Juvenile Sjögren's Syndrome

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Introduction

Primary Sjögren's syndrome (pSS) is a multisystemic autoimmune disease characterized by progressive lymphocytic and plasma cell infiltrations in exocrine glands, especially salivary and lacrimal glands leading to glandular atrophy and loss of function. The disease is also named autoimmune exocrinopathy and autoimmune epithelitis since it primarily affects exocrine glands, and salivary gland epithelial cells play a central role in its pathogenesis. The disease predominantly affects postmenopausal women, while it may rarely have a disease onset in infants, children, and adolescents [3]. The clinical presentation in children can be widely broad and may involve other organs besides exocrine glands, including musculoskeletal, dermatologic, hematologic, renal, pulmonary, cardiovascular, gastrointestinal, and nervous systems. Children with pSS can develop other well-defined autoimmune diseases coincidentally, which contribute to a more mysterious presentation and diagnostic challenge.

Terminology

Currently, there are no unified terminology and no specific age limit of pSS in children. Juvenile Sjögren's syndrome, pediatric Sjögren's syndrome, childhood-onset of Sjögren's syndrome, and pediatric primary Sjögren's syndrome are terminologies used in the literature. Children with three different age groups, including 16 years or younger, 18 years or younger, and 19 years or younger, have been described [3–5]. The term "Juvenile Sjögren's syndrome" (JSS) is used for the syndrome in children with or without other associated autoimmune diseases throughout this chapter.

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Historical Perspective

Henrik Sjögren reported a 49-year-old woman and four other cases with dry eyes, dry mouth, and arthritis, who were initially diagnosed with keratoconjunctivitis sicca in 1930 [6]. The first case of JSS was documented in a 17-year-old girl presenting with pain and scratching sensation of her eyes, keratitis sicca, positive Schirmer's test, and recurrent painful swelling of eyelids and left face, without evidence of lacrimal and salivary gland infection in 1938 [7]. The second case of JSS was described much later in 1965 in a 10-year-old girl who initially developed recurrent swelling and tenderness of bilateral parotid glands and subsequently developed arthritis of small joints with increasing gamma globulin, α2 macroglobulin, haptoglobin, and ceruloplasmin [8].

Epidemiology

JSS is an uncommon disease with difficulty to quantify [2, 9, 10]. The rarity of the disease may be related to the difficulty of the diagnosis in this age group. Children with JSS have a higher frequency of affecting male and non-white patients than ASS [11]. The frequency of childhood-onset primary SS is approximately 1% of patients with primary SS, and the mean age at the first signs or symptoms and at the time of diagnosis is somewhere between 13.2 and 14.2 years based upon a recent international cohort study [4]. Most patients are female with a male-to-female ratio of 1:8.5 [4]. The prevalence rate of JSS in Japan is 1.25 per 100,000 children under 16 years of age, and a mean age of onset is 11 years with male-to-female ratio of 1:4.7 [12]. The crude annual incidence rate of JSS per 100,000 children was 0.04 compared to 0.83 of juvenile rheumatoid arthritis, 0.47 of SLE, 0.16 of dermatomyositis/polymyositis, and 0.05 of mixed connective tissue disease [13]. The prevalence of SS in siblings is estimated to be 0.09% compared to 0.01% in the general population [14].

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Pathogenesis and Pathology

Hitherto, the etiology and pathogenesis in JSS remain unknown. It is postulated that environmental triggers, such as a viral infection in a genetically susceptible individual, contribute to disease development [14–16]. Both identical and dizygotic twins with JSS and ASS are reported [17–20]; however, genetic studies have not been performed. Specific genetic variants increasing the risk are identified in the major histocompatibility complex (MHC) and outside the MHC involving interferon pathway, NF-kB signaling, B- and T-cell function, and methylation [21, 22]. The genetic risk of JSS may overlap with other autoimmune diseases. Instrumental models in studying early events in mice reveal innate immune activation preceding adaptive immune activation. Environmental factors including EBV, CMV, hepatitis C, and HTLV1 infections can activate innate immunity and contribute to disease initiation and chronicity [23, 24]. Innate immune cells, including salivary gland epithelial cells (SGECs), dendritic cells, macrophages, natural killer (NK) cells, and mast cells, are implicated in the disease development [23]. Abnormal SGECs are considered a driver of the pathogenesis and the passive disease target in SS. In addition, increasing B-cell activating factor and adiponectin production, upregulating CD80 and CD86 expression, and HLA-DR by SGECs are associated with disease activity [25–28].

The complex interactions among the SGECs, environmental stimuli, and adaptive immunity resulting in tissue inflammation emerge as the disease pathogenesis throughout various disease stages [29]. A characteristic of histopathological findings in SS with periductal mononuclear infiltrates surrounding the SGECs implies particular immunological interactions among SGECs and other cells. The mononuclear cell infiltrates consist predominantly of CD4 + T cells and B cells with a small percentage of macrophages, interdigitating and follicular dendritic cells, and rare NK cells. Adaptive immune responses, including a progressive focal infiltration of T and B lymphocytes in the exocrine glands and the presence of autoantibodies and hypergammaglobulinemia, are well characterized. Activated T cells, especially the Th1 subset, are dominant in the early stages and produce inflammatory cytokines, which help B-cell differentiation and class switching. B cells are involved in the chronic inflammation phase by producing autoantibodies [30]. The inflammatory cells are significantly different depending on the disease severity. Typically, mild pathologic lesions have CD4 + T-cell predominance, and severe lesions show increased B-cell populations and decreased CD4+ T-cell populations [31]. These histopathologic findings remain unchanged with the interval of 3 ½–6 ½ years in ASS [32]. The hallmark of mononuclear cell infiltrates surrounding the ducts and acini in JSS is identical to ASS (Fig. 7.1) [33, 34].

Extraglandular involvement in SS can be periepithelial infiltrative processes and extraepithelial extraglandular involvement. The periepithelial mononuclear infiltrates with enriched CD4+ T cells are identified in extraglandular organs, including tubular epithelia in kidneys, airway epithelia of the bronchia, and bronchioles in lungs and ductal epithelia in the liver. These result in tubulointerstitial nephritis, distal renal tubular acidosis, bronchiolitis, interstitial lung disease, primary biliary cirrhosis, and autoimmune hepatitis in both ASS and JSS [35–39]. The extraepithelial extraglandular involvement develops after periepithelial infiltrates and is related to B-cell hyperactivity, hypergammaglobulinemia, and immune complex deposition contributing to cutaneous vasculitis or purpura, glomerulonephritis, peripheral neuropathy, cryoglobulinemia, and hypocomplementemia. The extraepithelial extraglandular involvement is associated with a higher risk of transformation to lymphoma in pSS [40].

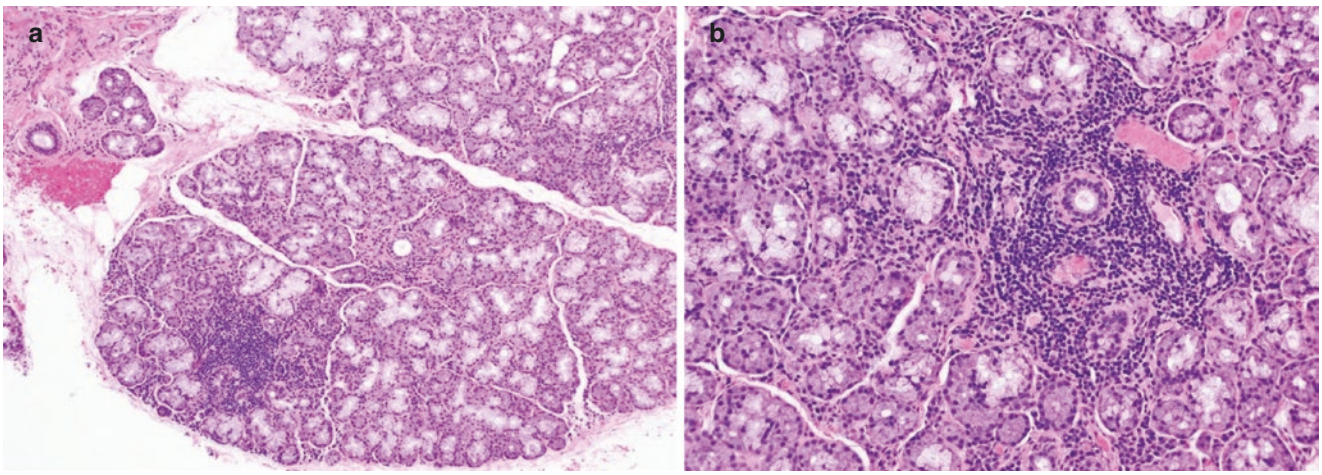

Fig. 7.1 Histopathological findings of minor salivary gland biopsy with periductal lymphocytic infiltrations from a child with JSS (H&E staining, **a**: magnification × 10; **b** magnification × 20)

Clinical Manifestations

Clinical presentations of JSS can be categorized into glandular and extraglandular manifestations. Major clinical features of JSS are recurrent or chronic parotitis, systemic symptoms, and extraglandular involvement with fewer sicca symptoms than in ASS [6]. Both xerostomia and xeropthalmia can be subclinical in children since the disease is relatively at an initial stage. Extraglandular symptoms can be the sole manifestation or precede and predominate over glandular symptoms [4].

Glandular Manifestations

Sialadenitis

Sialadenitis is defined as inflammation of the salivary glands. The diagnosis of sialadenitis is based upon clinical findings or imaging studies, or histopathologic findings [41]. Sialadenitis is detected in 35–53% of JSS cases [26, 38]. The most common clinical findings are recurrent or persistent unilateral or bilateral parotitis, including swelling, redness, pain of the parotid region, difficulties in mastication, and fever (Figs. 7.2a, b, and 7.3a), with or without submandibular involvement. Children with parotitis are typically younger and less likely to be female [3]. The parotitis is considered the earliest and predominant symptom of JSS, especially under 5 years of age [3, 12]. JSS with parotitis is likely diagnosed earlier than children without parotitis since the painful enlargement of parotid glands quickly brings to parent's attention, and a primary care provider quickly refers a child with parotitis to a pediatric rheumatologist or pediatric otolaryngologist [3].

Sicca Symptoms

Dry mouth (xerostomia) and dry eyes (xerophthalmia) are collectively described as sicca symptoms. The dryness representing glandular dysfunction requires a period of time for the symptoms to develop. Sicca symptoms in children are less common than in adults [3]. Adolescence has a higher prevalence of dry eye and dry mouth than preadolescence [4]. Sicca symptoms with dry eyes and dry mouth are reported in 24% of cases at the presentation [4]. The dryness increases over time following diagnosis. Dry mouth, the most common sicca symptom in JSS, is reported in 52% of cases. Dry eyes, the second most common sicca symptom, is reported in 48% of cases. Children with dry mouth and dry eyes are found in only 35% of cases [3].

The sicca symptoms are not significantly associated with parotitis [3]. It is not surprising that children deny sicca symptoms since they may not be fully aware of dryness symptoms or verbally express their symptoms. However, objective dryness can be identified based upon questioning dryness symptoms, sialometry, and ophthalmologic evaluation [3, 12].

Ranula

Ranula is a rare mucocele and a newly described clinical manifestation of JSS. It is caused by the extravasation of saliva due to damage or obstruction of sublingual glands or minor salivary glands or their ducts [42]. The etiology of ranula is still unknown. It is hypothesized that the lymphocytic infiltrates damage the ducts and induce extravasation of saliva and mucus accumulation [42]. Ranula may also be related to trauma, anatomical variations, and chronic disease of the sublingual glands [43]. Ranula can be an initial presenting symptom and help to diagnose JSS [38–40, 44]. Children with ranula should be evaluated for JSS with imaging studies, salivary gland ultrasound, or MRI.

Oral Manifestations

Early tooth decay and cavities, oral ulcers, peeling lips, angular cheilitis, erythematous mucosa, abnormal tongue with fissures, furrows, atrophic change or depapillated change, adherence of food to buccal surfaces, hypogeusia, dysphagia, recurrent oral candidiasis, and periodontal disease can be seen in JSS [45–9]. These oral symptoms have a negative impact on the quality of life of children. A diagnostic workup of JSS should be considered in any children with recurrent oral candidiasis and negative immunologic and genetic workup for primary immunodeficiency [51].

Ocular Manifestations

Children with JSS may experience specific ocular symptoms, including light sensitivity or photophobia, red eyes, bacterial conjunctivitis, eye fatigue, decreased visual acuity, a discharge in the eyes, a sensation of a film across the visual field, slower reading speeds, enlarged lacrimal gland related to chronic dacryoadenitis (Fig. 7.3b), superficial cornea erosion, filament keratitis, corneal ulceration, vascularization, opacification, and perforation [14, 47]. Other reports include uveitis and optic neuritis [14, 48].

Extraglandular Manifestations

Musculoskeletal Manifestations

Children with JSS commonly develop joint symptoms such as arthralgia, arthritis, or subclinical arthritis of large joint and small joints, including knees, hips, ankles, shoulders, wrists, elbows, hands, and feet [48]. Arthralgia is the most common extraglandular symptom and musculoskeletal complaint in JSS [3]. At the presentation, arthralgia and arthritis

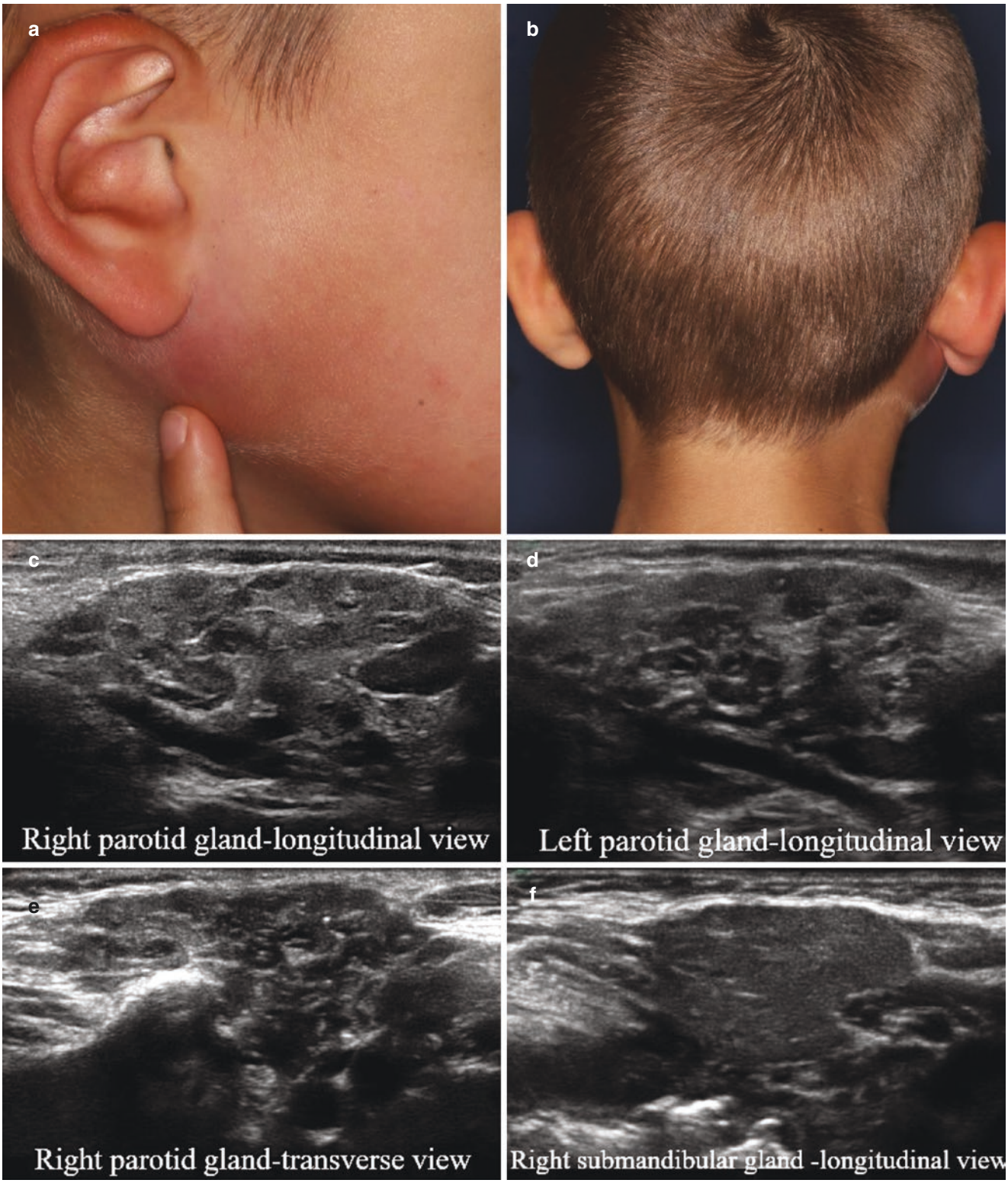

Fig. 7.2 Since 7 years of age, a 7-year-old boy has suffered from recurrent right parotitis (**a**, **b**) and xerostomia. His clinical presentation with negative anti-SSA/SSB mimics juvenile recurrent parotitis. The ultrasound images show a characteristic heterogeneity of the parenchyma with multiple anechoic/hypoechoic areas in both parotid glands with enlarged intraglandular lymph nodes (**c**–**e**). The submandibular gland showed mild heterogeneity and anechoic/hypoechoic areas (**f**). His labial salivary gland biopsy revealed a focus score of more than 4

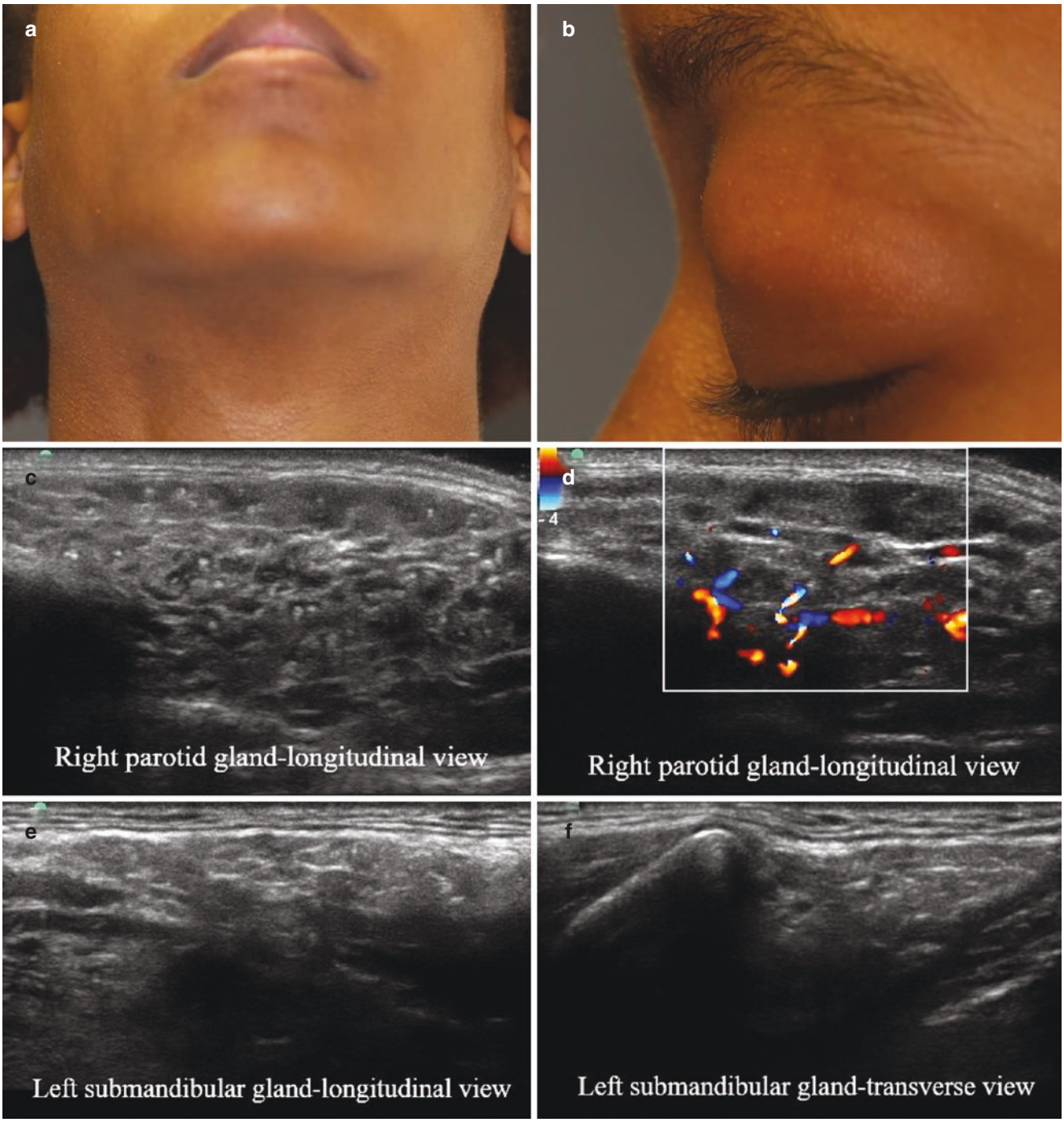

Fig. 7.3 A 14-year-old girl presented with chronic parotid swelling (**a**), bilateral lacrimal gland enlargement (**b**), fatigue, highly positive anti-SSA/SSB. She had abnormal ultrasound images of the parotid and submandibular glands ultrasound with multiple anechoic/hypoechoic appearances (**c**–**f**) and abnormal labial minor salivary gland biopsy with focus score > 12

are found in 10% and 2.6% of JSS cases [4]. The prevalence of arthralgia and arthritis in JSS is 54% and 24% [3]. The articular features may or may not be associated with a rheumatoid factor (RF) or anti-cyclic citrullinated peptide (CCP) antibody [48]. Myalgia and myositis are uncommon and reported in only 1–3% of cases [3, 4, 49]. Other musculoskeletal symptoms, including morning stiffness, tenosynovitis, enthesitis, tendinitis, low back pain, and osteoporosis, have been reported in JSS [48, 49]. Amplified musculoskeletal pain syndrome (AMPS) or juvenile fibromyalgia may be the earliest presenting symptoms of JSS. It is not uncommon for JSS with negative SS autoantibodies and generalized pain to be misdiagnosed as AMPS until glandular or extraglandular symptoms emerge.

Constitutional Manifestations

Constitutional symptoms including fever, fatigue, and weight loss are relatively common and found in 45% of cases [14]. The constitutional symptoms are reported in 5–22% of patients at the time of diagnosis [4]. Constitutional complaints may be the only presenting symptom. If the constitutional symptoms solely present at the disease onset with negative autoantibodies, the differential diagnoses are broad, and the diagnosis of JSS can be missed.

Lymphadenopathy

Abnormal lymph nodes in size, consistency, or number are found in JSS. Generalized or cervical lymphadenopathy may be an initial presenting symptom and sign of JSS and may mimic lymphoma [50]. The prevalence of lymphadenopathy is approximately 35%, and it is reported in 25% at the time of diagnosis of JSS [14]. Children with 9 years of age or younger are the most common age group with lymphadenopathy. The enlarged lymph node in JSS is typically less than 2 cm in diameter and is significantly associated with parotitis [3].

Hematologic Manifestations

Cytopenia in JSS is reported in the range of 15–28% of cases [14]. The findings are not significantly associated with parotitis or age onset [3, 4]. Both neutropenia (<1500) and lymphopenia (<1000) are the most common cytopenia, and autoimmune hemolytic anemia is the least common hematologic involvement [3].

Cutaneous Symptoms

Cutaneous manifestations reported in JSS are dry skin, erythematous rash, erythema multiforme, erythema nodosum, cutaneous vasculitis (Fig. 7.4a), Raynaud's phenomenon (Fig. 7.4b), chilblains (Fig. 7.4c), malar rash, and subacute cutaneous lupus (Fig. 7.5a, b). Approximately 12% of JSS have cutaneous symptoms at the time of diagnosis [4]. The prevalence of Raynaud's phenomenon in JSS is 15% [14]. Although the prevalence of overall cutaneous involvement is unknown, however, cutaneous manifestations are found in more than 25% of cases reported in a recent JSS study [51, 54].

Renal Manifestations

Renal manifestations at the time of diagnosis are 4.5% of cases [4]. The prevalence of renal involvement is 11% [14]. The primary kidney damage in JSS is tubulointerstitial nephritis, and the clinical features include proteinuria, hematuria, renal tubular acidosis, hypokalemia, glucosuria, or alkaline urine [55, 56]. Glomerular involvement was reported, including membranous glomerulonephritis, proliferative glomerulonephritis, and pauci-immune crescentic glomerulonephritis [56].

Neurologic manifestations

Neurologic involvement in JSS can be peripheral or central nervous systems [55]. The prevalence of neurologic manifestations is seen in 11% of JSS [14]. The symptoms vary, including fever, headache, lethargy, muscle weakness, ptosis, urinary incontinence, hypalgesia, difficulty with ambulation, gaze deviation, and mental disorder [56]. Specific neurologic diseases reported in JSS are aseptic meningitis, meningoencephalitis, brainstem encephalitis, autoimmune N-methyl-D-aspartate (NMDA) receptor encephalitis, autoimmune limbic encephalitis, optic neuritis, transverse myelitis/neuromyelitis optica spectrum, cranial neuropathy, peripheral neuropathy, polyradiculoneuritis, hemiplegia, hemiparesis, quadriparesis, seizure, autonomic neuropathy, ataxia, cerebral vasculitis, vertigo, migraines, hallucinations, depression, and psychosis [59].

Pulmonary Manifestations

Pulmonary involvement in JSS is uncommon and reported in 5–8% of patients [3, 14]. The respiratory manifestations in JSS are recurrent upper respiratory tract infections, chest pain, persistent cough, abnormal chest CT scan with interstitial lung disease, lymphocytic interstitial pneumonia, and pulmonary nodules [17]. Severe pulmonary hypertension [53], pulmonary hemorrhage [56], and idiopathic pulmonary hemosiderosis in JSS were reported [54, 58–60].

Gastrointestinal and liver manifestations

Gastrointestinal and liver involvement reported in JSS are recurrent abdominal pain, gastroparesis, atrophic gastritis, chronic gastritis, hepatomegaly, nonalcoholic steatohepatitis, autoimmune hepatitis, elevated pancreatic enzymes, and chronic pancreatitis [12, 14, 59–62].

Polyautoimmunity

Polyautoimmunity is the presence of more than one well-defined autoimmune disorder in a single patient [57, 58, 63]. Multiple autoimmune syndrome is the presence of three or more coexisting autoimmune diseases [64]. A cross-sectional polyautoimmunity study in children with autoimmune diseases revealed 44% of children diagnosed with a second autoimmune disease within 2 years, suggesting a necessity of assessment for polyautoimmunity in children with autoimmune diseases [65].

Polyautoimmunity reported in ASS is relatively common, with a prevalence of 33–52% [62, 63]. Children with JSS may have coexisting autoimmune disorders or polyautoimmunity as same as ASS. The prevalence of polyautoimmunity in JSS is 13–14%. The commonly reported autoimmunity in JSS is 8–12% of SLE and 2% mixed connective tissue diseases (MCTDs) [3, 54]. Juvenile idiopathic arthritis (JIA) [3, 52, 61, 64], anti-phospholipid syndrome [65], autoim-

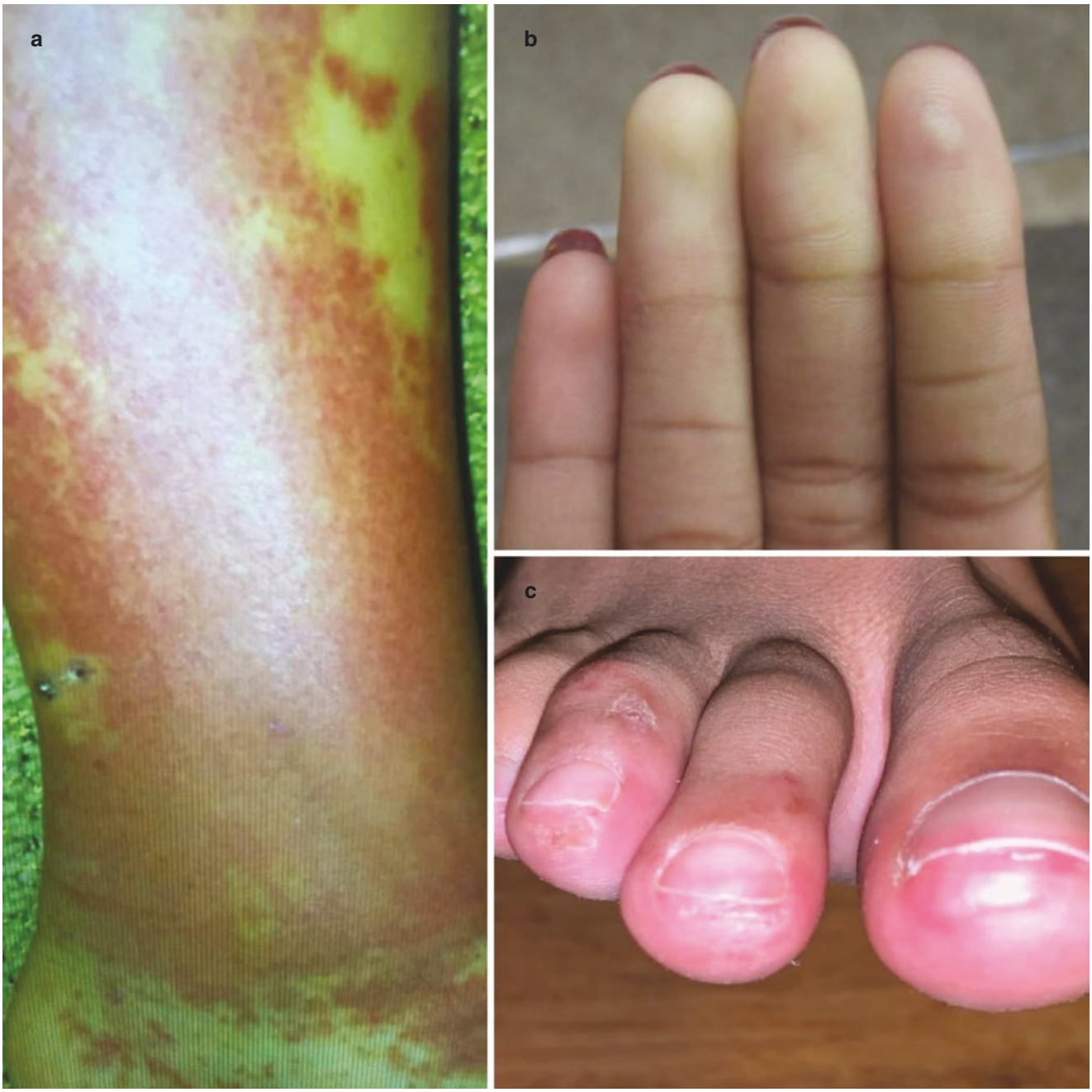

Fig. 7.4 (**a**) An 11-year-old girl with JSS and chronic parotitis presented with cutaneous vasculitis and purpura rash on bilateral lower legs and ankles. (**b**) A 16-year-old girl presented with Raynaud's phenomenon and healed digital ulcers, highly positive ANA, anti-SSA, hypergammaglobulinemia, and abnormal labial minor salivary gland biopsy with a high focus score. (**c**) An 18-year-old girl with JSS and recurrent parotitis developed swollen toes with red patches and small blisters of both feet. The skin biopsy revealed papillary edema with dense perivascular lymphocytic infiltrates in the superficial and mid-dermal layers as a characteristic of chilblains or pernio

mune hepatitis [66], Hashimoto's thyroiditis, Graves' disease [67], type 1 diabetes mellitus [68], and autoimmune encephalitis are all reported in JSS.

Historically, pSS accompanied by other systemic autoimmune diseases has been termed "secondary SS [69]." Polyautoimmunity has replaced secondary SS when patients with pSS are found with another well-defined autoimmune disorder fulfilling validated classification criteria [82, 73]. Labeling pSS associated with other autoimmune diseases as secondary SS is discouraged since patients with secondary SS are commonly under-recognized, undertreated, and under-researched. They are often excluded from clinical trials [82].

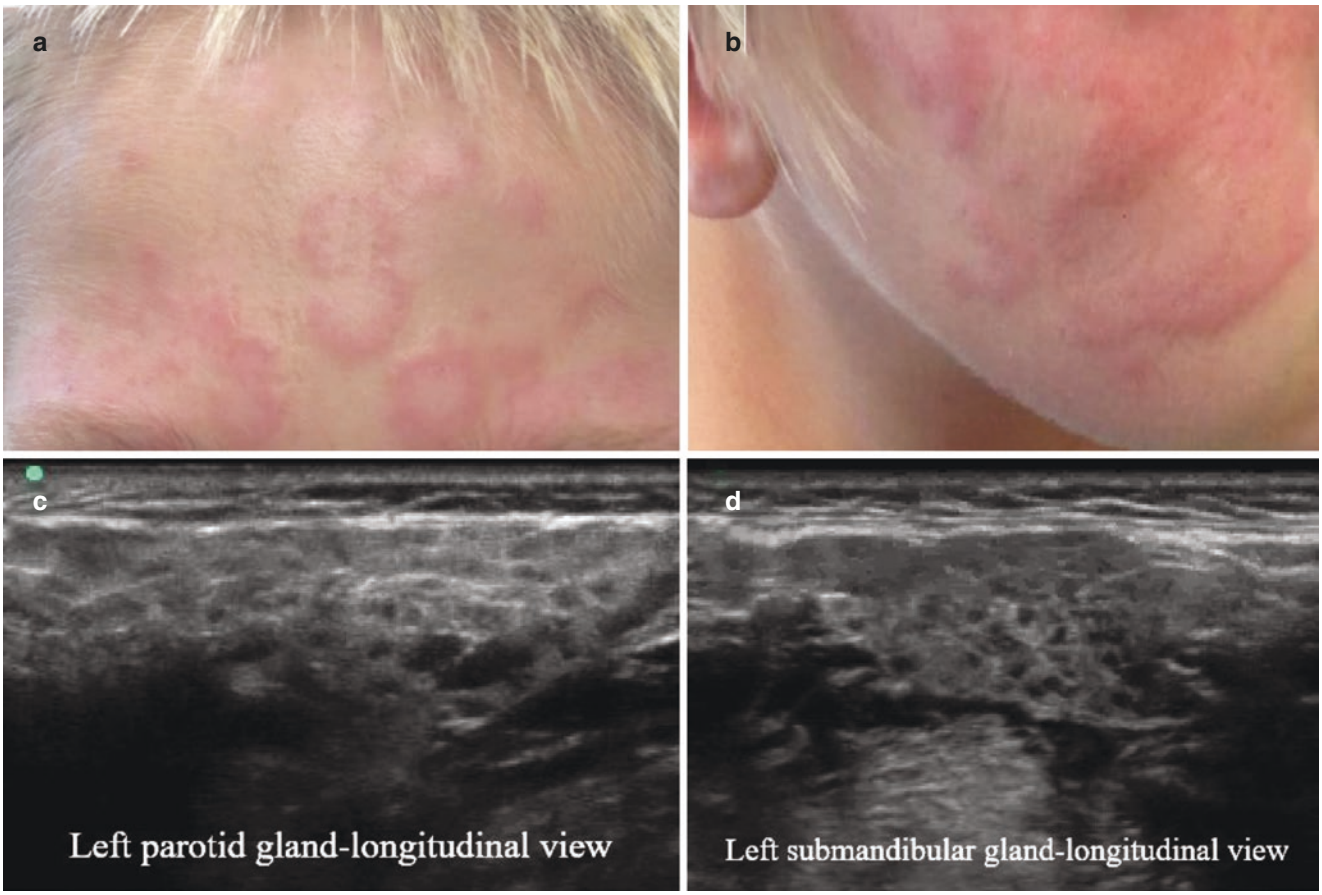

Fig. 7.5 A 10-year-old boy presented with multiple erythematous annular plaques on forearms, forehead (**a**), and cheeks (**b**) for 8 months and recurrent parotitis. The rash worsened after sun exposure. He also suffered from xerostomia and xerophthalmia. His blood tests revealed a hypergammaglobulinemia and highly positive autoantibodies, including ANA, anti-SSA-52, anti-SSB-60, anti-SSB, rheumatoid factor with normal complement, and negative anti-Smith and anti-double-stranded DNA. Both parotid glands and submandibular glands were heterogeneous with multiple anechoic/hypoechoic areas (**c**, **d**). His minor labial minor salivary gland biopsy showed a high focus score > 7, and a skin biopsy revealed subacute cutaneous lupus

Rare Manifestations

Rare manifestations including pericarditis [49, 71, 74], Kawasaki-like syndrome [66], hearing loss [49], vaginal dryness, vulvovaginitis [46, 70], dyspareunia, and psychosis [72, 75] were reported in JSS.

Laboratory Manifestations

Pediatricians refer children with positive autoantibodies or children with perplexing symptoms and negative autoantibodies to pediatric rheumatologists (76). ANA, anti-RoSSA/anti-LaSSB, rheumatoid factor, and immunoglobulins are commonly obtained for the initial workup of a suspected case of JSS. Understanding the clinical implications and limitations of the tests is necessary. Whether the persistent positive autoantibodies in asymptomatic patients will develop JSS or other autoimmune diseases is still unknown.

Antinuclear Antibody (ANA)

ANA is a primary autoantibody test in the diagnostic of JSS and other systemic autoimmune diseases. Indirect immunofluorescence on HEp-2, a human epithelial cell line, is the most common technique used for the ANA test. A positive test indicates at least one autoantibody reacting with a component of the cell nucleus. The positive ANA is the most common positive autoantibody in JSS found in 69–93% of cases (Table 7.1) with the specificity of 71% [78]. JSS cases may have negative ANAs; therefore, a negative ANA result does not exclude the diagnosis of JSS.

Anti-Ro/SSA and La/SSB Antibodies

The most common positive antinuclear antibodies in SS are antibodies directed against autoantigens Ro/SSA and La/SSB. Anti-Ro/SSA and anti-La/SSB antibodies react with

Table 7.1 A summary of laboratory manifestations from four large cohorts and a literature review-based cohort

Autoantibodies and immunologic test	Basiaga [3] (n = 300)	Literature review-based cohort (Marino) [81] (n = 240)	Ramos-Casals [4] (n = 158)	Hammenfors [52] (n = 67)	Thatayatikom [82] (n = 27)
ANA	88%	89%	90%	93%	69%
Anti-SSA/Ro	74%	82%	83%	75%	56%
RF	60%	70%	68%	45%	33%
Hypergammaglobulinemia	54%	84%	NA	NA	NA
Anti-SSB/La	45%	62%	62%	40%	15%
Anti-dsDNA	13%	N/A	N/A	N/A	17%
Neutropenia or lymphopenia	11%	N/A	N/A	N/A	N/A
Leukopenia	N/A	27%	N/A	N/A	N/A
Thrombocytopenia	5%	22%	N/A	N/A	N/A
Anemia	N/A	55%	N/A	N/A	N/A
Cryoglobulin	3%	N/A	5%	N/A	N
Low C3	N/A	N/A	14%	N/A	N/A
Low C4	N/A	N/A	14%	N/A	N/A
Early Sjogren antibodies	N/A	N/A	N/A	N/A	56%

the antigens in extracts from salivary and lacrimal glands, and they are found in both sera and lacrimal fluid of SS patients [73, 74]. The anti-Ro/SSA represents two distinct autoantibodies that react with two non-homologous proteins, Ro/SSA52 and Ro/SSA60 [80]. Both Ro/SSA52 and Ro/SSA60 are localized to different cell compartments and have various clinical associations. The Ro/SSA52 antigen does not bind directly to RNA; both Ro/SSA60 and La/SSB antigens bind directly [75]. The Ro/SSA52 is found on the cytoplasmic membrane or in small blebs during apoptosis. It is implicated in protein ubiquitination, pro-inflammatory states, and apoptosis mechanisms [79, 81, 83]. The anti-Ro/SSA 52 antibody is commonly positive because the antigen is accessible and ubiquitous. The Ro/SSB60 binds to small cytoplasmic RNA and forms small cytoplasmic ribonucleoprotein complexes with an essential function in cell survival after irradiation with the ultraviolet and protective role of autoimmune response [79, 81]. The diagnostic performance of anti-Ro52 and anti-Ro60 has never been studied in children with JSS.

Various methods of anti-Ro/SSA and anti-La/SSB detection have been used with nonequivalence results. RNA precipitation is the gold standard method with the highest sensitivity and specificity. Counter-immunoelectrophoresis, immunodiffusion, enzyme-linked immunosorbent assay (ELISA), and multiplex bead assay are commonly used in commercial laboratories. The positive anti-Ro/SSA and/or anti-La/SSB antibodies in children are associated with SS, SLE, subacute cutaneous lupus, neonatal lupus with congenital heart block and systemic sclerosis, idiopathic inflammatory myositis, autoimmune liver disease (primary biliary cirrhosis and type 1 autoimmune hepatitis), and celiac disease [79, 83].

The anti-Ro/SSA antibody is detected in 56–83% of children with JSS (Table 7.1) with the specificity of 95% [78]. The positive anti-La/SSB is less common than the positive anti-Ro/SSA. The anti-La/SSB antibody is detected in 16–62% of JSS cases (Table 7.1) with specificity of 96% [78]. Although both anti-Ro/SSA and anti-La/SSB are commonly positive, an isolated anti-La/SSB positivity with negative anti-Ro/SSA can be seen in JSS [3]. JSS with positive anti-Ro/SSA and/or anti-La/SSB may have a negative ANA [77]. A diagnosis of JSS in children with negative anti-Ro/SSA and anti-La/SSB antibodies is not eliminated since 22% of cases have negative anti-Ro/SSA and anti-La/SSB antibodies [3]. International studies of JSS revealed a negative correlation of parotitis with the positivity of anti-Ro/SSA [3] and a positive correlation of abnormal salivary gland ultrasound and the positivity of anti-Ro/SSA and anti-La/SSB [54]. The association between anti-Ro/SSA and anti-La/SSB positivity and the disease course or the disease severity has never been studied.

Rheumatoid Factor (RF)

RF is an antibody directed against the Fc portion of immunoglobulin G. The positive RF is commonly seen in 33–70% of JSS cases (Table 7.1). The positive RF in JSS is associated with parotitis and abnormal salivary gland ultrasound [3, 54].

Hypergammaglobulinemia

Polyclonal hypergammaglobulinemia is the result of increased B-cell activation in SS [78]. The elevated IgG is found in 54–84% of JSS cases (Table 7.1).

Early Sjögren's Syndrome Autoantibodies (eSjAs)

eSjAs are novel autoantibodies including salivary protein 1 (SP1), carbonic anhydrase IV (CA6), and parotid secretory protein (PSP), with three immunoglobulin isotypes (IgG, IgA, and IgM) for each antibody, totaling nine antibodies.

The autoantibodies initially were detected in IL-14 α transgenic mice and subsequently have been documented in ASS with negative anti-Ro/SSA antibody.

eSjAs are found in children with and without JSS [76, 82, 85]. The eSjAs may be the only autoantibody detected in some JSS cases with abnormal minor salivary gland biopsy. Among these antibodies, anti-CA6 IgG is the most prevalent. The sensitivity and specificity of eSjAs in JSS based upon the 2016 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria are 56% and 27% [76, 86]. The diagnostic performance of eSjAs should be re-evaluated in differentiating JSS from non-JSS when the age-specific classification criteria of JSS are available.

Other Laboratory Findings

Cytopenia is common in JSS with reports of anemia 55%, leukopenia 27%, thrombocytopenia 5%, and neutropenia 11%. A positive anti-double-stranded DNA (dsDNA) antibody can be detected in 13–17% of SS cases. It is unknown whether JSS with positive anti-dsDNA will develop SLE or polyautoimmunity in the future. Cryoglobulin is reported in 3–5% of JSS cases. Hypocomplementemia with low C3 and low C4 is found in 14% of cases. Other autoantibodies reported in JSS are anti-alpha-fodrin antibody [79], anti-muscarinic acetylcholine receptor M3 antibody [80], thyroglobulin antibody, thyroid peroxidase antibody, anticentromere, antimitochondrial, anti-cardiolipin antibodies, anti-β2 glycoprotein 1, and lupus anticoagulant.

Diagnosis and Classification Criteria

The most common symptom that alerts parents and caregivers is a painful enlargement of parotid glands related to recurrent or persistent parotitis. Unfortunately, misrecognition of parotitis as cervical lymphadenitis, especially in young children, is common. History of sicca symptoms should be asked. Since children may not complain of oral dryness, the following questions are recommended to assess dry mouth: (1) Do you need to drink water when eating dry foods like crackers or bread? (2) Are you worried about bad breath? (3) Have you ever experienced pain and or enlargement of the parotid gland? (4) Do you have dental caries or stomatitis, or ranula? (5) Have you noticed a change in your sense of taste? [12]. Isolated dry mouth is more common than isolated dry eyes or the combined dry mouth and dry eyes [3]. In the early stage of the disease, the oral cavity appears moist. The absence of saliva pooling in the floor of the mouth and frothy saliva are the signs of the disease progression. The oral mucosa is dry and glazed with fine wrinkles in the advanced stage. If the tongue sticks to the palate, it indicates extreme oral dryness [83].

The early detection and recognition of JSS can be challenging due to the lack of realization and verbal expression by pediatric patients, the absence of reliable oral and ocular dryness measurements in young children, and the unavailability of the validated JSS-specific diagnostic criteria. The extraglandular manifestations may be misdiagnosed as infectious, immunodeficiency, other autoimmune-associated, or hematologic/oncologic diseases. Since most pediatricians and pediatric specialists are not familiar with the extraglandular presentations of JSS, a delay in diagnosis and treatment is not uncommon. The diagnosis, therefore, requires a high index of suspicious and clinical expertise of pediatric rheumatologists. Certain clinical manifestations and abnormal laboratory findings listed in Tables 7.2 and 7.3 provide clues and diagnostic workup for JSS.

The 2016 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria have been used in children (Table 7.4); however, they have never been evaluated for applicability in children. Children with JSS can be underdiagnosed or misdiagnosed using the 2016 ACR/EULAR classification criteria, especially in children with extraglandular manifestations or subclinical xerostomia and xerophthalmia. Only 33–77% of children had fulfilled the criteria when all five criteria items were tested in two recent international studies [3, 56]. It

Table 7.2 Clinical manifestations and laboratory findings suggestive of JSS

1. Systemic symptoms	Fever, general malaise, lymphadenopathy, morning stiffness, body pain of unknown origin
2. Extraglandular manifestations	Joint pain/arthritis, rash such as erythema annular, purpura, thyroid adenoma,
3. Exocrine gland symptoms	Recurrent parotid swelling, frequent dental caries, mouth soreness, aphthous stomatitis, ranula, recurrent red eyes, a sensation of foreign body in the eye, eye itchiness, drinking a lot of water during meals, bad breath, no tears, and other similar issues
4. Abnormal laboratory findings (positive more than twice with an interval period of at least 3 months)	Elevation amylase, hypergammaglobulinemia Leukocytopenia or lymphocytopenia Increased erythrocyte sedimentation rate
5. Concomitant diseases	Hashimoto's thyroiditis, aseptic meningitis, interstitial nephritis, thrombocytopenic purpura, uveitis Other connective tissue diseases (especially systemic lupus erythematosus, mixed connective tissue disease, and polyarticular juvenile idiopathic arthritis) Fibromyalgia syndrome, chronic fatigue syndrome, and other similar diseases
6. Family history of autoimmune diseases	Sjögren's syndrome

Adapted from [87]

Table 7.3 Diagnostic workup for suspicious cases

Screening tests	Complete blood cell count, erythrocyte sedimentation rate, serum amylase, IgG, antinuclear antibody, rheumatoid factor, urinalysis (protein, occult blood, pH)
Serologic test	Anti-Ro/SSA antibody, anti-La/SSB antibody
Salivary gland function	Saliva production: unstimulated whole saliva measurement, stimulated whole saliva measurement
Lacrymal gland function	Tear production: Schirmer's test Conjunctiva or corneal epithelial damage: ocular staining
Salivary imaging studies	Ultrasonography, parotid gland sialography (conventional method or MR sialography), salivary gland scintigraphy
Biopsy	Labial minor salivary gland biopsy, lachrymal gland biopsy

Adapted from [87]

Table 7.4 The 2016 ACR/EULAR classification criteria

Item	Description	Weight/ score
Focus score of ≥1 (minor labial salivary gland biopsy)	A score determined by the number of mononuclear cell infiltrates containing ≥50 inflammatory cells per 4 mm^2	3
Positive anti-Ro/ SSA	Only anti-Ro/SSA60 antibodies have to be considered; isolated anti-Ro/ SSA52 antibodies are not specific for Sjögren's syndrome	3
Ocular staining score of ≥5	A score determined by an ophthalmologist on examination with fluorescein and lissamine green staining; scores range from 0 to 12, with higher scores indicating greater severity	1
Schirmer's test of ≤5 mm per 5 min in at least 1 eye	An assay for measuring tear production by inserting filter paper on conjunctiva in the lower eyelid and assessing the amount of moisture on the paper	1
Unstimulated whole salivary flow of ≤0.1 ml per min	Measuring the rate of salivary flow by collecting saliva in a tube for at least 5 min after the patient has swallowed	1
A diagnosis of pSS is defined as a score of ≥4		

Adapted from [89]

should be noted that there are three diagnostic criteria of JSS published; however, the criteria have never been validated [71, 87, 88].

Differential Diagnosis

Salivary gland diseases including juvenile recurrent parotitis, bacterial sialadenitis, HIV infection, viral sialadenitis, tuberculous sialolithiasis, IgG4-mediated disease, sarcoidosis, enlarged submandibular glands associated with cystic fibrosis, and benign salivary gland tumors should be differentiated from JSS in children presenting with enlarged salivary glands [87]. Juvenile idiopathic arthritis, systemic vasculitis, SLE, mixed connective tissue disease, systemic infections, leukemia, lymphoma, and primary immunodeficiency should be considered in JSS presenting with extraglandular symptoms.

Treatment

There are no specific treatment guidelines for JSS, and most of the therapy follows the regimens applied for ASS. Certain aspects, including growth, development, cosmetics, and mental health, should be considered in children. Treatment of glandular manifestations, including nonsteroidal anti-inflammatory drugs, acetaminophen, and systemic glucocorticoid, can relieve the salivary gland pain and swelling. Antibiotics can be prescribed if there is a concern of concurrent bacterial infections. Sialoendoscopy with saline or glucocorticoid irrigation may be effective in children with chronic or persistent sialadenitis. Pilocarpine hydrochloride and cevimeline hydrochloride are considered for xerostomia. Artificial tears and hyaluronic acid-containing topical eye drops are recommended for xeropthalmia [84].

Treatment of extraglandular diseases depends upon the symptoms, specific organ involvement, and severity of the affected organs. Pediatric rheumatologists commonly prescribe hydroxychloroquine for myalgia, arthralgia, arthritis, fever, fatigue, skin rash, and glandular symptoms. Methotrexate is considered for NSAID-resistant arthralgia/ arthritis. Disease-modifying anti-rheumatic drugs (DMARDs) or biologicals such as methotrexate, azathioprine, mycophenolate, tacrolimus, rituximab, belimumab, and abatacept may all be considered with a short course of systemic corticosteroid or pulse corticosteroid therapy [52, 84].

Prognosis

There are insufficient data on JSS regarding the disease prognosis. It is unknown whether the early detection and treatment of JSS can alter the disease course and minimize complications in adults. The risk of non-Hodgkin's lymphoma (NHL) development in JSS is unknown. However, the risk of NHL, especially mucosa-associated lymphoid tissue lymphoma (MALT), in ASS is 6–20 times greater than in the general population [88]. There are five reported cases of JSS with lymphoma, including a primary gastric B-cell MALT lymphoma in a 13-year-old girl [89], 2 cases of extranodal marginal zone B-cell lymphoma of salivary glands in a 14-year-old boy and a 16-year-old boy [90], and 2 cases of MALT of salivary glands in a 15-year-old girl and a 15-year-old boy [91].

References

1. Parisis D, Chivasso C, Perret J, Soyfoo MS, Delporte C. Current state of knowledge on primary Sjögren's syndrome, an autoimmune exocrinopathy. J Clin Med. 2020;9(7):doi:10.3390/jcm9072299.
2. Mavragani CP, Moutsopoulos HM. The geoepidemiology of Sjögren's syndrome. Autoimmun Rev. 2010;9(5):A305–10. https://doi.org/10.1016/j.autrev.2009.11.004.
3. Basiaga ML, Stern SM, Mehta JJ, Edens C, Randell RL, Pomorska A, Irga-Jaworska N, Ibarra MF, Bracaglia C, Nicolai R, Susic G, Boneparth A, Srinivasalu H, Dizon B, Kamdar AA, Goldberg B, Knupp-Oliveira S, Antón J, Mosquera JM, Appenzeller S, O'Neil KM, Protopapas SA, Saad-Magalhães C, Akikusa JD, Thatayatikom A, Cha S, Nieto-González JC, Lo MS, Treemarcki EB, Yokogawa N, Lieberman SM. Childhood Sjögren syndrome: features of an international cohort and application of the 2016 ACR/EULAR classification criteria. Rheumatology (Oxford, England). 2020;60:3144. https://doi.org/10.1093/rheumatology/keaa757.
4. Ramos-Casals M, Acar-Denizli N, Vissink A, Brito-Zerón P, Li X, Carubbi F, Priori R, Toplak N, Baldini C, Faugier-Fuentes E, Kruize AA, Mandl T, Tomiita M, Gandolfo S, Hashimoto K, Hernandez-Molina G, Hofauer B, Mendieta-Zerón S, Rasmussen A, Sandhya P, Sene D, Trevisani VFM, Isenberg D, Sundberg E, Pasoto SG, Sebastian A, Suzuki Y, Retamozo S, Xu B, Giacomelli R, Gattamelata A, Bizjak M, Bombardieri S, Loor-Chavez RE, Hinrichs A, Olsson P, Bootsma H, Lieberman SM. Childhood-onset of primary Sjögren's syndrome: phenotypic characterization at diagnosis of 158 children. Rheumatology (Oxford, England). 2021;60:4558. https://doi.org/10.1093/rheumatology/keab032.
5. Tomiita M, Saito K, Kohno Y, Shimojo N, Fujikawa S, Niimi H. The clinical features of Sjögren's syndrome in Japanese children. Acta Paediatr Jpn. 1997;39(2):268–72. https://doi.org/10.1111/j.1442-200x.1997.tb03597.x.
6. Wollheim FA. Henrik Sjögren and Sjögren's syndrome. Scand J Rheumatol Suppl. 1986;61:11–6.
7. Rucker CW. Keratitis Sicca: report of a case. Arch Ophthalmol. 1938;19(4):584–5. https://doi.org/10.1001/archopht.1938.00850160110007.
8. O'Neill EM. Sjogren's syndrome with onset at 10 years of age. Proc R Soc Med. 1965;58(9):689–90. https://doi.org/10.1177/003591576505800909.
9. Cimaz R, Casadei A, Rose C, Bartunkova J, Sediva A, Falcini F, Picco P, Taglietti M, Zulian F, Ten Cate R, Sztajnbok FR, Voulgari PV, Drosos AA. Primary Sjögren syndrome in the paediatric age: a multicentre survey. Eur J Pediatr. 2003;162(10):661–5. https://doi.org/10.1007/s00431-003-1277-9.
10. Condé K, Guelngar CO, Barry MC, Atakla HG, Mohamed A, Cissé FA. Sjögren's syndrome in children: about 15 cases in Guinea Conakry. Eur J Med Res. 2021;26(1):66. https://doi.org/10.1186/s40001-021-00534-6.
11. Virdee S, Greenan-Barrett J, Ciurtin C. A systematic review of primary Sjogren's syndrome in male and paediatric populations. Clin Rheumatol. 2017;36(10):2225–36. https://doi.org/10.1007/s10067-017-3745-z.
12. Tomiita M, Kobayashi I, Itoh Y, Inoue Y, Iwata N, Umebayashi H, Okamoto N, Nonaka Y, Hara R, Mori M. Clinical practice guidance for Sjögren's syndrome in pediatric patients (2018) – summarized and updated. Mod Rheumatol. 2021;31(2):283–93. https://doi.org/10.1080/14397595.2020.1816319.
13. Fujikawa S, Okuni M. A nationwide surveillance study of rheumatic diseases among Japanese children. Acta Paediatr Jpn. 1997;39(2):242–4. https://doi.org/10.1111/j.1442-200x.1997.tb03592.x.
14. Ciurtin C, Cho Y, Al-Obaidi M, Jury EC, Price EJ. Barriers to translational research in Sjögren's syndrome with childhood onset: challenges of recognising and diagnosing an orphan rheumatic disease. Lancet Rheumatol. 2021;3(2):e138–48. https://doi.org/10.1016/S2665-9913(20)30393-3.
15. Nezos A, Mavragani CP. Contribution of genetic factors to Sjögren's syndrome and Sjögren's syndrome related lymphomagenesis. J Immunol Res. 2015;2015:754825. https://doi.org/10.1155/2015/754825.
16. Nakamura H, Kawakami A. What is the evidence for Sjögren's syndrome being triggered by viral infection? Subplot: infections that cause clinical features of Sjögren's syndrome. Curr Opin Rheumatol. 2016;28(4):390–7. https://doi.org/10.1097/bor.0000000000000287.
17. Houghton KM, Cabral DA, Petty RE, Tucker LB. Primary Sjögren's syndrome in dizygotic adolescent twins: one case with lymphocytic interstitial pneumonia. J Rheumatol. 2005;32(8):1603–6.
18. Lee WS, Yoo WH. Primary Sjögren's syndrome in monozygotic twins. Int J Rheum Dis. 2014;17(5):578–9. https://doi.org/10.1111/1756-185x.12398.
19. Thatayatikom A, Bhattacharyya I, Elder ME, Cha S. The first case of monozygotic twin boys with nearly identical features of Sjögren's syndrome. Rheumatology (Oxford). 2020;59(3):687–8. https://doi.org/10.1093/rheumatology/kez428.
20. Bolstad AI, Haga HJ, Wassmuth R, Jonsson R. Monozygotic twins with primary Sjögren's syndrome. J Rheumatol. 2000;27(9):2264–6.
21. Bombardieri M, Argyropoulou OD, Ferro F, Coleby R, Pontarini E, Governato G, Lucchesi D, Fulvio G, Tzioufas AG, Baldini C. One year in review 2020: pathogenesis of primary Sjögren's syndrome. Clin Exp Rheumatol. 2020;38 Suppl 126(4):3–9.
22. Bordron A, Devauchelle-Pensec V, Le Dantec C, Capdeville A, Brooks WH, Renaudineau Y. Epigenetics in primary Sjögren's syndrome. Adv Exp Med Biol. 2020;1253:285–308. https://doi.org/10.1007/978-981-15-3449-2_11.
23. Kiripolsky J, McCabe LG, Kramer JM. Innate immunity in Sjögren's syndrome. Clin Immunol (Orlando, Fla). 2017;182:4–13. https://doi.org/10.1016/j.clim.2017.04.003.
24. Nakamura H, Shimizu T, Kawakami A. Role of viral infections in the pathogenesis of Sjögren's syndrome: different characteristics of Epstein-Barr virus and HTLV-1. J Clin Med. 2020;9(5):1459. https://doi.org/10.3390/jcm9051459.
25. Ittah M, Miceli-Richard C, Eric Gottenberg J, Lavie F, Lazure T, Ba N, Sellam J, Lepajolec C, Mariette X. B cell-activating factor of the tumor necrosis factor family (BAFF) is expressed under stimulation by interferon in salivary gland epithelial cells in primary Sjögren's syndrome. Arthritis Res Ther. 2006;8(2):R51. https://doi.org/10.1186/ar1912.
26. Katsiougiannis S, Kapsogeorgou EK, Manoussakis MN, Skopouli FN. Salivary gland epithelial cells: a new source of the immunoregulatory hormone adiponectin. Arthritis Rheum. 2006;54(7):2295–9. https://doi.org/10.1002/art.21944.
27. Manoussakis MN, Dimitriou ID, Kapsogeorgou EK, Xanthou G, Paikos S, Polihronis M, Moutsopoulos HM. Expression of B7 costimulatory molecules by salivary gland epithelial cells in patients with Sjögren's syndrome. Arthritis Rheum. 1999;42(2):229–39. https://doi.org/10.1002/1529-0131(199902)42:2<229::AID-ANR4>3.0.CO;2-X.
28. Mingueneau M, Boudaoud S, Haskett S, Reynolds TL, Nocturne G, Norton E, Zhang X, Constant M, Park D, Wang W, Lazure T, Le Pajolec C, Ergun A, Mariette X. Cytometry by time-of-flight immunophenotyping identifies a blood Sjögren's signature correlating with disease activity and glandular inflammation. J Allergy Clin Immunol. 2016;137(6):1809–1821.e1812. https://doi.org/10.1016/j.jaci.2016.01.024.
29. Verstappen GM, Pringle S, Bootsma H, Kroese FGM. Epithelial-immune cell interplay in primary Sjögren syndrome salivary gland pathogenesis. Nat Rev Rheumatol. 2021;17:333. https://doi.org/10.1038/s41584-021-00605-2.

30. Chivasso C, Sarrand J, Perret J, Delporte C, Soyfoo MS. The Involvement of Innate and Adaptive Immunity in the Initiation and Perpetuation of Sjögren's Syndrome. Int J Mol Sci. 2021;22(2):doi:10.3390/ijms22020658.
31. Christodoulou MI, Kapsogeorgou EK, Moutsopoulos HM. Characteristics of the minor salivary gland infiltrates in Sjögren's syndrome. J Autoimmun. 2010;34(4):400–7. https://doi.org/10.1016/j.jaut.2009.10.004.
32. Kapsogeorgou EK, Christodoulou MI, Panagiotakos DB, Paikos S, Tassidou A, Tzioufas AG, Moutsopoulos HM. Minor salivary gland inflammatory lesions in Sjögren syndrome: do they evolve? J Rheumatol. 2013;40(9):1566–71. https://doi.org/10.3899/jrheum.130256.
33. McGuirt WF Jr, Whang C, Moreland W. The role of parotid biopsy in the diagnosis of pediatric Sjögren syndrome. Arch Otolaryngol Head Neck Surg. 2002;128(11):1279–81. https://doi.org/10.1001/archotol.128.11.1279.
34. Saad Magalhães C, de Souza Medeiros PB, Oliveira-Sato J, Custódio-Domingues MA. Clinical presentation and salivary gland histopathology of paediatric primary Sjögren's syndrome. Clin Exp Rheumatol. 2011;29(3):589–93.
35. Gupta S, Ferrada MA, Hasni SA. Pulmonary manifestations of primary Sjögren's syndrome: underlying immunological mechanisms, clinical presentation, and management. Front Immunol. 2019;10:1327. https://doi.org/10.3389/fimmu.2019.01327.
36. François H, Mariette X. Renal involvement in primary Sjögren syndrome. Nat Rev Nephrol. 2016;12(2):82–93. https://doi.org/10.1038/nrneph.2015.174.
37. Skopouli FN, Barbatis C, Moutsopoulos HM. Liver involvement in primary Sjögren's syndrome. Br J Rheumatol. 1994;33(8):745–8. https://doi.org/10.1093/rheumatology/33.8.745.
38. Matsumoto T, Morizane T, Aoki Y, Yamasaki S, Nakajima M, Enomoto N, Kobayashi S, Hashimoto H. Autoimmune hepatitis in primary Sjogren's syndrome: pathological study of the livers and labial salivary glands in 17 patients with primary Sjogren's syndrome. Pathol Int. 2005;55(2):70–6. https://doi.org/10.1111/j.1440-1827.2005.01790.x.
39. Bogdanović R, Basta-Jovanović G, Putnik J, Stajić N, Paripović A. Renal involvement in primary Sjogren syndrome of childhood: case report and literature review. Mod Rheumatol. 2013;23(1):182–9. https://doi.org/10.1007/s10165-012-0633-x.
40. Tzioufas AG, Voulgarelis M. Update on Sjögren's syndrome autoimmune epithelitis: from classification to increased neoplasias. Best Pract Res Clin Rheumatol. 2007;21(6):989–1010. https://doi.org/10.1016/j.berh.2007.09.001.
41. Virdee S, Greenan-Barrett J, Ciurtin C. A systematic review of primary Sjögren's syndrome in male and paediatric populations. Clin Rheumatol. 2017;36(10):2225–36. https://doi.org/10.1007/s10067-017-3745-z.
42. Francis CL, Larsen CG. Pediatric sialadenitis. Otolaryngol Clin N Am. 2014;47(5):763–78. https://doi.org/10.1016/j.otc.2014.06.009.
43. Sato K, Yoshida Y, Sakai K, Shibui T, Hashimoto K, Baba A, Nomura T. Sjögren's syndrome and ranula development. Oral Dis. 2019;25(6):1664–7. https://doi.org/10.1111/odi.13130.
44. Means C, Aldape MA, King E. Pediatric primary Sjögren syndrome presenting with bilateral ranulas: a case report and systematic review of the literature. Int J Pediatr Otorhinolaryngol. 2017;101:11–9. https://doi.org/10.1016/j.ijporl.2017.07.019.
45. Takagi Y, Hashimoto K, Katayama I, Eida S, Sumi M. Juvenile primary Sjögren's syndrome with ranula: is ranula a clinical sign that leads to early detection of Sjögren's syndrome? Oral Radiol. 2021;37(2):328–35. https://doi.org/10.1007/s11282-020-00473-8.
46. Sardenberg F, Goursand D, Polletto LT, Vale MP, Zarzar PM, Paiva SM. Oral manifestations and treatment of a child with Sjogren's syndrome. J Dent Child (Chic). 2010;77(2):102–5.
47. Rojas-Rodriguez J, Garcia-Carrasco M, Ramirez ES, Romero-Rodriguez F, Ramos-Casals M, Rojas-Serrano J, Terrazas-Ramirez A. Optic neuropathy in a child with primary Sjögren's syndrome. Rev Rhum Engl Ed. 1998;65(5):355–7.
48. Shabana K, Okamoto N, Sugita Y, Shindo K, Murata T, Tamai H, Fujiwara K. The findings of musculoskeletal ultrasonography on primary Sjögren's syndrome patients in childhood with articular manifestations and the impact of anti-cyclic citrullinated peptide antibody. Mod Rheumatol. 2019;29(5):821–8. https://doi.org/10.1080/14397595.2018.1530849.
49. Schuetz C, Prieur AM, Quartier P. Sicca syndrome and salivary gland infiltration in children with autoimmune disorders: when can we diagnose Sjogren syndrome? Clin Exp Rheumatol. 2010;28(3):434–9.
50. Buonuomo PS, Maurizi P, Bracaglia C, Margani G, Riccardi R. Primary Sjögren's syndrome mimicking lymphoma in a pediatric patient. A rare and possibly misdiagnosed condition. Minerva Pediatr. 2009;61(1):119–22.
51. Thatayatikom A, Thatayatikom S, Carr S, Ezmigna D, Paim-Marquest L, Bhattacharyya I, Cha S. Juvenile Sjogren's syndrome with extraglandular manifestations mimicking immunodeficiency diseases. J Clin Immunol. 2021;41(suppl 1):S117.
52. Hammenfors DS, Valim V, Bica B, Pasoto SG, Lilleby V, Nieto-González JC, Silva CA, Mossel E, Pereira RMR, Coelho A, Bootsma H, Thatayatikom A, Brun JG, Jonsson MV. Juvenile Sjögren's syndrome: clinical characteristics with focus on salivary gland ultrasonography. Arthritis Care Res. 2020;72(1):78–87. https://doi.org/10.1002/acr.23839.
53. Zhang X, Zeng X. Severe pulmonary hypertension in pediatric primary Sjögren syndrome: a case report. J Clin Rheumatol. 2007;13(5):276–7. https://doi.org/10.1097/RHU.0b013e318156e46e.
54. Iijima N, Torii Y, Ito S, Hiramatu K, Suzuki M, Ito T, Senda Y. A case of idiopathic pulmonary hemosiderosis recurrent after remission of fifteen years and associated with Sjögren's syndrome. Nihon Kyobu Shikkan Gakkai Zasshi. 1988;26(11):1191–4.
55. Zhao J, Chen Q, Zhu Y, Zhao M, Liu J, Zhang Z, Gong X. Nephrological disorders and neurological involvement in pediatric primary Sjogren syndrome: a case report and review of literature. Pediatr Rheumatol Online J. 2020;18(1):39. https://doi.org/10.1186/s12969-020-00431-y.
56. Wang C, Simpkin C, Vielkind M, Galambos C, Lin C, Liptzin DR, Curran ML. Childhood-onset Sjögren syndrome presenting as pulmonary hemorrhage. Pediatrics. 2021;148(2) https://doi.org/10.1542/peds.2020-042127.
57. Malagón C, Gomez MDP, Mosquera C, Vargas C, Gonzalez T, Arango C, Martin L, Perez P, Amaya-Uribe L, Molano-Gonzalez N, Anaya JM. Juvenile polyautoimmunity in a rheumatology setting. Autoimmun Rev. 2019;18(4):369–81. https://doi.org/10.1016/j.autrev.2018.11.006.
58. Anaya JM, Rojas-Villarraga A, Mantilla RD, Arcos-Burgos M, Sarmiento-Monroy JC. Polyautoimmunity in Sjögren syndrome. Rheum Dis Clin N Am. 2016;42(3):457–72. https://doi.org/10.1016/j.rdc.2016.03.005.
59. Kashiwagi Y, Hatsushika T, Tsutsumi N, Go S, Nishimata S, Kawashima H. Gastrointestinal and liver lesions in primary childhood Sjögren syndrome. Clin Rheumatol. 2017;36(6):1433–5. https://doi.org/10.1007/s10067-017-3599-4.
60. Saulite V, Sharma P. EP32 gastroparesis in Sjögren's syndrome. Rheumatol Adv Pract. 2020;4(Supplement_1):rkaa052.031. https://doi.org/10.1093/rap/rkaa052.031.
61. Lovell DJ, Huang B, Chen C, Angeles-Han ST, Simon TA, Brunner HI. Prevalence of autoimmune diseases and other associated conditions in children and young adults with juvenile idiopathic arthritis. RMD Open. 2021;7(1) https://doi.org/10.1136/rmdopen-2020-001435.
62. Amador-Patarroyo MJ, Arbelaez JG, Mantilla RD, Rodriguez-Rodriguez A, Cárdenas-Roldán J, Pineda-Tamayo R, Guarin MR, Kleine LL, Rojas-Villarraga A, Anaya JM. Sjögren's syndrome at

the crossroad of polyautoimmunity. J Autoimmun. 2012;39(3):199–205. https://doi.org/10.1016/j.jaut.2012.05.008.
63. Lockshin MD, Levine AB, Erkan D. Patients with overlap autoimmune disease differ from those with 'pure' disease. Lupus Sci Med. 2015;2(1):e000084. https://doi.org/10.1136/lupus-2015-000084.
64. Simon TA, Harikrishnan GP, Kawabata H, Singhal S, Brunner HI, Lovell DJ. Prevalence of co-existing autoimmune disease in juvenile idiopathic arthritis: a cross-sectional study. Pediatr Rheumatol Online J. 2020;18(1):43. https://doi.org/10.1186/s12969-020-00426-9.
65. John A, Jayaraman D, Gunabooshanam B, Janarthanan M. Secondary antiphospholipid syndrome in an adolescent girl with sjögren syndrome. Indian J Rheumatol. 2021;16(2):238–9. https://doi.org/10.4103/injr.injr_255_20.
66. Bartunkova J, Sediva A, Vencovsky J, Tesar V. Primary Sjogren's syndrome in children and adolescents: proposal for diagnostic criteria. Clin Exp Rheumatol. 1999;17(3):381–6.
67. Miyagawa S, Tanaka M, Okamoto S, Ishihara T, Nakajima M, Taira K, Yoshioka A, Asada H. Autoimmune thyroid disease in anti-Ro/SS-A-positive children with annular erythema: report of two cases. Br J Dermatol. 2004;150(5):1005–8. https://doi.org/10.1111/j.1365-2133.2004.05926.x.
68. Krzewska A, Ben-Skowronek I. Effect of associated autoimmune diseases on type 1 diabetes mellitus incidence and metabolic control in children and adolescents. Biomed Res Int. 2016;2016:6219730. https://doi.org/10.1155/2016/6219730.
69. Kollert F, Fisher BA. Equal rights in autoimmunity: is Sjögren's syndrome ever 'secondary'? Rheumatology (Oxford). 2020;59(6):1218–25. https://doi.org/10.1093/rheumatology/keaa009.
70. Rojas-Villarraga A, Amaya-Amaya J, Rodriguez-Rodriguez A, Mantilla RD, Anaya JM. Introducing polyautoimmunity: secondary autoimmune diseases no longer exist. Autoimmune Dis. 2012;2012:254319. https://doi.org/10.1155/2012/254319.
71. Watanabe S, Abe Y, Tokunaga W, Kato M, Komori A, Kobayashi H, Nishimaki H, Masuda S, Morioka I. Pericarditis as an initial manifestation of Sjögren syndrome in a child: a case report. Medicine Case Rep Study Protocols. 2021;2(1):e0031. https://doi.org/10.1097/md9.0000000000000031.
72. Hammett EK, Fernandez-Carbonell C, Crayne C, Boneparth A, Cron RQ, Radhakrishna SM. Adolescent Sjogren's syndrome presenting as psychosis: a case series. Pediatr Rheumatol Online J. 2020;18(1):15. https://doi.org/10.1186/s12969-020-0412-8.
73. Yoshimi R, Ueda A, Ozato K, Ishigatsubo Y. Clinical and pathological roles of Ro/SSA autoantibody system. Clin Dev Immunol. 2012;2012:606195. https://doi.org/10.1155/2012/606195.
74. Kyriakidis NC, Kapsogeorgou EK, Tzioufas AG. A comprehensive review of autoantibodies in primary Sjögren's syndrome: clinical phenotypes and regulatory mechanisms. J Autoimmun. 2014;51:67–74. https://doi.org/10.1016/j.jaut.2013.11.001.
75. Robbins A, Hentzien M, Toquet S, Didier K, Servettaz A, Pham BN, Giusti D. Diagnostic utility of separate anti-Ro60 and anti-Ro52/TRIM21 antibody detection in autoimmune diseases. Front Immunol. 2019;10:444. https://doi.org/10.3389/fimmu.2019.00444.
76. Defendenti C, Atzeni F, Spina MF, Grosso S, Cereda A, Guercilena G, Bollani S, Saibeni S, Puttini PS. Clinical and laboratory aspects of Ro/SSA-52 autoantibodies. Autoimmun Rev. 2011;10(3):150–4. https://doi.org/10.1016/j.autrev.2010.09.005.
77. Negrini S, Emmi G, Greco M, Borro M, Sardanelli F, Murdaca G, Indiveri F, Puppo F. Sjögren's syndrome: a systemic autoimmune disease. Clin Exp Med. 2021; https://doi.org/10.1007/s10238-021-00728-6.
78. Nocturne G, Mariette X. B cells in the pathogenesis of primary Sjögren syndrome. Nat Rev Rheumatol. 2018;14(3):133–45. https://doi.org/10.1038/nrrheum.2018.1.
79. Maeno N, Takei S, Imanaka H, Oda H, Yanagi K, Hayashi Y, Miyata K. Anti-alpha-fodrin antibodies in Sjögren's syndrome in children. J Rheumatol. 2001;28(4):860–4.
80. Nakamura Y, Wakamatsu E, Matsumoto I, Tomiita M, Kohno Y, Mori M, Yokota S, Goto D, Ito S, Tsutsumi A, Sumida T. High prevalence of autoantibodies to muscarinic-3 acetylcholine receptor in patients with juvenile-onset Sjögren syndrome. Ann Rheum Dis. 2008;67(1):136–7. https://doi.org/10.1136/ard.2007.072421.
81. Marino A, Romano M, Giani T, Gaggiano C, Costi S, Singh R, Mehta JJ, Lieberman SM, Cimaz R. Childhood Sjogren's syndrome: an Italian case series and a literature review-based cohort. Semin Arthritis Rheum. 2020; https://doi.org/10.1016/j.semarthrit.2020.11.004.
82. Thatayatikom A, Jun I, Bhattacharyya I, Berg K, Lee YJ, Kim Y, Adewumi A, Zhang W, Thatayatikom S, Shah A, Beal C, Modica R, Elder ME, Cha S. The diagnostic performance of early Sjögren's syndrome autoantibodies in juvenile Sjögren's syndrome: the University of Florida Pediatric Cohort Study. Front Immunol. 2021;12(2373) https://doi.org/10.3389/fimmu.2021.704193.
83. Kassan SS, Moutsopoulos HM. Clinical manifestations and early diagnosis of Sjögren syndrome. Arch Intern Med. 2004;164(12):1275–84. https://doi.org/10.1001/archinte.164.12.1275.
84. Tomiita M, Kobayashi I, Itoh Y, Inoue Y, Iwata N, Umebayashi H, Okamoto N, Nonaka Y, Hara R, Mori M. Clinical practice guidance for Sjögren's syndrome in pediatric patients (2018) – summarized and updated. Mod Rheumatol. 2020;31:283. https://doi.org/10.1080/14397595.2020.1816319.
85. Yokogawa N, Lieberman SM, Sherry DD, Vivino FB. Features of childhood Sjogren's syndrome in comparison to adult Sjogren's syndrome: considerations in establishing child-specific diagnostic criteria. Clin Exp Rheumatol. 2016;34(2):343–51.
86. Shiboski CH, Shiboski SC, Seror R, Criswell LA, Labetoulle M, Lietman TM, Rasmussen A, Scofield H, Vitali C, Bowman SJ, Mariette X. 2016 American College of Rheumatology/European league against rheumatism classification criteria for primary Sjögren's syndrome: a consensus and data-driven methodology involving three international patient cohorts. Arthritis Rheumatol (Hoboken, NJ). 2017;69(1):35–45. https://doi.org/10.1002/art.39859.
87. Iro H, Zenk J. Salivary gland diseases in children. GMS current topics in otorhinolaryngology, head and neck surgery 13:Doc06. 2014. https://doi.org/10.3205/cto000109.
88. Sebastian A, Madej M, Sebastian M, Butrym A, Woytala P, Hałoń A, Wiland P. Prevalence and clinical presentation of lymphoproliferative disorder in patients with primary Sjögren's syndrome. Rheumatol Int. 2020;40(3):399–404. https://doi.org/10.1007/s00296-020-04522-7.
89. Fukumoto Y, Hosoi H, Kawakita A, Yamamoto S, Akioka S, Hibi S, Matsumura T, Tokiwa K, Sawada T. 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(1):49–56. https://doi.org/10.2177/jsci.23.49.
90. Collado P, Kelada A, Cámara M, Zeft A, Flagg A. Extranodal marginal zone B cell lymphoma: an unexpected complication in children with Sjögren's syndrome. Reumatol Clin. 2018;14(4):227–9. https://doi.org/10.1016/j.reuma.2017.01.015.
91. Tesher MS, Esteban Y, Henderson TO, Villanueva G, Onel KB. Mucosal-associated lymphoid tissue (MALT) lymphoma in association with pediatric primary Sjogren syndrome: 2 cases and review. J Pediatr Hematol Oncol. 2019;41(5):413–6. https://doi.org/10.1097/mph.0000000000001321.