

Sicca syndrome and salivary gland infiltration in children with autoimmune disorders: when can we diagnose Sjögren's syndrome?

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Abstract

Objectives

To analyse the initial presentation and outcome of children with a diagnosis of childhood-onset Sjögren's syndrome (SS) in a paediatric referral care center. To study whether the diagnosis was made in accordance with the most recent criteria of paediatric SS and to compare our patients to those reported in the literature.

Methods

We retrospectively analysed the clinical, histological and laboratory features of patients seen over a period of 15 years and diagnosed with SS before the age of 16.

Results

Eight patients had a diagnosis of SS in childhood and were followed for up to 14 years. Diagnosis of SS was based on histological evidence of salivary gland involvement in all patients with or without presence of specific autoantibodies (anti-SSA and -SSB). Sicca syndrome as a presenting symptom occurred in only 2/8 of children, recurrent parotid swelling in 3/8; whereas anti-SSA/SSB antibodies and typical salivary-gland histology were found in 6/8 patients. Five children fulfilled the proposed paediatric criteria for SS. Three patients did not fulfill the paediatric criteria but disclosed typical histology findings. Two patients developed overlapping lupus nephritis or autoimmune hepatitis years following diagnosis of SS.

Conclusion

Childhood-onset SS is an heterogeneous disease in its presentation and outcome. The diagnosis may be discussed in some patients who do not fulfill the proposed diagnosis criteria, even though they disclose sicca syndrome and typical immunologic and histological findings. Some patients with typical SS may develop overlapping lupus disease over time.

Key words

Sjögren's syndrome, juvenile, child, sicca syndrome, parotitis, classification criteria

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Introduction

Sjögren's syndrome (SS) is a chronic inflammatory systemic autoimmune disorder characterised by lymphocytic infiltration of the lachrymal and salivary glands leading to xerophthalmia, xerostomia and systemic production of autoantibodies. This syndrome is often complicated by extraglandular manifestations (1, 2). Unlike associated SS which occurs in the context of another autoimmune disease, primary SS may occur as an isolated disorder. In adults, SS is not uncommon. Primary SS occurs with a prevalence of 0,1-0,4% in the Caucasian population. Conversely, in childhood and early adulthood SS is an extremely rare autoimmune condition. Several retrospective studies have been published including single case reports and literature reviews reporting up to 189 children (3-8). Diagnostic criteria for adult patients were redefined in 2002 as American European consensus group (AECG) criteria (9). In children, however, criteria are more difficult to establish as autoantibodies often appear late in the course of the disease. Clinical hallmarks are recurrent parotid enlargement and non-specific signs and symptoms (2, 3, 5), often but not always followed by sicca syndrome, especially in associated SS (10).

Patients and methods

All 8 patients reviewed in this series were seen at a single paediatric referral care center (1100 patient consultations/year) over a period of 15 years and the diagnosis of SS was proposed. Charts were reviewed retrospectively. We analysed the clinical, immunologic and laboratory features.

Results

Six girls and one boy had a diagnosis of primary SS. Diagnosis of SS was based in all cases on histological evidence of salivary gland involvement with or without the presence of specific autoantibodies (anti-SSA and -SSB). Histology was performed according to the Chisholm-Mason scale requiring more than one focus of lymphocytes per 4 mm² for a positive result, a focus being an aggregate of 50 or more lymphocytes and histiocytes (11).

One girl was first diagnosed with oligoarticular-onset JIA, with anti-nuclear antibodies (ANA) but no anti-SSA or -SSB antibodies at disease onset: she was later diagnosed with associated SS (12). Age and manifestations at onset were highly variable (Table I). There was a delay of 6 months to 13.5 years (median 2.5 years) from the first symptoms to the time of histological diagnosis. Sicca syndrome was noted in 5 patients (xerophthalmia in 4 and xerostomia in 2), recurrent parotid swelling occurred in 3 patients. Laboratory manifestations showed marked inflammation and elevated serum levels of IgG in all patients. Autoantibodies (anti-SSA and anti-SSB) were present in 6 of 8 patients with positive ANA. Extraglandular manifestations were pericarditis, aseptic meningitis as well as hepatic, renal, pulmonary and muscular involvement (Table I). To illustrate the variability of presentation at onset we hereafter briefly describe the clinical history of the 7 patients with a diagnosis of primary SS. The case of a girl who developed associated SS fourteen years after oligoarticular-onset JIA has been reported previously (12). However, we have also summarised her case and included the latest follow-up.

Patient 1

A 4-year-old girl of Caribbean origin presented with repeated episodes of a nodular erythematous rash on her legs of two days duration. Skin biopsy showed leucocytoclastic vasculitis. At age 7 she developed photophobia. Four years later she also complained of ocular and oral sicca syndrome as well as tendinitis. Diagnosis of SS was based on salivary gland biopsy and immunological findings (Table I). At the last follow-up she was doing well apart from sicca syndrome and occasional tendinitis under hydroxychloroquine (HQ) treatment.

Patient 2

A 5-year-old Caucasian girl presented with talalgia, morning stiffness and arthritis. Recurrent ear-nose-and throat infections led to tonsillectomy and adenoidectomy at age six. Routine biology revealed moderate thrombocyto-

Competing interests: none declared.

Table 1. Patient characteristics.

| Patient no. | Sex | Ethnic origin | Age at disease onset (in years) | Age at diagnosis (in years) | First symptoms at disease onset | Sicca syndrome at onset | Recurrent parotid swelling | Age at last follow-up (in years) | Additional symptoms | IgG (g/l) | ANA | Anti-SSA Ro52/60 | Schirmer test | Salivary gland biopsy (Chisholm grade) |
|-------------|-----|---------------|---------------------------------|-----------------------------|---------------------------------|-------------------------|----------------------------|----------------------------------|---|-----------|--------|------------------|-----------------|---|
| 1 | f | CAR | 4 | 11 | erythema nodosum | no | no | 18 | photophobia tendinitis | 37 | 1:3200 | 1237/2438 | 2162 | 4 |
| 2 | f | CAU | 5 | 7 | arthritis thrombocytopenia | no | no | 10 | ocular and oral dryness | 32 | 1:1600 | 16172 | 4129 | 4 |
| 3 | f | MOR | 0.5 | 6 | neonatal lupus fever arthritis | no | no | 9 | aseptic meningitis superficial keratitis | 12 | neg. | neg. | neg. | 3 |
| 4 | f | CAR | 12 | 13 | Raynaud hepatitis | no | no | 19 | polymyositis pericarditis oral dryness | 28 | 1:1600 | 94 [#] | 52 [#] | 3 |
| 5 | m | ALG | 2 | 12 | uveitis | yes | no | 13 | | 8 | 1:200 | 1520 | neg. | lymphocytic infiltration not classified |
| 6 | f | ALG | 10 | 10 | keratitis parotitis weight loss | yes | yes | 12 | deafness | 10 | neg. | neg. | neg. | lymphocytic infiltration not classified |
| 7 | f | ALG | 8 | 11 | arthralgia fever | no | yes | 19 | pericarditis parotitis renal involvement hepatitis | 40 | 1:800 | 955 | 1329 | 3 |
| 8 | f | CAU | 1.5 | 15 | arthritis | no | yes | 28 | parotitis ocular and oral dryness renal involvement | 23 | 1:1250 | 1121/1528 | 2611 | 4 |

Al: autoimmune; CAU: Caucasian; MOR: Morocco; ALG: Algeria; CAR: Caribbean; ND: not documented. [#]EIA titre positive > 20, *subjective ocular dryness. Positive results: SSA/Ro52>500cpm, SSA/Ro60>225cpm, SSB>180cpm in radioligand assay.

Table II. Comparison of patients' characteristics with the literature according to the proposed diagnostic criteria for juvenile SS (2, 3).

| | | Hôpital Necker series n=8 | Literature (reviewed in [3-5, 8]) n=189 |
|---|---|---------------------------------|--|
| Clinical symptoms | Oral (dry mouth, recurrent parotitis or enlargement of parotid glands) | 5/8 | 113/189 (60%) |
| | Ocular (recurrent conjunctivitis without obvious allergic or infectious etiology, keratoconjunctivitis sicca) | 5/8 | 87/174 (50%) |
| | Other mucosal (recurrent vaginitis, gastric hyposecretion, dryness pharynx, nares) | 0/8 | 6/16 (38%) |
| | Systemic (fever of unknown origin, noninflammatory arthralgias, hypokalemic paralysis, abdominal pain) | 3/8 | 35/121 (29%) |
| Immunological features | Presence of at least 1 of anti-SSA, anti-SSB, high titer ANA, RF | 6/8 | 147/186 (79%) |
| Other laboratory abnormalities or additional investigations | Biochemical (elevated serum amylase) | NA | 13/14 (93%) |
| | Hematologic (leukopenia, high ESR) | 7/8 | 41/51 (80%) |
| | Immunological (polyclonal hyperimmunoglobulinemia) | 6/8 | 74/106 (70%) |
| | Nephrological (renal tubular acidosis) | 1/8 | 3/23 (13%) |
| | Histological proof of lymphocytic infiltration of salivary glands or other organs | 8/8 | 83/103 (80%) |
| | Objective documentation of ocular dryness (Bengal red staining, Schirmer test) | 4/6 | 93/154 (60%) |
| Criteria for pSS fulfilled | Objective documentation of parotid gland involvement (sialography) | 0/0 | 71/85 (84%) |
| | presence of ≥ 4 juvenile pSS criteria according to Bartunkova (2) | 5/7* | 49/64 (76%) |
| | Presence of ≥ 4 American-European consensus criteria including either anti-SSA or anti-SSB or histopathology | 1/7* | 26/64 (41%) |
| | Presence of ≥ 4 American-European consensus criteria (modifying oral symptom criteria to include recurrent or persistent salivary gland swelling in childhood) | 2/7* | 34/66 (51%) |

*The patient who was classified as having secondary SS was excluded from this analysis; NA: not available.

penia (42.000/ μ l). Four months later she presented with asthenia, fever and arthritis of her toes and forefeet. She responded partially to NSAIDs. Oral and ocular sicca syndrome appeared at around 7 years and treatment with HQ was started. She was clinically stable with a thrombocyte count of 100.000/ μ l until 5 months ago, when she presented with arthritis of the toes and skin eruption responsive to steroid treatment. At a recent follow-up she presented asthenia and problems with her schooling.

Patient 3

In the neonatal period, lupus-like skin lesions had been noted in this girl of Moroccan origin. At 6 months, she presented with fever and arthralgias. Upon hospitalisation she was found to have aseptic meningitis and arthritis which stabilised under treatment with NSAIDs. At around 6 years of age she complained of visual discomfort. Superficial keratitis was diagnosed. A presumptive diagnosis of SS was confirmed by typical salivary gland histology. At the last follow-up at the age of 9, she was stable under NSAIDs.

Patient 4

A 12-year-old girl of Carribean origin was referred for asthenia. Laboratory testing revealed elevated liver enzymes (4 to 5 times the normal limit) without cholestasis. Liver histology showed mild portal lymphoplasmocytic infiltrates pointing towards a possible autoimmune hepatitis. Marked, polyclonal serum hypergammaglobulinemia was present but no autoantibody was found. One month later she developed myositis characterised by muscle weakness affecting the shoulder girdle and pelvic muscles with CK levels above 10000 U/l. EMG showed pathologic myogenic anomalies. Echocardiography revealed moderate pericardic effusion. No muscle biopsy was performed as a panel of experts considered that the available clinical and histological features (salivary gland and liver biopsies) were convincing enough to consider myositis as an additional autoimmune feature. The diagnosis of inclusion body myositis was not considered due to the paediatric onset. The patient received regular immunoglobuline infusions in addition to intravenous corticosteroids. She also devel-

oped oral sicca syndrome confirmed by immunological and histological findings. Moreover, clinical Raynaud's syndrome was present. Microangiopathy was documented on nailfold capillaroscopy. The patient was stable at the latest follow-up under regular IVIG with no additional immunosuppressive therapy.

Patient 5

A 2-year-old boy of Algerian origin presented with a brief history of redness of his right eye, abdominal pain, diarrhea as well as weight loss (-2 kg within 1 year). He also complained of arthralgia. Salivary gland biopsy was performed to exclude granulomatous disease and revealed lymphocytic infiltrations, which together with positive anti-SSA antibodies led to the diagnosis of SS. He was lost to follow-up at the age of 13 years when his disease was clinically stable.

Patient 6

A 10.5-year-old girl from Algeria had a 3-month history of episodic swelling of her eyelids with periocular erythema. At presentation she had ulcerative kera-

titis and ocular sicca syndrome. Two months later she developed fever, abdominal pain and bilateral parotid swelling. Her symptoms including oral sicca syndrome responded well to corticoid therapy, but 3 weeks later – still under steroid treatment – she suddenly developed ataxia and hearing loss. Cogan syndrome was not excluded by several Ear-Nose and Throat specialists, however no definitive conclusion could be drawn. Salivary gland biopsy confirmed SS. This patient was lost to follow-up at the age of 12.

Patient 7

An 11-year-old girl of Algerian origin presented with a three year history of fatigue, arthralgias and Raynaud's syndrome. On admission her laboratory parameters showed systemic inflammation, and she was found to have pericarditis. At age 15 she developed repeated parotid swelling. Diagnosis of SS was based on histology of salivary glands and controlled with NSAID and HQ. One year later she presented with asthenia and jaundice. No infectious cause was identified and biopsy confirmed autoimmune hepatitis. ANA and anti-ds DNA were present leading to a diagnosis of SS with overlapping lupus disease. At the latest follow-up, the patient was treated by azathioprin and had stopped corticosteroids.

Patient 8

A 18-month-old Caucasian girl first presented with oligoarticular onset juvenile arthritis. Iridocyclitis was discovered at the onset of arthritis. At 9 years of age an extension of joint involvement occurred with 9 joints affected. She received MTX for 4 years with excellent response and low dose steroids to control uveitis. When she was 15 she developed salivary gland swelling with oral sicca syndrome and reactivation of arthritis. SS was confirmed by histology and typical autoantibody profile. Retrospectively the switch of the antinuclear antibodies specific for SS had occurred at age 14. As shown in Table 1 she later developed renal involvement with moderate renal insufficiency. Biopsy showed interstitial lymphocytic infiltration and mild fibrosis.

At the last follow-up the patient was in excellent condition on low dose steroids apart from oral and ocular sicca syndrome.

Discussion

Our series shows a large variability of symptoms in children diagnosed with SS. It illustrates the initial difficulties in defining a diagnosis due to a set of nonspecific symptoms not always suggestive of paediatric SS. Infectious recurrent parotitis is not uncommon in children, whereas paediatric SS is extremely rare. In addition, the association of recurrent parotitis and xerostomia-xerophthalmia may not always be applicable to the diagnosis of paediatric SS, either for a lack of sensitivity within the first phase of the disease or a difficulty in correctly assessing mild mucosal dryness in children. Of note, neither widespread dental caries nor other objective symptoms of oral dryness was recorded in our patients, and in most cases the diagnosis of oral dryness was based on a subjective feeling by the patient. Retrospectively all patients had a positive salivary gland histology (lymphocyte infiltration with Chisholm grade 3 or 4 in most cases), which we considered as a confirmation of the diagnosis of paediatric SS in the absence of any validated diagnosis criteria. In all but one patient the disease accompanied or followed extraglandular manifestations of autoimmunity like Raynaud's syndrome or arthritis. Some patients later developed extraglandular manifestations such as polyarthritis, hepatitis or glomerulonephritis with overlapping lupus disease in some cases, as has also been reported in adult onset SS (13). The association of SS, autoimmune hepatitis and myositis has also been previously described (14). Hematologic abnormalities affecting one or more cellular lineages, as in one patient of this series presenting with thrombocytopenia, are frequent manifestations of autoimmune connective tissue diseases, which may be related in some cases to disease activity (15). Age at onset, family history of autoimmune diseases, associated autoimmune manifestations and complications do not differ significantly from previously

published data in paediatric onset SS (Table II). Nevertheless, whereas recurrent parotid swelling was observed in the majority of children in several publications (16-18), this symptom was only present in 3/8 patients of our series. Also, oral sicca syndrome was rare compared to a Canadian cohort (25% vs. 60% (3)). Of note, our patients were from highly diverse ethnic origin, with only 2 children from Caucasian ethnicity, however the incidence of ethnicity on SS clinical presentation is unknown.

Existing criteria for SS syndrome were not always helpful for establishing the diagnosis in our series, even several years after the inaugural symptoms. Only one of our 7 patients with primary SS fulfilled the international consensus criteria of adult disease (9) and five patients fulfilled the suggested criteria for paediatric patients (2). According to the AECG criteria, 4 of 6 criteria including a positive biopsy sample or specific antibody positivity, or 3 out of the 4 objective criteria are required for the diagnosis of SS in adults (9). In our cohort there was histological evidence of salivary gland involvement in all patients. Sialography, ultrasound or MRI studies were not systematically performed. Although all children presented with either the typical histologic salivary gland involvement or antibodies to SS-A/SS-B, none of them fulfilled all 3 additional criteria (ocular and oral symptoms, objective evidence of dry eyes). The discrepancy between the clinical diagnosis of SS and classification according to the AECG criteria in the paediatric population has been noted elsewhere (2, 3, 5). Importantly paediatric populations often lack sufficient disease criteria for other diseases such as SLE compared to adults, as some symptoms may only develop with age (19-20). A recent review analysing over 100 children with primary SS concluded that compared to expert clinical diagnosis only 75% of patients would be diagnosed according to the existing classification systems (3). Salivary gland histology can be considered to be a rather objective and specific parameter (21). However, even when analysed by experienced pathologists, specificity

and sensitivity of the biopsy are reported to be only around 80%. In particular, salivary gland specimens can be infiltrated by lymphocytes in 20% of patients with other autoimmune disorders such as SLE. Furthermore non-specific sialadenitis was found in a healthy control population (22). In our cohort 6/8 children had typical salivary glands changes (grade 3 or 4 of the Chisholm scale (11)), whereas the two remaining patients showed lymphocytic infiltration compatible with the diagnosis of SS. A follow-up assessment in children with moderate salivary glands lymphocytic infiltration would be worthwhile as serial studies show significant progression of histological findings in at least 50% of adult patients with sicca syndrome (23).

In summary, clinical presentation of childhood onset SS is highly diverse and diagnostic criteria are therefore not easily established. In our cohort we did not find recurrent parotid swelling to be contributive to an early diagnosis. Sicca syndrome was present in less than 2/3 of our patients at the onset of the disease. However, testing for ocular dryness seems to be a useful criterion – especially the easily performed Schirmer's test. Parotid ultrasonography and more recently magnetic resonance sialography are less invasive than salivary gland biopsies in evaluating parotid gland damage and certainly valuable in experienced hands. These methods however remain to be evaluated prospectively. In childhood-onset SS, careful follow-up is required as some patients may develop visceral involvement with overlapping lupus features years after being diagnosed with SS.

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