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CASE REPORT

Pediatric Sjogren syndrome with distal renal tubular acidosis and autoimmune hypothyroidism: an uncommon association

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Abstract A 14-year-old female came with the history of sudden onset weakness; during work up, she was found to have hyperchloremic metabolic acidosis with normal anion gap and normal renal function suggesting the possibility of renal tubular acidosis (RTA). On further evaluation of RTA, she had positive antinuclear antibody, anti-Ro, and anti-La antibodies. On nuclear scan of salivary glands, her left parotid gland was nonfunctional. Her parotid biopsy revealed dilated interlobular ducts engulfed by lymphoid cells. She also had autoimmune hypothyroidism as suggested by raised TSH and positive anti-TPO antibodies. At admission, her serum potassium levels were low and she was treated with intravenous potassium chloride. After she recovered from acute hypokalemic paralysis, she was started on oral potassium citrate along with phosphate supplements, hydroxychloroquine, oral prednisolone and thyroxine supplements. Over the next 6 months, she has significant reduction in the dosage of potassium, bicarbonate and phosphate and gained 3 kg of weight and 3.5 cm of height. As primary Sjogren syndrome itself is rare in pediatric population and its association with renal tubular acidosis is even rarer, we suggest considering Sjogren syndrome as a differential diagnosis during the RTA work-up is worth trying.

Keywords Renal tubular acidosis · Pediatric Sjogren syndrome · Autoimmune hypothyroidism

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Introduction

Sjogren syndrome is an autoimmune rheumatic disease of unknown etiology characterized by focal mononuclear cell infiltration of exocrine glands. While primary Sjogren syndrome occurs alone, secondary Sjogren syndrome occurs with other rheumatological diseases, mainly systemic lupus erythematosus. In spite of being a disease of exocrine glands, extraglandular features are not uncommon in primary Sjogren syndrome especially in pediatric age group which itself may be the presenting feature [1]. Incidence of Sjogren syndrome varies from 0.2 to 3.0 % in different geographical populations [2, 3].

Renal tubular acidosis in primary Sjogren syndrome is reported in 13 pediatric cases till date. Hypokalemic paralysis as a sole presenting feature of Sjogren syndrome in pediatric cases is rare. Here, we describe an adolescent girl who presented with hypokalemic paralysis secondary to distal RTA and delayed puberty and found to have autoimmune thyroiditis with Sjogren syndrome.

Case report

14-year-old female presented to casualty with history of inability to stand after getting up from bed in the morning so was rushed to hospital. There was no preceding history of diarrhea, vomiting, upper respiratory tract infection, rashes over body, polyuria, polydipsia, salt craving, and visual and hearing disturbances.

Though there was a history of poor weight and height gain for the last 4 years for which she was started on some ayurvedic medicine, the nature of which could not be established.

On clinical examination, her vital signs were stable with heart rate of 70/min, respiratory rate of 20/min and blood

Table 1 First-line investigations and second-line investigations

Parameter	Value	Units	Ref range
Hemoglobin	13.7	g/dL	12–15
Erythrocyte sedimentation rate	33	mm in first hour	0–20
Blood urea	15	mg/dL	<35
Serum creatinine	0.4	mg/dL	0.46–0.81
Serum sodium	136	mEq/L	135–145
Serum potassium	1.8	mEq/L	3.5–5.5
Serum calcium	7.7	mg/dL	8.6–10
Serum phosphorus	2.3	mg/dL	2.7–4.5
Serum magnesium	1.6	mg/dL	1.8–2.6
Total serum protein	6.7	g/dL	6.0–7.9
Serum albumin	3.2	g/dL	3.2–5.1
Alanine transferase	37	U/L	<40
Aspartate transferase	31	U/L	<40
Serum creatine kinase	93	U/L	<145
Blood pH	7.25	–	7.35–7.45
Urine pH	7.5	–	4.6–8.0
Blood anion gap	13.2	–	10–14
Urine anion gap	+3	–	Positive value
Urine Na^+	65	mEq/L	<20
Urine K^+	15	mEq/L	0–10
Urine chloride	77	mEq/L/day	110–250
Parameter	Value	Units	Ref range
Ultrasound KUB	Bilateral nephrocalcinosis		
X-ray right knee AP	Mild diffuse osteopenia		
iPTH	103.8	pg/mL	
25(OH) vitamin D	22.1	ng/mL	>30
Urinary aminoacidogram	Normal excretion of amino acids in Urine	Two-dimensional thin layer chromatography	
Urinary beta2 microglobulin 24 h urine	2371	ng/mL	<300
24 h calcium excretion	189	mg/day	<4 mg/kg/day
24 h phosphorus excretion	500	mg/day	400–1300
FT3-RIA	4	pM/L	2.5–5.8
FT4-RIA	12.2	pM/L	11.5–23
TSH-IRMA	60	μU/mL	0.2–5.1
Anti-TPO antibody	315.2	IU/mL	<5.6
Anti-thyroglobulin antibody	279	IU/mL	<20
		Chemiluminescence	
Serum IgG immunoturbidometry	3631	mg/dL	700–1600
Serum IgA immunoturbidometry	337	mg/dL	70–400
Serum IgM immunoturbidometry	136	mg/dL	40–230
ANA	Positive	ELISA	Negative
Anti-Ro/SS-A	109.82	EIA	<20
Anti-La/SS-B	117.79	EIA	<20
Anti-smith antibody	3.07	EIA	<20
Anti-U1 RNP antibody	2.86	EIA	<5
Rheumatoid factor latex agglutination test	Positive in 1:16 dilution (128 IU/mL)	–	Negative
C3 Immunoturbidometry	123.64	mg/dL	90–180
C4 Immunoturbidometry	19.81	mg/dL	10–40

Table 1 continued

Parameter	Value	Units	Ref range
tTG–IgA	4.12	EIA	<20
HBsAg	Negative	ECLIA	Negative
Anti-HCV antibody	Negative	ECLIA	Negative
Ultrasound neck	Coarse thyroid echo texture with suggestion of poorly defined lesion within left lobe thyroid		
Scintigraphy of salivary glands	Absent uptake of radiotracer in the left parotid gland		
	Other salivary glands are normally visualized		
Tc 99 scan of thyroid	Grade I diffuse thyroid enlargement with preserved trapping function. Pattern is suggestive of inflammatory thyroid disease in hypothyroid state		
Parotid gland biopsy	Lymphoepithelial lesion right parotid gland and dilated interlobular ducts engulfed by lymphoid cells		
Eye evaluation	Schirmer's test—normal in both eyes		
Ear evaluation	Normal pure tone audiometry in both ears		
Karyotyping	46,XX	G bands by trypsin and Giemsa staining	46XX for Female 46XY for Male

Table 2 Primary Sjogren's syndrome (pSS) in children and adolescents: proposal for diagnostic criteria

I. Clinical symptoms
1. Oral: recurrent parotitis or enlargement of parotid gland
2. Ocular: recurrent conjunctivitis without obvious allergic or infectious etiology, keratoconjunctivitis sicca
3. Other mucosal: recurrent vaginitis
4. Systemic: (a) fever of unknown origin; (b) non-inflammatory arthralgias; (c) hypokalemic paralysis; (d) abdominal pain

II. Immunological abnormalities

Presence of at least one of the following antibodies: anti-SS-A, anti-SS-B, high titer of ANA (speckled type), rheumatoid factor.

III. Other laboratory abnormalities or additional investigations
1. Biochemical: elevated serum amylases (parotic isoenzyme, pancreatic isoenzyme or both)
2. Hematological: leucopenia, high ESR
3. Immunological: polyclonal hyperimmunoglobulinemia
4. Nephrological: renal tubular acidosis (incapacity of spontaneous or challenged acidification of urine)
5. Histological proof of lymphocytic infiltration of salivary glands or other organs (i.e., liver biopsy)
6. Objective documentation of ocular dryness (Bengal red staining or Schirmer's test)
7. Objective documentation of parotid gland affection (sialography)

IV. Exclusion of all other autoimmune diseases

pressure of 110/80 mmHg. On central nervous system examination, patient was conscious and oriented to time place and person, and there was no evidence of any cranial nerve paralysis. Motor tone was decreased in all the four limbs and deep tendon reflexes were of grade 2/5 in all the four limbs. Bilateral plantar response was flexor and sensory system did not reveal any positive findings. Rest of systemic examination did not reveal any abnormality.

Preliminary investigations revealed severe hypokalemia with hyperchloremic normal anion gap metabolic acidosis and normal renal function indicating the possibility of renal tubular acidosis (RTA). On further evaluation, RTA patient was found to have hypophosphatemia, hypercalciuria, low-molecular-weight proteinuria. Her urinary pH was 7.5. Her ultrasound abdomen revealed nephrocalcinosis. Urinary aminoacidogram was normal but she had hyperphosphaturia. Rest of the other (Complete blood count with peripheral smear, liver function test, creatine phospho kinase chest X-ray and electrocardiogram) investigations were normal. Her formal assessment of hearing and vision was normal.

Patient was treated with potassium chloride infusion along with injectable sodium bicarbonate. She improved gradually as her serum potassium and serum bicarbonate level improved. After the improvement in acidosis, her serum calcium levels started falling, so calcium

Table 3 Reported cases of primary Sjogren's syndrome presenting as renal tubular acidosis

References	Age(years)/ Sex	Presenting features	Renal tubular acidosis type	Renal comorbidity	Thyroid involvement	Immunosuppression	Follow-up years	Renal outcome
Shioji et al.	14/Female	Growth failure, rickets	Proximal	Not specified	No	ND	1.5	Stabilized
Zhang et al.	13/Female	Periodic paralysis	Not specified	Diabetes insipidus	Not specified	Not specified		ND
Chang et al.	15/Female	Periodic paralysis	Distal	Diabetes insipidus	No	Prednisolone	3	ND
Kobayashi et al.	10/Female	Renal calcification	Distal	Nephrocalcinosis	Not specified	Methylprednisolone and cyclophosphamide	5	Stabilized
Zawadzki	15/Female	Gait disturbances	Distal	Not specified	Not specified	Cyclophosphamide and prednisolone	20 months	Stabilized
Bartunkova et al.	10/Female	Ileus	Proximal + Distal	Not specified	Not specified	Methylprednisolone and cyclosporin A	8	Unstable
Shi and He	12/Female	Fever headache	Not specified	Not specified	Not specified	Prednisolone	ND	Stabilized
Zeng et al.	17/Female	Dysphagia, paralysis	Not Specified	Not specified	Not specified	Prednisolone	ND	Stabilized
Liu and Li	14/Female	Growth failure, paralysis	Distal	Diabetes insipidus	Not specified	Prednisolone	1.5	Improved
Ohlson et al.	8/Female	Dehydration, hypokalemia	Distal	Not specified	No	Methylprednisolone and methotrexate	ND	ND
Skalova et al.	16/Female	Paralysis	Distal	Not specified	No	Prednisolone and cyclosporin A	ND	Stabilized
Maripuri et al.	13/Female	Not specified	Distal	Not specified	Not specified	Prednisolone	28 months	Stabilized
Bogdanovic et al.	13/Female	Nephrocalcinosis	Proximal + Distal	Diabetes insipidus, Nephrocalcinosis	Not specified	Prednisolone, azathioprine and mycophenolate mofetil	6	Unstable
Our Report	14/Female	Hypokalemic paralysis and growth failure		Nephrocalcinosis	Autoimmune thyroiditis	Prednisolone	6 months	Stabilized

ND no data

supplements were given along with phosphate supplements for hypophosphatemia.

On evaluation of short stature, she was found to be hypothyroid for which she was started on oral levothyroxine.

Apart from above medications, patient was also started on hydroxychloroquine and oral prednisolone at a dose of 1 mg/kg followed by tapering of dose. After the addition of steroid, her bicarbonate, potassium and phosphate requirements have reduced significantly. At 6-month follow-up visit, she has gained 3 kg of weight and 3.5 cm of height Table 1.

Discussion

The occurrence of Sjogren syndrome is rare in childhood and in its primary form only single case reports or small groups of patients have been reported. Its presentation in pediatric age group is different from adults and recurrent parotid swelling is the most common presentation. No specific diagnostic criteria have been established for Sjogren syndrome in childhood. Clinical symptoms and the diagnostics performed in childhood do not fulfill the classical diagnostic criteria which are successfully used for adults. So J.Bartu°nvková et al. [4] proposed diagnostic criteria for juvenile primary Sjogren syndrome, Table 2.

Renal involvement in pediatric primary Sjogren syndrome itself is rare and primary Sjogren syndrome presenting as renal tubular acidosis is even rarer limited to only few case reports [5] Table 3.

Tubulointerstitial nephritis remains the most common presentation of renal involvement in primary Sjogren syndrome leading to distal renal tubular acidosis and less commonly to proximal renal tubular acidosis [6].

Renal tubular acidosis is a group of transport defects secondary to reduced proximal tubular reabsorbtion of bicarbonate or distal tubular secretion of protons or both. Renal tubular acidosis is characterized by normal anion gap hyperchloremic metabolic acidosis. Renal tubular acidosis in childhood presents as growth retardation, failure to thrive, and polyuria, polydipsia as the main presenting complaint, and symptoms (weakness and paralysis) related to hypokalemia are rare but at times they are the presenting features in pediatric age group. Management of renal tubular acidosis relies on correcting acidosis and other electrolyte abnormalities [7].

Patients suffering from primary Sjogren syndrome may develop other autoimmune diseases as well, Hashimoto's autoimmune thyroiditis being the most frequent. Sjögren's syndrome and chronic thyroiditis are common disorders in adults, but the information in childhood is scarce [8].

Autoimmune thyroiditis may be diagnosed prior to the onset of primary Sjogren syndrome, at the same time as primary Sjogren syndrome or it may develop during the later years [9].

Prevalence of autoimmune thyroiditis in patients with primary Sjogren syndrome varies according to the geographical location. In a large Hungarian Cohort, 6.2 % patients with primary Sjogren syndrome had thyroid dysfunction [9].

Patients affected by co-occurrence of primary Sjogren syndrome and autoimmune hypothyroidism have a milder clinical phenotype of primary Sjogren syndrome envisaging a lower risk factors for the development of lymphoma [10].

Presence of autoimmune thyroiditis in patients with primary Sjogren syndrome is a well-known association but we could not find a pediatric literature on association of autoimmune thyroiditis, renal tubular acidosis and primary Sjogren syndrome in a same patient. To best of our knowledge, this is a first case report having this kind of association in pediatric patient. According to the adult literature, primary Sjogren syndrome-associated thyroiditis is found more frequently in females with a prevalence of 7 % [3] and they also have milder phenotype [10]. In adult onset, primary Sjogren syndrome renal involvement resulting in renal tubular acidosis is fairly common, but in pediatric age group it is limited to few case reports [6].

Tubulointerstitial nephritis remains the most common presentation of renal involvement in primary Sjogren syndrome [11] which is often characterized by distal renal tubular acidosis and less commonly proximal renal tubular acidosis.

Steroids are the cornerstone of the therapy in patients with renal involvement, while other treatments include hydroxychloroquine, cyclophosphamide, methotrexate, azathioprine, mycophenolate mofetil and calcineurin inhibitors. In rare cases, plasma exchange and rituximab may be of some value in improvement of symptoms for short duration without affecting the long-term outcome [12, 13].

According to the case series by Maripuri [14], early treatment by immunosuppressive therapy appears to maintain or improves renal function in primary Sjogren syndrome patients with renal involvement. We suggest that patients should be closely monitored for signs and symptoms of infection during steroid use.

Conflict of interest All the authors have declared no competing interest.

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