Features of childhood Sjögren's syndrome in comparison to adult Sjögren's syndrome: considerations in establishing child-specific diagnostic criteria

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Abstract

Objective

To describe the clinical features of childhood Sjögren's syndrome (SS) in comparison to adult SS and to evaluate possible child-specific modifications to existing adult criteria for use in diagnosing childhood SS.

Methods

We retrospectively identified children (age <18 years) with SS and compared the clinical, laboratory, and histopathological features of these children based on presence or absence of parotitis. We compared these features to adults with SS and evaluated the applicability of existing classification criteria in diagnosing childhood SS. Child-specific modifications to existing criteria were evaluated.

Results

Twenty-six children were included in our childhood SS group. Sixteen children had parotitis at or before presentation. Absence of parotitis was associated with greater degree of organ damage based on SS disease damage index. Compared to 413 adult SS patients, childhood SS was more commonly associated with parotitis, positive serologies, neurologic and nephrologic manifestations, and non-specific features (fever, lymphadenopathy) but less commonly associated with dry mouth and dry eyes. Only a minority of these children met previously established criteria for adult SS. Inclusion of child-specific features such as parotitis and the presence of any focal lymphocytic sialadenitis on minor salivary gland biopsy increased the proportion of children meeting these criteria.

Conclusion

Childhood SS features may be different than adult SS features necessitating child-specific criteria for better diagnosis of childhood SS, a key step towards better understanding the features, prognosis, and outcomes in this disease.

Key words
Sjögren's syndrome, paediatrics, child, diagnosis, parotitis

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Introduction

Sjögren's syndrome (SS) is a chronic autoimmune disease primarily affecting lacrimal and salivary glands but with potential to extend to other organs as well. Thus Sjögren's syndrome has the potential to cause considerable morbidity and decreased quality of life (1-8). Sjögren's syndrome is well-characterised in adults, although the best classification criteria for adult Sjögren's syndrome continue to be debated (9-14). Currently the most widely used criteria are those of the 2002 revised American–European Consensus Group (AECG) (9); however, the 1999 revised Japanese criteria are still widely used in Japanese studies (12), and the American College of Rheumatology (ACR) recently endorsed a new set of criteria proposed by the Sjögren's International Collaborative Clinical Alliance (13). These three criteria identified similar groups of adult SS patients with considerable overlap (15, 16).

Childhood SS was reported as early as the 1960s (17) but is generally considered to be rare. More recently, it has become clear that parotitis is the most frequent manifestation in childhood SS (18-23) and that paediatric cases may be underdiagnosed due to lack of typical sicca symptoms at presentation (18, 20, 23-25). Accordingly, the classification criteria for adult Sjögren's syndrome may not be adequate for paediatric use (22), and modifications of the AECG criteria for use with childhood SS have not improved sensitivity to adult standards (22, 26). The Japanese and ACR criteria have not, to our knowledge, been evaluated in children. Child-specific criteria have been proposed (18); however, even these have a sensitivity of only 76% for diagnosing childhood SS (18, 22, 26). In this study, we retrospectively identified and reviewed childhood SS patients diagnosed and followed at a single institution, compared these paediatric patients based on the presence or absence of parotitis, then compared our childhood SS patients to a large group of adult SS patients from a single institution, and evaluated the applicability of existing criteria for diagnosing childhood SS. Moreover, we modified the adult criteria to include child-specific features and discuss a framework for moving forward with development of diagnostic criteria for childhood SS.

Materials and methods

Childhood SS patients

Medical records between 1998 and 2008 at The Children's Hospital of Philadelphia were retrospectively reviewed for children <18 years old with a suspected diagnosis of SS (ICD-9 710.2). Patients were included in the childhood SS group if diagnosed with SS by a paediatric rheumatologist and followed for a minimum of 1 year with no subsequent alternate diagnosis. Patients with other autoimmune diseases were not excluded. The study was approved by the Institutional Review Boards at the Children's Hospital of Philadelphia and the University of Pennsylvania.

The systematic evaluation included documentation of signs, symptoms, unstimulated salivary flow rates, serologies, scintigraphy results, ophthalmologic evaluation for dry eyes, labial minor salivary gland (LSG) biopsy results, and extraglandular manifestations. SS disease damage index (SSDDI) was calculated for each child (27). Detailed histopathological analysis of a subset of these children was recently published (28).

Adult SS patients

Data for adult SS patients were retrieved from the University of Pennsylvania SS database. This database includes data from a retrospective chart review of patients ≥18 years old who met the AECG classification criteria for SS and were seen for at least 2 visits. Many of these patients also met the ACR criteria for SS and were included in a later validation study (13). All adult patients underwent a complete history and physical examination, whole mouth sialometry, salivary scintigraphy, serologies, other routine labs and, when necessary, LSG biopsy (9). All patients had an unanesthetised Schirmer test, fluorescein corneal staining, fluorescein tear break-up time and ocular surface staining (lissamine green or rose Bengal) as part of the evaluation.

Evaluation of established criteria and child-specific modifications

We evaluated the applicability of the existing adult (ACR (13), AECG (9), and Japanese (12)) criteria and the previously proposed diagnostic criteria for juvenile primary SS (18) (Table I) using our childhood Sjögren's syndrome group. We did not exclude patients with other autoimmune diseases as required for diagnosis of primary Sjögren's syndrome. Child-specific modifications of these criteria include two changes:

1. adding parotitis (defined as acute or subacute painful swelling of the parotid gland(s)) to the objective criteria for salivary gland dysfunction in AECG (and removing it from the oral symptoms item), as an alternate to positive ocular surface staining (*i.e.* parotitis and/or positive ocular staining) in the ACR criteria, and to the objective oral item in the Japanese criteria;
2. changing the definition of positive histopathology to any FLS (*i.e.* focus score >0 foci/4 mm^2) in each criterion (28).

Statistical analysis

Patients with missing data in a particular category were excluded from analysis of that category. Statistical analyses were performed with JMP10.0.2 (JMP Software). Fisher's exact test was used for contingency table analyses to compare categorical variables. Wilcoxon rank sum test was used to compare continuous variables (focus score and SSDDI).

Results

Features of childhood SS

Twenty-six patients were included in the childhood SS group (Table II). All patients were diagnosed with SS by a paediatric rheumatologist (the current gold standard), followed for a minimum of 1 year, and had either positive serologies (anti-SSA/Ro, anti-SSB/La, or positive ANA and positive RF) or histopathology consistent with current adult criteria for SS. Twenty-four (92.3%) patients were female. The median (range) age at diagnosis was 12.3 (4-17.8) years. The median (range) follow-up time was 3 (1–11) years. The chief complaint at the initial paediatric rheumatology visit at which childhood SS was considered included 11 (42.3%) patients with parotid swelling, 6 (23.1%) with joint pain, 3 (11.5%) with neurological abnormality, 3 (11.5%) with nephrological abnormality, 2 (7.7%) with dry mouth and dry eyes, and 1 (3.8%) with purpura. While only 2 presented with the chief complaint of dry mouth or dry eyes, a comprehensive review of systems revealed 9 (34.6%) patients with dry

Table I. Criteria for classification or diagnosis of Sjögren's syndrome*.

Category	AECG	Japanese	ACR	Juvenile SS
Clinical symptoms	1. Dry eyes 2. Dry mouth (including parotitis)			1. Recurrent parotitis or parotid enlargement 2. Recurrent conjunctivitis (non-allergic and non-infectious) or keratoconjunctivitis sicca 3. Recurrent vaginitis 4. Systemic: fever of unknown origin, arthralgias, hypokalemic paralysis, or abdominal pain
Objective	3. At least one of: a. Schirmer test ≤5 mm/5 min b. van Bijsterveld score ≥ 4 (any ocular dye) 4. At least one of: a. Unstimulated whole salivary flow ≤1.5 ml/15 min b. Parotid sialography with diffuse sialectasias without obstruction of major ducts c. Salivary scintigraphy (delayed uptake, decreased concentration, delayed excretion of dye)	1. Schirmer test ≤5 mm/5 min AND at least one of: a. van Bijsterveld score ≥3 (rose bengal) b. positive fluorescein staining test 2. At least one of: a. Abnormal sialography ≥ Stage I b. Decreased salivary secretion (≤10 ml/10 min chewing gum test or ≤2 g/2 min Saxon test) AND decreased salivary function on scintigraphy	1. Keratoconjunctivitis sicca with ocular staining score ≥3 (lissamine green + fluorescein)	5. Ocular dryness (ocular staining or Schirmer test) 6. Abnormal sialography 7. Elevated serum amylase 8. Leukopenia or elevated ESR 9. Hyperimmunoglobulinaemia (polyclonal) 10. Renal tubular acidosis
Serology	5. Anti-Ro/SSA and/or anti-La/SSB autoantibodies	3. Anti-Ro/SSA and/or anti-La/SSB autoantibodies	2. At least one of: a. Anti-Ro/SSA and/or anti-La/SSB b. Positive RF and ANA ≥1:320	11. At least one of: anti-SSA, anti-SSB, high titer ANA (speckled pattern), RF
Histopathology	6. Focal lymphocytic sialadenitis with focus score ≥1 lymphocytic focus per 4 mm^2 glandular tissue	4. At least one of: a. Focal lymphocytic sialadenitis with focus score ≥1 lymphocytic focus per 4 mm^2 glandular tissue b. Focal lymphocytic dacryoadenitis with focus score ≥1 lymphocytic focus per 4 mm^2 glandular tissue	3. Focal lymphocytic sialadenitis with focus score ≥1 lymphocytic focus per 4 mm^2 glandular tissue	12. Lymphocytic infiltration of salivary glands or other organs
Diagnosis or Classification Requirements	Classification requires: 4 of 6 items including at least 1 of histopathology or serology OR 3 of 4 objective items (#3-6)	Diagnosis requires: at least 2 of 4 items	Classification requires: at least 2 of 3 items	Diagnosis requires: at least 4 of 12 items

*modified from AECG (9), Japanese (12) ACR (13), Juvenile (18, 22, 26) SS criteria. For additional specifications of these criteria or descriptions of tests please see references.

Table II. Summary of characteristics of childhood Sjögren's syndrome cohort (n=26)*.

Patient ID	Age at dx (y)	Sex	PolyAI	Dry mouth¥	Parotitis	Caries	Dry eyes¥	Abnormal Schirmer test	Abnormal ocular stain	Abnormal salivary flow	Abnormal salivary scan	SSA/SSB	ANA§	RF	LSG biopsy	Extra-glandular (whole course)‖	Follow-up (y)	SSDDI
1	9.5	F	SLE	N	N	N	Y	N	N	ND	ND	SSA	Pos	Neg	2.2	R	1	0
2	11	F	JIA	Y	N	Y	Y	ND	ND	Y	ND	Neg	Pos	Neg	1	J, N, R, S, U	7	6
3	11.3	F	-	N	N	N	N	ND	ND	ND	ND	SSA/SSB	Pos	ND	0.8	N, R	5	2
4	12.8	F	-	N	N	N	N	N	ND	ND	ND	SSA/SSB	Pos	Neg	0.4	J, N	2	2
5	14.8	F	-	Y	N	Y	N	N	N	ND	ND	SSA/SSB	Pos	Pos	1.2	H, J, L	1	0
6	15.8	F	-	Y	N	N	Y	ND	ND	ND	ND	SSA/SSB	Pos	Neg	2.3	J, L, R	2	2
7	16.1	F	thyroid	N	N	N	Y	ND	N	ND	ND	SSA	Neg	Pos	ND	F, H, J, R	3	0
8	16.3	F	thyroid	Y	N	Y	Y	Y	Y	Y	ND	Neg	Pos	ND	1	F, J	1	2
9	17.4	F	-	N	N	Y	Y	Y	Y	ND	ND	SSA/SSB	Pos	ND	ND	J, L	1	1
10	17.8	F	-	N(→Y)	N	N	N(→Y)	N	N	ND	ND	SSA/SSB	Pos	Neg	0.7	J	2	2
11	4	F	SLE	Y	Y	Y	Y	ND	ND	Y	Y	Neg	Pos	Pos	ND	J, L	11	1
12	5.8	M	SLE	Y	Y	Y	Y	ND	ND	ND	ND	Neg	Pos	Neg	Pos¶	J, L, S, U	5	0
13	7.6	F	-	Y	Y	Y	Y	Y	N	ND	ND	SSA/SSB	Pos	Pos	ND	F, L	8	1
14	8.8	F	-	Y	Y	Y	Y	Y	N	ND	ND	SSA	Pos	ND	2	F, L, N, S	3	1
15	9.1	F	-	Y	Y	Y	N	ND	N	ND	ND	SSA/SSB	Pos	Pos	ND	H, L	5	0
16	10.6	F	-	N	Y	Y	N	ND	ND	ND	ND	SSA/SSB	Pos	Pos	1.2		1	0
17	10.8	F	-	N	Y	N	N	Y	ND	Y	ND	SSA	Pos	Pos	ND		1	2
18	10.9	F	psoriasis	Y	Y	Y	N	N	N	ND	ND	SSA/SSB	Pos	Pos	ND		2	0
19	11.7	F	-	N	Y	Y	N(→Y)	Y	Y	ND	ND	SSA/SSB	Pos	Pos	ND	F	5	2
20	11.9	F	-	N(→Y)	Y	N	N	ND	N	ND	ND	SSA	Pos	Pos	0.9	F, L, N, S	2	0
21	13.2	F	-	Y	Y	N	Y	ND	Y	ND	ND	SSA/SSB	Pos	Pos	ND	J, L	3	0
22	13.4	F	-	N	Y	N	N	N	ND	ND	ND	SSA/SSB	Pos	Pos	1.1	J, L	5	0
23	14.5	F	-	Y	Y	Y	Y	N	ND	ND	ND	SSA/SSB	Pos	Pos	2.7	J	2	0
24	14.5	M	-	Y	Y	N	N	N	N	Y	ND	SSA/SSB	Pos	Pos	0.5		3	1
25	15.6	F	morphea	Y	Y	Y	Y	N	N	N	Y	SSA/SSB	Pos	Pos	ND	J, N	4	1
26	17.6	F	-	Y	Y	Y	Y	N	N	N	Y	SSA/SSB	Pos	Pos	ND	H, J, L	5	0
Total		24 F/2 M	8/26	17/26	16/26	15/26	16/26	6/16	4/16	5/7	3/3	22/26	25/26	16/22	15/15	22/26		

*ANA: antinuclear antibody; dx: diagnosis; LSG: labial salivary gland; N: no/absent; ND: not done; Neg: negative; PolyAI: polyautoimmunity; Pos: positive; RF: rheumatoid factor; Y: yes/present; y: years; SSDDI: Sjögren's syndrome disease damage index. ¥N(→Y), developed after diagnosis. §Pos ANA defined as titer ≥1:160. ‖F: fever; H: haematological (leukopenia, lymphopenia); J: arthritis/arthralgias; L: lymphadenopathy; N: neurological (optic neuritis, neuromyelitis optica, meningoencephalitis, cranial neuropathy, autonomic dysfunction); R: nephrological (nephrocalcinosis, renal tubular acidosis, interstitial nephritis); S: rash; U: uveitis. ¶diffuse lymphoplasmacytic infiltrate with lymphoepithelial lesions consistent with late SS. This is consistent with SS and FS>1 (coalescence of individual foci makes exact enumeration not possible).

mouth or dry eyes as part of the initial SS manifestations and an additional 9 (34.6%) who developed dry mouth or dry eyes after initial SS symptoms but prior to diagnosis. Thus, at diagnosis, 18 (69.2%) of our patients had dry mouth or dry eyes (Table II). Following diagnosis, an additional 3 (11.5%) patients developed dry mouth or dry eyes. Parotitis was also more prevalent at diagnosis, occurring in an additional 5 children beyond the 11 with parotid swelling as their chief complaint. Thus, 61.5% of our childhood SS patients experienced parotitis. Fifteen (58%) children had multiple dental caries, 11 with parotitis and 4 without parotitis. Of these children with multiple caries, most (12 of 15) had dry mouth symptoms on review of systems; however, 3 children with multiple caries had no sensation of dry mouth.

Extraglandular end-organ damage included neurological damage (3 with CNS involvement and 1 with autonomic dysfunction) and nephrological damage (2 with nephrocalcinosis and 2 with renal tubular acidosis). One patient who developed progressive lymphadenopathy required repeated biopsies to rule-out lymphoma. One patient developed pyogenic parotitis. Polyautoimmunity occurred in eight children (Table II).

Features of childhood SS based on presence or absence of parotitis

While parotitis is the most common feature in childhood SS (18-23), nearly 40% of our childhood SS patients did not have parotitis (Table II). To determine if features among childhood SS patients differ based on the presence or absence of parotitis, we compared clinical, laboratory, and histopathological features of these two subsets within our childhood SS group (Table III). The no parotitis group was older at diagnosis (p=0.035). Other glandular manifestations and evaluations did not differ significantly between the groups. A non-statistically significant increase in dry mouth and dental caries was noted in the parotitis group. However, interestingly, all children with LSG biopsies (including 8 patients without parotitis) had FLS. Extraglandular manifestations occurred in all children in the non-parotitis group, but only nephrological manifestations were significantly higher in this group (p=0.004). SSDDI were higher in the non-parotitis group (p=0.042), in which the majority of children showed SSDDI >1 (6 of 10 compared to 2 of 16 in the parotitis group; p=0.026 by Fisher's exact test). Positive RF was more common in the parotitis group (p=0.004), while the other serologies did not differ significantly between the groups. Of note, all children in both groups were positive for ANA or anti-SSA. Comparison of children with and without parotitis limited only to those with primary Sjögren's syndrome (*i.e.* excluding those with SLE, JIA, or morphea) again resulted in increased age, increased nephrological manifestations, and increased SSDDI in the no parotitis group along with increased RF positivity in the parotitis group (not shown). In addition, the increase in joint pain manifestations in the no parotitis group became statistically

Table III. Manifestations, laboratory findings and organ damage in patients with childhood SS based on presence or absence of parotitis*.

	Parotitis (n=16)	No Parotitis (n=10)	$p^{¥}$
Demographics			
Age, mean ± SD	11.2±3.6	14.3±2.9	0.035
Female, %	87.5	100	0.508
Glandular manifestations			
Dry eyes, %	56.2	70	0.683
Dry mouth, %	75	50	0.234
Any sicca, %	81.2	80	1.000
Dental caries, %	68.8	40	0.228
Schirmer's I test, %	40 (4/10)	33.3 (2/6)	1.000
Rose bengal or fluorescein test	20 (2/10)	33.3 (2/6)	0.604
Unstimulated whole salivary flow <0.1ml/min, %	60 (3/5)	100 (2/2)	1.000
Abnormal scintigraphy, %	100 (3/3)	-	
LSG biopsy FS ≥ 1, %	66.7 (4/6)	62.5 (5/8)	1.000
LSG biopsy FS >0, %	100 (6/6)	100 (8/8)	1.000
Extra-glandular manifestations			
Any, %	75	100	0.136
Joint pain, %	43.8	80	0.109
Lymphadenopathy, %	56.2	30	0.248
Neurological, %	18.8	30	0.644
Fever, %	25	20	1.000
Nephrological, %	0	50	0.004
Haematological, %	12.5	20	0.625
Dermatological, %	18.8	10	1.000
Laboratory features			
Anti-SSA and/or Anti-SSB, %	87.5	80	0.625
Anti-nuclear antibodies (ANA), %	100	90	0.385
ANA or anti-SSA, %	100	100	1.000
Rheumatoid factor, %	93.3 (14/15)	28.6 (2/7)	0.004
Organ damage			
SSDDI, mean (95% confidence interval)	0.6 (0.2-1.0)	1.7 (0.4-3.0)	0.042

*Numbers include patients with indicated manifestations during the course of disease (not limited to symptoms at diagnosis). FS: focus score; LSG: labial salivary gland; SS: Sjögren's syndrome; SSDDI: SS disease damage index. ¥Wilcoxon rank sum test (age and SSDDI) or Fisher's exact test.

significant (p=0.024). Thus, the overall differences noted in Table III are not likely due to the inclusion of both primary and secondary Sjögren's syndrome.

Features of childhood SS in comparison to adult SS

To identify the differences between childhood and adult SS that might account for the inadequacy of the AECG criteria in diagnosing childhood SS (22, 26), we compared clinical, laboratory, and histopathological features of our childhood SS patients with a large group of adult SS patients (Table IV). In adult SS, 381 patients had SS alone, while 32 had SS along with another autoimmune disease (13 with limited scleroderma, 10 with rheumatoid arthritis, 4 with systemic lupus erythematosus, 2 with undifferentiated connective tissue disease, 1 with diffuse scleroderma, 1 with mixed connective tissue disease, and 1 with dermatomyositis). Dry eyes and dry mouth were more common in adult SS while parotitis was more common in childhood SS. Only 2/3 of our childhood SS patients with LSG biopsies had focus scores ≥1 focus/4 mm^2, but all had evidence of FLS with at least one focus present (*i.e.* focus score >0 foci/4 mm^2) as previously reported for a subset of these patients (28). Extraglandular manifestations such as fevers, lymphadenopathy, neurological and nephrological abnormalities, and serological abnormalities (anti-SSA/SSB antibodies, ANA and RF) were all more common in childhood SS than in adult SS. When secondary Sjögren's syndrome patients (adults and children) were excluded, comparable differences in these parameters were again noted (not shown) except for the increased occurrence of neurological and nephrological manifestations in children, which were no longer statistically significantly different (p=0.253 and p=0.052, respectively). Thus, the majority of differences in children compared to adults were not due to the inclusion of both primary and secondary Sjögren's syndrome in our adult and childhood SS groups.

Childhood SS involved a similar degree of organ damage based on comparable SSDDI. Lymphoma was not found in childhood SS patients but one patient (patient 12) developed progressive lymphadenopathy requiring frequent biopsies. Of note, one adult SS patient with bacterial parotitis at age 15 and diagnosis of SS at age 18 (persistent parotid swelling, dry mouth, dry eyes, abnormal salivary nuclear scan, and positive anti-SSA and anti-SSB antibodies) subsequently developed lymphoma at age 21.

Evaluation of criteria for diagnosis of childhood SS

Previous studies demonstrated poor sensitivity of the AECG criteria for use with childhood SS (22, 26), but the evaluation of Japanese and ACR criteria has not been reported. In evaluating these criteria and their applicability to our childhood SS patients, we first noted that among our 26 subjects, none had undergone all of the testing required to evaluate the sensitivity of these criteria. This may reflect the decreased regularity in performing functional salivary and lacrimal gland testing in children. Ocular tests were performed in 20 of the 26 subjects, with abnormalities found in only 7 (Table II). Among these 20 children, only 12 underwent both Schirmer and ocular surface staining, but none had ocular surface staining scores reported as required by the adult SS criteria. Thus none of the children met the ocular staining items in the ACR, AECG, or Japanese criteria. The only remaining objective ocular item that could be met was the abnormal Schirmer test item. Salivary function testing was performed less frequently (7 of 26 patients), with abnormalities reported in all 7, but with both salivary flow and salivary scans performed for only 3. LSG biopsy was performed in

15 of the 26 children with abnormalities found in all of the samples. In the absence of complete data sets, we could not evaluate the sensitivities of the established criteria; however, based on the available data (which we believe reflects data commonly available in paediatric rheumatology practice), we determined the number and percentage of children meeting each criterion (Table V). Only 9 (34.6%) of our childhood SS patients met the AECG criteria, 7 (26.9%) met the ACR criteria, 7 (26.9%) met the Japanese criteria, and 22 (84.6%) met the previously proposed diagnostic criteria for juvenile SS (Table V). Only three patients failed to meet any of these four criteria. Thirteen patients fulfilled at least one of the three adult criteria: three patients met all three criteria, four met the ACR criteria and the Japanese criteria, and six met only the AECG criteria. None met only the ACR criteria or only the Japanese criteria. Notably, 10 out of the 13 children who did not meet any of the adult criteria met the proposed juvenile SS criteria.

Table IV. Demographics, manifestations, laboratory findings and organ damage in patients with childhood SS and adult SS*.

	Childhood SS (n=26)	Adult SS (n=413)	$p^{¥}$
Demographics			
Age, mean ± SD	12.4±3.6	54.4±13.7	
Female, %	92.3	92.5	1.000
Glandular manifestations			
Dry eyes, %	61.5	84.8	0.005
Dry mouth, %	65.4	88.6	0.003
Parotitis, %	61.5	23.7	<0.001
Schirmer's I test < 5 mm/5 min, %	37.5 (6/16)	49.1 (114/232)	0.443
Unstimulated whole salivary flow <0.1ml/min, %	71.4 (5/7)	43.6 (143/328)	0.248
Abnormal salivary scintigraphy, %	100 (3/3)	74.4 (160/215)	0.574
LSG biopsy FS ≥1, %	66.7 (10/15)	84.3 (102/121)	0.142
Extra-glandular manifestations			
Joint pain, %	53.9	57.1	0.839
Lymphadenopathy, %	46.2	15.5	<0.001
Neurological, %	23.1	9.2	0.035
Fever, %	23.1	1.9	<0.001
Nephrological, %	19.2	3.9	0.005
Inflammatory eye disease (uveitis), %	7.7	1.9	0.113
Interstitial lung disease, %	0	1.2	1.000
Laboratory features			
Anti-SSA and/or Anti-SSB, %	84.6	56.6 (188/332)	0.006
Anti-nuclear antibodies, %	96.2	68.6 (205/299)	0.001
Rheumatoid factor, %	72.7 (16/22)	41.4 (79/191)	0.006
Organ damage			
SSDDI, mean (95% confidence interval)	1.0 (0.5-1.5)	1.0 (0.9-1.1)	0.987

*Numbers include patients with indicated manifestations during the course of disease (not limited to symptoms at diagnosis). FS: focus score; LSG: labial salivary gland; SS: Sjögren's syndrome; SSDDI: SS disease damage index. ¥Wilcoxon rank sum test (age and SS damage index) or Fisher's exact test.

Child-specific modification of adult criteria

We considered which child-specific features of the disease were not captured in the adult criteria and might therefore be appropriate to add to the adult criteria to render it more child-specific. We included parotitis as an objective item of salivary involvement for both the AECG and Japanese criteria, and as an alternate to ocular surface staining as the non-histologic/non-serologic item in the ACR criteria (*i.e.* to meet this ACR criteria item one must have ocular staining score ≥3 OR parotitis). While parotitis is already incorporated into the subjective oral symptoms item in the AECG criteria, we felt it should be an independent objective item (and no longer included in the oral symptoms item) in considering the diagnosis of childhood Sjögren's syndrome. Additionally, we redefined positive histopathology as any FLS (*i.e.* focus score >0 foci/4 mm^2) based on our recent study demonstrating FLS to be extremely rare in LSG biopsies of non-SS patients but present within all of the childhood SS specimens we analysed (28). With these modifications, the proportion of children meeting the modified paediatric criteria increased, but only the Japanese and ACR criteria improved significantly (Table V and not shown). Despite these improvements, the modified paediatric criteria performed no better than the previously proposed juvenile SS criteria.

Discussion

In adults, SS is well-accepted as a potentially devastating disease with considerable risk for development of systemic manifestations and decreased quality of life (29, 30). With validated diagnostic and classification criteria, studies of adult SS have led to a better understanding of specific risk factors for adverse outcomes including lymphoma and death (8, 30-32). Whether similar risk factors may predict outcomes in childhood SS is not known. In order to begin to characterise childhood SS prevalence, prognosis, and outcomes, we need to establish highly sensitive diagnostic or classification criteria. Children with SS rarely present with the complaints of dry eyes or dry mouth, the hallmark symptoms of adult SS. Interestingly, though, a majority of our childhood SS group had some degree of dry eyes or dry mouth on extensive questioning for review of systems. Without these classic adult SS symptoms as the chief complaint, a high index of suspicion is required to diagnose childhood SS. Based on this study and others, childhood SS should be considered in any child presenting with recurrent parotitis, the most common presentation of childhood SS (18-23). Interestingly, in our study, children without parotitis showed more organ damage as measured by SSDDI, suggesting that absence of parotitis may be a poor prognostic factor. However, children without parotitis were diagnosed at an older age and, thus, may have had longer duration of inflammation prior to diagnosis and treatment.

Table V. Evaluation of existing, proposed, and child-modified criteria for childhood SS patients*.

Patient ID	Established Criteria			Proposed Juvenile SS Criteria	Child SS-Modified (parotitis, FS>0)		
	Japanese	AECG	ACR		Japanese	AECG	ACR
1	+	-	+	+	+	-	+
2	-	+	-	+	-	+	-
3	-	-	-	-	+	-	+
4	-	-	-	-	+	-	+
5	+	-	+	-	+	-	+
6	+	+	+	+	+	+	+
7	-	-	-	+	-	-	-
8	-	+	-	+	-	+	-
9	-	-	-	+	-	-	-
10	-	-	-	-	+	-	+
11	-	-	-	+	-	-	+
12	-	-	-	+	+	+	+
13	-	+	-	+	+	+	+
14	+	+	+	+	+	+	+
15	-	-	-	+	+	-	+
16	+	-	+	+	+	+	+
17	-	+	-	+	+	+	+
18	-	-	-	+	+	-	+
19	-	-	-	+	+	+	+
20	-	-	-	+	+	+	+
21	-	-	-	+	+	+	+
22	+	-	+	+	+	+	+
23	+	+	+	+	+	+	+
24	-	-	-	+	+	+	+
25	-	+	-	+	+	+	+
26	-	+	-	+	+	+	+
TOTAL +	7	9	7	22	21	16	22
TOTAL %	27	35	27	85	81	62	85

*Criteria details listed Table I. Child-modified criteria include parotitis as an objective oral feature and a focus score (FS) >0 foci/4 mm^2 as definition for positive histopathology within the parameters of the indicated criteria (see text for details). + indicated meets criteria, - indicates does not meet criteria.

Thus, whether the absence of parotitis or the later diagnosis is responsible for the increase in organ damage remains to be determined, and whether pre- or post-pubescent status plays a role is not yet known. Besides recurrent parotitis, childhood SS should be considered in any child with sicca symptoms or unexplained recurrent dental caries (33, 34) and in children with unexplained kidney disease (renal tubular acidosis, interstitial nephritis, glomerulonephritis) (35, 36), neurological abnormalities such as NMO (37-39), unexplained fevers, arthritis/arthralgias, or rash (*e.g.* purpura, annular erythema) (20, 25).

When childhood SS is suspected clinically, the appropriate workup should ensue. While establishment of childhood SS diagnostic criteria will ultimately guide the specific testing, serological evaluation will be a key part of the childhood SS workup especially given the recent study demonstrating positive serologies years before diagnosis of SS in adults (40). In our group of childhood SS patients, all children were positive for either anti-SSA or ANA. Positive ANA and/or anti-SSA is not unique to our group and has been reported in multiple studies of childhood SS (18, 19, 21-26, 33, 36). However, some children with SS are negative for ANA, anti-SSA, and anti-SSB, yet demonstrate FLS on LSG biopsy (26, 34). Thus, a negative serologic workup should not necessarily preclude the diagnosis of childhood SS, and further investigation may be warranted. Ideally, identification of additional SS-relevant autoantibodies will result in a panel of serologies with high negative predictive value. A recent study identified additional SS-relevant autoantibodies positive in a number of otherwise seronegative adult SS patients (41); however, the relevance of such antibodies in childhood SS remains to be determined. In the absence of such a panel of serologic tests with high negative predictive value for childhood SS, further workup including a combination of imaging, measurement of exocrine gland function, and histopathological analyses should all be considered essential in the workup of childhood SS. We have recently demonstrated that the presence of any FLS on minor labial salivary gland biopsy is suggestive of childhood SS (28). Evaluations for exocrine gland function such as the Schirmer test, salivary flow quantitation, and ocular staining may be appropriate; however, child-specific normal ranges are not well defined. Moreover, if we could define and diagnose childhood SS prior to exocrine gland dysfunction then perhaps we could eventually alter the course of the disease and prevent exocrine gland dysfunction by means of immunomodulatory therapies. MR sialography (42, 43) and salivary gland ultrasound (44) can be abnormal in children and may provide sufficient evidence for childhood SS diagnosis with the more invasive histopathological analysis of minor labial salivary glands reserved for children who have inconclusive imaging or other features requiring a more definitive diagnostic test. Notably, salivary gland ultrasonography is a non-invasive tool to assess parotid gland involvement in children with Sjögren's syndrome as recently demonstrated for three children with recurrent parotitis due to childhood Sjögren's syndrome (44). Whether similar characteristic ultrasonographic findings might also help in diagnosing childhood Sjögren's syndrome in the absence of parotitis is not yet known but is worth evaluating.

Regarding diagnostic criteria, we evaluated the existing criteria as well as these criteria with child-specific modifications and found that the modified ACR criteria performed best overall with the modified Japanese criteria performing nearly as well. However, neither performed superior to the previously proposed juvenile SS criteria (18), which, in our study, performed better than previously noted (22, 26). We propose that future childhood SS diagnostic and classification criteria should be developed based on these objective criteria to include a combination of objective oral, ocular, serological, and histopathologi-

cal manifestations, requiring at least two of these (including at least one of either serological or histopathological features) for a positive diagnosis. The optimal items for each of these categories remain to be further evaluated in children. Objective evidence of salivary gland disease should include recurrent parotitis (non-infectious, observed by a physician) or findings on salivary gland imaging. Recurrent or persistent parotid swelling is suggestive of SS but can also have other aetiologies such as benign recurrent parotitis, mumps, diffuse infiltrative lymphocytosis syndrome (HIV), sarcoidosis, and IgG4-related disease, all of which should be considered and ruled-out as clinically appropriate.

Lacrimal gland disease may be measured by positive ocular staining, though positive ocular staining was noted in only 4 of the 16 children evaluated in our childhood SS group, suggesting that ocular manifestations may be less common in childhood SS or, alternatively, that positive ocular staining may be a later manifestation. Whether decreased saliva and decreased tears should be included remains to be determined and should be prospectively evaluated in children. Serological criteria should include a combination of ANA and anti-SSA antibodies perhaps with the addition of other autoantibodies. However, whether including anti-SSB, RF, or other autoantibodies (41, 45, 46) will provide additional diagnostic or prognostic value is not yet known. Histopathological findings should include FLS on LSG biopsy or biopsy of other salivary or lacrimal glands if tissue was procured for other purposes such as to rule out lymphoma. Further study to determine whether any FLS on LSG biopsies is adequate for childhood SS should be performed, though our preliminary study suggests this may be sufficient as we detected only one focus of lymphocytic infiltrate in only one sample from our 8 non-SS control LSG biopsy specimens (28).

Limitations of our study include a relatively small patient sample size, lack of non-SS control patients for specificity calculations, lack of an independent childhood SS group to evaluate sensitivities of child-specific modifications to the adult criteria, retrospective data collection, and several missing data points. Since an objective gold standard for the diagnosis of childhood SS is absent, formal expert consensus methodology should be used to develop preliminary diagnostic and classification criteria for childhood SS. The establishment of an international Childhood SS Working Group will aid in these pursuits.

In summary, child-specific criteria for childhood SS are greatly needed for further characterisation of this potentially devastating disease and to fill the wide gaps in our knowledge of optimal treatments and long-term outcomes for children with Sjögren's syndrome. Both increasing awareness of childhood SS and establishing more sensitive criteria will facilitate earlier diagnosis and studies to evaluate prognosis including the risk for developing lymphoma.

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