Manometric assessment of impaired esophageal motor function in primary Sjögren's syndrome

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Abstract

Objective

To evaluate by manometry the esophageal motility changes in patients with primary Sjögren's syndrome (SS).

Methods

Esophageal manometry was carried out in 25 (F/M: 22/3) primary SS patients with systemic manifestations and in 42 control subjects. The primary SS patients also completed a dysphagia scoring questionnaire and underwent whole salivary flow measurements.

Results

As compared with the controls the primary SS patients exhibited a decreased lower esophageal sphincter (LES) pressure ($p < 0.01$) and a prolongation of LES relaxations ($p < 0.02$). In the esophageal body (EB) a decreased peristaltic velocity ($p < 0.01$), an increased duration of contractions ($p < 0.01$) and a higher occurrence of simultaneous waves ($p < 0.01$) were detected.

Since decreased peristaltic velocity was the most frequent motor abnormality (11/25 cases), two groups of patients were formed for further analysis: patients with a decreased (group I, n = 11) and patients with a normal (group II, n = 14) peristaltic velocity. The SS patients with a decreased EB propagation velocity (≤ 2.7 cm/s, group I) displayed more significantly decreased pressures ($p < 0.01$) and more prolonged relaxation times ($p < 0.05$) in the LES, with higher rates of simultaneous contractions on dry swallows ($p = 0.05$) in the EB, as compared with those who had a normal peristaltic velocity (group II). Of the clinical parameters, the decreased EB peristaltic velocity was associated with a smaller whole saliva production both in the basal state and after stimulation. Furthermore, this group of patients had a significantly higher liquid requirement for swallowing than those who had normal peristaltic velocities ($p = 0.05$).

Conclusions

Primary SS patients with systemic manifestations exhibit several esophageal motility abnormalities. In this study, a decreased EB peristaltic velocity was the most common manometric change, and showed an association with impaired saliva production and higher liquid requirement for swallowing, but not with the laboratory parameters or with the systemic manifestations of the disease.

Key words

Primary Sjögren's syndrome, esophageal manometry.

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Introduction

Primary Sjögren's syndrome (SS) is a chronic autoimmune inflammatory disorder of unknown etiology. The obligatory involvement of the salivary and lacrimal glands results in xerostomia and keratoconjunctivitis sicca. Besides these local glandular manifestations, other organs (e.g. gastrointestinal, respiratory tract, joints, etc.) are often affected (1,2). Although the patients often complain of difficulties in swallowing, to date only a few studies have been performed to evaluate the esophageal motor function in the disease (3-8).

The aim of our study was to conduct a manometric assessment of esophageal motility changes in patients with primary SS.

Materials and methods

Patient population

Twenty-five primary SS patients (22 women, 3 men) with systemic symptoms were studied in 1997 and 1998. All of these patients met the criteria of the European Community Study Group (9). At the time of the examination, the mean age was 55 (range 31-75) years, and the mean duration of the disease was 14 (range 2-30) years. The manometric examinations were performed in random sequence reflecting the visits of the patients to our outpatient unit, in all of those patients who agreed to the investigations and who gave their signed informed consent.

Esophageal manometric study

Esophageal motility was investigated after an overnight fasting period, by standard, water-perfusion esophageal manometry in each subject, in a recumbent position (Polygraph HR, Synectics Medical, Sweden) according to the protocol of Castell (10-12). For the procedure, a four-channel, low-compliance, nasoesophageal catheter was applied. The competence of the lower esophageal sphincter (LES) was estimated by a station pull-through technique. Esophageal body (EB) function was studied by measuring the amplitude, duration and propagation velocity of the contractions, and the frequency of simultaneous waves after wet (5 cm^3 of room-temperature tap water) and dry swallows. Ten swallows of each type were performed at least 30 seconds apart. In the upper esophageal sphincter (UES), the pressure profile and relaxation were studied. In the pharynx (PHX) the amplitude of the contractions was measured, with analysis of the UES-PHX coordination. Polygram UGI edition 5.06C2 (Gastrosoft Inc., Sweden) software was used for the computer-assisted analysis of the tracings.

The control group (n = 42) for the manometric examinations consisted of healthy volunteers and of patients admitted to the hospital because of minor abdominal complaints, who did not exhibit any upper gastrointestinal symptoms, all of whom likewise gave their signed informed consent. These latter patients did not suffer from metabolic disorders or autoimmune connective tissue diseases. The normal ranges obtained from these controls (mean ± SD, see Table II for details) corresponded to the internationally accepted values (13).

During the evaluation of EB function, the results were considered pathologic overall only when abnormal values were present at all 4 points: 3, 8,13 and 18 cm above the LES, respectively. Prior to the manometric examinations, the presence of organic esophageal diseases (webs, strictures and malignancies) was excluded by upper gastrointestinal endoscopy in all cases.

Symptom analysis

On the day of the manometric study, the patients were requested to complete a symptom scoring questionnaire in relation to their swallowing problems. Swallowing difficulty, i.e. dysphagia, comprises symptoms ranging from a moderate sensation of slowing of the esophageal passage to the typical feeling of the sticking of solid foods or even liquids. The patients were asked about the typical site (from the mouth to the cardia) and the frequency of dysphagia (0: no dysphagia; 1: less than one episode of dysphagia/week; 2: one or more episodes of dysphagia/week,3: one or more episodes of dysphagia/day; 4: one or more episodes of dys-

phagia/meal; and 5: problems at each swallow), the quality of food sticking (solids, liquids or both), the typical food causing a symptom, the requirement of liquid for swallowing (0: never, 1: sometimes, and 2: always), the presence of odynophagia (pain associated with swallowing) (0: never, 1: occasionally, and 2: regularly), and the frequency of aspiration during a meal (0: never, 1: less than one episode/ week, 2: one or more episodes/week, 3: one or more episodes/day, and 4: one or more episodes/meal).

Evaluation of salivary function

Both the unstimulated (basal) and the stimulated whole saliva production were measured in all patients. The salivation test was carried out under standardized conditions between 9 and 11 a.m. Patients were instructed to fast before the procedure. Neither eating nor drinking nor smoking was allowed for at least 1 1/2 hours before the saliva collection.

For the study, a sterile absorbent gauze was placed between the lower lip and the teeth of the patient, who was sitting in an upright position leaning slightly forward. Patients were not allowed to swallow, masticate or speak during the examination. Both unstimulated and stimulated whole saliva collection lasted for 10 minutes. During the stimulated saliva production, 1 drop of 2% citric acid solution was placed on the surface of the tongue at the beginning and in the fifth minute of the examination.

The difference in the weights of the gauze before and after the procedures gave the amount of saliva produced. When the methods were established earlier, we also determined the saliva production in 96 non-SS subjects. With our method, the unstimulated saliva production is considered to be reduced if it is ≤1.0 ml in 10 minutes, and the stimulated production is abnormally low if it is ≤4.0 ml in 10 minutes.

Histology

A lower lip biopsy was performed in 23 of the 25 patients for histological examination of the minor salivary glands. The result was considered positive if at least one focus of ≥50 mononuclear inflammatory cells per 4 mm^2 was found (9). The lip biopsies were carried out several months or even years prior to this esophageal manometric study.

Laboratory investigations

Routine laboratory and immunoserological examinations were performed in all patients: antinuclear antibody (ANA; indirect immunofluorescence on rat liver substrate), IgM rheumatoid factor (latex test, positive if titer ≥ 1:40), anti-native DNA (radioimmunoassay), anti-SSA, anti-SSB, anti-RNP and anti-Sm antibodies (enzyme-linked immunosorbent assay; Immuno DOT), and concentrations of complement C3 (rocket immunoelectrophoresis).

Statistics

The chi-square test and Student's t-test were used for statistical analysis. The latter was applied with the Welch correction if the variances differed.

Results

Of the main clinical manifestations which appeared during the course of the disease, parotid enlargement occurred in 15 of the 25 patients (60%), articular involvement in 19 (76%), purpura in 7 (28%) and Raynaud's phenomenon in 13 (52%). Renal tubular acidosis was diagnosed in 7 patients (28%), including 2 patients with histologically proved tubulointerstitial nephritis. Lower airway involvement was found in 10 patients (40%), with lung fibrosis in 7 (mild in 5, advanced in 2) of the 10, verified by high-resolution computed tomography.

Of the laboratory changes, leukopenia (with or without anemia) was detected in 13 cases (52%), hypergammaglobulinemia in 15 (60%), IgM rheumatoid factor positivity in 23 (92%) and ANA positivity in 15 (60%). Anti-SSA antibody positivity was found in 20 (80%) patients [alone in 8 (32%), and coupled with anti-SSB antibody positivity in 12 (48%)] and anti-SSB antibody positivity in 13 (52%) cases [alone in 1 (4%) and together with anti-SSA antibody positivity in 12 (48%)]. The histology of the minor salivary glands was indicative of SS in all biopsied patients.

The symptom evaluation revealed some grade of dysphagia [score: 2.7 ± 1.37 (mean ± SD)] in all but 2 patients (23/25, 92%) (Table I). Of these 23 patients, 22 had swallowing difficulties for only solids, and 1 for both solids and liquids. The patients predominantly stated that their dysphagia was situated in the upper esophageal (9/23) or pharyngeal region (5/23), whereas symptoms relating to the mid-esophagus were reported in 4/23 cases.

The most typical foods causing swallowing problems were bread and other bakery products (17/23, 74%). Meat or other solid foods (fruits,potato, cheese, etc.) were reported less frequently (6/23, 26%). All but one patient with dysphagia needed the aid of liquids to help them swallow solids, 17 had a constant, and 5 an occasional need for this (score: 1.68 ± 0.56 mean ± SD). Episodes of odynophagia occurred in 11 of the 25 patients (in 5 regularly and in 6 occasionally), giving an overall score of 0.67 ± 0.82 (mean ± SD). Aspiration was rare. At least daily episodes were reported by only 1 patient, and 3 patients had weekly episodes (score: 0.58 ± 0.88, mean ± SD).

Both basal and stimulated saliva production were reduced in 23/25 (92%) patients. One patient displayed an impairment of stimulated secretion only. Normal saliva secretion was detected in 1 patient.

Of the studied manometric parameters, the mean LES pressures were significantly lower ($p < 0.01$), and the relaxation times were significantly prolonged ($p < 0.02$) as compared with the controls (Table II). However abnormally low LES pressures were found in 9/25, and prolonged relaxation in 8/25 cases.

In the EB, an increased duration of peristaltic contractions, a decreased propagation velocity and a higher rate of simultaneous contractions were observed for dry and wet swallows ($p < 0.01$, Table II). The duration of peristaltic contractions was abnormally long in 10/25 cases for wet swallows, and less frequently (7/25) for dry swallows. The rate of simultaneous contractions exceeded the normal rate in 7 patients for wet swallows, and in 4

Table I. Distribution of different locations of dysphagia in patients with primary SS.

Dysphagia	No. of pts.
Present	23/25 (92%)
Location	
Mouth	3/23 (13%)
Pharynx	5/23 (22%)
Upper third of esophagus	9/23 (39%)
Middle third of esophagus	4/23 (17%)
Lower third of esophagus	1/23 (4.5%)
Cardia/diaphragm	1/23 (4.5%)

patients for dry swallows. The rate of simultaneous contractions for dry swallows correlated with the frequency of dysphagia. Patients with at least daily episodes of dysphagia (score ≥ 3) had significantly more simultaneous contractions for dry swallows, than those with fewer episodes (score ≤ 2). The rates were 19.7 ± 25.5% vs. 3.3 ± 7.1%, (mean ± SD), $p < 0.05$, respectively. This difference was not seen for wet swallows. Concerning the amplitude of the peristaltic waves, the values for the patients appeared to be similar to those for the controls.

In the upper region of the esophagus(at the level of the UES and the PHX) the manometric standards indicated no differences in the studied parameters between the primary SS patients and the controls (Table II).

As a decreased EB peristaltic velocity was the predominant motor abnormality, two groups of patients were formed for further study: those with normal and those with abnormal values (Table III). In group I (11 patients), each patient had a decreased (≤ 2.7 cm/s) esophageal peristaltic velocity, while the patients in group II (14 patients) had normal values. The LES pressure was found to be significantly lower ($p < 0.01$) and the LES relaxation significantly longer ($p < 0.05$) in group I than in group II. We also observed a higher rate of simultaneous contractions in the EB in group I for dry swallows ($p = 0.05$), whereas this difference was not seen for wet swallows. There was no statistical difference between the two groups as concerns the values of the amplitude and duration of the EB contraction, and the studied parameters of the UES-PHX region.

Both the unstimulated and the stimulated whole saliva production were significantly lower in group I ($p < 0.05$ for both) than in group II (Table IV).

The characteristics of the dysphagia were identical in the two groups, with the exception of one parameter: the group I patients had a significantly higher liquid requirement for swallowing than the patients in group II, with scores of 1.91 ± 0.30 vs. 1.50 ± 0.65; (mean ± SD), $p = 0.05$, respectively (Table IV).

The distributions of the systemic manifestations of primary SS, the results of routine and immunological laboratory tests and the studied demographic parameters (age and duration of the disease) did not demonstrate any statistically significant difference between the two groups.

Table II. Manometric differences in esophageal motility between primary SS patients and controls (mean ± SD).

LES	Primary SS (n = 25)		Control (n = 42)		p	
Pressure (mm Hg)*	20 ± 8		26 ± 7		< 0.01	
Relaxation time (s)	9.7 ± 2.1		8.6 ± 1.4		< 0.02	
EB peristaltic wave	**DS**	**WS**	**DS**	**WS**	**DS**	**WS**
Duration above the LES (s) at						
3 cm.	4.7 ± 1.1	4.8 ± 0.8	3.6 ± 1.0	3.7 ± 0.9	< 0.01	< 0.01
8 cm.	4.5 ± 1.1	4.7 ± 0.9	3.2 ± 0.8	3.4 ± 0.7	< 0.01	< 0.01
13 cm.	4.0 ± 0.9	3.9 ± 0.7	3.2 ± 0.7	3.1 ± 0.6	< 0.01	< 0.01
18 cm.	3.3 ± 0.7	3.5 ± 1.0	2.5 ± 0.7	2.6 ± 0.6	< 0.01	< 0.01
Propagation velocity (cm/s)	2.8 ± 0.8	2.6 ± 0.6	3.7 ± 0.9	3.3 ± 0.6	< 0.01	< 0.01
Simultaneous contractions (%)	14 ± 22	10 ± 12	5 ± 12	1 ± 3	0.05	< 0.01
Amplitude above the LES (mm Hg) at						
3 cm.	71 ± 38	105 ± 40	86 ± 35	113 ± 34	ns	ns
8 cm.	69 ± 35	92 ± 35	66 ± 35	99 ± 29	ns	ns
13 cm.	53 ± 31	67 ± 30	50 ± 22	65 ± 26	ns	ns
18 cm.	41 ± 30	46 ± 30	51 ± 35	59 ± 32	ns	ns
UES Pressure (mmHg)*	66 ± 27		73 ± 29		ns	
Relaxation time (s)	1.43 ± 0.39		1.54 ± 0.31		ns	
PHX Contraction amplitude (mm Hg)	45 ± 15		42 ± 16		ns	
UES-PHX Coordination (s)	-0.15 ± 0.09		-0.15 ± 0.05		ns	

LES: lower esophageal sphincter; EB: esophageal body; DS: dry swallow; WS: wet swallow; UES: upper esophageal sphincter; PHX: pharynx; ns: not significant.
* Mean pressure in high-pressure zone of sphincter.

Table III. Manometric abnormalities associated with an impaired EB peristaltic velocity in patients with primary SS.

	Group I Impaired (≤ 2.7 cm/s) EB peristaltic velocity (n=11)	Group II Normal (> 2.7 cm/s) EB peristaltic velocity (n=14)	P
LES pressure (mm Hg, mean ± SD)	15 ± 6	24 ± 8	< 0.01
LES relaxation time (s, mean ± SD)	10.7 ± 2.5	9.0 ± 1.4	< 0.05
Rate of simultaneous contractions in EB (%, mean ± SD)	DS: 25 ± 29 WS: 10 ± 14	DS: 6 ± 6 WS: 10 ± 11	0.05 ns

EB: esophageal body; DS: dry swallow; WS: wet swallow; ns: not significant.

Discussion

Although swallowing difficulties are common in patients with primary SS, the first report on esophageal abnor-

Table IV. Results of saliva production and esophageal symptom analysis in primary SS patients with or without an impaired esophageal body (EB) peristaltic velocity.

Saliva production	Group I Impaired EB peristaltic velocity (n = 11)	Group II Normal EB peristaltic velocity (n = 14)	P
Basal whole saliva volume (ml/10 min, mean ± SD)	0.23 ± 0.17	0.67 ± 0.76	< 0.05
Stimulated whole saliva volume (ml/10 min, mean ± SD)	0.44 ± 0.29	1.45 ± 1.60	< 0.05
Symptom	**Group I Impaired EB peristaltic velocity (n = 11)**	**Group II Normal EB peristaltic velocity (n = 14)**	**P**
Frequency of dysphagia episodes (symptom score, mean ± SD)	2.60 ± 1.51	2.71 ± 1.33	NS
Frequency of odynophagia episodes (symptom score, mean ± SD)	0.70 ± 0.82	0.64 ± 0.84	NS
Liquid requirement for swallowing (symptom score, mean ± SD)	1.91 ± 0.30	1.50 ± 0.65	0.05
Frequency of aspiration (symptom score, mean ± SD)	0.90 ± 0.88	0.36 ± 0.84	NS

malities was published only in 1967 (5). Since then, a number of studies have been carried out, but the results are still controversial. The high prevalence of dysphagia is explained as a consequence either of the lack of saliva or of esophageal dysmotility (3-5, 8, 14). Less often, in approximately 10% of the cases, upper esophageal webs have also been reported (5, 6). In contrast, esophageal motility measurements failed to reveal any specific dysmotility patterns in SS (3-5, 7). Grande *et al*. found no manometric differences between SS patients and controls, except for a decrease in the distal esophageal peristaltic velocity for dry swallows in SS patients with dysphagia. Their other finding, that patients with SS have a significantly higher LES pressure than controls, may be questionable, since their value (15.6 mm Hg) was at the lower end of the internationally accepted normal range (4, 13). Anselimo *et al*. studied 27 patients and detected only an increased number of simultaneous contractions when severe dysphagia was present (3). In contrast, Palma *et al*. observed no significant differences in EB motility (7).

Our results are in accordance with the literature as regards the prevalence of dysphagia (70-90%) in primary SS. On the other hand, we observed an impaired EB peristaltic velocity in nearly half of the patients (44%), which appeared to be the predominant esophageal motor abnormality. This alteration was coupled with a mild decrease in the LES pressure and a prolongation of the LES relaxation time, which has not been described previously.

We must note that the absolute values of LES pressure and relaxation time were on the borderline of the internationally accepted normal ranges (13) and the normal ranges in our laboratory. Additionally, other esophageal motor abnormalities, such as a prolonged duration of peristaltic contractions and an increased rate of simultaneous contractions in the EB, were also found in our patients. Most of our patients had a markedly diminished salivary function, which was even more prominent in the group with an impaired esophageal peristaltic velocity. Anselimo *et al*. (3) did not find a correlation between saliva production and esophageal motor disorders. The difference from our results could be explained by the less markedly diminished saliva production in their patients, and/or by the fact that the various parameters in the esophageal motility measurements were not compared individually with the saliva production.

Similarly as in the series of other investigators, the manometric abnormalities of the esophageal function did not correlate with the presence of the different systemic manifestations, the laboratory findings or the demographic parameters of our primary SS patients. The questionnaire analysis revealed a higher liquid requirement for swallowing in patients with an impaired peristaltic velocity and saliva production. This suggests that both esophageal motor abnormalities and a diminished salivary function are factors in the development of swallowing difficulties in primary SS. As there are data indicating a parasympathetic dysfunction in SS (15), its role in the development of an esophageal motor disturbance and/or decreased saliva production can not be ruled out.

To summarize, our examinations revealed that several esophageal motility abnormalities can be found in primary SS patients with systemic manifestations. A decreased EB peristaltic velocity was the most common manometric change, which showed an association with the impaired saliva production and with the higher liquid requirement for swallowing, but not with the laboratory parameters or the systemic manifestations of the disease.

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