A case of atelosteogenesis type III with bladder stone and proteinuria

Maiko Okada¹, Hiroko Sasaki¹, Atsuko Koge¹, Shoko Ohashi¹, Yoshinori Fujinaka¹, Ken Masunaga¹, Itsuro Takigawa¹, Akinori Hashiguchi², Midori Awazu³

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Abstract
Atelosteogenesis is a chondrodysplasia characterized by severe short-limbed dwarfism with multi-joint dislocation and specific facial features caused by mutations in the gene encoding filamin B. We report a case of atelosteogenesis type III with a large bladder stone and proteinuria. He had hematuria at age 3 years, which was found to be due to kidney stones and hypercalciuria. Hypercalciuria was thought to be due to excessive intake of protein and sodium in addition to immobilization from the original disease. Kidney stones formed, moved to the bladder after the patient became able to sit up. The bladder stone became enlarged due to urinary tract infection. Proteinuria was also detected, which gradually worsened with a glomerular pattern. Surgical removal of the bladder stone and the kidney biopsy were performed concomitantly. The stone consisted of calcium phosphate and magnesium ammonium phosphate. The kidney biopsy showed minor abnormalities. Postural proteinuria was considered to be the cause since he kept sitting position during the day. As he started to move by shuffling, proteinuria decreased. Bladder stone and proteinuria should be born in mind when seeing patients assuming a long-term sitting position.

Introduction
Atelosteogenesis is a disease caused by mutations of FLNB gene encoding filamin B characterized by severe short-limbed dwarfism. FLNB-related disorders include atelosteogenesis type I, Larsen syndrome, spondyloepimetaphyseal dysplasia, and atelosteogenesis type III. We report a case of atelosteogenesis type III who had bladder stone and proteinuria. While there have been no reports of kidney disease in these disorders⁴, filamin is an actin cross-linking protein, which functions as a scaffold for intracellular signaling pathway and protein transporting pathway⁵. Since filamin is ubiquitously expressed⁶, we speculated that proteinuria could be related to atelosteogenesis type III. No renal pathology was detected, however, which led to the diagnosis of postural proteinuria. The bladder stone may also be related to the sitting position of the patient.

Case Report
The patient boy is the first child of a 33-year-old mother. There is no family history of skeletal- or kidney disorders. The patient was born at 38 weeks’ gestation with a birth weight of 2612 g (–0.7 SD) and a length 37.0 cm (–4.7 SD). He had an extreme shortening of limbs, clubfoot, mild scoliosis, characteristic face, and cleft palate. He required ventilation management for severe tracheomalacia and glossoptosis, and tracheotomy was performed on day 118. Phenobarbital was used for sedation for approximately one month before and after tracheotomy. Genetic testing was performed and the diagnosis of atelosteogenesis type III was made. There was a

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650th cytosine to thymine base substitution in exon of FLNB gene which resulted in an amino acid changes from 217th proline to leucine. He was discharged home on day 216 with a ventilator and on tube feeding. He was on oral iron therapy for seven months and on erythromycin for chronic lung disease. Diuretics or vitamin D supplements had not been administered. The patient was receiving regular formula. He started solid food at 9 months, and tube feeding and formula feeding were stopped at 1 year and 4 months and formula at 2 years, respectively. He began to use a seating support system since 2 years and was mostly in the sitting position during the day since age 3 years and 5 months. There had been no history of urinary tract infection up to that time. At 3 years and 6 months, he developed macroscopic hematuria. On physical examination, his height was 81 cm (±4.3 SD), weight was 10.28 kg (±2.5 SD). Blood pressure was 102/78 mmHg. Physical examination was unremarkable except for the known deformities. Laboratory data showed Table 1. Ultrasonography showed two kidney stones, one with the diameter 7 mm in the pelvis of the right kidney and the other with the diameter 7 mm in the pelvis of the left kidney. The renal pelvis and calyces of left kidney was dilated. There was no bladder stones or entrapment of the left renal vein. The cause of hematuria was considered to be urolithiasis. In consultation with a pediatric urologist, we decided to wait for the natural excretion of stones by enhancing water intake. After 2 months, however, a bladder stone of 10 mm was observed whereas the stone in the left kidney was no longer found. The dilation of renal pelvis and calyces of the left kidney disappeared. After confirming the bladder stone administration of trichlormethiazide 0.06 mg/kg/day was started, but hypercalciuria continued with calcium-to-creatinine ratio of 0.13–0.59 g/g. Uric acid-to-creatinine ratio was 1.5 mg/mg (reference range 1–3 yrs.< 1.08 mg/mg), and magnesium-to-creatinine ratio was 0.25 mg/mg (reference range>0.3 mg/mg). We increased trichlormethiazide to 0.1 mg/kg/day. Also, since his salt intake was 4–5 g/day and protein intake 60 g/day because of his unbalanced food preference, we provided nutrition instruction. The urinary protein-to-creatinine ratio ranged from 0.3 to 3.0 g/g and panaminociduria was noted. Urinary immunoglobulin G (IgG)-to-creatinine ratio was 0.2–0.3 mg/g and the protein selectivity index was 0.06. Urine α₁-microglobulin-to-creatinine ratio was 0.05 mg/mg (reference range<0.6 mg/g), β₂-microglobulin-to-creatinine ratio was 0.2–0.6 mg/g (reference range<0.3 mg/g), and N-acetyl-β-glucosaminidase-to-creatinine ratio was 0.07–0.2 U/g (reference range<5.8 U/g). At 4 years and 11 months, the diameter of the bladder stone increased to 19 mm (Fig. 1). Oral administration of sodium citrate was started. The patient began to feel pain at the time of urination at 5 years and 1 month. His urine analysis showed many white blood cells and urine culture was positive for Enterococcus species. He was treated with intravenous ampicillin and cefotaxime for 5 days followed by oral amoxicillin. A post-treatment urine culture was negative. Neither lower urinary tract obstruction nor vesicoureteral reflux disease was observed on voiding cystourethrography at 5 years and 1 month. At age 5 years and 2 months, transurethral bladder lithotripsy was performed concomitantly with a needle.

| Table 1 | Laboratory results at initial |
|---------|-------------------------------|
| WBC     | 11000 /μl                   |
| RBC     | 531×10⁴ /μl                 |
| Hemoglobin | 13.4 g/dl                  |
| Platelet | 36.0×10⁴ /μl                |
| pH      | 7.440                        |
| pCO₂    | 35.8 mmHg                    |
| HCO₃⁻   | 23.8 mEq/L                   |
| Urea nitorogen | 15.9 mg/dl             |
| Serum creatinine | 0.22 mg/dl            |
| Uric acid | 4.4 mg/dl                  |
| Total protein | 7.4 g/dl                |
| Albumin  | 4.4 g/dl                    |
| Serum sodium | 139 mEq/L               |
| Serum pottasium | 3.9 mEq/L             |
| Serum chloride | 106 mEq/L              |
| Serum calcium | 9.9 mg/dl                 |
| Serum phosphate | 4.9 mg/dl              |
| Serum magnesium | 2.1 mg/dl                |
| intact PTH | 12 pg/ml                   |
| 1,25-(OH)³ Vitamin D | 70 pg/ml              |

CBC, complete blood count; WBC, white blood cells; RBC, red blood cells; PTH, parathyroid hormone; HPF, high power field.
biopsy of the kidney. The bladder stone was completely removed but kidney stones remained. The bladder stone consisted of calcium phosphate (44%) and magnesium ammonium phosphate (36%). In the kidney specimen, 21 glomeruli were contained, all showing minor abnormalities (Fig. 2). Tubular atrophy or interstitial lesions were not observed. Glomerular density and size were normal. Immunofluorescence and electron microscopy studies were not performed because glomeruli were absent in the sample. Since no glomerular lesions were found, postural proteinuria was suspected. As he started to move by shuffling, proteinuria decreased. At age 6 years and 9 months, the urinary protein-to-creatinine ratio was 0.27 g/g, and hematuria was absent. Since urine was collected using a bag in the sitting position, it was not possible to evaluate the change in urine protein by postural changes. Ultrasonography showed three stones with the diameter 9 mm, 5 mm, and 4 mm in the pelvis of the right kidney at age 7 years and 2 months. No stones were found in the left kidney or the bladder. In the sitting position, the left renal vein could not be identified due to gastrointestinal gas. Compression of the left renal vein was not demonstrated in a supine position.

**Discussion**

We reported a patient with atelosteogenesis type III who had bladder stone and proteinuria. Atelosteogenesis type III is caused by a mutation in the gene FLNB, and is characterized by severe short-limbed dwarfism with multi-joint dislocation, clubfeet, and specific facial features such as cleft palate. Neither urolithiasis including bladder stone nor kidney disease has been reported in FLNB-related disorders.

Pediatric urolithiasis has underlying disorder in 60 to 80 percent of cases. Urinary stone formation is multifactorial processes depending on environmental conditions, metabolic disorders, nutrition, infection as well as the patient’s anatomical abnormalities. Bladder stones are rare in pediatric urolithiasis. Bladder stones are usually associated with bladder outlet obstruction, anatomical abnormalities, neurogenic bladder, chronic bacteriuria or catheters. In our case, kidney stones were probably due to hypercalciuria as the cause of which immobilization is most likely. High sodium intake probably contributed to hypercalciuria. After becoming able to sit, a bladder stone appeared. Analysis of the stone revealed its composition to be calcium phosphate and magnesium ammonium phosphate. The latter is associated with urinary tract infection. While there was no history of febrile urinary tract infection, there was an episode of urinary tract infection. The alkalization of urine for urolithiasis may have enhanced the formation of struvite.

In our patient, proteinuria was observed intermittently since the appearance of hematuria and became persistent since 4 years and 6 months. Renal parenchymal lesions were suspected since urine protein-to-creatinine ratio increased to 3 g/g and since IgG was detected in the urine. The filamin is an actin cross-linking protein and the actin cytoskeleton plays an important role in the structure and function of podocytes.
We speculated that the filamin mutation had an effect on renal function. No pathology was found, however, and the proteinuria was considered to be postural. Postural proteinuria is a benign condition and the most frequent cause of proteinuria in children, especially in adolescents. Postural proteinuria is mainly of glomerular origin, and has been reported to contain low molecular weight proteins as well as amino acids as seen in our patient. The mechanism of postural proteinuria is proposed to be, at least in part, the left renal vein entrapment following movement from supine to an upright posture. Proteinuria was not observed when he was mainly in a supine position. Since approximately 3 years and 5 months, he spent most of the time sitting. We considered that this change in posture caused proteinuria. Of note, his urine was collected in the sitting position. The left renal vein compression was not demonstrated by repeated ultrasonography. This could be because ultrasonography was performed in a supine position. An upright position is recommended along with Doppler sonography in diagnosing left renal vein entrapment.

Conclusion

In conclusion, we reported a patient with atelosteogenesis type III complicated with a bladder stone and proteinuria. Urolithiasis due to hypercalciuria secondary to immobilization is not uncommon in recumbent patients. The bladder stone developed probably around a stone that passed through the ureter from the kidney after he assumed a sitting position. The urinary tract infection contributed the building of the stone. The proteinuria was thought to be postural due also to the sitting position. Since long-term survivors of atelosteogenesis type III and other similar diseases are increasing, these complications should be watched for.

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Conflict of interest

The authors have declared that no conflict of interest exists.

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