

Sonographic evaluation of salivary glands in Juvenile Sjögren's Syndrome

Guissa VR¹, Martinelli EL², Brandão LMKR², Garcia LD², Provenza JR², Mendonça JA²

ACTA REUMATOL PORT. 2018;43:61-65

ABSTRACT

Introduction: Sjögren's syndrome in childhood is a rare autoimmune disease and mostly under-diagnosed. The aim of this study is to highlight the importance of ultrasonographic assessment of the salivary glands in children with recurrent parotitis and positive autoantibodies. Two cases of ultrasonographic patterns typical of Sjögren's syndrome described below.

Case 1: Female, 7-year-old, reporting for 2 years recurrent parotitis, xerophthalmia, xerostomia, polyarthralgia and fever. Immunological tests were positive for antinuclear antibodies, rheumatoid factor, anti-SSA/Ro and anti-SSB/La. Salivary glands ultrasound was consistent with Grade 4 by the B-mode method and the spectral Doppler with presence of intense Power Doppler signal and decreased vessels internal resistance, supporting the diagnosis of juvenile Sjögren's syndrome.

Case 2: Female, 10 years old, reporting recurrent parotitis for 1 year and polyarthritis for 10 days. The supplementary tests revealed positive antibodies for Sjögren's syndrome. Salivary glands Ultrasound and Spectral Doppler were consistent with chronic and active inflammatory process of the salivary glands in the juvenile Sjögren's syndrome.

Discussion: Salivary glands ultrasound can be a useful exam in the diagnosis of juvenile Sjögren's syndrome.

Keywords: Juvenile Sjögren syndrome; Parotitis; Salivary Glands Ultrasound; Autoimmune diseases; Childhood.

INTRODUCTION

Juvenile Sjögren's Syndrome (JSS) is a rare autoimmune disease that mainly affects children and adolescents salivary and lacrimal glands, mostly under diagnosed due to the different initial clinical manifestations and evolution along the course of the disease, when compared to adult's Sjögren's syndrome (SS). Isolated recurrent parotitis is the most common clinical manifestation during childhood, and may be primary or associated with other autoimmune rheumatic diseases, such as juvenile systemic lupus erythematosus (SLE), juvenile idiopathic arthritis, and juvenile systemic sclerosis¹⁻³. Exocrinopathy extended to the skin, the respiratory and urogenital systems may also occur, as well as extraglandular and systemic manifestations. With regard to the distribution by gender, there is a predominance of the disease in female pediatric patients (F: M = 5-7: 1), as well as in the adult population⁴.

Recent studies in adults show that the salivary glands ultrasound (SGU) detect glandular changes typical of SS, and can be a useful exam in the diagnosis and follow-up of patients with positive antibodies, showing 89% sensitivity and 85% specificity⁵⁻⁹. The same ultrasonographic findings can be found in JSS, and although few studies have been published so far, it is suggested that its application may become a new tool to help in the diagnostic aid for children and adolescents with recurrent parotitis and classic laboratory abnormalities¹⁰.

Between January 2007 and October 2017, 664 pediatric patients were admitted to the Rheumatology Department of the *Pontifícia Universidade Católica* of Campinas (PUC-Campinas). Out of these patients, 2 (0.30%) were diagnosed with JSS, exhibiting recurrent parotitis, positive autoantibodies and ultrasound changes of salivary glands, typical of this syndrome. These two cases are described below. This study was approved by the Ethics Committee of the University Hospital.

1. Pediatric Rheumatology Department, Pontifícia Universidade Católica de Campinas.

2. Rheumatology Department, Pontifícia Universidade Católica de Campinas.

CASE REPORTS

CASE 1

A 7-year-old white female patient was admitted to the Rheumatology Department of the PUC-Campinas, reporting recurrent bilateral parotitis, recurrent tooth decay, early loss of deciduous teeth, dry eyes, symmetrical inflammatory polyarthralgia of small and large joints, intermittent fever and impaired weight gain for 2 years. Diagnosis of idiopathic thrombocytopenic purpura for 2 months was reported; the patient was then treated with an infusion of immunoglobulin and prednisone 5mg/day. No oral ulcers, alopecia, cutaneous lesions, neurological, cardiac involvement, respiratory, abdominal or urogenital symptoms were reported. The patient's weight and height were in the 25th percentile and physical examination found no alterations. Laboratory exams revealed hemoglobin 12.4 g/dL, hematocrit 37%, white blood cell count 4.300/ mm³ (48% neutrophils, 46% lymphocytes, 1% eosinophils, 5% monocytes), platelets 198.000/ mm³, C-reactive protein (CRP) 48 mg/L (normal < 0.5), erythrocyte sedimentation rate (ESR) 42 mm/1st hour (normal < 11), amylase 97 U/L (normal < 80), urea 30 mg/dL (normal 16.6-48.5), creatinine 0.40 mg/dL (normal 0.53-0.79), aspartate aminotransferase (AST) 32 IU/L (normal 0-32), alanine aminotransferase (ALT) 9 IU/L (normal 0-33), lactate dehydrogenase (LDH) 232 U/L (314-333), glucose 79 mg/dL (normal <110), normal urinalysis, negative 24-hour urine protein excretion, C3 121 mg/dL (normal 90-180) and C4 14 mg/dL (normal 10-40). Serologic tests for viral infections were negative (Hepatitis virus B and C, Epstein-Barr virus, Cytomegalovirus, Toxoplasmosis, Parvovirus, Parvovirus, Human immunodeficiency virus and Hu-

man T-Lymphotropic Virus). Immunological tests were positive for antinuclear antibodies (ANA): 1/640 (nuclear fine speckled pattern), rheumatoid factor (RF) 640 IU/mL (normal 1-14), anti-SSA (Ro) 240 U/mL (normal < 10) and anti-SSB (La) 320 U/mL (normal <10) and negative for other serum antibodies: anti-double stranded DNA (anti-dsDNA), anti-Sm, anti-RNP, IgG and IgM anticardiolipin, direct Coombs (DC) and anti-cyclic citrullinated peptide (anti-CCP). The echocardiogram demonstrated normal ventricular function, without pericardial effusion. Chest and abdomen computed tomography showed no evidence of any lymph node pathology or visceromegaly. The ophthalmologic exam was consistent with bilateral *keratoconjunctivitis sicca*. SGU of parotid, submandibular and sublingual glands was performed with the MyLabTM 50 Esaote Ultrasound (Brazil, São Paulo), equipped with high-frequency linear transducer (12 MHz) for the B-mode and *Power Doppler* frequency ranging from 6.6 to 8.0 MHz. The B-mode method evidenced irregular contours, hypoechogenic areas > 6mm and multiple calcifications with echogenic bands with decrease in the size of the glands; the posterior gland border was not visible, consistent with Grade 4^{7,8}. In addition, spectral Doppler detected intense signal of *Power Doppler* (PD) and decreased internal resistance (IR) of mean \pm Standard Deviation (SD) of 0.42 ± 0.08 (Figure 1). Based on clinical, serological and ultrasonographic findings, the diagnosis of primary JSS was established. Due to the systemic signs and symptoms, treatment with hydroxychloroquine was indicated (5mg/kg/day). The patient remained asymptomatic for only 2 months, with a new relapse of the febrile condition and polyarthralgia, maintaining evidence of positive inflammatory activity; a treatment with a combi-

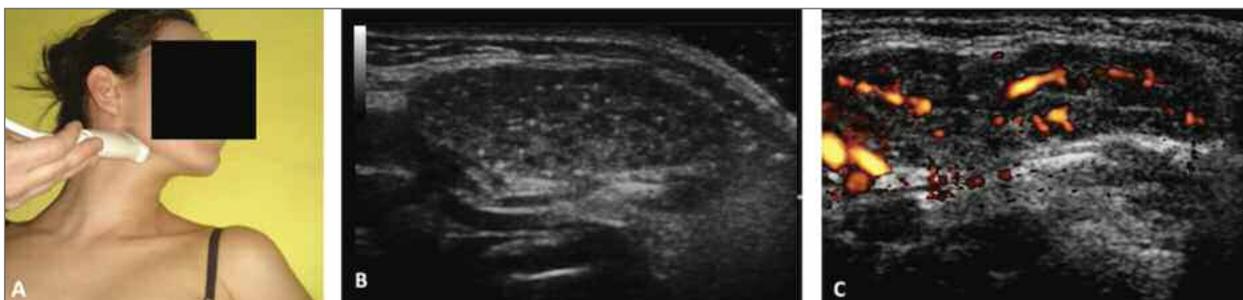


FIGURE 1. Female, 7-year-old, exhibiting salivary glands ultrasound with Grade 4 by the B-mode method, intense power Doppler signal and decreased vessels internal resistance, supporting the diagnosis of juvenile Sjögren's syndrome. A. Illustrative probe position to evaluate salivary glands. B. Salivary glands classified as Grade 4: irregular contours, several hypoechogenic areas, multiple calcifications with echogenic bands, decrease of the glands size. C. Increased power Doppler signal.

nation of hydroxychloroquine and azathioprine (2 mg/kg/day) was then indicated. The case evolved with clinical and laboratorial remission; however, 6 months later the patient presented a thrombotic event, positive antiphospholipid antibodies, hypocomplementemia, fulfilling the new international classification criteria for SLE, according to The Systemic Lupus International Collaborating Clinics (SLICC)¹¹, supporting the diagnosis of JSS associated to juvenile SLE.

CASE 2

A 10-year-old female black patient, with a sickle cell trait, recurrent bilateral parotitis for one year, symmetric polyarthritis of large joints, and fatigue in the previous 10 days was admitted. Sicca symptoms, fever or other systemic manifestations were not reported. Physical examination showed weight and height in the 75th percentile and wrists, elbows and knees' arthritis.

Supplementary investigations revealed: hemoglobin 10.7 g/dL, hematocrit 31%, white blood cell count 4.140/mm³ (40% neutrophils, 49% lymphocytes, 3% eosinophils, 8% monocytes), platelets 317.000/mm³, CRP 1.0 mg/L, ESR 59 mm 1st hour, amylase 127 U/L, glucose 72 mg/dL, normal urinalysis, proteinuria 0.07 g/24h, C3 109 mg/dL, C4 18 mg/dL, CH50 163 U/mL (normal 60-265), IgG 2632 mg/dL (normal 570-1320), IgA 300 mg/dL (normal 65-240), IgM 143 mg/dL (normal 60-175). Serologic tests for viral infections were negative. Immunological tests were positive for ANA: 1/640 (nuclear fine speckled pattern), RF 61 IU/mL, anti-Ro > 240 U/mL, anti-La > 320 U/mL and negative for other serum antibodies: anti-dsDNA, anti-Sm, anti-RNP, IgG and IgM anticardiolipin, DC and anti-CCP. Tomography of the chest and abdomen and echocardiogram were within normality. Schirmer s test and rose bengal unchanged. SGU: parotid and

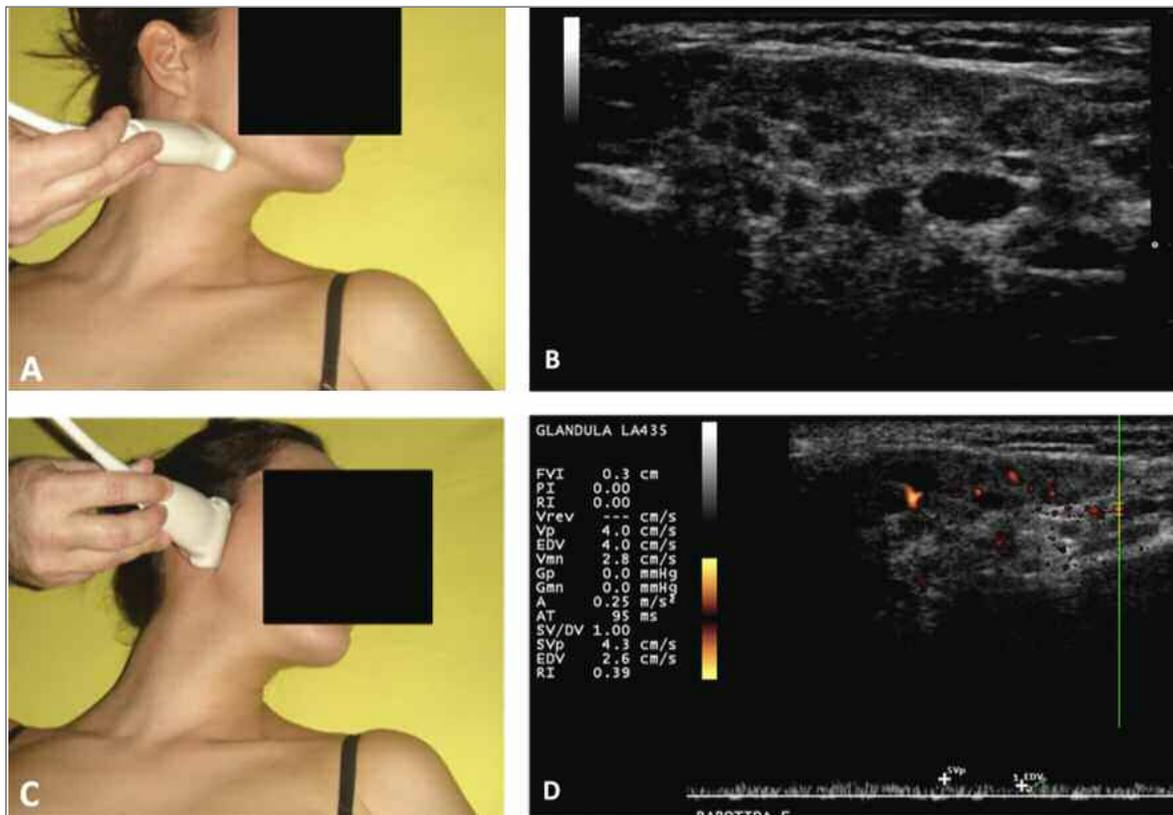


FIGURE 2. Salivary glands Ultrasound and Spectral Doppler of a female, 10-year-old patient, consistent with chronic and active inflammatory process of the salivary glands in the juvenile Sjögren's syndrome. A. Illustrative probe position to evaluate the submandibular glands. B. Classified as Grade 4: irregular contours, several hypoechogenic areas, multiple calcifications with echogenic bands, decrease in the size of the glands. C. Illustrative probe position to evaluate the parotid glands. D. Esppectral Doppler indicating IR equal to 0.39.

submandibular glands consistent with Grade 4 and sublingual with Grade 1^{7,8} (regular edges, small hypoechogenic areas and absence of echogenic bands) and presence of intense PD signal and decreased IR, with mean \pm SD 0.48 ± 0.07 , consistent with active inflammatory process of the JSS (Figure 2). The patient was submitted to labial salivary gland biopsy (LSGB), with a representative sample of glandular tissue, which demonstrated usual histological analysis, absence of acinar atrophy or lymphocytic inflammatory infiltrate. After the exclusion of chronic infections, neoplastic and secondary autoimmune diseases, the clinical, serological and ultrasonographic findings supported the diagnosis of primary JSS and the therapeutic indication. Treatment with a non-hormonal anti-inflammatory drug was initiated (naproxen), with remission of joint signs and symptoms within 10 days; however, 2 months later, the patient showed recurrence of bilateral parotitis, positive inflammatory activity tests, and initiated hydroxychloroquine (5mg/kg/day). The patient progressed clinically stable until the sixth month of treatment, when she presented with a new episode of parotitis (fifth episode), associated with fever and ankles and knees arthritis. The indication was then a combination of hydroxychloroquine with azathioprine (2 mg/kg/day); the patient remained clinically asymptomatic and with normal laboratory controls during the last 17 months of the outpatient follow-up.

DISCUSSION

In recent years, ultrasound indications in pediatric rheumatologic patients have been widely discussed in the literature, making it a valuable tool for the extension of rheumatologic physical examination, detection of acute and subacute inflammatory activity in organs and tissues, as well as a potential guideline in local therapeutic interventions. In addition to proven diagnostic sensitivity, ultrasound evidenced advantages over other imaging methods because it is safe, non-invasive, does not require pediatric patient sedation and is relatively inexpensive^{12,13}.

Although ultrasound is not currently included in the diagnostic criteria for SS, ultrasound plays an important role in the evaluation of salivary glands of adult rheumatologic patients and may increase the sensitivity and accuracy of the diagnosis; it is also expected to be an evaluation method of patient's prognosis and treatment^{5-7,9}. By means of the B-mode method, it is

possible to semi-quantify the salivary glands in relation to parenchyma homogeneity, echogenicity, gland size and posterior glandular border, classifying the degree of glandular involvement, according to the scoring system suggested by Cornec and De Vita et al.^{7,8}, ranging from Grade 0 (normal salivary glands) to Grade 4 (diffuse structural damage of the glandular parenchyma), identifying the presence of glands degeneration, fibrosis and calcification. In addition, spectral Doppler is a recent method that allows detection of the inflammatory process through the measurement of internal resistance of vessels, complementing the structural glandular evaluation^{7,14}.

The diagnosis of JSS is challenging since recurrent parotitis, which is the most common clinical manifestation of affected children, normally precedes oral, ocular, extra-glandular and systemic symptoms in years, and may mimic infections, immunodeficiencies, other autoimmune and neoplastic diseases; those conditions must be excluded in order to confirm the diagnostic^{1,3,15,16}. However, biochemical, hematological, immunological and histological findings follow the typical patterns of the syndrome in adults, such as the presence of autoantibodies (ANA, anti-Ro, anti-La, RF), ESR increase and lymphocytic infiltration in exocrine glands^{1,3,17,18}.

The lack of validated diagnostic criteria for the SS in this age group and the syndrome's initial clinical peculiarities mentioned above support the discussion about the applicability of SGU as a new, noninvasive and low risk diagnosis method, provided the patients assessed carry immunological markers suggestive of chronic autoimmune inflammation of the exocrine glands.

As in the two cases reported above, Nieto-González et al¹⁰ reported the case of 3 pediatric patients who were diagnosed with primary JSS, based on the sonographic findings of salivary glands in children with recurrent parotitis, positive autoantibodies and negative chronic infections and lymphoproliferative diseases. None of those patients underwent salivary gland biopsy and all of them progressed with clinical improvement after starting treatment with a non-hormonal anti-inflammatory drug and/or hydroxychloroquine. In a multicenter study with 40 pediatric patients diagnosed with primary JSS, all of them had positive autoantibodies and the most common initial clinical symptom was recurrent parotitis (72.5%). Joint involvement was reported in 10-57.7%, fever in 10% and fatigue in 7.5% of children affected. Only two patients were evaluated ultrasonographically, and both

exhibited images consistent with a chronic inflammatory process of the salivary glands⁴. Positive ultrasonographic data of salivary glands have also been reported in a 2-years and 7-month-old patient diagnosed with primary JSS who presented xerophthalmia, xerostomia, arthralgia, recurrent parotitis, positive ANA and RF, and biopsy of minor salivary glands with histological pattern typical of the disease¹⁹. Although few studies in JSS reported 100% positive findings in the salivary gland biopsies of the evaluated patients, there are no comparative studies between the ultrasound findings of the salivary glands and the histological patterns found in the biopsies in the JSS^{18,19}. In a recent study in adults with confirmed SS, out of the 20 patients with positive antibodies and ultrasonographic findings suggestive of the disease, 5 showed LSGB without alterations²⁰. Therefore, in the case #2 reported above, normal biopsy does not invalidate the diagnosis, since the patient presented with the main clinical manifestations of the disease in childhood, positive autoantibodies, exclusion of infectious and neoplastic diseases, and clinical remission throughout the treatment.

In conclusion, although ultrasound is not validated as a diagnostic criterion for JSS, ultrasonographic patterns typical of the disease were found in the patients evaluated above, who exhibited clinical and immunological characteristics suggestive of the syndrome, supporting the diagnosis and early treatment, determinants of good prognosis of the disease in that pediatric age group. For the purpose of this study, it is suggested that all the children and adolescents affected have their salivary glands evaluated through ultrasonography. Besides being a potential tool for diagnosis, ultrasound can screen more accurately those patients who should actually undergo invasive and risky supplementary examinations for diagnostic classification.

CORRESPONDENCE TO

Vanessa Ramos Guissa
 Rua Dr. Sampaio Ferraz, 750, apartamento 22 B
 E-mail: vanessaguissa@gmail.com

REFERENCES

1. Longhi BS, Appenzeller S, Centeville M, Gusmão RJ, Marini R. Primary Sjögren's syndrome in children: is a family approach indicated? *Clinics (São Paulo)* 2011; 66: 1991-1993.
2. Baszis K, Toib D, Cooper M, French A, White A. Recurrent parotitis as a presentation of primary pediatric Sjögren syndrome. *Pediatrics* 2012; 129: 179-182.
3. Singer NG, Tomanova-Soltys I, Lowe R. Sjögren's syndrome in childhood. *Curr Rheumatol Rep* 2008; 10: 147-155.
4. Cimaz R, Casadei A, Rose C et al. Primary Sjögren syndrome

- in the paediatric age: a multicentre survey. *Eur J Pediatr* 2003; 162: 661-665.
5. Saied F, Włodkowska-Korytkowska M, Ma li ska M, et al. The usefulness of ultrasound in the diagnostics of Sjögren's syndrome. *J Ultrason* 2013; 13: 202-211.
6. Hammenfors DS, Brun JG, Jonsson R, Jonsson MV. Diagnostic utility of major salivary gland ultrasonography in primary Sjögren's syndrome. *Clin Exp Rheumatol* 2015; 33: 56-62.
7. Cornec D, Cornec D, Jousse-Joulin S, Marhadour T. Salivary gland ultrasonography improves the diagnostic performance of the 2012 American College of Rheumatology classification criteria for Sjögren's syndrome. *Rheumatology (Oxford)* 2014; 53: 1604-1607.
8. De Vita S, Lorenzon G, Rossi G, Sabella M, Fossaluzza V. Salivary gland echography in primary and secondary Sjögren's syndrome. *Clin Exp Rheumatol* 1992; 10: 351-356.
9. Theander E, Mandl T. Primary Sjögren's syndrome: diagnostic and prognostic value of salivary gland ultrasonography using a simplified scoring system. *Arthritis Care Res (Hoboken)* 2014; 66: 1102-1107.
10. Nieto-González JC, Monteagudo I, Bello N, Martínez-Estupiñan L, Naredo E, Carreño L. Salivary gland ultrasound in children: a useful tool in the diagnosis of juvenile Sjögren's syndrome. *Clin Exp Rheumatol* 2014; 32: 578-580.
11. Petri M, Orbai AM, Alarcón GS et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. *Arthritis Rheum* 2012; 64: 2677-2686
12. Hernández-Díaz C, Ventura-Ríos L, Gutiérrez M, Roth J. Ultrasonography in pediatric rheumatology in Latin America. Expanding the frontiers. *Clin Rheumatol* 2016; 35: 1077-1080.
13. Laurell L, Court-Payen M, Boesen M, Fasth A. Imaging in juvenile idiopathic arthritis with a focus on ultrasonography. *Clin Exp Rheumatol* 2013; 31: 135-148.
14. Mendonça JA. Ultrassonografia em Reumatologia: uma extensão do exame físico. Rio de Janeiro: Livraria e editora Revinter LTDA, 2014: 55.
15. Houghton K, Malleson P, Cabral D, Petty R, Tucker L. Primary Sjögren's syndrome in children and adolescents: are proposed diagnostic criteria applicable? *J Rheumatol* 2005; 32: 2225-2232.
16. Shabana K, Okamoto N, Shindo K, Murata T, Tamai H, Fujiwara K. Musculoskeletal ultrasound findings of articular manifestations on juvenile primary sjogren's syndrome. *Pediatr Rheumatol Online J* 2014 Published Online First: 17 September 2014. doi: 10.1186/1546-0096-12-S1-P37.
17. Breda L, Nozzi M, De Sanctis S, Chiarelli F. Laboratory tests in the diagnosis and follow-up of pediatric rheumatic diseases: an update. *Semin Arthritis Rheum* 2010; 40: 53-72.
18. Saad Magalhães C, de Souza Medeiros PB, Oliveira-Sato J, Custódio-Domingues MA. Clinical presentation and salivary gland histopathology of paediatric primary Sjogren's syndrome *Clin Exp Rheumatol* 2011; 29: 589-593.
19. De Oliveira MA, De Rezende NP, Maia CM, Gallottini M. Primary Sjögren syndrome in a 2-year-old patient: role of the dentist in diagnosis and dental management with a 6-year follow-up. *Int J Paediatr Dent* 2011; 21: 471-475.
20. Astorri E, Sutcliffe, Richards PS, et al. Ultrasound of the salivary glands is a strong predictor of labial gland biopsy histopathology in patients with sicca symptoms. *J Oral Pathol Med* 2016; 45: 450-454.