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G.E. Legger[1], M.B. Erdtsieck[1], L. de Wolff[2], A.J. Stel[2], L.I. Los[3], G.M. Verstappen[2], F.K.L. Spijkervet[4], A. Vissink[4], B. van der Vegt[5], F.G.M. Kroese[2], W. Armbrust[1], S. Arends[2], H. Bootsma[2]

[1]*Department of Paediatric Rheumatology,* [2]*Department of Rheumatology and Clinical Immunology,* [3]*Department of Ophthalmology,* [4]*Department of Oral and Maxillofacial Surgery,* [5]*Department of Pathology and Medical Biology, University of Groningen, University Medical Center Groningen, The Netherlands.*

Geertje E. Legger, MD
Margit B. Erdtsieck, MD
Liseth de Wolff, MD
Alja J. Stel, MD, PhD
Leonoor I. Los, MD, PhD
Gwenny M. Verstappen, PharmD, PhD
Fred K.L. Spijkervet, DMD, PhD
Arjan Vissink, MD, DMD, PhD
Bert van der Vegt, MD, PhD
Frans G.M. Kroese, PhD
Wineke Armbrust, MD, PhD
Suzanne Arends, PhD
Hendrika Bootsma, MD, PhD

Please address correspondence to:
Geertje Legger,
Department of Paediatric Rheumatology, University Medical Centre Groningen, PO Box 30.001, 9700 RB Groningen, The Netherlands.
E-mail: g.e.legger@umcg.nl

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ABSTRACT

Objective. *Primary Sjögren's syndrome (pSS) is a rare disease in paediatric patients. Presenting symptoms differ from those in adult patients. The aim of this study was to evaluate presenting symptoms, classification criteria and clinical assessments, including salivary gland ultrasonography (SGUS), at disease onset in paediatric and adult patients with pSS.*

Methods. *Data of 23 paediatric- and 33 adult-onset patients with pSS were obtained from our standardised multidisciplinary REpSULT and RESULT cohorts, respectively. Clinical, patient-reported, serological, functional, biopsy and SGUS parameters were compared.*

Results. *In paediatric-onset pSS (pedSS) patients, recurrent parotid gland swelling (91% vs. 49%, p<0.001) and fever (30% vs. 3%, p=0.006) were more often present than in adult-onset patients. In contrast, sicca symptoms of mouth (52% vs. 79%, p=0.046) and eyes (26% vs. 73%, p<0.001) were less common in pedSS patients. In paediatric patients, the entry criteria of the ACR/EULAR classification were most often met due to activity in the glandular domain of the ESSDAI. When applying the ACR/EULAR classification criteria, only 78% of pedSS fulfilled these criteria compared to 100% of adult patients. Abnormal glandular function tests had a greater contribution to fulfilling the criteria in adults, while the biopsy had a greater contribution in paediatric patients. Anti-SSA/Ro serology had similar contribution for both cohorts. SGUS Hocevar score was significantly higher in paediatric compared to adult patients (median 25 vs. 18, p=0.004).*

Conclusion. *PedSS has a different presentation than adult-onset pSS. Recurrent parotid gland swelling in paediatric patients should alert clinicians to the potential presence of pSS.*

Introduction

Primary Sjögren's syndrome (pSS) is a chronic, systemic auto-immune disease characterised by involvement of exocrine glands. In adults, mainly the lacrimal and salivary glands are involved, resulting in sicca symptoms (1, 2). Predominantly females are affected with a female to male ratio of 9:1. The disease is typically diagnosed in the fourth or fifth decade of life (3, 4). Although relatively rare, pSS may also develop in children (5). The prevalence and prognosis of paediatric onset pSS (pedSS) are not yet clear. A recent study stated that 1.3% of patients with pSS have a paediatric onset of pSS (5). For adults, the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria were developed in 2016 to define a homogeneous population of patients with pSS for research purposes (6. 7). Although these classification criteria can be helpful in the diagnosis of pSS, the gold standard for diagnosing patients with pSS is still the diagnosis of the treating physician. Due to a lack of child specific criteria, the ACR/EULAR criteria are also used for classifying pedSS. It is not entirely known how accurate these adult criteria are for pedSS patients.

The presenting symptoms in pedSS differ from those in adults with pSS. Paediatric patients present more often with non-specific extra-glandular manifestations like fever and arthralgias (8). Furthermore, paediatric patients present less often with sicca complaints (5), which is one of the patient-reported entry criteria for the ACR/EULAR classification, and more often with recurrent parotid gland swelling (9, 10). The latter is currently only included in the ACR/EULAR criteria as an entry criterium embedded in the glandular domain

of the EULAR SS disease activity index (ESSDAI), when parotid, submandibular or lacrimal gland swelling is assessed by clinical examination (6, 7). As a consequence, paediatric patients who do not show such enlargement while visiting the physician will not fulfill the ACR/EULAR entry criteria for pSS when sicca symptoms are mild or absent. Although not (yet) incorporated in the classification criteria for pSS, salivary gland ultrasonography (SGUS) is a non-invasive, inexpensive and widely available method to visualise the major salivary glands (11). Several studies in patients with pSS have assessed the potential role of SGUS in the diagnosis and classification of pSS (12). Our recent study in adults with pSS showed that a positive SGUS in combination with the presence of anti-SSA/Ro antibodies predicts a positive classification according to the ACR/EULAR criteria, but a negative SGUS does not exclude classification (11). In pedSS, scarce research data is available, but a recent study shows an association between anti-SSA/Ro positivity and a positive SGUS score, similar to adults (13). However, an optimal cut-off score for an abnormal SGUS in pedSS remains undetermined.

The aim of this study was to evaluate the presenting symptoms, classification criteria and clinical assessments, including SGUS, of paediatric pSS and adult patients with pSS at the onset of the disease. This will be of value to diagnose the disease at an earlier stage and in more paediatric patients. Even though pSS cannot be cured at the moment, diagnosing patients sooner is of interest because preventive care and accurate treatment may restrain irreversible damage.

Materials and methods

Patient cohorts

This exploratory study was performed at the University Medical Center Groningen (UMCG), Netherlands, a tertiary referral hospital with a Sjögren's syndrome expertise centre. Regarding the care of patients suspected to have pSS, there is a unique collaboration between different departments at the UMCG. The REgistry of Pediatric Sjögren's Syndrome LongiTudinal (REpSULT) cohort started in 2020 and includes patients with confirmed or suspected pSS according to the (paediatric) rheumatologist, when the age of onset is ≤16 years. The REgistry of adult Sjögren's Syndrome LongiTudinal (RESULT) (14) cohort started in 2016 and includes patients with a confirmed or suspected pSS according to the rheumatologist, when the age of onset is >16 years. Both cohorts have been set up to identify clinical parameters and biomarkers that determine and predict the longitudinal course of pSS. The presence of standardised cohorts for both paediatric and adult patients within the UMCG makes it possible to compare presenting symptoms, classification criteria and clinical assessments at disease onset between these groups.

Consecutive patients of the REpSULT and RESULT cohort were included in this study if the clinical diagnosis of pSS was confirmed according to the (paediatric) rheumatologist and if they were diagnosed ≤1 year after their first visit at the UMCG. For both cohort studies, approval was obtained from the Medical Ethics Committee of the UMCG (REpSULT METC 2019/541 and RESULT METC 2014/491). All subjects provided informed consent.

Assessments

Clinical characteristics included age, gender and symptoms at onset of pSS. Presenting symptoms of different systemic autoimmune diseases like pSS, systemic lupus erythematosus and mixed connective tissue disease were collected from the medical records. Patients completed the American-European Consensus Group (AECG) classification criteria questionnaire consisting of six questions regarding oral and ocular sicca symptoms (15). This questionnaire consists of the same five questions which are included in the ACR/EULAR entry criteria, with the addition of a question regarding recurrent or persistent salivary gland swelling. Systemic disease activity was measured using the EULAR Sjögren's syndrome disease activity index (ESSDAI) (6).

Serological parameters were determined, including presence of antinuclear antibodies (ANA), anti-SSA/-SSB antibodies, rheumatoid factor (RF) level and total immunoglobulin G (IgG) level. Tear gland function (data of the most affected eye) was assessed using the Schirmer's test and Ocular Staining Score (OSS) (16). Salivary gland function tests included unstimulated and stimulated (by chewing) whole saliva flow rate (UWSFR and SWSFR) (17). Glandspecific unstimulated and stimulated (by 2% citric acid solution) saliva from the parotid glands and the submandibular/sublingual glands were collected by using Lashley cups and by syringe aspiration, respectively. If available, parotid and/or labial salivary gland biopsies were evaluated for focal lymphocytic infiltrates, germinal centres, lymphoepithelial lesions, IgA/IgG plasma cell shift, MALT lymphoma and the Chisholm score was calculated (18-21). B-mode SGUS was performed using the MyLabTwice scanner (Esaote), equipped with a high-resolution linear probe (4–13 MHz). All US images were scored real-time by trained readers. The scoring system by Hocevar *et al*. (22) was applied (range 0–48), including the components of parenchymal echogenicity, homogeneity, presence of hypoechogenic areas, hyperechogenic reflections, and clarity of the salivary gland border in both parotid and submandibular salivary glands. A total Hocevar score of ≥15 was considered positive in both paediatric and adult patients due to a lack of child-specific cut off scores (14).

Statistical analysis

Statistical analyses were performed using IBM Statistical Packages for Social Sciences (SPSS), version 23. Descriptive statistics were described as number (%) of patients for categorical parameters and mean (standard deviation; SD) or median (interquartile range; IQR) for normally or non-normally distributed continuous parameters. The separate items of the ACR/EULAR classification criteria were scored, and a total score was calculated. A score of ≥4 was considered as meeting the classification criteria for pSS (7). To compare symptoms and characteristics between paediatric and adults patients with pSS,

Fisher's Exact or Chi-Square test, Independent Samples t-test and Mann-Whitney U-test were used as appropriate. *p*-values <0.05 were considered statistically significant.

Results

In total 23 pedSS patients from the REpSULT cohort were included, of whom 18 (78%) patients were female *versus* 81% in the adult group (p=1.00), and median age was 13 (IQR 11-15) years. Paediatric patients were diagnosed between 2008 and 2020 (only three before 2015). In total 33 adult-onset patients with pSS from the RESULT cohort were included, of whom 27 (81%) patients were female and median age was 50 (IQR 31-63) years. All adult patients were diagnosed between 2016 and 2020.

Table I. Prevalence of presenting symptoms in paediatric *vs*. adult patients with a clinical diagnosis of pSS.

Characteristic	Paediatric cohort, n=23	Adult cohort, n=33	*p*-value
Recurrent parotid gland swelling (uni-or bilateral)	21 (91.3)	16 (48.5)	**0.001**
Dry mouth	12 (52.2)	26 (78.8)	**0.046**
Dry eyes	6 (26.1)	24 (72.7)	**0.001**
Arthralgia	14 (60.9)	23 (69.7)	0.572
Myalgia	2 (8.7)	11 (33.3)	0.052
Fatigue	13 (56.5)	18 (54.5)	1.000
Fever	7 (30.4)	1 (3.0)	**0.006**
Lymphadenopathy	5 (21.7)	8 (24.2)	1.000
Skin involvement*	6 (26.1)	4 (12.1)	0.288
Sun allergy	3 (13.0)	5 (15.2)	1.000
Raynaud's phenomenon	10 (43.5)	13 (39.4)	0.789
Mouth ulcers	4 (17.4)	5 (15.2)	1.000
Alopecia	0 (0.0)	0 (0.0)	N/A
Neurological symptoms	0 (0.0)	7 (21.2)	**0.034**
Pulmonary symptoms	0 (0.0)	2 (6.1)	0.507

Data are presented as number of patients (%). Numbers in bold indicate significant *p*-value.
*defined as the presence of acute or chronic cutaneous lupus or cutaneous vasculitis.
N/A: not available.

Presenting symptoms

In pedSS patients, the most frequent presenting symptoms were recurrent parotid gland swelling, arthralgias, fatigue, dry mouth, fever and Raynaud's phenomenon (Table I). Recurrent parotid gland swelling (91% *vs*. 49%, p=0.001) and fever (30 % *vs*. 3%, p=0.006) were more often present among paediatric patients, in comparison with adult-onset patients. In contrast, sicca symptoms of the mouth (52% *vs*. 79%, p=0.046) and particularly the eyes (26% *vs*. 72%, p=0.001) were less common in paediatric patients.

Fulfillment of ACR/EULAR entry criteria for pSS

Of the pedSS patients, 96% fulfilled the ACR/EULAR entry criteria for pSS (defined as scoring positive on one of the five AECG questions and/or any activity in one ESSDAI domain), compared to 100% of the adult-onset patients (p=0.23). The pedSS patient, who did not meet the entry criteria scored four points on the ACR/EULAR classification criteria (three points for anti-SSA/Ro positivity and one point for abnormal UWSFR).

Regarding AECG questions, only 57% of the pedSS patients fulfilled the entry criteria by scoring positive on one of the five AECG (sicca-related) questions, compared to 91% of the adult-onset patients (p=0.004). The original AECG questions comprises an additional question about recurrent salivary gland swelling. This question is not included in the ACR/EULAR patient reported entry criteria for pSS, but almost all paediatric patients scored positive on this question (91% *vs*. 48% adults, p<0.001).

Regarding the ESSDAI items as entry criterium for ACR/EULAR criteria, 91% of the pedSS patients and 94% of the adult-onset patients had any activity in at least one ESSDAI domain. Paediatric patients mainly scored on the glandular domain (any activity in 70% of the patients), which is scored when parotid, submandibular or lachrymal gland swelling is present at the moment of the clinical examination. Other frequently active domains were the biological domain (48%) and the constitutional domain (24%). Adult patients mainly scored on the biological domain (82%), glandular domain (46%) and haematological domain (39%) (Table II).

Fulfillment of the ACR/EULAR classification criteria for pSS

Fewer pedSS patients met the ACR/EULAR classification (defined as a score of ≥4 when the weight from the five criteria of the ACR/EULAR classification criteria are summed) criteria at disease onset compared to adults (78% *vs*. 100%, p=0.009). The four paediatric patients who did not fullfil the ACR/EULAR classification criteria all scored three points on the ACR/EULAR criteria. Two of these four patients had a positive biopsy (FS≥1.0) and the other two were anti-SSA/Ro seropositive, but had no positive glandular tests. All four presented with recurrent parotid gland swelling and arthralgias. Three out of four patients reported sicca complaints and Raynaud's phenomenon. All patients were ANA positive and three patients were RF positive.

Anti-SSA/Ro antibodies were positive in the majority of paediatric and adult patients (87% *vs*. 94%). Although not statistically significant, pedSS patients scored less often positive on the objective glandular tests compared to adults (Schirmer's test, OSS and UWSFR). Biopsy results showed a focus score ≥1 in most paediatric and adult patients (94% *vs*. 87%). In paediatric patients, the biopsy results played a major role in fulfilling the ACR/EULAR classification criteria. Without the biopsy, only half of the paediatric patients fulfilled the criteria (44% compared to 76% of adults) (Table II).

Additional diagnostic tests

Detailed results for laboratory testing, ophthalmic evaluation, sialometry, salivary gland biopsy and ultrasound are

Table II. Prevalence of fulfilment of the separate ACR/EULAR classification criteria in paediatric *vs*. adult patients with a clinical diagnosis of pSS. Data are presented as number of patients (%).

ACR/EULAR entry and classification criteria	Abnormal or positive result		*p*-value
	Paediatric cohort, n=23	Adult cohort, n=33	
Entry criteria			
AECG questions			
Have you had daily, persistent, troublesome dry eyes for more than 3 months?	5 (21.7)	23 (74.2)#	**<0.001**
Do you have a recurrent sensation of sand or gravel in the eyes?	4 (17.4)	18 (58.1)#	**0.005**
Do you use tear substitutes more than 3 times a day?	3 (13.0)	10 (31.3)^	0.193
Have you had a daily feeling of dry mouth for more than 3 months?	12 (52.2)	27 (81.8)	**0.037**
Do you frequently drink liquids to aid in swallowing dry food?	11 (47.8)	22 (66.7)	0.198
*Have you had recurrently or persistently swollen salivary glands (as an adult)?**	21 (93.1)	17 (51.5)	**0.003**
ESSDAI domains			
Constitutional domain	8 (34.8)	8 (24.2)	0.549
Lymphadenopathy domain	4 (17.4)	4 (12.1)	0.704
Glandular domain	16 (69.6)	15 (45.5)	0.103
Articular domain	5 (27.1)	5 (15.2)	0.725
Cutaneous domain	2 (8.7)	0 (0.0)	0.164
Pulmonary domain	1 (4.3)	1 (3.0)	1.000
Renal domain	0 (0.0)	0 (0.0)	N/A
Muscular domain	0 (0.0)	0 (0.0)	N/A
Peripheral nervous system domain	0 (0.0)	3 (9.1)	0.261
Central nervous system domain	0 (0.0)	0 (0.0)	N/A
Haematological domain	2 (8.7)	13 (39.4)	**0.014**
Biological domain	11 (47.8)	27 (81.8)	**0.010**
ACR/EULAR criteria			
Anti-SSA/Ro antibodies	19 (82.6)	29 (93.9)	0.215
OSS ≥5 in at least one eye	1 (4.3)	7 (21.2)	0.123
Schirmer ≤ 5 mm in at least one eye	6 (31.6)*	18 (56.3)^	0.146
USWFR ≤0.1 ml/min	9 (45.0)*	21 (63.6)	0.255
Salivary gland biopsy (focusscore ≥1)	17 (94.4)+	26 (86.7)#	0.637

Missing data: ^0-5%, #5-10%, *10-20%, + 20-30%.
Numbers in bold indicate significant *p*-value. Data are presented as number of patients (%).
N/A: not available; ACR/EULAR: American College of Rheumatology/European League Against Rheumatism; AECG: American-European Con**sensus** Group; OSS: ocular staining score; USWFR: unstimulated whole salivary flow rate.
*Not included in ACR/EULAR entry criteria.

presented in Table III. There were no significant differences between pedSS and adult-onset patients with pSS with respect to the laboratory testing. There was a tendency that pedSS patients had higher levels of RF compared to adult onset patients (median 50, (IQR 17-99) *vs*. 24, (2.5-62), *p*=0.14). SWSFR was significantly lower in paediatric patients compared to adults (median 0.40, (IQR 0.21–0.63) *vs*. 0.69, (0.34–1.11), *p*=0.018). However, there was no significant difference in UWSFR (median 0.12, (IQR 0.03–0.27) *vs*. 0.07, (0.02–0.15), *p*=0.2). Paediatric patients showed a higher Schirmer's test score compared to adult patients (median 18, (IQR 5-24) *vs*. 5, (3-11), *p*=0.06), indicating better tear gland function. The OSS was somewhat lower in paediatric patients (median 1.0, (IQR 0.0-2.0) *vs*. 2.0 (1.0-4.0), *p*=0.06), indicating less ocular surface disease.

No significant differences in salivary gland biopsies (lymphoepithelial lesions, germinal centers and IgA/IgG plasma cell shift) were observed between paediatric and adult patients. Based on the biopsy results and clinical symptoms, there were two paediatric and no adult patients with a mucosa associated lymphoid tissue (MALT) lymphoma (11% *vs*. 0%, *p*=0.14).

Paediatric patients showed significantly higher SGUS scores with a median total Hocevar of 25 (IQR 22-29) *vs*. 18 (11-28), *p*=0.004). SGUS scores were more often abnormal (Hocevar ≥15: 95% *vs*. 65%, *p*=0.018) compared to adult patients. In paediatric patients, Hocevar score of the parotid glands was higher than Hocevar score of the submandibular (SM) and sublingual (SL) glands (median 14 (IQR 10-16) *vs*. 8 (IQR 6-14), which was less pronounced in adults (median 12 (IQR 10-14) *vs*. 10 (IQR 5-13). When comparing the individual components of the Hocevar score, paediatric patients showed significantly higher scores for parenchymal echogenicity, homogeneity, presence of hypoechogenic areas, and hyperechogenic reflections (data not shown).

Association between biopsy abnormalities and SGUS scores

For both paediatric and adult patients with pSS, total Hocevar score was significantly higher when biopsy results were abnormal. Hocevar scores were significantly higher in paediatric and adult patients with an abnormal Chisholm focus score (adults only), presence of lymphoepithelial lesions, germinal centres and IgA/IgG shift (Fig. 1).

The cut-off score for an abnormal SGUS in adults is defined as Hoce-

Table III. Prevalence of additional test results in paediatric *vs*. adult patients with clinical diagnosis of pSS.

Examination	Results of examination		*p*-value
	Paediatric cohort n=23	Adult cohort n=33	
Laboratory testing			
ANA abnormal, n (%)	22 (95.7)	27 (87.1)#	0.380
SSB abnormal, n (%)	13 (56.5)#	19 (57.6)^	1.000
Rheumatoid factor, median (IQR)	50.0 (17.0 – 99.0)	24.0 (2.5-62.0)	0.138
Rheumatoid factor abnormal, n (%)	19 (82.6)	24 (72.7)	0.525
Immunoglobulin G, median (IQR)	17.6 (14.1 – 23.9)*	19.6 (12.0 – 25.0)	0.909
Sialometry			
UWSFR, median (IQR)	0.12 (0.03 – 0.27)*	0.07 (0.02 – 0.15)	0.201
SWSFR,median (IQR)	0.40 (0.21 – 0.63)#	0.69 (0.34 – 1.11)^	**0.018**
Unstimulated parotid saliva flow rate, median (IQR)	0.00 (0.00– 0.01)#	0.01 (0.00 – 0.02)	0.079
Stimulated parotid saliva flow rate, median (IQR)	0.03 (0.004 – 0.06)#	0.03 (0.01 – 0.09)	0.294
Unstimulated SM/SL saliva flow rate, median (IQR)	0.10 (0.03 – 0.20)#	0.05 (0.01 – 0.13)	0.125
Stimulated SM/SL saliva flow rate, median (IQR)	0.19 (0.06 – 0.35)#	0.09 (0.09 – 0.27)	0.256
Ophthalmic evaluation			
Schirmer's test, median (IQR)	18.0 (5.0 – 24.0)*	5.0 (3.0 – 10.8)^	0.061
OSS, median (IQR)	1.0 (0.0 – 2.0)	2.0 (1.0– 4.0)	0.058
Salivary gland biopsy[a]			
Lymphoepithelial lesions present, n (%)	13 (68.4)*	17 (56.7)#	0.550
Germinal centres present, n (%)	5 (31.3)$	10 (33.3)#	1.000
IgA/IgG plasma shift present, n (%)	14 (77.8)+	22 (71.0)#	0.743
Suggestive for MALT lymphoma, n (%)	2 (11.1)+	0 (0.0)#	0.136
SGUS			
Total Hocevar score, median (IQR)	25.0 (22.0 – 29.0) *	18.0 (11.0 – 28.0)#	**0.020**
Total Hocevar score abnormal, n (%)	18 (94.7) *	20 (64.5)#	**0.018**

[a]Paediatric patients: 17 (81%) parotid gland biopsies and 4 (19%) labial gland biopsies; adult patients 26 (84%) parotid gland biopsies and 5 (16%) labial gland biopsies.
Missing data: ^0-5% #5-10%, *10-20%, + 20-30%, $30-35%. Numbers in bold indicate significant *p*-value.
IQR: interquartile range; ANA: antinuclear antibodies; IgA/IgG: immunoglobulin A/immunoglobulin G; OSS: ocular staining score; UWSFR: unstimulated whole salivary flow rate; SWSFR: stimulated whole salivary flow rate; SM/SL: submandibular/sublingual; MALT: mucosa-associated lymphoid tissue.

var score of ≥15. In the adult cohort, patients with normal biopsy results based on Chisholm score, presence of lymphoepithelial lesions or IgA/IgG shift had a median Hocevar score of <15 (ranging from 10 to 12), whereas patients with abnormal biopsy results based on any of the items had a median Hocevar score of ≥15 (ranging from 20 to 25). In the paediatric cohort median Hocevar score was ≥15 for both groups with normal and abnormal pathological findings (ranging from 20 to 24 for normal *vs*. 26 to 28 for abnormal biopsy results; Fig. 2). In the total paediatric cohort, there was only one patient with a Hocevar score <15.

Discussion

This cross-sectional, observational study compared presenting symptoms and diagnostic test results between paediatric- and adult-onset patients with pSS. We showed that pedSS patients present more often with recurrent parotid gland swelling and fever, and less often with sicca symptoms than adult patients. When applying the ACR/EULAR entry criteria in paediatric patients, these were most often met due to the presence of any activity in the glandular domain of the ESSDAI. The ACR/EULAR classification criteria were fulfilled most often due to a positive biopsy result in paediatric patients. Except for SWSFR and SGUS scores, laboratory tests, functional tests and biopsy results were very similar between the two cohorts. In pedSS patients SWSFR was significantly lower and the median total Hocevar score was higher compared to adults. Furthermore, more pedSS patients had an abnormal total Hocevar score.

In our cohort, patient reported recurrent parotid gland swelling was present in 91% of the paediatric patients, compared to 49% of adult patients. In the scarce literature available on paediatric onset pSS, recurrent parotid gland swelling is seen as an important feature, with a prevalence ranging from 50% to 75% (5, 8, 10, 23). A possible explanation for the high prevalence of recurrent parotid swelling in our cohort might be that it was scored as subjective symptom (reported by the patients), while other studies only scored parotid gland swelling when parotid enlargement was observed by a physician. A major challenge in diagnosing pSS in paediatric patients is to distinguish recurrent parotitis or recurrent parotid gland swelling as the first symptom of pSS from juvenile recurrent parotitis (24-26), a disease with an unknown origin, which presents during childhood, but eventually is self-limiting. Illustrative of the fact that differentiating between juvenile recurrent parotitis and recurrent parotid gland swelling associated with pSS can be difficult, is a study which demonstrated that 5 of 20 paediatric patients who presented to a paediatric otolaryngology or rheumatology clinic with the diagnosis of juvenile recurrent parotitis were eventually diagnosed with pSS (9). Another

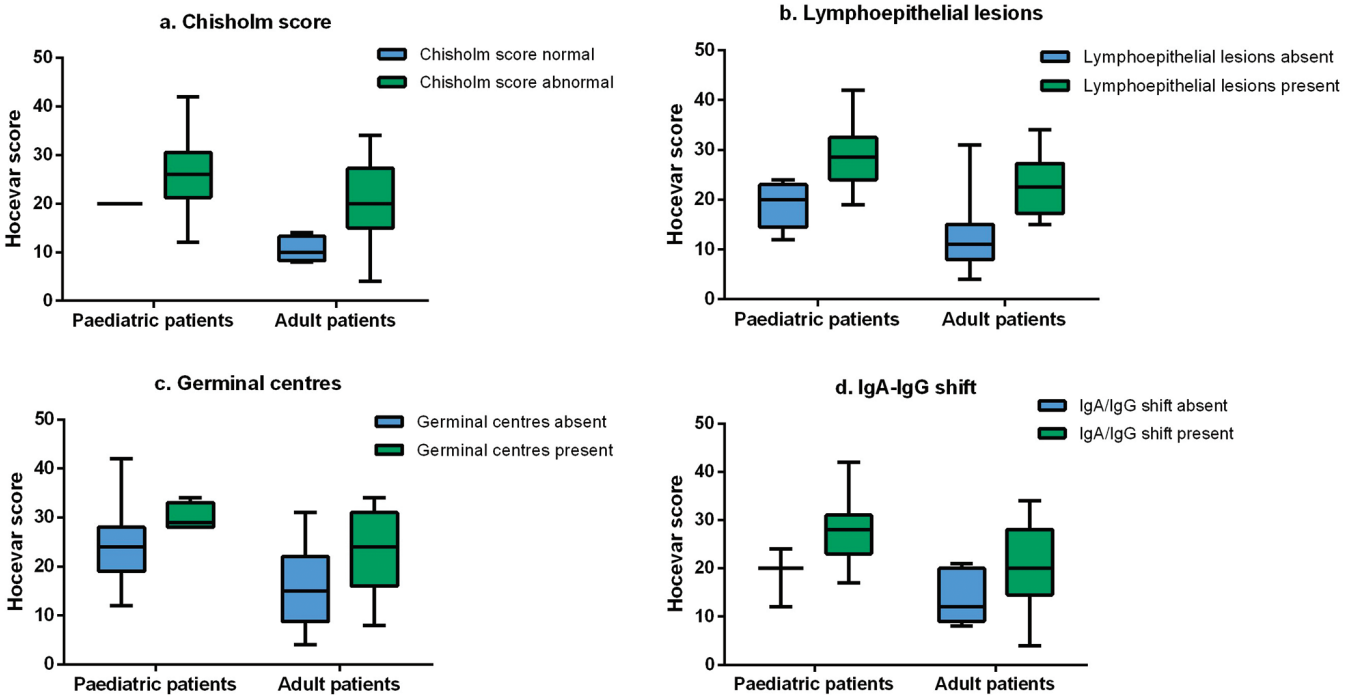

Fig. 1. Association between SGUS Hocevar total scores and parotid or labial biopsy results for paediatric and adult patients.
a: Chisholm score, paediatric patients: normal; median 20 (IQR20-20) abnormal; median 26 (IQR21-31); p=0.533, adult patients: normal; median 10 (IQR8-13), abnormal; median 20 (IQR15-27; p=0.019. **b**: Lymphoepithelial lesions, paediatric patients: normal; median 20 (IQR15-23), abnormal; median 29 (IQR24-33); p=0.008, adult patients: normal; median 12 (IQR 8-22), abnormal; median 23 (16-22); p=0.006. **c**: Germinal centres, paediatric patients: normal: median 24 (IQR19-28), abnormal; median 29 (IQR28-33); p=0.038; adult patients: normal; median 15 (IQR11-24), abnormal; median 25 (IQR17-31); p=0.109. **d**: IgA/IgG shift, paediatric patients: normal median 20 (IQR12-20), abnormal; median 28 (IQR23-31); p=0.082; adult patients: normal; median 12 (IQR10-19), abnormal; median 24 (IQR15-29), p=0.036.

interesting finding was that fever was seen in 30% of the paediatric patients, compared to 3% of the adult patients. The exact mechanism of this finding is not yet clear. A possible reason for this difference might be that more inflammation is present in the paediatric population, but this is not supported by differences in the general inflammation markers, C-reactive protein (CRP) levels and/or erythrocyte sedimentation rates (ESR), between adult and paediatric patients (data not shown).

With regard to subjective symptoms, sicca symptoms were less common in the paediatric cohort compared to the adult cohort (ocular sicca 26% *vs*. 72%, oral sicca 52% *vs*. 79%). In adults, sicca symptoms are the most familiar signs for physicians to consider pSS, but in paediatric patients these symptoms occur less often. The entry questions for the ACR/EULAR criteria only address sicca symptoms. Although (recurrent) parotid gland swelling seems to be an important feature of pedSS, there is no entry question in the ACR/EULAR entry criteria addressing glandular swelling. The other possibility to meet the ACR/EULAR entry criteria, is the presence of any activity in one of the ESSDAI domains. Although parotid gland swelling is represented in the glandular domain of the ESSDAI, the (paediatric) rheumatologist needs to observe and objectify the glandular enlargement (6). As a consequence, paediatric patients who do not show such enlargement while visiting the physician would not fulfill the entry criteria when sicca symptoms are mild or absent. Our results show that 70% of paediatric patients with pSS had objective activity in the glandular domain of the ESSDAI, while 91% of the patients reported recurrent parotid gland swelling.

No significant differences in serological parameters (anti SSA/Ro antibodies, ANA, RF and IgG levels) were found between the two populations. Notably, a relatively high proportion of our adult cohort (82%) showed activity in the biological domain of the ESSDAI compared to other adult pSS cohorts (27). The absence of a significant difference between our two populations might be caused by the relatively high scores in our adult population. Nonetheless, two-thirds of the paediatric patients were positive for RF and the overall RF titre tended to be higher compared to adults. Previous studies showed that the presence of RF and anti-SSA in healthy persons increases with age and the percentage of healthy children with positive RF and/or anti-SSA/Ro antibodies is considered to be low (28, 29). In adult patients, RF is also related to other auto-immune diseases like rheumatoid arthritis, and is therefore not specific for diagnosing pSS (30). However, RF could be an important feature in diagnosing pedSS, mainly because RF is not often found in other auto-immune diseases in paediatric patients. For example, juvenile idiopathic arthritis (JIA) is associated with RF in only 5% of cases (31). While patients with pedSS and SLE can present with similar symptoms, a positive RF titre is rare (5% at diagnosis) in paediatric patients with SLE (32).

When applying the ACR/EULAR classification criteria, only 78% of the pae-

diatric patients fulfilled these criteria while 100% of the adult patients fulfilled the criteria. Moreover, the paediatric and adult patients scored positive on different criteria items. In line with the lower frequency of sicca symptoms in pedSS, significantly less paediatric patients scored positive on the objective glandular tests (Schirmer's test, OSS, UWSFR) compared to the adults. Furthermore, our study showed that paediatric patients have a different sialometric pattern compared to adults, with a higher UWSFR and a lower SWSFR. The cut-off values of the sialometry tests used for diagnosing pSS are only validated for adults. In adult patients a UWSFR of ≤0.1 ml/min and a SWSFR of ≤0.7 ml/min are considered abnormal (33-35). Studies into saliva secretion rates in healthy paediatric patients show a similar salivary flow pattern as in healthy adults, with an equal or slightly higher UWSFR and SWSFR (5, 36, 37), therefore we interpreted the data of paediatric and adult patients in the same manner. Studies in adults with pSS show that the submandibular (SM) and sublingual (SL) glands are first affected (38), which mainly influences UWSFR. Our data suggest that SWSFR declines before the UWSFR in pedSS patients. Considering parotid glands are mostly responsible for SWSFR (36), a possible explanation is that in pedSS parotid glands are more affected. This is strengthened by the high prevalence of recurrent parotid gland swelling in the paediatric cohort. We therefore suggest that the SWSFR is more valuable for diagnosing pedSS than the UWSFR.

While glandular function tests played a relatively minor role in the classification of pedSS, the biopsy results played a major role and were decisive for fulfillment of the ACR/EULAR criteria in almost half of the patients. No significant differences in the results of the salivary gland biopsies were observed between paediatric and adult patients. However, histopathological evaluation was based only on H&E staining and more quantitative parameters, such as the area fraction of infiltration and T- and B-cell numbers, were not yet evaluated. Since a salivary gland biopsy is an invasive and burdensome procedure for paediatric patients, this is not a suitable method for broad screening of a rare disease like pedSS, but should only be applied in children with a strong clinical suspicion of pSS.

A potential alternative to a salivary gland biopsy for evaluating patients with pSS is SGUS, which has been studied intensively in adult patients in recent years (39). In the present study, total Hocevar scores were significantly higher in paediatric compared to adult patients. When applying the proposed cut-off value for adults, SGUS was also more often abnormal in paediatric patients and they showed a median Hocevar score of ≥15 in case of normal and abnormal pathological biopsy findings. Our data show that paediatric patients have higher total Hocevar scores, especially for the parotid glands. Paediatric patients scored higher on all the components of the Hocevar score, except for the clarity of the salivary gland border (data not shown). One possibility might be that glands of paediatric patients are more inflamed. Another explanation is that salivary glands of paediatric patients are still in development and therefore appear different on SGUS compared to salivary glands of adult patients. Studies into SGUS in paediatric patients are scarce, and no studies have been performed to determine a cut-off score for abnormal SGUS in the paediatric population.

The limited power of this study and the lack of inclusion of clinically suspected or healthy children impedes proposition of diagnostic or classification criteria for pedSS. However, this study gives an insight into which measurements should be subjected to further study. All patients underwent extensive multidisciplinary diagnostic testing at their disease onset. Therefore, this study could address several items in more depth than other studies have done so far (5, 8-10, 13). The results in our study suggest that adding the AECG question about recurrent or persistent salivary gland swelling as an entry criterion, and SWSFR and SGUS with paediatric specific cut-off scores to the ACR/EULAR classification criteria may lead to a higher accuracy of these criteria in paediatric patients. Validation of other diagnostic measurements than those currently included in the ACR/EULAR classification criteria (*e.g.* SWSFR, SGUS) should be conducted in a study including patients with recurrent parotid gland swelling related to pedSS and idiopathic juvenile recurrent parotitis to identify items which can distinguish between these diseases. Furthermore, additional research with healthy children as controls to determine an SGUS cut-off score for paediatric patients should be conducted.

To conclude, this study showed that pedSS has a different presentation than adult-onset pSS. Paediatric patients with pSS present more often with symptoms of major salivary gland involvement, expressed by recurrent parotid gland swelling, decreased SWSFR and higher Hocevar scores Currently, the ACR/EULAR criteria are used in pedSS patients for classification, but further research should be performed to determine sensitivity and specificity of current and new diagnostic measurements to optimise a criteria set specific for pedSS patients. In paediatric patients with recurrent parotid gland swelling without a clear cause, in combination with additional symptoms like oral sicca, arthralgias, Raynaud's phenomenon, fatigue or fever, pedSS should be considered. Our advice is that in these patients, serologic analyses (anti-SSA and RF) should be performed first. Furthermore, SGUS may play a role in diagnosing pedSS patients, but specific studies into normal and abnormal values for the paediatric population should be conducted. When the diagnosis of pSS remains uncertain, a biopsy can be useful and should be performed.

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