ΣΤΟΜΑ 1998; 26 : 197-203

Sjogren's syndrome: A review article

J. GIDARAKOU[1], L. PAPANAOUM[1]
Laboratory of Stomatology, Aristotle University of Thessaloniki, Greece
Director: Prof. P. Papanagiotou

Σύνδρομο Sjogren: Βιβλιογραφική ανασκόπηση

Ι. ΓΙΔΑΡΑΚΟΥ[1], Λ. ΠΑΠΑΝΑΟΥΜ[1]
Εργαστήριο Στοματολογίας του Αριστοτελείου Πανεπιστημίου Θεσσαλονίκης
Διευθυντής: Καθ. Παν. Παπαναγιώτου

SUMMARY

Sjogren's Syndrome was first reported in 1933. It is considered to be an autoimmune disease, while genetic factors, several viruses and other environmental parameters may be implicated in the initiation and development of the syndrome. The characteristic triad of the symptoms is comprised of xerostomia, xerophthalmia and degenerative lesions in the joints. Many organs and systems of the organism may be affected, thus making the diagnosis of the syndrome difficult. The diagnostic process includes numerous parameters and tests; at present there are seven published criteria proposed to be used for the diagnosis of Sjogren's Syndrome. Clinical indications show an increased risk of malignancy for patients with Sjogren's Syndrome, as premalignant and malignant changes in the salivary glands are reported. The treatment is symptomatic, as the exact etiology of the syndrome remains unknown. As different organs and systems can be affected, each patient receives different treatment. Radical therapy is imperative only to those patients experiencing severe functional disorders or life-threatening complications.

KEY WORDS: Sjogren's syndrome, autoimmune, xerostomia

ΠΕΡΙΛΗΨΗ

Η νόσος του Sjogren ανακοινώθηκε για πρώτη φορά το 1933. Θεωρείται αυτοάνοση νόσος, ενώ γενετικοί παράγοντες, διάφοροι ιοί και άλλες περιβαλλοντικές παράμετροι μπορούν να εμπλέκονται στην έναρξη και την εξέλιξη του συνδρόμου. Η χαρακτηριστική τριάδα των συμπτωμάτων περιλαμβάνει την ξηροφθαλμία, την ξηροστομία και εκφυλιστικές αλλοιώσεις από τις αρθρώσεις. Επιπρόσθετα, αναφέρεται ξηρότητα στο ρινικό βλεννογόνο, στο φάρυγγα και στην ανώτερη αναπνευστική οδό, με συνέπεια οι ασθενείς να υποφέρουν από βρογχίτιδα, πνευμονία και επίσταξη. Λιγότερο συχνά παρατηρείται χρόνια ηπατική βλάβη, δυσλειτουργίες του κεντρικού νευρικού συστήματος, πορφύρα, πολυμυοπάθεια και διαταραχές των ανοσοσφαιρινών. Καθώς πολλά όργανα και συστήματα του οργανισμού μπορεί να επηρεαστούν, η διάγνωση του συνδρόμου καθίσταται δύσκολη. Η διαγνωστική διαδικασία περιλαμβάνει μια πληθώρα από παραμέτρους και τεστ που διαθέτουν άλλοτε άλλη ευαισθησία. Προς το παρόν υπάρχουν επτά δημοσιευμένα κριτήρια που χρησιμοποιούνται για τη διάγνωση της νόσου. Κλινικές ενδείξεις δείχνουν αυξημένο κίνδυνο εμφάνισης κακοήθειας στο σύνδρομο Sjogren, καθώς αναφέρονται προ-κακοήθεις και κακοήθεις αλλοιώσεις στους σιαλογόνους αδένες. Σχετικά σύνηθες εύρημα είναι η εμφάνιση ψευδολεμφώματος ή κακοήθους λεμφώματος στα αρχικά ή μετέπειτα στάδια της νόσου. Η θεραπεία του συνδρόμου είναι συμπτωματική, εφόσον η αιτιολογία του παραμένει άγνωστη. Καθώς διαφορετικά όργανα και συστήματα προσβάλλονται σε κάθε περίπτωση, η θεραπευτική αγωγή είναι διαφορετική για κάθε ασθενή. Η ξηροστομία αντιμετωπίζεται συμπτωματικά κυρίως με τη χορήγηση τεχνητού σάλιου ή σιαλαγωγών φαρμάκων. Τα

ΛΕΞΕΙΣ ΚΛΕΙΔΙΑ: Σύνδρομο Sjogren, αυτοάνοσο, ξηροστομία

Received at 19.3.98. Accepted at 27.4.98.
[1] Fifth-year student in the Dentistry School

Στάλθηκε στις19.3.98. Εγκρίθηκε στις 27.4.98.
[1] Πεμπτοετής φοιτητής της Οδοντιατρικής Σχολής

τεχνητά δάκρυα και ειδικές ενυδατικές αλοιφές χρησιμοποιούνται για την αντιμετώπιση της ξηροφθαλμίας. Πιο ριζική θεραπεία απαιτείται για εκείνους μόνον τους ασθενείς που υποφέρουν από έντονες λειτουργικές διαταραχές ή εμφανίζουν επιπλοκές που θέτουν τη ζωή τους σε κίνδυνο. Τα κορτικοστεροειδή μετριάζουν τα έντονα φλεγμονώδη συμπτώματα και η κυκλοφωσφαμίδη βελτιώνει τη λειτουργία των εξωκρινών αδένων σε ορισμένους ασθενείς. Η χρήση αυτών των φαρμάκων περιορίζεται σε εκείνους τους ασθενείς που παρουσιάζουν έντονες ρινικές, δερματικές ή πνευμονικές εκδηλώσεις.

INTRODUCTION

Sjogren's Syndrome (SS) is an autoimmune disorder, which affects many systems of the organism and is characterized by generalized desiccation, exocrine hypofunction and serological abnormalities[1]. It was first identified by a Swedish physician, Hhenrik Sjogren in 1933[1]. Sjogren's Syndrome was primarily characterized by the typical triad xerostomia, keratoconjunctivitis sicca (KCS) and rheumatoid arthritis[2,3,4]. It is a chronic disorder, with its major clinical manifestations resulting from changes in the exocrine glands[5,6]. Due to the fact that the Sjogren's Syndrome represents an immunologic attack on exocrine organs, the term «autoimmune exocrinopathy» has been proposed[5,7,8,9,10,11,12].

It has been suggested that genetic factors and specifically certain HLA class II antigens have increased prevalence in Sjogren's Syndrome patients[13]. HLA-DR antigens on epithelial cells in the exocrine glands may play a role in the initiation or perpetuation of the autoimmune reactions[14,15]. Moreover some studies have proposed that environmental factors are responsible for the syndrome or are associated to it[5,13]. Indirect evidence has supported a role for herpeviruses [especially Epstein-Barr virus(EBV)] and a potential role for retroviruses[12,16]. Other viruses have been proposed as being associated with SS. These include human retrovirus type 6 (Fox et al., 1993)[17] and HTLV-1 as well as the hepatic C virus (HCV)[5,18,19,20,21,22,23]. Nevertheless a consistent picture does not emerge from the studies of viruses and their relation to SS. There is no direct, solid evidence of a pathogenic role for viruses in this disease in humans[5]. Thus the etiology of the syndrome remains obscure.

There are two types of Sjogren's Syndrome, the primary and the secondary type[5]. Primary SS involves the eyes and the mouth, while patients with secondary SS may have a connective tissue disease such as rheumatoid arthritis, lupus, polymyositis (inflammation of the muscles), scleroderma (thickening and stiffening of the skin- abnormality of the collagen) or polyartiritis nodosa (inflammation of the arteries)[14]. Primary SS presents characteristic inflammatory cell involvement of both salivary and lacrimal glands; on the other hand, the secondary type includes another defined connective tissue disease, in addition to exocrine disorder[5]. Both types lead to exocrine dysfunction and tissue loss of the affected organ[3]. Other researchers discern three forms of the particular syndrome: a primary form (sicca complex), a secondary form accompaning rheumatoid arthritis or occasionally another connective tissue disease and a third form characterized mainly by lymphoproliferation of either a benign infiltrative or a malignant nature[13]. However, in all forms of the syndrome the histopathological feature that prevails is the lymphocytic proliferation

The Sjogren syndrome shows no discrimination or eclectic appearance in any race[3]. It is most commonly diagnosed in middle-aged females4,24. SS of the young people has however been rarely described and the clinicopathologic features in young patients have not been well described[25]. Nevertheless, it is reported that the syndrome may be more rife among young people than previously suspected[4,10,26,27].

CLINICAL FEATURES

The most common early symptom includes progressive development of dry eyes (keratoconjunctivitis sicca) or dry mouth (xerostomia) in a patient with rheumatoid arthritis or the more rapid development of a severe oral and ocular dryness (the sicca complex) often accompanied by episodic parotitis in an otherwise healthy individual[3].

Xerostomia is attributed to the atrophic procedures taking place in the parenchyma of the major salivary glands. Out of 50% of the cases with SS the parotid glands display inflammatory swelling and have a dough-like texture. This symmetrical, often recurrent condition be may also accompanied by fever, tenderness or erythema. Enlargement of the remaining major glands is more rare[3,4,28].

In some cases dysphagia is reported.The oral mucosa is dry, red, while pseudomembranes and ulcers may be present. The tongue is also dry and reddish; the lips often have angular cheilitis. In later stages and due to the atrophy of the epithelium, the oral mucosa and the

tongue gradually become smooth and glossy[4]. The distressing symptoms of salivary insufficiency include: difficulty with chewing, swallowing and phonation, adherence of food to buccal surfaces, fissures and ulcers of the tongue, buccal membrane and lips (particularly at the corners of the lips), the need for frequent ingestion of liquids (particularly at meal times) and rampant dental caries due to xerostomia. Dryness may also involve the nose, the posterior pharynx, the larynx and the tracheobronchial tree; as a result the patients suffer from hoarseness, epistaxis and recurrent otitis media, bronchitis or even pneumonia[3].

As far as the ophthalmic lesions are concerned, the most prevalent symptom is the KSC, which is characterized by the decrease in the production and alteration in the quality of the tears, foreign body sensation and dryness, accompanied by hyperemia of the oral mucosa and the keratoid tissue[7,11]. The eyes are described as feeling «sandy» or «gritty». Other symptoms include photosensitivity, eye fatigue, itching and a «filmy» sensation that interferes with vision[3,4].

Besides salivary and lacrymal glands, the normal function of other exocrine glands may also be radically affected. This can lead to loss of pancreatic secretions, dermal dryness, lack of vaginal secretion, hypo- or achlorhydria and renal abnormalities[3,4,29,30].

Joints are also affected. Some of the lesions which may appear are rheumatoid arthritis, subacute arthritis and multiarthritis. All joints can be affected, but the vertebral column may be selectively affected. In further, during the last stages the whole system of the joint is bound to be destroyed due to degenerative process[4].

Raynaud's phenomenon occurs in 20% of the patients, while in approximately 5% chronic thyroiditis of the Hashimoto's type is found[3]. Autoimmune thyroid disease and involvement of the peripheral nervous system are also reported[31,32,33,34].

As a whole, the most prevalent clinical symptoms of the SS are presented in the following table I[3]:

TABLE I

Clinical Presentation of Sjogren's syndrome

1. Sicca Symplex - xerophthalmia and xerostomia
2. Rheumatoid arthritis or other connective tissue disorder
3. Salivary gland enlargement
4. Purpura - nonthrombocytopenic; hyperglobulinemic; vasculitis
5. Renal tubular acidosis or other tubular disorder
6. Polymyopathy; Neuropathy -peripheral or cranial, particularly trigeminal
7. Central nervous system disorder
8. Chronic liver disease
9. Chronic pulmonary disease
10. Pseudolymphoma ; Lymphoma local or generalized
11. Immunoglobulin disorder - Cryoglobulinemia; macroglobulinemia

DIAGNOSTIC CRITERIA OF SJOGREN'S SYNDROME

Sjogren's Syndrome is often referred to as the «great mimicker», because its symptoms often imitate other diseases[1]. Various parameters have been used in the diagnosis of the SS. Salivary gland biopsy, sialography, ultrasonography, Schirmer's test, positive Waaler-Rose reaction, Latex-test, Coombs-test and the parotid salivary flow rate[4,6,35,36,37,38,39,40,41,42,43,44]. Biopsy of a minor salivary gland is usually used as a safe and easy diagnostic method[6,45,46,47]. A positive labial gland biopsy showing focal accumulation of mononuclear cells and periductal lumphocytic infiltration has been considered to be rather specific for Sjogren's Syndrome[14,48,49]. Sialochemical examinations may be used in order to help the diagnostic process[7,44]. Sialography reveals narrow salivary ducts and prolonged detention of the substance used in this diagnostic process[4,6]. Ultrasonography uses ultra-sounds in order to depict the lesions in the exocrine glands[36,40]. Schirmer's test is used in the diagnosis of KCS. It is a test of tear production, in which a piece of filter paper is inserted over the conjunctival sac of the lower lid with the end of the paper hanging down, thus measuring the moisture on the projecting paper[4,36]. The Waaler-Rose test is an agglutination test for rheumatoid factor (RF) using tanned sheep red blood cells (SRBC) coated with subagglutinating amounts of rabbit anti-SRBC IgG antibody[36]. Another test is the Latex-test, which is used in order to detect the presence of specific antibodies. It is a type of agglutination test in which antigen to a given antibody is absorbed to latex particles and mixed with a solution for agglutination of these latex[4]. Coombs-test is used to detect the presence of nonagglutinating antibodies against red cells. It uses anti-human globulin antibody to agglutinate red blood cells coated with the nonagglutinating antibody.

The parotid salivary flow is measured by stimulating secretion with citric acid; normally, 1-

2 ml of saliva per minute are gathered in middle-aged patients[6]. At present there are seven published criteria proposed for the diagnosis of Sjogren's Syndrome (Daniels, 1996)[50,51]. The most commonly used criteria are the ones from the Copenhagen group (Manthorpe et al., 1986)[52], the Scripps Institute (Fox et al., 1986a)[53] and a European study group (Vitali et al., 1993)[54]. There are marked differences in the tests used and the sensitivity of these tests. The results may be influenced by the definition of Sjogren's Syndrome used in the study, while comparison of the studies is complicated by differing diagnostic criteria for Sjogren's Syndrome[5].

MALIGNANT-PREMALIGNANT CHANGES IN SALIVARY GLANDS

Autoimmune disorders are known to be associated with malignant lymphoma (Santana and Rose, 1992)[55]. In some cases autoimmune diseases may complicate the lymphoma, but more often malignancy arises in the context of chronic lymphoproliferative disorders, which are thought to have an autoimmune basis (Isaacson and Spencer, 1993)[56]. These include, for example, chronic gastritis (possibly leading to gastric cancer), Hashimoto's thyroiditis and Sjogren's Syndrome[3,5].

Bunin and Talal (1963)[57] first reported the association between SS and lymphoma; it was shown that the risk of lymphoma development in SS is increased 44-fold (Kassan, Moutsopoulos 1978)[58], which apart from Hashimoto's thyroiditis (Holm et al., 1985)[59] appears to be the highest risk of any of the autoimmune diseases.

Pseudomalignant or malignant lymphoproliferation may be present initially or may develop in later stages of the illness. Most lymphomas belong to the B-cell lineage, as demonstrated by immunophenotyping and immunogenotyping (Zulman et al., 1978)[60]. These cells frequently have irregular cleaved nuclei and resemble centrocytes (Hyjek et al., 1982)[61]. Pseudolymphoma is an intermediate stage in the transition from benign to malignant lymphoproliferation[3]. This term was used to describe a clinically suspicious lymphoproliferation in the salivary tissues, where a diagnosis of lymphoma could not be established definitely[65].

Other clinical indications of an increased risk of malignancy include persistent or greatly increased parotid swelling, generalized lymphathenopathy and splenomegaly[3].

TREATMENT

Because of the unknown etiology of SS, there is only a symptomatic treatment available, which alleviates discomfort associated with the symptoms and limits the damaging local effects of chronic xerostomia and xerophthalmia.

Xerostomia is one of the main symptoms. It is relieved by chewing gum, drinking water and eating sugar-free candies given as sialagoges in order to stimulate the secretion of saliva[3], providing that there remains some glandular activity intact[62].

Drugs may occasionally be used to stimulate saliva flow, but generally they are not very effective and have many side-effects[62].

Due to the decrease in the saliva flow, the patient must be encuvased instructed in order to keep his teeth clean, so as to reduce the danger of dental caries[16]. This may be obtained by lessening the sugar intake and by controlling the formation of dental plaque. High level of oral hygiene is required, while topical fluoride application is helpful[3,4].

Infections of the oral cavity are not rare and are attributed to the atrophic epithelium. Oral candidiasis is very common to patients with SS; it may be treated with anitfungal tablets for a prolonged course with separate treatment of dentures[3,6].

Patients are also prone to mouth ulcers. Chlorexidine mouthwash helps them heal more rapidly. The antiseptic is used in a relatively low concentration as the mucosa is quite sensitive[4,62].

As far as the eyes are concerned, ocular dryness responds to the use of artificial tears. A variety of «tear substitutes» is available. Soft contact lenses may be used to protect the cornea, but increase the risk of infection. Saran wrap occlusion or diving goggles may be worn at night in an attempt to provide tear evaporation. Topical steroid use should be avoided unless specifically indicated, because cornea thinning and subsequent perforation is bound to occur[3].

Lubricant ointments, especially to night, can be of great help in some patients in whom symptoms are not put under control despite frequent use of drops[62].

Inflammation of the conjunctiva may be proven catastrophic for the ocular surface. Nowadays a new approach is being tried in order to reduce the risk of inflammation and the subsequent unfavorable consequences. Such agents used contain cyclosporin and bendezac ly-

sine[62].

Some medicines must be avoided to be prescribed to SS patients. Medication possessing anticholinergic effects reduce the activity of the autonomous nervous supply of the lachrymal glands. Antihistamines and a few travel sickness pills may inhibit tear secretion, so they must not be used by patients suffering from eye dryness[62].

Moreover, diuretics, antihypertension drugs and antidepressants may further diminish lachrimal and salivary secretion[3].

The atmospheric environment exercises an effect to the rate of evaporation; thus, hot, dry summer days, air conditioned rooms and frosty winter days are not indicated for dry eye sufferers because of low humidity. Room humidifiers and plenty of plants with large leaves indoors may be practical ways of increasing humidity[62].

More radical therapy including corticosteroid or immunosupressive drugs and use of radiation is necessary only to those patients with severe functional disorders or life-threatening complications. Cyclophosphamide has improved exocrine gland function in some individuals and decreased extraglandular lymphoid infiltrates. Nevertheless, as malignant lymphoma may appear as an implication of the syndrome, radiation and immunosupressive therapy using corticosteroid drugs is better not used. This treatment is restricted to those patients with severe renal, skin or pulmonary manifestations[3,6].

In conclusion, Sjogren's Syndrome is an autoimmune disease, the etiology of which is not very clear, as specific autoimmunogen and pathogenic autoantibodies have not yet been identified in either the primary or secondary form of the syndrome. Many diagnostic tests have been proposed, but the results may vary as each method uses different criteria. Future research studies will be directed at identifying the environmental factors that initiate the disease, mechanisms of tolerance which are overcome as the disorder develops and more optimal therapies to restore glandular function and reverse the autoimmune process.

We would like to thank our supervisor, lecturer Mrs. Belazi, as her help and guidance were indispensable for the completion of this article.

REFERENCES

1. Sjogren H. Zur Kenntnis der Keraticonjunctivitis sicca, Keratitis filiformis bei Hypofunktion der Tranendrusen. Acta Ophth K'hvn 1933; 2: 151.
2. Tohru S, Hiroshi F, Makoto A, Akemi M, Masanobu S, Akira S, Shigeta M. Periductal lympocytic infiltration of salivary glands in Sjogren's Syndrome with relation to clinical and immunologic findings. Oral Surg Med Oral Pathol 1991; 71:179-83.
3. Tatal N. Overview of Sjogren's Syndrome. J Dent Res, February 1987; 66: 672-4.
4. Papanagiotou P. Stomatology: Diagnosis and Treatment concerning diseases of the oral mucous. Third Edition, Thessaloniki 1994; p.186-90.
5. Fox PC, Speight PM. Current concepts of autoimmune exocrinopathy: immunologic mechanisms in the salivary pathology of Sjogren's Syndrome. Crit Rev Oral Biol Med 1996; 7: 144-58.
6. Karakasis D. Lessons of maxilofacial surgery, part three. First Edition, Thessaloniki, 1986; 248-51.
7. Bloch K. et al. Sjogren's Syndrome, Medicine, 1965; 44:187.
8. Bertram U. Xerostomia. Clinical aspects, pathology and pathogenesis. Acta Odont Scand 1967; 25: 126.
9. Sheern, M.: Sjogren's Syndrome. W. Saunders Co., Philadelphia 1974.
10. Sussman R, Stewart S, Stoopack J, Jerold Th. Sjogren's Syndrome. An autoimmune disease. J Oral Surg 1972; 30: 23.
11. Shafer W, Hine M. and Levy B. A text book of oral pathology, 3rd edition. W. B. Saunders Co., Philadelphia, 1974.
12. Gardiner P. Primary Sjogren's Syndrome. Baillieries Clin Rheumatol, February, 1993; 7: 59-77.
13. Fox R.I. Sjogren's Syndrome: immunobiology of exocrine gland dysfunction. Adv Dent Res, April, 1996; 10: 35-40.
14. Thorn JJ, Oxholm P. Sialochemistry in Sjogren's Syndrome: a review. J Oral Pathol Med 1989; 18:457-68.
15. Fox R.I. Bumol T, Fantozzi R, Schreiber R. Expression of histocompatibility antigen HLA-DR salivary gland epithelial cells in Sjogren's Syndrome. Arthritis Rheum 1986; 29: 1105-11.
16. Mariette X. Sjogren's Syndrome and viruses. Rev Med Intern 1994; 15: 601-6.
17. Fox R.I, Luppi M, Kang H, Ablshi D, Josheps S. Detection of high levels of human herpes virus-6 DNA in a lymphoma of a patient with Sjogren's Syndrome (letter). J Rheumatol 1993; 20 : 764-5.
18. Wen S. et al.: Association of Epstein-Barr virus (EBV) with Sjogren's Syndrome: differential EBV expression between epithelial cells and lymphocytes in salivary glands. Am J Pathol Nov. 1996; 149: 1511-7.
19. Pinheiro Sr. et al.: HTLV-1 associated uveitis, myelopathy, rheumatoid arthritis and Sjogren's Syndrome. Arq Neuropsiquiatr Dec 1995; 53: 777-81.
20. Rigby Sp, et al. Absence of HTLV-1 tax in Sjogren's Syndrome (letter). Arthritis Rheum., Sep. 1996; 39: 1609-11.
21. Nishioka K. HTLV-1 arhtropathy and Sjogren's Syndrome. J. Acquir. Immune Defic Syndr Hum Retrovir-

ol, 13 Suppl., 1996; 1: S57-62.
22. Porter Sr, et al. Lack of association between hepatitis C virus and Sjogren's Syndrome. Oral Dis, June 1996; 2: 183-4.
23. Boscagli A, Hatron Py, Canva-Delcambre V, Hachulla E. Janin A, Paris C, Devulder B. Sicca syndrome and hepatitis C virus infection: a Gougerot-Sjogren pseudo-syndrome? Rev Med Intern 1996; 17: 375-80.
24. Gorlin R, Pindborg J, Cohen M. Syndromes of the head and neck. 2nd Ed. Mc.Graw-Hill, New York, 1976.
25. Tohru S, Hiroshi F, Noriyuki T, Masa-aki H, Masanobu S. Akira A. Sjogren's Syndrome in the adolescent, report of four cases. Oral Surg, Oral Pathol 1994; 77: 368-72.
26. Anderson D. Sjogren's Syndrome in the young. Report of a case. J Oral Med 1982; 37/1: 21.
27. Chudwin D. et al. Spectrum of Sjogren's Syndrome in children. J Pediatr 1981; 98: 213.
28. Yazawa, Y., Okada, K., Fukui, J., Kitanishi, T., Kitajima, K.: Clinical features of Sjogren's Syndrome. Nippon-Jibiinkoka-Gakkai-Kaiho, Apr. 1997; 100: 429-35.
29. Ostuni Pa. et al.: Pancreatic exocrine involvement in primary Sjogren's Syndrome. Scand J Rheumatol 1996; 27: 74-81.
30. D'Ambrosi A, Verzola A, Gennaro P, Gatto S, Cattelani M, La-Corte R. Functional reserve of the exocrine pancreas in Sjogren's Syndrome. Recenti. Prog Med Jan 1997; 88: 21-5.
31. Scofield Rh. Autoimmune thyroid disease in systematic lupus and Sjogren's Syndrome. Clin Exp Rheumatol 1996; 14: 321-30.
32. Rodeir G et al.: Involvements of the peripheral nervous system and primary Gougerot-Sjogren's Syndrome. Rev Med Interne 1996; 17: 558-62.
33. Panthumchinda K.: Multiple cranial palsies as a presenting symptom in primary Sjogren's Syndrome. J Med Assoc Thai, 1989; 72: 291-4.
34. Heylen A, Devogelaer Jp, Noel H, Nagant-De- Deuxchaisnes C. Axonal polyneuropathy without vasculitis, follicular lymphoma and primitive sicca syndrome. A rare association. Clin Rheumatol 1990; 9: 84-7.
35. Laskaris G. Colored Atlas of Stomatology (Diagnosis-Therapy). Autoimmune Diseases, p. 162, Athens, January 1986.
36. Papanagiotou I. Medical Microbiology and Immunobiology. Thessaloniki, 1994; Volume A. p. 243-5.
37. Daniels Te, et al. Is sialography effective in diagnosing the salivary component of Sjogren's Syndrome? Adv Dent Res 1996; 10: 25-8.
38. Sreenby Lm, et al. The use of whole saliva in the differential diagnosis of Sjogren's Syndrome. Adv Dent Res 1996; 10: 17-24.
39. Xu Kp, et al.: Biopsy of labial salivary glands and lacrimal glands in the diagnosis of Sjogren's Syndrome. J Rheumatol 1996; 23: 76-82.
40. Makula E, et al.: Parotid gland ultrasonography as a diagnostic tool in primary Sjogren's Syndrome. Br J Rheumatol 1996; 35: 972-9.
41. Vitali C, Giuggioli C, Monti P, Rossi G, Wu Dh, d'Ascanio A, Chiellini S, Gabriele M, Bombardieri S. Statistical evaluation of different clinical and serological parameters for the diagnosis of Sjogren's Syndrome. Clin Exp Rheumatol 1989; 7: 191-5.
42. Morais D, Perusse R. Sjogren's Syndrome and differential diagnosis of parotid hypertrophy. J Can Dent Assoc 1991; 57: 135-9.
43. Vitali C, Bombardieri S, Moutsopoulos Hm, Balestrieri G, Bencivelli W, Bjerrum Kb, Braga S, Coll J, de-Vita S, et al. Preliminary criteria for the classification of Sjogren's Syndrome. Results of a prospective concerted action supported by the European Community. Arthritis Rheum 1993; 36: 340-7.
44. Andonopoulos, Ap., Tzanakakis, Gn., Christophidou, M.: Light microscopy of dried saliva in the evaluation of xerostomia of the sicca syndrome. A preliminary report. J Rheumatol 1992; 19: 1390-2.
45. Tarpley TM, Anderson LG,and White CL. Minor salivary gland involvement in Sjogren's Syndrome. Oral Surg 1974; 37: 64-74.
46. Greenspan JS, et al. The histopathology of Sjogren's Syndrome in labial salivary gland biopsies. Oral Surg 1974; 37: 212-229.
47. Meloni F, Transi Mg, Nigro D, Belli S, Bernardi A, Botazzi M, Valesini G. La biopsia delle ghiandole salivari minori nella sindrome di Sjogren. Clin Ter 1990; 135: 367-72.
48. Sreebny L, Xing Zhu W. Whole saliva and the diagnosis of Sjogren's Syndrome: an evaluation of patients who complain of dry mouth and dry eyes. Part 2: Immunologic findings. Gerontology 1996; 13:44-8.
49. Daniels Te. Labial salivary gland biopsy in Sjogren's Syndrome. Assessment of a diagnostic criterion in 362 suspected cases. Arthritis Rheum 1984; 27: 147-56.
50. Daniels Te. Sjogren's Syndrome: Clinical spectrum and current diagnostic controversies. Adv Dent Res 1996; 10: 3-8.
51. Fox RI, Saito I. Criteria for diagnosis of Sjogren's Syndrome. Rheum Dis Clin North Am 1994; 20: 391-407.
52. Mantherpe, R., Oxholm, P., Prause, Ju., Schiodt, M.: The Copenhagen criteria for Sjogren's Syndrome. Scand J Rheumatol 1986; (Suppl. 61): 19-21.
53. Fox Ri, Robinson Ca, Curd Jg, Kozin F. Howell, Sjogren's Syndrome: Proposed criteria for classification. Arthritis Rheum 1986a; 29: 577-85.
54. Vitali C, Bombardieri S, Moutsopoulos Hm, Bencivelli W, Bernstein Rm, et al. Preliminary criteria for the classification of Sjogren's Syndrome. Results of a prospective concerted action supported by the European Community. Arthritis Rheum 1993; 36: 340-7.
55. Santana V, Rose Wr. Neoplastic lymphoproliferation in autoimmune disease: An updated review. Clin Immunol Immunopathol 1992; 63: 295-213.
56. Isaacson Pg, Spencer J. Autoimmunity and malignancy. In: Isenberg DA, Horsefall AC, editors. Oxford: BIOS Scientific Publishers Ltd 1993; 189-201.
57. Bunim Jj, Talal N. The association of malignant lym-

phoma with Sjogren's Syndrome. Trans Assoc Am Phys 1963 76: 54-6.
58. Kassan Ss, Thomas Tl, Moutsopoulos Hm, Hoover R, Kimberly Rp, Budman Dr. Increased risk of lymphoma in sicca syndrome. Ann Inter Med 1978; 89: 888-92.
59. Holm Le, Blomgren H, Lowhagen T. Cancer risks in patients with chronic lumphocytic thyroiditis. N Engl J Med 1985; 312: 601-4.
60. Zulman J, Talal N. Evidence that the malignant lymphoma of Sjogren's Syndrome is a monoclonal B-cell neoplasm. N Engl J Med 1987; 299: 1215-20.
61. Hyjek E, Smith Wj, Isaacson Pg. Primary B-cell lymphoma of salivary glands and its relationship to myoepithelial sialoadenitis. Human Pathol 1988; 19: 766-76.
62. British Sjogren's Syndrome Association : Sjogren's Syndrome: An advisory guide for patients and doctors, 1993; 7-26.