

# Two Pediatric Patients with Herbal Medicine-Induced Nephrotic Syndrome

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Nephrotic syndrome (NS) is a common chronic disease in children; in 90 percent of cases, the condition is primary (idiopathic). Toxic nephropathy can be induced by herbal medicines, and is mainly manifested as tubulointerstitial nephritis and rarely, as glomerulopathy. Here in, we describe two cases of steroid-sensitive NS, which developed after the patients received herbal medicines. A 5-year-old boy and an 8-year-old girl were separately admitted within a short time period with acute onset of generalized edema, proteinuria, hypoalbuminemia, and hypercholesterolemia. Each patient had previously taken herbal medicine, which had been prescribed by different oriental medical clinics for different conditions. The patients were diagnosed with herbal medicine-induced NS and were treated empirically by a standard steroid therapy, with subsequent resolution of their NS. One patient relapsed, but her NS again responded to steroid therapy. We described two unusual cases of prototypical pediatric, steroid-sensitive NS, which was presumed to be minimal-change disease that developed after the administration of herbal medicines. We also reviewed the literature.

**Key words:** Nephrotic syndrome, Herbal medicine, Pediatrics.

## Introduction

Nephrotic syndrome (NS) is a common chronic glomerular disease in children. It is characterized by a primary increase in the permselectivity barrier of the glomerular capillary wall, leading to passage of proteins through the defective filtration barrier, and severe proteinuria of more than 40 mg/m<sup>2</sup>/hour, or a spot (random) urinary protein-to-creatinine ratio of more than 2 mg/mg<sup>1-3</sup>). Although nephrotic syndrome is associated with many types of renal disease, the most common form (90%) in children is primary (idiopathic) nephrotic syndrome, which develops in the absence of features of nephritis or of associated primary extrarenal disease<sup>1,2</sup>. Less commonly, childhood nephrotic syndrome can be associated with inflammatory or autoimmune disease; or develop as a result of ischemic insult, infection, drugs, or inherited renal disease<sup>1-3</sup>).

Complementary and alternative medicine (CAM) is commonly used, especially in Asia. Many consumers have the perception that “natural” products are harmless; therefore, they readily depend on CAM. In Korea, traditional

Chinese (Korean) herb(al) medicine is a substantial component of the medical industry, and many Koreans have a positive or over credulous attitude toward traditional Chinese (Korean) herb medicine<sup>4</sup>. Therefore, adverse effects of herb medicines are rarely reported by patients who have taken them.

It is true that the incidence rates of minimal-change nephrotic syndrome are declined, at the same time, CAM is still frequently used. The minimal-change nephrotic syndromes which are caused by immunologic infection and inflammation are decreased. On the other hand, herbal medicine-induced nephrotic syndrome is still observed which has different immunopathogenesis from above. Here, we present two children who manifested unusual signs of steroid-sensitive nephrotic syndrome (SSNS), probably minimal-change disease, after ingestion of herb medicines that were taken for different conditions.

## Case report

### 1. Case 1

A previously healthy 5-year-old boy was admitted to our hospital with a 3-day history of eyelid edema and proteinuria. He had taken herb medications every winter for the past 4 years, and most recently starting 10 days prior to admission. He was prescribed herb medications consisting of ephedra alkaloids, gypsum (hydrated calcium sulfate), *Ziziphus jujuba* var. *inermis*, and licorice (the root of *Glycyrrhiza glabra*) to suppress his appetite so that he would lose weight. The medications were discontinued 4 days prior to admission because he developed a rash. He had no history of prior hospitalization or surgery, nor family history of renal disease.

On admission, he appeared acutely ill; however, his vital signs were unremarkable. His body weight was 28 kg, which was 2 kg heavier than his usual weight. Except for eyelid edema, his physical findings were unremarkable, and no rash was apparent. Blood biochemistry testing revealed a normal serum creatinine level (30.94  $\mu\text{mol/L}$ ), hypoalbuminemia (1.5 g/dL), and hypercholesterolemia (516 mg/dL). Peripheral blood analysis showed thrombocytosis (471,000 / $\mu\text{L}$ ) without eosinophilia; the serum electrolyte levels were unremarkable. Urinalysis showed 4+ albumin

without hematuria or pyuria. The urinary protein-to-creatinine ratio (mg/mg) was significantly elevated at 11.9 mg/mg. Autoantibody and complement screening, antistreptolysin O titer, and hepatitis B surface antigen were all negative. We thought that his clinical (SSNS) and laboratory features were consistent with minimal-change nephrotic syndrome (MCNS) rather than other nephritic syndrome pathologic types, and therefore began empirical oral steroid therapy (deflazacort) at 2.4 mg/kg/day in divided doses without performing a renal biopsy. After 8 days of therapy, the patient's urinary protein-to-creatinine ratio was 0.18 mg/mg. He has been asymptomatic for more than 16 months, without further signs of relapse (Fig. 1A).

### 2. Case 2

A previously healthy 8-year-old girl was admitted to our hospital at about the same time as Case 1, with a 5-day history of periorbital swelling and generalized edema. Two weeks before admission, she took oral medications for a few days for fever, nausea, and vomiting. Because her illness did not improve, she was prescribed herb medications consisting of citrus peel, *Cyperus rotundus* (purple nutsedge), *Inula helenium*, dried trifoliolate orange, gromwell, licorice, and ginger that she took for six days. She had no history of prior hospitalization or surgery. Her grandfather had end-stage renal disease caused by a severe urinary tract infection.

On admission, she appeared acutely ill. However, with the exception of generalized edema, her vital signs (blood pressure 110/70 mmHg, body temperature 36.9°C), physical parameters, and physical findings were unremarkable. Blood biochemistry testing revealed normal serum creatinine (56.58  $\mu\text{mol/L}$ ), low albumin level (2.5 g/dL) and hypercholesterolemia (370 mg/dL). Peripheral blood analysis and serum electrolyte levels were unremarkable. Urinalysis showed 4+ albumin, microscopic hematuria (red blood cells [RBCs] 10-19/high-power field), 94% dysmorphic RBCs, 10% G1 cells, and no pyuria. The urinary protein-to-creatinine ratio was significantly elevated at 7.8 mg/mg (normal <0.2 mg/mg). Autoantibody and complement screening, antistreptolysin O titer, and hepatitis B surface antigen were all negative.

The patient was prescribed oral steroid therapy (deflazacort) at 2.4 mg/kg/day in divided doses. Because she responded

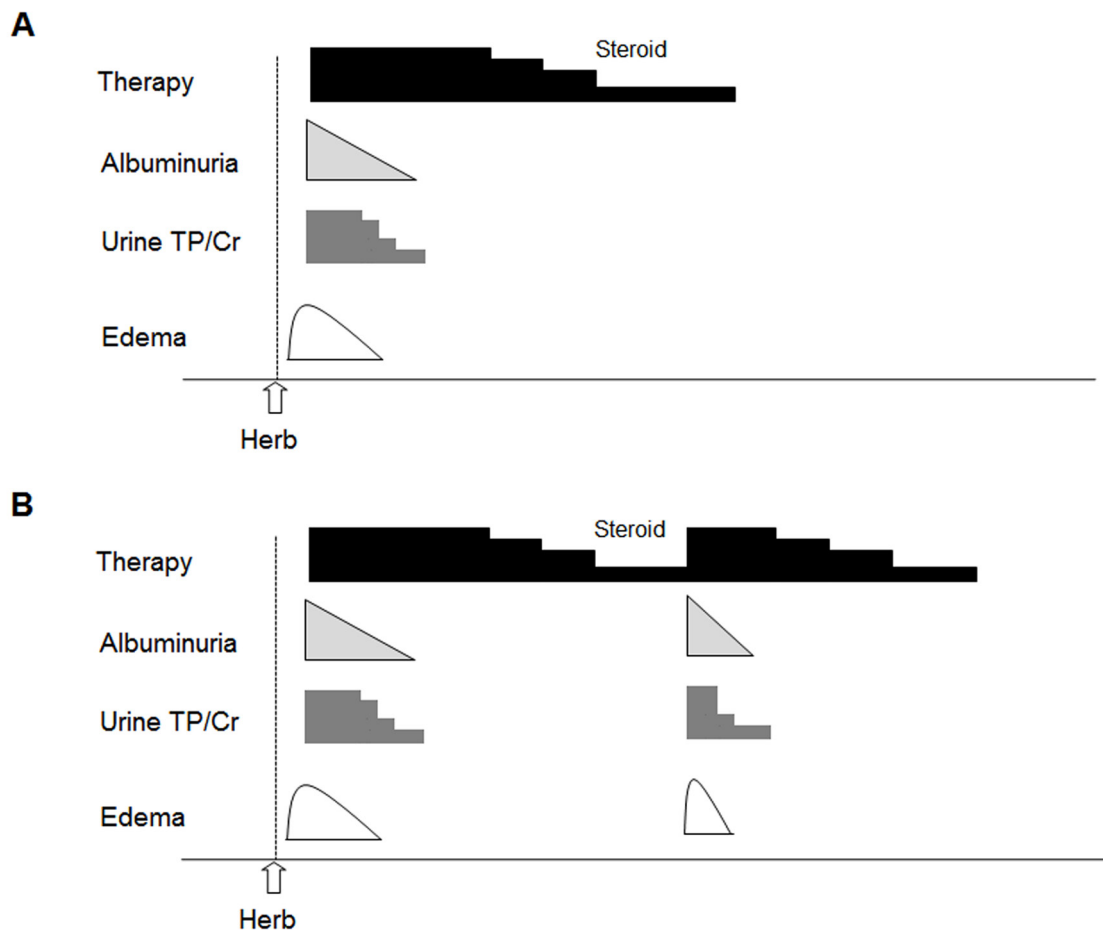


Fig. 1.A and B denote the sequential clinical and laboratory features of Case 1 and Case 2, respectively. TP, total protein;Cr, creatinine.

to steroid therapy and did not appear to have renal impairment, we did not perform a renal biopsy. After 10 days of therapy, her urinary protein-to-creatinine ratio was 0.18 mg/mg. As she underwent steroid tapering (10 mg of deflazacort as a single dose, alternate days), she developed a relapse, with periorbital swelling and albuminuria. We increased the dosage of deflazacort, and two and half weeks later, her periorbital swelling and albuminuria disappeared. She has been well for more than 7 months, without further signs of relapse, including microscopic hematuria (Fig. 1B).

## Discussion

The kidney is very susceptible to xenobiotic and environmental toxins because of its unique anatomical and physiological features. The pathogenesis of drug-induced

nephropathy includes direct cytotoxic damage to kidney structures and indirect damage due to changes in renal hemodynamics (cyclo-oxygenase inhibition), immune-mediated processes, production of endogenous nephrotoxins, and nephrolithiasis<sup>5,6</sup>. The clinical manifestations of drug-induced nephropathy vary, ranging from mild reduction in renal function that includes hematuria, proteinuria (NS), and nephrolithiasis; to severe, progressive signs of renal toxicity, resulting in end-stage renal disease<sup>2,5,6</sup>. However, drug-induced nephropathy usually presents as interstitial nephritis, and acute tubular necrosis usually presents as Chinese herb nephropathy (CHN). Acute interstitial nephritis (AIN) is a hypersensitivity reaction mediated by both humoral and cell-mediated mechanisms<sup>5,6</sup>. Signs and symptoms of the disease occur within hours to months after drug administration. Renal manifestations include acute renal failure, eosinophiluria,

proteinuria, glycosuria, hematuria, and decreased tubular reabsorption of phosphorus<sup>5,6</sup>. Herb medicine rarely induces glomerulopathy, and there have been several reports that drug-induced NS in children is very unusual, compared to common drug-induced AIN in children<sup>7-9</sup>. The patients described in the previous reports needed renal biopsy because of steroid resistance or renal failure. The biopsied renal tissues showed characteristics of both AIN (interstitial edema and cell infiltration with detachment of tubular cells) and MCNS (podocyte foot process effacement). However, we did not performed biopsy before starting medication as usual. Either of our case patients had no features of gross hematuria, hypertension, renal insufficiency or age of less than one year old or more than 12 years old which are the indication of renal biopsy.

CAM use is highly prevalent throughout the world. Several reports around the world have described cases of CHN predominantly associated with tubulointerstitial damage. Most patients showed evidence of tubular dysfunction, which was manifested as low-molecular-weight proteinuria, glycosuria, aseptic leukocyturia, and Fanconi syndrome<sup>10</sup>. Aristolochic acid from *Aristolochia contorta*-associated CHN is the most comprehensively studied alternative medicine<sup>11</sup>; however, none of the known ingredients of the medications taken by our cases contained aristolochic acid. However, ephedra alkaloids and licorice, which were ingredients of the medications taken by our patients, are known to be nephrotoxic dietary supplements. Ephedra is commonly used to treat allergic rhinitis, asthma, hypotension, and weight loss. Ephedra-associated nephrotoxicity can lead to nephrolithiasis, in addition to ephedrine-, norephedrine-, and pseudoephedrine-induced stone formation<sup>12</sup>. Licorice has antibiotic and anti-inflammatory effects, and has been used to treat gastrointestinal disorders. Licorice can cause renal tubular injury, which leads to prolonged hypokalemia; and acute kidney injury, which leads to hypokalemic rhabdomyolysis in the setting of pseudoaldosteronism<sup>13</sup>.

The other herbal components prescribed to our patients have been known to be effective for various clinical conditions. *Cyperus rotundus* extracts were found to have anti-inflammatory, peripheral analgesic, antioxidant, and immunostimulatory effects; which may be ascribed to their contents, including flavonoids, and polyphenols such

as tannin<sup>14</sup>. The extracts of *Inula helenium* have tumor cell-specific toxicity by stimulating apoptosis in tumor cells<sup>15</sup>.

Our patients developed signs of NS, and the nephrotoxicants may have been other unknown components of the herbal medicines they received. Identifying the nephrotoxic ingredients of alternative medicines such as herb medicines remains difficult because of the absence of standardization and information on their drug interactions between the active components of the herbal medicines. Drug interactions can be augmented by underlying predisposing conditions of the patient, such as dehydration; and contamination of the herb medicines changes in prescribed herbal remedies<sup>10</sup>. From our case, we can hypothesize that various herbal remedies can activate the immunological mechanism inducing nephrotic syndrome which need to be investigated consistently.

In our case report, we described children who developed steroid-sensitive (SS) NS after the administration of herb medicines, which is quite unusual. Our patients may be the first reported cases of SSNS induced by herb medicines. Our cases had early signs of NS, including albuminuria, hypercholesterolemia, hypoalbuminemia, and normal serum creatinine level, which can be typically detected on NS. Their proteinuria subsequently increased to the level considered to indicate NS, and both patients achieved remission within 2 weeks of steroid treatment. Although the second patient showed transient microscopic hematuria, her relapsed NS suggests the diagnosis of idiopathic NS instead of secondary NS or AIN. In addition, our patients show neither hypertension nor gross hematuria which are the major evidence of interstitial nephritis. In conclusion, herb medicines induced rather than caused idiopathic NS instead of secondary nephrotoxic proteinuria in our patients, and the response of their NS to steroid treatment suggests that the pathologic condition might have been MCNS, although the major type of drug-induced NS is membranous nephropathy.

### Conflict of interest

No potential conflict of interest relevant to this article was reported.

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