Oesophageal and anorectal involvement in systemic sclerosis: a systematic assessment high resolution manometry

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ABSTRACT

Objective. *In systemic sclerosis (SSc), oesophageal and anorectal involvements are frequent and often associated with each other. In clinical practice, oesophageal explorations are often prescribed, while anorectal explorations are rarely proposed and therefore, under-recognised. However, it is well documented in the literature that early detection of anorectal dysfunction could delay and/or prevent the onset of symptoms such as fecal incontinence (FI). The main objective was the systematic evaluation and detection of oesophageal and anorectal involvements in SSc patients.*

Methods. *In this monocentric retrospective study, all patients with SSc addressed in the Department of Functional Digestive Explorations, North Hospital, Marseille for oesophageal and anorectal explorations were included. Self-Questionnaires, evaluating the symptoms and quality of life, were filled by patients during their visit. Explorations were performed on the same day: high resolution oesophageal manometry (EHRM), 3 Dimensional high resolution anorectal manometry (3DHRARM) and endo anal sonography (EUS).*

Results. *44 patients (41 women), mean age 59.8±12 years, were included. With regard to the symptoms, 45.5% of patients had gastro-oesophageal reflux disease (GERD), 66.9% dysphagia, 65.9% constipation and 77.3% FI. The incidence of oesophageal dismotility was 65.9%, anorectal and both upper and lower dysfunction were 43.2%. More than 89% patients with abnormal explorations (EHRM, 3DHRARM or both) were symptomatic. Duration of SSc and altered quality of life was correlated with the severity of digestive involvement.*

Conclusion. *Anorectal dysfunction appears to be closely linked to oesophageal involvement in SSc. Their routine screening is undoubtedly essential to limit the occurrence of severe symptoms such as FI.*

Introduction

Systemic sclerosis (SSc) is a heterogeneous autoimmune disease with a prevalence ranging from 50 to 200 cases per million, characterised by fibrosis of skin and internal organs, microvascular alteration and immune dysregulation. Its pathogenesis remains unknown, but there are many arguments for an initial vascular mechanism (1, 2). SSc preferentially affects women between 45 and 64 years. Two main subtypes of SSc are described depending on the extent of skin fibrosis: diffuse cutaneous SSc (DSSc) and limited cutaneous SSc (LSSc) (3, 4). Antinuclear antibodies are present in the serum of more than 85% patients, some of them being specific for SSc (anti-centromere antibodies (ACA), anti-topoisomerase I or anti-Scl70 antibodies (antiScl70), and anti-RNA polymerase III antibodies). Autoantibodies patterns are directly related to the severity and extent of organ involvement (5-7). For example, Roman *et al*. showed that oesophageal dismotility was strongly associated with positive anti-Scl70 antibodies (8-10). However, when considering the disease as a whole, it has been noticed that involvement of the digestive system is extremely common and has been observed in 75-90% of cases, mainly affecting the oesophagus and the anorectal function (11, 12). However, oesophageal involvement is usually well-documented, whereas anorectal dysfunction remains probably underdiagnosed as it is not systematically assessed even though current literature shows that oesophageal and anorectal disorders are often present together (13, 14). Since 2009, the French High Health Authority recommends physi-

cians to perform oesophageal manometry in the patient's initial assessment, whereas anorectal investigations were only recommended in patients complaining of fecal incontinence (FI) (15). The use of new high resolution manometric probes (oesophageal and anorectal) increases the diagnostic accuracy. Thus, it could be argued that i) a systematic screening with high resolution manometric probes could allow early diagnosis of anorectal involvement in poorly symptomatic patients, ii) early assessment could help in developing earlier therapeutic strategies to reduce the occurrence of FI that significantly alters the patient's quality of life (16). Our primary objective was to systematically assess oesophageal and anorectal dysfunctions in SSc patients using high-resolution manometric probes. Our secondary objective was to correlate digestive damages to the following parameters: symptoms, subtype and duration of the disease, serological profile and impact on the quality of life.

Methods

Patients

In this single-centre retrospective study, from December 2012 to June 2014, all patients with diffuse or limited SSc, referred for oesophageal and anorectal investigations in our Digestive Physiological Unit (Marseille, France) were eligible. The inclusion criteria were: age ≥18 years, and diffuse or limited SSc diagnosed by an expert physician. The exclusion criteria were: age <18 years, organic pathology of the oesophagus, stomach, colon or rectum detected by clinical examination or endoscopy, previous digestive surgery, any disability preventing the carrying out of the investigations, neurological disease. The demographic data and characteristics of the disease were collected (age, sex, duration of the disease, subtype of SSc, other organ involvement and serological profile).

According to the French law, this retrospective study was performed in accordance with the 1975 Declaration of Helsinki.

Questionnaires

In our practice, before the investigations, all the patients are asked, in the waiting room, to answer self-completed questionnaires. The following symptomatic questionnaires are used: GERD-Q for gastro-oesophageal reflux disease (GERD) (17-19), DYMUS for dysphagia (20), KESS for constipation (21), WEXNER for FI (16) and MOS-SF36 for quality of life (22).

Functional digestive investigations

All patients underwent the three following investigations on the same day: Esophageal High Resolution Manometry (EHRM), 3D High Resolution Anorectal Manometry (3DHRAM), Endoanal Ultrasonography (EUS).

EHRM was performed using a solid-state high resolution catheter with 36 solid-state sensors spaced at 1 cm intervals from one another (Sierra Scientific Instruments Inc, Los Angeles, CA). Each sensor is circumferentially sensitive. The EHRM catheter was passed trans-nasally in a patient following a 6 hours fast-period and positioned to record from hypopharynx to the stomach. The manometry examination included a 30-second period to assess basal sphincter pressure followed by ten 5-ml water swallows done at regular intervals. The data were analysed using ManoView® analysis software (Sierra Scientific Instruments, Inc) (23).

EUS was performed in the left lateral decubitus position. A rigid linear rectal probe with 7 MHz frequency was used. A longitudinal and axial study was done. An internal anal sphincter atrophy (IAS) was defined as a thick less than 1 mm (24, 25).

3DHRARM was performed using a high resolution 3D probe with 256 pressure sensors. Studies were done in the left lateral decubitus position, without previous enema. The data was analysed using ManoViewTM® analysis software (Given Imaging). The data recorded was: Mean resting anal pressure (MRP) and Mean squeeze anal pressure (MSP), Recto Anal Inhibitory Reflex (RAIR), and rectal sensibility (26).

Statistical analysis

The data analysis was treated with the software SPSS v. 17.0. The significant threshold was fixed to 5%. A descriptive analysis of the population was done. The continuous parameters were presented under the shape of averages and standard deviations, qualifying parameters and proportions. The functional scores were transformed into binary variables from available thresholds in the literature. The quality of life's scores were calculated by means of the algorithm supplied by the designers. Subgroups of patients were constituted: with or without oesophageal/anorectal or both oesophageal and anorectal involvement. The comparisons between these various subgroups were made by mean of Chi2 or Digher tests.

Results

Patient cohort

Forty-four patients (41 women) of mean age 59.8±12 years were included in this retrospective study from December 2012 to June 2014. The individual cohort characteristics are described in Table I.

Questionnaires

Forty-four patients answered the different questionnaires. GERD was observed in 20 patients (45.5%), dysphagia in 25 patients (56.9%), constipation in 29 patients (65.9%) and a FI in 34 patients (77.3%). A significant reduced physical and social quality of life was, similarly, observed considering the results of MOS SF36 questionnaires. As a matter of fact, the mean PCS score (physical component) was 37.9 and the mean MCS score (psychological com-

Table I. Demographic and patients characteristics.

Type of SSc	n=44
Diffuse n (%)	16 (36.4%)
Limited n (%)	28 (63.6%)
Age of SSc	n=44
Age average of SSc (years)	9.2 ± 8.3
< 5 years n (%)	17 (39.6%)
5 à 10 years n (%)	11 (25%)
>10 years n (%)	16 (36.4%)
Digital ulcerations n (%)	23 (52.3%)
Renal impairment n	0
Pulmonary fibrosis n (%)	8 (18.2%)
Pulmonary arterial hypertension (PAH) n (%)	2 (4.7%)
Antibodies:	n=44
Anti-Scl 70 n (%)	18 (40.9%)
Anti-centromere n (%)	17 (38.6%)

ponent) was 36.6, considering that normal physical and psychological statement is 100. Three patients were totally asymptomatic.

Investigations

Results of EHRM, EUS and 3DHRARM are detailed in Table II. A typical SSc oesophageal manometric involvement at EHRM was observed in 29 patients (65.9%). An IAS atrophy was observed in 19 patients (43.2%) with the EUS. Nineteen patients (43.2%) had both an oesophageal involvement and an IAS atrophy (Table II).

Symptoms and involvement

Data are presented in Table III. Twenty-six patients (89.7%) with typical oesophageal involvement at EHRM were symptomatic. Symptoms included: GERD, dysphagia, or both. Eighteen patients (94.7%) with IAS atrophy had lower digestive symptoms: constipation, FI, or both. Anorectal dysfunction was always associated with oesophageal functional abnormalities. All the patients with oesophageal functional involvement had IAS atrophy. Seventeen patients (89.5%) with both oesophageal and anal involvements at functional or morphological investigations had digestive symptoms: upper GI symptoms in 94.1%, lower GI symptoms in 94.1% and both upper and lower GI symptoms in 88.2%.

Statistical associations

Patients with IAS atrophy were significantly older than patients without (65.2±9.7 *vs*. 56±12.1 years, $p<0.005$), but there was no difference in age for patients with or without oesophageal involvement.

More DSSc patients than LSSc had an oesophageal involvement (respectively 58.6% and 41.4%, NS). Conversely, anorectal and combined upper and lower GI involvement was more frequent in LSSc patients (57.9% *vs* 42.1% and 52.9% *vs*. 47.1%, NS). The duration of SSc was significantly higher in cases associated with oesophageal dysmotility (11.9±9 *vs*. 3.5±1.6 years, $p<0.05$), anorectal dysfunction (13.9±9.5 *vs*. 5.1±5.6 years, $p<0.05$) and combined upper and lower GI involvement (14.6±9.7 *vs*. 5.7±5.1 years, $p<0.05$). Prevalence of anti-Scl70 and anti-centromere antibodies was not significantly different when patients with esophageal, anorectal or combined involvement were compared to patients without such involvements. A significant association between the presence of digital ulcers and combined anorectal and oesophageal involvement was observed ($p<0.01$). No significant association was observed in cases of isolated oesophageal and

Table II. Investigations' results.

EHRM	n = 44
LES hypotonia n (%)	33 (75%)
Absent peristaltism of inferior oesophagus 2/3 n (%)	29 (65.9%)
Absent peristaltism + LES hypotonia n (%)	29 (65.9%)
EUS	n = 45
IAS atrophy n (%)	19 (43.2%)
Sphincteria rupture n (%)	19 (43.2%)
Both n (%)	13 (29.5%)
Only EAS n (%)	2 (4.5%)
Only IAS n (%)	4 (9.1%)
Pelvic static trouble n (%)	20 (45.5%)
3DHRARM	n = 44
Resting anal pressure (IAS) average (mmHg)	55.7 ± 26.5
IAS hypotonia n (%)	27 (61.4%)
Squeeze anal pressure average (mmHg)	97.8 ± 58.6
Decreased squeeze anal pressure n (%)	18 (40.9%)
Decreased rectal sensibility n (%)	6 (13.6%)
Altered RAIR n (%)	12 (27.3%)
IAS hypotonia + atrophy n (%)	17 (38.6%)
IAS atrophy + EHRM involvement n (%)	19 (43.2%)
IAS atrophy/hypotonia + EHRM involvement n (%)	17 (38.6%)

Table III. Symptoms and investigations' results.

Oesophageal involvement	
Typical EHRM involvement	n = 29
Asymptomatic n (%)	3 (10.3%)
GERD n (%)	18 (62.1%)
Dysphagia n (%)	20 (69%)
GERD AND Dysphagia n (%)	12 (41.4%)
GERD AND/OR Dysphagia n (%)	26 (89.7%)
Anorectal involvement	
EUS typical involvement (IAS atrophy)	n = 19
Asymptomatic n (%)	1 (5.3%)
Constipation n (%)	14 (73.7%)
Fecal incontinence n (%)	18 (94.7%)
Constipation AND fecal incontinence n (%)	14 (73.7%)
Constipation AND/OR fecal incontinence n (%)	18 (94.7%)
IAS atrophy and hypotonia n	n = 17
Asymptomatic n (%)	1 (5.9%)
Constipation n (%)	13 (76.5%)
Fecal incontinence n (%)	16 (94.1%)
Constipation AND fecal incontinence n (%)	13 (76.5%)
Constipation AND/OR fecal incontinence n (%)	16 (94.1%)
Both oesophageal and anorectal involvement	
EHMR typical involvement + IAS atrophy	n = 19
Asymptomatic n (%)	0
Oesophageal symptomatology n (%)	18 (94.7%)
Anorectal symptomatology n (%)	18 (94.7%)
Both oesophageal and anorectal symptoms n (%)	17 (89.5%)
EHRM typical involvement + IAS atrophy/hypotonia	n = 17
Asymptomatic n (%)	0
Oesophageal symptomatology n (%)	16 (94.1%)
Anorectal symptomatology n (%)	16 (94.1%)
Both oesophageal and anorectal symptoms n (%)	15 (88.2%)

anorectal involvement. No association was found between pulmonary hypertension and skin fibrosis extension and oesophageal and/or anorectal involvements.

In the presence of IAS atrophy, "physical capacity" dimensional score (16.5 *vs*. 27 without atrophy, $p<0.05$) and PCS score (19 *vs*. 26.8 without atrophy, $p<0.05$) were reduced significantly. Furthermore, in cases of IAS atrophy, "social quality of life" dimensional score was reduced (17.8 *vs*. 26.1, $p<0.05$). A significant reduced physical quality of life was observed in case of oesophageal involvement associated or not to IAS atrophy ($p<0.05$).

Symptomatic IAS atrophy was significantly related to patients'age (64.9±9.9 *vs*. 56.2±12.2 years, $p<0.05$). No association was found between anal sphincter rupture and anorectal symptoms in case of IAS atrophy.

Discussion

In this study we present and describe the cases of 44 SSc patients with systematic assessment of oesophageal and anorectal involvement in our investigational department. To our knowledge, this work is the first one using high resolution manometry for both oesophageal and anorectal assessment.

Dysphagia and GERD were the most common oesophageal symptoms, observed in about 50% of cases, similar to what was previously reported in the literature (27-29). All patients of our study were under medications: PPi often associated with prokinetics. Furthermore, a high prevalence of typical manometric oesophageal dysfunction was observed (65.9%), in the range reported in the literature from 55.1% to 90% (8, 14, 30-33). Also comparable to our results, Roman *et al*. observed oesophageal involvement by EHRM in 55.1% of cases, 89.7% of them being symptomatic (GERD and/or dysphagia) (8). Lock *et al*. studied the predictive value of oesophageal symptoms (heartburn or dysphagia) on oesophageal motor impairment and reported a positive predictive value of 62%. This low correlation between symptoms and functional alteration at the investigational level may justify, according to the authors, a systematic manometric screening in SSc patients (33). In our study, half of patients had upper digestive symptoms whereas 29/44 (66%) had EHRM typical SSc pattern, justifying a systematic manometric screening. However, there was probably a recruitment bias in our study as patients consulted in our department for digestive investigations, and thus they were more prone to have digestive symptoms in comparison to SSc patients consulting in other medical departments.

The frequency of constipation in our series was 65.9%, similar to the frequency reported in other studies (34, 35). FI was found in 77.3% of cases and mainly concerned gas incontinence. The FI frequency was higher when compared to data reported in the literature (ranging from 11.5 to 53%) (34, 36-39). This high rate of FI in our study may partly be explained by the recruitment of our department and by the use of a systematic screening questionnaire focused on anorectal symptoms.

In our study, 43.2% of patients presented anorectal dysfunction taking only into account the criterion of IAS atrophy and 38.6% had both IAS atrophy and hypotonic resting anal sphincter pressure. Marie *et al*. estimated the prevalence of anorectal dysfunction to be between 50 to 70% (11). For a few years now, many authors have demonstrated that EUS accurately diagnoses IAS atrophy in SSc patients, making it a suitable criterion to determine the SSc-related anal lesion. Engel *et al*. were the first, in 1994, to describe the IAS atrophy in 2 patients with SSc and FI (40). Many studies have subsequently described the sonographic sign with significant results in incontinent SSc patients (39, 40, 41).

In 2011, Thoua *et al*. found IAS atrophy among both symptomatic and asymptomatic SSc patients (42). In our study, 94.7% of patients having an IAS atrophy suffered from FI. Hypotonic resting anal sphincter pressure, reflecting IAS function, was significantly associated with IAS atrophy (Table II). Hypotonic resting anal sphincter pressure is not specific of SSc aetiology but has often been reported in the literature by classical anorectal manometry before the contribution of the EUS and 3DHRARM. Several studies have described hypotonic resting anal sphincter pressure in incontinent or constipated patients (35, 36, 38). In a series of 17 SSc patients, Chiou *et al*. reported a 35% incidence of asymptomatic patients having abnormal anorectal manometry (36). In the present study, only one patient was asymptomatic in the presence of IAS atrophy (Table III).

27.3% of patients had impaired RAIR (decreased or absent) (Table II). Data in the literature reported various frequency of RAIR impairment, from 10 to 87% of SSc patients with or without incontinence (13, 34, 36, 37, 43). In the present study, 13.6% of patients had a decreased rectal sensibility (Table II). Our results are consistent with the few studies reporting a decreased rectal sensibility in SSc (42, 44).

To summarise our results, anorectal dysfunction in SSc seems to be defined by several abnormalities detected by EUS and 3DHRAM, the more representative being IAS atrophy and low resting anal sphincter pressure. RAIR impairment and decreased rectal sensibility also appear to participate in SSc related involvement. These last two abnormalities suggest an early neuropathic involvement resulting from vascular (ischaemia of the vasa nervorum) or fibrotic (nerve fibers cut by excessive deposits of collagen) damages.

94.1% of patients with anorectal dysfunction were symptomatic in our study with a higher incidence of incontinence (94.1%) compared to constipation (76.5%) (Table III). In the literature, the overall incidence of anorectal dysfunction in incontinent patients is lower than 40-84% (33, 43, 45). Engel *et al*. explored two incontinent patients and Daniel *et al*. one constipated patient with both conventional manometry and EUS and found a typical involvement (40, 41). Basilico *et al*. reported 35% of abnormal manometry in SSc constipated patients (35).

In our study, 38.6% of patients had both oesophageal and anorectal involvements. Anorectal dysfunction was always associated with oesophageal functional abnormalities, whereas oesophageal dysfunction could be iso-

lated, as seen in nine patients (20.5%). An earlier oesophageal involvement occurring in SSc disease could be suggested. Few studies assessing the relationship between these two involvements gave discordant conclusions. Lock and *al*. studied oesophageal and anorectal function using conventional manometry in 26 SSc patients and did not find any correlation (37). In Lepri *et al*. series, 14 of the 59 patients with very early SSc (23.7%) had a combined impairment showing the early gastro intestinal involvement in SSc (46). Finally, Hamel-Roy *et al*. found a strong correlation between LES and RAIR amplitude in a series of 26 SSc patients (13). This correlation can be in part explained by the functional and histological similarities, particularly in the SSc fibrosis process, between LES and IAS. At the early stage of the disease, the fibrous proliferation develops in the submucosal, the muscularis mucosae and the rectal wall, causing a decreased rectal compliance with possible RAIR impairment and hypotonic resting anal sphincter pressure. Later on, smooth muscle atrophy resulting from local ischaemic phenomena may cause an anal incontinence (2).

As similarly described by other authors, we found a significant association between the duration of the disease (but not with the age of patients) and the presence of oesophageal involvement, suggesting an increased incidence of oesophageal alteration with the duration of the disease. Few authors reported this correlation (27, 47, 48). By contrast, the significant association in our study between the duration of SSc and anorectal or combined dysfunctions has not been reported in the literature.

In our series, the presence of digital ulcers was significantly associated with combined oesophageal and anorectal involvement. To our knowledge, such association has never been reported in the literature. However, other significant associations have been described in literature such as oesophageal involvement and skin lesions (8) or lung disease (49), which could not be confirmed in our work. The type of SSc (DSSc and LSSc) had no significant impact on esophageal, anorectal involvements (nor the two combined). In contrast, other authors such as Roman and *al*. found a significant association between oesophageal involvement and DSSc (8, 49-51). To date, association between SSc subtypes and anorectal or combined dysfunctions have not been reported.

The serological profile was not significantly related to the presence of esophageal, anorectal or combined impairment, despite a higher incidence of anti-Scl70 patients in each group (data not shown). However, several studies have demonstrated a strong association between oesophageal motor impairment and positive anti-Scl70 antibodies (8-10, 47). Roman and *al*. even suggested in cases of positive anti Scl70 SSc patients not to perform manometry and to immediately propose endoscopy, with the aim of looking for complication (oesophagitis, Barett oesophagus (BE), oesophageal adenocarcinoma) (8). Indeed, recent studies reported between 7 to 13% of BE in SSc patients (51, 52) and Wipff *et al*. reported first an increased risk of oesophageal adenocarcinoma in SSc patients compared to general population (incidence of 0,7% per year *vs*. 0,45%) (53).

Finally, in our work, patient's age was not correlated with the presence of an oesophageal dysfunction. However, a higher age was significantly associated with the presence of IAS, mainly in symptomatic patients (constipation and / or incontinence). It could be argued that some degree of IAS fibrosis could be related to physiological atrophia due to aging (54).

In our study, mean scores of quality of life for each of the 8 dimensions, MOS SF36 components, were generally low, reflecting the social, mental and physical impacts of SSc. The physical impact was higher in the presence of an esophageal, anorectal or both combined impairment. Social life was significantly affected in the presence of anorectal dysfunction. In the literature, other studies have used the SF36 as a tool for clinical evaluation and the evaluation of the quality of life of SSc patients. Georges and *al*. found a correlation between patients' quality of life (physical and social impact) and severity of clinical involvement of the disease (55). In 2012, a Canadian literature review emphasise the impaired quality of life in SSc patients with gastrointestinal involvement (12).

Recently, a new comprehensive and self-completed questionnaire for the assessment of gastrointestinal involvement in scleroderma patients has been validated. The UCLA Scleroderma Clinical Trial Consortium Gastrointestinal Tract (UCLA SCTC GIT 2.0) has 7 multi-item scales: Reflux, Distension/ Bloating, Diarrhoea, Fecal Soilage, Constipation, Emotional Well-being, and Social Functioning and a total gastro intestinal tract or GIT score (56, 57).

In terms of critical appraisal of our work, the main limiting factors of our study are the small cohort size of SSc patients recruited and its retrospective design.

Conclusion

Oesophageal, anorectal and combined impairment are common in SSc. In our study, anorectal dysfunction was always associated with oesophageal involvement, but the latter could be isolated, suggesting the possibility of an earlier oesophageal impairment in the disease history. A systematic oesophageal screening by EHRM at the initial disease evaluation should be performed, due to the risk of oesophagitis, BE and oesophageal adenocarcinoma. The results of the current study suggest that this screening may be extended to anorectal explorations. Symptoms collected with self-completed questionnaires pointed out the high number of incontinent patients. FI is a "taboo" symptom and is difficult to detect by a simple examination. This justifies proposing 3DHRARM and EUS, both complementary investigations, which provide diagnostic accuracy and a gain for further management. An early management of anorectal dysfunction could prevent or at least delay the onset of severe FI. A prospective study with oesophageal and anorectal systematic assessment in SSc patients could help validate the interest of an earlier diagnosis of these digestive involvements in order to prevent potentially disabling symptoms.

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Key messages

- High frequences of symptomatic patients with abnormal explorations results at EHRM, 3DHRARM and EUS.
- Anorectal dysfunction always associated with oesophageal involvement in SSc patients in this study..
- Necessary routine oesophageal and anoretal dysfunction screening to limit occurrence of severe symptoms such as fecal incontinence and preserve quality of life.

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