

Sjögren's syndrome in relation to pernicious anaemia and idiopathic Addison's disease

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Lymphocytic infiltration of the gastric mucosa in chronic gastritis is associated with the development of pernicious anaemia in a proportion of cases (Anderson, Buchanan, and Goudie, 1967). More than 40 per cent. of patients suffering from pernicious anaemia can be shown to have antibodies to gastric parietal cells (Irvine, Davies, Delamore, and Williams, 1962; Markson and Moore, 1962; Taylor, Roitt, Doniach, Couchman, and Shapland, 1962; Irvine, 1963a). It occurred to the investigators that the lymphocytic infiltration in chronic gastritis might be similar to that found in the lacrimal and salivary glands in Sjögren's syndrome and it is to be noted that a series of patients suffering from this disease was found to have a high incidence of autoantibodies to gastric parietal cells (Buchanan, Cox, Harden, Glen, Anderson, and Gray, 1966). Furthermore, patients suffering from pernicious anaemia have a high incidence of thyroglobulin antibodies (Irvine and others, 1962; Markson and Moore, 1962; Taylor and others, 1962; Doniach, Roitt, and Taylor, 1963) as do patients with Sjögren's syndrome (Anderson, Goudie, Gray, and Buchanan, 1961; Bloch, Buchanan, Wohl, and Bunim, 1965).

Sjögren's syndrome consists of the triad of keratoconjunctivitis sicca, xerostomia, and rheumatoid arthritis (Sjögren, 1933) or other connective tissue diseases such as systemic lupus erythematosus (Ramage and Kinnear, 1956; Bain, 1960), polyarteritis nodosa (Ramage and Kinnear, 1956), progressive systemic sclerosis (Ramage and Kinnear, 1956), and polymyositis (Bloch and others, 1965).

The first purpose of this investigation was to determine the prevalence of Sjögren's syndrome in patients suffering from proven pernicious anaemia.

In idiopathic Addison's disease there is atrophy of both adrenal cortices with loss of most of the cortical cells, lymphocytic and plasma cell infiltration, and minimal fibrosis. Chronic thyroiditis, which demonstrates similar histological changes, is present in approximately 50 per cent. of patients with idiopathic Addison's disease examined *post mortem* (Wells, 1930; Sloper, 1953; Bloodworth, Kirkendall, and Carr, 1954). Primary myxoedema has occurred with idiopathic Addison's disease with sufficient frequency to warrant the term Schmidt's syndrome (Schmidt, 1926). In addition, the chronic thyroiditis found in idiopathic Addison's disease is associated with thyroid microsomal antibodies in about 30 per cent. of the patients studied (Blizzard and Kyle, 1963; Irvine,

1963a) and thus is probably of the autoimmune type. Pernicious anaemia has been reported in idiopathic Addison's disease (Blizzard and Kyle, 1963; Irvine, 1963b; Kra and Barile, 1964). Gastric mucosal biopsies reveal a high incidence of chronic gastritis in patients with idiopathic Addison's disease (Feyrter and Klima, 1952; Smith, Delamore, and Williams, 1961). In addition, gastric parietal cell antibodies are more prevalent in idiopathic Addison's disease than in tuberculous cases (Irvine, 1963b). There is, therefore, strong evidence, clinical, histological, and immunological, pointing to an association between idiopathic Addison's disease, chronic thyroiditis, and chronic gastritis (which predisposes to pernicious anaemia).

Antibodies to salivary duct epithelium have been reported in patients with idiopathic Addison's disease (Blizzard and Kyle, 1963) and similar antibodies have been detected in patients with Sjögren's disease (Bertram and Halberg, 1964; Halberg, Bertram, Söborg, and Nerup, 1965; MacSween, Goudie, Anderson, Armstrong, Murray, Mason, Jasani, Boyle, Buchanan, and Williamson, 1967).

The second purpose of this investigation, therefore, was to determine the prevalence of Sjögren's syndrome in patients suffering from idiopathic Addison's disease.

Material and methods

PATIENTS

169 patients (120 female, 49 male) comprising three groups (pernicious anaemia, idiopathic Addison's disease, and hospital controls) were included in the survey (the mean age and age range are shown in Table I). All of the patients were examined for evidence of keratoconjunctivitis sicca. The patients in the first two groups had been investigated as in-patients. Together with the help of the original case records and further specific examinations, evidence of rheumatoid arthritis, thyroid disease, and salivary duct atrophy was collected. Most of the hospital control patients were attending as out-patients and were not suffering from any disease known to have an autoimmune basis.

Group I Pernicious anaemia (77 patients: 40 female, 37 male)

Four of these had rheumatoid arthritis by the American Rheumatism Association criteria (Ropes, Bennett, Cobb, Jacox, and Jessar, 1958). Two had Hashimoto's thyroiditis (Buchanan, Alexander, Crooks, Koutras, Wayne, Anderson, and Goudie, 1961) and one had idiopathic Addison's disease (Anderson and others, 1967). One patient had thyrotoxicosis as well as rheumatoid arthritis and another had thyrotoxicosis.

Group II Idiopathic Addison's disease (primary adrenal atrophy) (20 patients: 15 male, 5 female)

The diagnosis was based on the exclusion of obvious causes, *e.g.* tuberculosis for extensive and irreversible destruction of the cortex of the adrenal glands (Anderson and others, 1967), and on the detection of antibodies to adrenal cortical cells (Anderson, Goudie, Gray, and Timbury, 1957; Blizzard and Kyle, 1963; Goudie, Anderson, Gray, and Whyte, 1966).

Group III Hospital controls (72 females)

These were patients attending clinics associated with the Western and Royal Infirmaries, Glasgow. None of the variety of general medical conditions from which they suffered had any known association with pernicious anaemia, thyroid disease, or autoimmune disorders.

Table I Keratoconjunctivitis sicca in pernicious anaemia and idiopathic Addison's disease (primary adrenal atrophy)

Clinical groups	No. of patients	Age (yrs)		Schirmer's test (mm. at 5 minutes)						Keratoconjunctivitis sicca	
		Mean	Range	5		5-9		10-14		No.	Per cent.
				No.	Per cent.	No.	Per cent.	No.	Per cent.		
Pernicious anaemia	77	62.5 ± 11.1	20-82	11	14.1	14	18.0	12	14.2	6	7.7
Addison's disease	20	36.6 ± 6	20-45	—	—	—	—	1	5.0	—	—
Hospital controls	72	51.9	31-74	5	6.9	10	13.9	6	8.3	5	6.9

METHODS

Antibodies to parietal cells

These were tested using the indirect immunofluorescence technique for the detection of gastric auto-antibodies. Antigen was prepared from frozen unfixed sections of normal gastric fundal mucosa (Taylor and others, 1962).

Autoantibodies to thyroglobulin

These were tested by a precipitin test using the Ouchterlony-Elekpate 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). Autoantibody to thyroid microsomes was measured by an immunofluorescence technique on unfixed frozen sections of thyroid slices (Holborow, Brown, Roitt, and Doniach, 1959).

Other laboratory data

Waler-Rose, latex particle, and haemoglobin tests were recorded in the patients suffering from pernicious anaemia.

Examination for Sjögren's syndrome

Each patient underwent a complete ophthalmic examination. This included a Schirmer I tear test using standardized sterile strips developed by Halberg and Berens (Contactisol Inc., Lindenhurst, New York, U.S.A.). Patients with less than 15 mm. of wetting at 5 minutes had a Schirmer II tear test using 10 per cent. ammonia held by the patient for 5 minutes at 6 in. from the nose (Williamson, Cant, Mason, Greig, and Boyle, 1967). Keratoconjunctivitis sicca was diagnosed when the Schirmer II test gave less than 5 mm. wetting after 5 minutes and when there was strongly positive staining with the vital dye rose bengal 1 per cent., punctate or filamentary, of the conjunctivae and/or corneae.

Sialography

This was performed on four patients who gave a history of dryness of the mouth and throat and who had clinical xerostomia (Park and Mason, 1966).

Results

EXAMINATION FOR SJÖGREN'S SYNDROME

The results of the examination for keratoconjunctivitis sicca are summarized in Table I. A small number of patients in Group I (pernicious anaemia) and Group III (hospital controls) were suffering from keratoconjunctivitis sicca. Although the incidence of the ocular disease was higher in Group I than Group III the difference was not significant.

Most of the patients who demonstrated a reduced Schirmer I tear test, unprovoked by ammonia, had pernicious anaemia. The average age of the anaemia group of patients was 62.5 years, 10 years more than the hospital control patients, and this may account for the apparent fall in tear secretion in the anaemia group.

None of the patients with idiopathic Addison's disease had keratoconjunctivitis sicca.

Four of the patients with pernicious anaemia had xerostomia but normal sialograms.

Table II summarizes the principal findings in those patients who had pernicious anaemia and evidence of Sjögren's syndrome.

Table II Summary of findings in patients with pernicious anaemia, keratoconjunctivitis sicca, and/or xerostomia

Patient no.	Pernicious anaemia	Keratoconjunctivitis sicca	Xerostomia	Rheumatoid arthritis	Hashimoto's thyroiditis	Idiopathic Addison's disease
1	+	+	0	+	0	0
2	+	+	+	0	+	0
3	+	+	0	0	+	+
4	+	+	+	0	0	0
5	+	+	0	0	0	0
6	+	+	0	0	0	0
7	+	0	+	0	0	0
8	+	0	+	0	0	0

The first four patients listed (Table II) had evidence of involvement of other diseases. Patient 1 had rheumatoid arthritis, patient 2 xerostomia and Hashimoto's thyroiditis, patient 3 Hashimoto's thyroiditis and idiopathic Addison's disease, and patient 4 xerostomia.

Three other patients had pernicious anaemia and rheumatoid arthritis but no evidence of keratoconjunctivitis sicca. One of the patients with pernicious anaemia and rheumatoid arthritis also suffered from thyrotoxicosis.

OTHER INVESTIGATIONS

A family history of pernicious anaemia was obtained from fourteen (18.2 per cent.) of the 77 patients suffering from this disease and a history of thyroid disorders in eight (10.4 per cent.).

There was no history of pernicious anaemia or thyroid disease in the families of those suffering from idiopathic Addison's disease.

25 (32.4 per cent.) of the 77 patients with pernicious anaemia had palpable thyroid glands. In twenty patients the glands were soft, in five firm. Two of the firm glands lay beneath operation scars, one for thyrotoxicosis, the other for Hashimoto's thyroiditis. Five of the patients with pernicious anaemia had proven thyroid disease; two had Hashimoto's thyroiditis, two thyrotoxicosis, and one primary myxoedema.

LABORATORY DATA

All of the patients with pernicious anaemia were receiving Cytamen injections, the mean current haemoglobin being 11.5 ± 2.1 g./100 ml.

Antibody to gastric parietal cells was detected in the sera of 35 (77 per cent.) of 46 patients, antibodies to thyroid microsomes in eighteen (39 per cent.) of 46 patients, and tanned red cell titres were positive in thirteen (28 per cent.) of 46 patients suffering from pernicious anaemia.

Discussion

This study shows no increased prevalence of keratoconjunctivitis sicca in patients suffering from pernicious anaemia (Table I). The prevalence is higher than in Sjögren's series (Sjögren, 1933), in which his nineteen patients were distributed among 36,000 hospital patients (0.05 per cent.), and in the ophthalmic control series of de Roeth (1945) in which he found 0.2 per cent. of 6,200 patients with keratoconjunctivitis sicca. However, in neither series was the age and sex distribution recorded. The number of patients suffering from proven autoimmune thyroid disease who develop keratoconjunctivitis sicca is also no higher than in a hospital control group (Williamson and others, 1967). In the present series, it is interesting to observe that two of the six patients with pernicious anaemia and keratoconjunctivitis sicca also had autoimmune thyroiditis—Hashimoto's disease (Table II)—and that one of them in addition had idiopathic Addison's disease. However, it is accepted that a patient with any one organ-specific disease has a higher than normal tendency to develop another organ-specific disorder (Anderson and others, 1967). In Sjögren's syndrome there are organ-specific features in that there is specific destruction of the lacrimal and salivary glands. Nevertheless, a non-organ-specific connective tissue disorder, usually rheumatoid arthritis, is present in over 50 per cent. of patients with Sjögren's syndrome (Bloch and others, 1965). In this series one of the pernicious anaemia patients who had keratoconjunctivitis sicca was also suffering from rheumatoid arthritis. Three others with rheumatoid arthritis and pernicious anaemia did not have Sjögren's syndrome.

The number of patients with xerostomia was no higher than in the hospital control group reported previously (Williamson and others, 1967).

No cases of Sjögren's syndrome were detected among the twenty patients who had a primary diagnosis of idiopathic Addison's disease. Their mean age (36.6 years) is, however, much younger than either the pernicious anaemia group or the hospital control group. One patient in the pernicious anaemia series who had idiopathic Addison's disease and keratoconjunctivitis sicca has been discussed already.

The prevalence of gastric parietal cell antibodies and thyroglobulin antibodies, however, is increased in Sjögren's syndrome (Buchanan and others, 1966; Anderson and others, 1961; Bloch and others, 1965). Both of these antibodies occur with increased frequency in pernicious anaemia (Irvine and others, 1962; Markson and Moore, 1962; Taylor and others, 1962; Irvine, 1963a; Doniach and others, 1963) and in idiopathic Addison's disease (Blizzard and Kyle, 1963; Irvine, 1963b). Thyroglobulin antibodies are more frequent 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), both of which may be associated with established keratoconjunctivitis sicca. The absence of an increased prevalence of keratoconjunctivitis sicca in pernicious anaemia or in idiopathic Addison's disease in contrast to that in autoimmune systemic disorders is consistent, however, with the concept that pernicious anaemia and idiopathic Addison's disease are organ-specific disorders.

Summary

77 patients with pernicious anaemia and twenty with idiopathic Addison's disease were examined for keratoconjunctivitis sicca by Schirmer tear tests, staining of the conjunctiva and cornea by rose bengal dye, and slit-lamp examination. The prevalence of keratoconjunctivitis sicca in these patients was no higher than in 72 hospital controls. Sialography was performed on four patients who had xerostomia but no abnormalities were detected.

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