Case Report

Diagnosis of adenine phosphoribosyltransferase deficiency as the underlying cause of renal failure in a renal transplant recipient

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Introduction

Adenine phosphoribosyltransferase (APRT) deficiency is a rare inborn error of metabolism first described in the UK in 1976 [1]. It is inherited as an autosomal recessive trait and the gene is located on chromosome 16. APRT is a salvage enzyme that normally catalyses the conversion of adenine to adenine monophosphate using PP-ribose-P. Deficiency results in adenine accumulation with conversion to and excretion of 2,8-dihydroxyadenine (2,8-DHA) in the urine. 2,8-DHA is protein-bound in plasma, but is extremely insoluble in urine at any pH. Tubular crystal deposition can occur associated with marked interstitial fibrosis and/or urolithiasis. Since its original description, APRT deficiency has been recognized increasingly as a cause of chronic renal failure. We report a case of APRT deficiency that was diagnosed after renal transplantation. This has led to specific treatment for the patient to reduce the risk of further crystal and stone formation in the transplanted kidney. Also, additional family members with the condition have been identified through family screening.

Case

A 23-year-old male of Pakistani origin was transferred from another hospital for a cadaver renal transplant in January 2003. The cause of his chronic renal failure was classified as unknown. He had a small right kidney with multiple renal calculi and a relatively normal-sized left kidney. Renal biopsy, which was not reviewed in our centre, was reported as showing chronic interstitial nephritis with non-specific crystal deposition. Following the transplant there was immediate graft function and over the next few weeks he passed small stones in his urine. Analysis of the stones by infrared spectroscopy (Thermo Nicolet Avatar 360 FT-IR) showed that they were composed of 2,8-DHA. Urine was not analysed for 2,8-DHA, as this is not routinely available in our hospital. Studies on lysed and intact red cells with radiolabelled adenine using methods previously described [2] showed significant but reduced APRT activity. Residual APRT activity was 6.9 nmol/mgHb/h (control range: 16–32 nmol/mgHb/h). There was 95% conversion of radiolabelled adenine in intact erythrocytes. We considered these results attributable to transfusion with three units of packed cells 2 months previously. Repeat analysis 7 months later revealed 0 nmol/mg Hb/h APRT activity, confirming this suspicion.

He was treated with a high fluid intake, allopurinol 100 mg daily and a low purine diet. Over the following month he developed allograft dysfunction with serum creatinine slowly rising to 361 μmol/l. Renal biopsy revealed chronic interstitial nephritis with crystals consistent with 2,8-DHA (Figure 1). The patient’s allopurinol has been increased to 300 mg daily and he has been encouraged to increase his fluid intake and to avoid purine-rich foods. Serum creatinine has gradually fallen to 262 μmol/l.

His family was offered screening by assaying red blood cell APRT activity. It was found that both his mother and father, who are first cousins, were carriers of the condition. Of his four siblings, one brother is unaffected and two sisters are considered to be carriers with reduced erythrocyte APRT activity. APRT activity in the remaining brother (aged 29) was undetectable, indicating he is homozygous for the condition. He is asymptomatic, does not live locally and has been advised that he should be investigated for any renal involvement.
Discussion

We describe a case of APRT deficiency that presented with progressive unexplained renal failure and subsequently received a cadaver renal transplant. The diagnosis of APRT deficiency was made only after renal transplantation. This led to active management of the underlying condition with a high fluid intake, low purine diet and allopurinol to reduce the risk of progressive chronic renal failure due to recurrent disease (which has developed) in the allograft. In addition, it has also led to family screening. The latter has identified four carriers and an additional affected sibling.

There have been four other reported cases worldwide of recurrent dihydroxyadenine stone formation in renal transplant recipients [3–6]. In all cases, the diagnosis was made only after transplantation.

Although APRT is a rare inborn error of metabolism, it can lead to stone formation and chronic renal failure. Consequently, it is particularly important that the nephrology community are aware of this disorder as a potential cause of unexplained renal disease. Early diagnosis can prevent the onset of renal disease in asymptomatic siblings and, where renal disease has already developed, intervention is imperative and can lead to improvement in renal function. The condition may (a) be misdiagnosed, as conventional laboratory methods of stone analysis frequently incorrectly identify the stones as uric acid, or (b) with the advent of lithotripsy to treat renal stones without seeking an underlying cause, never be recognized [7]. 2,8-DHA lithiasis is also probably under-diagnosed in the general population. The heterozygous frequency in Caucasians has been estimated to be between 0.4% and 1.1% [8]. This would suggest that there should be approximately 750 homozygotes in the UK with APRT deficiency. This is likely to be higher in communities where matings are not random, as in this case where the parents were first cousins. Iceland, with 23 homozygotes from 16 families among a total population of 267 000, has the largest number on a per capita basis, illustrating a founder effect [9]. Of these, ~15% would be asymptomatic [10], yet prior to this report only seven patients have been identified in the UK, two of which progressed to dialysis and transplantation. The finding of 25 cases in France is attributed to more efficient stone analysis [7].

Though rare, a high index of suspicion is required, especially in young patients presenting with
unexplained renal failure and renal stone disease. Potentially, renal failure can be prevented, reversed or arrested. Should the condition go unrecognized and the patient is subsequently transplanted, early diagnosis and treatment is essential to help preserve renal allograft function. Genetic counselling for family members is also vital, not only to prevent disease progression in affected siblings, but also for carriers within the family.

The message from this report is that:

(i) Early recognition is crucial because allopurinol and a high fluid intake will prevent the formation of the nephrotoxic 2,8-DHA.

(ii) Preliminary diagnosis can be made from the characteristic round brown crystals in the urine deposit by anyone with a microscope [11].

(iii) Correct diagnosis from erythrocyte enzyme assay will be masked by recent blood transfusion.

The necessity to improve clinical awareness and limit the morbidity in this treatable disorder is underlined by the fact that such cases are still being found.

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References


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