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COMMUNICATIONS

SJÖGREN'S SYNDROME AND THYROID DISEASE*†

BY

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SJÖGREN'S syndrome is a chronic benign systemic disease of unknown aetiology which involves principally the lacrimal and salivary glands and may occasionally also affect the naso-pharyngeal, buccal, oesophageal, and tracheo-broncheal glands and the sweat glands (Sjögren, 1943, 1951; Stoltze, Hanlon, Pease, and Henderson, 1960; Bloch, Buchanan, Wohl, and Bunim, 1965). The majority of patients studied have underlying connective tissue disease such as rheumatoid arthritis, systemic lupus erythematosus, progressive systemic sclerosis, polymyositis, or polyarteritis nodosa (Bloch and Bunim, 1963; Bloch and others, 1965), each of which is characterized by circulating autoantibodies to cells or cell constituents.

Anderson, Gray, Beck, and Kinnear (1961); Bunim (1961); Bloch and Bunim (1963); Anderson, Beck, Bloch, Buchanan, and Bunim (1965), have also shown that the prevalence of thyroglobulin autoantibodies is increased in patients with Sjögren's syndrome, but the corresponding prevalence of Sjögren's syndrome in patients with autoimmune thyroid disease has not been evaluated. The histological features of autoimmune thyroiditis, Hashimoto's thyroiditis, and spontaneous myxoedema and those of the lacrimal and salivary glands in Sjögren's syndrome are, however, very similar, as first noted by Hashimoto (1912). For this reason it appeared to be important to determine whether the two conditions occur together with significant frequency. Since thyroid autoantibodies are also found in patients with thyrotoxicosis (Roitt and Doniach, 1958; Buchanan, Alexander, Crooks, Koutras, Wayne, Anderson, and Goudie, 1961; Buchanan, Koutras, Crooks, Alexander, Brass, Anderson, Goudie, and Gray, 1962; Anderson, Gray, Middleton, and Young, 1964), the incidence of Sjögren's syndrome in this disorder was also determined. In each group of patients the incidence of Sjögren's syndrome was compared with that in a group with simple goitre and that in another control group of hospital patients.

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Lacrimal gland function is difficult to assess accurately even where the gland is healthy, and routine biopsy is not a practical procedure; the most reliable clinical indication of lacrimal gland involvement is the presence of kerato-conjunctivitis sicca which is readily diagnosed and this is the index we have used in the investigation. Examination of the salivary glands was also made in a large number of patients by means of sialography and the incidence of abnormalities was determined.

Material and Methods

Patients

339 female patients comprising five groups were examined for kerato-conjunctivitis sicca. The mean age and age range are shown in Table I.

TABLE I

KERATO-CONJUNCTIVITIS SICCA IN THYROID DISEASE

Clinical Groups	Number of Patients	Age (yrs)		Schirmer's Test (mm. at 5 minutes)						Kerato-conjunctivitis Sicca	
				5		5–9		10–14			
		Mean	Range	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
Hashimoto's Thyroiditis	83	55·0	37–75	5	6·0	11	13·3	7	8·4	3	3·6
Primary Hypothyroidism	69	67·0	33–74	6	8·7	12	17·3	5	7·2	5	7·2
Thyrotoxicosis	68	43·2	16–66	7	10·3	1	1·4	—	—	6	8·6
Simple Goitre	46	39·5	15–67	2	4·3	—	—	5	11·0	2	4·3
Hospital Controls	72	51·9	31–74	5	6·9	10	13·9	6	8·3	5	6·9

Group 1. Hashimoto's Thyroiditis (*83*).—The diagnosis was based on five patients on histological examination of the gland using the criteria of Joll (1939) and in the remaining 78 on the presence of a positive precipitin test for antithyroglobulin autoantibodies in a euthyroid or hypothyroid patient (Buchanan and others, 1961). Three of these patients were hypothyroid when studied, but the remaining eighty were receiving 0·2 mg. sodium thyroxine and were euthyroid when studied. Four had "definite" rheumatoid arthritis by the American Rheumatism Association criteria (Ropes, Bennett, Cobb, Jacox, and Jessar, 1958).

Group 2. Spontaneous Primary Hypothyroidism (*69*) (hypothyroidism without a goitre).—The diagnosis was based on the clinical and laboratory criteria described by Wayne (1960) and Wayne, Koutras, and Alexander (1964). Ten patients were hypothyroid when examined and the remaining 59 were receiving 0·2–0·3 mg. sodium thyroxine and were euthyroid. Four had "definite" rheumatoid arthritis by the American Rheumatism Association criteria (Ropes and others, 1958).

Group 3. Thyrotoxicosis (*68*).—21 patients had become hypothyroid following radioactive iodine (^{131}I) therapy; twenty of them were euthyroid at the time of examination and were receiving 0·2–0·3 mg. sodium thyroxine per day and the other was hypothyroid. The remaining 47 were euthyroid following antithyroid drug therapy, subtotal thyroidectomy, or ^{131}I therapy.

Group 4. Simple Goitre (*46*).—All these were euthyroid, and none had systemic disease.

Group 5. Hospital Controls (*72*).—These were all women attending as outpatients at the clinics associated with the Western and Royal Infirmaries, Glasgow. They had a variety of general medical conditions, none of which, however, had any known association with thyroid disease or autoimmune disorders.

Methods

Autoantibodies to Thyroglobulin were tested by a precipitin test using the Ouchterlony-Elekplate technique (Anderson, Buchanan, Goudie, and Gray, 1962) and by the tanned red cell haemagglutination test using thyroglobulin-coated formalized tanned sheep red cells (Burroughs Wellcome), (Fulthorpe, Roitt, Doniach, and Couchman, 1961). The lowest serum dilution tested in the tanned red cell haemagglutination test was 1 in 16. Autoantibody to thyroid "microsomes" was measured by an immunofluorescence technique on unfixed frozen sections of thyroid slices (Holborow, Brown, Roitt, and Doniach, 1959), using test serum diluted one in four in the first layer.

Examination for Sjögren's Syndrome.—Each patient underwent an ophthalmic examination. This included a Schirmer I test using the standardized sterile strips developed by Halberg and Berens (Contactisol Inc. Lindenhurst, New York, U.S.A.). The wetting of the paper strip was read at 5 minutes and the mean of the two eyes was recorded. Patients with less than 15 mm. wetting were subjected to a Schirmer II test, using 10 per cent. ammonia held by the patient for 5 minutes 6 in. from the nose. Rose bengal 1 per cent. was instilled into the conjunctival sac of each eye and immediately followed by irrigation with normal sterile saline; the patients were then examined by a Zeiss or Haag-Streit slit lamp for punctate and filamentary keratitis. Staining over the area previously in contact with the Schirmer filter paper was ignored. Kerato-conjunctivitis sicca was diagnosed when the Schirmer II test gave less than 5 mm. wetting after 5 minutes and when there was associated strongly positive rose bengal staining of the conjunctivae and/or corneae. To minimize bias in this study the medical diagnosis was not known to the ophthalmologists until after the eye examinations were complete.

Sialography.—This was performed in 109 patients, 41 with Hashimoto's thyroiditis, 32 with primary hypothyroidism, and 36 control subjects. A hydrostatic technique was employed, using Triosil "45" (sodium metrizoate) as a contrast medium. Apparatus consisting of a 20 ml. glass syringe, polythene tubing, and a tapered catheter was used to convey the contrast medium to the duct and gland. The glass syringe was set at a fixed height above the patient's head (70–90 cm.). The contrast medium flowed into the gland using only the force of gravity and therefore a relatively constant pressure was obtained (Park and Mason, 1966). This method rarely led to over-filling and was less painful for the patient. The water-soluble contrast medium is rapidly expelled from the gland and therefore a secretory phase film was exposed 5 minutes after the filling phase was complete. Between the two phases, the patient was asked to suck a slice of lemon to stimulate salivary flow.

Results

The results of the ophthalmological examination are summarized in Table I. Only a small minority in each group had definite kerato-conjunctivitis sicca. The highest prevalence was found in Group 3 treated thyrotoxicosis (8·6 per cent.), but this was not significantly different from that in Group 5 hospital controls (6·9 per cent.). The 43 patients treated with ^{131}I therapy were re-assessed separately (Table II, overleaf). Six of those with kerato-conjunctivitis sicca came from this group and none of the remaining 25 treated by drugs and/or surgery had kerato-conjunctivitis sicca. No correlation was, however, found between the presence of kerato-conjunctivitis sicca and the number of doses, total dosage of ^{131}I, or the interval since the last dose of ^{131}I.

None of the 83 patients with Hashimoto's thyroiditis and none of the four with primary hypothyroidism plus rheumatoid arthritis had kerato-conjunctivitis sicca.

TABLE II

RELATION OF KERATO-CONJUNCTIVITIS SICCA TO THE NUMBER OF DOSES AND TOTAL DOSAGE OF RADIOACTIVE IODINE (^{131}I) THERAPY IN THYROTOXIC PATIENTS

No. of Patients	No. of Doses of ^{131}I	Mean and Range of ^{131}I Doses (mc.)		No. with Kerato-conjunctivitis Sicca
		Mean	Range	
15	1	9·1	8–10	2
18	2	18·7	16–20	3
10	3	29·1	24–30	1

None of the five patients with Hashimoto's thyroiditis in whom the diagnosis was confirmed by biopsy had kerato-conjunctivitis sicca.

Abnormal sialograms were found in eighteen cases: seven (16 per cent.) of the 41 patients with Hashimoto's thyroiditis, five (16 per cent.) of the 32 with primary hypothyroidism, and in six (16 per cent.) of the 36 in the hospital control group (Table III). Only two patients with Hashimoto's thyroiditis showed globular sialectasis, the remaining patients having only minor abnormalities consisting of punctate sialectasis with or without intermediate duct changes. Mild xerostomia was found in sixteen of these eighteen patients. None had a history or clinical evidence of salivary gland enlargement. Two of the hospital control subjects had unexplained xerostomia but normal sialograms. None of the patients with Hashimoto's thyroiditis or with primary myxoedema who had rheumatoid arthritis had xerostomia or abnormal sialograms.

TABLE III

RESULTS OF SIALOGRAPHY IN CASES OF HASHIMOTO'S THYROIDITIS AND PRIMARY HYPOTHYROIDISM, AND IN HOSPITAL "CONTROLS"

Clinical Group	No. of Patients	Sialographic Abnormalities					No. with Abnormal Sialograms and Xerostomia	No. with Abnormal Sialograms and Salivary Gland Enlargement
		Total		Punctate	Punctate with Intermediate Duct Changes	Globular		
		No.	Per cent.					
Hashimoto's Thyroiditis	41	7	16	3	2	2	6	0
Primary Hypothyroidism	32	5	16	3	2		4	0
Hospital Controls	36	6	16	4	2		6	0

Discussion

This study shows no increased prevalence of kerato-conjunctivitis sicca in patients with proven autoimmune thyroid disease (Table I). The prevalence is higher than that in an ophthalmic control series of 6,200 (0·2 per cent.) in the United States (de Roetth, 1945), but the age and sex distribution of de Roetth's patients was not recorded. The number of patients with xerostomia and sialographic abnormalities consistent with Sjögren's disease affecting the parotid glands was also no higher in the groups with Hashimoto's thyroiditis and primary hypothyroidism respectively than in the hospital control group (Table III).

The prevalence of kerato-conjunctivitis sicca in patients with thyrotoxicosis (8·6 per cent.) was higher, but not significantly higher, than in the patients with simple goitre (4·3 per cent.) and the hospital controls (6·9 per cent.). 64 per cent. of

the patients with thyrotoxicosis received treatment with ^{131}I therapy, but no correlation was found between the number of doses or the total amount of ^{131}I given. One of us (Williamson, unpublished observations) has detected significant amounts of ^{131}I in tears one hour after a therapeutic dose of ^{131}I given to thyrotoxic patients. It does not appear, however, that this results in subsequent irradiation damage to the lacrimal and accessory lacrimal glands of the eye. It is of interest to note, however, that irradiation parotitis and xerostomia have been noted in patients receiving similar doses of ^{131}I therapy for thyrotoxicosis (Chapman and Maloof, 1955).

The prevalence of thyroglobulin autoantibodies in patients with Sjögren's syndrome is, however, increased (Anderson and others, 1961; Bunim, 1961; Bloch and Bunim, 1963; Anderson and others, 1965), and thyroglobulin autoantibodies have also been reported to occur with increased frequency in the connective tissue diseases, rheumatoid arthritis (Anderson and others, 1961; Bloch and others, 1965), and systemic lupus erythematosus (Anderson and others, 1961; Hijmans, Doniach, Roitt, and Holborow, 1961), all of which may be associated with established kerato-conjunctivitis sicca. The absence of an increased prevalence of kerato-conjunctivitis sicca in autoimmune thyroid disorders in contrast to that in autoimmune systemic disorders may, however, be consistent with the concept that autoimmune thyroiditis is an organ specific disorder.

Summary

83 patients with Hashimoto's thyroiditis, 69 with primary hypothyroidism, and 68 with thyrotoxicosis were examined for kerato-conjunctivitis sicca by Schirmer tear tests, staining of the conjunctiva and cornea by rose bengal dye, and slit-lamp examination. The prevalence of kerato-conjunctivitis sicca in these patients was no higher than in 46 patients with simple goitre and in 72 hospital controls matched for age and sex. Sialography was performed in 41 patients with Hashimoto's thyroiditis, 23 with primary hypothyroidism, and 36 of the hospital controls. Sialographic abnormalities suggestive of Sjögren's syndrome were found as frequently in the hospital controls as in the patients with Hashimoto's thyroiditis and primary hypothyroidism.

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