[7,27]. A minority of patients treated experience stone recurrence[7,27]. Non-compliance or an insufficient dose of XDH inhibitor should be suspected in these patients or if there is no marked reduction in crystalluria.

CONCLUSION

APRT deficiency is a potentially severe condition that tends to be overlooked, especially in adults. A high index of suspicion for APRT deficiency and performing the appropriate investigations are mandatory in patients with recurrent urolithiasis and decreased renal function. There are few examples of diseases that can lead to complications as severe as irreversible renal failure but that can be efficiently treated with one pill a day. No stone should be left unturned in the effort to better recognize APRT deficiency and thereby enabling early and effective therapeutic intervention.

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