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SHORT REPORT

Nephrotic syndrome occurring during tiopronin treatment for cystinuria

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Abstract Cystinuria is an autosomal recessive disorder characterized with abnormal tubular reabsorption of cystine and dibasic amino acids leading to cystine urolithiasis. The classical form is caused by mutations in the SLC3A1 gene (OMIM 220100). The cornerstone of the treatment is high hydration and alkalization of the urine to achieve urine pH between 7.0 and 7.5, at which point, cystine solubility in the urine is optimal. These measures very often fail, and thus addition of sulfhydryl agents like penicillamine and tiopronin (mercaptopropionyl glycine) is recommended. Herein, we report a 3-year-old boy with cystinuria resulting in recurrent nephrolithiasis requiring surgery and extracorporeal shock wave lithotripsy. Nine months after introduction of tiopronin, the boy manifested generalized edema, oliguria, and biochemical indices of nephrotic syndrome. Tiopronin was withdrawn, and the boy was given only supportive treatment. Within 10 days, he entered into clinical and biochemical remission. Pediatricians should be aware of this adverse effect of tiopronin, and therefore, testing of the urine with strips or sulfosalicylic acid at least once weekly at home may be very helpful for early detection of proteinuria.

Keywords Cystinuria · Nephrolithiasis · Nephrotic syndrome · Proteinuria · Tiopronin

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Introduction

Cystinuria is an autosomal recessive disorder characterized with abnormal reabsorption of cystine and dibasic amino acid namely lysine, ornithine, and arginine in the proximal renal tubules and the intestine. If not diagnosed and treated properly, cystinuria results in recurrent urolithiasis with significant morbidity due to obstruction, infection, and repeated surgical intervention [17]. Often, the stones are treated surgically, as extracorporeal shock wave lithotripsy is not sufficiently efficient in cystinuria patients [4, 8, 16]. The mainstream treatment is high hydration and alkalization of the urine aiming to achieve urine pH between 7.0 and 7.5 (at which point, the cystine solubility in the urine is optimal). These measures often fail, and thus addition of sulfhydryl agents like penicillamine and tiopronin is recommended. These drugs reduce cystine to a more soluble cysteine disulfide. Unfortunately, both drugs have significant side effects, nephrotic syndrome being the most severe. In this report, we describe a boy with cystinuria who developed nephrotic syndrome during treatment with mercaptopropionyl glycine (tiopronin).

Case report

A 3-year-old boy was referred to the Children's Hospital after an episode of macroscopic hematuria. Ultrasound examination revealed bilateral nephrolithiasis. There was hydronephrosis of the right kidney due to obstruction with 17 mm calculus in the pyelon. Intravenous urography confirmed the findings of the ultrasound study. Dynamic study with Tc-99mDTPA generated an obstructive curve over the right kidney without response to furosemide. The boy underwent open surgery, and the calculus in the right

kidney was removed. Metabolic investigation revealed positive nitroprusside reaction 3+. The analysis of the stone with infrared spectroscopy confirmed the cystine content of the stone. Urinary amino acid analysis showed pathologic excretion of cystine and dibasic amino acids (cystine: creatinine ratio was 324 μmol/mmol; normal, <20). The child was prescribed alkali therapy (potassium citrate, 0.1 g/kg/day) and high hydration (2 l/1.73 m^2) in order to achieve specific gravity of the early morning urine sample less than 1,010. At the age of 4 years, ultrasound examination detected several calculi in both kidneys. The child was referred to the University Children's Hospital Heidelberg where combined treatment with extracorporeal shock wave lithotripsy and litholapaxy resulted in complete elimination of all calculi in both kidneys. Besides standard alkali therapy, treatment with tiopronin at the dose of 10 mg/kg was initiated. Nine months after introduction of tiopronin, the child developed generalized edema. The hematology parameters were normal, but urinalysis showed proteinuria 3+ and many red blood cells in the urinary sediment. Serum biochemistry revealed urea 5.0 mmol/l, creatinine 35 μmol/l, uric acid 118 μmol/l, Na 143 mmol/l, K 5.0 mmol/l, Ca 1.9 mmol/l, P 1.7 mmol/l, Mg 0.7 mmol/l, total protein 47 g/l, albumin 20 g/l, AST 28 U/l, ALT 15 U/l, ALKP 143 U/l, GGT 9 U/l, bilirubin 11 μmol/l, cholesterol 9.3 mmol/l, triglycerides 1.1 mmol/l, and CPK 133 U/l. Serological test for antinuclear factor, rheumatoid factor, and HBs antigen was negative. Daily urinary excretion of total protein was 1.43 g (98 mg/kg; nephrotic range, >50 mg/kg). The child was given only symptomatic treatment with low salt diet and furosemide. Sodium bicarbonate was discontinued, and alkali therapy continued with potassium citrate. Within 10 days, complete clinical and biochemical remission ensued, the child decreased his weight from 16.5 to 14.5 kg, his urine was protein free, and serum proteins were normalized. Alkali treatment was continued. During the follow-up, his urinalysis did not show presence of proteinuria neither hematuria. There was no evidence for new calculi.

Discussion

Tiopronin is a drug used to treat cystinuria when the condition leads to stone formation. The drug is preferred to D-penicillamine for its lower prevalence of adverse effects. Both drugs have the same mechanism of action, i.e., they contain a thiol compound that reacts with cystine to form a soluble mixed disulfide. Since this drug was used in the past for treatment of rheumatoid arthritis, most adverse effects, and in particular proteinuria and nephrotic syndrome, were reported in patients with rheumatism [2, 5, 7, 9, 10, 14]. The most common side effects of tiopronin are cutaneous (pruritus, erythema, and pemphigus) and stomatitis observed in 46 out of 140 (32.8%) patients with rheumatoid arthritis treated with tiopronin [14]. Few patients may develop transitory hematological abnormalities like thrombocytopenia and leukopenia. Gastrointestinal disorders and dysgeusia are also reported. It is uncertain if cholestasis and muscle disorders, which were noticed during treatment with tiopronin, are caused by this drug [14]. The most severe adverse effect of tiopronin is nephrotic syndrome.

Ambanelli et al. [2] had followed 50 patients with rheumatoid arthritis who had been treated with tiopronin for 15.4 months. Five patients developed proteinuria, and four of them manifested full-blown nephrotic syndrome. Proteinuria and nephrotic syndrome resolved spontaneously 2–5 weeks after withdrawal of the drug. In the above reported series by Sany et al. [14], proteinuria was observed in five patients and nephrotic syndrome in three patients. Discontinuation of the tiopronin resulted in resolution of proteinuria in all patients [14].

Other reports also describe nephrotic syndrome in cystinuria patients treated with tiopronin [1, 3, 11–13, 15]. Ferraccioli et al. reported the biopsy findings of six patients who developed nephrotic syndrome during treatment with tiopronin [6]. The majority of patients had membranous glomerulonephritis, while one patient had mesangioproliferative glomerulonephritis and one patient glomerulonephritis with segmental deposits in the mesangium. Lecoules et al. observed a 73-year-old patient who developed severe nephrotic syndrome during treatment with tiopronin [9]. The histology revealed minimal glomerular lesions. The patient went into spontaneous complete remission 5 weeks after discontinuation of the drug. Although nephrotic syndrome induced by tiopronin may be very severe, in majority of cases, symptomatic treatment and withdrawal of the drug are sufficient measures.

Our patient presented with moderately severe nephrotic syndrome. Restriction of salt and water and careful use of diuretics and alkalizing agents were sufficient intervention to control edema and to prevent formation of calculi during the oliguric phase. Although furosemide increases the diuresis, its effect on lowering urine pH may favor cystine precipitation. Potassium citrate is preferred over sodium bicarbonate since the later may worsen edema.

In conclusion, we present a pediatric patient with cystinuria and secondary nephrotic syndrome caused by tiopronin therapy. It is likely that tiopronin interferes with the podocytes function, although the mechanism is not known yet. Careful symptomatic treatment and monitoring of the patient is very important until entering spontaneous remission. Testing of the urine with strips or sulfosalicylic acid at least once weekly may be very helpful for early detection of proteinuria in patients receiving tiopronin.

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Conflicts of interest None.

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