Case report

J Korean Soc Pediatr Nephrol 2012;16:126-131
DOI: http://dx.doi.org/10.3339/jkspn.2012.16.2.126

ISSN 1226-5292 (print)
ISSN 2234-4209 (online)

신성요붕증과 신세뇨관산증을 동반한 일차성 쇠그렌 증후군의 1례

가톨릭대학교 의과대학 소아과학교실

최종원 · 정유진 · 서진순 · 박소현 · 고대균

A Pediatric Case of Primary Sjögren's Syndrome Associated with Nephrogenic Diabetes Insipidus and Renal Tubular Acidosis

Jong Won Choi, M.D.,
You Jin Jung, M.D.,
Jin Soon Suh, M.D.,
So Hyun Park, M.D.,
and Dae Kyun Koh, M.D.

Department of Pediatrics, The Catholic University of Korea, College of Medicine, Seoul, Korea

Corresponding Author: So Hyun Park
Department of Pediatrics, The Catholic University of Korea, College of Medicine, Seoul, Korea
Tel: 031)249-8158, Fax: 031)257-9111
E-mail: nicedoc@catholic.ac.kr

*All authors have no conflicts of interest to disclose

Received: 18 March 2012
Revised: 15 June 2012
Accepted: 20 June 2012

Sjögren's syndrome (SS) is an autoimmune disorder primarily affecting the salivary and lacrimal glands. In addition, extra-glandular manifestations involving the lungs, liver, kidneys, pancreas, skin and central nervous system were reported in patients with SS. These extra-glandular manifestations are not rare in adult patient, but are very rare in pediatric SS. Renal manifestations are relatively common in adult SS, but are rarely reported in childhood SS. We experienced a girl with primary SS manifested with nephrogenic diabetes insipidus and renal tubular acidosis.

Key words: Sjögren's syndrome; Diabetes insipidus; Renal tubular acidosis; Child

Introduction

Sjögren's syndrome (SS) is an autoimmune disease involving the salivary and lacrimal glands which is associated with the presence of autoantibodies [1]. Primary SS is characterized by dry mouth and dry eyes; secondary to autoimmune dysfunction of the exocrine glands without evidence of other autoimmune diseases, whereas secondary SS can occur in association with other autoimmune diseases [1]. The prevalence of SS is estimated to be from 0.5 to 5 %. Although the disorder usually occurs in midlife, it may also be seen in children and elderly patients. It primarily affects the exocrine glands, however, non-exocrine organ systems such as skin, lungs, gastrointestinal tract, central and peripheral nervous systems, musculoskeletal system and the kidneys can be also affected [1]. These extra-glandular manifestations have been studied best

in adult-onset SS [2], although several reports have also documented in pediatric patients [3]. Due to the rare incidence of extra-glandular manifestations in children, the diagnosis and management are usually inferred from adult patients' experience. Among the extra-glandular manifestations, renal disease was reported in 4% of adults with primary SS [4], and renal tubular acidosis (RTA) was the predominant form [1]. In rare occasions, hypokalemic paralysis is the first presenting symptom of primary SS [5]. In pediatric patients, several reports regarding renal tubular acidosis in primary SS have been published [6, 7]. However, to the best of our knowledge, there has been no report to date about a pediatric case of primary SS with nephrogenic diabetes insipidus (DI) in Korea. Herein we report a girl with primary SS with chronic tubular interstitial nephritis manifested by nephrogenic DI and distal RTA.

Case report

Her urine output was exceeding four liters a day and she also had a history of dry mouth and generalized weakness since twelve years of age.age twelve. She experienced unexplained hair loss and palpable purpura on lower extremities for 8 months prior to admission. She had lost 6 kg over several months and had amenorrhea for 3 months. She had no family history of autoimmune disease. Her blood pressure was 100/60 mmHg, pulse rate was 75/min, respiratory rate was 20/min, and body temperature was 36.4℃ on admission. Her height was 154.8 cm, and body weight was 44 kg. She had dry mouth and lips, eczema on posterior region of the neck and palpable purpura on lower extremities. Further interview revealed that she had dry eyes for more than 5 or 6 months. There were no other abnormalities in the lungs, heart and abdomen. Radiologic imaging showed no definite abnormalities on simple abdominal X-ray. Initial laboratory results revealed serum sodium level of 143.7 mEq/L, potassium 2.7 mEq/L, chloride 118.3 mEq/L, blood urea nitrogen (BUN) 21.4 mg/dL, serum creatinine (Cr) 1.3 mg/dL, arterial pH 7.195, and bicarbonate 12.2 mmol/L. Urinalysis revealed pH 6.5, specific gravity (S.G.) 1.005, and negative glucose. In urine chemistry analysis, sodium was 31.2 mEq/L, potassium was 7.1 mEq/L, and chloride was 23.5 meq/L. Creatinine and calcium in the urine was 10.3 mg/dL, and 2.0 mg/dL. The plasma anion gap was 13.2, whereas the urinary anion gap was 14.8. These results suggested normal anion gap metabolic acidosis with positive urinary anion gap and although we did not try bicarbonate challenge test, we made the diagnosis of distal RTA. Her creatinine clearance was decreased to 31.3 mL/min/1.73m^2, and estimated glomerular filtration rate (GFR) was 56.8 mL/min/1.73m^2.

The water deprivation test was conducted on the second day of admission. Laboratory findings before test were serum sodium of 143.4 mEq/L, serum osmolality 291 mOsm/kg, urine S.G. 1.000, and urine osmolality 79 mOsm/kg. After four hours, she complained of nausea and dizziness, and presented with up to 5 % of weight loss. The lab findings at that moment showed serum sodium level of 146.5 mEq/L, urine S.G. 1.005, and urine osmolality 87 mOsm/kg. Her total urine output was 950 mL during the 4 hours and it was not concentrated during water deprivation. We injected vasopressin but urine S.G. was still 1.005. The serum antidiuretic hormone (ADH) level was 22 pg/mL (0-6.7 pg/mL). Therefore, we made the diagnosis of nephrogenic DI.

Thyroid function tests revealed all values within normal reference and negative for thyroid autoantibodies.

Immunologic studies showed that immunoglobulin G was elevated to 3798 mg/dL. The serum autoimmune study tested positive for rheumatoid factor (RF) (229.0 IU/mL), anti-nuclear antibody (ANA) (>1:1600), anti-SS-A and anti-SS-B. However anti-double stranded-DNA antibody was negative. Serum CH 50, C3 and C4 levels were 47.7 U/mL, 128 mg/dL and 30 mg/dL, respectively.

Ophthalmologic consultation commented on no specific findings except for dry eyes although Schirmer test was not conducted. Renal ultrasound showed normal kidney, and salivary scan with technisium-99m pertechnetate showed homogeneous uptake but decreased excretion after stimulation in both parotid glands. The patient met four criteria for SS and

there was no evidence of other autoimmune disease. Therefore, we diagnosed her with primary SS. Kidney biopsy was performed and revealed interstitial fibrosis and tubular atrophy with sparing glomeruli.

Based on these findings, the patient was diagnosed as having primary SS with chronic tubular interstitial nephritis manifested as nephrogenic DI and distal RTA. She was treated with topical lubricant for her dry eyes, thiazide and indomethacin for nephrogenic DI, and potassium chloride and oral bicarbonate solution for RTA. Her symptoms such as polyuria and polydipsia and the laboratory abnomalities gradually improved and she was discharged with the above medications on the twelfth hospital day. . During follow-up, thiazide and indomethacin doses were reduced gradually. After discharge, she still had generalized weakness, polyuria and polydipsia and her serum sodium level between 131 and 143.6 mEq/L. However, despite oral potassium supplement, serum potassium mainly remained between 2.2 and 2.9 mEq/L. 9 months after discharge, her serum urea nitrogen and creatinine was 49.5 mg/dL and 2.1 mg/dL, respectively. She was started on intravenous methylprednisolone 750 mg for three consecutive day, then the dose was changed to oral prednisolone 1 mg/kg and tapered gradually for the next 3 months. After 1 year since her diagnosis, she had profound facial hair and still had generalized weakness. Her laboratory findings deteriorated to serum urea nitrogen level of 42.2 mg/dL and creatinine level of 2.5 mg/dL. Prednisolone was restarted and she was transferred to tertiary hospital for further management.

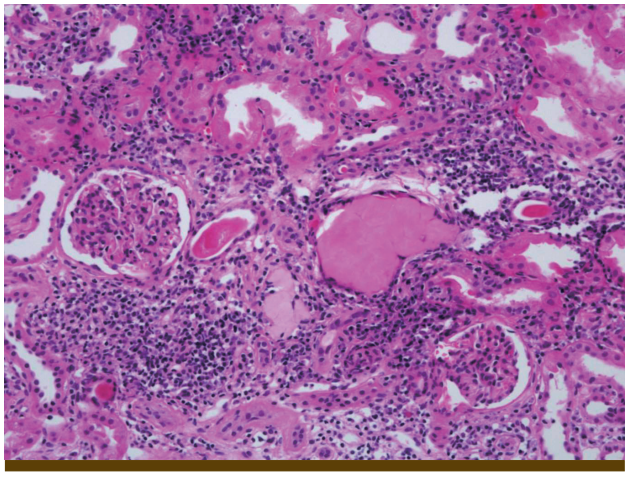

Fig. 1. Renal biopsy shows chronic tubulointerstitial nephritis. The interstitium shows interstitial fibrosis, tubular atrophy and mononuclear cell infiltration. Glomeruli do not show pathologic changes (PAS staining, magnification; x200).

Discussion

SS is a well known autoimmune disease that affects middle aged women. The diagnostic criteria of SS include 6 of the followings: (1) ocular symptoms, (2) oral symptoms, (3) evidence of keratoconjunctivitis sicca, (4) focal sialoadenitis by minor salivary gland biopsy, (5) instrumental evidence of salivary gland involvement, and (6) presence of SS-A or SS-B autoantibodies. The diagnosis of primary SS can be made if a patient presents with more than 4 of the above 6 criteria proposed by American-European Consensus group (AEC) [8].

In children, the most common manifestation at the onset of the disease is either parotid swelling or sicca syndrome [6]. However, in this case the chief complaints were progressive polyuria and polydipsia, not dry eye or dry mouth. Although our patient had dry eye and dry mouth on admission, she did not have salivary gland swelling. She might have had salivary or lacrimal gland symptoms before the renal disease developed, but she probably did not recognize those symptoms. The salivary scan showed decreased excretion in both parotid glands, and antibodies to SS-A and SS-B were both positive in this case. These signs and laboratory findings met the AEC criteria for SS, and we diagnosed her with primary SS [8].

Involvement of extra-glandular organs, such as lung, liver or nervous system, can be seen in primary SS. Pulmonary involvement is relatively common in primary SS, cough caused by xerotrachea occurs in 40 to 50% of the patients [1]. Although our patient did not have these manifestations, mild autoimmune hepatitis and peripheral neuropathy can also occur in primary SS. Purpura is a vasculitis manifestation of SS that has been reported in approximately 15% of SS patients [1] and our patient had recurrent purpura for several months. Subtypes may range from hypersensitivity vasculitis to necrotizing form

[9].

Diverse renal abnormalities such as nephrogenic DI and RTA have been known in SS and are not rare in adult SS; however, in the absence of clinical disease, renal metabolic studies usually reveal mild disturbances in the tubular function [10]. Impaired urine concentrating ability varying in degrees of severity, is the most frequently associated renal symptom in primary SS in both adults and children [10,11]. In adult SS, the incidence of nephrogenic DI was previously reported to be from 16 to 82% [10]. The defective concentrating capacity of the kidney is usually overlooked, because this form of acquired nephrogenic DI is frequently mild and some patients show only modest reduction of concentrating ability [10]. Although Severe DI is rarely reported, Shearn et al. reported profound polyuria and polydipsia in a patient with SS [12]. In primary SS, only 13 pediatric case reports of renal disease have been documented[6, 13]. Bogdanovic et al, recently reported a 13-year-old girl, otherwise asymptomatic except with distal RTA and nephrogenic DI secondary to primary SS associated tubulointerstitial nephritis [13]. Their patient had also bilateral medullary nephrocalcinosis and hypercalciuria accompanied by hypocitraturia, and had positive ANA and anti SS-A antibodies. The kidney biopsy revealed interstitial lymhocytic infiltrates but neither tubular atrophy nor interstitial fibrosis was present [13]. Although the exact pathogenic mechanisms of RTA in SS have not yet been elucidated, the absence of H+-ATPase in the cortical collecting tubule with proton pump failure have been described[14].

Nephrogenic DI may exist as an isolated abnormality in SS, but in many of the reported cases it has been associated with other tubular abnormalities including RTA [15]. Pessler et al. reported 12 cases of RTA in pediatric SS [11]. Three of them had DI at diagnosis but the symptom resolved in all 3 cases.

Glomerulonephritis is another manifestation of SS [15]. In East Asia, there were two reports of renal involvement of primary SS in children recently. Jung et al. reported primary SS with mesangial proliferative glomerulonephritis in 11 year old boy [7]. And Ito et al. reported two case of primary SS developed after IgA nephropathy [16].

In so far, tubulointerstitial nephritis has been known to be more common than glomerulonephritis in primary SS.

Kidney biopsies showed interstitial mononuclear cell infiltrates without significant glomerular changes in many cases [13], but in this case kidney biopsy revealed both interstitial fibrosis and tubular atrophy and the glomeruli spared. Talal et al. [17] noted CD 8+ lymphocytic infiltrates in patients suffering from renal tubular acidosis and glomerulonephritis in primary SS.

Serologic abnormalities are frequent in SS, including increased immune reactivity to ANA, RF, anti-smooth muscle antibodies, anti-SS-A antibodies, anti-SS-B antibodies, anti-parietal cell gastric antibodies, antiperoxidase antibodies and anti-Tg antibodies, as well as low C4 and cryoglobulinemia [2]. In primary SS, antibodies to SS-A and SS-B are present in 75% and 40% of the patients, respectively; two thirds of SS patients have positive ANA and RF activity [1]. In this presented case, she tested positive for anti-SS-A antibodies, anti-SS-B antibodies, ANA and RF. However, ds-DNA antibody as well as thyroid autoantibodies were negative and C3 level was within normal range. She did not have manifestations suggesting other autoimmune disease.

Conclusively, our patient had profound polyuria with diluted urine which did not respond to water deprivation and vasopressin injection. Also, she had normal anion gap metabolic acidosis and kidney biopsy finding showed chronic interstitial nephritis. She also had sicca symptoms and antibodies to SS-A and SS-B. Therefore, she was diagnosed with distal RTA and acquired nephrogenic DI due to chronic tubulointerstitial nephritis associated with primary SS.

The treatment of primary SS associated renal symptoms in children often requires corticosteroids and/or immunosuppressive agents for a period of time just as in adults [11, 18]. It is an established theory that management of acquired nephrogenic DI primarily consists of identifying and treating the underlying disorder and in most instance this would be sufficient to reverse the condition and relieve polyuria. However, in patients with long-standing tubular damage, the condition may be

irreversible and in such cases, thiazide and nonsteroidal anti-inflammatory drugs could be beneficial [19, 20]. In this case, since primary SS is the underlying disorder of nephrogenic DI and RTA, immunosuppressive agents like steroid should be considered to improve the symptoms at initial diagnosis. But unfortunately we started the treatment for nephrogenic DI with potassium supplement, thiazide and indomethacin first, and then later followed by additive steroid treatment.

Life-long alkali and electrolyte supplementation is needed for RTA in order to preserve growth and to prevent complications [11]. Long term outcome of renal involvement in pediatric primary SS is usually, but not always good [11].

In conclusion, we report the first pediatric case of nephrogenic DI and RTA in primary SS in Korea.

한글요약

쇠그렌 증후군은 주로 침샘과 눈물샘을 침범하는 자가면역 질환으로, 폐나 간, 콩팥, 췌장, 피부, 신경계 등의 다른 장기 역시 침범하여 임상 증상을 나타내기도 한다. 성인의 경우 이런 다른 장기와 관련된 증상은 드물지 않으나 소아에서는 매우 드물다고 알려져 있다. 특히 콩팥을 침범한 쇠그렌 증후군은 성인의 경우 비교적 흔하지만 소아는 매우 드문데, 이에 본 저자들은 신성 요붕증과 신세뇨관 산증을 주 증상으로 진단한 소아의 일차성 쇠그렌 증후군 1례를 경험하였기에 보고한다.

References

1) Carsons S. Sjögren's syndrome. In: Firestein GS, Budd RC, Harris ED Jr., McInnes IB, Ruddy S, Sergent JS, editors. Textbook of Rheumatology. 8 th ed. Philadelphia:Elsevier Saunders, 2008:1149-68.
2) Garcia-Carrasco M, Ramos-Casals M, Rosas J, Pallares L, Calvo-Alen J, Cervera R, et al. Primary Sjögren's syndrome: clinical and immunologic disease patterns in a cohort of 400 patients. Medicine 2002;81:270-80.
3) Kobayashi I, Furuta H, Tame A, Kawamura N, Kojima K, Endoh M, et al. Complications of childhood Sjögren's syndrome. Eur J Pediatr 1996;155:890-4.
4) Goules A, Masouridi S, Tzioufas AG, Ioannidis JP, Skopouli FN, Moutsopoulos HM. Clinically significant and biopsy-documented renal involvement in primary Sjögren's syndrome. Medicine 2000;79:241-9.
5) Ohtani H, Imai H, Kodama T, Hamai K, Komatsuda A, Wakui H, et al. Severe hypokalaemia and respiratory arrest due to renal tubular acidosis in a patient with Sjögren's syndrome. Nephrol Dial Transplant 1999;14:2201-3.
6) Cimaz R, Casadei A, Rose C, Bartunkova J, Sediva A, Falcini F, et al. Primary Sjögren's syndrome in the paediatric age: a multicentre survey. Eur J Pediatr 2003;162:661-5.
7) Jung SK, Park KH, Yim HE, Yoo KH , Hong YS, Lee JW, et al. Primary Sjögren's syndrome with mesangial proliferative glomerulonephritis and IgA deposits in a child. Pediatr Nephrol 2010;25:567-8.
8) Vitali C, Bombardieri S, Jonsson R, Moutsopoulos HM, Alexander EL, Carsons SE, et al. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis 2002;61:554-8.
9) Tsokos M, Lazarou SA, Moutsopoulos HM. Vasculitis in primary Sjögren's syndrome. Histologic classification and clinical presentation. Am J Clin Pathol 1987;88:26-31.
10) Shiozawa S, Shiozawa K, Shimizu S, Nakada M, Isobe T, Fujita T. Clinical studies of renal disease in Sjögren's syndrome. Ann Rheum Dis 1987;46:768-72.
11) Pessler F, Emery H, Dai L, Wu YM, Monash B, Cron RQ, et al. The spectrum of renal tubular acidosis in paediatric Sjögren's syndrome. Rheumatology 2006;45:85-91.
12) Shearn MA, Tu WH. Nephrogenic diabetes insipidus and other defects of renal tubular function in Sjögren's syndrome. Am J Med 1965;39:312-8.
13) Bogdanovic R, Basta-Jovanovic G, Putnik J, Stajic N, Paripovic A. Renal involvement in primary Sjogren syndrome of childhood: case report and literature review. Mod Rheumatol. 2012:Apr 7. [Epub ahead of print].
14) Cohen EP, Bastani B, Cohen MR, Kolner S, Hemken Ph, Gluck SL. Absence of H+-ATPase in cortical collecting tubules of a patient with Sjögren's syndrome and distal renal tubular acidosis. J Am Soc Nephrol 1992;3:264-70.
15) Janson RW, Arend PW. Renal disorders associated with systemic sclerosis, rheumatoid arthritis, Sjögren's syndrome, and polymyositis-dermatomyositis. In: Schrier RW, editor. Diseases of the kidney and urinary tract 8th ed. Philadelphia: Lipincott williams & wilkins, 2007;1712-13.
16) Ito S, Kamei K, Ikoma M. Primary Sjögren syndrome that developed after IgA nephropathy. Pediatr Nephrol 2010;25:1579-80.
17) Talal N, Zisman E, Schur PH. Renal tubular acidosis, glomerulonephritis and immunologic factors in Sjögren's syndrome. Arthritis Rheum 1968;11:774-86.

18) Ohlsson V, Strike H, James-Ellison M, Tizard EJ, Ramanan AV. Renal tubular acidosis, arthritis and autoantibodies: primary Sjögren's syndrome in childhood. Rheumatology 2006;45: 238-40.

19) Khanna A. Acquired nephrogenic diabetes insipidus. Semin Nephrol 2006;26:244-8.

20) Garofeanu CG, Weir M, Rosas-Arellano MP, Henson G, Garg AX, Clark WF. Causes of reversible nephrogenic diabetes insipidus: a systematic review. Am J Kidney Dis 2005;45:626-37.