

Chapter

Sialoendoscopy in Juvenile Recurrent Parotitis That Could Be Primary Pediatric Sjogren's Syndrome

*Brigida Iorio, Roberto De Luca, Gianpaolo Tartaro
and Giuseppe Colella*

Abstract

Parotid swelling often is encountered in the pediatric population, essentially acute and self-limiting, which usually represents viral or bacterial infections. Less common etiologies include juvenile recurrent parotitis (JRP) or pneumoparotid or anatomic abnormalities. Sjögren's syndrome is common in JRP (40% almost). Levels of suspicion for an autoimmune disorder should be maintained for children affected by JRP, particularly in bilateral glands involvement in order to optimize diagnoses and facilitate treatment. Cytological examination of saliva, which is normally in children is acellular, shows granulocytes, lymphocytes, and in some cases 50% of bacteria. Sialoendoscopy typically shows whitish ductal walls and the presence of stenosis without evidence of solid obstructions and/or mucous membranes. Sialoendoscopic treatment can improve symptoms thanks to local anti-inflammatory therapy and sialoendoscopic washing.

Keywords: juvenile recurrent parotitis (JRP), Sjögren's syndrome (SS), sialoendoscopy, pediatric parotitis, sialoadenitis

1. Introduction

Juvenile recurrent parotitis (JRP) was firstly described by Rose in 1953 [1]. The prevalence of JRP in children is 10 times lower than in adults, yet it is the second leading cause of inflammatory salivary gland disease in children after mumps, and the differential diagnosis between them is difficult in young children [2].

JRP is defined when a minimum of 2 and maximum of 30 episodes per year of painful parotid inflammation occur, usually associated with fever, swelling, and erythema of the overlying skin gland [3, 4].

Sjögren's syndrome (SS) is an idiopathic systemic autoimmune disease affecting exocrine glands with classic symptom complex of dry eyes (xerophthalmia) and dry mouth (xerostomia). Extraglandular involvement in SS may affect many systems such as renal, central nervous system, and vascular and hematological ones. 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. Conversely, in

childhood and early adulthood SS is an extremely rare autoimmune condition (only 147 cases described in literature) [5, 6].

We hypothesized a higher prevalence of pSS in our young patients and we adopted a protocol with clinical, laboratory, and endoscopic examination. Sialoendoscopy has gained an increasing role in both diagnosis and treatment of JRP in a pediatric age. After its introduction in 1991 for the treatment of salivary disorders in adults, sialoendoscopy has also been validated as a safe technique in JRP treatment by Nahieli and Marchal [2, 7].

2. Clinical findings

2.1 JRP

JRP clinical symptoms include intermittent, usually unilateral swelling of the parotid gland, which occurs suddenly (over minutes or hours) and may persist for days or weeks [8]. The first episode typically occurs in scholar age, between 3 and 6 years, more often in males [9].

The etiopathology of JRP remains obscure; many factors have been suggested for the development of JRP including retrograde infection of the duct, viral or bacterial infection, autoimmune disease [10], disrupted enzyme activity [11], dental occlusion disorders [8, 12, 13], hypogammaglobulinemia, immunoglobulin A deficiency, and immunoglobulin G3 deficiency [14, 15]. These theories subtend a phagocyte dysfunction and humoral immunodeficiency. Another hypothesis considers JRP as mucosa-associated lymphoid tissue disorder, hyperplastic cells surrounding the ducts in a manner similar to chronic inflammatory disorders. The recurrent non-suppurative ductal inflammation in JRP leads to a squamous ductal metaplasia, progressive parotid atrophy, and insufficient salivary outflow throughout the ductal system [16].

Histologically, there are intraductal cystic dilatations of peripheral ducts with periductal lymphocytic infiltration, called sialectasis [2]. The ecstatic ducts are usually 1–2 mm in diameter and typically have a white appearance of the ductal layer without the healthy blood vessel coverage, when compared with a normal gland [9]. This aspect is believed to be the characteristic of JRP.

The diagnosis is based on the clinical history, and clinical examination shows parotidomegaly with or without mucopurulent salivary secretion from the Stensen's duct with papilla hyperemia. Diagnosis is confirmed by ultrasound and sialography [17, 18]. Some studies also describe the use of magnetic resonance (MR), MR-sialography, characterized by T1-weighted hypointensity and T2-weighted hyperintensity; MR and MR-sialography, and CT and sialo-CT are reserved for special cases in which expansionary diseases may be suspected [19].

Thanks to reproducible, safe, and economic rule salivary gland ultrasonography in the most used imaging, especially in childrens. Choi [20], Blatt [21], and Xie [17] proposed classification on sialographic images: Glandular homogeneity and the presence of hypoechogenic areas were evaluated and graded (range 0–3).

Grades 0–1 were considered to correspond to normal/nonspecific changes and grades 2–3 to correspond to pathologic changes.

Treatments in acute are based on antibiotics and anti-inflammatory corticosteroid therapy; rule of low-dose preventive corticosteroid was not confirmed. Chronic management intercurrent periods are based on massage, warmth, chewing gum use, and sialogogues. Sialography reduces frequency of acute episodes but also sialoendoscopy is useful in diagnostic and treatment of JRP. Many authors underline a reduction of episodes [2, 22, 23]. In summary, JRP is 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 obstructive parotid gland sialiectasis. Although the affected gland demonstrates distal duct sialiectasis, 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 is more commonly repeated every 3–4 months. Some recent studies (Houghton et al.) suggest that some symptoms, including recurrent conjunctivitis and mumps, if added to the diagnostic criteria encoded by AECG 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 manifested [24].

2.2 Juvenile Sjögren's syndrome

Juvenile Sjögren's syndrome is extremely rare; the average presentation time is around 10 years and affects 77% of girls. Juvenile Sjögren's syndrome begins with major salivary gland swelling but can involve in 50% of patient many organ systems with neurologic, dermatologic, musculoskeletal, vascular, gastrointestinal, respiratory manifestations. There are no criteria for Juvenile Sjögren's syndrome and the use of adult criteria has not been validated. Recently, ultrasound criteria were developed compared with promising results both with salivary gland biopsy and with seroprevalence of antibodies anti-Ro/SSA and anti-La/SSB. Homogeneity and the presence of hypoechogenic zones and cystic areas were evaluated by ultrasound of the parotid and submandibular glands on a scale from 0 to 3 where the degree 0–1 corresponds to normal and degrees 2 and 3 to the pathological changes [25]. Primary SS is a difficult diagnosis in childhood because of different presentation of symptoms. There are specific laboratory findings as lymphocytic infiltration of exocrine glands, hypergammaglobulinemia, anti-Ro/SSA, and anti-La/SSB antibodies but the manifestations of oral dryness are rarer and appear later, mainly concerning dry and cracked lips and tongue depapillation [26].

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) [24] have been validated for adults and include six 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 four 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) cannot 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. [27] were not validated because pediatric patients rarely have sicca syndrome or xerophthalmia at presentation (almost always present in the adult with 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. 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 bilateral involvement in order to timely recognize this disease and to facilitate treatment and screening for complications.

Treatment of pSS is based on anti-inflammatory and immunosuppressive drugs especially in patients with muscle and joint pain; salivary substitutes and cholinergic stimulators can be applied locally through oral dry [26].

2.3 Clinical experience

We reported our experience in the sialoendoscopic management of JRP that represents a valid and effective treatment.

We enrolled 16 consecutive patients aged between 5 and 17 years (mean 7.5), 10 males and 6 females, referred to 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 5 years. They 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 the presence or absence of autoantibodies suggestive of autoimmune disease, we analyzed typical SS antibodies (SS-A, SS-B, anti-dsDNA, anti-Sm, anti-RNP), antinuclear antibody (ANA), rheumatoid factor (RF). Ultrasound images were characterized by areas of ectasia and hypoechoic spots or sialoendoscopic features of whitish ductal walls, ectasia, and stenosis. Seven of 16 patients, 4 males and 3 females, with a mean age of 9.57 years, reported SS clinical and laboratories signs.

Exclusion criteria were the 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.

Patients thus selected were diagnosed with JRP and were treated with sialoendoscopy (intraductal wash of saline solution and steroids) or other anti-inflammatory drugs (**Figures 1** and **2**).

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.

The endoscopic-assisted procedures were performed in the ambulatory operating suite. After detection of the impaired gland, a local anesthesia with lidocaine 2% to the orifice region and a gradual dilatation of the duct orifice were performed, (thanks to increasing diameter lacrimal probes from 0000 to 0 size) and also with a standard salivary dilator. In this way, we reached 1.3 mm diameter, matching the outer diameter of the sialoendoscope diagnostic unit (Erlangen Sialoendoscope—Karl Storz). The larger (1.6 mm diameter) scopes were introduced as needed. The diagnostic unit 0.8 mm was introduced into the duct and was advanced forward, until reaching the ductal system and thanks to continuous lavage with isotonic saline solution. The plaques were washed out, and any structures were dilated. Mucous plugs and debris were removed with irrigation or with a forceps if necessary. At the end of the procedure, the ductal system was irrigated with a steroid- solution of Besamethasone, under direct vision while withdrawing the scope in order to treat the inflammation of the ductal epithelium (sialodochitis) and to promote the dilatation of ductal structures. In the post-operative, we prescribed Rovamycine 3000 U.I. every 12 hours for one week. The follow-up period was at least 12 months to 5 years. In all 16 patients, sialoendoscopic treatment was effective. We reported only 2 patients with a recurrence at 5 and 3 years, respectively. Seven of 16 patients (43,75%) presented SS features. In contrast to other cases of JRP resolution, the symptoms were not immediate, but an average of three sialoendoscopic treatments; the patients identified had the following characteristics (**Table 1**).



Figure 1.
Sialoendoscopic treatment in young patient.



Figure 2.
Sialoendoscopic image of duct.

pSS is probably underdiagnosed in childhood, as the mode of presentation can be large and are not rare long delays in diagnosis. And likely that some patients diagnosed with PSS in adulthood have experienced the onset of symptoms during

Pat	Age	Sex	Onset age (Months)	Symptoms	US	Endoscopic findings	Antibodies	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	negative RF, ANA, SSA, SSB, Sm, and RNP	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	negative RF, ANA, SSA, SSB, Sm, and RNP	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 footprint, ectasia of the duct system	positive RF; positive ANA; high-titer antibodies to SSA and SSB; negative anti-dsDNA, Sm, and RNP	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.	negative RF, ANA, SSA, SSB, Sm, and RNP	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	positive ANA; elevated SSA and SSB; negative anti-dsDNA, Sm, and RNP	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	negative RF, ANA, SSA, SSB, Sm, and RNP	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	negative RF, ANA, SSA, SSB, Sm, and RNP	Success at 18 months

Table 1. Clinical, ultrasound, endoscopic, and laboratory features of patients with suspected SS.

Adult	Children
Classic symptoms: xerostomia, xerophthalmia, and glans swelling	Atypical symptoms: gland swelling, tongue depapillation, dry and cracked lips
	Our experience: Swelling 7/7100% Dry mouth 7/7100% Dry eyes 4/7 57,14% SS antibodies 2/7 28,57%

Table 2.
Presentation differences in adults and children.

childhood. In fact, the clinical presentation of pSS in childhood may differ from the clinical presentation in adulthood (**Table 2**). The cases of pediatric PSS are reported to have a higher incidence of recurrent parotitis and a lower incidence of xerostomia and xerophthalmia. We found dry eyes in four patients. Laboratory and pathological findings in children with SS are positive antinuclear antibody (ANA) of 80% and autoantibodies to nuclear antigens Ro/SSA and La/SSB2 of only 70–75% [27]. In our experience, we have detected the presence of specific antibodies in only two patients.

In pediatric recurrent parotitis, laboratory evaluation and sialoendoscopy may be very helpful. 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 systemic lupus erythematosus, SLE, or another connective tissue disease) [5].

3. 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, especially no responsive to sialoendoscopic treatment. We have to consider pSS when JRP is assessed, despite the rareness of condition. Typical sign of sialiectasis is the same in JRP and in pSS as ultrasonography ones. Antibodies are not in all patients: anti-Ro/SSA 29% seronegativity and anti-La/SSB 33%; similarly, eye dryness is present in just over half of patients.

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. Reid et al.'s theory of ascending infections from the upper respiratory tract would merit a multicenter study of prevalence in patients undergoing adenotonsillectomy that should slow down the frequency of the disease. Our intention is to verify this deduction in the near future. 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 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.

In the majority of our patients, it is suggested that sialoendoscopy can offer a minimally invasive and gland-preserving approach to obstructive salivary glands diseases; this technique is proven to be safe, suitable in children under local anesthesia and able to improve swelling, pain, and social life.

Conflict of interest

The authors declare no conflict of interest. Neither author nor any member of their families received any material or financial gain or personal advancement in the production of this manuscript. We have read the Helsinki Declaration and have followed the guidelines in this investigation. For each patients, we have written parent's contents.

Notes/thanks/other declarations

Thanks to our young patients.

Author details

Brigida Iorio^{1*}, Roberto De Luca¹, Gianpaolo Tartaro² and Giuseppe Colella²

1 Maxillofacial Surgery Unit, Department of Medical, Surgical and Dental Speciality, Campania University "Luigi Vanvitelli" Naples, and Department of Neuroscience, Reproductive and Odontostomatologic Sciences, University of Naples Federico II, Naples, Italy

2 Maxillofacial Surgery Unit, Department of Medical, Surgical and Dental Speciality, Campania University "Luigi Vanvitelli" Naples, Italy

*Address all correspondence to: brigida.iorio@libero.it; brigida.iorio82@gmail.com

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