

Case Report

An expanded syndrome of dRTA with hearing loss, hyperoxaluria and beta2-microglobulinuria

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Abstract

We describe a 7-month-old male with atypical features of autosomal recessive distal renal tubular acidosis (dRTA) with sensorineural hearing loss. Uncharacteristically, he presented with mild acidosis, hypokalaemia and hypocalciuria as well as unilateral sensorineural hearing loss. Subsequent investigations led to the discovery of both hyperoxaluria and beta2-microglobulinuria, thereby expanding the differential diagnosis to include both primary hyperoxaluria and Dent disease. Two mutations in the *ATPVI1B1* gene, one of which was novel, confirmed the diagnosis of dRTA. We consider the overlapping features of and diagnostic dilemmas involved in making a diagnosis of dRTA, primary hyperoxaluria and Dent disease in patients with infantile nephrocalcinosis. We highlight the occurrence of hyperoxaluria and low-molecular-weight proteinuria in patients with dRTA and propose that the phenotype of autosomal recessive dRTA with sensorineural hearing loss be broadened to include both hyperoxaluria and increased urinary excretion of beta2-microglobulin.

Keywords: *ATPVI1B1*; distal renal tubular acidosis; hyperoxaluria; low-molecular-weight proteinuria; sensorineural hearing loss

Introduction

Primary distal renal tubular acidosis (MIM #267300, #602722 and #179800) (dRTA) is an inherited condition characterized by systemic acidosis as a result of the inability of the distal tubule to adequately acidify the urine. Failure to thrive, polyuria, polydipsia, hypercalciuria, nephrocalcinosis and hypokalaemia are common presenting signs in infancy. Sensorineural hearing loss may be found in some patients depending on which gene is mutated. Rarely, patients with proven dRTA have been reported to have hyperoxaluria [1,2], hyperaminoaciduria [1], low-molecular-weight proteinuria [2], hypophosphataemia and hypouricaemia [2].

The primary hyperoxalurias (MIM #259900 and #260000) are autosomal recessive inborn errors of glyoxylate metabolism, which result in markedly increased oxalate

synthesis by the liver. Increased urinary oxalate excretion, normal-to-low urine calcium excretion, nephrocalcinosis, recurrent nephrolithiasis and progressive renal disease are the predominant clinical features. Nephrocalcinosis is a frequent presenting finding in infancy and early childhood [3], although failure to thrive, renal failure, anaemia and acidosis may also occur in this age group.

Dent disease (MIM #300009) is an inherited condition characterized by low-molecular-weight proteinuria, nephrocalcinosis, hypercalciuria and nephrolithiasis. The defect is in proximal tubular function, and glucosuria, aminoaciduria, metabolic acidosis and hypophosphataemia may all occur as part of an associated partial Fanconi syndrome [4–6]. In a minority of patients, the Dent phenotype results from a mutation in the *OCRL* gene which is also involved in the oculocerebrorenal syndrome of Lowe [7]. The clinical presentation is often insidious with many patients remaining asymptomatic throughout childhood; however, nephrocalcinosis, hypercalciuria and low-molecular-weight proteinuria are not uncommon findings in infancy [4].

Case report

A 7-month-old boy was referred for evaluation of nephrocalcinosis. A renal ultrasound was performed after he failed newborn hearing screen of the right ear.

Family history

A paternal second cousin developed renal failure, of unknown aetiology in childhood. The paternal grandfather and great-grandfather had multiple renal calculi. Both parents were healthy.

Physical examination

Height was 63.6 cm (10th percentile), weight 6.3 kg (<5th percentile) and blood pressure 107/67 mmHg. There were no dysmorphic features. He had normal eyes, ears and neck, normal cardiac abdominal and genital examination, no birthmarks, and normal reflexes.

Laboratory studies

Initial serum concentrations were as follows: sodium 140 mmol/L (normal 133–140 mmol/L), potassium 3.0 mmol/L (normal 4.1–5.8 mmol/L), chloride 110 mmol/L (normal 96–106 mmol/L), carbon dioxide 19 mmol/L (normal 20–26 mmol/L), creatinine 0.3 mg/dL (normal 0.1–0.4 mg/dL) and calcium 10.4 mg/dL (normal 9.2–10.4 mg/dL). Further studies showed: urine pH 8.5, urine calcium/creatinine ratio <0.06, serum phosphorus 5.2 mg/dL (normal 3.8–6.5 mg/dL), serum magnesium 2.1 mg/dL (normal 1.5–2.5 mg/dL) and urine beta2-microglobulin 218 431 µg/g Cr (normal <300 µg/g Cr).

Imaging studies

The renal ultrasound showed normal-sized kidneys for age and height. The right measured 5.45 cm, and the left measured 5.26 cm. There was no hydronephrosis. No calculi were visualized. There was bilateral medullary nephrocalcinosis.

Audiometry

Auditory brainstem response at 3 months of age revealed normal low frequency (500–1000 Hz) hearing sensitivity and a mild-to-moderate high frequency (2000–4000 Hz) hearing loss on the right with normal hearing sensitivity on the left. At 16 months, otoacoustic emission testing of the left ear was normal.

Course

After the initial evaluation primary hyperoxaluria, dRTA and Dent disease remained as the most likely diagnoses. The acidosis was corrected with 3–4 mEq/kg of Bicitra. The importance of early confirmation led us to pursue primary hyperoxaluria as the primary diagnosis. The first urine oxalate:creatinine ratio was 808 mg/g (normal <280 mg/g). A confirmatory oxalate:creatinine level was also elevated at 397 mg/g. A urine hyperoxaluria panel revealed an elevated glycolate:creatinine of 76 mg/g (normal <61 mg/g) and a normal glycerate:creatinine of 52 mg/g (normal <57 mg/g) suggestive of primary hyperoxaluria type I (PH1). Pyridoxine was initiated and titrated up to 65 mg per day (8 mg/kg). Genetic analysis did not reveal any mutations in the *alanine:glyoxylate aminotransferase* (PH1) and *glycolate reductase/D-glycerate dehydrogenase* (PH2) genes. After 1 month of pyridoxine therapy, the oxalate:creatinine ratio remained elevated at 629 mg/g. A liver biopsy showed normal hepatic alanine:glyoxylate aminotransferase activity : 44 µmol/h/mg protein (normal 19.1–47.9), normal glycolate reductase/D-glycerate dehydrogenase activity 100 nmol/min/mg protein (normal 23–207), and normal alanine:glyoxylate aminotransferase and glycolate reductase/D-glycerate dehydrogenase immunoreactivity staining, thereby excluding primary hyperoxaluria as a possible diagnosis. At 13 months of age, the urine oxalate:creatinine ratio normalized to 146 mg/g; however, the beta2-microglobulinuria (28 396 µg/g Cr) persisted. The initial hypocalciuria (urine calcium/creatinine ratio <0.06) occurred at a time of mild systemic acidosis

(carbon dioxide 19 mmol/L). Surprisingly, hypercalciuria (calcium/creatinine ratio 0.65) developed 1 month later after the acidosis was corrected. Genetic analysis of the *ATP6V1B1* gene showed two different mutations, one of which was novel, thereby confirming the diagnosis of autosomal recessive dRTA with unilateral sensorineural hearing loss.

Discussion

Primary dRTA is caused by a defective vacuolar H⁺-ATPase located at the apical surface of the α-intercalated cells in the distal tubule. The *ATP6V1B1* gene encodes the B1 subunit of the H⁺-ATPase. At least 25 different mutations in *ATP6V1B1* have been identified in autosomal recessive dRTA with deafness [8–14]. Our patient is a compound heterozygote with a new mutation that has not previously been described. The novel mutation located in exon 14 is a result of a 2-bp duplication at position 1401 (1401_1402dupGT) resulting in a premature stop codon at position 487 (467fs487X). Ruf *et al.* [14] described a patient with a nearby point mutation at position 1443 (G1443A) resulting in a missense mutation at position 463 (R463H). This new discovery likely highlights the importance of this region of exon 14 in proper H⁺-ATPase functionality. The patient's second mutation was a single base-pair insertion at position 1156 (1156insC), which results in a frameshift mutation, and a premature stop codon at position 441. Karet *et al.* [8] described two patients with single base-pair insertions at position 1152 (1152insC), and Stover *et al.* [10] described three patients with single base pair insertions at position 1158 (1158insC), all resulting in frameshift mutations and an identical premature stop codon at position 441 (fsX441). Although it is very unlikely, given the clinical picture, it remains possible that both mutations occurred on the same allele and are therefore not the cause of our patient's phenotype. Unfortunately, due to financial restrictions, we were unable to test the parents.

The differential diagnosis for infantile nephrocalcinosis includes prematurity, furosemide use, hypercalcaemia, hypervitaminosis D, Bartter syndrome, familial hypomagnesaemia with hypercalciuria and nephrocalcinosis (FHHNC), dRTA, primary hyperoxaluria, and Dent disease [4,15]. Most of these conditions were quickly excluded in our patient as he was not premature, had not been exposed to furosemide, had no alkalosis, and had normal serum calcium and magnesium levels. dRTA, primary hyperoxaluria and Dent disease remained as possible diagnoses. The features consistent with dRTA included acidosis, hypokalaemia and sensorineural hearing loss, but the unilateral hearing loss, hypocalciuria and the mild degree of acidosis made the diagnosis doubtful. Although the severity of hearing loss associated with *ATP6V1B1* mutations can be asymmetrical, this is the first reported case to our knowledge with unilateral involvement [16]. Whether the hearing loss might eventually develop bilaterally remains to be seen. Evidence for primary hyperoxaluria included significantly elevated urine oxalate/creatinine ratios, elevated urine glycolate levels and the absence of hypercalciuria. Dent disease also remained a possibility given the low-molecular-weight proteinuria and mild acidosis.

There are several reports of atypical presentations of dRTA in children with generalized aminoaciduria [2,17], low-molecular-weight proteinuria [2,17,18], hypophosphataemia with hyperphosphaturia [2,17], hypouricaemia and hyperuricosuria [2,17], and hyperoxaluria [1,2]. The mechanisms by which patients with dRTA develop proximal tubular dysfunction and hyperoxaluria are unclear. Interestingly, the B1 subunit encoded by the mutated *ATP6V1B1* gene seen in our patient is not expressed in proximal tubular cells [19]. Igarashi *et al.* [18] described four patients with dRTA and low-molecular-weight proteinuria. They hypothesized that the chronic hypokalaemia results in tubular insults and accounts for the dysfunction. This seems unlikely given the young age and relatively mild degree of hypokalaemia in our patient. Conversely, primary hyperoxaluria has been infrequently associated with dRTA [20,21]; however, the majority of cases were from the pre-genomic era and may have been cases of atypical dRTA with secondary hyperoxaluria. Low-molecular-weight proteinuria can also be a feature of primary hyperoxaluria after renal damage has occurred, although this is not typically a primary finding [22]. Rare reports of Dent disease associated with hyperoxaluria have been described in which the patients were initially misdiagnosed as having primary hyperoxaluria [22]. We speculate that the hyperoxaluria seen in some patients with dRTA and Dent disease might contribute to the focal glomerulosclerosis and end-stage renal failure seen in older patients with these conditions [5,23].

The limits of our current diagnostic and screening capabilities contribute to the difficulty in screening for these conditions. The inability of most centres to perform acid load tests renders the confirmation of mild or incomplete RTA very difficult. Clearly, it is impractical to evaluate all of these cases genetically, and therefore, cases are undoubtedly being missed. Furthermore, although children with primary hyperoxaluria type I characteristically demonstrate normal-to-low urine calcium excretion [3] and those with Dent disease and dRTA typically have elevated calcium excretions, the hypercalciuria in both Dent disease and dRTA has been shown to be inconstant findings [5,13]. In addition, although measurement of oxalate in a timed 24-h urine collection is strongly preferred for the diagnosis of PH [3], it is impractical in very young patients, and random spot urine collections with an oxalate/creatinine ratio can be used to estimate oxalate excretion [3]. Since random urine oxalate/creatinine ratios are subject to variability, it is recommended to repeat the urine oxalate/creatinine ratio several times as well as measuring urine glycolate and L-glycerate prior to confirming the diagnosis [3]. However, as demonstrated with our patient, these tests may be unable to reliably differentiate primary hyperoxaluria from secondary causes of hyperoxaluria such as prematurity, high oxalate diets, gastrointestinal diseases and dRTA [24]. Interestingly, our patient was placed on soy-based formula for vomiting and failure to thrive prior to diagnosis. It is possible that the intermittent emesis, which occurred prior to initiating alkali therapy, contributed to the uncharacteristic mild acidosis at presentation. We speculate that the urine oxalate excretion normalized at 13 months as a result of

transitioning from infant soy formula to whole milk and table foods.

In this report, we describe a novel mutation in the *ATP6V1B1* gene resulting in autosomal recessive dRTA with unilateral sensorineural hearing loss. In addition, we highlight the important overlapping features of and diagnostic dilemmas involved in making a diagnosis of dRTA, primary hyperoxaluria and Dent disease in patients with infantile nephrocalcinosis. Specifically, we draw attention to the relatively under-appreciated occurrence of hyperoxaluria and low-molecular-weight proteinuria in these patients. We also recommend caution with regard to consumption of high oxalate formulas and foods in patients with RTA. Finally, we recommend that the phenotype of patients with autosomal recessive dRTA with sensorineural hearing loss should be broadened to include hyperoxaluria and increased urinary excretion of beta2-microglobulin.

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Conflict of interest statement. None declared.

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