CASE REPORT

Distal Renal Tubular Acidosis Associated with Celiac Disease and Thyroiditis

AMIT KUMAR SATAPATHY, SAPNA MITTAL AND VANDANA JAIN
From Department of Pediatrics, All India Institute of Medical Sciences, New Delhi, India.

Correspondence to: Dr Vandana Jain, Additional Professor, Division of Pediatric Endocrinology, Department of Pediatrics, AIIMS, New Delhi 110 029, India. drvandanajain@gmail.com
Received: December 21, 2015; Initial review: March 07, 2016; Accepted: July 13, 2016.

Background: Association of distal renal tubular acidosis (RTA) with autoimmune diseases is extremely rare in children.**Case Characteristics:** 12-year-old girl with distal RTA. Despite resolution of acidosis on bicarbonate, she continued to have poor growth and delayed puberty. Investigations revealed autoimmune thyroiditis and celiac disease. **Outcome:** Levothyroxine and gluten-free diet were initiated. Child gained height and weight and had onset of puberty after gluten withdrawal. **Messages:** Distal RTA in children may rarely be of autoimmune etiology.

Keywords: *Autoimmune diseases, Hypothyroidism, Metabolic acidosis, Refractory rickets.*

Distal renal tubular acidosis (RTA) is an important cause of refractory rickets and failure to thrive in children. Rarely, distal RTA may be of autoimmune etiology, as suggested by its association with other autoimmune conditions such as Sjogren syndrome, systemic lupus erythematosus (SLE) and Hashimoto's thyroiditis. Herein we present a girl with distal RTA with celiac disease and thyroiditis.

CASE REPORT

A 12-year-old girl with vitamin-D resistant rickets was referred to us. Her height and BMI were 121.5 cm and 13.4 kg/m^2 (both below the 3rd centile). The child had been born to a non-consanguineous couple, with no significant past or family history. Investigations revealed high serum 25OHD, normal anion gap metabolic acidosis, hypokalemia and alkaline urine (***Table* I**), suggesting a possibility of renal tubular acidosis. Further tests revealed bilateral nephrocalcinosis and hypercalcuria. Phosphaturia and generalized aminoaciduria were absent. Urinary-Blood CO_2 after bicarbonate loading test also favoured the diagnosis of distal RTA. Child was started on oral bicarbonate at the dose of 2 meq/kg/day along with potassium supplementation and hydrochlorthiazide.

On follow-up, rachitic changes resolved and blood gas and serum potassium normalized, but growth continued to be poor, with delayed bone age and delayed puberty. Thyroxine supplementation was initiated in view of persistent mild elevation of TSH, borderline low T4 and positive anti-thyroperoxidase (anti-TPO) antibodies (49.8 IU/mL, normal <30IU/mL), but no improvement in growth was noted.

Child was also observed to have pallor on subsequent visits. Peripheral smear showed microcytic hypochromic anemia. Anti-endomysial antibodies were strongly positive. Duodenal biopsy revealed changes compatible with Marsh 3 criteria for celiac disease. Child was started on gluten-free diet at 13.5 years of age, after which she

TABLE I LABORATORY PARAMETERS AT INITIAL PRESENTATION AND AFTER 24 MONTHS

	Initial presentation	*Follow up (24 months)*
Hemoglobin (g/dL)	8.9	10.4
Calcium (mg/dL)	8.2	9.3
Phosphate (mg/dL)	2.3	5.3
SAP (IU/L)	1489	1052
Creatinine (mg/dL)	0.5	0.4
pH	7.31	7.34
HCO_3 (mEq/L)	14.8	19.3
K^+ (mEq/L)	3.2	3.8
$FePO_4$ (%)	24	18
TMP GFR	2.6	2.6
Ur calcium (mg/kg/d)	6	13
Ur calcium/creatinine ratio	0.4	0.7
Ur pH	6.3	6.9
T4 (ng/ml)	5.9	7.5
TSH (mIU/L)	7.8	0.87

$FePO_4$: Fractional excretion of phosphate; *Ur; Urinary; SAP*: *Serum alkaline phosphatase.*

showed dramatic improvement in height velocity. Presently, at 16 years of age, child is on gluten-free diet along with soda bicarbonate, potassium and thyroxine supplements. She has no bony deformities, her height is 150 cm, BMI is 16 kg/m^2 and she has attained menarche.

We considered the possibility that celiac disease itself may have led to rickets and hypokalemia due to malabsorption. However, lack of response to injectable vitamin D, persistence of rickets despite high serum 25OHD levels, and presence of metabolic acidosis and nephrocalcinosis went against this hypothesis. A trial of reduction in dose of alkali supplement resulted in reappearance of metabolic acidosis. Hence, our final diagnosis is distal RTA (of possible autoimmune etiology), with celiac disease and hypothyroidism due to Hashimoto's thyroiditis. Anti-nuclear antibody (ANA) was negative for the child. Child is under regular follow up and we are vigilant for the appearance of other associated autoimmune manifestations.

DISCUSSION

Distal RTA is a rare condition and no estimate of its prevalence in Indian population is available. Inherited form of distal RTA is most commonly due to autosomal recessive mutations in genes encoding subunits of the vacuolar H^+ATPase, resulting in impaired transporter function in the renal tubule [2].

Acquired impaired transporter function of the H^+ secreting machinery is more common in adults, and is often associated with autoimmune conditions like Sjögren syndrome [3]. Other autoimmune diseases such as SLE [4], primary biliary cirrhosis [5], autoimmune hepatitis [6], thyroiditis and pernicious anemia [7] are also uncommonly associated with distal RTA. The exact target of autoimmunity in the pathogenesis of distal RTA is not clear. In patients with primary Sjögren syndrome, inhibitory autoantibodies against the enzyme carbonic anhydrase II have been reported [3], and in patients with distal RTA and pernicious anemia, antibodies against intercalated cells with possible cross-reactivity against structures containing the gastric H1/K1-ATPase pump have been reported [7].

Our patient had an association of celiac disease with autoimmune thyroiditis and distal RTA. Patients with celiac disease commonly have other autoimmune conditions as well. This is probably secondary to a generalized abnormal immunological response to gluten-derived protein, leading to production of several auto-antibodies. Type 1 diabetes and autoimmune thyroiditis are the most commonly associated autoimmune conditions with celiac disease. Other associated conditions include Graves disease, IgA nephropathy, autoimmune hepatitis, primary sclerosing cholangitis and gluten ataxia [8]. HLA DQ2 and HLA DQ8 are strongly associated with celiac disease and screening of HLA subtype can be used to predict the future occurrence of celiac disease in patients with type 1 diabetes or thyroiditis [8].The association of celiac disease with Sjogren syndrome and distal RTA in an adult has been reported previously [9], but the association of celiac disease with distal RTA without Sjogren syndrome in children has not been previously reported.

To conclude, we wish to emphasize that distal RTA, although usually a primary inherited condition in children, can be secondary to autoimmunity, and be associated with other autoimmune diseases.

Contributors: VJ, AS: managed the case; AS, SM, VJ: prepared the manuscript; VJ: critical revisions, and will act as guarantor.
Funding: None; *Competing interest*: None stated.

REFERENCES

1. Krieger NS, Frick KK, Bushinsky DA. Mechanism of acid-induced bone resorption. Curr Opin Nephrol Hypertens. 2004;13:423-36.
2. Karet FE. Inherited distal renal tubular acidosis. J Am Soc Nephrol. 2002;13: 2178-84.
3. Takemoto F, Hoshino J, Sawa N, Tamura Y, Tagami T, Yokota M, *et al*. Autoantibodies against carbonic anhydrase II are increased in renal tubular acidosis associated with Sjogren syndrome. Am J Med. 2005;118:181-4.
4. Li SL, Liou LB, Fang JT, Tsai WP. Symptomatic renal tubular acidosis (RTA) in patients with systemic lupus erythematosus: an analysis of six cases with new association of type 4 RTA. Rheumatology (Oxford). 2005;44:1176-80.
5. Komatsuda A, Wakui H, Ohtani H, Masai R, Okuyama S, Nimura T, *et al*. Tubulointerstitial nephritis and renal tubular acidosis of different types are rare but important complications of primary biliary cirrhosis. Nephrol Dial Transplant. 2010;25:3575-79.
6. Golding Pl, Mason AS. Renal tubular acidosis and autoimmune liver disease. Gut. 1971;12:153-7.
7. Gaarder PI, Heier HE. A human autoantibody to renal collecting duct cells associated with thyroid and gastric autoimmunity and possibly renal tubular acidosis. Clin Exp Immunol. 1983;51:29-37.
8. Lundin KE, Wijmenga C. Coeliac disease and autoimmune disease-genetic overlap and screening Nat. Rev Gastroenterol Hepatol. 2015;12:507-15.
9. Fracchia M, Galatola G, Corradi F, Dall'Omo AM, Rovera L, Pera A, *et al*. Coeliac disease associated with Sjögren's syndrome, renal tubular acidosis, primary biliary cirrhosis and autoimmune hyperthyroidism. Dig Liver Dis. 2004;36:489-91.