CASE REPORT

Primary Sjögren's syndrome in children: Is a family approach indicated?

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INTRODUCTION

Sjögrens syndrome (SS) is a chronic autoimmune disease primarily affecting the lachrymal and salivary glands with varying degrees of systemic involvement. SS can be isolated (primary SS or pSS) or associated with other autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus, or scleroderma (secondary SS). pSS predominantly affects middle-aged women and is uncommon in childhood.[1-4] In addition to being underdiagnosed, clinical manifestations are often different in children when compared to adults. Recurrent parotid swelling is a common feature observed in children with pSS (37, 5–100%).[2] Oral and ocular involvement, however, is present in a minority of children, especially at the onset of disease (23–80%).[2] Pathologic and laboratory findings are similar to those found in adults and include characteristic lymphocytic infiltration of the exocrine glands, the presence of hypergammaglobulinemia, an elevated erythrocyte sedimentation rate (ESR), and the presence of autoantibodies (such as anti-Ro/SSA, anti-La/SSB, antinuclear antibody (ANA), and rheumatoid factor (RF)[4-6]). Although pSS is an autoimmune disease, familial incidence of pSS is infrequently reported.[6-8]

We report the occurrence of pSS in two siblings and in their mother and review the literature on multiplex pSS families.

CASE REPORTS

Patient 1 - A 9-year-old girl with a one-year history of bilateral recurrent enlargement of the parotid gland was sent to the rheumatology unit. She denied having dry mouth, dry eyes, or any systemic symptoms. Upon examination, she was healthy with a weight in the 75th percentile and a height in the 90th percentile. Her physical examination was unremarkable, except for the presence of a bilateral, painful parotid enlargement. The physician also identified sialadenitis upon sialography and a positive Schirmers test upon ophthalmological evaluation. The patient was negative for RF and antinuclear antibodies (ANA), but positive for anti-Ro. Antibodies against La, double-stranded DNA (anti-dsDNA), and Sm were also negative. Her white blood cell counts (WBCs) and ESR were normal, and no hypergammaglobulinemia was observed. A minor salivary gland biopsy showed diffuse lymphocytic infiltration.

Patient 2 - During medical evaluation, the mother of the patient mentioned that her other 8-year-old daughter also had a two-year history of recurrent parotid gland swelling. The patient denied having dry mouth, dry eyes, or any systemic symptoms. Her physical exam was unremarkable. The patient had a normal Schirmer's test and did not have any evidence of chronic sialadenitis upon sialography. Her laboratory test results revealed that she was positive for RF, ANA, Ro, and La antibodies as well as negative for anti-dsDNA and anti-Sm. The patient displayed normal WBC and ESR, but exhibited polyclonal hypergammaglobulinemia. A salivary gland biopsy revealed lymphocytic sialadenitis with more than four lymphoid foci (4 mm^2 in size), which was compatible with SS.

Patient 3 - The mother was 28 years in age and complained of persistent dry mouth, photophobia, and dry eyes after two years of her daughters' follow-up. Her physical exam was unremarkable. She was negative for RF, positive for ANA, and anti-Ro, had a normal WBC and ESR, and presented no hypergammaglobulinemia. Ophthalmological examination revealed positive results both on Schirmer's test and the Rose Bengal test. Her salivary gland scintigraphy revealed deficient drainage of her left parotid gland, and her salivary gland biopsy showed no evidence of diffuse lymphocytic infiltration.

DISCUSSION

pSS is a well-known autoimmune disease that predominantly affects middle-aged women. pSS is diagnosed following the Revised International Classification Criteria for Sjögren's Syndrome from the American-European Group and includes six items: (I) presence of ocular symptoms, (II) presence of oral symptoms, (III) evidence of keratoconjunctivitis sicca, (IV) focal sialadenitis upon minor salivary gland biopsy, (V) instrumental evidence of salivary gland involvement, and (VI) presence of SSA or SSB autoantibodies. Diagnosis of pSS requires 4 of the six criteria.[5,9] As there are no specific diagnostic criteria for pSS in children, and the adult criteria are often used. The

No potential conflict of interest was reported.

Table 1 - Case reports of familial Sjögren's Syndrome.

Reference	Cases	Comment
Coverdale[20]	Father and daughter	
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Bloch et al.[21]	Mothers of two patients	
Camus et al.[22]	Mother and daughter	Both had KS and intermittent parotid gland enlargement Association with familial scleroderma
Koivukagas et al.[23]	Two sisters	Association with achalasia of the esophagus
Simila S et al.[24]	Two siblings	KS(1,2), X(1,2), achalasia (1,2), gastric hyposecretion (1,2)
Besana et al.[25]	Identical twins	Bilateral dacryiadenitis; KS
Ostuni et al.[26]	Identical twins	PS(1,2), KS(1)
Houghton et al.[6]	Dizygotic twins	PS (1,2), X (1), LIP (1)
Bolstad et al.[27]	Monozygotic twins (1,2) and the mother (3)	X, KS, salivary gland dysfunction (1,2); X, KS, dry nose, dry skin, dry cough, RP (3)
Boling et al.[15]	Two siblings	Hemolytic anemia, no association with HLA-DR3
Lichtenfeld et al.[8]	Four siblings	Association with primary salivary gland lymphoma
Sábio et al.[19]	Dizygotic siblings (1,2,3) and the mother (4)	X and KS (1,2,3,4), PS (1)

Ks: keratoconjunctivitis sicca; X: xerostomia, PS: parotid swelling; RP: Raynaud's phenomenon.

diagnosis of childhood SS may be difficult because the classical diagnostic criteria that are successfully used for adults are often not fulfilled by children at disease onset.

The onset of disease may not only be different in children, but also characterized by nonspecific symptoms. Frequently, salivary gland enlargement or recurrent parotitis is observed; sicca symptoms are rarely referred.[2] Laboratory signs are present early during the course of disease and include hypergammaglobulinemia, positive tests for anti-SS-A and/or anti-SSB, a high titer of speckled antinuclear antibodies, and/or the presence of rheumatoid factor.[10]

pSS is rare in children and adolescents.[4,6,11] During a three-year study, Cimaz et al.[2] collected data on 40 patients from ten different centers worldwide. The most common manifestation reported in their study was recurrent parotid swelling (72.5%) at the onset of disease, whereas ocular and/or oral symptoms were only found in a minority of children. Other clinical signs and symptoms observed at disease onset were arthritis (10%), fever (10%), fatigue (7.5%), and submandibular swelling (5%). Similar results were observed in other reports.[6,12]

The differential diagnosis of recurrent parotitis is broad in children and includes mechanical, infectious, malignant, and inflammatory etiologies.[6] It is important to note that in both the children in this case study, recurrent parotitis was the initial clinical manifestation of pSS. Therefore, recurrent parotitis should alert the clinician to the possibility of pSS.[6,12]

Familial cases of pSS are rare (Table 1).[6,8,19-27] Lichtenfeld et al. described one patient with SS in whom a primary parotid gland lymphoma subsequently developed.[8] Moreover, two of four siblings had evidence of SS, and the authors suggested that genetic influences may facilitate the development of SS. Houghton et al. reported pSS in dizygotic adolescent twins; recurrent parotitis was the initial clinical manifestation in both parents.[6] The authors proposed that pSS is likely a polygenic disorder resulting from several genes interacting with environmental factors. Some studies of pSS showed that it has a strong association with HLA-DR3.[6,13,14] However, recent studies have suggested that pSS is a complex, polygenic disorder sharing common genetic determinants with related autoimmune diseases, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA).[14] Recent advances in SLE and RA provide valuable insights into the potential genetic complexity of SS.[14] Several families with multiplex SS have also been described,[6,15,16] and relatives often have other autoimmune diseases, such as SS (12%), autoimmune thyroid disease (AITD) (14%), RA (14%), and SLE (5%–10%).[17,18]

In conclusion, although pSS is a complex genetic disorder, familial cases of SS are rarely reported. In children, pSS may be underdiagnosed because of the lack of classic sicca symptoms. However, pSS should be included in the differential diagnosis of recurrent parotid swelling, and when diagnosed, siblings should be evaluated.

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AUTHOR CONTRIBUTIONS

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