Primary Sjögren's Syndrome in Children and Adolescents: Are Proposed Diagnostic Criteria Applicable?

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ABSTRACT. ***Objective.*** To compare the proposed criteria for the diagnosis of primary Sjögren's syndrome (pSS) in childhood to the validated American-European Consensus Group (AECG) classification criteria for pSS in adults.

Methods. Charts of 7 children with pSS seen at British Columbia's Children's Hospital (BCCH) and data on 128 children identified through Medline in the English language literature between 1963 and 2003 were reviewed for pediatric and AECG criteria for pSS. The presence of ≥ 4 criteria was required to satisfy the respective classification criteria. The expert clinical opinion of pediatric rheumatologists was considered the gold standard for diagnosis.

Results. A total of 24/62 (39%) cases satisfied the AECG criteria; 47/62 (76%) satisfied the proposed pediatric criteria. Inclusion of recurrent parotitis increased the sensitivity of the pediatric clinical criteria. From the cases, 78/133 (59%) satisfied the pediatric oral symptom criteria; only 6/78 (8%) had xerostomia in the absence of recurrent parotitis. There was no reported case of recurrent conjunctivitis in the absence of keratoconjunctivitis sicca. We found 101/130 (78%) cases had at least one positive autoantibody test result [antinuclear antibodies (ANA), rheumatoid factor (RF), SSA, SSB]; 78/123 (63%) had autoantibodies to SSA or SSB.

Conclusion. The AECG adult criteria for pSS should not be applied to children as the sensitivity is unacceptably low. The inclusion of recurrent parotitis increases the sensitivity of the pediatric criteria, and recurrent parotitis should alert the clinician to the possibility of pSS. The inclusion of recurrent conjunctivitis did not improve the sensitivity over the AECG ocular criteria. The addition of ANA and RF to the AECG criteria did not change the number of patients satisfying the criteria for pediatric pSS. (J Rheumatol 2005;32:2225–32)

Key Indexing Terms:
PRIMARY SJÖGREN'S SYNDROME CLASSIFICATION
DIAGNOSIS PEDIATRIC PAROTITIS

Sjögren's syndrome (SS) is an idiopathic systemic autoimmune disease affecting predominantly the exocrine glands, with the classic symptom complex of dry eyes (keratoconjunctivitis sicca) and dry mouth (xerostomia). Extraglandular involvement in SS may include interstitial pneumonitis, interstitial nephritis, isosthenuria or renal tubular acidosis, thyroiditis, central nervous system involvement, vasculitis, and an increased incidence of lymphoma[1,2].

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Dr. Houghton is a Pediatric Rheumatology Fellow at the University of British Columbia and is supported by The Arthritis Society.

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Accepted for publication June 7, 2005.

Primary SS (pSS) may occur as an isolated disorder, but secondary SS in association with another autoimmune disease is more common. PSS is most prevalent in women in their fourth and fifth decades; it is uncommonly reported in childhood, with about 130 cases in the literature[3-5]. PSS is probably underdiagnosed in childhood; the spectrum of presentation can be broad and long delays in diagnosis are not uncommon. It is likely that some patients diagnosed with pSS in adulthood experienced symptom onset in childhood. The clinical presentation of pSS in childhood may differ from the clinical presentation in adulthood. Cases of pediatric pSS are reported to have a higher incidence of recurrent parotitis and a lower incidence of sicca complex symptoms[5-13]. Pathological and laboratory findings in children with SS are similar to those found in adults, with characteristic lymphocytic infiltration of exocrine glands and the presence of hypergammaglobulinemia, elevated erythrocyte sedimentation rate (ESR), positive antinuclear antibodies (ANA), and autoantibodies to the nuclear antigens Ro/SSA and La/SSB[2].

There are several proposed sets of diagnostic criteria for

adult pSS[14-16]. The revised European Community Study Group classification criteria proposed by the American-European consensus group (AECG) have been validated for adults and include 6 items: ocular symptoms, oral symptoms, evidence of keratoconjunctivitis sicca, focal sialoadenitis by minor salivary gland biopsy, instrumental evidence of salivary gland involvement, and presence of SSA or SSB autoantibodies. The presence of 4 of the criteria, with the exclusion of patients who have negative autoantibodies or minor salivary gland biopsy, was found to have a sensitivity of 89.5% and specificity of 95.2%[14].

Criteria for the diagnosis of pSS in children have been suggested by Bartunkova, *et al*[3], but they have not been validated. The introduction of pediatric criteria is important, as it is well recognized that children do not present with typical sicca symptoms[5-13]. These proposed pediatric criteria differ from the AECG criteria by the inclusion of parotid enlargement or recurrent parotitis in childhood as additional oral symptoms, and recurrent conjunctivitis as an additional ocular symptom. They also include elevated amylase, distal renal tubular acidosis, leukopenia, elevated ESR, the presence of ANA and RF, and hypergammaglobulinemia as additional biochemical and serological criteria. We report our recent clinical experience with pediatric pSS and summarize the clinical manifestations and immunologic and laboratory data of our patients, as well as those reported in the literature. We evaluate the diagnostic utility of the proposed pediatric criteria for pSS[3].

MATERIALS AND METHODS

This is a retrospective chart review study with analysis of the clinical, immunologic, and laboratory features of our pediatric pSS cases and other reported cases of pediatric pSS.

Patients. All patients with a diagnosis of pSS currently being followed through the pediatric rheumatology clinic at British Columbia's Children's Hospital (BCCH) were reviewed. We also reviewed BCCH hospital charts from 1993 to 2003 of all patients admitted either to hospital or to surgical daycare with an ICD-10 code for SS or sialoadenitis.

Literature review. All case reports and case series of pSS in childhood reported in the English language literature between 1963 and 2003 identified through Medline were reviewed.

Exclusion criteria were the presence of other identified autoimmune disease or the presence of autoantibodies suggestive of another primary autoimmune disease (anti-dsDNA, anti-Sm, anti-RNP), sarcoidosis, graft versus host disease (GVHD), past head and neck radiation, and known human immunodeficiency virus infection or hepatitis C infection.

Data collection, by retrospective chart review or by extraction of information from individual publications, included demographic, clinical, immunologic, and other laboratory information that incorporated items from both the proposed pediatric criteria and adult criteria for pSS.

Few reports have complete data; therefore, depending on the availability of data for each criterion, the denominator used for analysis varies. The following clinical indicators were recorded: ocular symptoms (dry eyes, keratoconjunctivitis sicca, and recurrent conjunctivitis without obvious allergic or infectious etiology); oral symptoms (presence of dry mouth, recurrent parotitis or enlargement of parotid gland); systemic symptoms (fever of unknown origin, noninflammatory arthralgias or arthritis, abdominal pain, hypokalemic paralysis); and extraglandular symptoms (neurologic, pulmonary, renal, Raynaud's phenomena). Laboratory measures included: RF, ANA, SSA and SSB, immunoglobulins, ESR, complement C3 and C4, white blood cell count, and urinalysis. Additional investigations included documentation of ocular dryness (Schirmer test, Rose-Bengal stain); evidence of parotid involvement (scintiscan, sialography); and histological evidence of lymphocytic infiltration of the minor salivary glands or other organs. The presence of 4 or more pediatric pSS criteria or 4 or more AECG criteria was required to satisfy the respective classification criteria. The expert clinical opinion of pediatric rheumatologists was considered the gold standard for diagnosis.

RESULTS

Seven patients with a clinical diagnosis of pSS have been followed in the BCCH pediatric rheumatology program since 2001. No additional cases were identified on review of BCCH inpatient records from 1993 to 2003: no patient was discharged with an ICD-10 code for SS; 32 were discharged with an ICD-10 code for sialoadenitis but were excluded [infectious parotitis (n = 25), recurrent parotitis with negative SSA and SSB (n = 5), parotitis as adverse drug reaction (n = 1), GVHD (n = 1)].

Cases

Patient 1. A 12-year-old Caucasian girl was referred for evaluation of 3 episodes of right-side parotitis occurring over a 16 month period. She denied dry eyes, dry mouth, or dysphagia and had no other systemic complaints. There was no family history of autoimmune or rheumatic disorders. Her general examination was unremarkable; gross clinical examination revealed normal production of saliva and tears. Investigations showed a strongly positive RF; positive ANA; positive SSA and SSB; negative Sm and RNP; normal complement; elevated ESR, amylase, IgG, and IgM levels; and normal urinalysis. At the parents' request, no treatment was initiated; she did not return for followup.

Patient 2. A Canadian First Nations girl was initially evaluated at age 10 years with a recent history of localized right facial swelling and tenderness that had been preceded by 3 days of wrist and proximal interphalangeal joint pain. Previously, she had 3 similar episodes of right-side facial swelling without associated joint pain. All these episodes resolved spontaneously within 1–2 weeks. She had no other systemic complaints. Her history was unremarkable aside from a tonsillectomy at age 7 years and nonspecific musculoskeletal complaints. She had a paternal great aunt and 2 paternal aunts with systemic lupus erythematosus (SLE) and a paternal aunt with rheumatoid arthritis. Other than bilateral enlarged anterior cervical lymph nodes, the general examination was unremarkable. Investigations showed positive RF and ANA; elevated SSA and SSB; negative anti-dsDNA, Sm, and RNP; normal complement, ESR, and immunoglobulin levels; and normal urinalysis. A minor salivary gland biopsy showed nonspecific focal lymphoplasmacytic infiltrate of duct epithelium. Two months after the initial assessment, she complained of increasing fatigue, dry mouth, and

intermittent arthralgias of the metacarpophalangeal joints. She was given prednisone and hydroxychloroquine, which significantly improved her energy level and arthralgias. However, her xerostomia persisted and she had new onset of ocular sicca symptoms. She continued taking hydroxychloroquine while prednisone was tapered and discontinued. Over the next 14 months, she had persistent xerostomia, a discrete episode of parotid swelling, recurrent arthralgias without arthritis, new onset of diffuse abdominal pain, and episodes of depression. She was lost to followup at age 16 years.

Patient 3. A 13-year-old Vietnamese-Canadian girl was admitted to hospital with fever, parotid swelling, and intermittent headaches. Episodes of painful, bilateral parotid swelling had occurred annually since age 7 years. *H. parainfluenza* was cultured from Stenson's duct during the last episode. She denied sicca symptoms or dysphagia. Interestingly, her twin sister had milder episodes of bilateral recurrent parotid gland swelling without ever requiring hospitalization. On examination, she appeared well apart from swollen parotid glands. Investigations showed a strongly positive RF; positive ANA; high titer antibodies to SSA and SSB; negative anti-dsDNA, Sm, and RNP; elevated ESR; elevated amylase; and elevated IgG, IgA, and IgM. She was started on prednisone and hydroxychloroquine, with complete resolution of parotid swelling and no further recurrences.

Patient 4. An 8-year-old Caucasian girl was referred for evaluation of recurrent painful, bilateral parotitis with low grade fever. She had a history of 2 similar episodes over a 6 month period. She was later diagnosed with keratoconjunctivitis sicca; she denied having oral sicca symptoms. Aside from a ruptured appendix at age 2 and a subsequent bowel obstruction, her medical history was not significant. There was no family history of autoimmune disease. Physical examination results were within normal limits. Investigations showed a strongly positive RF; positive ANA; high titer antibodies to SSA and SSB; negative anti-dsDNA, Sm, and RNP; elevated amylase; normal complement, ESR, and immunoglobulin levels; and normal urinalysis. Schirmer's test was decreased bilaterally (OD 2 mm, OS 6 mm). Although her parotids remained slightly enlarged over 5 months of followup, she had no recurrent painful episodes. She was treated with hydroxychloroquine and lubricant eye drops.

Patient 5. A 9-year-old Caucasian girl was initially assessed at age 5 years following 6 episodes of recurrent parotitis occurring over a 10 month period. The episodes were accompanied by fever, were sometimes bilateral, and resolved within a few days. She also complained of transient groin and lower abdominal pain, diffuse arthralgias of the hip and jaw, and a sandpaper-like rash on her trunk unassociated with the parotitis. Apart from one hospitalization with enlarged tonsils, mild epistaxis, and conjunctivitis, her general health was excellent. Her mother has Crohn's disease and her paternal grandmother died of SLE. The physical examination was within normal limits. Investigations showed elevated SSA and SSB; negative anti-dsDNA, Sm, and RNP; elevated amylase, ESR, and IgG; and normal urinalysis. A minor salivary gland biopsy revealed a moderate chronic inflammatory infiltrate and sialogram showed widespread sialectasis within the distal left parotid ducts and blocked distal right parotid ducts. Over a 5 month period, she had increased anorexia and fatigue and several more episodes of parotid swelling with low grade fevers. She also had more frequent episodes of epistaxis, diffuse abdominal pain, myalgias, and rash. She was given hydroxychloroquine; over the past 26 months of therapy she has had only occasional flares of parotid swelling and intermittent myalgias.

Patient 6. A 13-year-old Caucasian girl was referred for positive autoantibodies to SSA and SSB. She had a 30 month history of episodic anaphylactoid reactions associated with urticaria, angioedema of the lips and tongue, numbness of the throat, and severe abdominal cramps. For each episode she was given antihistamines but a specific etiology was not identified. On review of systems, she noted dry mouth; dysphagia; episodic chest pains; chronic nausea, heartburn, and intermittent diarrhea alternating with constipation; and 3 episodes of microscopic hematuria associated with dysuria and frequency. Family history revealed her mother has multiple sclerosis and possible juvenile idiopathic arthritis. Investigations showed a positive ANA; elevated SSA and SSB; negative anti-dsDNA, Sm, and RNP; normal complement levels; elevated ESR; and microscopic hematuria. No treatment was initiated at first. She was started on hydroxychloroquine 12 months later with resolution of her xerostomia and dysphagia, with no additional anaphylactoid episodes or new symptoms.

Patient 7. A 15-year-old Canadian First Nations boy was referred with hallucinations and high titers of antibodies to SSA and SSB. The laboratory tests were performed prior to initiation of psychotropic therapy. He had no musculoskeletal complaints and denied having sicca symptoms. There was no known family history of rheumatic disease. Physical examination was unremarkable. Other investigations showed a positive ANA; positive RNP; negative Sm and anti-dsDNA; and immunoglobulin levels were normal. No treatment for SS was initiated and on reassessment, his psychiatric symptoms had improved. He had no new symptoms, but high titer SSA and SSB antibodies persisted.

Tables 1 and 2 summarize the clinical and laboratory data of our 7 patients. The mean age of symptom onset was 8 years, 10 months (range 5–14 yrs), the mean age of diagnosis was 11 years, 7 months (range 6–15 yrs), and the mean time from symptom onset to diagnosis was 2 years, 9 months (range 0–8 yrs).

Table 1. Clinical features in our 7 patients with primary Sjögren's syndrome.

Patient	Sex	Ethnicity	Age at Symptom Onset, yrs	Age at Diagnosis, yrs	Recurrent Parotitis or Enlargement of Parotid	Oral Sicca Symptoms	Keratoconjunctivitis Sicca	Recurrent Conjunctivitis	Extraglandular Manifestations	Treatment	Response to Treatment
1	F	Caucasian	11	12	Yes	Yes	No	No	None	None	—
2	F	First Nation	7	15	Yes	Yes	Yes	No	Arthralgias, fatigue, abdominal pain	Hydroxychloroquine, 4 months prednisone	Initial improvement in fatigue and arthralgia; one recurrence of parotid swelling and persistent dry mouth
3	F	Vietnamese	7	13	Yes	No	No	No	None	Prednisone, hydroxychloroquine	Excellent; disease currently inactive
4	F	Caucasian	7	8	Yes	No	Yes	No	None	Hydroxychloroquine	No further parotitis episode
5	F	Caucasian	5	6	Yes	No	No	No	Arthralgias, abdominal pain, fatigue	Ibuprofen, hydroxychloroquine	Excellent; disease currently inactive
6	F	Caucasian	10	13	No	Yes	No	No	Arthralgias, episodic chest pain, GI complaints, dysuria & frequency	Hydroxychloroquine	Resolution of xerostomia and dysphagia with no additional anaphylactic episodes or new symptoms
7	M	First Nation	14	14	No	No	No	No	Hallucinations	Divalproex and quetiapine for psychotic episodes	Improvement of psychotic symptoms and no new symptoms

Table 2. Investigations and results in our 7 patients with primary Sjögren's syndrome.

Patient	Salivary Gland Biopsy	Elevated Amylase	Schirmer/Rose Bengal Stain	RF*	ANA*	SSA/SSB*	Anti-dsDNA, anti-Sm, anti-RNP, C3/C4*	ESR Elevated or leukopenia	IgG/IgM/IgA, g/l*	Urinalysis
1	NR	Yes	NR	1280	1:1280	Pos/Pos**	Negative	Yes	21.52/3.41/3.89	Normal
2	Pathologic	NR	NR	1280	1:1280	1333/1479	Negative	No	15.20/2.32/1.55	Normal
3	NR	Yes	NR	1280	1:1280	1333/1344	Negative	Yes	27.30/2.32/3.22	NR
4	NR	Yes	Pathologic	1280	1:640	1132/64	Negative	No	13.50/1.20/1.44	Normal
5	Pathologic	Yes	NR	NR	1:320	653/71	Negative	Yes	18.6/1.92/2.35	Normal
6	NR	NR	NR	NR	1:1280	1158/531	Negative	Yes	9.30/1.77/1.67	Trace blood
7	NR	NR	NR	NR	1:1280	1269/296	RNP positive (42)	No	15.70/1.00/1.60	NR

NR: not recorded. * Normal values: RF positive (> 20), SSA (0–46), SSB (0–14), Sm (0–40), RNP (0–40). ** Titers not quantified (partial identity). Normal values: IgG (7.16–17.11 g/l), IgA (0.47–2.49 g/l), IgM (0.15–1.88 g/l).

Review of the literature identified a further 128 cases of childhood pSS in case reports and small case series. Table 3 lists the proposed clinical, immunologic, and laboratory criteria for pSS in children and shows the frequency of each criterion for our case series, and for the 128 reported cases. For the "other" reported cases data were frequently incomplete; therefore, depending on the availability of data for each criterion, the denominator used for analysis varies. Table 4 lists the AECG classification for pSS in adults.

Adult criteria (AECG) for pSS were fulfilled by 1/7 (14%) of BCCH patients and 24/62 (39%) of all reported patients, compared to 5/7 (71%) and 47/62 (76%), respectively, satisfying the proposed pediatric criteria. The inclusion of recurrent parotitis or enlargement of the parotid gland in the pediatric criteria increased the sensitivity. The AECG oral symptom criteria include recurrent or persistent enlargement of the salivary glands as an adult, thus excluding children. If we interpreted the AECG criteria to include

Table 3. Proposed diagnostic criteria for juvenile primary Sjögren's syndrome.

	Case Series, n = 7	Literature, n = 128	Total (%)	References
I. Clinical symptoms				
1. Oral (dry mouth, recurrent parotitis or enlargement of parotid glands)	6/7	72/126	78/133 (59)	3–5, 7–13, 17–20, 22, 24–31
2. Ocular (recurrent conjunctivitis without obvious allergic or infectious etiology, keratoconjunctivitis sicca)	2/7	50/111	52/118 (44)	3–5, 9, 11–13, 17, 18, 20–22, 24, 27, 28, 31, 32
3. Other mucosal* (recurrent vaginitis)	0/1	6/15	6/16 (38)	3, 20, 29
4. Systemic (fever of unknown origin, noninflammatory arthralgias, hypokalemic paralysis, abdominal pain)	3/7	31/113	34/120 (28)	3–5, 7–9, 11–13, 19, 21, 22, 24–27, 29, 31–34
II. Immunologic abnormalities (presence of at least 1 of: anti-SSA, anti-SSB, high titer ANA, RF)	7/7	94/123	101/130 (78)	3–5, 7–9, 11–13, 19, 21, 22, 24–27, 29, 31–34
III. Other laboratory abnormalities or additional investigations.				
1. Biochemical (elevated serum amylase)	4/4	9/10	13/14 (93)	3, 27
2. Hematologic (leukopenia, high ESR)	4/7	36/43	40/50 (80)	3–5, 7, 8, 11, 13, 19, 25–27, 29, 30, 32–35
3. Immunologic (polyclonal hyperimmunoglobulinemia)	3/7	70/98	73/105 (70)	3–5, 7, 8, 10, 11, 13, 19, 22, 24–29, 32, 34–36
4. Nephrological (renal tubular acidosis)	0/7	2/15	2/22 (9)	3
5. Histological proof of lymphocytic infiltration of salivary glands or other organs	2/2	77/97	79/99 (80)	3–5, 7, 8, 10, 11, 13, 17–19, 22, 24–29, 31, 32, 34–36
6. Objective documentation of ocular dryness (Bengal red staining, Schirmer test)	1/1	57/100	58/101 (57)	4, 5, 9–11, 13, 17–22, 24, 26–29, 32, 35, 36
7. Objective documentation of parotid gland involvement (sialography)	1/1	69/83	70/84 (83)	4, 9–11, 18, 19, 22, 24–27, 29, 34,35
IV. Exclusion of all other autoimmune disease	7/7	128/128	135/135 (100)	
Presence of 4 or more juvenile pSS criteria (%)	5/7 (71)	42/55 (76)	47/62 (76)	
Presence of 4 or more American-European consensus criteria including either anti-SSA or anti-SSB, or histopathology (%)	1/7 (14)	23/55 (42)	24/62 (39)	
* Presence of 4 or more American-European consensus criteria (modifying oral symptom criteria to include recurrent or persistent salivary gland swelling in childhood) (%)	3/7 (43)	27/55 (49)	30/62 (48)	

* 3 = Recurrent vulvovaginitis, 2 = gastric hyposecretion, 1 = dryness pharynx, nares.

Table 4. American-European Consensus Group criteria for the classification of primary Sjögren's syndrome (adults)[14].

Ocular symptoms	Definition: a positive response to at least one of the following 3 questions: 1. Have you had daily, persistent, troublesome dry eyes for more than 3 months? 2. Do you have recurrent sensation of sand or gravel in the eyes? 3. Do you use tear substitutes more than 3 times a day?
Oral symptoms	Definition: a positive response to at least one of the following 3 questions: 1. Have you had a daily feeling of dry mouth for more than 3 months? 2. Have you had recurrent or persistently swollen salivary glands as an adult? 3. Do you frequently drink liquids to aid in swallowing dry foods?
Ocular signs	Definition: objective evidence of ocular involvement, determined on the basis of a positive result on at least one of the following 2 tests: 1. Schirmer test, without anesthesia (< 5 mm in 5 minutes) 2. Rose-Bengal score or other ocular dye score (> 4 according to the van Bijsterveld scoring system)
Histopathological features	Definition: focus score > 1 on minor salivary gland biopsy (focus defined as an agglomeration of at least 50 mononuclear cells; focus score defined as the number of foci in 4 mm^2 of glandular tissue)
Salivary gland involvement	Definition: objective evidence of salivary gland involvement, determined on the basis of a positive result on at least one of the following 3 tests: 1. Salivary scintigraphy 2. Parotid sialography 3. Unstimulated salivary flow (< 1.5 ml in 15 minutes)
Autoantibodies	Definition: presence of at least one of the following serum autoantibodies: 1. Antibodies to Ro/SSA or La/SSB antigens
For primary SS	The presence of any 4 of the 6 items as long as either serology (autoantibodies) or histopathology is positive
Exclusion criteria	Preexisting lymphoma, HIV, hepatitis C, sarcoidosis, graft versus host disease

children the sensitivity of these criteria improves from 39% to 48%. This is still much lower than 76% for the proposed pediatric criteria, primarily due to the AECG obligatory criterion of positive serology (SSA or SSB) or histopathology (biopsies not performed on all patients). We found 78/133 (59%) patients satisfied the pediatric oral symptom criteria; 72/78 (92%) children fulfilling pediatric oral symptom criteria had recurrent parotitis or enlargement of parotid gland. Only one BCCH patient and 5 reported in the literature had xerostomia in the absence of recurrent parotitis or enlargement of the parotid gland.

In total, 52/118 (44%) patients satisfied the AECG ocular symptom criteria. The addition of recurrent conjunctivitis in the pediatric criteria did not increase the sensitivity; there were no reported cases of recurrent conjunctivitis in the absence of keratoconjunctivitis sicca. Among these, 34/120 (28%) reported systemic symptoms including fever, noninflammatory arthralgias, or abdominal pain.

In total, 58/101 (57%) patients had evidence of keratoconjunctivitis sicca documented by a positive Schirmer test or Bengal red staining; 70/84 (83%) had positive sialography or scintigraphy; biochemical evidence of parotid involvement with elevated serum amylase was reported in 13/14 (93%). In total, 101/130 (78%) had at least one positive autoantibody result (ANA, RF, SSA, SSB); 78/123 (63%) had autoantibodies to SSA or SSB. Twenty-one patients had a positive ANA or RF and negative SSA and SSB; one patient had positive ANA[28] and one patient had positive ANA and RF[33] in the absence of reported antibodies to SSA or SSB. Although the inclusion of ANA and RF in addition to AECG criteria of SSA and SSB autoantibodies increased the number of patients reporting positive autoantibodies, it ultimately did not change the number of patients satisfying pediatric or AECG criteria for pSS. Leukopenia or an elevated ESR was reported in 40/50 (80%) and renal tubular acidosis in 2/22 (9%). Minor salivary gland histology was suggestive of SS in 79/99 (80%).

DISCUSSION

PSS is infrequently recognized in children compared to adults, yet many adults diagnosed with this condition are likely to have had symptom onset in childhood. Criteria for diagnosing pSS in adults are not sensitive enough to distinguish this disease in childhood. In children the disease course may be much more insidious and it may be many years before they develop the endstage characteristics that are included as criteria in the AECG classification. The proposed criteria for diagnosis of pSS in children include recurrent parotitis, which is a more characteristic feature of disease in children than sicca symptoms. If one assumes that expert clinical diagnosis is the gold standard for diagnosis of pSS in children, 24/62 (39%) of all reported patients fulfilled the AECG pSS criteria compared to 47/62 (76%) fulfilling the proposed pediatric criteria. Neither composite criterion is very sensitive compared to the gold standard of a pediatric rheumatologist. A sensitivity of at least 80% is generally agreed to be necessary for classification or diagnostic criteria. The discrepancy in sensitivity is partly accounted for by the absence of sicca symptoms and the presence of parotitis in the majority of pediatric patients. The AECG oral symptom criteria include recurrent or persistent enlargement of the salivary glands as an adult, thus excluding children. The sensitivity of the AECG criteria improves to 48% with the inclusion of recurrent or persistent enlargement of the salivary glands as a child or adult; however, this still does not approach the sensitivity of the proposed pediatric criteria due to the obligatory criterion including positive serology or histopathology.

Classification criteria are often applied clinically as diagnostic criteria. However, unless the sensitivity and specificity of classification criteria approach 100%, patients will be misclassified or effectively misdiagnosed. Classification criteria often include specific criteria (manifestations characteristic of the disease in question), as well as nonspecific criteria (manifestations common to other diseases). Diagnostic criteria tend to consist of a constellation of symptoms or signs commonly seen in a particular disease. Classification criteria are often used to identify a homogeneous population of patients for study purposes, whereas diagnostic criteria are used to determine the presence or absence of a particular disease[23]. Despite these differences we sought to determine whether the proposed pediatric diagnostic criteria might be more sensitive than the validated adult classification criteria. We found that neither composite criterion was very sensitive when compared to the gold standard of a pediatric rheumatologist's clinical diagnosis. In the pSS population misclassification is especially problematic at onset of disease and early in disease course, when classic symptoms and signs are often not manifest. The endstage ocular and oral symptoms, objective evidence of keratoconjunctivitis sicca, and instrumental evidence of salivary gland involvement are not helpful in establishing early diagnosis. Diagnosis often relies on histologic proof of chronic lymphocytic infiltration of exocrine glands and on positive autoantibodies, both of which can be associated with false positives and negatives[15]. Further, due to the absence of sicca symptoms and invasive features of testing, not all children with pSS in the differential diagnosis undergo biopsy or testing for exocrine dysfunction. It may indeed be beneficial for children to have serial investigations to determine early dysfunction of the lacrimal or parotid glands, as dysfunction may antedate symptomatology.

This study has several limitations. We acknowledge the inherent difficulties of a retrospective study of literature-reported cases over a 40 year time period. Several of the larger case series did not report individual characteristics; therefore the data could not be extracted on individual patients. Many of the earlier case reports and case series did

not evaluate nuclear antigens to SSA and SSB as the technology was not available. However, of the 23 patients with either a positive ANA or RF in the absence of a reported or positive SSA or SSB, only 8 cases had sufficient information to evaluate the composite criteria and no patient fulfilled or did not fulfill either pediatric or revised AECG criteria based on the presence or absence of immunologic abnormalities.

In summary, despite the improved sensitivity of the proposed pediatric criteria for pSS over the AECG criteria, nearly one-quarter of patients in our review would still be misclassified. Nonetheless, the inclusion of recurrent parotitis and enlargement of the parotid gland increases the sensitivity of the pediatric clinical criteria. The inclusion of recurrent conjunctivitis in the pediatric criteria did not improve the sensitivity of the AECG ocular criteria and may be omitted. The inclusion of ANA and RF in addition to AECG criteria of SSA and SSB autoantibodies increased the number of patients reporting positive autoantibodies, but ultimately did not change the number of patients satisfying pediatric criteria for pSS. Therefore, the utility of ANA and RF in the pediatric criteria is uncertain. The inclusion of non-disease-specific criteria such as elevated ESR and polyclonal hypergammaglobulinemia undoubtedly increases the sensitivity of the pediatric pSS criteria, but probably at the expense of decreased specificity. The acute-phase response is common to many rheumatic diseases and is not specific for pSS.

Accurate diagnosis of pSS in the pediatric population is difficult. Recurrent parotitis should alert the clinician to the possibility of pSS. The proposed pediatric criteria lack sensitivity and clinical utility. Until validated diagnostic criteria are available, clinical acumen will prevail as the gold standard. Prospective multicenter studies are needed to further characterize pSS in the pediatric population, and to better define and develop appropriate classification criteria. Consideration should be given to the inclusion of specific obligatory criteria such as the presence of SSA or SSB autoantibodies or classic histopathology changes on minor salivary gland biopsy. The development of an international database would enable epidemiologic and clinical study.

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