

Juvenile Recurrent Parotitis: Could be a Primary Pediatric Sjogren Syndrome?

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Abstract

Objective: To alert the clinician suspecting of an autoimmune disorder like Sjogren Syndrome for children affected by recurrent parotitis, particularly in case of bilateral involvement in order to timely recognize this disease and to facilitate the treatment and the screening for complications.

Materials and Methods: All patients with recurrent parotid swelling between 0 and 14 years, 7 in total referred to the Multidisciplinary Department of Medical and Dental Specialities, Division of Oral and Maxillofacial Surgery (Università degli Studi della Campania Luigi Vanvitelli, Naples, Italy) in the last 2 years, were subjected to clinical, serological, microbiological and ultrasound screening for excluding tumors or infectious diseases. In patients thus selected were diagnosed with Juvenile Recurrent Parotitis and were treated with sialoendoscopy (intraductal wash of saline solution and steroids) or other anti-inflammatory drugs. From the formulation of diagnosis, patients were subjected to careful follow-up checks with 6, 12 and 18 months during which they proceeded to repeat initial serological screening if the endoscopic or systemic therapy became ineffective.

Results: **Patient 1:** Following interventional sialoendoscopy treatment with mechanical dilation and washing with physiological solution and cortisone, showed remission at 18 months. **Patient 2:** Following interventional sialoendoscopy treatment with mechanical dilation and washing with physiological solution and cortisone showed remission at 18 months. **Patient 3:** She took prednisone and hydroxychloroquine, with complete resolution of parotid swelling and no further recurrences. **Patient 4:** Following endoscopic treatment with mechanical dilation and washing with physiological solution and cortisone did not show relapse after 18 months. **Patient 5:** She took hydroxychloroquine 12 months later with resolution of parotitis symptoms. **Patient 6:** Following interventional sialoendoscopy treatment with mechanical dilation and washing with physiological solution and cortisone showed remission at 18 months. **Patient 7:** Following the interventional sialoendoscopy treatment with mechanical dilation and washing with physiological solution and cortisone showed remission of relapse at 18 months.

Conclusions: Recurrent parotitis should alert the clinician to the possibility of pSS especially if it does not respond to treatment with anti-inflammatory therapy and sialoendoscopic washing.

Introduction

Parotid swelling is frequently encountered in the pediatric population. Typically acute and self-limiting, usually represents viral (epidemic mumps, *Epstein-Barr virus*, *Adenovirus*, *Coxsackievirus*, Influenza, HIV, *Cytomegalovirus*) or bacterial (*Staphylococcus aureus*, *Streptococcus*) infection. Less common etiologies include Juvenile Recurrent Parotitis (JRP) or pneumoparotid or anatomic abnormalities, such as calculi or tumors. Less frequent etiologies include autoimmune diseases such as Sjögren Syndrome (SS) or sarcoidosis [1].

Sjögren's Syndrome (SS) is an idiopathic systemic autoimmune disease affecting predominantly the exocrine glands, with the classic symptom complex of dry eyes (keratoconjunctivitis sicca) and dry mouth (xerostomia). Extraglandular involvement in SS may include interstitial pneumonitis, interstitial nephritis, isosthenuria or renal tubular acidosis, thyroiditis, central nervous system involvement, vasculitis, and an increased incidence of lymphoma. Primary SS (pSS) occurs with a prevalence of 0.1-0.4% in the Caucasian population with a female predominance in the fourth and fifth decades of their lives. Conversely, in childhood and early adulthood SS is an extremely rare autoimmune condition (only 147 cases described in literature) [2,3]. There are several proposed sets of diagnostic criteria for adult pSS. The revised European Community Study Group classification criteria proposed by the American-European Consensus Group (AECG) [4] have been validated for adults and include 6 items: ocular symptoms, oral symptoms, evidence of keratoconjunctivitis sicca, focal sialoadenitis by minor salivary gland biopsy, instrumental evidence of salivary gland involvement, and presence of SSA or SSB autoantibodies. In adults the presence of 4 of the criteria, with the exclusion of patients who have negative autoantibodies or minor salivary gland biopsy was found to have a sensitivity of 89.5% and specificity of 95.2%. The proposed diagnostic criteria for Sjogren's syndrome in adults (formulated by the European Community Study Group and later revisited by the American-European Consensus Group Criteria) can't be applied for the diagnosis in children because they have an unacceptably low sensitivity. Further, the criteria for the diagnosis of juvenile pSS suggested by Bartunkova et al. [5] were not validated because pediatric patients rarely have sicca syndrome or xerophthalmia at presentation (almost always present in the adult with

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pSS) and autoantibodies often appear late in the course of the disease but often present with parotid symptomatology (mainly intended as swelling and pain) as evidenced by studies carried out by Baszis et al. [5] and by our clinical experience. According to our opinion, levels of suspicion for an autoimmune disorder should be maintained for children affected by recurrent parotitis, particularly in case of bilateral involvement in order to timely recognize this disease and to facilitate the treatment and the screening for complications.

Materials and Methods

All patients with recurrent parotid swelling between 0 and 14 years, 7 in total, 4 males 3 females, with a mean age of 9.57 years, referred to the Multidisciplinary Department of Medical and Dental Specialities, Division of Oral and Maxillofacial Surgery (Università degli Studi della Campania Luigi Vanvitelli, Naples, Italy) in the last 2 years, were subjected to clinical, serological, microbiological and ultrasound screening for excluding tumors or infectious diseases.

We have therefore included children with remitting unilateral or bilateral swelling of the parotid region, that may last from a few days to months; with presence or absence of autoantibodies suggestive of autoimmune disease (SS-A, SS-B, anti-dsDNA, anti-Sm, anti-RNP), ultrasound image characterized by areas of ectasia and hypoechoic spots or sialoendoscopic features of whitish ductal walls, ectasia and stenosis.

Exclusion criteria were presence of viral markers, neoformations detectable with methods of imaging, the acclaimed presence of autoimmune disease, sarcoidosis, Graft Versus Host Disease (GVHD), past head and neck radiation, and known human immunodeficiency virus infection or hepatitis C infection.

In patients thus selected were diagnosed with Juvenile Recurrent Parotitis and were treated with sialoendoscopy (intraductal wash of saline solution and steroids) or other anti inflammatory drugs.

Table 1: Patients demographic, clinical and diagnostical features.

Pz	Age	Sex	Onset age (Months)	Symptoms	US	Endoscopic findings	Outcome	Follow up
1	6	M	6	Right parotid swelling dry eyes, dry mouth, dysphagia	inhomogeneous parenchyma, multiple hypoechoic areas and hypoechoic spots	whitish ductal walls, moderate stenosis, mucous fibrinous material in the main duct	Fav	Success at 18 months
2	9	M	12	Right parotid swelling, dry eyes, dry mouth, or dysphagia	inhomogeneous parenchyma, multiple hypoechoic areas and hypoechoic spots	whitish ductal walls, moderate stenosis, mucous fibrinous material in the main duct	Fav	Success at 18 months
3	12	F	84	Left parotid swelling, fever, intermittent headaches. Sicca syndrome symptoms, dysphagia.	inhomogeneous parenchyma, multiple hypoechoic areas and intraglandular adenopathy	parenchymal inflammation, fibrosing footpring, ectasia of the duct system	Fav	Immediate success
4	12	M	24	Bilateral parotid swelling dry eyes, dry mouth, dysphagia	inhomogeneous parenchyma	whitish ductal walls, mucous fibrinous material in the main duct.	Fav	Success at 18 months
5	13	F	12	Right parotid swelling dry mouth; dysphagia	inhomogeneous parenchyma, multiple hypoechoic areas and intraglandular adenopathy	whitish ductal walls, mucous fibrinous material in the main duct	Fav	Success at 12 months
6	8	F	12	Bilateral parotid swelling dry eyes, dry mouth, dysphagia	parenchyma, multiple hypoechoic areas and hypoechoic spots	whitish ductal walls, moderate stenosis, mucous fibrinous material in the main duct	Fav	Success at 18 months
7	7	M	4	Left parotid swelling dry eyes, dry mouth, dysphagia	inhomogeneous parenchyma, multiple hypoechoic areas and hypoechoic spots	whitish ductal walls, moderate stenosis, mucous fibrinous material in the main duct	Fav	Success at 18 months

From the formulation of diagnosis, patients were subjected to careful follow-up checks with 6, 12 and 18 months during which they proceeded to repeat initial serological screening if the endoscopic or systemic therapy became ineffective.

Results

The patients identified had the following characteristics (Table 1):

Patient 1

A 6-year-old Caucasian boy was referred for evaluation of several episodes of right-side parotitis occurring over a 6 month period. He denied dry eyes, dry mouth, or dysphagia and had no other systemic complaints. There was no family history of autoimmune or rheumatic disorders. His general examination was unremarkable; gross clinical examination revealed normal production of saliva and tears. Investigations showed a negative RF, ANA, SSA, SSB, Sm and RNP; normal complement; elevated ESR and normal urinalysis. Ultrasound image characterized by inhomogeneous parenchyma, multiple hypoechoic areas and hypoechoic spots. Sialoendoscopic features of whitish ductal walls, moderate stenosis, mucous fibrinous material in the main duct. Following interventional sialoendoscopy treatment with mechanical dilation and washing with physiological solution and cortisone, showed remission at 18 months (Figure 1).

Patient 2

A 9-year-old Caucasian boy with a story of right-side parotitis occurring 4 times in a year with spontaneous resolution. He denied dry eyes, dry mouth, or dysphagia and had no other systemic complaints. There was no family history of autoimmune or rheumatic disorders. His general examination was unremarkable; gross clinical examination revealed normal production of saliva and tears. Investigations showed a negative RF, ANA, SSA, SSB, Sm and RNP; normal complement; elevated ESR and normal urinalysis. Ultrasound image characterized by inhomogeneous parenchyma, multiple hypoechoic areas and hypoechoic spots. Sialoendoscopic features of

whitish ductal walls, moderate stenosis, mucous fibrinous material in the main duct. Following interventional sialoendoscopy treatment with mechanical dilation and washing with physiological solution and cortisone showed remission at 18 months.

Patient 3

A 12-year-old girl was admitted to hospital with fever, parotid swelling, and intermittent headaches. Episodes of painful, bilateral parotid swelling had occurred annually since age 7 years. She denied sicca syndrome symptoms or dysphagia. On examination, she appeared well apart from swollen parotid glands. Investigations showed a strongly positive RF; positive ANA; high titer antibodies to SSA and SSB; negative anti-dsDNA, Sm, and RNP; elevated ESR; elevated amylase; and elevated IgG, IgA, and IgM. Ultrasound image was characterized by inhomogeneous parenchyma, multiple hypoechoic areas and intraglandular adenopathy. Sialoendoscopic features of chronic parenchymal inflammation, fibrosing footpring, ectasia of the duct system. She took prednisone and hydroxychloroquine, with complete resolution of parotid swelling and no further recurrences.

Patient 4

A 12 year-old boy was referred for evaluation of several episodes of bilateral parotitis occurring over a 24 months. He denied dry eyes, dry mouth, or dysphagia and had no other systemic complaints. There was no family history of autoimmune or rheumatic disorders. His general examination was unremarkable; gross clinical examination revealed normal production of saliva and tears. Investigations showed a negative RF, ANA, SSA, SSB, Sm and RNP; normal complement; elevated ESR and normal urinalysis. Ultrasound image characterized by inhomogeneous parenchyma. Sialoendoscopic features of whitish ductal walls, mucous fibrinous material in the main duct. Following

endoscopic treatment with mechanical dilation and washing with physiological solution and cortisone did not show relapse after 18 months.

Patient 5

A 13-year-old Caucasian girl was referred for positive autoantibodies to SSA and SSB. She denied dry mouth; dysphagia. Family history revealed her mother has multiple sclerosis and possible juvenile idiopathic arthritis. Investigations showed a positive ANA; elevated SSA and SSB; negative anti-dsDNA, Sm, and RNP; normal complement levels; elevated ESR; and microscopic hematuria. Ultrasound image was characterized by inhomogeneous parenchyma, multiple hypoechoic areas and intraglandular adenopathy. Sialoendoscopic features of chronic parenchymal inflammation, fibrosing footpring, ectasia of the duct system. No treatment was started at first. She took hydroxychloroquine 12 months later with resolution of parotitis symptoms.

Patient 6

A 8-year-old Caucasian girl with a story of bilateral parotitis occurring 3 times in a year with spontaneous resolution. She denied dry eyes, dry mouth, or dysphagia and had no other systemic complaints. There was no family history of autoimmune or rheumatic disorders. Her general examination was unremarkable; gross clinical examination revealed normal production of saliva and tears. Investigations showed a negative RF, ANA, SSA, SSB, Sm and RNP; normal complement; elevated ESR and normal urinalysis. Ultrasound image characterized by inhomogeneous parenchyma, multiple hypoechoic areas and hypoechoic spots. Sialoendoscopic features of whitish ductal walls, moderate stenosis, mucous fibrinous material in the main duct. Following interventional sialoendoscopy treatment with mechanical dilation and washing with physiological solution and cortisone showed remission at 18 months.

Patient 7

A 7-year-old Caucasian boy was referred for evaluation of several episodes of left-side parotitis occurring over a 4 months period. He denied dry eyes, dry mouth, or dysphagia and had no other systemic complaints. There was no family history of autoimmune or rheumatic disorders. His general examination was unremarkable; gross clinical examination revealed normal production of saliva and tears. Investigations showed a negative RF, ANA, SSA, SSB, Sm and RNP; normal complement; elevated ESR and normal urinalysis. Ultrasound image characterized by inhomogeneous parenchyma, multiple hypoechoic areas and hypoechoic spots. Sialoendoscopic features of whitish ductal walls, moderate stenosis, mucous fibrinous material in the main duct. Following the interventional sialoendoscopy treatment with mechanical dilation and washing with physiological solution and cortisone showed remission of relapse at 18 months.

Discussion

For these reasons in patients 1-2-4-6-7 were diagnosed JRP, a clinical condition characterized by parotid gland recurrent episodes of pain and swelling, usually accompanied by fever and malaise determined by inflammation. This condition affects infants and children between 3 and 6 years old, with a clear preference for the male and usually disappears at puberty. It is associated with not

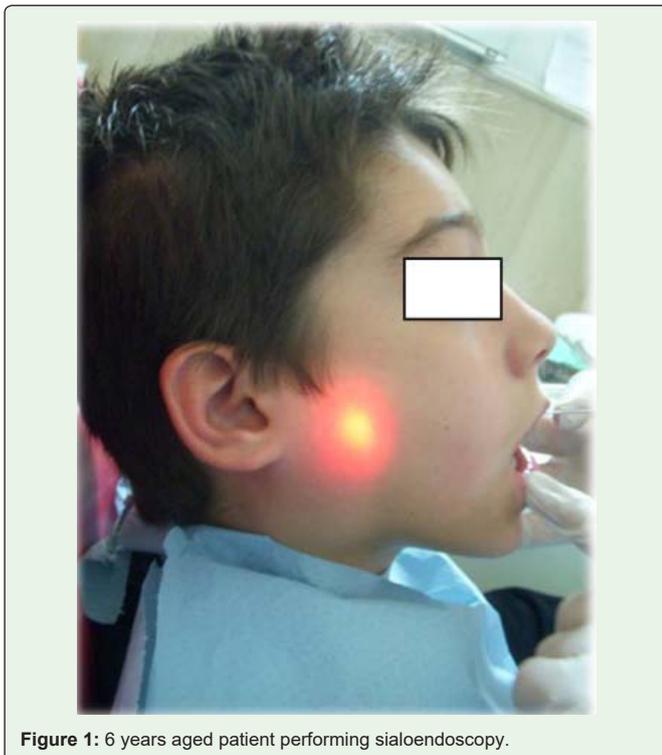


Figure 1: 6 years aged patient performing sialoendoscopy.

obstructive parotid gland sialectasies. The etiology is unknown despite many studies about it. Although the affected gland demonstrate distal duct sialectasies, it seems there is evidence of obstruction in most cases. Symptoms are generally unilateral, when bilaterals are always marked on one side. The number of occurrences individually varies but are more commonly repeated every 3-4 months, while at puberty are reduced gradually until it disappears altogether. Painful swelling is usually associated with fever; symptoms persist from a few days to 2 weeks but resolves spontaneously, independently of any treatment [6]. At sialography (whose role is becoming secondary to ultrasound) typical pattern is constituted by sialectasic jets and globular scattered throughout the gland, usually bilateral even in cases in which the symptomatic presentation is unilateral (but still smaller and fewer where there is the procession of symptoms). US is recommended at the beginning and in the follow-up, constantly shows hypoechoic areas that correspond to areas of sialectasia episode demonstrated by sialography (Figure 2). Sialoendoscopy typically puts in evidence whitish ductal walls and presence of stenosis without evidence of solid obstructions and/or mucous membranes [17,18] (Figure 3). Cytological examination of saliva, which is normally in children is acellular, shows granulocytes, lymphocytes, and in some cases 50% of bacteria (aerobic and anaerobic cocci). Histological examination revealed around the interlobular dilated ducts, organized numerous lymphocytes in lymphoid follicles and a cylindrical pseudo stratified epithelium with areas of hyperplasia and metaplasia. Some recent studies (see Houghton et al. [2,7,8]) suggest that some symptoms, including recurrent conjunctivitis and mumps, if added to the diagnostic criteria encoded by AECG [4] greatly increase the sensitivity of the latter in the diagnosis of pSS in the child. In the pSS population misclassification is especially problematic at disease onset and early in disease course, when classic symptoms and signs are often not manifest. The end stage ocular and oral symptoms, objective evidence of keratoconjunctivitis sicca, and instrumental evidence of salivary gland involvement are not helpful in establishing early diagnosis. As a rule the pSS is prevalent in women in the fourth and fifth decades, but it is commonly reported during childhood, with about 147 cases reported in the literature [8]. This is because it is probably under-diagnosed in childhood, as the mode of presentation can be large and are not rare long delays in diagnosis.



Figure 2: US peculiar findings: increased volume of parotid, inhomogeneous hypoechoic structure characterized by notes of moderate fibrosis.

And likely that some patients diagnosed with pSS in adulthood have experienced the onset of symptoms during childhood. In fact, the clinical presentation of pSS in childhood may differ from the clinical presentation in adulthood. The cases of pediatric pSS are reported to have a higher incidence of recurrent parotitis and a lower incidence of xerostomia and xerophthalmia [9]. Laboratory and pathological findings in children with SS are similar to those found in adults, with the characteristic lymphocytic infiltration of the exocrine glands and the presence of hypergammaglobulinemia, increased Erythrocyte Sedimentation Rate (ESR), positive Antinuclear Antibody (ANA) and autoantibodies to nuclear antigens Ro/SSA and La/SSB2.

In pediatric recurrent parotitis, laboratory evaluation and sialoendoscopy may be very helpful [10,11]. A combination of positive ANA, RF, SS-A, and SS-B; hypergammaglobulinemia; elevated amylase (parotid or pancreatic); elevated ESR and suggestive chronic inflammatory endoscopic patterns are suspicious for SS (however, the presence of anti-double-stranded DNA antibodies or hypocomplementemia raises the concern for other systemic autoimmune disorders, such as SLE or another connective tissue disease) [12,13].

Even in the absence of xerophthalmia, objective testing may be able to document evidence of subclinical disease. These include the Schirmer test (wetting of filter paper strip to quantify tear production, abnormal being less than 5 mm in 5 minutes) and rose bengal or fluorescein staining to identify corneal erosions.

In unclear cases, parotid ultrasound, sialography, or biopsy of a minor salivary gland (sublingual) may be useful.

Therapy for symptomatic relief can be very helpful, including artificial tears, nasal saline douches, sialogogues (lemon drops), and parasympathomimetics such as pilocarpine. Treatment under the care of a rheumatologist may include nonsteroidal anti-inflammatory drugs for symptomatic relief of parotitis or corticosteroids for systemic inflammation or extraglandular involvement.

Long-term therapy with immunomodulating agents, such as hydroxychloroquine, methotrexate, mycophenolate mofetil, or cyclophosphamide, is often helpful and may be necessary, depending on the extent and severity of organ involvement [14-16].

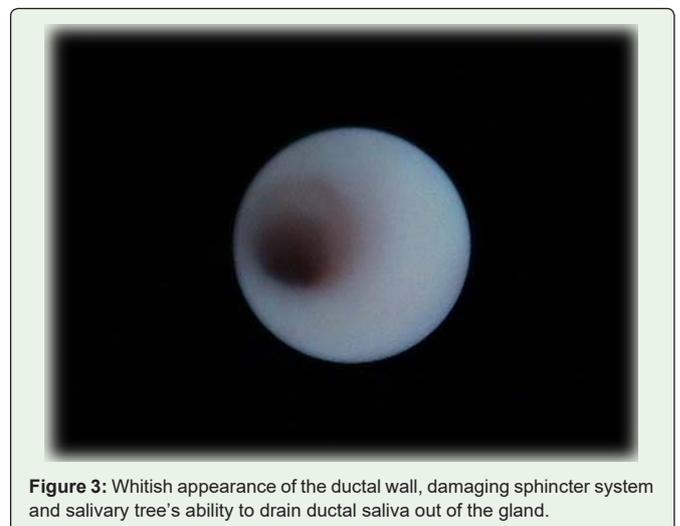


Figure 3: Whitish appearance of the ductal wall, damaging sphincter system and salivary tree's ability to drain ductal saliva out of the gland.

Conclusion

In summary, parotitis is a frequently encountered pediatric problem. Although infection, recurrent juvenile parotitis, and anatomic abnormalities are more common etiologies, primary pediatric SS should be considered when encountering a patient with recurrent parotitis.

These patients typically exhibit a distinctive laboratory and autoantibody profile and will benefit from early referral to a pediatric rheumatologist for treatment and monitoring for disease complications. Accurate diagnosis of pSS in the pediatric population is difficult. Recurrent parotitis should alert the clinician to the possibility of pSS especially if it does not respond to treatment with anti-inflammatory therapy and sialoendoscopic washing. The proposed pediatric criteria lack sensitivity and clinical utility. Until validated diagnostic criteria are available, clinical acumen will prevail as the gold standard. Prospective multicenter studies are needed to further characterize pSS in the pediatric population, and to better define and develop appropriate classification criteria. Consideration should be given to the inclusion of specific obligatory criteria such as the presence of SSA or SSB autoantibodies or classic histopathology changes on minor salivary gland biopsy. The development of an international database would enable epidemiologic and clinical study.

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