RHEUMATOLOGY

Rheumatology 2021;60:4558–4567
doi:10.1093/rheumatology/keab032
Advance Access publication 26 January 2021

Original article

Childhood-onset of primary Sjögren's syndrome: phenotypic characterization at diagnosis of 158 children

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Abstract

Objectives. To characterize the phenotypic presentation at diagnosis of childhood-onset primary SS.
Methods. The Big Data Sjögren Project Consortium is an international, multicentre registry using worldwide data-sharing cooperative merging of pre-existing clinical SS databases from the five continents. For this study, we

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Submitted 5 August 2020; accepted 12 November 2020

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selected those patients in whom the disease was diagnosed below the age of 19 years according to the fulfilment of the 2002/2016 classification criteria.

Results. Among the 12 083 patients included in the Sjögren Big Data Registry, 158 (1.3%) patients had a childhood-onset diagnosis (136 girls, mean age of 14.2 years): 126 (80%) reported dry mouth, 111 (70%) dry eyes, 52 (33%) parotid enlargement, 118/122 (97%) positive minor salivary gland biopsy and 60/64 (94%) abnormal salivary US study, 140/155 (90%) positive ANA, 138/156 (89%) anti-Ro/La antibodies and 86/142 (68%) positive RF. The systemic EULAR Sjögren's syndrome disease activity index (ESSDAI) domains containing the highest frequencies of active patients included the glandular (47%), articular (26%) and lymphadenopathy (25%) domains. Patients with childhood-onset primary SS showed the highest mean ESSDAI score and the highest frequencies of systemic disease in 5 (constitutional, lymphadenopathy, glandular, cutaneous and haematological) of the 12 ESSDAI domains, and the lowest frequencies in 4 (articular, pulmonary, peripheral nerve and CNS) in comparison with patients with adult-onset disease.

Conclusions. Childhood-onset primary SS involves around 1% of patients with primary SS, with a clinical phenotype dominated by sicca features, parotid enlargement and systemic disease. Age at diagnosis plays a key role in modulating the phenotypic expression of the disease.

Key words: Sjogren's syndrome, epidemiology, autoimmune diseases, paediatrics, childhood

Rheumatology key messages

- The estimated frequency of childhood-onset primary SS is around 1% of patients.
- Systemic phenotype is clearly dominated by glandular involvement, followed by articular, lymphadenopathy and constitutional involvement
- No essential difference exists in the SS phenotype between young-onset and childhood-onset patients

Introduction

Primary SS is a systemic autoimmune disease most commonly diagnosed in middle-aged women, with a frequency ranging between 0.01 and 0.72% [1]. The autoimmune damage mainly targets the exocrine glands, which are infiltrated by lymphocytes (focal sialadenitis) [2]. Over 95% of patients present with oral and/or ocular dryness [3], but may also develop a large number of organ-specific manifestations (systemic SS) [4]. The key immunological markers are anti-Ro antibodies, the most specific, and cryoglobulins and hypocomplementaemia, the main prognostic markers [5].

Although primary SS can occur at all ages, it is diagnosed between 30 and 60 years in two-thirds of patients [3]. Paediatric onset of the disease is rarely reported, and there is no information about how frequent the paediatric presentation is. In addition, a clear view of how the disease presents in children is difficult to obtain due to the scarce and heterogeneous available data. The main series published until now are characterized by a heterogeneous methodology, using a variable definition of the paediatric age (from 14 to 18 years), including up to 50% of patients not fulfilling the current classification criteria and mixing the inclusion of primary and associated forms of the disease. As an example, in the largest series reported (67 cases) [6], only approximately half the cases fulfilled the current SS classification criteria and 12% were patients diagnosed with other concomitant systemic autoimmune diseases.

Understanding how primary SS presents/manifests at earlier ages (both glandular and extraglandular) would help paediatricians to more promptly identify the disease [7]. In the absence of established classification criteria specific for SS in children, along with the notions that SS in children is not pathophysiologically distinct from SS in adults and that childhood-onset primary SS is part of the epidemiological continuum of the disease, we chose to focus our study on children who met the current classification criteria [8, 9] established for use in classifying SS in adults.

Therefore, the aim of this study was to characterize the phenotypic presentation at diagnosis of childhood-onset primary SS in a large international, multi-ethnic cohort of patients in comparison with the adult-onset phenotype.

Methods

Patients

The Big Data Sjögren Project Consortium is an international, multicentre registry designed in 2014 to take a 'high-definition' picture of the main features of primary SS using worldwide data-sharing cooperative merging of pre-existing clinical SS databases from leading centres in clinical research in SS from the five continents [3, 10, 11]. Databases from each centre are harmonized into a single database by applying the data-cleaning pre-processing techniques. Descriptive statistics and data visualization methods are used in order to detect

outliers, data errors, missing data and influential observations [12]. A double-checking process correcting errors and completing missing information is carried out to minimize incomplete and erroneous data. Inclusion criteria are the fulfilment of the 2002 classification criteria [8] and/or 2016 ACR/EULAR criteria [9]. Diagnostic tests for SS were carried out according to the recommendations of the European Community Study Group [13]. The study was approved by the Ethics Committee of the Coordinating Centre (Hospital Clinic, Barcelona, Spain, registry HCB/2015/0869). Patients who agreed to participate gave written informed consent.

Definition of variables

Disease diagnosis was defined as the time when the attending physician confirmed fulfilment of the 2002/2016 criteria. For this study, we selected those patients in whom the disease was diagnosed below the age of 19 years. Because the members of the Project are physicians who care for adult patients, the coordinator of each centre travelled to the referral paediatric centres to include paediatric cases with active follow-up, in order to avoid selection bias by excluding younger children who were not yet referred to the adult departments.

The main disease features at this time (criteria fulfilment), as well as the first signs and symptoms at presentation, were retrospectively collected from the patient records and analysed. The following clinical variables were selected for harmonization and further refinement:

i. Epidemiological features: age, gender, ethnicity, country of residence.
ii. Clinical features at presentation: first signs and symptoms suggesting an autoimmune disease.
iii. Systemic activity: systemic involvement at diagnosis was classified and scored according to the EULAR Sjögren's syndrome disease activity index (ESSDAI) [14], the clinical ESSDAI (clinESSDAI) [15, 16] and the DAS [17].
iv. Diagnostic approach: fulfilment of the 2002/2016 criteria items, parotid US study.
v. Immunological profile: ANA, anti-Ro/La antibodies, RF, complement C3 and C4 levels, cryoglobulins.

Statistical analysis

Descriptive data are presented as mean and S.D. for continuous variables and numbers and percentages (%) for categorical variables. Disease patterns for three paediatric age at diagnosis subsets (5–9, 10–14, 15–18 years) and five 18-year age at diagnosis groups ($\leq$18, 19–36, 37–54, 55–72, $\geq$73 years) were compared according to the gender, ethnicity, diagnostic tests for SS, immunological markers and systemic involvement. The χ^2 test was used to compare categorical variables and analysis of variance test was used to compare continuous variables. Data visualization techniques were used to summarize information. To handle missing data due to non-evaluated features, 'available case analysis' was assumed. All significance tests were two-tailed and values of $P < 0.05$ were considered significant. *P*-values were adjusted for multiple comparisons using the false discovery rate correction. All analyses were conducted using the R V.3.5.0 for Windows statistical software package (https://www.R-project.org/).

Results

Among the 12 083 patients included in the Sjögren Big Data Registry, 158 (1.3%) patients were diagnosed at an age below 19 years (supplementary Fig. S1, available at *Rheumatology* online). Of these 158 patients, 80 (50.6%) have been included in the previously published cohorts and 78 (49.4%) were new patients included only in this cohort. They were 136 (86%) girls and 22 (14%) boys, with a mean age at first sign or symptom suggestive of the disease of 13.2 (S.D. 3.2) years and of 14.2 (S.D. 3.5) years at the time of diagnosis of primary SS (Table 1).

TABLE 1 Epidemiological and clinical features of 158 patients with primary SS diagnosed in childhood

Variable	Patients with pSS diagnosed in childhood ($n = 158$)
Sex and age	
Sex (female)	136 (86.1)
Age at diagnosis (mean ± S.D.)	14.2 ± 3.5
Age at first sign/symptom ($n = 29$)	13.2 ± 3.2
Ethnicity	
White	107 (67.7)
Asian	26 (16.5)
Hispanic	19 (12)
Black/African American	4 (2.5)
Others	2 (1.3)
Geolocation	
Europe	104 (65.8)
America	29 (18.4)
Asia	24 (15.2)
Africa	1 (0.6)
Signs and symptoms at presentation	
Glandular enlargement	54/151 (35.8)
Dry mouth + dry eyes	36/151 (23.8)
Isolated dry mouth or dry eyes	33/151 (21.9)
Fever	18/151 (11.9)
Arthralgias	15/151 (9.9)
Skin involvement	14/151 (9.3)
Fatigue	7/151 (4.6)
RP	7/151 (4.6)
Peripheral lymphadenopathies	5/151 (3.3)
Arthritis	4/151 (2.6)
Cytopenias	4/151 (2.6)
RTA	2/151 (1.3)
Myalgias	1/151 (0.7)

Values are represented as mean ± S.D. for continuous variables and numbers (percentages) for categorical variables. pSS: primary SS.

The first signs and symptoms that led to the suspicion of an autoimmune disease are summarized in Table 1.

Despite not being presenting complaints, 126 (80%) children reported dry mouth and 111 (70%) dry eyes at the time of diagnosis. With respect to the diagnostic approach, abnormal ocular tests were reported in 51% in those studied by Schirmer's test and 35% in those studied using ocular dye tests, while abnormal oral tests were reported in 78% of those studied by unstimulated whole salivary flows and 81% of those studied by parotid scintigraphy (Table 2). Minor salivary gland biopsy showed Chisholm Mason grades 3–4 (i.e. focus score $\geq$1 focus/4 mm^2) in 118 (97%) out of 122 patients biopsied, while salivary US study was abnormal in 60 (94%) out of 64 patients (Table 2). With respect to the immunological profile at the time of diagnosis, the most frequent abnormalities consisted of positive ANA (90%), anti-Ro antibodies (83%), positive RF (68%) and anti-La antibodies (62%) (Table 2). All patients fulfilled both the 2002 and 2016 criteria except three (2%) who had anti-La antibodies in the absence of anti-Ro antibodies and in whom fulfilment of the 2016 criteria could not be confirmed because a salivary gland biopsy was not performed.

With respect to systemic phenotype, the mean total ESSDAI score at diagnosis of the entire cohort was 7.1

Table 2 Diagnostic tests, immunological markers and systemic activity at the time of diagnosis

Variable	Patients with pSS diagnosed in childhood (n = 158)
Diagnostic tests	
Abnormal ocular tests (any)	72/125 (57.6)
Schirmer's test	63/123 (51.2)
Rose bengal score/other ocular dye score	27/76 (35.5)
Abnormal oral diagnostic tests (any)	80/98 (81.6)
Unstimulated whole salivary flow	62/79 (78.5)
Parotid sialography	16/18 (88.9)
Salivary scintigraphy	17/21 (81)
Positive minor salivary gland biopsy	118/122 (96.7)
Abnormal salivary US study	60/64 (93.8)
Immunological profile	
ANA positive	140/155 (90.3)
RF positive	96/142 (67.6)
Positive anti-Ro/La antibodies	138/156 (88.5)
Anti-Ro antibodies	129/156 (82.7)
Anti-La antibodies	96/155 (61.9)
Low C3 levels	20/138 (14.5)
Low C4 levels	19/136 (14)
Positive cryoglobulins	3/64 (4.7)
Systemic activity	
Mean ESSDAI score (n = 155)	7.1 $\pm$ 6.7
DAS	
Low	72/155 (46.5)
Moderate	57/155 (36.8)
High	26/155 (16.8)
Activity subsets	
No activity (ESSDAI = 0)	16/155 (10.3)
No high activity in any domain	128/155 (82.6)
High activity in at least 1 domain	11/155 (7.1)
ESSDAI domains (score $\geq$1)	
Constitutional	34/155 (21.9)
Lymphadenopathy	39/155 (25.2)
Glandular	73/155 (47.1)
Articular	41/155 (26.5)
Cutaneous	19/155 (12.3)
Pulmonary	8/155 (5.2)
Renal	7/155 (4.5)
Muscular	3/155 (1.9)
PNS	0/155 0
CNS	1/155 (0.6)
Haematological	44/155 (28.4)
Biological	84/155 (54.2)

Values are represented as mean $\pm$ S.D. for continuous variables and numbers (percentages) for categorical variables. pSS: primary SS; ESSDAI: EULAR Sjögren's syndrome disease activity index; PNS: peripheral nervous system.

(S.D. 6.7); 90% of patients had systemic activity at diagnosis (global ESSDAI score ≥1) (Table 2). The clinical domains containing the highest frequencies of active patients included the glandular (47%), articular (26%) and lymphadenopathy (25%) domains. There was only one (0.6%) patient who presented with lymphoma at the time of primary SS diagnosis. The distribution of the degree of activity (no activity, low, moderate and high) in the entire cohort for each domain is summarized in supplementary Table S1, available at *Rheumatology* online, and the association of the main variables at diagnosis with systemic activity is summarized in supplementary Table S2, available at *Rheumatology* online.

Table 3 compares the disease patterns at diagnosis according to the three paediatric age subsets (<10, 10–14, >14 years). These analyses revealed some similarities and some differences including an increase in Whites ($P = 0.003$), a higher frequency of reported dry eyes ($P = 0.026$) and a lower frequency in lymphadenopathy ($P = 0.003$) in the older group compared with the other two younger groups. In addition, patients diagnosed at 10–14 years showed the highest systemic activity phenotype, with a higher frequency of anti-Ro antibodies ($P = 0.042$), a higher global mean ESSDAI ($P = 0.017$) and a higher frequency of systemic activity at the constitutional domain ($P = 0.004$). Using 15 as the cut-off resulted in increased frequency of low C3 levels ($P = 0.049$) and an increased frequency of patients with no systemic activity ($P = 0.012$) in the older compared with younger group (supplementary Table S3, available at *Rheumatology* online).

Table 4 compares the disease pattern of childhood-onset primary SS with adult patients grouped in intervals of 18 years. Childhood-onset primary SS showed a higher frequency of affected male sex and non-White patients, a lower frequency of sicca features with a lower frequency of abnormal ocular tests but a higher frequency of abnormal oral tests and positive salivary gland biopsy (Fig. 1A). With respect to immunological profile, childhood-onset disease patients showed the highest frequencies of positive autoantibodies and the lowest frequency of cryoglobulins among all the age subsets (Fig. 1B). With respect to systemic disease, the highest mean ESSDAI score was observed in childhood patients, who also showed the highest frequencies of systemic disease in 5 (constitutional, lymphadenopathy,

Table 3 Differences in the pattern expression of primary SS according to the three paediatric age subsets

Variable	5–9 years ($n = 23$)	10–14 years ($n = 47$)	15–18 years ($n = 88$)	*P*-value
Gender (female)	21 (91.3)	37 (78.7)	78 (88.6)	0.210
Ethnicity (White)	9 (39.1)	31 (66)	67 (76.1)	**0.003**
Dry eye	12 (52.2)	30 (63.8)	69 (78.4)	**0.026**
Dry mouth	15 (65.2)	36 (76.6)	75 (85.2)	0.085
Abnormal ocular tests	7/17 (41.2)	25/42 (59.5)	40/66 (60.6)	0.335
Positive minor salivary gland biopsy	21/22 (95.5)	33/33 (100)	64/67 (95.5)	0.464
Abnormal oral diagnostic tests	6/8 (75)	30/34 (88.2)	44/56 (78.6)	0.455
Abnormal salivary ultrasound study	10/11 (90.9)	24/25 (96)	26/28 (92.9)	0.816
Anti-Ro antibodies	15 (65.2)	41/46 (89.1)	73/87 (83.9)	**0.042**
Anti-La antibodies	14 (60.9)	31/46 (67.4)	51/86 (59.3)	0.655
ANA-positive	21 (91.3)	44/46 (95.7)	75/86 (87.2)	0.290
RF-positive	12/19 (63.2)	31/45 (68.9)	53/78 (67.9)	0.900
C3 low	1/21 (4.8)	4/45 (8.9)	15/72 (20.8)	0.079
C4 low	6/21 (28.6)	4/45 (8.9)	9/70 (12.9)	0.092
Positive cryoglobulins	1/8 (12.5)	1/15 (6.7)	1/41 (2.4)	0.430
ESSDAI total (mean ± S.D.)	5.8 ± 4.5	9.4 ± 8.7	6.1 ± 5.6	**0.017**
DAS (high)	2 (8.7)	13 (27.7)	11/85 (12.9)	0.051
High activity in at least 1 domain	1 (4.3)	5 (10.6)	5/85 (5.9)	0.510
ESSDAI domains (score ≥1)				
Constitutional	2 (8.7)	18 (38.3)	14/85 (16.5)	**0.004**
Lymphadenopathy	11 (47.8)	15 (31.9)	13/85 (15.3)	**0.003**
Glandular	11 (47.8)	27 (57.4)	35/85 (41.2)	0.200
Articular	5 (21.7)	10 (21.3)	26/85 (30.6)	0.437
Cutaneous	1 (4.3)	8 (17)	10/85 (11.8)	0.309
Pulmonary	1 (4.3)	4 (8.5)	3/85 (3.5)	0.456
Renal	0 0	2 (4.3)	5/85 (5.9)	0.481
Haematological	5 (21.7)	13 (27.7)	26/85 (30.6)	0.699
Biological	15 (65.2)	28 (59.6)	41/85 (48.2)	0.236

Statistically significant differences ($P < 0.05$) are shown in bold. Values are represented as mean ± S.D. for continuous variables and numbers (percentages) for categorical variables. ESSDAI domains that are muscular, peripheral nervous system and CNS are not analysed (fewer than five active patients per domain). ESSDAI: EULAR Sjögren's syndrome disease activity index.

TABLE 4 Differences in the pattern expression of primary SS according to the five 18-year age groups

Variable	≤18 years (*n* = 158)	19–36 years (*n* = 1701)	37–54 years (*n* = 4591)	55–72 years (*n* = 4684)	≥73 years (*n* = 921)
Gender (female)	136 (86.1)	1625 (95.5)	4302 (93.7)	4361 (93.1)	845 (91.7)
Ethnicity (White)	107 (67.7)	1073/1674 (64.1)	3130/4476 (69.9)	3529/4468 (79)	756/877 (86.2)
Dry eye	111 (70.3)	1498 (88.1)	4229 (92.1)	4403 (94)	840 (91.2)
Dry mouth	126 (79.7)	1532 (90.1)	4282 (93.3)	4447 (94.9)	892 (96.9)
Abnormal ocular tests	72/125 (57.6)	1151 (67.7)	3298 (71.8)	3342 (71.3)	592 (64.3)
Positive minor salivary gland biopsy	118/122 (96.7)	1001/1160 (86.3)	2601/3223 (80.7)	2868/3501 (81.9)	537/663 (81)
Abnormal oral diagnostic tests	80/98 (81.6)	958 (56.3)	2681 (58.4)	2962 (63.2)	637 (69.2)
Anti-Ro antibodies	129/156 (82.7)	1480/1682 (88)	3505/4535 (77.3)	3172/4641 (68.3)	604/919 (65.7)
Anti-La antibodies	96/155 (61.9)	953/1674 (56.9)	2072/4503 (46)	1874/4626 (40.5)	359/915 (39.2)
ANA-positive	140/155 (90.3)	1472/1640 (89.8)	3594/4356 (82.5)	3289/4326 (76)	645/845 (76.3)
RF-positive	96/142 (67.6)	820/1348 (60.8)	1846/3752 (49.2)	1580/3665 (43.1)	309/725 (42.6)
C3 low	20/138 (14.5)	259/1406 (18.4)	563/3766 (14.9)	349/3715 (9.4)	73/727 (10)
C4 low	19/136 (14)	232/1398 (16.6)	535/3763 (14.2)	435/3712 (11.7)	109/733 (14.9)
Positive cryoglobulins	3/64 (4.7)	60/730 (8.2)	134/2055 (6.5)	177/2068 (8.6)	28/388 (7.2)
ESSDAI total (mean ± S.D.)	7.1 ± 6.7	6.2 ± 6.6	6.0 ± 7.3	5.8 ± 7.7	6.1 ± 7.4
ESSDAI domains (score ≥1)					
Constitutional	34/155 (21.9)	191/1621 (11.8)	458/4416 (10.4)	380/4430 (8.6)	74/860 (8.6)
Lymphadenopathy	39/155 (25.2)	211/1625 (13)	410/4423 (9.3)	290/4440 (6.5)	52/863 (6)
Glandular	73/155 (47.1)	389/1621 (24)	961/4416 (21.8)	846/4430 (19.1)	121/860 (14.1)
Articular	41/155 (26.5)	558/1621 (34.4)	1743/4416 (39.5)	1585/4430 (35.8)	250/859 (29.1)
Cutaneous	19/155 (12.3)	181/1625 (11.1)	422/4423 (9.5)	349/4440 (7.9)	78/863 (9)
Pulmonary	8/155 (5.2)	97/1625 (6)	420/4422 (9.5)	545/4440 (12.3)	130/863 (15.1)
Renal	7/155 (4.5)	101/1621 (6.2)	196/4416 (4.4)	162/4430 (3.7)	32/860 (3.7)
Muscular	3/155 (1.9)	20/1621 (1.2)	102/4416 (2.3)	111/4430 (2.5)	19/860 (2.2)
PNS	0/1550	55/1621 (3.4)	240/4416 (5.4)	293/4430 (6.6)	74/860 (8.6)
CNS	1/155 (0.6)	29/1621 (1.8)	72/4416 (1.6)	84/4430 (1.9)	17/860 (2)
Haematological	44/155 (28.4)	387/1611 (24)	981/4365 (22.5)	858/4368 (19.6)	200/843 (23.7)
Biological	84/155 (54.2)	1009/1584 (63.7)	2205/4276 (51.6)	1911/4301 (44.4)	370/846 (43.7)

All comparisons were statistically significant ($P < 0.05$) except for positive cryoglobulins ($P = 0.117$), total ESSDAI ($P = 0.069$), muscular domain ($P = 0.058$) and CNS ($P = 0.691$). Values are represented as mean ± S.D. for continuous variables and numbers (percentages) for categorical variables. ESSDAI: EULAR Sjögren's syndrome disease activity index; PNS: peripheral nervous system.

glandular, cutaneous and haematological) out of the 12 ESSDAI domains, and the lowest frequencies in 4 (articular, pulmonary, peripheral nerve and CNS) (Fig. 1C). There is a differentiated trend in the frequency of patients with active organ-specific ESSDAI domains according to the age group at diagnosis; while some organs follow a predominant steady decreasing frequency pattern (constitutional, lymphadenopathy and glandular), others showed a predominant steady increasing pattern (pulmonary and neuromuscular) from the youngest to the older group ages (Fig. 2).

Discussion

A significant challenge of diagnosing primary SS is recognizing that the disease can occur in people of any age. Although the disease is diagnosed predominantly in middle-aged people, the epidemiology of primary SS is a continuum and the disease has been diagnosed in people aged from 2 [18] to 97 years [10]. The data available until now suggest that primary SS is a very rare disease in children. In comparison with adult-onset disease, both the number of studies and the number of reported cases of childhood-onset SS is very limited, with only six studies including >20 cases [6, 19–23] (supplementary Table S4, available at *Rheumatology* online). In this study, we used a different methodological approach from previous studies. Firstly, we included only cases fulfilling the current classification criteria for the disease [8, 9] searching for those cases included in the Sjögren Big Data cohort diagnosed in childhood, and secondly, we requested the cooperative involvement of paediatricians who included children currently followed in paediatric departments to ensure a complete epidemiological coverage of potential cases. For the first time, we can estimate the real frequency of childhood-onset disease (around 1%), confirming that primary SS is a disease that is exceptionally diagnosed in children.

Previous studies have defined the clinical phenotype of childhood-onset SS as mainly dominated by parotid involvement more than by sicca features, often using a clinical diagnosis more than the current SS classification criteria (Supplementary Table S4, available at

Fig. 1 Radar charts

Radar charts showing variations in glandular involvement (**A**), immunological profile (**B**) and ESSDAI scores (**C**). ESSDAI: systemic EULAR Sjögren's syndrome disease activity index.

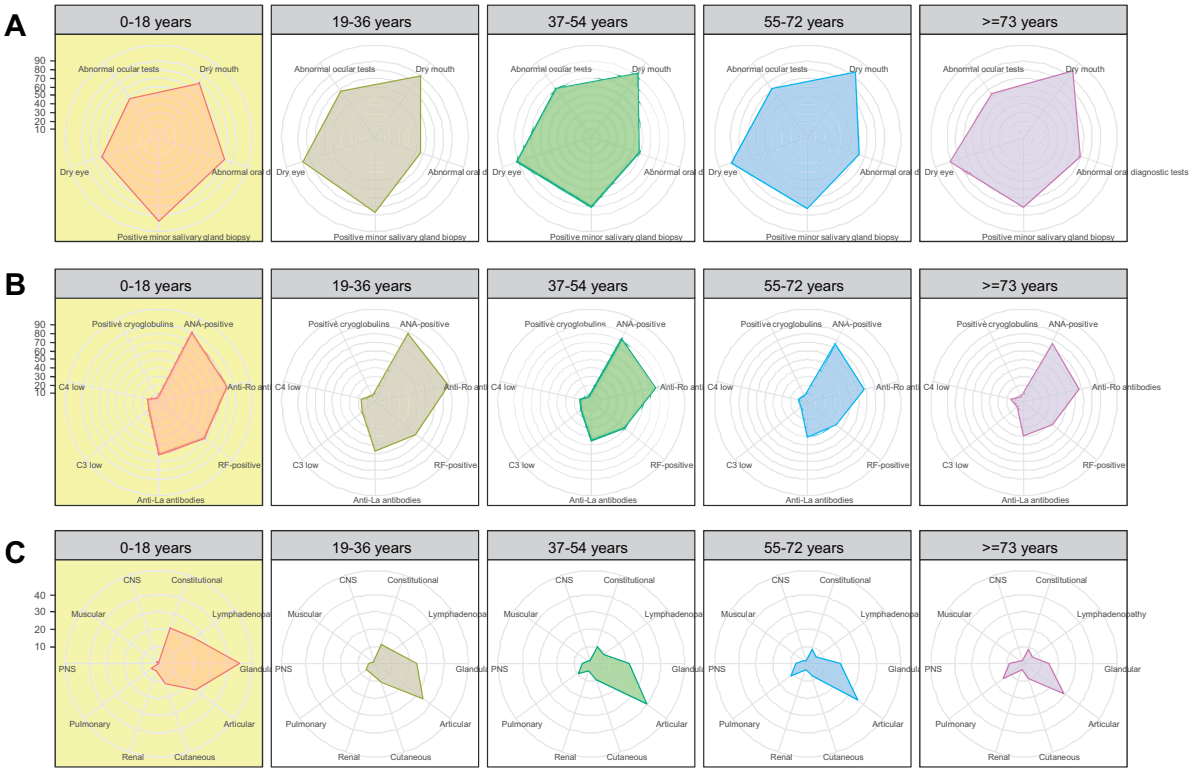
Rheumatology online). Our study, made under the methodological umbrella of the fulfilment of current criteria, showed a predominant phenotype much closer to that reported in young adult patients, with sicca symptoms being more frequent than salivary gland enlargement (80% and nearly 50%, respectively). Despite this, salivary gland enlargement remains a prominent feature of childhood-onset primary SS, affecting one out of two children. In these children, it is important to distinguish onset of SS from recurrent parotitis of childhood, an idiopathic disease affecting the parotid glands reported as the most common parotid disease in childhood after mumps [24]. There are significant differences between recurrent parotitis of childhood and SS, especially in the immunological profile (ANA, RF, Ro and/or La antibodies), which was reported in 96% of our cases of childhood primary SS, while in recurrent parotitis of childhood patients, the frequency ranges from 4 to 16% [25, 26].

Classification criteria for SS in children are not uniformly agreed upon by paediatricians [27] and diagnostic tests used for diagnosing glandular dysfunction in adults are not validated in children. Among ocular tests, Schirmer's test is most frequently carried out in children with SS, with around 70% of cases showing abnormal results [19, 23]. For the study of salivary gland dysfunction, salivary gland US is a non-invasive test that may evaluate the glandular damage of salivary glands and that can be very useful in both adults and children. In the largest study reported, Hammenfors *et al.* [6] evaluated 67 patients with childhood-onset SS in whom US was carried out at a mean age of 16 years (including an undetermined number of cases evaluated above the age of 18 years): pathologic salivary gland US findings were observed in 41 (61%) cases, while in our study, the rate was higher (94%). The low rate of positive findings reported by Hammenfors *et al.* [6] could be explained by the fact that <60% of cases fulfilled the current classification criteria, as well as by the significant variation among countries. But the two key diagnostic markers supporting a diagnosis of SS are, as happens in adults, a positive test for Ro autoantibodies and the finding of a focal lymphocytic sialadenitis in the salivary gland tissue, because they are the most specific diagnostic tests. In previous studies, salivary gland biopsy was positive in 82% of children (supplementary Table S4, available at *Rheumatology* online), while in our study the frequency rose to 97%. With respect to immunological markers, anti-Ro/SSA antibodies were found in >70% of patients and anti-Ro/SSA and/or anti-La/SSB in 80% of childhood SS patients in previous studies [27]. In our study, nearly 90% of our cases were positive for Ro/La antibodies, highlighting the key role of these autoantibodies in diagnosing primary SS in children.

According to our data, childhood primary SS is undeniably a systemic disease (90% of our cases had systemic activity at the time of diagnosis, defined as an ESSDAI score of 1 or higher), as happens in adults. The age at diagnosis is a key determinant of the expression of systemic disease in primary SS, and a recent study in our international cohort showed that the highest systemic scores were reported in patients diagnosed at 18–35 years [10]. In addition, age at diagnosis also modulated how frequent the involvement of individual organs was at the time of diagnosis. A younger diagnosis was associated with an increased risk of presenting activity at diagnosis in some clinical domains (constitutional, lymphadenopathy, glandular, cutaneous, renal), but a decreased risk of presenting activity in others (pulmonary and neurological domains). In childhood-onset primary SS, systemic phenotype is clearly dominated by glandular involvement (in nearly 50% of our patients), followed by articular, lymphadenopathy and constitutional involvement, a very close phenotypic scenario to that reported in young-onset people [10].

The inclusion criteria that we used in this study (primary cases meeting the current criteria) may explain some of the main findings, such as the higher percentages of positive diagnostic tests (salivary flow, salivary gland US, autoantibodies or salivary gland biopsy) in comparison with previous childhood SS studies (supplementary Table S4, available at *Rheumatology* online). However, meeting the criteria may exclude an earlier stage of disease that is not captured through these criteria [28, 29]. This is especially significant for Ro-negative children with a high suspicion of having a primary SS, because it is unclear whether these autoantibodies could be appearing later, although salivary gland biopsy will play a key role in such cases in confirming SS. In Ro-negative children with a normal histopathological analysis, the disease can be reasonably discarded. But as happens in adults, the criteria are designed to classify and not to diagnose on clinical grounds, and some children could have an abnormal biopsy with focal sialadenitis but not fulfilling the

FIG. 2 Frequency of patients with active organ-specific ESSDAI domains according to the five 18-year age groups



(**A**) Organs with a predominant decreasing pattern; (**B**) organs with a predominant increasing pattern; (**C**) organs with a mixed pattern. ESSDAI: systemic EULAR Sjögren's syndrome disease activity index.

classification criteria (a focus score <1, but >0) [30]. Only long-term follow-up studies of individuals diagnosed with primary SS during childhood will confirm whether these patients will develop a full SS during the follow-up. These studies will also be helpful for defining the prognosis of the childhood-onset SS. In our cohort, only one (0.6%) case showed a lymphoma coincident with the diagnosis of primary SS. Although lymphoma development has been reported in some children with SS [31–34], whether the risk is similar to or greater than that in adults is not yet known.

The study has some limitations. With a retrospective design analysing pre-existing data obtained from medical records, a recall bias cannot be discarded. The retrospective use of the ESSDAI score (which was published in 2010) also means that some laboratory parameters were not available at diagnosis in all patients. In addition, the physician assessment and the referral patterns from each centre may influence how systemic disease is scored. The predominant presence of European patients (due to the origin of the project in the EULAR SS Group) could also limit the generalization of the results in non-European populations due to the small size of some ethnic subpopulations, such as Black/African-American patients, and further studies may be necessary to confirm their relevance in these patients.

In summary, childhood-onset primary SS involves around 1% of patients with primary SS, with a clinical phenotype dominated by sicca features, parotid enlargement and systemic disease. Our results indicate that no essential difference exists in SS between young-onset and childhood-onset patients, suggesting that the specific features seen in childhood-onset disease may reflect an early stage of SS. Therefore, childhood-onset SS should be considered an epidemiological subset with a specific pattern of presentation as happens with other epidemiological subsets (elderly patients, male patients) more than a differentiated disease from adult-onset primary SS, highlighting the key role of the age at diagnosis on modulating the phenotypic expression of the disease from childhood to elderly ages. Paediatric-specific normative values for these diagnostic tests and paediatric-specific classification criteria are needed, as well as international collaborative studies to better define and understand the natural history of SS in children, and to determine what features accurately could predict a worse progression.

Acknowledgments

Other members of the Sjögren Big Data Consortium who have contributed to this work: B. Kostov (Department of Statistics and Operational Research,

Universitat Politècnica de Catalunya; Primary Healthcare Transversal Research Group, IDIBAPS, Barcelona, Spain); I.-F. Horvath, A. Szanto (Division of Clinical Immunology, Faculty of Medicine, University of Debrecen, Debrecen, Hungary); R. Seror, X. Mariette (Center for Immunology of Viral Infections and Autoimmune Diseases, Assistance Publique—Hôpitaux de Paris, Hôpitaux Universitaires Paris-Sud, Le Kremlin-Bicêtre, Université Paris Sud, INSERM, Paris, France Paris, France); M. Kvarnstrom, M. Wahren-Herlenius (Department of Medicine, Solna, Division of Experimental Rheumatology, Karolinska Institutet, and Karolinska University Hospital, Stockholm); S. Praprotnik (Department of Rheumatology, University Medical Centre, Ljubljana, Slovenia); R. Solans (Department of Internal Medicine, Hospital Vall d'Hebron, Barcelona, Spain); G. Nordmark (Rheumatology, Department of Medical Sciences, Uppsala University, Uppsala, Sweden); D. Hammenfors, J.G. Brun (Department of Rheumatology, Haukeland University Hospital, Bergen, Norway); T.A. Gheita (Rheumatology Department, Kasr Al Ainy School of Medicine, Cairo University, Egypt); F. Atzeni (IRCCS Galeazzi Orthopedic Institute, Milan and Rheumatology Unit, University of Messina, Messina, Italy); B. Armagan, L. Kilic, U. Kalyoncu (Department of Internal Medicine, Hacettepe University, Faculty of Medicine, Ankara, Turkey); T. Nakamura, Y. Takagi (Department of Radiology and Cancer Biology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan); S. Consani (Clinica Medica 3 – Universidad de la Republica, Hospital Maciel, Montevideo, Uruguay); F. Olivera Solorzano (Department of Paediatric Rheumatology, Unidad de Especialidades Médicas. Secretaría de la Defensa Nacional, México DF, México).

Supplementary data

Supplementary data are available at *Rheumatology* online.

Disclosure statement: The authors have declared no conflicts of interest.

Funding: This work was supported by Grants Fondo de Investigaciones Sanitarias (INT15/00085 to M.R.-C.) and Hospital Clinic Barcelona (Ajut per a la Recerca Josep Font to P.B.-Z.).

Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

References

1 Brito-Zerón P, Baldini C, Bootsma H *et al.* Sjögren syndrome. Nat Rev Dis Prim 2016;2:16047.

2 Mariette X, Criswell LA. Primary Sjögren's syndrome. N Engl J Med 2018;378:931–9.

3 Brito-Zerón P, Acar-Denizli N, Zeher M *et al.* Influence of geolocation and ethnicity on the phenotypic expression of primary Sjögren's syndrome at diagnosis in 8310 patients: a cross-sectional study from the Big Data Sjögren Project Consortium. Ann Rheum Dis 2017;76: 1042–50.

4 Ramos-Casals M, Brito-Zerón P, Sisó-Almirall A *et al.* Primary Sjogren syndrome. BMJ 2012;344:e3821–e3821.

5 Brito-Zeron P, Retamozo S, Ramos-Casals M. Phenotyping Sjögren's syndrome: towards a personalised management of the disease. Clin Exp Rheumatol 2018;36: 198–209.

6 Hammenfors DS, Valim V, Bica BERG *et al.* Juvenile Sjögren's syndrome: clinical characteristics with focus on salivary gland ultrasonography. Arthritis Care Res (Hoboken) 2020;72:78–87.

7 Lieberman SM. Childhood Sjögren syndrome: insights from adults and animal models. Curr Opin Rheumatol 2013;25:651–7. doi:10.1097/BOR.0b013e328363ed23

8 Vitali C, Bombardieri S, Jonsson R *et al.* Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis 2002;61:554–8.

9 Shiboski CH, Shiboski SC, Seror R *et al.*; the International Sjögren's Syndrome Criteria Working Group. 2016 American College of Rheumatology/ European League Against Rheumatism classification criteria for primary Sjögren's syndrome. Ann Rheum Dis 2017;76:9–16.

10 Brito-Zeron P, Acar-Denizli N, Ng W-F *et al.* Epidemiological profile and north-south gradient driving baseline systemic involvement of primary Sjögren's syndrome. Rheumatology (Oxford) 2020;59:2350–9.

11 Acar-Denizli N, Kostov B, Ramos-Casals M. The Big Data Sjogren Consortium: a project for a new data science era. Clin Exp Rheumatol 2019;37: 19–23.

12 Gibert K, Sànchez-Marrè M, Izquierdo J. A survey on pre-processing techniques: relevant issues in the context of environmental data mining. AI Commun Eur J Artif Intell 2016;29:627–63.

13 Vitali C, Bombardieri S, Moutsopoulos HM *et al.* Preliminary criteria for the classification of Sjögren's syndrome. Results of a prospective concerted action supported by the European Community. Arthritis Rheum 1993;36:340–7.

14 Seror R, Ravaud P, Bowman SJ *et al.* EULAR Sjögren's syndrome disease activity index: development of a consensus systemic disease activity index for primary Sjögren's syndrome. Ann Rheum Dis 2010;69: 1103–9.

15 Seror R, Meiners P, Baron G *et al.* Development of the ClinESSDAI: a clinical score without biological domain. A tool for biological studies. Ann Rheum Dis 2016;75: 1945–50.

16 Seror R, Bowman SJ, Brito-Zeron P *et al.*; on behalf of the EULAR Sjögren;s Task Force. EULAR Sjögren's syndrome disease activity index (ESSDAI): a user guide. RMD Open 2015;1:e000022.

17 Seror R, Bootsma H, Saraux A *et al.* Defining disease activity states and clinically meaningful improvement in

primary Sjögren's syndrome with EULAR primary Sjögren's syndrome disease activity (ESSDAI) and patient-reported indexes (ESSPRI). Ann Rheum Dis 2016;75:382–9.

18 De Oliveira MA, De Rezende NPM, Maia CMF *et al.* Primary Sjögren syndrome in a 2-year-old patient: role of the dentist in diagnosis and dental management with a 6-year follow-up. Int J Paediatr Dent 2011;21:471–5.

19 Stiller M, Golder W, Döring E *et al.* Primary and secondary Sjögren's syndrome in children–a comparative study. Clin Oral Investig 2000;4:176–82.

20 Cimaz R, Casadei A, Rose C *et al.* Primary Sjögren syndrome in the paediatric age: a multicentre survey. Eur J Pediatr 2003;162:661–5.

21 Yokogawa N, Lieberman SM, Sherry DD *et al.* Features of childhood Sjögren's syndrome in comparison to adult Sjögren's syndrome: considerations in establishing child-specific diagnostic criteria. Clin Exp Rheumatol 2016;34: 343–51.

22 Kobayashi I, Okura Y, Ueki M *et al.* Evaluation of systemic activity of pediatric primary Sjögren's syndrome by EULAR Sjögren's syndrome disease activity index (ESSDAI). Mod Rheumatol 2019;29:130–3.

23 Tomiita M, Saito K, Kohno Y *et al.* The clinical features of Sjögren's syndrome in Japanese children. Acta Paediatr Jpn Overseas Ed 1997;39:268–72.

24 Saarinen R, Kolho K-L, Davidkin I *et al.* The clinical picture of juvenile parotitis in a prospective setup. Acta Paediatr 2013;102:177–81.

25 Leerdam CM, Martin HCO, Isaacs D. Recurrent parotitis of childhood. J Paediatr Child Health 2005;41:631–4.

26 Hara T, Nagata M, Mizuno Y *et al.* Recurrent parotid swelling in children: clinical features useful for differential diagnosis of Sjögren's syndrome. Acta Paediatr 1992;81: 547–9.

27 Singer NG, Tomanova-Soltys I, Lowe R. Sjögren's syndrome in childhood. Curr Rheumatol Rep 2008;10: 147–55.

28 Houghton K, Malleson P, Cabral D *et al.* Primary Sjögren's syndrome in children and adolescents: are proposed diagnostic criteria applicable? J Rheumatol 2005;32:2225–32.

29 McGuirt WF, Whang C, Moreland W. The role of parotid biopsy in the diagnosis of pediatric Sjögren syndrome. Arch Otolaryngol Head Neck Surg 2002;128:1279–81.

30 Yokogawa N, Lieberman SM, Alawi F *et al.* Comparison of labial minor salivary gland biopsies from childhood Sjögren syndrome and age-matched controls. J Rheumatol 2014;41:1178–82.

31 Buonuomo PS, Maurizi P, Bracaglia C *et al.* Primary Sjögren's syndrome mimicking lymphoma in a pediatric patient. A rare and possibly misdiagnosed condition. Minerva Pediatr 2009;61:119–22.

32 Collado P, Kelada A, Cámara M *et al.* Extranodal marginal zone B cell lymphoma: An unexpected complication in children with Sjögren's syndrome. Reumatol Clin 2018;14:227–9.

33 Fukumoto Y, Hosoi H, Kawakita A *et al.* Sjögren's syndrome with MALT (mucosa-associated lymphoid tissue) lymphoma in a 13-year-old girl: a case report. Nihon Rinsho Meneki Gakkai Kaishi 2000;23:49–56. [].

34 Tesher MS, Esteban Y, Henderson TO *et al.* Mucosal-Associated Lymphoid Tissue (MALT) lymphoma in association with pediatric primary Sjögren syndrome: 2 cases and review. J Pediatr Hematol Oncol 2019;41: 413–6.