Clinical presentation and salivary gland histopathology of paediatric primary Sjögren's syndrome

C. Saad-Magalhães[1], P.B. de Souza Medeiros[1], J. Oliveira Sato[1], M.A. Custódio Domingues[2]

Departments of [1]Paediatrics and [2]Pathology, Botucatu Medical School, São Paulo State University (UNESP), Brazil.

Abstract

Objective

Explore the presentation, diagnostic criteria and exocrine gland histopathology of paediatric primary Sjögren's syndrome (PPSjS).

Methods

A case series of 8 children is reported and American-European Consensus Group (AECG-2002) criteria were examined, as well as minor labial salivary and lachrymal gland biopsies, which were scored by a pathologist blinded to outcome. For all cases, connective tissue diseases and parotid-related infectious disease were excluded.

Results

Age at onset varied from 5–13 years old; 6 were females, all followed from diagnosis up to the last visit (1–10 years). The main features at presentation were recurrent tender parotid swelling and sialectasis imaging, with decreased salivary function assessed by Tc-99 scintigraphy. Mild sicca symptoms were observed in 4/8 cases. Systemic features, including fatigue, myalgia, arthritis, tenosynovitis, joint contractures, transient Raynaud's and high ESR, were recorded at onset. Autoantibody profile was unremarkable for diagnosis, while lymphocytic infiltration of labial salivary glands and sialectasis were observed in all biopsies (8/8). In lachrymal glands, massive lymphocytic infiltration and lymphocytic gastritis were observed during complementary assessment. Flares were treated with low dose steroids and long-term use of hydroxychloroquine (5/8), although only 3/8 fulfilled AECG-2002 diagnostic criteria, throughout the disease course.

Conclusion

PPSjS is rare, slowly progressive and its early presentation is variable. Standardised diagnostic algorithms should include recurrent parotid swelling and early diagnosis should rely mostly on salivary and lachrymal gland histopathology in this age group.

Key words

children, focal sialadenitis, recurrent parotitis, sialectasis, Sjögren's syndrome

Claudia Saad-Magalhães, MD PhD
Priscila B. de Souza Medeiros, MD
Juliana Oliveira Sato, MD
Maria A. Custódio Domingues, MD PhD

Please address correspondence and reprint requests to:
Claudia Saad-Magalhães,
Associate Professor,
Paediatric Rheumatology Unit,
Botucatu Medical School,
São Paulo State University - UNESP,
18618-970 Brazil.
E-mail: claudi@fmb.unesp.br

Received on December 3, 2010; accepted in revised form on January 10, 2011.

© Copyright CLINICAL AND EXPERIMENTAL RHEUMATOLOGY 2011.

Competing interests: none declared.

Introduction

Primary Sjögren's syndrome is rare in childhood and may have different clinical presentations from adult Sjögren's syndrome (1, 2). The development of paediatric diagnostic criteria and standardised outcome measures are in demand and, overall, the syndrome may be underdiagnosed and undertreated (3). According to previously published series (4-13), it is slowly progressive and a standardised diagnostic algorithm needs to include recurrent parotid swelling.

This case-series report aimed to outline and evaluate clinical features, salivary gland functional assessment, laboratory and biological markers, histopathology and diagnostic criteria in a paediatric series of primary Sjögren's syndrome.

Methods

A retrospective case-notes review study was conducted in a single centre. Analysis of clinical and immunological features and histopathological scoring was conducted by a pathologist blinded to outcome.

All patients with a conclusive or suspected diagnosis of primary Sjögren's syndrome, attending the paediatric rheumatology outpatient clinic of a reference hospital, followed from 1997 to 2009, were included. Signs, symptoms and investigations were outlined in order to fulfill diagnostic criteria according to the American-European Consensus Group (AECG-2002) (14). All patients underwent differential diagnosis to exclude parotid-related infections.

Clinical indicators of ocular and oral symptoms were recorded. Ocular symptoms (dry eyes, recurrent conjunctivitis) were confirmed by an ophthalmologist using age-appropriate tests. Oral symptoms (recurrent parotitis, parotid swelling) and all related extraglandular features were recorded and compared. Parotid gland imaging by ultrasound was recommended in all cases with parotid swelling or recurrent tender parotitis (15).

Histopathology examination was performed by minor salivary gland biopsy on the intraoral border of the lower lip, under local anesthesia. This procedure is considered safe (16), although limited tissue sample quantity was observed in those of younger age. An average "focus score" was determined using at least 50 lymphocytes in a 4 mm^2 surface for a focus score ≥1. Focus scores were classified as follows: grade 0, absence of histological alterations; grade 1, mild lymphocytic infiltrate; grade 2, moderate lymphocytic infiltrate; grade 3, formation of lymphoid nodule; and grade 4, presence of more than one lymphoid nodule (17, 18). Grades 3 and 4 are indicative of Sjögren's syndrome. Other tissue samples, such as lachrymal glands or gastric mucosa, were obtained following specific indication.

Results

Eight cases were diagnosed as Paediatric primary Sjögren's syndrome (PPsjS) by the attending physician, although only 3/8 fulfilled AECG criteria (14). Age at onset varied from 5-13 years of age, 6 patients were female and follow-up varied from 1 to 10 years. Patient clinical features are outlined in Table I. Ocular symptoms were present in 5/8 patients, represented mainly by recurrent conjunctivitis. Allergic conjunctivitis was excluded and all were treated with humidifier eye drops. Mild oral symptoms were observed in 3/8 cases, with complications involving dental caries. Salivary function analysis was only possible by salivary gland scintigraphy. In cases of functional impairment, the uptake and release of technetium Tc-99 pertechnetate was diminished. Although scintigraphy is costly and unspecific, other functional assessments have age limitations. All cases with recurrent parotitis underwent ultrasound imaging, which indicated sialectasis. Systemic features, such as fatigue, myalgia, tenosynovitis, high ESR were recorded, and were dominant symptoms in 3/8 patients, at onset. Joint contractures were observed in 2/8 patients, osteoporotic fractures in 1/8 and transient Raynaud's in 3/8. Autoantibody profile was unremarkable in determining diagnosis, while lymphocytic infiltration of labial glands and sialectasia was present in all biopsies (8/8), although only 5 had focus scoring compatible with Sjögren's syndrome definite diagnosis. In lachrymal

Table I. Systemic and glandular features and diagnostic criteria fulfilled according to the American-European Consensus Group (AECG-2002) in a paediatric series.

Case	1	2	3	4	5	6	7	8
Gender	Female	Female	Female	Male	Female	Female	Female	Male
Clinical features	Arthralgia, Myalgia Osteomalacia Migraine, Raynaud's Lymphocytic gastritis	Anemia, Arthritis, Tenosynovitis Dry skin, Eczema Enlarged lymph nodes Raynaud's	Fatigue, Polyarthritis, Tenosynovitis Corneal abrasions	Recurrent Parotitis	Recurrent Parotitis	Swollen parotid glands Enlarged lymph nodes Raynaud's	Recurrent orbital swelling	Recurrent Parotitis
ESR	High	High	High	High	Normal	High	High	Normal
ANA titers	Negative	1: 83, 920	1: 10, 240	1: 640	1: 160	1:160	Negative	Negative
Rheumatoid Factor	Positive	Positive	Positive	Positive	Negative	Positive	Negative	Negative
Other autoantibodies	Negative	anti-Scl 70	Anti-DNA, anti-Sm, anti-ENA RNP low titres	Negative	Negative	Negative	ANCA-myelopero-xidase	Negative
Immunoglobulin*	–	High IgG, IgM, IgA, IgE	High IgA and IgG	–	High IgA	High IgM Low IgA	–	
Subjective ocular symptoms	Yes	Yes	Yes	No	Yes	No	Yes	No
Objective oral symptoms	Yes	Yes	Yes	No	No	No	No	No
Objective ocular signs I. Schirmer I test ≤5mm/ 5min II. Rose Bengal score ≥4	Dry eyes	Dry eyes	Dry eyes	Dry eyes	No	–	Dry eyes	–
Focus score in lower lip biopsy ≥1	Grade 3	Grade 4	Grade 4	Grade 3	Grade 1	Grade 4	Grade 1	Grade 1
Objective salivary gland involvement (at least one) I. Salivary gland scintigraphy II. Parotid sialography III. Sialometry	I-Scintigraphy decreased function	I-Scintigraphy decreased function	I-Scintigraphy decreased function	–	I-Scintigraphy normal function	I-Scintigraphy normal function	I-Scintigraphy decreased function	I-Scintigraphy decreased function
Anti SSA/SSB autoantibodies	SSA +	SSA +	Negative	SSA +	Negative	–	Negative	Negative
AECG criteria (2002)	Yes	Yes	Yes	No	No	No	No	No

(-): test not performed, ESR: erythrocyte sedimentation rate, ANA: antinuclear antibodies, (*) abnormal values according to reference for age.

glands, massive lymphocytic infiltration (Fig. 1. I and J) and lymphocytic gastritis (Fig. 1. H) were also observed in cases 7 and 1, respectively (Table I). High titer positivity for ANA and Rheumatoid Factor (Latex test) was verified in 5/8 and 4/8 patients, respectively. Treatment included non-steroidal antiinflammatory drugs, low dose steroids and hydroxychloroquine (5/8). Of note, one patient presenting with recurrent orbital swelling (Table I, case 7) showed a prompt response to a short course of high dose prednisone.

The retrospective review of labial salivary gland histopathology, conducted by a pathologist who was blinded to outcome, indicated lymphocyte infiltration in all samples. One limitation observed during the analysis of the tissue samples collected from the younger patients, was the small quantity of collected material. Despite this limitation, a variable spectrum of plasma cells and lymphocyte infiltrates, sialectasis and gland tissue atrophy was observed and described (Fig. 1). The only lachrymal gland biopsy obtained showed massive lymphocyte infiltration, consisting of organized follicles with germinative centers. Gastric mucosa was examined in one female patient due to symptomatic gastritis, revealing specific lymphocytic infiltration.

Discussion

Sjögren's syndrome is a chronic inflammatory systemic autoimmune disorder mainly affecting exocrine glands, particularly the salivary and lachrymal glands, which results in sicca syndrome, a glandular dysfunction that may represent end-stage organ-damage. Diagnosis requires special consideration in paediatrics, to avoid delay. The spectrum of clinical manifestations, in agreement with previous series reports (4-13) and a systematic review (12), indicates it is slowly progressive. It has also been shown that Sjögren's syndrome phenotype in children seems much more variable than adults.

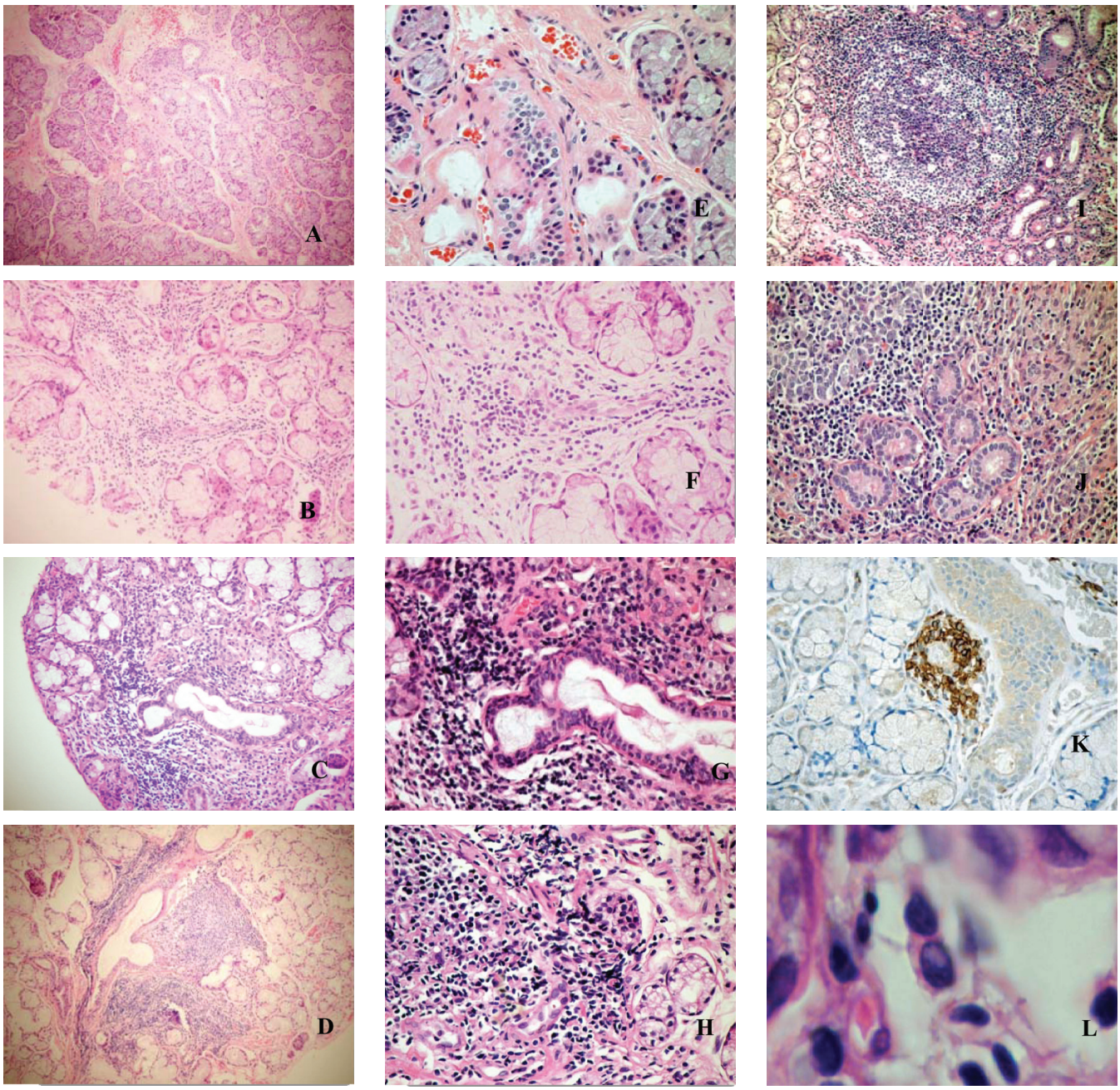

Fig. 1. Minor labial salivary gland histopathology grade and Sjögren syndrome: **A**) grade 1, mild lymphocytic infiltrate; **B**) grade 2, moderate lymphocytic infiltrate; **C**) grade 3, formation of lymphoid nodule; **D**) grade 4, presence of more than one lymphoid nodule. 200x HE. **E**) Interstitial sclerosis. **F**) Lymphoid infiltrate **G**) Sialectasis. 400x HE. **H**) Gastric mucosa showing lymphoid infiltrate permeating the glandular epithelium of the muscular layer. 400x HE. **I** and **J**) Lachrymal gland compromised by intense lymphoid infiltrate with formation of lymphoid follicles and germinative centres. 200x HE. **K**) CD20 expression in the interstitial lymphoid infiltrate of salivary glands. 400x IMH. **L**) Plasmocyte exhibiting Dutcher bodies. 1000x HE.

Comparative review resulted in the application of the more sensitive criteria proposed (9, 12, 13). Similar to other reports, diagnosis in the present series relied on expert opinion and investigations conducted according to a standardized care protocol, including consideration of recurrent parotitis as an important feature. The AECG-2002 (14, 19) classification criteria were fulfilled in only 3 out of 8 cases for conclusive Sjögren's syndrome diagnosis. The remaining cases did not reach such criteria due to absence of sicca symptoms. However, other clinical features, including parotid or lachrymal gland swelling, non-specific autoantibodies, histopathology of minor labial salivary glands and abnormal exocrine function, were compatible with early diagnosis of Sjögren's syndrome, according to the physician's evaluation. Lower frequency of SSA-SSB autoantibodies occurred, but positive ANA, Rheumatoid factor and hypergammaglobulinemia were observed more frequently.

Systemic complications (20, 21), such as interstitial nephritis, thyroiditis, meningoencephalitis, interstitial lung disease, purpura and polyclonal hyper-

gammaglobulinemia were not observed, but it has to be acknowledged that this is a small series with a relatively short follow-up.

One case presented recurrent orbital swelling and the initial biopsy of the lachrymal glands revealed massive lymphocyte infiltration. This case might have been classified as the previously named Mikulicz's syndrome (22), but no mild or suspected salivary gland involvement was observed. Apart from the series from 1927 mentioned above and isolated reports, the prevalence of this condition in paediatric patients is unknown.

Differential diagnosis includes recurrent, non-autoimmune parotitis in children, infectious parotitis and tumors. All these conditions were excluded by serology and imaging exams. Benign recurrent parotitis of childhood is a common cause of parotid swelling (23, 24). It is more frequent in boys from 3-6 years of age and the recurrent parotitis tends to cease near puberty. Congenital dilatation of salivary ducts may contribute to its pathogenesis and other salivary infections, including HIV, Epstein-Bar and coxsackie virus, may be also involved. Diffuse infiltrative lymphocytosis syndrome in HIV-infected children may be clinically indistinguishable from that caused by Sjögren's syndrome (21).

In the present series, it was considered that recurrent parotitis may precede Sjögren's syndrome (24, 25) in the same way Sjögren syndrome itself may precede other autoimmune disease, by several years (13). All patients underwent minor labial salivary gland assessment and scoring by an expert pathologist, as well as other specific investigations and a close follow-up.

There is no controlled therapeutic study involving paediatric patients; thus, hydroxychloroquine was prescribed for most patients following current recommendations for adults to control disease progress, reserving immunosuppressive treatment for life-threatening extraglandular manifestations (26).

Histopathology was important in all cases, regardless of clinical criteria, and this finding is in agreement with a previous series by Schuetz *et al*. (13). The most prominent pathological finding was focal lymphocyte infiltration of salivary glands in a periductal distribution and epithelial infiltration with B cell hyperplasia. The extreme disease expression of the Sicca complex, observed only in case 2, correlated with histological grade, periductal fibrosis and gland atrophy (Fig. 1. E).

In view of the limited knowledge regarding long-term outcome, the findings obtained suggest that these cases, even if incomplete according to current classification criteria or specific diagnosis, support that children with recurrent parotid swelling, irrespective of the presence or absence of Sicca syndrome, should be considered part of the paediatric spectrum of Sjögren syndrome.

References

1. DROSOS AA, TSIAKOU EK, TSIFELAKI NT, POLITI EN, SIAMAPOLOU-MOVRIDOU A: Subgroups of primary Sjögren syndrome. Sjögren's syndrome in male and paediatric Greek patients. *Ann Rheum Dis* 1997, 56: 333-5.
2. STILLER M, GOLDER W, DÖRING E, BIEDERMAN T: Primary and secondary Sjögren's syndrome in children: a comparative study. *Clin Oral Invest* 2000, 4: 176-82.
3. VENABLES PJW: Sjögren's syndrome. *Best Pract Res Clin Rheumatol* 2004, 18: 313-29.
4. FRANKLIN DJ, SMITH RJ, PERSON DA: Sjögren's syndrome in children. *Otolaryngol Head Neck Surg* 1986; 94: 230-5.
5. MIZUNO Y, HARA T, HATAE K *et al*.: Recurrent parotid gland enlargement as an initial manifestation of Sjögren syndrome in children. *Eur J Pediatr* 1989; 148: 414-6.
6. HARA T, NAGATA M, MIZUNO Y, URA Y, MATSUO M, UEDA K: Recurrent parotid swelling in children: Clinical features useful for differential diagnosis of Sjögren's syndrome. *Acta Paediatr* 1992; 81: 547-9.
7. ANAYA JM, OGAWA N, TALAL N: Sjögren's syndrome in childhood. *J Rheumatol* 1995; 22: 1152-8.
8. OSTUNI PA, IANNIELLO A, SFRISO P, MAZZOLA G, ANDRETTA M, GAMBARI PF: Juvenile onset of primary Sjögren's syndrome: report of 10 cases. *Clin Exp Rheumatol* 1996; 14: 689-93.
9. BARTUNKOVA J, SEDIVA A, VENKOVSKY J, TESAR V: Primary Sjögren's syndrome in children and adolescents: proposal of diagnostic criteria. *Clin Exp Rheumatol* 1999; 17: 381-6.
10. THOURET MC, SIRVENT N, TRIOLO V, MONTHEILH C, MICHIELS J, BOUTTÉ P: [Primary Gougerot-Sjögren syndrome in a 13-year-old girl]. *Arch Pediatr* 2002; 9: 142-6.
11. SINGER NG, TOMANOVA-SOLTYS I, LOWE R: Sjögren's syndrome in childhood. *Curr Rheumatol Rep* 2008; 10: 147-55.
12. 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: 2225-32.
13. SCHUETZ C, PRIEUR A, QUARTIER P: Sicca syndrome and salivary gland infiltration in children with autoimmune disorders: when can we diagnose Sjögren syndrome? *Clin Exp Rheumatol* 2010; 28: 434-9.
14. MANTHORPE R: Sjögren's syndrome criteria. *Ann Rheum Dis* 2002; 61: 482-4.
15. HOCEVA A, AMBROZIC A, ROZMAN B, KVEDER T, TOMSIC M: Ultrasonographic changes of major salivary glands in primary Sjögren's syndrome. Diagnostic value of a novel scoring system. *Rheumatology* 2005; 44: 768-72.
16. CAPORALI R, BONACCI E, EPIS O, BOBBIO-PALLAVICINI F, MOBINI P, MONTECUCCO M: Safety and usefulness of minor salivary gland biopsy: retrospective analysis of 502 procedures performed in a single centre. *Arthritis Rheum* 2008; 59: 714-20.
17. WATERHOUSE JP, DONIACH I: Post-mortem prevalence of focal lymphocytic adenitis of the submandibulary salivary glands. *J Path Bact* 1966; 91, 53-64.
18. CHRISHOLM DM, MASON DK: Labial salivary gland biopsy in Sjögren's disease. *J Clin Pathol* 1968; 21: 656-60.
19. VITALI C, BOMBARDIERI S, MOUTSOPOULOS HM *et al*.: Preliminary criteria for the classification of Sjögren's syndrome: results of a prospective concerted action supported by European Community. *Arthritis Rheum* 1993; 36: 340-7.
20. KOBAYASHI I, FURUTA H, TAME A *et al*.: Complications of childhood Sjögren syndrome. *Eur J Pediatr* 1996; 155: 890-94.
21. 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; 32:1603-6.
22. SCHAFFER AJ, JACOBSEN AW: Mikulicz's syndrome: a report of 10 cases. *Am J Dis Child* 1927; 34: 327-46.
23. LEERDAM CM, MARTIN HCO, ISAACS DJ: Recurrent parotitis of childhood. *J Paediatr Child Health* 2005; 41: 631-4.
24. ALLEN R, MUNRO J: Recurrent parotitis and Sjögren Syndrome. *J Paediatr Child Health* 2003; 39: 157-62.
25. TANAKA H, ONODEA N, ITO R *et al*.: Subclinical Sjögren's syndrome: a significant 67gallium accumulation in the orbits and parotid glands. *Acta Paediatr Jpn* 1998; 40: 621-3.
26. FOX RI, DIXON R, GUARRASI V, KRUBEL S: Treatment of primary Sjögren's syndrome with hydroxychloroquine. *Lupus Suppl* 1996: S31-6.