Adenine Phosphoribosyltransferase Deficiency: An Underdiagnosed Cause of Lithiasis and Renal Failure

Giuseppina Marra • Paolo Gilles Vercelloni • Alberto Edefonti •
Gianantonio Manzoni • Maria Angela Pavesi • Giovanni Battista Fogazzi •
Giuseppe Garigali • Lionel Mockel • Irene Ceballos Picot

Received: 26 July 2011 / Revised: 5 September 2011 / Accepted: 7 September 2011 / Published online: 21 December 2011
© SSIEM and Springer-Verlag Berlin Heidelberg 2011

Abstract We describe an infant affected by adenine phosphoribosyltransferase (APRT) deficiency diagnosed at 18 months of age with a de novo mutation that has not been previously reported. APRT deficiency is a rare defect of uric acid catabolism that leads to the accumulation of 2,8 dihydroxyadenine (2,8-DHA), a highly insoluble substance excreted by the kidneys that may precipitate in urine and

form stones. The child suffered from renal colic due to a stone found in the peno-scrotal junction of the bulbar urethra. Stone spectrophotometric analysis allowed us to diagnose the disease and start kidney-saving therapy in order to avoid irreversible chronic kidney damage. APRT deficiency should always be considered in the differential diagnosis of pediatric urolithiasis.

Introduction

APRT deficiency is a rare defect of uric acid catabolism that leads to the accumulation of 2,8 dihydroxyadenine (2,8-DHA), a highly insoluble substance excreted by the kidney that may precipitate in urine (Bouzidi et al. 2007; Simmonds 2003). The disease is due to a mutation in the APRT gene and is inherited in an autosomal recessive manner (Tischfield and Ruddle 1974). The small number of patients diagnosed in contrast with the mutation frequency in general population suggests that it is a still underdiagnosed disease (Ceballos-Picot et al. 1992). It is not only an uncommon cause of renal stones but can also cause chronic renal failure and lead to dialysis as other lithogenic diseases such as cistinuria and primary hyperoxaluria. Furthermore, unless promptly diagnosed and treated, it may even recur in a transplanted kidney (Benedetto et al. 2001; Bollée et al. 2010; Edvardsson et al. 2001; Stratta et al. 2010). Most of the published case reports concern adults (Simmonds 2003), but it is very important to recognize and treat the disease as soon as possible in order to reduce lithiasic episodes and prevent its potential long-term consequences. A correct diagnosis can be made by following a diagnostic workup but a high index of suspicion is necessary.

The authors Giuseppina Marra and Paolo Gilles Vercelloni equally contributed to the article.

Communicated by: Jean-Marie Saudubray.

Competing interests: None declared.

G. Marra (✉) • P.G. Vercelloni • A. Edefonti
Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico,
UO Pediatric Nephrology, Via Commenda 9, 20122, Milano, Italy
e-mail: gimarra@hotmail.com

G. Manzoni
Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico,
UO Pediatric Surgery, Via Commenda 9, 20122, Milano, Italy

M.A. Pavesi
Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico,
UO Pediatric Radiology, Via Commenda 920122, Milano, Italy

G.B. Fogazzi • G. Garigali
Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico,
UO Nephrology, Via Commenda 9, 20122, Milano, Italy

L. Mockel • I.C. Picot
Laboratory of Metabolic Biochemistry, Necker-Enfants Malades
Hospital, Assistance Publique-Hôpitaux de Paris, Rue de Sevres,
Paris, France

We here describe a patient with APRT deficiency who was diagnosed during infancy and was due to a *de novo* mutation that has not been previously reported.

Case Report

AP was born in the 29th week of gestation by cesarean delivery due to placenta praevia in an uneventful twin pregnancy. The neonatal period was characterized by cardiorespiratory distress and jaundice, which required ICU admission and CPAP and phototherapy. A number of perinatal renal ultrasound (US) examinations revealed micropapillary calcifications probably related to his prematurity without any urinary tract dilatation or other alteration of the renal parenchyma (Fig. 1a). His twin sister had a similar clinical history and showed the same renal findings, which disappeared spontaneously during the first few months of life. In our patient, they remained unchanged (Fig. 1b) and subsequently assumed the appearance of nephrocalcinosis.

At the age of 8 months, he developed a symptomatic upper urinary tract infection. When he was 16 months old, a renal US examination revealed multiple bilateral radiolucent apico-papillary and peripheral stones with diameters ranging from 2 to 5 mm. Two months later, he suffered an acute episode of renal colic, after which two small stones were found in a nappy and a further two were observed by US in the pelvis of both kidneys. Two weeks later, he presented acute urine retention with stranguria and oliguria, and a stone was palpable at the peno-scrotal junction of the bulbar urethra. He underwent an emergency endoscopic

evaluation with stone fragmentation and lithotripsy, and was eventually referred to our hospital for nephrological and metabolic evaluation.

The hematological (acid-base balance, parathormone, electrolytemia, renal function) and urinary examinations showed no signs of tubulopathy or major metabolic diseases causing urolithiasis: aminoaciduria and cystinuria, ossaluria and citraturia were normal; calciuria/creatininuria was 0.27 (95th percentile = 0.56), phosphaturia/creatininuria 2.13 (95th percentile = 3.95), magnesiuria/creatininuria 0.19 (95th percentile = 0.37), and uricuria/creatininuria 0.96 (normal value <1).

A semiquantitative spectrophotometric analysis of the removed stone revealed a curve very similar to that of 2,8-DHA (Fig. 2), adenine phosphoribosyltransferase (APRT) deficiency was suspected, and it was found that the patient's red blood cells did not show any APRT activity. Genetic analysis of the APRT gene confirmed the diagnosis of APRT deficiency, and showed that the patient was composite heterozygous for two mutations: a known mutation c.84C>A localized on exon 2 and leading to the substitution p.Asp28Glu at protein level, and a never previously described deletion (g.347_372del26) located at the exon2/intron2 junction.

In the meantime, medical therapy was started with allopurinol 10 mg/kg day combined with hydropinic therapy.

The child is now 3 years old and has normal renal function. The micropapillary deposits disappeared 1 year after the beginning of therapy (Fig. 1c); the residual pelvic stone is unchanged in size (<5 mm), and no new 2,8-DHA

Fig. 1 Ultrasound images before therapy at 3 (a) and 9 months of age (b), and after 1 year of therapy (c)

Fig. 2 Spectrophotometry of the surgically extracted stone

stones have formed. Furthermore, no 2,8-DHA crystals were ever found in the many follow-up searches of urine sediment.

After the initial diagnosis was established, the whole family underwent a complete APRT enzymatic and genetic evaluation. The father and twin sister of the index case had a low residual erythrocyte APRT activity (7% and 38%, respectively). Both of them had the c.84C>A mutation heterozygously but not the deletion and various renal US examinations revealed that they both had normal kidneys and urinary tract and no crystalluria. The APRT activity of the index case's mother was normal and no genetic abnormalities were found. This familial investigation revealed that the c.84C>A mutation found in the first allele of the index case was inherited from the father and that the g.347_372del26 deletion in the second allele was a de novo mutation.

Discussion

APRT is a purine salvage enzyme present in all human cells that is encoded by a gene located on chromosome 16q24 (Tischfield and Ruddle 1974; Simmonds 2003), which was cloned in 1987. It normally catalyzes the conversion of adenine to adenosine monophosphate but, in the case of APRT deficiency, adenine is catabolised to 2,8-DHA, a highly insoluble substance that is responsible for crystalluria, nephrolithiasis, and intratubular deposition with or without symptoms. The subsequent renal damage is characterized by chronic tubulointerstitial nephritis with progressive sclerosis and chronic renal failure until the terminal phase, which usually develops during adulthood. The treatment of this disease consists of hydropinic therapy and a low purine diet combined with a daily 10 mg/kg dose of allopurinol. Unlike in the case of other renal stones, it is not necessary to acidify or alkalinize urine because 2,8-DHA precipitates at every pH. The therapy is relatively simple and effective and, in many cases, its prompt administration stops damage progression (Edvardsson et al. 2001; Bollée et al. 2010; Stratta et al. 2010).

This seems to be our patient's case because the micro-papillary deposits disappeared in less than 6 months and no new stones have formed but, in many other published cases, the disease was not diagnosed until the kidney had been irreversibly damaged (Bollée et al. 2010; Edvardsson et al. 2001) or even after a recurrence in a transplanted kidney (Benedetto et al. 2001; Bollée et al. 2010; Edvardsson et al. 2001; Stratta et al. 2010). The diagnostic phase is therefore crucial, and the extremely small number of cases reported by now is in contrast with a homozygosity at APRT locus estimated between 1 in 50,000 and 1 in 100,000. The most plausible explanation for this was that APRT deficiency may be largely unrecognized by clinicians involved in the treatment of patients with urolithiasis and/or renal failure (Bollée et al. 2010; Bouzidi et al. 2007; Ceballos-Picot et al. 1992).

We believe that APRT deficiency should be suspected in every child with renal stones, especially if they are radiolucent and there is no evidence of hyperuricuria, as in our case. The stones may occasionally be radiopaque because of the presence of calcium salts, but the diagnosis is suggested by examining the urinary sediment, which shows 2,8-DHA crystals (Bouzidi et al. 2007; Ceballos-Picot et al. 1992) in about 96% of untreated patients (Edvardsson et al. 2001). These crystals are typically round and reddish-brown with a Maltese cross pattern under polarized light, but an experienced laboratory is required to recognize them (Bouzidi et al. 2007).

In our case, the diagnosis was directly suggested by the spectrophotometric stone analysis. The other methods usually used in clinical practice, such as a murexide test, colorimetry reaction or thermo-gravimetric analysis cannot distinguish them from uric acid stones (Ceballos-Picot et al. 1992).

The diagnosis can be confirmed by measuring APRT activity in red blood cells and undertaking a genetic analysis. In our rare case, the disease manifested itself in very early infancy, but we cannot say whether the de novo mutation may have been responsible for its early clinical expression. The familial genetic study showed that the father and sister were heterozygous carriers of the same

previously reported mutation and, respectively, showed 7% and 38% residual enzymatic activity. It is interesting to note that despite this low level (especially in the father) there was no evidence of crystalluria or any US signs of nephrocalcinosis or stones, thus confirming that heterozygotes are usually completely asymptomatic.

In conclusion, pediatric lithiasis (especially in the first years of life) is a relatively rare condition, and may be a major indicator of high morbidity congenital or metabolic disorders that could be diagnosed and treated, sometimes with good clinical results. For this reason, a multidisciplinary approach is always mandatory in every case of child with urinary stones: obviously, the first step in the management of these patients is to relieve pain and undertake appropriate imaging to enable a decision as to whether and how to remove the stones or resolve obstruction. The second step, similarly mandatory, is the metabolic evaluation. APRT deficiency can be diagnosed by means of a urinary sediment examination, an affordable and reliable method that should represent the first diagnostic step in every child with lithiasis. However, a correct diagnosis requires a high index of suspicion that is possible only with a good knowledge of the disease.

Support: the molecular studies for the diagnosis of APRT and HPRT deficiencies are supported by the Association Lesch-Nyhan Action and the Association Malaury.

Dr Vercelloni's work has been sponsored by a research fund "Ricerca Corrente anno 2011" thanks to Fondazione IRCCS Ca'Granda Ospedale Maggiore Policlinico Milano.

Acknowledgements We thank Véronique Droin for her technical assistance in APRT enzymatic activity determination.

Take-Home Message

Pediatric lithiasis (especially in the first years of life) is a relatively rare condition, and may be a major indicator of

high morbidity congenital or metabolic disorders that could be diagnosed and treated, sometimes with good clinical results. For this reason, a multidisciplinary approach including a scrupulous metabolic evaluation is always mandatory in every case of child with urinary stones. APRT deficiency can be diagnosed by means of a urinary sediment examination, an affordable and reliable method that should represent the first diagnostic step in every child with lithiasis. However, a correct diagnosis requires a high index of suspicion that is possible only with a good knowledge of the disease.

References

- Benedetto B, Madden R, Kurbanov A, Braden G, Freeman J, Lipkowitz G (2001) Adenine phosphoribosyltransferase deficiency and renal allograft dysfunction. *Am J Kidney Dis* 37(5): E37
- Bollée G, Dollinger C, Boutaud L, Guillemot D, Bensman A, Harambat J, Deteix P, Daudon M, Knebelmann B, Ceballos-Picot I (2010) Phenotype and genotype characterization of adenine phosphoribosyltransferase deficiency. *J Am Soc Nephrol* 21(4):679–688
- Bouzidi H, Lacour B, Daudon M (2007) 2,8-Dihydroxyadenine nephrolithiasis: from diagnosis to therapy. *Ann Biol Clin (Paris)* 65(6):585–592
- Ceballos-Picot I, Perignon JL, Hamet M, Daudon M, Kamoun P (1992) 2,8-Dihydroxyadenine urolithiasis, an underdiagnosed disease. *Lancet* 339:1050–1051
- Edvardsson V, Palsson R, Olafsson I, Hjalpottir G, Laxdal T (2001) Clinical features and genotype of adenine phosphoribosyltransferase deficiency in Iceland. *Am J Kidney Dis* 38(3):473–480
- Simmonds HA (2003) Adenine phosphoribosyltransferase deficiency. *Orphanet Encyclopedia*. www.orpha.net
- Stratta P, Fogazzi GB, Canavese C, Airolidi A, Fenoglio R, Bozzola C, Ceballos-Picot I, Bollée G, Daudon M (2010) Decreased kidney function and crystal deposition in the tubules after kidney transplant. *Am J Kidney Dis* 56(3):585–590, Epub 2010 Mar 19
- Tischfield JA, Ruddle FH (1974) Assignment of the gene for adenine phosphoribosyltransferase to human chromosome 16 by mouse-human somatic cell hybridization. *Proc Natl Acad Sci U S A* 71:45–49