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Results of a Nationwide Multicenter Study in Childhood Sjögren Disease

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ABSTRACT. ***Objective***. This nationwide, multicenter study was conducted to assess the demographic and clinical features, treatment regimens, and prognosis of primary Sjögren disease (SjD) in childhood.

Methods. This retrospective study included a total of 81 patients < 18 years of age from 21 pediatric rheumatology centers. Among these, 51 patients fulfilled the diagnosis of childhood SjD according to the 2016 American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) classification criteria. The remaining 30 patients—who did not fully meet these criteria but exhibited clinical and laboratory findings suggestive of SjD—were categorized as at risk for childhood SjD to highlight diagnostic challenges and the spectrum of early presentations, based on comprehensive clinical evaluation by experienced pediatric rheumatologists.

Results. The cohort consisted of 81 patients (85.2% female, 14.8% male) with a median age at symptom onset of 11.4 years and a median follow-up of 24 months. Common clinical manifestations included dry mouth, dry eyes, arthralgia, fatigue, and parotitis. Fifty-one of the 81 patients met the 2016 ACR/EULAR classification criteria, whereas the remaining 30 were classified as an at-risk group. The most common clinical findings in the at-risk group were xerostomia (90%), arthralgia (56.7%), fatigue (50%), and dry eyes (43.3%). Dry mouth and peripheral nervous system involvements were found to be higher in patients categorized as at risk ($P = 0.03$ and $P = 0.02$, respectively).

Conclusion. The current classification criteria for childhood SjD appear to be inadequate, highlighting the need for pediatric-specific criteria that more accurately reflect the distinct clinical patterns observed in children.

Key Indexing Terms: autoimmune diseases, childhood, parotitis, Sjögren disease

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Sjögren disease (SjD) is a systemic autoimmune disease that primarily targets the exocrine glands. This leads to dryness of mucosal surfaces due to lymphocytic infiltration of the related tissues.[1] In a systematic review and metaanalysis, the incidence of SjD was estimated to be 6.9 per 100,000 person-years at risk, whereas the pooled prevalence in the total population was 60.8 cases per 100,000 people, with a higher incidence in female individuals than male individuals.[2] The frequency of the disease in children is significantly lower, representing approximately 1% of all primary SjD diagnoses.[3] One prevailing theory in its etiopathogenesis is that of autoimmune epithelitis, which presumes that the inflamed tissue in SjD comprises the epithelial cells of exocrine glands. These cells function as antigen-presenting cells, initiating an immune response. Autoantigens expressed by the epithelium, such as SSA/Ro and SSB/La, provoke abnormal responses from T cells and B cells. This leads to an increase in cytokines and chemokines, resulting in chronic inflammation and, ultimately, exocrinopathy and parenchymal involvement in the exocrine glands, causing loss of physiological function.[4]

Despite established classification criteria and advanced treatment options for adults, significant limitations remain in the classification, diagnosis, and treatment of pediatric cases due to the rarity of the disease and pediatric-specific limitations in diagnostic testing, such as ocular staining scores and salivary flow rates.[5-7] Consequently, the diagnosis of childhood SjD can often be delayed. The rarity of the disease not only delays diagnosis but also poses challenges in establishing an accurate diagnosis, selecting appropriate treatments, screening for complications such as malignancy, and providing counseling on long-term outcomes.

This multicenter study conducted in Türkiye aims to assess the demographic, clinical, and laboratory features; treatment regimens; and prognosis of childhood SjD, marking the first description to our knowledge of the disease characteristics on a nationwide scale in childhood.

METHODS

This retrospective study included 81 patients who were diagnosed with primary SjD before the age of 18, and who were followed up at 21 pediatric rheumatology centers across various provinces in Türkiye. These patients either met the 2016 American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) criteria for SjD[5] or were diagnosed with SjD based on expert opinion.[8,9] The patients who did not fully meet these criteria were categorized as at risk for childhood SjD based on comprehensive clinical evaluation by experienced pediatric rheumatologists, supported by laboratory (ie, antinuclear antibody [ANA], anti-SSA/Ro, anti-SSB/La, rheumatoid factor [RF] positivity), imaging (salivary gland ultrasound [SGUS]), and histopathological (minor salivary gland [MSG] biopsy) findings. Certain adult classification components, such as ocular staining scores and salivary flow rates, were not routinely assessed due to practical pediatric-specific limitations.

We collected demographic data including sex, age at symptom onset, age at diagnosis, and pubertal status, along with clinical features such as presenting symptoms and additional accompanying symptoms. Laboratory analyses included acute-phase reactants (C-reactive protein [CRP], erythrocyte sedimentation rate [ESR]), complete blood count, complement levels (C3 and C4), immunoglobulins, and immunological variables including ANA, anti-dsDNA, anti-SSA/Ro, anti-SSB/La, and RF. Laboratory tests performed at the time of initial diagnosis and the last visit were included in the study.

The study evaluated adherence to the 2016 ACR/EULAR diagnostic criteria, with radiological examinations focusing on salivary glands and disease activity assessed at initial and final visits. Intermediate follow-up assessments of disease activity were limited due to retrospective data collection inconsistencies. The duration of patient follow-up, treatment regimens, and prognoses were also documented. Patients were categorized into 2 age groups based on developmental stages: preadolescence (≤ 10 years) and adolescence (> 10 years) according to the American Academy of Pediatrics.[10] Thus, the study sought to investigate whether the clinical features of this disease, known to differ between children and adults, also show variability within the pediatric age group, potentially highlighting distinct patterns in preadolescence and adolescence.

MSG biopsy results were classified according to the Chisholm and Mason criteria.[11] The classification according to the Chisholm and Mason criteria was performed in accordance with standard care protocols. Disease activity was measured at the time of diagnosis and at the final visit using the EULAR Sjögren Syndrome Disease Activity Index (ESSDAI). The ESSDAI's 12 domains—constitutional, lymphadenopathy, glandular, articular, cutaneous, muscular, renal, pulmonary, peripheral nervous system, central nervous system, hematological, and biological—were assessed for each patient. Activity levels were defined as low (scores < 5), moderate (scores 5-13), and high (scores ≥ 14).[12]

Statistical analysis. Statistical analysis was conducted using SPSS version 25.0 (IBM SPSS Statistics 25 Software). Continuous variables were reported as median with minimum and maximum values, whereas categorical variables were presented as frequencies and percentages. The Shapiro-Wilk test was applied to assess the normality in distribution of numeric variables. Differences between independent groups were analyzed using the Mann-Whitney *U* test, and categorical variables were compared using the chi-square test. Logistic regression analysis was performed to assess the relationship between laboratory variables and the ESSDAI domains with the highest scores. The logistic regression model included laboratory test results (acute-phase reactants, complement levels, immunoglobulins, and immunological variables) as covariates, and the results were reported as odds ratios with 95% CIs. Statistical significance was determined at a *P* value threshold of 0.05 in all tests.

RESULTS

Demographic, clinical, and laboratory data in all patients. The study cohort consisted of 81 patients, of whom 69 (85.2%) were female and 12 (14.8%) were male. The median ages at symptom onset and diagnosis were approximately 11.4 years (range 2.4-17.1) and 12.5 years (range 5.8-18), respectively. The median duration from symptom onset to diagnosis was

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Table 1. The characteristics of 81 pediatric patients diagnosed with primary SjD or categorized as at risk.[a]

Clinical Signs and Symptoms	Values
Dry mouth	62 (76.5)
Dry eyes	51 (63)
Arthralgia	47 (58)
Dry eyes + dry mouth	39 (48.1)
Fatigue	37 (45.7)
Parotitis	36 (44.4)
Peripheral LAP	29 (35.8)
Arthritis	25 (30.9)
Rash	23 (28.4)
Malar rash, n/N	1/23
Discoid rash, n/N	1/23
Erythema multiforme, n/N	1/23
Purpura, n/N	2/23
Papular, n/N	2/23
Nonspecific, n/N	16/23
Myalgia	19 (23.5)
Weight loss	18 (22.2)
Fever	16 (19.8)
Raynaud phenomenon	16 (19.8)
CNS involvement	7 (8.6)
CNS vasculitis, n/N	1/7
Transverse myelitis, n/N	1/7
Autoimmune encephalitis, n/N	1/7
Epileptic seizures, n/N	2/7
Demyelinating plaques, n/N	3/7
PNS involvement	4 (4.9)
Neuropathy, n/N	3/4
Facial paralysis, n/N	1/4
Pulmonary involvement	3 (3.7)
ILD, n/N	1/3
Persistent cough, n/N	1/3
Shortness of breath, n/N	1/3
Renal involvement	8 (9.8)
TIN, n/N	2/8
TIN + RTA, n/N	1/8
Proteinuria, n/N	8/8
Psychosis	1 (1.2)

Laboratory Features at Diagnosis	Values
Complete blood count test[b]	
Anemia	13 (16)
Thrombocytopenia	5 (6.2)
Leukopenia	5 (6.2)
Autoantibodies	
Positive ANA	69 (85.2)
Positive anti-SSA/Ro	55 (67.9)
Positive RF, n/N (%)	26/73 (35.6)
Positive anti-SSA/Ro and anti-SSB/La	27 (33.3)
Positive anti-SSB/La	26 (32.1)
Positive anti-dsDNA	3 (3.7)
Acute-phase reactants	
Elevated ESR	45 (55.6)
Elevated CRP	28 (34.6)
Complements	
Low C4	11 (13.6)
Low C3	10 (12.3)
IgG, n/N (%)	
Elevated IgG	13/64 (20.3)
Low IgG	2/64 (3.1)
Other variables	
Elevated amylase	30 (37)
Proteinuria[c]	8 (9.9)

ESSDAI Domains	
Articular	35 (43.2)
Glandular	35 (43.2)
Lymphadenopathy	31 (38.3)
Constitutional	31 (38.3)
Biological	21 (25.9)
Cutaneous	14 (17.3)
Central nervous system	8 (9.9)
Hematological	7 (8.6)
Renal	6 (7.4)
Muscular	2 (2.5)
Pulmonary	3 (3.7)
Peripheral nervous system	2 (2.5)

Values are expressed as n (%) unless otherwise indicated. [a] At-risk group: patients who did not fully meet the adult classification criteria but exhibited clinical and laboratory findings suggestive of childhood SjD, classified based on comprehensive pediatric clinical evaluation. [b] Anemia: hemoglobin ≤ 2.5th percentile for age and sex; thrombocytopenia: platelet count < 150×10^9/L; leukopenia: white blood cell count < 4×10^9/L. [c] Proteinuria: spot urine protein/creatinine ratio > 0.2 mg/mg. ANA: antinuclear antibody; CNS: central nervous system; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; ESSDAI: European Alliance of Associations for Rheumatology Sjögren Syndrome Disease Activity Index; ILD: interstitial lung disease; LAP: lymphadenopathy; PNS: peripheral nervous system; RF: rheumatoid factor; RTA: renal tubular acidosis; SjD: Sjögren disease; TIN: tubulointerstitial nephritis.

12 months (range 1-114). A moderate negative correlation was observed between the age at symptom onset and the duration from symptom onset to diagnosis (r –0.52, $P < 0.001$). The most common clinical findings reported in at least half of the patients were dry mouth, dry eye, arthralgia, fatigue and parotitis, in descending order of frequency (Table 1). When analyzing SjD in children by sex, parotitis was present in 39.1% of female patients compared to 75% of male patients, which was statistically significant ($P = 0.02$). Further, myalgia-related symptoms were reported only in girls.

Of the 81 patients, 51 (63%) met the ACR/EULAR classification criteria for SjD. The Schirmer test was positive in 46 patients (56.8%). MSG biopsy was performed in 51 patients (63%), of whom 35 (68.6%) exhibited grade 3 or 4 changes according to the Chisholm and Mason classification. SGUS were performed in 49 patients (60.5%), with 41 (83.7%) showing inflammatory changes consistent with the disease. Salivary gland scintigraphy was performed in 3 patients, all of whom demonstrated technetium-99m pertechnetate decreased uptake, indicative of glandular dysfunction. The most frequently detected autoantibodies were ANA, followed by anti-SSA/Ro, RF, and anti-SSB/La (Table 1).

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The most common clinical findings in 30 patients categorized as at risk for childhood SjD based on expert clinical evaluation were xerostomia (90%), arthralgia (56.7%), fatigue (50%), and dry eyes (43.3%; Table 2). Rash, parotitis, and arthritis were present in approximately 30% of patients, whereas Raynaud phenomenon was observed in 23.3%. Parotitis was present in 10/12 patients (83%) on SGUS. MSG biopsy was performed in 15 patients who did not meet the diagnostic criteria. Biopsy findings were consistent with grade 2 in 10 patients and grade 1 in 3 patients according to the Chisholm and Mason classification. Eighty percent of patients were ANA positive, 56.7% were anti-SSA/Ro positive, 29% were RF positive, and 20% were anti-SSB/La positive. The characteristics of patients categorized as at risk were presented in Table 3. Patients meeting the diagnostic criteria were compared with those categorized as at risk. The median age at symptom onset was lower among patients who fulfilled the diagnostic criteria compared to those who did not. Elevated ESR ($P = 0.01$), positive Schirmer test ($P < 0.001$), positive MSG biopsy ($P < 0.001$), parotitis ($P = 0.045$), and dry eyes ($P = 0.01$) were found to be statistically significantly higher in patients meeting the diagnostic criteria. Dry mouth ($P = 0.03$) and peripheral nervous system (PNS; $P = 0.02$) involvement were found to be statistically significantly higher in patients categorized as at risk (Table 2).

ESSDAI domains and associated conditions. ESSDAI is a scoring system that evaluates disease activity across 12 domains. At the time of diagnosis, the clinical domains with the highest frequencies of active disease were as follows: articular (43.2%), glandular (43.2%), lymphadenopathy (38.3%), and constitutional (38.3%; Table 1). The median ESSDAI score at the time of diagnosis was 8 (range 0-36), decreasing to 0 (range 0-21) by the last visit. Intermediate follow-up assessments were limited due to retrospective data collection inconsistencies. The last-visit ESSDAI score exhibited a weak positive correlation with the age at symptom onset (r 0.26, $P = 0.02$) and a moderate positive correlation with the initial ESSDAI score (r 0.53, $P < 0.001$). When the ESSDAI scores at the last visit were evaluated, 74.7% of patients had achieved low disease activity. We analyzed factors that could influence disease activity using logistic regression analysis based on ESSDAI scores. Anti-SSB/La positivity was found to be a statistically significant and increasing risk factor for disease presence in the constitutional domain compared to anti-SSB/La negativity. Specifically, the presence of anti-SSB/La was associated with a 4.26-fold increased risk of disease in the constitutional domain compared to when it was absent (Table 4). The other relevant increasing risk factors identified were as follows: elevated ESR and amylase levels (constitutional domain); positivity for anti-SSA/Ro and elevated amylase levels (lymphadenopathy domain); positivity for anti-SSA/Ro, anti-SSB/La, and elevated CRP, ESR, and amylase levels (glandular domain); positivity for elevated ESR (biological domain); and positivity for anti-SSB/La (hematological domain; Table 4).

Treatment and outcome. Hydroxychloroquine (HCQ) was the most commonly prescribed medication, used by 87.3% of patients. Corticosteroids were the second most prevalent treatment: pulse steroids were used by 5 patients (6.3%) and oral steroids by 30 patients (38%). Among other disease-modifying antirheumatic drugs (DMARDs), methotrexate (MTX) was used in 14 patients (17.7%), azathioprine (AZA) in 8 (10.1%), mycophenolate mofetil (MMF) in 6 (7.6%), cyclophosphamide (CYC) in 4 (5.1%), and rituximab (RTX) in 2 (2.5%). Additionally, 2 patients received intravenous IgG therapy. The median duration of treatment was 20.5 months (range 1-120), with a median follow-up duration of 24 months (range 2-128 months). Two patients were lost to follow-up. One patient diagnosed with autoimmune encephalitis died due to aspiration pneumonia as a result of recurrent epileptic seizures and subsequent ventilator-associated pneumonia. She was not receiving immunosuppressive treatment during this period. Notably, no malignancies were observed in any of the patients during the study's follow-up period. A positive response to treatment was observed in 96.2% of patients. The positive response to treatment was evaluated based on the opinion of the pediatric rheumatologist who monitored and managed the patients' treatment. Three patients who were evaluated as unresponsive to treatment based on expert opinion also demonstrated high disease activity in their ESSDAI scores at the last visit. Two of these patients had neurological involvement, whereas 1 patient was nonadherent to treatment. Response to treatment is defined in all centers in Türkiye, according to the criteria recommended by the Turkish Pediatric Rheumatology Association, and all participating centers have agreed on this issue. Accordingly, the criteria for a complete response are as follows: resolution of symptoms, normalization of laboratory markers, and absence of new organ damage, ensuring no progression of damage to organs affected by the disease.

Comparisons according to age groups. At the time of diagnosis, 34 patients (42%) were preadolescents, whereas 47 (58%) were adolescents (Table 5). A substantial majority of the male patients (83%) were in the preadolescent group. The interval between symptom onset and diagnosis was notably longer for preadolescents. Clinically, parotitis and peripheral lymphadenopathy were more commonly observed in preadolescents, whereas arthritis, arthralgia, myalgia, rash, and Raynaud phenomenon were more prevalent in adolescents. No significant differences were noted in the prevalence of dry eyes and dry mouth between the 2 groups. When comparing the ESSDAI domains by age, the glandular domain scored significantly higher in preadolescents, whereas the articular and renal domain was higher in adolescents. At the last visit, the median ESSDAI score was 0 for preadolescents and 1 for adolescents.

In terms of laboratory findings, amylase and CRP levels were significantly higher in preadolescents, whereas other laboratory variables did not show significant differences between the groups (Table 5). Regarding the ACR/EULAR classification criteria, 73.5% of preadolescents and 55.3% of adolescents fully met the criteria. However, the difference between these groups was not statistically significant, indicating no superiority of 1 group over the other in meeting the criteria ($P = 0.09$). In 84% of preadolescents and 53.8% of adolescents, MSG biopsy results were identified as grade 3 or 4 changes according to the Chisholm and Mason classification. The frequency of positive biopsy results was significantly higher in preadolescents. No

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Table 2. The characteristics of pediatric patients meeting the ACR/EULAR classification criteria and patients categorized as at risk for childhood SjD.

	At-Risk Group[a], n = 30	Patients Meeting the ACR/EULAR Classification Criteria, n = 51	*P*
Demographic findings			
Female sex	27 (90)	42 (82.4)	ND
Male sex	3 (10)	9 (17.6)	ND
Age at symptom onset, yrs, median (min-max)	13.1 (3-17)	10.3 (2.4-17.1)	**0.02**
Age at diagnosis, yrs, median (min-max)	14.3 (5.8-17.5)	12.1 (5.9-18)	ND
Duration between symptom onset and diagnosis, mos, median (min-max)	9 (1-50)	13 (1-114)	ND
Duration of patient follow-up, mos, median (min-max)	23 (2-128)	32 (3-105)	ND
Clinical signs			
Parotitis	9 (30)	27 (52.9)	**0.045**
Arthritis	9 (30)	16 (31.4)	ND
Arthralgia	17 (56.7)	30 (58.8)	ND
Myalgia	4 (13.3)	15 (29.4)	ND
Peripheral lymphadenopathy	8 (26.7)	21 (41.2)	ND
Rash	10 (33.3)	13 (25.5)	ND
Raynaud phenomenon	7 (23.3)	9 (17.6)	ND
Dry eyes	13 (43.3)	38 (74.5)	**0.01**
Dry mouth	27 (90)	35 (68.6)	**0.03**
Fever	4 (13.3)	12 (23.5)	ND
Fatigue	15 (50)	22 (43.1)	ND
Weight loss	7 (23.3)	11 (21.6)	ND
Renal tubular acidosis	1 (3.3)	0 (0)	ND
Tubulointerstitial nephritis	2 (6.7)	1 (2)	ND
CNS involvement	5 (16.7)	2 (3.9)	ND
PNS involvement	4 (13.3)	0 (0)	**0.02**
Pulmonary involvement	1 (3.3)	2 (3.9)	ND
Psychiatric symptoms	1 (3.3)	0 (0)	ND
Laboratory test			
Elevated amylase	8 (32)	22 (43.1)	ND
Positive anti-SSB/La	6 (20)	20 (39.2)	ND
Positive ANA	24 (80)	45 (88.2)	ND
Elevated CRP	7 (23.3)	21 (41.2)	ND
Elevated ESR	11 (36.7)	34 (66.7)	**0.01**
Diagnostic test			
Positive SGUS, n/N (%)	10/12 (92.6)	31/37 (83.8)	ND
Positive MSG biopsy, grade 3 or 4, n/N (%)	2/15 (13.3)	33/36 (91.7)	**< 0.001**
Positive Schirmer test	7 (25)	39 (76.5)	**< 0.001**
Positive anti-SSA/Ro	17 (56.7)	38 (74.5)	ND
ESSDAI score, median (min-max)			
At the time of diagnosis	9 (0-34)	8 (0-36)	ND
At last visit	0 (0-21)	0 (0-19)	ND
ESSDAI domains at the time of diagnosis			
Glandular	9 (30)	26 (51)	ND
Articular	12 (40)	23 (45.1)	ND
Renal	3 (10)	3 (5.9)	ND
Constitutional	8 (26.7)	23 (45.1)	ND
Lymphadenopathy	9 (30)	22 (43.1)	ND
Cutaneous	7 (23.3)	7 (13.7)	ND
Pulmonary	1 (3.3)	2 (3.9)	ND
Muscular	0 (0)	2 (3.9)	ND
PNS	2 (6.7)	0 (0)	ND
CNS	6 (20)	2 (3.9)	**0.047**
Hematological	1 (3.3)	6 (11.8)	ND
Biological	9 (30)	12 (23.5)	ND
Outcome			
Remission	26 (92.9)	50 (98)	ND
Not in remission	2 (7.1)	1 (2)	ND

Values are n (%) unless otherwise specified. [a]The at-risk group refers to patients who did not fully meet the adult ACR/EULAR classification criteria but exhibited clinical, laboratory, and/or histopathological findings suggestive of childhood SjD, classified based on comprehensive pediatric clinical judgment. ACR: American College of Rheumatology; ANA: antinuclear antibody; CNS: central nervous system; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; ESSDAI: EULAR Sjögren Syndrome Disease Activity Index; EULAR: European Alliance of Associations for Rheumatology; MSG: minor salivary gland; ND: no statistically significant difference; PNS: peripheral nervous system; SGUS: salivary gland ultrasound.

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Table 3. The characteristics of pediatric patients categorized as at risk for childhood SjD[a] based on expert clinical evaluation.

Age at the Time of Diagnosis, Sex	Clinical Findings	Laboratory and Diagnostic Findings	Positive Classification Criteria, Total Score (ACR/EULAR 2016)
5.8 yrs, male	Recurrent parotitis, dry mouth, peripheral LAP	MSG biopsy grade 2, positive SGUS, positive ANA, positive anti-SSA/Ro	Positive anti-SSA/Ro, 3
7.2 yrs, female	Recurrent parotitis	Positive anti-SSA/Ro, positive ANA, positive anti-dsDNA, high amylase	Positive anti-SSA/Ro, 3
7.4 yrs, female	Seizure, autoimmune encephalitis, dry eyes, dry mouth, fatigue, fever	Positive anti-SSA/Ro, high CRP, high ESR, anemia	Positive anti-SSA/Ro, 3
9 yrs, female	Recurrent parotitis, dry eyes, dry mouth, fever, fatigue	Positive ANA, positive anti-SSA/Ro, positive anti-SSB/La, positive SGUS	Positive anti-SSA/Ro, 3
9.2 yrs, female	Recurrent parotitis, fever, arthralgia, peripheral LAP	MSG biopsy grade 4, positive SGUS	MSG biopsy grade 4, 3
9.2 yrs, female	Recurrent parotitis, dry mouth	MSG biopsy grade 2, positive SGUS, high ESR, positive RF, positive ANA, positive anti-SSA/Ro, positive anti-SSB/La	Positive anti-SSA/Ro, 3
9.4 yrs, female	Dry eyes, dry mouth, arthritis, arthralgia, rash	MSG biopsy grade 2, positive Schirmer test, positive SGUS, positive ANA	Positive Schirmer test, 1
9.5 yrs, female	Parotitis, dry eyes, fatigue, arthralgia, myalgia, LAP	Positive ANA, positive anti-SSA/Ro, high CRP, high ESR, high amylase, positive SGUS	Positive anti-SSA/Ro, 3
11 yrs, female	Recurrent parotitis, dry eyes, dry mouth, peripheral LAP, RP	MSG biopsy grade 2, positive anti-SSB/La	No positive diagnostic criteria
11.8 yrs, female	Dry eyes, fatigue, weight loss, arthritis, arthralgia, rash, RP	Positive anti-SSA/Ro, positive ANA, positive RF, positive anti-dsDNA, anemia, leukopenia, high CRP, high ESR	Positive anti-SSA/Ro, 3
12.3 yrs, female	Arthritis, arthralgia, TIN, anemia	Positive anti-SSA/Ro, positive anti-SSB/La, positive ANA, high CRP, high ESR, proteinuria, hematuria	Positive anti-SSA/Ro, 3
12.5 yrs, male	Dry eyes, dry mouth	MSG biopsy grade 2, positive Schirmer test	Positive Schirmer test, 1
13.3 yrs, female	Dry eyes, dry mouth, fever, fatigue, arthritis, arthralgia, myalgia, polyneuropathy	Positive Schirmer test, high ESR, low C3	Positive Schirmer test, 1
13.4 yrs, female	Recurrent parotitis, dry eyes, dry mouth	Positive SGUS, high CRP, high amylase	No positive diagnostic criteria
14 yrs, female	Dry mouth, fatigue, arthralgia, rash, RP	MSG biopsy grade 2, positive anti-SSA/Ro, positive anti-SSB/La, positive ANA, positive RF	Positive anti-SSA/Ro, 3
14.5 yrs, female	Dry mouth, fatigue, weight loss, ataxia, transverse myelitis, axonal polyneuropathy	Positive anti-SSA/Ro, positive ANA, high ESR, high CRP, low C3	Positive anti-SSA/Ro, 3
14.8 yrs, female	Dry mouth, fatigue, weight loss, arthritis, arthralgia, hair loss, oral ulcer	MSG biopsy grade 2, positive anti-SSA/Ro, positive ANA, positive RF, low C3, high amylase, proteinuria	Positive anti-SSA/Ro, 3
15 yrs, female	Dry eyes, dry mouth, fatigue, arthritis, arthralgia, rash	MSG biopsy grade 1, positive anti-SSA/Ro, positive ANA	Positive anti-SSA/Ro, 3
15.5 yrs, female	Dry mouth, rash, RP	MSG biopsy grade 2, positive anti-SSA/Ro, positive ANA	Positive anti-SSA/Ro, 3
15.9 yrs, female	Dry mouth, parotitis, RP, dental caries	Positive anti-SSA/Ro, positive ANA, positive RF, positive anti-dsDNA, positive SGUS, high ESR, high amylase, low C3	Positive anti-SSA/Ro, 3
16.2 yrs, female	Dry eyes, dry mouth, peripheral LAP, facial paralysis, demyelinating plaque	MSG biopsy grade 2, positive Schirmer test, positive SGUS, positive ANA	Positive Schirmer test, 1
16.2 yrs, female	Dry eyes, fatigue, arthralgia, myalgia	MSG biopsy grade 2, positive Schirmer test, positive ANA	Positive Schirmer test, 1
16.3 yrs, female	Dry mouth, fatigue, weight loss, arthralgia, rash, RTA, TIN, proteinuria	Positive ANA, high ESR, high CRP, anemia, high IgG	No positive diagnostic criteria
16.3 yrs, male	Dry mouth, fatigue, weight loss, arthralgia, peripheral LAP, rash	Positive anti-SSB/La, positive ANA, positive RF	No positive diagnostic criteria
16.6 yrs, female	Dry eyes, dry mouth, RP, fatigue, psychosis	Positive Schirmer test, positive ANA, low C4	Positive Schirmer test, 1
16.7 yrs, female	Dry mouth, fatigue, arthritis, arthralgia, RP, LAP	Positive anti-SSA/Ro, positive ANA, low C4	Positive anti-SSA/Ro, 3
16.8 yrs, female	Dry mouth, arthritis, arthralgia, rash	MSG biopsy grade 3, positive ANA, positive RF, low C4, low C3	MSG biopsy grade 3, 3

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Table 3. Continued.

Age at the Time of Diagnosis, Sex	Clinical Findings	Laboratory and Diagnostic Findings	Positive Classification Criteria, Total Score (ACR/EULAR 2016)
16.9 yrs, female	Dry mouth, fatigue, weight loss, arthralgia, myalgia, diplopia, sensory neuropathy	MSG biopsy grade 1, positive anti-SSA/Ro, positive ANA, high ESR	Positive anti-SSA/Ro, 3
16.9 yrs, female	Dry eyes, dry mouth, arthritis, arthralgia	MSG biopsy grade 1, positive Schirmer test, positive SGUS, positive ANA, anemia	Positive Schirmer test, 1
17.5 yrs, female	Dry mouth, arthralgia, rash, RP	Positive anti-SSA/Ro, positive ANA, positive RF	Positive anti-SSA/Ro, 3

The ocular staining score and salivary flow rate mentioned in the diagnostic criteria were not assessed in pediatric patients. [a] The at-risk group refers to patients who did not fully meet the adult ACR/EULAR classification criteria but exhibited clinical, laboratory, and/or histopathological findings suggestive of childhood SjD, classified based on comprehensive pediatric clinical judgment. ACR: American College of Rheumatology; ANA: antinuclear antibody; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; EULAR: European Alliance of Associations for Rheumatology; LAP: lymphadenopathy; MSG: minor salivary gland; RF: rheumatoid factor; RP: Raynaud phenomenon; RTA: renal tubular acidosis; SGUS: salivary gland ultrasound; SjD: Sjögren disease; TIN: tubulointerstitial nephritis.

Table 4. Logistic regression analysis of laboratory variables associated with increased risk of activity in ESSDAI domains.

Risk Factors	Constitutional		Lymphadenopathy		Glandular		Articular		Biological		Hematological	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Positive anti-SSA/Ro	2.77 (0.96-7.98)	0.06	**3.76 (1.24-11.42)**	**0.02**	**2.81 (1.02-7.76)**	**0.046**	1.33 (0.51-3.45)	0.55	1.72 (0.55-5.36)	0.35	3.06 (0.34-26.84)	0.31
Positive anti-SSB/La	**4.26 (1.58-11.46)**	**0.004**	1.62 (0.62-4.20)	0.32	**3.03 (1.15-7.96)**	**0.02**	1.19 (0.46-3.0)	0.71	0.80 (0.26-2.37)	0.69	**6.31 (1.13-35.09)**	**0.04**
Positive anti-dsDNA	0.76 (0.06-8.83)	0.83	NA	NA	0.65 (0.05-7.49)	0.73	0.61 (0.05-7.10)	0.67	1.40 (0.12-16.29)	0.79	NA	NA
Elevated CRP	1.34 (0.52-3.42)	0.54	2.11 (0.82-5.41)	0.12	**4.88 (1.82-13.09)**	**0.002**	1.52 (0.60-3.83)	0.37	1.23 (0.43-3.45)	0.69	1.47 (0.30-7.08)	0.63
Elevated ESR	**2.87 (1.10-7.45)**	**0.03**	1.81 (0.72-4.56)	0.20	**2.59 (1.03-6.51)**	**0.04**	1.69 (0.69-4.14)	0.25	**4.85 (1.46-16.15)**	**0.01**	2.12 (0.38-11.60)	0.39
Elevated amylase	**3.70 (1.39-9.84)**	**0.01**	**3.32 (1.26-8.72)**	**0.02**	**12.72 (4.14-39.09)**	**< 0.001**	0.72 (0.28-1.84)	0.50	1.15 (0.40-3.32)	0.79	0.23 (0.02-2.01)	0.18

The logistic regression model included laboratory variables as covariates: anti-SSA/Ro, anti-SSB/La, anti-dsDNA positivity, CRP elevation, ESR elevation, and elevated amylase levels. Values in bold are statistically significant, defined by a *P* value < 0.05. CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; ESSDAI: European Alliance of Associations for Rheumatology Sjögren Syndrome Disease Activity Index; NA: not applicable; OR: odds ratio.

significant differences were observed in positive Schirmer test results or antibody positivity (Table 5).

DISCUSSION

In this nationwide, multicenter study, we present data from 81 cases of childhood SjD, marking the first study to our knowledge of its scope in Türkiye. Historically, since the first case was reported in the 1960s, the majority of publications have featured small case series, with only 7 studies reporting > 30 cases.[3,8,9,13-16]

Childhood SjD manifests more frequently in girls than in boys, with a reported ratio of 3:1 to 12:1.[16,17] The average age at diagnosis typically ranges between 10 and 14 years, with the earliest reported onset as young as 3 months.[3,8,9,13,17-19] In our cohort, the male-to-female ratio was approximately 1:6, and the median and youngest ages at diagnosis were 12.5 years and 5.8 years, respectively. The presence of parotitis is reported as 1 of the most common nonsicca manifestations in childhood SjD.[3,8,9,13,14,17,18] Despite not all patients meeting the ACR/EULAR classification criteria—which is common in pediatric studies, where rates of fulfillment have a wide range from 23% to 97%—our findings are similar to those in the literature.[8,9,13] Methodologies in these studies show considerable heterogeneity. Some rely solely on expert opinion for patient inclusion, others on classification criteria, and some, like ours, incorporate both. This variance underscores the need for new classification criteria specifically tailored to childhood SjD.

SGUS has emerged as a valuable diagnostic tool, offering a noninvasive, easily applicable, and effective method.[20,21] In our study, approximately 84% of the SGUS performed revealed inflammatory signs in the parotid glands, indicative of structural changes typically manifested as glandular parenchymal heterogeneity. Ultrasound findings are not only associated with glandular involvement but also with systemic disease and immunological variables, as evidenced by their correlation with hyposalivation, gland swelling, and the presence of autoantibodies.[15,20,22] Further research confirms that severe glandular changes on SGUS,

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Table 5. The characteristics of pediatric patients with primary SjD according to developmental age groups (preadolescents and adolescents).

	Preadolescent, n = 34	Adolescent, n = 47	*P*
Demographic findings			
Female sex	24 (70.6)	45 (95.7)	**0.002**
Male sex	10 (29.4)	2 (4.3)	
Duration between symptom onset and diagnosis, mos, median (min-max)	23 (1-114)	8 (1-40)	**< 0.001**
Duration of follow-up, mos, median (min-max)	27.5 (3-105)	24 (2-128)	ND
Clinical signs			
Parotitis	27 (79.4)	9 (19.1)	**< 0.001**
Arthritis	5 (14.7)	20 (42.6)	**0.01**
Arthralgia	13 (38.2)	34 (72.3)	**0.002**
Myalgia	4 (11.8)	15 (31.9)	**0.04**
Peripheral lymphadenopathy	17 (50)	12 (25.5)	**0.02**
Rash	4 (11.8)	19 (40.4)	**0.01**
Raynaud phenomenon	3 (8.8)	13 (27.7)	**0.04**
Dry eyes	22 (64.7)	29 (61.7)	ND
Dry mouth	24 (70.6)	38 (80.9)	ND
Dry eyes + dry mouth	16 (47.1)	23 (48.9)	ND
Fever	9 (26.5)	7 (14.9)	ND
Fatigue	12 (35.3)	25 (53.2)	ND
Weight loss	4 (11.8)	14 (29.8)	ND
Renal tubular acidosis	0 (0)	1 (2.1)	ND
Tubulointerstitial nephritis	0 (0)	3 (6.4)	ND
CNS involvement	2 (5.9)	5 (10.6)	ND
PNS involvement	0 (0)	4 (8.5)	ND
Autonomic symptoms	0 (0)	1 (2.1)	ND
Pulmonary involvement	1 (2.9)	2 (4.3)	ND
Psychiatric symptoms	0 (0)	1 (2.1)	ND
Laboratory test			
Elevated amylase	20 (58.8)	10 (23.8)	**0.002**
Positive anti-SSB/La	11 (32.4)	15 (31.9)	ND
Positive anti-SSA/Ro and anti-SSB/La	10 (29.4)	17 (36.2)	ND
Positive ANA	28 (82.4)	41 (87.2)	ND
Elevated CRP	16 (47.1)	12 (25.5)	**0.04**
Elevated ESR	21 (61.8)	24 (51.1)	ND
Diagnostic test			
Positive ACR/EULAR classification criteria	25 (73.5)	26 (55.3)	ND
Positive salivary gland ultrasound, n/N (%)	25/27 (92.6)	16/22 (72.7)	ND
Positive MSG biopsy, grade 3 or 4, n/N (%)	21/25 (84)	14/26 (53.8)	**0.02**
Positive Schirmer test	17 (50)	29 (64.4)	ND
Positive anti-SSA/Ro	25 (73.5)	30 (63.8)	ND
ESSDAI score, median (min-max)			
At the time of diagnosis	8 (0-28)	9 (0-36)	ND
At last visit	0 (0-21)	1 (0-21)	ND
ESSDAI domains			
Glandular	23 (67.6)	12 (25.5)	**< 0.001**
Articular	10 (29.4)	25 (53.2)	**0.03**
Renal	0 (0)	6 (12.8)	**0.04**
Constitutional	14 (41.2)	17 (36.2)	ND
Lymphadenopathy	16 (47.1)	15 (31.9)	ND
Cutaneous	3 (8.8)	11 (23.4)	ND
Pulmonary	2 (5.9)	1 (2.1)	ND
Muscular	0 (0)	2 (4.3)	ND
PNS	0 (0)	2 (4.3)	ND
CNS	2 (5.9)	6 (12.8)	ND
Hematological	1 (2.9)	6 (12.8)	ND
Biological	9 (26.5)	12 (25.5)	ND
Outcome			
Remission	33 (97.1)	43 (95.6)	ND
Not in remission	1 (2.9)	2 (4.4)	ND

Values are expressed as n (%) unless otherwise indicated. Preadolescent refers to patients ≤ 10 years, whereas adolescent refers to patients > 10 years. ACR: American College of Rheumatology; ANA: antinuclear antibody; CNS: central nervous system; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; ESSDAI: EULAR Sjögren Syndrome Disease Activity Index; EULAR: European Alliance of Associations for Rheumatology; ND: no statistically significant difference; PNS: peripheral nervous system; SjD: Sjögren disease.

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particularly in conjunction with positive autoantibodies, are indicative of more extensive systemic involvement.

ANA and anti-SSA/Ro positivity are critical serological markers in both childhood and adult SjD. Reports indicate these abnormalities are more prevalent in children than in adults.[18] In the Sjögren Big Data Project Consortium, which examined 10,500 adult patients, ANA was the most frequently positive immunological marker at 79%, followed by anti-SSA/Ro at 73%, RF at 48.5%, and anti-SSB/La at 45%.[23] Similar to adult patients, the hierarchy of positive immunological markers in children—ANA, anti-SSA/Ro, RF, and anti-SSB/La—was consistent in our study and comparable to other pediatric studies.[3,8,9,15,16] As a marker of inflammation, ESR plays a more prominent role in childhood SjD, often supported by pediatric research findings. Marino et al[17] reported that elevated ESR is a more common inflammatory marker in children than elevated CRP levels, although patients with parotitis generally exhibited higher CRP levels. In our study, high ESR was more frequent than high CRP. However, elevated CRP levels were statistically associated with an increased glandular domain score, indicating significant glandular involvement. This suggested that although ESR was typically a superior marker of inflammation in SjD, CRP's role became more critical in cases with glandular involvement, predominantly seen in the preadolescent group.

ESSDAI is a validated tool designed to assess disease activity in adult patients with primary SjD. However, its application in childhood SjD presents several limitations. Childhood SjD is rare and often exhibits distinct clinical manifestations compared to adults, such as more frequent parotid gland enlargement and less severe systemic involvement, which may not be fully captured by ESSDAI. Additionally, the lack of pediatric-specific validation studies for ESSDAI limits its reliability and accuracy in this population. Constitutional, articular, and lymphadenopathy domains were reported as the most dominant in ESSDAI at the time of diagnosis, particularly the glandular domain.[3] In our study, the glandular domain and the articular domain were dominant. Immunological markers have been previously reported to significantly influence systemic involvement at diagnosis, with antibody-positive patients showing higher mean ESSDAI scores.[23,24] In the study by Brito-Zerón et al,[23] anti-SSA/Ro positivity was associated with increased activity in constitutional, cutaneous, hematological, and biological ESSDAI domains. In contrast, anti-SSB/La positivity was linked to increased activity in constitutional, lymphadenopathy, glandular, cutaneous, renal, muscular, hematological, and biological domains. ANA positivity correlated with increased activity in lymphadenopathy, cutaneous, hematological, and biological domains, whereas RF positivity was associated with higher activity in glandular, articular, cutaneous, hematological, and biological domains.[23] Further, it was observed in another study that parotitis is more common in patients positive for anti-SSA/Ro and anti-SSB/La, and anti-SSA/Ro positivity was associated with anemia. Although not statistically significant, lung involvement tended to occur more frequently in individuals who were positive for anti-SSA/Ro.[8] Given the lack of pediatric-specific disease activity indices, future studies should aim to validate ESSDAI or develop pediatric-appropriate tools.

Regarding the time lag to diagnosis, in our study, the preadolescent group had a significantly longer duration between symptom onset and diagnosis. This may be attributed to less apparent or specific disease manifestations in younger children compared to adolescents, who often exhibit more recognizable symptoms such as dry eyes and mouth. Additionally, musculoskeletal involvement in adolescents likely leads to earlier diagnosis, as these symptoms are more straightforward to identify. Clinical findings varied by age, with parotitis and peripheral lymphadenopathy more common in preadolescents, whereas arthritis, arthralgia, myalgia, rash, and Raynaud phenomenon were more frequent in adolescents. These findings underscore the clinical variations of SjD in childhood, suggesting that the current classification criteria may not adequately address the heterogeneous nature of the disease in younger populations. The surprising lack of difference in sicca symptoms between the 2 age groups may be attributed to the parents' failure to associate these symptoms with any disease or their inability to recognize them, which could mask the expected age-related variation.

An intriguing aspect of our study was the significant predominance of the male sex in the preadolescent age group, exceeding 80%. This dominance may be linked to the higher incidence of parotitis among male children during these years. Notably, the presence of parotitis was statistically significant and frequently observed in the preadolescent group, affecting 75% of male individuals.

Despite the absence of specific treatment protocols for children, the most common medications in pediatric cases include corticosteroids, HCQ, nonsteroidal antiinflammatory drugs, and conventional and biological DMARDs in selected cases. HCQ is frequently used for symptoms such as parotitis, articular involvement, and fatigue. MTX is often used for articular involvement and AZA is used in cases with liver involvement or as maintenance therapy for renal conditions, whereas CYC and RTX are reserved for severe cases with neurological, renal, and pulmonary manifestations in the literature.[25-27]

Our study had several limitations, primarily owing to its retrospective design. Due to retrospective data collection, intermediate disease activity assessments were limited. The absence of pediatric-specific diagnostic criteria necessitated categorizing some patients as at risk based on expert clinical judgment. Further, the evaluation of treatment response was limited by the lack of an objective variable, leading to assessments being made according to the treating physician's judgment. Another limitation is the risk associated with multiple comparisons, which could lead to an increased chance of type I errors. Despite these limitations, this study constitutes the largest cohort of childhood SjD from Türkiye.

Childhood SjD presents a broad spectrum of clinical manifestations, with parotitis being notably common. Early detection of glandular dysfunction is essential, making SGUS an increasingly crucial diagnostic tool, particularly in pediatric patients. Given the frequent early presentation of male children with parotitis, incorporating this manifestation into the classification criteria for childhood SjD should be considered.

Autoantibodies significantly influence the disease phenotype. Pediatric patients with positive specific autoantibodies, even in the absence of typical SjD clinical features, should be monitored closely for the emergence of clinical symptoms over

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time. Further, pediatric patients categorized as at risk for childhood SjD require careful and continuous monitoring due to their potential progression to definitive SjD.

In conclusion, the current classification criteria for childhood SjD appear to be inadequate, highlighting the need for pediatric-specific criteria that more accurately reflect the distinct clinical patterns observed in children. Raising awareness of the broad spectrum of signs and symptoms in childhood SjD is essential to facilitate earlier diagnosis and intervention. A better understanding of these unique clinical characteristics will ultimately contribute to improved patient outcomes. Future multicenter and collaborative studies should focus on validating and establishing pediatric-specific classification criteria that incorporate the age-related phenotypic diversity of childhood SjD.

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CONTRIBUTIONS

All authors contributed to data acquisition and interpretation and provided critical revisions of the manuscript. All authors approved the final version of the manuscript.

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COMPETING INTERESTS

The authors declare no conflicts of interest relevant to this article.

ETHICS AND PATIENT CONSENT

This retrospective study was conducted in accordance with Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. It was approved by the Pamukkale University Ethics Committee (approval no. 2023/390341). Informed consent forms were obtained from all parents/patients.

DATA AVAILABILITY

The data supporting the findings of this study are available from the corresponding author, upon reasonable request.

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