The Journal of Laryngology and Otology
November 1986. Vol. **100.** pp. 1299–1305

Sjögren's syndrome

by

A. G. D. MARAN, M.D., F.R.C.S., F.A.C.S., (Edinburgh)

It is a great honour to be invited to give the thirty-first Yearsley Lecture some 28 years after my old chief, Dr Simson Hall, gave his lecture on the mobilization operation in the treatment of otosclerosis. It is also a great pleasure to commemorate Dr Yearsley's memory because, among his many other attributes, he had connections with both Edinburgh and St Andrew's. Although Yearsley was primarily an otologist and although 24 out of the previous 30 lectures have been related to otology, your committee has allowed me some licence in order to talk about Sjögren's disease which has attracted a great deal of interest in the last 15 years, for 3 reasons.

Firstly, it displays the widest range of autoantibodies in any disease process; secondly, it is the second commonest autoimmune disease after rheumatoid arthritis; and finally, it presents a model which is of research interest in the aetiology of cancer. Although it is primarily dealt with by rheumatologists, immunologists and oral surgeons, the otolaryngologist will see these patients not only with sialosis but also with nasal crusting, epistaxis, dysphagia, hoarseness and serous otitis media. Any physician faced with one feature of the syndrome should look for the multiple other features and should identify the disease as accurately as possible because of the known increased incidence of lymphoma.

History

At a meeting of the Society for Scientific Medicine in Koningsberg in 1888, Mikulicz presented the case of a 42-year-old Prussian farmer with a 7-month history of lacrimal and then sub-maxillary and parotid swelling without kerato-conjunctivitis sicca (KCS) or xerostomia. He removed two-thirds of the submandibular mass and found infiltration with small round cells and 2 months later he removed the residue. The condition then resolved and he published the case in 1892 in German but only in 1937 was it reproduced in the English language. His description was so partially correct that the aetiology was expanded over the next 20 years and conditions such as tuberculosis, gout, syphilis, sarcoid, lymphoma and leukaemia were added to make it Mikulicz's syndrome.

In 1925, Gougerot, a French dermatologist, described 3 patients with progressive atrophy of salivary glands, lacrimal glands, nasal, laryngeal and vulval glands. This was the first indication that the condition was a sicca syndrome.

In 1933, Henrik Sjögren, a Stockholm ophthalmologist, described the triad of xerostomia, KCS and arthritis. He reported clinical and histological findings in 19 women with xerostomia and KCS of whom 13 had chronic arthritis.

Based on the 1985 Yearsley Lecture.

https://doi.org/10.1017/S002221510010101X Published online by Cambridge University Press

Morgan and Castleman (1953) showed that, because of identical histological findings, Mikulicz's disease/syndrome was not a distinct and pathological entity but one manifestation of Sjögren's syndrome which was a more generalised symptom complex.

In 1952, Dr. Godwin described a lesion called benign lymphoepithelial lesion. Whether this exists or not is still a subject for debate but while most immunologists and haematologists hold the view that it is merely part of Sjögren's disease, Dr. Batsakis (1979) supports the view that it can occur as a local salivary gland disease. It is a pathological process that arises in the intralobular ducts like a punctate parotitis. As the ducts dilate their cells disrupt and epidermoid metaplasia begins. Lymphocytes aggregate around the ducts and the lumens become obliterated. Dr. Godwin thought that this was related to a lymphoreticular proliferative disease and his predictions have turned out to be correct. It is not yet clear whether a benign lymphoepithelial lesion evolves to malignancy or whether it is a part of an immunological disorder which is going to lymphoproliferative disease anyway.

Classification

1. Primary Sjögren's disease or the sicca syndrome consists of xerostomia and xerophthalmia without an associated connective tissue disease. These patients are often extremely disturbed by the dryness of the mouth and frequently show psychiatric disturbances. This type is frequently associated with a variety of extra-glandular manifestations.
2. Secondary Sjögren's syndrome shows the complete triad and in 48 per cent of cases the accompanying autoimmune disorder is rheumatoid arthritis. Also involved in this way may be systemic lupus, scleroderma, polymyositis, primary biliary cirrhosis, autoimmune liver disease, chronic graft versus host disease and a number of other rarer autoimmune disorders.
3. Benign lymphoepithelial lesion is limited to the salivary glands and has the same pathological processes of dilated ducts, flattened and disrupted cells and epidermoid metaplasia. This may proceed not only to lymphoma but also, in rare instances, to carcinoma.
4. Aggressive lymphocyte behaviour. This was described by Strand and Talal (1980) and this type is associated with widespread organ infiltration with lymphocytes together with prominent lymphadenopathy, termed pseudolymphoma. The chance of developing lymphoma is very much increased in this type.

Prevalence

There is a predilection for middle-aged and elderly females. In elderly persons in Scotland there is a high prevalence (16.7 per cent) of KCS which is equal in males and females. Xerostomia is also common in elderly females (18.2 per cent) but less common in elderly males (2.8 per cent). A definite sicca syndrome can be found in 3.5 per cent of females and 2.8 per cent of males over the age of 80. There is no association between the prevalence of autoantibodies and KCS or xerostomia in these people, suggesting that senile atrophy of the secretory apparatus rather than immunological injury is the underlying aetiology (Whaley *et al.*, 1972).

The incidence of KCS and rheumatoid arthritis is 11 per cent whereas xerostomia only occurs in 1 per cent. It is now obvious that sub-clinical inflammation of the salivary gland is almost universal in patients with connective tissue diseases although the extent of tissue destruction is often insufficient to produce the overt sign of secretory insufficiency. Autopsy examination of submandibular glands in patients with rheumatoid arthritis shows lymphocytic infiltrates in all cases (Waterhouse and Doniach, 1966).

Clinical Features

Sjögren's syndrome is a multi-system disease involving almost every system in the body.

https://doi.org/10.1017/S002221510010101X Published online by Cambridge University Press

1. *Oral Symptoms*

The main oral symptoms are dryness of the mouth which in turn alters the bacterial oral population causing dental caries and stomatitis and glossitis. Secondary candidiasis is an accompanying feature. Severe xerostomia may cause lip cracking and chronic ulceration of the lip, angular stomatitis and fissuring and ulceration of the tongue and atrophy of the oral mucosa.

2. *Ocular Symptoms*

The diagnosis of kerato-conjunctivitis sicca is made by identifying keratitis with Rose Bengal dye and slit lamp examination; the sicca element is measured by a Schirmer's test. Some patients may have Sjögren's syndrome with normal tear secretion and may have only pronounced lacrimal gland enlargement.

The patient complains of a foreign body sensation in the eye, burning, redness, itchiness, photosensitivity and an inability to tolerate contact lenses if worn.

3. *Salivary Gland Symptoms*

Contrary to popular teaching in otolaryngology, Sjögren's syndrome is not primarily a disease of the major salivary glands and, in a study of 171 patients with Sjögren's syndrome, intermittent salivary gland enlargement was present in only 21.6 per cent. Persistent salivary gland enlargement was found in only 4.1 per cent and 74.3 per cent had no clinical salivary gland enlargement (Whaley *et al.*, 1973). Patients who do have parotid gland involvement have a poor prognosis because they have a higher chance of developing lymphoma. It must, therefore, be considered whether or not a parotidectomy is warranted in patients with Sjögren's syndrome who present with enlarged parotid glands on a diagnostic basis.

4. *Respiratory Tract*

In the upper respiratory tract nasal crusting, dryness, epistaxis, serous otitis media, hoarseness and a dry throat have all been described (Bloch *et al.*, 1965; Doig *et al.*, 1971).

In the lower respiratory tract, cough with the inability to get rid of tough tenacious sputum going on to atalectasis and fibrosis and pneumonia with effusion, have all been described. Diffuse interstitial fibrosis can occur due to lymphoid infiltration of the pulmonary interstitium and the type of infiltrate may range from the benign lymphocytic interstitial luminitis through pseudolymphoma to malignant lymphoma (Weisbrot, 1976; Strimlan *et al.*, 1976).

5. *Gastrointestinal Tract*

Dryness of the pharynx and oesophagus make mild dysphagia very common and post-cricoid webs have been described (Doig *et al.*, 1971) Achlorhydria has been described and gastric biopsies from patients with Sjögren's syndrome have shown chronic inflammatory cell infiltration of the mucosa (Jebavy *et al.*, 1961). Abnormal oesophageal motility may also occur (Rameriz-Mata, 1975).

Atrophic gastritis is reasonably common in Sjögren's syndrome but overt pernicious anaemia occurs in only 3.5 per cent of Sjögren's syndrome patients. Sjögren's syndrome involving the stomach differs from true pernicious anaemia because there is no increased incidence of Sjögren's syndrome in pernicious anaemia (Williamson *et al.*, 1950).

6. *Pancreas*

Acute pancreatitis, chronic relapsing pancreatitis and pancreatic calcification have all been described. Investigation of pancreatic function in these patients with secretin and pancreozymin suggests that widespread or subclinical pancreatic disease is a common feature of Sjögren's syndrome (Hradsky *et al.*, 1967).

7. *Liver*

Hepatomegaly is found in 18–23 per cent of Sjögren's syndrome patients but, following the introduction of mitochondrial antibody

https://doi.org/10.1017/S002221510010101X Published online by Cambridge University Press

test as a marker and autoimmune liver disease, it is becoming increasingly obvious that autoimmune liver disease is a feature of Sjögren's syndrome. There is also histological evidence of peripheral lymphocytic infiltration features indistinguishable from clinically obvious primary biliary cirrhosis (Doniach and Walker, 1969).

8. *Kidney*

Sjögren's syndrome patients may develop renal tubular defects and acute glomerulonephritis. There is diminished resorption of uric acid, aminoaciduria and glycosuria (Talal *et al.*, 1968).

9. *Thyroid*

There is an increased incidence of autoimmune thyroiditis in Sjögren's disease. A clinical thyroid disease occurs in 10–14 per cent of patients (Bloch *et al.*, 1965). There is no increased incidence of Sjögren's disease in patients with autoimmune thyroid disease, however.

10. *Other Systems*

In the skin, xerodermia, vulval dryness, vitiligo and lipodystrophy have been described. In the central nervous system, trigeminal neuropathy, facial paralysis and other cranial neuropathies are listed and Raynaud's phenomenon has been frequently seen.

Bloch *et al.*, (1965) first drew attention to the penicillin and gold allergy these patients suffer and there has also been a high incidence of allergic reactions to levamisole noted (Balint *et al.*, 1977).

Investigations

1. *History*

The disease is commoner in middle-aged females and is much commoner in northern Europe than southern Europe. The patient will complain of a dry eye with its complications and a dry mouth with its complications. They may complain of nasal dryness and sinus discomfort and difficulty in getting rid of chest secretions. They may be deaf from serous otitis media and will probably show evidence of a connective tissue disorder like rheumatoid arthritis.

2. *Examination*

A general medical examination is done as well as an otolaryngology examination. To measure the dryness of the eye, a Schirmer's test is done and values of less than 5 mm. of tearing in 5 minutes are considered abnormal.

Salivary flow rates are measured with Carlsson Crittenden cups with maximal stimulation with lemon juice. A flow rate of less than 0.5 ml. per minute suggests a xerostomia.

3. *Radiology*

A sialogram will often show evidence of globular sialectasis. The findings vary from major to minor and sialography does not hold a diagnostic specificity in this condition. It does, however, lend some important pointers to the aetiology. It was in 1955 that Thackray first pointed out that globular sialectasis was different from fusiform sialectasis. Whereas fusiform sialectasis represents a true degeneration of the gland, globular sialectasis represented the escape of the radio-opaque media through the ducts and alveoli to sit as globules in the stroma of the parotid gland. It is thus a demonstration of 'leaky' ducts and more will be said of this later.

4. *Biopsy*

The definitive diagnostic test is the sublabial biopsy which is carried out under local anaesthetic. At least 4 globules of fat must be removed from the back of the lower lip and the specimen must be graded histologically according to Greenspan *et al.*, (1974) and Tarplay *et al.*, (1974). According to this grading,

https://doi.org/10.1017/S002221510010101X Published online by Cambridge University Press

which is on a 1:4 basis, the pathologist must count foci of lymphocytes; one focus is defined as an aggregate of 50 or more lymphocytes, histiocytes or plasma cells per HP field.

Biopsy of the major salivary glands is not as helpful as a sublabial biopsy although the recent availability of monoclonal antibodies to parotid gland may change this.

Immunopathology

It is not known whether the widespread immunological abnormalities in this condition are of immediate clinical relevance or are *in vitro* epiphenomena. What is certain, however, is that they do provide clues to the aetiology of the condition.

There is a raised ESR and diffuse elevation of all 3 major serum immunoglobulins. Ninety per cent have antinuclear antibodies, 80 per cent have antibodies to gammaglobulin, 30 per cent have rheumatoid arthritis-associated nuclear antigens and 15 per cent have rheumatoid arthritis precipitins. Rheumatoid arthritis, alone or with Sjögren's syndrome, is associated with HLA-DR4 antigens and the sicca syndrome is associated with HLA-DR3 antigens. Precipitating antibodies to 2 nuclear antigens SS-A and SS-B are closely associated with Sjögren's syndrome of the sicca variety (Isenberg *et al* 1982; Alexander *et al.* 1983).

The main immunological problem in Sjögren's disease is a defect in the T suppressor cell activity which may interfere with the production of essential antibodies (Fox *et al.*, 1982; Isenberg *et al.*, 1984). A decrease in the suppressor cell activity allows the escape of autoantibody secreting clones of B cells.

The possibility that Sjögren's disease is viral-related has received attention. Even though the familial clustering of Sjögren's syndrome would support a role for an infectious aetiological agent, there is no evidence to support this. Cultures of saliva have failed to reveal a higher that expected prevalence of bacterial micoplasmal or viral agents. There is, however, one report on ultrastructural studies of the bronchial epithelium of a patient with Sjögren's syndrome which showed particles similar to the murine leukaemic type A virus particles associated with tumours in laboratory and wild mice (Sutinen and Huhti, 1977).

This raises the possible hypothesis of the duct being the antigen. It could be that the cytomegalovirus which is prevalent in northern Europe infects salivary tissue inducing the formation of rheumatoid factor and antinuclear factor. This in turn could stimulate B lymphocyte proliferation and periductal infiltration. This may be the explanation of the 'leaky' ducts that are often seen as globular sialectasis on sialography.

The models for studying malignant transformation in Sjögren's disease are the New Zealand black and white F1 mice. These mice develop lesions in the salivary and lacrimal glands which are indistinguishable from Sjögren's syndrome. They have defects of all cell-mediated immunity and have autoantibodies. If they survive long enough they develop lymphoma which are all non-Hodgkin's type and are almost exclusively extra-salivary. Immunological typing of the lymphoma indicates that they are monoclonal B cell neoplasms.

This is identical to the lymphoma that arises in the human. There is a 44 times greater than normal risk of developing lymphoma if a patient has the sicca syndrome and this is often likened to the 80 times greater than normal risk that immuno-suppressed transplant recipients have of developing tumours. In real terms this means that a patient with the sicca syndrome has a 1:6 chance of developing lymphoma.

The prognosis of a lymphoma in salivary tissue arising in the sicca syndrome is very gloomy. Very few survivors have been reported after 2 years. This is in contradistinction to other primary lymphomas arising in the salivary glands where 4 year survival rates of up to 90 per cent have been described (Nime *et al.*, 1976).

The other tumour that can develop is a carcinoma in a pre-existing benign lymphoepithelial lesion. Over 50 such cases have been reported and most have been in the parotid. None of these patients have had a past history of Sjögren's disease and 25 have been described in Eskimos. It takes the form of an

https://doi.org/10.1017/S002221510010101X Published online by Cambridge University Press

anaplastic carcinoma so typical that it has been called an Eskimoma.

Treatment

The main treatment of Sjögren's disease is symptomatic. For the dry eye, 0.5 per cent methyl cellulose drops are helpful and synthetic saliva often helps the dry mouth although sucking confectionery is probably as good. The patients need to have good dental care and there is perhaps a place for steroids in the treatment of recurrent parotitis.

As pointed out earlier, however, with the increased risk of lymphoma development, an enlarged parotid gland should certainly be biopsied and possibly removed for diagnostic purposes. The virtually fatal outcome of lymphoma developing in a Sjögren's disease may be a manifestation of the immunological background in which it arises but it may also be due to diagnostic delay. Certainly early parotidectomy can do little other than good, Similarly, if the patient presents with any enlarged neck nodes, they should also be biopsied. Chest and sinus symptoms should be investigated with the appropriate endoscope.

Conclusion

In conclusion, therefore, one can put forward a hypothesis for the causation of this very interesting autoimmune disease relating it to the cytomegalovirus infection and duct antigenicity. We must be aware that many of these patients may present early in the ENT department with dryness symptoms related to the nose or throat and/or serous otitis media. The diagnosis should be kept in mind with this type of patient since the risk of lymphoma development is so high and the transformation to lymphoma apparently so fatal at the moment. Early parotidectomy is recommended for those patients who develop parotomegaly.

References

ALEXANDER, B. L., ARNETT, F. C., PROVEST, T. T. and STEVENS, M. B. (1983) Sjögren's syndrome: association of anti-ro (SS-A) antibody with vasculitis, haematologic abnormalities and serologic hyperactivity. *Annals of Internal Medicine,* **98:** 155–159.

BALINT, G., GHOBAREY, A., CAPELL, H., MADKOUR, M., DICK, W. C., FERGUSON, M. M. and ANWAR, M. (1977) Sjögren's syndrome, a contraindication to levamisole treatment. *British Medical Journal,* **2:** 1386–1387.

BATSAKIS, J. G. (1979) Tumours of the head and neck—Second edition. Williams and Wilkins, Baltimore, p. 108.

BLOCH, K. J., BUCHANAN, W. W. and WOHL, M. J. (1965) Sjögren's syndrome, a clinical, pathological and seriological study of 62 cases. *Medicine,* **44:** 187–231.

DOIG, J. A., WHALEY, K., DICK, W. C., NUKI, G., WILLIAMSON, J. and BUCHANAN, W. W. (1971) Otolaryngological aspects of Sjögren's syndrome. *British Medical Journal,* **4:** 460–463.

DONIACH, D. and WALKER, J. G. (1969) A unified concept of autoimmune hepatitis. *Lancet,* **1:** 813–815.

FOX, R. L., CARSTENS, S. A., FONG S., ROBINSON, C. A., HOWELL, F. and VAUGHEN, J. H. (1982) Use of monoclonal antibodies to analyse peripheral blood and salivary gland lymphocyte upsets in Sjögren's syndrome. *Arthritis and Rheumatic Diseases,* **25:** 419-426.

GODWIN, J. T. (1952) Benign lymphoepithelial lesion of the parotid gland; report of 11 cases. *Cancer,* **5:** 1089–1103.

GOUGEROT, H. (1925) Progressive et atrophie des glands salivaires et muqueuses de la Bouche de conjunctives. *Bulletin de la Societe Francaise Dermatologie Syphilographie,* **32:** 376–381.

GREENSPAN, J. S., DANIELS, T. E., TALAL, N. and SYLVESTER, R. A. (1974) Histopathology of Sjögren's syndrome in labial salivary gland biopsies. *Oral Surgery,* **37:** 217–229.

HRADSKY, M., BARTOS, V. and KELLER, O. (1967) Pancreatic function in Sjögren's syndrome. *Gasteroenterologia,* **108:** 252–260.

ISENBERG, D. A., HAMMOND, L., FISHER, C., GRIFFITHS, M., STEWART, J. and BATTAZZO, G. F. (1982) Predictive value of SS-B precipitating antibodies in Sjögren's syndrome. *British Medical Journal,* **284:** 1738–1740.

ISENBERG, D. A., ROWE, D., TOOKMAN, A., HOPP, A., GRIFFITHS, M., PAICE, E., STEWART, J. and BEVERLEY, P. L. (1984) An immunohistological study of secondary Sjögren's syndrome. *Annals of Rheumatic Diseases,* **43:** 470–476.

JEBAVY, M., VON HRADSKY, M. and HEROUT, V. (1961) Gastric biopsy in patients with Sjögren's syndrome. *Zetoschrift für Medizin,* **43:** 16–930.

MIKULICZ, J. (1937) Concerning peculiar symmetrical disease of lacrimal and salivary glands. *Medical Classics,* **2:** 165–186.

https://doi.org/10.1017/S002221510010101X Published online by Cambridge University Press

MORGAN, W. S. and CASTLEMAN, B. A. (1953) Clinical pathologic study of Mikulicz's disease. *American Journal of Pathology,* **29:** 471–503.

NIME, F. A., COOPER, H. S. and EGGLESTON, J. C. (1976) Primary malignant lymphomas of the salivary glands. *Cancer,* **37:** 906–912.

RAMERIZ-MATA, M. (1975) Abnormal oesophageal motility in primary Sjögren's syndrome. *Journal of Rheumatology,* **3:** 63–69.

SJÖGREN, H. (1933) Zur kenntnis der kerato conjunctivitis sicca. *Acta Ophthalmologica,* Supplement II, 1–151.

STRAND, V. and TALAL, N. (1980) Advances in the diagnosis and concept of Sjögren's syndrome. *Bulletin of Rheumatic Diseases,* **30:** 1046–1052.

STRIMLAN, C. V., ROSENOW, E. C. and DIVERTIE, M. V. (1976) Pulmonary manifestations of Sjögren's syndrome. *Chest,* **70:** 354–361.

SUTINEN, S. and HUHTI, E. (1977) Ultrastructure of lymphoid interstitial pneumonia. Virus like particles in broncheolar epithelium of a patient with Sjögren's syndrome. *American Journal of Clinical Pathology,* **67:** 328–333.

TALAL, N., ZISMAN, E. and SCHUR, P. H. (1968) Renal tubular acidosis, glomerulonephritis and immunologic factors in Sjögren's syndrome. *Arthritis and Rheumatic Diseases,* **11:** 774–781.

TARPLAY, T. M., ANDERSON, L. G. and WHITE, C. L. (1974) Minor salivary gland involvement in Sjögren's syndrome. *Oral Surgery* **37:** 64–74.

THACKRAY, A. C. (1955) Sialectasis. *Archives of the Middlesex Hospital,* **5:** 151–159.

WATERHOUSE, J. P. and DONIACH, I. (1966) Postmortem prevalence of focal lymphocytic adenitis of the submandibular salivary gland. *Journal of Pathology and Bacteriology,* **91:** 53–64.

WEISBROT, I. M. (1976) Lymphomatoid granulomatosis of the lung associated with a long history of benign lymphoepithelial lesions of the salivary glands and lymphoid interstitial luminitis. Report of a case. *American Journal of Clinical Pathology,* **66:** 792–797.

WHALEY, K., WILLIAMSON, J. and WILSON, T. (1972) Sjögren's syndrome and autoimmunity in a geriatric population. *Age,* **1:** 197–201.

WHALEY, K., WILLIAMSON, J. and CHISHOLM, D. (1972) Sjögren's syndrome. Sicca components. *Quarterly Journal of Medicine,* **42:** 279–285.

WILLIAMSON, J., PATERSON, R. W., MCGAVIN, D. D., GREIG, W. R. and WHALEY, K. (1970) Sjögren's syndrome in relation to pernicious anaemia and idiopathic Addison's disease. *British Journal of Ophthalmology,* **54:** 31–36.

Address for correspondence:
Dr. A. G. D. Maran,
Department of Otolaryngology,
The Royal Infirmary,
Edinburgh,
EH3 9YW.

https://doi.org/10.1017/S002221510010101X Published online by Cambridge University Press

https://doi.org/10.1017/S002221510010101X Published online by Cambridge University Press