

Celiac disease in children with urolithiasis

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SUMMARY: Menekşe E, Selimoğlu MA, Temel İ, Tabel Y, Gürgöze M. Celiac disease in children with urolithiasis. *Turk J Pediatr* 2012; 54: 382-386.

There are a few studies suggesting a relationship between celiac disease (CD) and kidney disease, but no study has investigated CD in patients with urolithiasis. In this study, we aimed to determine the prevalence of CD in infants and children with urolithiasis.

One hundred and eighty-seven infants and children (4 months-17 years) with urolithiasis, and 278 age- and sex-matched healthy children were included. CD was screened using tissue transglutaminase (tTG) immunoglobulin (Ig)A. Seropositive cases, whose parents gave consent, underwent upper gastrointestinal system endoscopy for duodenal biopsy.

Seven (3.7%) among those with urolithiasis and one (0.3%) among controls were positive for tTG IgA ($p=0.008$). Six of the urolithiasis group and one from the control group underwent upper gastrointestinal endoscopy. Intestinal biopsy revealed Marsh-Oberhuber type 1 intestinal lesions in two children. The other five had normal histology. Biopsy-proven CD was detected in two (1%) children with urolithiasis. The prevalence of biopsy-proven CD among all cases was 0.4%. When children were evaluated with respect to age factor, it was found that seropositivity in children younger and older than two years was not different (4% vs. 3.6%; $p=0.880$).

In this first study investigating CD prevalence in children with urolithiasis, we found a higher seropositivity for CD in children with urolithiasis compared to controls, but in terms of biopsy-proven CD, no difference was found.

Key words: celiac disease, children, urolithiasis.

Celiac disease (CD) is an autoimmune-like systemic disorder in genetically susceptible individuals perpetuated by gluten ingestion with manifestations in the intestine and in organs outside the gut¹. It is the most common cause of malabsorption, affecting children and adults for life. In classical-type CD, steatorrhea, abdominal distension and growth retardation occur. In recent years, the number of children with atypical CD has increased relative to typical ones, probably due to increased awareness of the atypical symptoms of the disease. Atypical involvement includes dermatological, hematological, endocrinological, neurological, and skeletal system findings¹.

There are a few studies suggesting a relationship between CD and kidney disease, most of which involve patients with immunoglobulin (Ig)A

nephropathy²⁻⁴. In two comprehensive studies on the relationship between CD and renal disease, it was reported that CD increased the risk of all types of kidney diseases, including renal stones^{5,6}. Although studies on the relationship between urolithiasis and CD have been gradually accumulated, most of them are still case reports or are adult studies⁷. To the best of our knowledge, there is no study investigating the relationship between urolithiasis and CD in children: CD prevalence in those with urolithiasis and vice versa. In this study, we aimed to determine the prevalence of CD in infants and children with urolithiasis.

Material and Methods

One hundred and eighty-seven infants and children with urolithiasis (aged 4 months

to 17 years) who were on gluten-containing diet for at least two months were included in the study. Two hundred and seventy-eight age- and sex-matched healthy children were included as controls. Symptoms and signs of the disease, nutritional, medical and family histories, anthropometric measurements, and the composition of the renal stones, if known, were recorded.

Blood samples of children were centrifuged at 3000 rpm for 15 minutes and stored at -20°C until test procedure. Tissue transglutaminase (tTG) IgA was tested by Brio brand, Seac Radim Company model 50041 device using micro-ELISA method (ImmuliSA anti-human tissue transglutaminase antibody IgA). Serum IgA level was studied in all cases using Dade Behring IgA test kit in order to exclude selective IgA deficiency.

Seropositive cases, whose parents gave permission, underwent upper gastrointestinal system endoscopy for duodenal biopsy. Marsh-Oberhuber classification was used for histological assessment.

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) for Windows version 16.0. Mann-Whitney U test, Yates-corrected chi-square test, Fisher's exact chi-square test, and Pearson's chi-square test were used.

The ethical committee of the medical faculty approved the study.

Results

Of children with urolithiasis, 80 were girls (42.8%) and 107 were boys (57.2%). The mean age of the patients was 4.90 ± 4.38 years, and 75 (40.1%) were under two years of age. Urinary system symptoms and symptoms that may suggest CD were investigated, and the following were recorded: altered urine color (49.2%), lateral pain (46%), nausea and vomiting (44.4%), dysuria (42.8%), anorexia (40.6%), paleness (34.2%), recurrent abdominal pain (27.3%), constipation (21.9%), growth retardation (17.6%), weight loss (17.6%), dental caries (13.9%), abdominal distension (12.8%), diarrhea (11.2%), seizures (8.6%), skin rash (5.3%), hair loss (3.7%), and paresthesia (1.1%).

Nutritional history revealed that mean duration of exclusive breastfeeding and mean introduction time of gluten-containing foods in patients were 4.47 ± 1.79 months (0-9 months) and 6.53 ± 1.99 months (2-12 months), respectively. Family history of the patients revealed consanguinity in 58 (31%), urolithiasis in 112 (59.9%), intermittent diarrhea in 15 (8%), constipation in 31 (16.6%), recurrent abdominal pain in 19 (10.2%), abdominal distension in 15 (8%), osteoporosis at a young age in 6 (3.2%), and presence of a close relative with CD in 1 (0.5%).

In 40 (21%) children, the composition of the stone could be determined. Of those, 29 (72%), 5 (12%), 4 (10%), and 2 (5%) had calcium oxalate, uric acid, cystine, and infection stones, respectively.

Among children with urolithiasis, 7 (3.7%) were positive for tTG IgA, and among controls, 1 (0.3%) was positive for tTG IgA ($p=0.008$). Of children who were found positive for tTG IgA, 87.5% were from the patient group and 12.5% were from the control group.

Serum IgA level was normal in all cases from the control group, but one case from the patient group had a low IgA level according to age (0.3% for patients, 0.021% for all cases). In the patient with IgA deficiency, tTG IgG and antigliadin antibody IgG were studied, and both were found negative.

Six seropositive children from the patient group and one from the control group underwent endoscopic duodenal biopsy, two of which revealed Marsh-Oberhuber type 1 intestinal lesions suggesting CD. The other five had normal small bowel histology. Biopsy-proven CD was detected in 2 (1%) children with urolithiasis. The prevalence of biopsy-proven CD among all cases was 0.4%.

When children were evaluated with respect to age factor, it was found that seropositivity between children younger and older than two years was not different (4% vs. 3.6%; $p=0.880$). However, both of the children with biopsy-proven CD were older than two years (8 and 9 years).

Seropositive and seronegative children with urolithiasis were compared with respect to the symptoms and nutritional, medical, and family history features. The same comparison was made between children with and without

biopsy-proven CD. While no difference was detected with respect to the seropositivity, recurrent abdominal pain ($p=0.020$) and dental caries ($p=0.012$) were more common in the biopsy-proven CD group. Mean duration of exclusive breastfeeding and the introduction of gluten-containing foods were not different when evaluated with respect to seropositivity or presence of histological damage ($p>0.05$).

Anthropometric measurements including weight for height, body mass index, weight and height z scores, and triceps and subscapular skinfold thickness were not different in seronegative and seropositive children ($p>0.05$).

Routine hematological and biochemical test results were also not different between those groups ($p>0.05$). In both seropositive and biopsy-proven patients, while the most common type of stone was calcium oxalate (3 patients), 1 was uric acid stone and 3 were undetermined.

Discussion

Celiac disease (CD) was first reported to be associated with urolithiasis in the 1970s. Ogilvie et al.⁸ investigated urinary outputs of oxalate, calcium and magnesium in children with intestinal disorders such as small bowel syndrome, CD and pancreatic dysfunction, and found that 58% and 67% of patients with intestinal disorders and CD, respectively, had hyperoxaluria. It was also stated in that report that in two patients, treatment of the underlying condition was accompanied by a return of oxalate excretion to normal⁸. That report is important in terms of its emphasis on the risk of renal stone development in children with intestinal disorders including CD.

A considerable amount of bile salts and fatty acids are absorbed from the jejunum and ileum. Problems in this region cause bile salts and fatty acids to pass through the colon, where they bind calcium and are excreted in that way. Meanwhile, oxalate is released and absorbed highly with the help of the permeability-increasing effect of bile acids. Dehydration secondary to diarrhea along with hyperoxaluria makes calcium oxalate stone formation likely.

Most of the studies and case reports of renal stones secondary to malabsorption are on ileal resection or jejunioileal bypass⁹⁻¹⁴. O'Leary et al.¹¹ detected urolithiasis in 20% of patients

with jejunioileal bypass. Similarly, in the three largest series consisting of patients with jejunioileal bypass, calcium oxalate stones were detected in 9.6%, 12.2%, and 5.5%, respectively¹²⁻¹⁴. In those patients, while levels of urinary calcium excretion were normal, oxalate excretion was 2-10 times higher than normal¹⁵.

Kidney stones have been reported in inflammatory bowel disease (IBD) as well. Gelzayd et al.¹⁶ reported the prevalence of calcium oxalate and uric acid stones as 7.2% in 885 cases with IBD. A five-year follow-up of 230 patients with urolithiasis revealed that 18 of them had a digestive system disease¹⁷. McConnell et al.¹⁸ found that two of 25 patients with Crohn's disease (8%) had urinary stones and 36% had hyperoxaluria.

Another malabsorption known to be associated with urolithiasis is cystic fibrosis. In a series of 140 patients with cystic fibrosis, renal stone was detected in eight, seven of which were calcium-oxalate stones¹⁹.

The relationship between CD and urolithiasis has been a subject receiving much less attention. In a very recent study, a 27% increased risk of urinary stone disease in CD was reported⁶. It was also shown that patients with CD were at a slightly increased risk of prior urinary stone disease⁶. Smith et al.⁹ found hyperoxaluria in six of 15 patients with CD and liver cirrhosis. Stauffer et al.²⁰ reported hyperoxaluria in two patients with CD, and when the amount of calcium in their diets was reduced, it was shown that urinary oxalate excretion was increased. McDonald et al.²¹ demonstrated that hyperoxaluria had a tendency to decrease under gluten-free diet (GFD). One case presented with renal colic but without gastrointestinal findings and was diagnosed as CD with serological and histological tests showing normalization of urinary oxalate excretion after three months under GFD⁷. That case underlines both exclusive urinary presentation of CD and the effect of GFD on the relief of hyperoxaluria⁷. In our patients who were both seropositive and biopsy-proven, the most common type of stone was calcium oxalate.

In our series, seropositivity in children with urolithiasis and controls was 3.7% and 0.3%, respectively. Biopsy-proven CD prevalence

was 1% among patients with urolithiasis. The seropositivity rate of the control group was similar to rates reported in our country before^{22,24}. Seropositivity despite normal intestinal mucosa may be interpreted as potential CD that needs follow-up for the possible development of intestinal lesions in the future. Alternatively, it may be speculated that autoantibodies may accompany urolithiasis. Relevant to that hypothesis, a study reported anti-SS-A antibodies in 10 patients with urolithiasis who were followed for five to 53 years²⁴. In another study, antinuclear antibody (ANA) was investigated in 197 patients with hypocitraturia and found positive in 18% and 1.5% of women and men, respectively²⁵. In the same study, 16% of women also had anti-SS-antibody positivity²⁵. Other than those two studies, there is no other study on the relationship between autoantibodies and urolithiasis. Interpreting seropositivity as potential CD leads to a suggestion that CD is more common in children with urolithiasis, which necessitates stronger proofs for a clear determination.

In conclusion, in this first study investigating CD prevalence in children with urolithiasis, we found a higher seropositivity for CD in children with urolithiasis compared to controls, but in terms of biopsy-proven CD, no difference was found. Since most of seropositive children had normal intestinal histology, a recommendation for screening children with urolithiasis for CD is not reasonable at present. Follow-up of those seropositive children may provide conclusive proof for the relationship between urolithiasis and CD.

Acknowledgement

This study was funded by İnönü University Scientific Research Projects Unit (No: 2009/29).

REFERENCES

- Maki M. Immune enteropathies. Celiac disease. In: Kleinman RE, Sanderson IR, Goulet O, Sherman PM, Mieli-Vergani G, Shneider BL (eds). *Walker's Pediatric Gastrointestinal Disease*. Hamilton: BC Decker Inc.; 2008: 319-327.
- Helin H, Mustonen J, Reunala T, Pasternack A. IgA nephropathy associated with celiac disease and dermatitis herpetiformis. *Arch Pathol Lab Med* 1983; 107: 324-327.
- Fornasieri A, Sinico RA, Maldifassi P, Bernasconi P, Vegni M, D'Amico G. IgA- antigliadin antibodies in IgA mesangial nephropathy. *Br Med J* 1987; 295: 78-80.
- Woodrow G, Innes A, Boyd SM, Burden RP. A case of IgA nephropathy with celiac disease responding to a gluten-free diet. *Nephrol Dial Transplant* 1993; 8: 1382-1383.
- Ludvigsson JF, Montgomery SM, Olen O, Ekblom A, Ludvigsson J, Fored M. Coeliac disease and risk of renal disease—a general population cohort study. *Nephrol Dial Transplant* 2006; 21: 1809-1815.
- Ludvigsson JF, Zingone F, Fored M, Ciacci C, Cirillo M. Moderately increased risk of urinary stone disease in patients with biopsy-verified coeliac disease. *Aliment Pharmacol Ther* 2012; 35: 477-484.
- Gama R, Schweitzer FA. Renal calculus: a unique presentation of coeliac disease. *BJU Int* 1999; 84: 528-529.
- Ogilvie D, McCollum JP, Packer S, et al. Urinary outputs of oxalate, calcium and magnesium in children with intestinal disorders. Potential cause of renal calculi. *Arch Dis Child* 1976; 51: 790-795.
- Smith LH, Fromm H, Hofmann AF. Acquired hyperoxaluria, nephrolithiasis and intestinal disease. *New Engl J Med* 1972; 286: 1371-1375.
- Dowling RH, Rose GA, Sutor DJ. Hyperoxaluria and renal calculi in ileal disease. *Lancet* 1971; 1: 1103-1106.
- O'Leary JP, Thomas WC Jr, Woodward ER. Urinary tract stone after small bowel bypass for morbid obesity. *Am J Surg* 1974; 127: 142-147.
- Fikri E, Cassella R. Jejunioleal bypass for massive obesity: results and complications in fifty-two patients. *Ann Surg* 1974; 179: 460-464.
- Danowski TS, Clare DW, Nolan S, et al. Prospective study of jejunioleal bypass in obesity. I. Clinical manifestations in first 5-7 months. *Obesity/Bariatric Med* 1975; 4: 108.
- Gregory JG, Starkloff EB, Miyai K, Schoenberg HW. Urologic complications of ileal bypass operation for morbid obesity. *J Urol* 1975; 113: 521-524.
- Dickstein SS, Frame B. Urinary tract calculi after intestinal shunt operation for the treatment of obesity. *Surg Gynecol Obstet* 1973; 136: 257.
- Gelzayd EA, Breuer RI, Kirsner JB. Nephrolithiasis in inflammatory bowel disease. *Am J Digest Dis* 1968; 13: 1027-1034.
- Coe FL, Kavalach AG. Hypercalcaemia and hyperuricosuria in patients with calcium nephrolithiasis. *New Engl J Med* 1974; 291: 1344-1350.
- McConnell N, Campbell S, Gillanders I, Rolton H, Danesh B. Risk factors for developing renal stones in inflammatory bowel disease. *BJU Int* 2002; 89: 835-841.
- Chidekel AS, Dolan TF Jr. Cystic fibrosis and calcium oxalate nephrolithiasis. *Yale J Biol Med* 1996; 69: 317-321.
- Stauffer JQ, Stewart RJ, Bertrand G. Acquired hyperoxaluria: relationship to dietary calcium content and severity of steatorrhea. *Gastroenterology* 1974; 66: 783.
- McDonald GB, Earnest DL, Admirand WH. Hyperoxaluria correlates with steatorrhea in patients

- with sprue. Gut 1977; 18: 561-566.
22. Ertekin V, Selimoğlu MA, Kardaş F, Aktaş E. Prevalence of celiac disease in Turkish children. J Clin Gastroenterol 2005; 39: 689-691.
 23. Dalgic B, Sari S, Basturk B, et al.; Turkish Celiac Study Group. Prevalence of celiac disease in healthy Turkish school children. Am J Gastroenterol 2011; 106: 1512-1517.
 24. Eriksson P, Denneberg T, Eneström S, Johansson B, Lindström F, Skogh T. Urolithiasis and distal renal tubular acidosis preceding primary Sjögren's syndrome: a retrospective study 5-53 years after the presentation of urolithiasis. J Intern Med 1996; 239: 483-488.
 25. Eriksson P, Denneberg T, Lundström I, Skogh T, Tiselius HG. Autoantibodies and primary Sjögren's syndrome in a hypocitraturic stone population. Scand J Urol Nephrol 1997; 31: 73-80.