Adenine Phosphoribosyltransferase Deficiency

Guillaume Bollée, Jérôme Harambat,† Albert Bensman,‡ Bertrand Knebelmann,§ Michel Daudon,‖ and Irène Ceballos-Picot¶*

Summary

Complete adenine phosphoribosyltransferase (APRT) deficiency is a rare inherited metabolic disorder that leads to the formation and hyperexcretion of 2,8-dihydroxyadenine (DHA) into urine. The low solubility of DHA results in precipitation of this compound and the formation of urinary crystals and stones. The disease can present as recurrent urolithiasis or nephropathy secondary to crystal precipitation into renal parenchyma (DHA nephropathy). The diagnostic tools available—including stone analysis, crystalluria, and APRT activity measurement—make the diagnosis easy to confirm when APRT deficiency is suspected. However, the disease can present at any age, and the variability of symptoms can present a diagnostic challenge to many physicians. The early recognition and treatment of APRT deficiency are of crucial importance for preventing irreversible loss of renal function, which still occurs in a non-negligible proportion of cases. This review summarizes the genetic and metabolic mechanisms underlying stone formation and renal disease, along with the diagnosis and management of APRT deficiency.

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*Association pour l'Utilisation du Rein Artificiel and Inserm U970, Paris, France; †Service de Pédiatrie, Centre Hospitalier Universitaire de Bordeaux, Centre de référence Maladies Rénales Rares du Sud Ouest, Bordeaux, France; ‡Service de Néphrologie Pédiatrique, Université Pierre et Marie Curie, APHP, Hôpital Armand Trousseau, Paris, France; §Service de Néphrologie and ¶Laboratoire de Biochimie Métabolique, Université Paris Descartes, Assistance Publique Hôpitaux de Paris, Hôpital Necker-Enfants Malades, Paris, France; and ‖Service d'explorations fonctionnelles Hôpital Tenon, Université Pierre et Marie Curie, Assistance Publique Hôpitaux de Paris, Paris, France

Correspondence: Dr. Guillaume Bollée, Association pour l'Utilisation du Rein Artificiel, rue du Bessin, 75015 Paris, France, and Dr. Irène Ceballos-Picot, Hôpital Necker, 149 rue de Sèvres, 75015 Paris, France. Email: gbollee@gmail.com or irene.ceballos@nck.ap-hop-paris.fr

Introduction

A partial deficiency of adenine phosphoribosyltransferase (APRT) was identified in healthy persons more than four decades ago by Kelley *et al.*, who described mutant forms of the enzyme and found the inheritance to be autosomal (1). In 1974, Cartier *et al.* identified for the first time a child with urolithiasis related to complete APRT deficiency. Both of his parents had partial APRT deficiency. The authors found the stones to be composed of a new compound: 2,8-dihydroxyadenine (DHA) (2). The autosomal-recessive inheritance of the disease was confirmed by Van Acker *et al.*, who reported on the manifestations of APRT deficiency in one family (3). In the Japanese population, the prevalence of DHA stones was found to be particularly high (4). APRT deficiency is a protean disease that can manifest not only as recurrent urolithiasis but also as crystalline nephropathy. Unfortunately, the diagnosis is often delayed by years after the onset of symptoms, and many patients have already developed irreversible renal failure when adequate treatment is implemented (5–8). There is a crucial need for earlier recognition and better management of APRT deficiency.

We review the genetic and metabolic mechanisms involved in APRT deficiency, along with the diagnosis and treatment of this condition.

Metabolic Mechanisms

The APRT enzyme is expressed in all tissues and provides the only pathway for the metabolic salvage of adenine resulting from polyamine biosynthesis and dietary sources (Figure 1) (9). APRT catalyzes the formation of 5′-adenosine monophosphate and inorganic pyrophosphate from adenine and 5-phosphoribosyl-1-pyrophosphate, allowing adenine to be detected only at low levels in blood and urine (10). In individuals lacking functional APRT, adenine is converted to 8-hydroxyadenine, which is further metabolized to DHA by xanthine dehydrogenase (XDH), previously known as xanthine oxydase (11). DHA has a high renal clearance, which may involve both filtration and tubular secretion (12). APRT deficiency therefore results in high urinary levels of DHA (3). DHA is extremely insoluble in urine and forms crystals, which can gather, grow, and form stones (3,13) or precipitate in renal parenchyma, causing crystalline nephropathy (5,6,8,14).

Although crystals and stones form secondarily to null APRT activity *in vivo*, two types of complete deficiency have been described, according to the level of APRT activity *in vitro* (10). APRT activity is usually measured in cell lysates using radiolabeled ^{14}C-adenine in a chromatographic assay (6). This technique does not detect any enzyme activity in individuals with type I APRT deficiency. Type I deficiency mainly affects white individuals but has been also reported in people originating from countries worldwide (6,7,15). In type II deficiency, which accounts for most cases in Japan (4), APRT has a reduced affinity for the cosubstrate 5-phosphoribosyl-1-pyrophosphate and the enzyme activity in cell lysates is about 25% of normal values (16). In fact, this classification applies only to *in vitro* phenomena in cell lysates and has no relevance in cultured cells (17,18) or *in vivo*. This classification has no known clinical significance because the manifestations of the disease are identical in the two types (4,6,7,16).

Genetics

The *APRT* gene located on chromosome 16q24 encompasses 2.8 kb of DNA, contains five exons, and has a coding region of 540 bp (19). Complete APRT

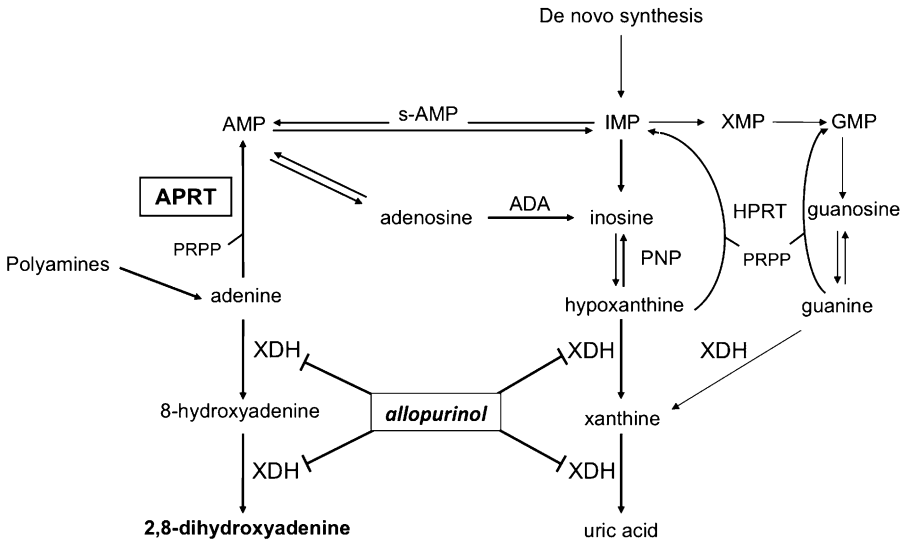

Figure 1. | **Adenine metabolism pathways and the role of adenine phosphoribosyltransferase (APRT).** In humans, adenine cannot be converted to adenosine as hypoxanthine to inosine; the only alternative pathway in APRT deficiency is oxidation of adenine to 2,8-hydroxyadenine by xanthine dehydrogenase (XDH). Allopurinol acts by inhibiting XDH, thus preventing 2,8-dihydroxyadenine synthesis. ADA, adenosine deaminase; AMP, adenosine monophosphate; GMP, guanosine monophosphate; HPRT, hypoxanthine phosphoribosyltransferase; IMP, inosine monophosphate; PNP, purine nucleoside phosphorylase; PRPP, 5-phosphoribosyl-1-pyrophosphate.

deficiency occurs in individuals carrying mutations in both copies of the *APRT* gene.

Mutant alleles responsible for type I have been classified as APRT*Q0, which encompasses a heterogeneous collection of mutations distributed along the coding sequence, including missense (19–22), non-sense (6,19,23), insertion or deletion (6,19,24,25), and mutation at the splice junction site leading to abnormal mRNA splicing (6,19,24,26). Patients with type I deficiency are homozygotes or compound heterozygotes for these mutations. Some mutations appear to be particularly frequent in certain populations. The IVS4+2insT mutation, corresponding to a single T insertion in the intron 4 splice donor site resulting in a truncated protein (24), accounted for 40% of mutations in our cohort (6). All probands carrying at least one IVS4+2insT mutation originated from France or other European countries, whereas IVS4+2insT was not detected in five families from other ethnic groups (6). The IVS4 +2insT mutation had been identified previously in several families from Europe and seems to be the most common cause of APRT deficiency in this population (10,19,24,27,28). Another common mutation is a missense (Asp65Val) found in British, Icelandic, and Spanish patients (6,20,27). Asp65Val mutation was found in the homozygous state in all 16 families reported in an Icelandic study (7).

Type II APRT deficiency is caused by a single mutant allele with a missense mutation in exon 5 (Met136Thr) referred to as APRT*J, which has been reported exclusively in the Japanese population (4,21). Patients with type II deficiency have the genotype APRT*J/APRT*J or, more rarely, APRT*J/APRT*Q0 (25). An exception to this is a missense mutation (V150F) reported in a patient of Polish origin, which produced an enzyme with null activity *in vivo* but residual activity *in vitro* (29). This observation suggests that type II deficiency may be rarely observed in non-Japanese populations.

Prevalence

APRT deficiency is often considered a very rare disease, although its worldwide prevalence remains largely unknown. Most cases and studies published arise from Japan and are rarely reported from other populations, except for the Icelandic and French cohorts (6,7). Considering the percentage of DHA stones among calculi analyzed in a large clinical laboratory in Japan, it was estimated that about 1/27,000 of the Japanese population had complete APRT deficiency; the incidence of heterozygotes was calculated to be higher than 1.2% (4). In white persons, the heterozygosity for APRT deficiency has an estimated frequency ranging from 0.4% to 1.2% from measurements of enzyme activity in healthy populations (30,31). Homozygosity causing complete APRT deficiency should therefore range between 1/50,000 and 1/100,000, which contrasts with the small number of cases recorded and suggests that the disease may be underdiagnosed (32). In the Necker Hospital laboratories, which are referral centers for urolithiasis and purine metabolism in France, the number of families and patients in whom complete APRT deficiency is diagnosed has notably increased in the last few years, rising to 55 families, probably as a result of increased awareness (Figure 2A).

The frequency of APRT deficiency might not be homogeneous among white populations because of the high frequency of certain mutations in some countries, such as IVS4+2insT in France and Asp65Val in Iceland. We found the IVS4+2insT mutation in 2 of 204 (0.98%) healthy newborn chromosomes (6), suggesting a high prevalence of this mutation in France. However, this result will have to be confirmed in a larger population sample. In Iceland, the prevalence is higher than 1/15.000, with 23 homozygotes among a population of around 300,000 (7).

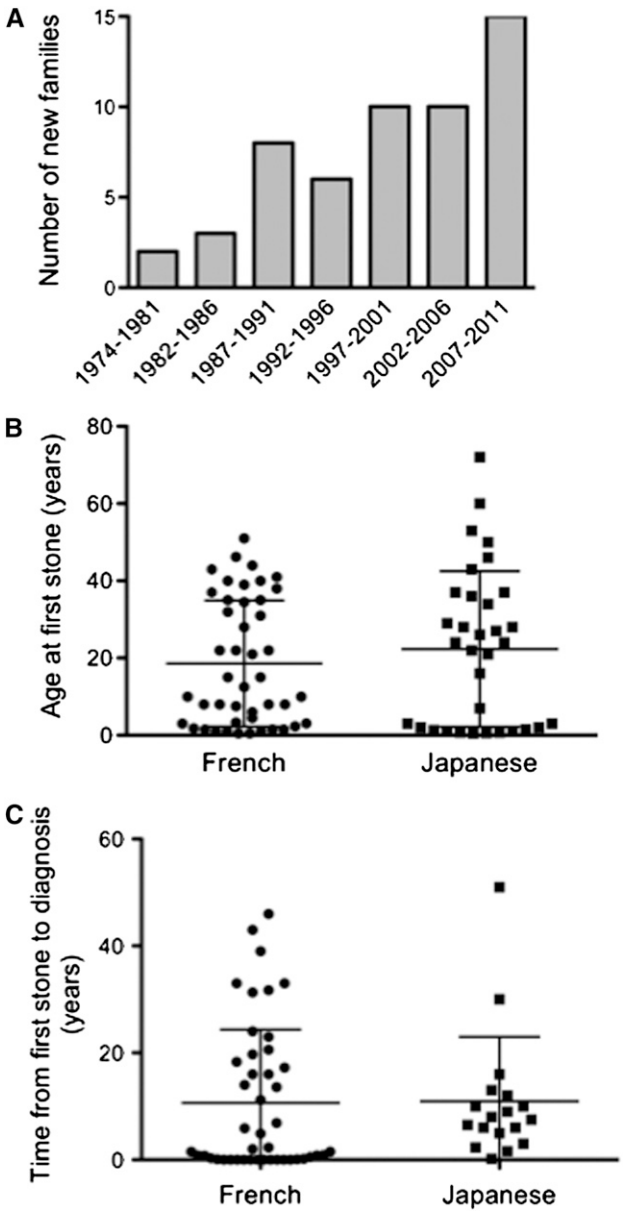

Figure 2. | Diagnosis of complete adenine phosphoribosyltransferase (APRT) deficiency. (A) Number of new families with complete APRT deficiency diagnosed in the laboratories of Necker Hospital, Paris, France, by time period since 1974. (B) Age at occurrence of first stone episode in one French (6) and two Japanese (pooled) (4,16) cohorts. Bars indicate mean ± SD. Mean age at first stone was 18.6±16.3 years in French patients (n=45) and 22.3±20.2 years in Japanese patients (n=33). (C) Time from first stone to diagnosis in the French (6) cohort and the Japanese (16) cohort. Mean time from first stone to diagnosis was 10.7±13.7 years in French patients (n=45) and 11±12.1 years in Japanese patients (n=18).

Clinical Presentation

Complete APRT deficiency often poses a diagnostic challenge not only because of variability of symptoms and age of onset but also lack of awareness. The disease can present with two types of clinical manifestations, which may occur together or separately: urolithiasis and crystalline nephropathy. Although APRT deficiency occurs in all cells, no extrarenal symptom has been reported in affected individuals.

Studies in European and Japanese populations have highlighted that APRT deficiency can present at any age. The age at diagnosis varies from infancy to older than 70 years (4,6,7,16). The disease can be diagnosed late, either because patients have remained free of symptoms for decades or because it has remained misdiagnosed despite recurrent urolithiasis. In the setting of familial screening, it is not unusual to detect complete APRT deficiency in individuals who are totally asymptomatic even as adults (6,7). The first urolithiasis episode may occur during the first few months after childbirth as well as later than the fifth decade (Figure 2B) (4,6,16). Reddish-brown diaper stains may be observed in infants (7). In both European and Japanese cohorts, several years or even decades sometimes elapsed before the diagnosis was made (Figure 2C) (6,7,16). Delayed diagnosis is less frequent when symptoms begin in children because urolithiasis is a much less common condition than in adults, which often alerts physicians to investigate the nature of the stone. In adults, confusion frequently occurs between DHA and uric acid stones, which are much more frequent and are radiolucent, like DHA stones. Of note, DHA stones may contain calcium salts, making them sometimes radiopaque (4,33).

DHA crystals can precipitate in renal tubules and interstitium and severely impair renal function. We propose the term "DHA nephropathy" for the crystalline nephropathy secondary to DHA precipitation. DHA nephropathy may present as an acute disease leading to renal failure in a few days or weeks or, more frequently, develop insidiously and cause progressive decline of renal function during a period of several years. Acute renal failure may be triggered by dehydration, which causes oliguria, urine supersaturation, and massive precipitation of DHA. In both European and Japanese cohorts, decreased renal function was observed in about one third of patients at time of diagnosis, and nearly 10% of patients had reached ESRD before diagnosis (4,6,7). DHA nephropathy may rarely occur in patients with no history of urolithiasis (7) and more frequently occurs in patients who showed only a few stone episodes, sometimes a long time ago (Figure 3, A and B).

In some catastrophic situations, APRT remains unrecognized and untreated after ESRD has occurred, allowing DHA nephropathy to recur after renal transplantation, which often leads to irremediable loss of allograft function within a few weeks, unless adequate therapy is rapidly implemented (5,8,34–36).

The reasons behind the variability in APRT deficiency phenotype are unclear. No correlation between phenotype and genotype has been reported to date. Perhaps this is not so surprising, given the probable complete loss of APRT activity in all homozygotes, whatever the mutation may be. However, the limited number of cases and the heterogeneity in patient management characterizing most of studies preclude the drawing of firm conclusions. Factors such as fluids and purine intake are likely to account for this variability. Individual differences in the effectiveness of crystallization inhibitors, such as osteopontin, may also modulate phenotype (37).

Although individuals with complete or partial APRT deficiency generally have normal plasma uric acid levels, hyperuricemia and gout have occasionally been reported in heterozygotes with partial APRT deficiency (38–40). This

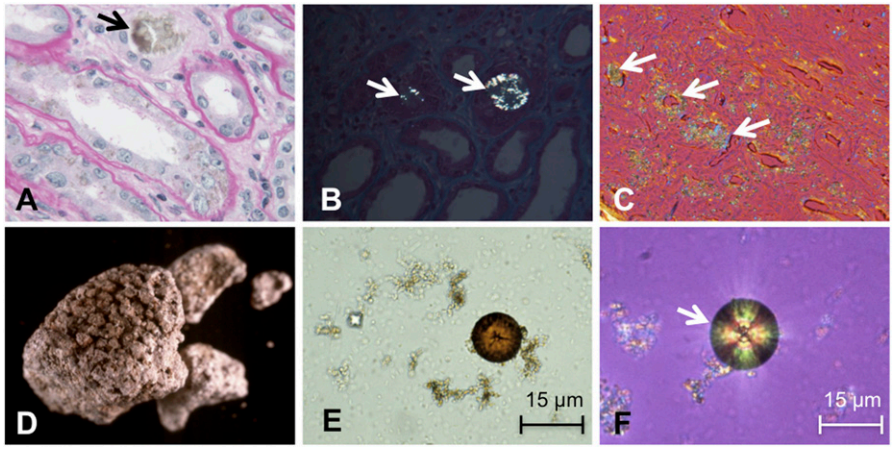

Figure 3. | Representative pictures of 2,8-dihydroxyadenine (DHA) nephropathy, stone, and crystals. (A–C) Images of renal biopsy specimens from a patient with DHA nephropathy secondary to adenine phosphoribosyltransferase (APRT) deficiency. The patient was a 64-year-old woman with renal failure who had experienced only one stone episode 33 years earlier. (A) Light microscopic view of renal biopsy specimen showing severe tubulointerstitial injury secondary to precipitation of crystals (arrows) (periodic acid-Schiff staining; original magnification, ×1000). (B) Polarized light view allows better visualization of crystals (arrows) (Masson trichrome staining; original magnification, ×400). (C) Polarized microscopic view shows multiple crystals (green and blue, arrows) in renal parenchyma (original magnification, ×400). Infrared analysis confirmed the DHA nature of crystals, and assay for APRT activity showed complete deficiency. (D) Morphologic aspect of DHA stones, which are reddish-brown and then turn gray when drying. DHA stones typically have a rough and bumpy surface that is soft and friable. Stones are beige to brown and show unorganized sections with porosities. (E) Nonpolarized image of DHA crystals in urine. (F) Typical aspect of DHA crystals by polarized microscopy; the crystals appear as round and reddish-brown, with characteristic central Maltese cross pattern (arrow).

association may not be fortuitous and will deserve closer examination.

Diagnosis

The diagnosis of APRT deficiency is primarily based on the identification of DHA, either by examination of crystals in urine or by stone analysis. Stones should be analyzed every time one is available by the combination of morphologic examination under stereomicroscope (Figure 3C) and infrared spectroscopy, which allows identification of DHA in all cases (41,42). Biochemical stone analysis fails to differentiate DHA from uric acid and cannot be relied on for diagnosis of APRT deficiency. Crystalluria examination by light and polarizing microscopy is a very useful, noninvasive, and inexpensive tool for the identification of DHA crystals (Figure 3D) (41,42). Crystalluria study is best performed in first-voided morning urine samples, which are the most concentrated. Quantification can be done by counting the number of crystals per volume unit (42), which is high in untreated patients (6). Infrared spectrophotometry should be also performed when DHA crystals are suspected or, more generally, when crystals of uncertain nature are seen. In our experience, crystalluria is very sensitive and specific, allowing the identification of homozygotes in 100% of cases. False-negative results have been rarely reported (7). As an invasive procedure, renal biopsy is theoretically not required. However, it often leads to diagnosis in cases of DHA nephropathy, APRT deficiency being an unexpected finding in most cases. Renal biopsy usually shows severe tubular injury and precipitation of crystals within tubular lumen and in renal interstitium (Figure 3A). The crystals may lack the typical features of DHA and their presence in renal parenchyma should never be dismissed. The best method is to characterize crystals in renal biopsy using polarizing microscopy and Fourier transform infrared microscopy (43,44). If the latter is not available, crystalluria and measurement of APRT activity assay may also lead to diagnosis.

Given that the DHA nature of stones or crystals is pathognomonic of APRT deficiency, measurement of APRT activity in erythrocytes lysates is not mandatory but is useful when available (45,46). In the United States, APRT activity assay availability is restricted to a few laboratories, such as the University of California San Diego Biochemical Genetics Laboratory. In type I APRT deficiency, which accounts for nearly all cases in non-Japanese patients, APRT activity is null. The only exception known to this is a peculiar mutation associated with residual activity *in vitro* reported in a patient of Polish origin (29). In type II, APRT activity is usually 15%–30% of normal activity (4). Individuals carrying one APRT*Q0 and one normal allele show significant decrease in APRT activity although still detectable. In 56 heterozygotes for APRT*Q0 tested in our laboratory, APRT activity ranged between 6% and 58% of normal activity, with a mean value of 28% (unpublished data). Heterozygotes for APRT*J cannot be distinguished from normal individuals because they have 50% to more than 65% of the mean activity of healthy persons, which overlaps with normal individual values since normal levels show significant variation (16,18).

The analysis of purine metabolites in urine may suggest the diagnosis if adenine level is increased. However, a standardized assay for quantification of DHA, which would be more specific, is not available.

The mutations involved may be determined by sequencing of PCR-amplified DNA, which can be readily performed given the small size of *APRT* gene (19). However, genetic testing should not be considered as a diagnostic tool. In our experience, 10% of mutations remain unidentified despite sequencing of the entire coding region and intron/exon junctions of the *APRT* gene (6). This may be explained by mutations located in promoter region or by large deletions in one allele.

When should APRT deficiency be suspected and diagnostic tests implemented? The possibility of APRT deficiency should be considered in all cases of urolithiasis in children, recurrent urolithiasis (especially if stones are radiolucent), and urolithiasis associated with renal dysfunction of uncertain cause. In such cases, adequate stone analysis should be performed whenever possible. Crystalluria is very useful, especially in the absence of stone available. Crystalluria may be used in routine clinical practice as a first-intention test for patients with unexplained renal dysfunction with no or low-grade proteinuria, even in the absence of history of urolithiasis. APRT activity assay is useful when no stone is available and crystalluria cannot be studied in a patient with crystalline nephropathy (*e.g.*, anuria). We also suggest that APRT activity should be systematically measured in patients with ESRD awaiting renal transplantation who have a history of urolithiasis, even if the stone episodes were old and rare, unless the etiology of renal failure or the nature of stones has been clearly established. A diagnostic algorithm for APRT deficiency is provided in Figure 4.

Management

No treatment has been shown to increase APRT activity. Treatment of APRT deficiency relies on allopurinol therapy, which acts by blocking XDH (Figure 1). In patients with DHA nephropathy, allopurinol therapy usually allows renal function to stabilize or improve and prevents recurrence after renal transplantation (6,7). The possibility of renal function recovery largely depends on the degree of acute tubular necrosis and chronic tubulointerstitial changes when treatment is initiated. All individuals with complete APRT deficiency, even asymptomatic, should be treated by allopurinol, given the risk for acute or insidious DHA nephropathy.

The usual dosage of allopurinol is 200–300 mg/d in adults and 5–10 mg/kg per day in children, which efficiently prevents the formation of crystals in most patients. Dosing must be adapted when renal function is impaired. This treatment is well tolerated in most patients, and children treated show normal growth and development (47). Febuxostat, another XDH inhibitor (48), may represent a

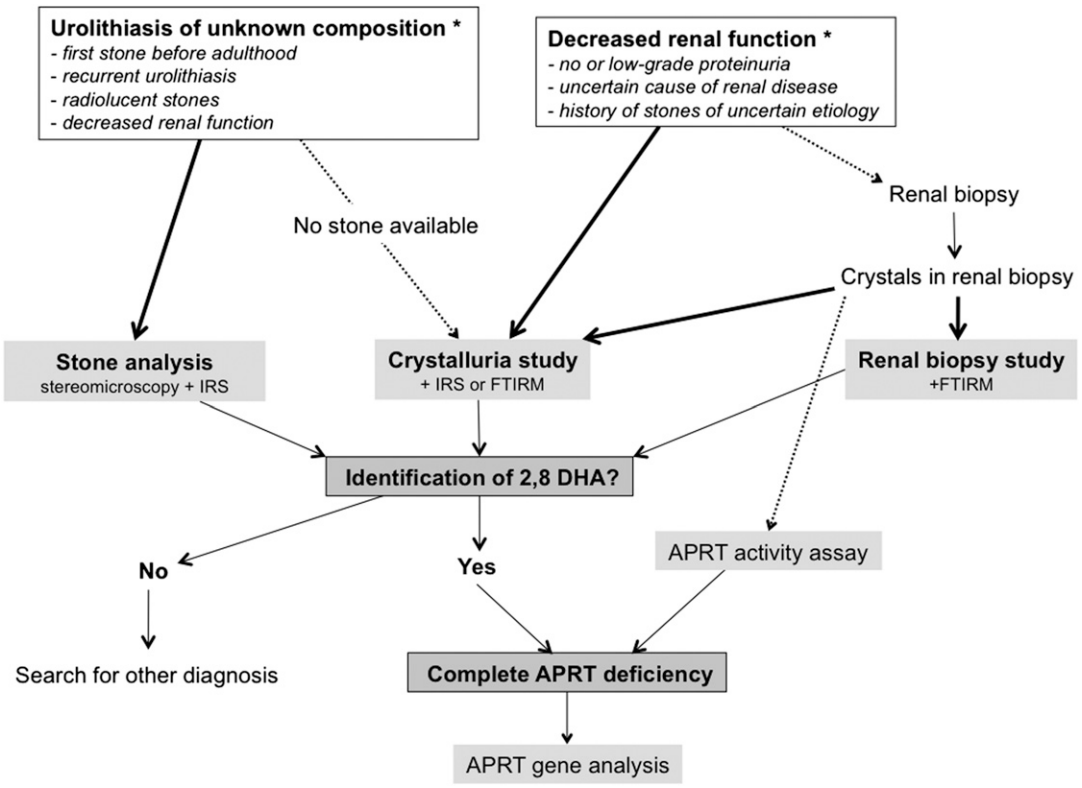

Figure 4. | **Recommended diagnostic algorithm for complete adenine phosphoribosyltransferase (APRT) deficiency.** Bold solid lines indicate the first intention tests for diagnosis of APRT deficiency; dotted lines indicate those that may be used as an alternative diagnostic tool. For crystalluria study, infrared spectrophotometry (IRS) can be used successfully to identify large amounts of crystals separated by centrifugation, and Fourier transform infrared microscopy (FTIRM) is useful to characterize very small amounts of crystals. *Complete APRT deficiency should be suspected especially in patients presenting with one or several of the clinical features indicated. DHA, 2,8-dihydroxyadenine.

potential alternative in allopurinol-intolerant patients, although its use has never been reported in APRT deficiency.

High fluid intake (at least 2.5 L of water per day in adults) and avoidance of purine-rich food should also be advised. Alkalization does not have to be recommended because DHA remains very insoluble at pH values below 8.5 (10). Decrease of crystalluria is usually observed under therapy and should be considered as an adequate response to treatment (6,47). We therefore recommend measuring crystalluria for treatment monitoring. Stones recur in a minority of patients despite treatment (6,47). Lack of adherence to treatment or insufficient dosing of allopurinol should be suspected in such situations or if crystalluria persists.

Familial Screening and the Question of Heterozygotes

Siblings of a patient with complete APRT deficiency have a 25% chance of being affected and must therefore be investigated. Crystalluria and, if possible, APRT activity assay should be performed in these individuals. If APRT activity assay is not available, it is prudent to repeat crystalluria study before ruling out the diagnosis. Genetic testing of siblings can also be useful, especially if the two mutations have been identified in the propositus. As discussed earlier, treatment should be implemented if complete deficiency is found.

Heterozygotes usually show normal amounts of DHA in urine despite partial APRT deficiency (3). In our experience, crystalluria is negative in heterozygotes and these individuals do not develop symptoms; therefore, allopurinol therapy is not indicated. However, this assumption was challenged by the report of a well documented case of DHA lithiasis in a patient carrying one mutant APRT*J and one normal allele (49). It remains unclear whether increased polyamine synthesis, which appears to be the main source of endogenous adenine (9), or high dietary purine intake can lead to DHA lithiasis in heterozygotes. It seems therefore prudent to systematically perform crystalluria analysis.

Conclusion

APRT deficiency may represent a unique example of a disease that potentially leads to renal failure but can be easily treated by taking a pill each day. Physicians should therefore leave no stone unturned when it comes to caring for patients with urolithiasis or renal disease. There is a need to make diagnostic tools, especially APRT activity assay, more available worldwide. Research programs, such as those conducted by the Rare Kidney Stone Consortium (www.rarekidneystones.org), will provide an opportunity to better understand and manage APRT deficiency.

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Disclosure

None.

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