Otolaryngological Aspects of Sjögren's Syndrome

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Summary

Twenty-two patients with Sjögren's syndrome uncomplicated by a connective tissue disorder, 31 with Sjögren's syndrome complicated by rheumatoid arthritis, and 21 with rheumatoid arthritis alone were studied with particular reference to changes in the ears and in the upper respiratory and digestive tracts.

Epistaxis, soreness and dryness of the throat, dysphagia, and hoarseness were common symptoms, and rhinitis sicca and postcricoid narrowing were not uncommon features of the Sjögren groups. Oesophagoscopy in one patient revealed a web identical to that found in Paterson/Brown Kelly syndrome; none of the patients, however, had an iron-deficiency anaemia or koilonychia. There was an increased frequency of deafness in all groups, and the deafness tended to be conductive in the Sjögren groups and sensorineural in the rheumatoid arthritis group.

Introduction

Sjögren's syndrome, first adequately described by Henrik Sjögren, the Swedish ophthalmologist, in 1933, is a chronic benign disorder predominantly affecting middle-aged or elderly women (Sjögren, 1943). The underlying morbidity is chronic inflammation of the lachrymal and salivary glands, which results in atrophy of the gland acini and therefore diminution of their secretory capacity. Clinically this is manifest as dryness of the eyes, or keratoconjunctivitis sicca, and dryness of the mouth, or xerostomia. About one-half to two-thirds of these patients have an associated connective tissue disease, usually rheumatoid arthritis, more rarely systemic lupus erythematosus, progressive systemic sclerosis, polyarteritis nodosa, or polymyositis (Bloch, Buchanan, Wohl, and Bunim, 1965).

Secretory insufficiency of the glands of the upper respiratory tract (Sjögren, 1943; Bloch *et al.*, 1965), stomach (Buchanan *et al.*, 1966), pancreas (Fenster, Buchanan, Laster, and Bunim, 1964; Hradský, Bartoš, and Keller, 1967), and the skin and vagina (Bloch *et al.*, 1965) has been shown to occur. Histological examination of the glands of lip (Chisholm and Mason, 1968; Whaley, Chisholm, Downie, Dick, and Williamson, 1968), palate (Bertram, 1967), nose (Sjögren, 1943), stomach (Jebavý, Hradský, and Herout, 1961), and skin (Ellman, Weber, and Goodier, 1951; Szanto, Farkas, and Gyulai, 1957) has shown chronic inflammatory infiltrates in the involved tissues. Though it is known that involvement of the upper respiratory tract may occur in Sjögren's syndrome, the prevalence of this complication is unknown, and, furthermore, the clinical

significance of such involvement is unknown. We therefore considered it valuable to investigate our patients with Sjögren's syndrome in an attempt to answer these questions.

Patients and Methods

Twenty-two patients with Sjögren's syndrome uncomplicated by a connective tissue disorder (sicca syndrome) (mean age 53.3 years, range 30-81 years), 31 patients with Sjögren's syndrome complicated by rheumatoid arthritis (mean age 51.4 years, range 31-78 years), and 21 patients with rheumatoid arthritis alone (mean age 51.7 years, range 34-70 years) were included in the study. None of the patients had been referred from an ear, nose, and throat department and none were known to have any ear, nose, or throat problems at the time of referral.

Sjögren's syndrome was diagnosed by using the criteria of Bloch *et al.* (1965), any two of the three major criteria—xerostomia, keratoconjunctivitis sicca, and the presence of a connective tissue disease—being required to make the diagnosis. Patients having xerostomia and keratoconjunctivitis sicca but without an associated connective tissue disease were said to have the sicca syndrome.

Oral Examination.—The clinical examination included questioning the patient closely for the presence of dryness of the mouth necessitating increased fluid intake to combat difficulty in mastication, swallowing, and conversation. Examination of the mouth for xerostomia, shown by absence of a pool of saliva under the tongue, atrophy of the lingual papillae, and oral mucosa, was performed. Sialography was carried out by the hydrostatic technique of Park and Mason (1966), and salivary flow rates were measured with a Carlsson-Crittenden cup.

Ophthalmological Examination.—Keratoconjunctivitis sicca was diagnosed when a patient had diminished lachrymation, shown by a subnormal Schirmer II tear test, and the presence of a punctate or filamentary keratitis on slit-lamp examination of the cornea after the instillation of one drop of rose bengal dye into the conjunctival sac. This procedure has been described in detail elsewhere (Williamson, Cant, Mason, Greig, and Boyle, 1967; Whaley *et al.*, 1969). Rheumatoid arthritis was diagnosed by using the diagnostic criteria of the American Rheumatism Association (Ropes, Bennett, Cobb, Jacox, and Jassar, 1958).

Examination of Nose.—All patients were questioned regarding symptoms of nasal dryness and crusting, and epistaxis. Examination of the nose under direct vision was undertaken to detect dryness, crusting, or atrophy of the nasal mucosa. The presence of septal perforations was also noted.

Examination of Pharynx.—Dryness and/or soreness of the throat and dysphagia were noted. The nasopharynx was viewed indirectly, as was the laryngopharynx. Dryness of the mucosa with crusting, especially in relation to the Eustachian tubes, and atrophy of the mucosa were looked for. The oropharynx was viewed directly. Patients complaining of dysphagia were examined radiologically with the barium swallow technique.

Examination of Larynx.—Hoarseness of the voice was documented, and on indirect laryngoscopy the vocal cords were examined for the presence of dryness or stickiness.

Examination of Ears.—Tinnitus, deafness, vertigo, and earache were all asked about, together with the use of salicylates. Examination of the external auditory meatus was made to assess the dryness of the canal and wax and the state of the tympanic membrane. Audiometry with a Peters SPD5 pure tone

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audiometer was carried out and repeated one week later. The results of the audiometric examination were graded as 1, 2, and 3, based on the results obtained by Hinchcliffe (1959a, 1959b) in various age groups. Group 1 contained patients who fell within the normal range for their age, group 2 consisted of patients within the maximum limits one would accept as probably being normal, and group 3 consisted of patients definitely having impaired hearing when compared with other people of the same age, and also those with a conductive deafness of any degree.

Results

The results of the study are set out in the Table. Two features of particular interest were the findings on examination of the larynx and on audiometric testing.

Symptoms and Clinical Signs in Patients Studied

Symptom	Sicca Syndrome (22)		Rheumatoid Arthritis and Sjögren's Syndrome (31)		Rheumatoid Arthritis Alone (21)	
	No.	%	No.	%	No.	%
<i>Symptoms</i>						
Nasal crusting and/or dryness	4	18.5	5	16.1	2	9.5
Epistaxis	7	31.8	11	35.5	2	9.5
Soreness and/or dryness of throat ..	18	81.8	20	64.5	4	19.0
Dysphagia	6	27.3	10	32.3	2	9.5
Hoarseness	6	27.3	6	19.4	2	9.5
Otalgia	1	4.5			1	4.8
Tinnitus	1	4.5	3	9.7	3	14.3
<i>Clinical Signs</i>						
Nasal dryness ..	10	45.5	15	48.4	3	14.3
Nasal crusting ..	12	54.5	18	58.1	3	14.3
Atrophy of nasal mucosa	3	13.6	3	9.7		
Perforation of nasal septum			2	6.5	1	4.8
Dryness of oropharynx	8	36.4	8	25.8	1	4.8
Viscid secretions on posterior pharyngeal wall	3	13.6	1	3.2		
Dryness of nasopharynx ..	1	4.5	9	29.1	1	4.8
Dryness of laryngopharynx ..	3	13.6	3	9.7	1	4.8
Dryness of vocal cords	5	22.7	1	3.2	1	4.8
Tenacious mucus over vocal cords			3	9.7		
Dryness of skin of external auditory meatus	2	9.1	3	9.7	2	9.5
Dry wax	2	9.1	3	9.7		
"Milky" appearance of tympanic membrane	2	9.1			1	4.8
Perforated tympanic membrane	2	9.1	2	6.5	1	4.8

Dysphagia was a symptom in six patients with the sicca syndrome, in 10 patients with Sjögren's syndrome complicated by rheumatoid arthritis, and in two with rheumatoid arthritis alone. Two patients with the sicca syndrome and two with Sjögren's syndrome complicated by rheumatoid arthritis had postcricoid narrowing on barium swallow examination (Fig. 1). None of these patients had koilonychia and none had iron-deficiency anaemia, though both patients with Sjögren's syndrome complicated by rheumatoid arthritis had a normochromic anaemia which is commonly associated with rheumatoid arthritis.

Hoarseness of the voice was not common in any of the three groups of patients, being present in only six with the sicca syndrome and in two with rheumatoid arthritis alone. Visual evidence of dryness of the vocal cords was seen in five patients with the sicca syndrome, one patient with Sjögren's syndrome and rheumatoid arthritis, and one with rheumatoid arthritis alone. In addition, three patients with Sjögren's syndrome and rheumatoid arthritis had thick tenacious secretion over the vocal cords.

FIG. 1—Left: Normal barium swallow. The arrow indicates the cricopharyngeal sphincter. Right: Barium swallow in a 58-year-old man with Sjögren's syndrome and rheumatoid arthritis. The x-ray film shows a cricopharyngeal web (arrowed). Oesophagoscopy confirmed the presence of a web. The patient had a normocytic normochromic anaemia with a haemoglobin concentration of 12.9 g/100 ml.

With the criteria outlined above it was found that of the 22 patients with the sicca syndrome four had grade 3 deafness. All had severe conduction deafness, but, in addition, one patient also had sensorineural deafness. Two patients had grade 2 deafness, and the remainder had normal hearing. None of these patients were on ototoxic drugs.

Six patients with rheumatoid arthritis and Sjögren's syndrome had grade 3 deafness, and three had grade 2 audiometric changes. Of the patients with severely impaired hearing, two had pure conduction deafness, one having a large perforation in the left tympanic membrane but without any abnormality of the opposite drum. Of the remainder three had sensorineural deafness and one combined conduction and sensorineural deafness.

Of the 21 patients with rheumatoid arthritis alone, nine had grade 3 deafness (only one conductive) and six had grade 2 audiometric changes.

One may conclude from these audiometric observations that impairment of hearing in patients with rheumatoid arthritis alone is rarely due to arthritic changes in the ossicles of the middle ear (Copeman, 1963) and probably is the result of ototoxic drugs. The prevalence of conduction deafness in patients with the sicca syndrome suggests that dryness of the mucous membranes of the middle ear and Eustachian tube may be a major precipitating factor. In patients with rheumatoid arthritis and Sjögren's syndrome both factors are likely to contribute to the production of deafness.

Discussion

The purpose of this study was to note the prevalence of secretory insufficiency of the exocrine glands in the nose, pharynx, larynx, and ears, and to discover to what extent they were responsible for symptoms. Nasal dryness and/or crusting were not very common complaints in any of the three clinical groups studied, though they were slightly more frequent in the two groups of patients with Sjögren's syndrome. In contrast

both nasal dryness and crusting were found on examination to be much commoner in patients with Sjögren's syndrome than in those with rheumatoid arthritis alone. This is probably the reason for the high incidence of epistaxis in the first two groups. Atrophy of the nasal mucosa was present only in those with Sjögren's syndrome, but was not particularly common, and perforation of the nasal septum was distinctly uncommon, which is somewhat surprising in view of the high prevalence of nasal crusting noted on examination. This, of course, may be because crusting gave rise to little symptomatology, though the high incidence of epistaxis is against this argument. Hypofunction of the nasal glands may be visualized by scanning the nasal cavity with a Picker-Magnascanner V, after the intravenous administration of radiotechnetium (^{99m}Tc). The normal scan (Fig. 2A) shows high uptake over the salivary glands, oral cavity, and nose, whereas the scan from a patient with Sjögren's syndrome (Fig. 2B) shows little uptake over these regions.

As nasal crusting and dryness were so common in patients with Sjögren's syndrome, we examined carefully four elderly

women patients with ozaena for evidence of Sjögren's syndrome, but none had clinical or serological evidence of the disease.

Soreness and dryness of the throat are common symptoms in patients with Sjögren's syndrome, unlike patients with rheumatoid arthritis alone, but objective evidence of dryness of the oropharynx was much less common, but still much commoner than in the rheumatoid arthritic group. Thick tenacious secretions on the posterior wall of the oropharynx together with food particles were uncommon, but were associated with difficulty in mastication, and all four patients needed to take a large amount of fluid with their meals. The nasopharynx was generally normal except in nine patients with rheumatoid arthritis complicated by Sjögren's syndrome, but in none was the Eustachian tube obstructed. We have twice seen elderly women patients during consultations at other hospitals who had had the sicca syndrome for several years, and were troubled by the onset of acute deafness, with an associated exudative otitis media. Examination of the nasopharynx in both cases showed large crusts covering the Eustachian tube. Removal of these crusts was followed by rapid recovery of hearing.

Dysphagia was not an uncommon symptom (see Table), and of the six patients in whom the dysphagia was severe enough to merit investigation, four had postcricoid narrowing similar to that seen in the Paterson/Brown Kelly syndrome. Oesophagoscopy, performed in one patient, showed a web identical to a sideropenic web, and the finding has been repeated in another patient after completion of the series. None of these patients had iron deficiency, as shown by haemoglobin level, packed cell volume, mean corpuscular haemoglobin concentration, or serum iron and iron-binding capacity. In addition, koilonychia was not present, but all had some degree of atrophy of the lingual papillae, and three patients with dentures had angular stomatitis.

Godtfredsen (1947) noted strictures at the entrance to the oesophagus in the barium swallow of 3 out of 23 patients with Sjögren's syndrome, but this was not confirmed by oesophagoscopy. This finding suggests that dysphagia in patients with Sjögren's syndrome should be taken seriously, as we do not know whether or not postcricoid webs in this condition are premalignant, as they are in sideropenic states. In this respect it is of interest that patients with Sjögren's syndrome have an unduly high prevalence of lymphoma, pseudolymphoma, and Waldenström's macroglobulinaemia (Talal and Bunim, 1964; Talal, Sokoloff, and Barth, 1967). If any of these patients do develop oesophageal carcinoma, then Sjögren's syndrome will rank with coeliac disease in its predisposition to both lymphoid and non-lymphoid neoplasms.

Hoarseness, a not infrequent symptom in patients with Sjögren's syndrome, was associated with the presence of dryness or tenacious mucus coating the vocal cords. Movement of the vocal cords was normal in all patients examined, suggesting that involvement of the cricoarytenoid joints in rheumatoid arthritis is rare.

Thus pathological changes are often present in the upper respiratory tract and ears in Sjögren's syndrome, but these are often asymptomatic, even when they are clinically obvious. Probably the most important result of this study is the finding that postcricoid pharyngeal webs are not unusual in patients with Sjögren's syndrome, and these patients should be closely followed up to see whether malignancy supervenes.

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2A

2B

FIG. 2—Radioactive (^{99m}Tc) scans of salivary glands in Sjögren's syndrome (below) and in a normal subject (above). The diminished uptake over the parotid (A) and submandibular (B) glands are obvious. Accumulation of the isotope is present in the oral (D) and nasal (C) cavities in the normal person. The scan in the Sjögren patient shows accumulation of the isotope in the thyroid.

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Further Experience with Azathioprine in Rheumatoid Arthritis

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Summary

Azathioprine has been shown to reduce the steroid requirements of patients with severe rheumatoid arthritis. Twenty-seven patients treated with azathioprine have now been followed up for 30 months. At the end of this period only 10 were still taking the drug. Maximum steroid reduction occurred within the first 12 months of treatment. Some steroid-sparing effect seemed to persist after the drug was stopped. There was no evidence that azathioprine prevented radiological deterioration. No deaths occurred and toxic effects always reversed on stopping the drug.

Introduction

Azathioprine has been used in the treatment of rheumatoid arthritis since 1964; the results of this therapy have recently been reviewed in detail by Currey (1971). Though many reports are encouraging it is unfortunate that most studies have been uncontrolled and are therefore difficult to assess. However, a double-blind controlled study of azathioprine against placebo in patients with rheumatoid arthritis carried out at the London Hospital has been reported (Mason *et al.*, 1969). It was found that steroid requirements were significantly reduced in the azathioprine-treated group after 12 months.

When the results of the trial were available it became unethical to withhold azathioprine from those patients in the placebo group who had failed to reduce steroid dosage, and a controlled follow-up was therefore impossible. The azathioprine-treated group has been followed for 30 months after entry to the trial and this report describes their progress.

Patients and Methods

The design of the trial was described in the original report (Mason *et al.*, 1969). Fifty-four patients with severe, sero-positive, erosive rheumatoid arthritis entered the trial and 49 received treatment for long enough to be analysed. Most had considerable functional impairment and all had been treated with at least 5 mg of prednisolone daily (range 5-20 mg) for six months. Steroid requirements were always kept at the lowest acceptable level and all patients were maintained on a stable dose for two months before starting the trial tablets.

Twenty-seven patients received azathioprine 2.5 mg/kg/day in divided doses. When the trial was completed and the nature of the treatment revealed, the clinicians were allowed to decide whether individual patients should continue to take azathioprine or not.

Results

Only 10 of the 27 azathioprine-treated patients were still taking the drug at 30 months; reasons for discontinuing azathioprine are shown in the Table.

Reasons for Withdrawal from Azathioprine (Original Number of Patients = 27)

Reasons for Withdrawal	No. of patients
Toxicity:	
Haematological { Neutropenia (neutrophils <2,500/mm ³)	3
{ Macrocytosis	1
{ Vomiting	1
Gastrointestinal { Gastric haemorrhage	1
Rash	1
No benefit	8
Preliminary to surgery	1
Transfer to another area	1
Total	17

Steroid Requirements.—Reduction in steroid requirement may be best expressed as a fall in the log dose. The effect of this transformation is to give similar weight to falls which are the same proportion of the starting dose, even though their absolute values may be different. The steroid requirements of the patients are shown in the Chart. There was a significant fall during the first 12 months of treatment ($P=0.05$, t test, 2-tailed). In order to define the period of maximum benefit in those patients who responded to azathioprine, a separate line shows the steroid requirements of the group, omitting eight patients who were withdrawn from treatment because of failure to respond. This shows more clearly that the maximum steroid reduction occurred during the first 12 months and after that

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