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Esophageal involvement in juvenile localized scleroderma: a pilot study

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Abbreviations:
LES: lower esophageal sphincter
JLS: juvenile localized scleroderma
JSS: juvenile systemic sclerosis
ANA: anti-nuclear antibody
RF: rheumatoid factor
GI: gastrointestinal
RI: reflux index
GER: gastroesophageal reflux.

Competing interests: none declared.

ABSTRACT

Objectives. *To evaluate the esophageal involvement in patients with juvenile localized scleroderma (JLS).*

Methods. *A cohort of patients with JLS underwent esophageal stationary manometry to evaluate esophageal motility and lower esophageal sphincter (LES) function, distal esophagus 24-hour pH-monitoring to detect gastroesophageal reflux (GER) and upper gastrointestinal (GI) endoscopy to evaluate the presence of esophagitis.*

Results. *Fourteen patients (10 female, mean age 13.3 yrs, mean disease duration 4.7 yrs), took part in the study. Ten had linear scleroderma, three deep morphea, and one generalized morphea. Esophageal abnormalities were found in 8/14 patients (57%): pathological acid exposure on 24-hour pH-monitoring was found in 7; non-specific esophageal motor abnormalities in 5 and endoscopy-proved esophagitis in 5 symptomatic patients. Interestingly, 5 out of 8 patients with esophageal abnormalities were found to be ANA positive, and 2 were also RF positive.*

Conclusion. *Esophageal involvement is not unusual in patients with juvenile localized scleroderma, even in the absence of specific symptoms. These preliminary findings, if confirmed in a larger cohort of patients, may support the indication for an extensive GI evaluation especially in presence of positive autoantibodies or specific GI symptoms.*

Introduction

Juvenile scleroderma syndromes are multisystem autoimmune diseases whose unifying characteristic is the presence of hard skin and the onset before 16 years of age. They can be separated into two main categories: those with skin sclerosis but no vascular or internal organ involvement, such as juvenile localized scleroderma (JLS), and those with diffuse skin sclerosis associated with internal organ involvement, such as Juvenile Systemic Sclerosis (JSS) (1).

Internal organs are frequently involved in JSS. Esophageal motility is impaired in approximately 75% to 90% of patients. Similarly, decreased motility has been described in the stomach, small intestine, colon and anorectal area, and can give rise to a significant morbidity (2, 3).

Little information is available on esophageal motility involvement in patients with JLS.

The aim of the present study was to evaluate the presence of esophageal involvement in a cohort of patients suffering from JLS.

Methods

Study subjects

The study involved 14 consecutive patients with JLS referred to University of Padova (Italy) Pediatrics Department from January 2003 until December 2003. Demographic characteristics included gender, age and disease duration at the time of GI evaluation. The clinical subtype was defined according to the Mayo Clinic classification criteria (1). This classification gathers the different varieties of JLS into five groups: plaque morphea (PM), generalised morphea (GM), bullous morphea (BM), linear scleroderma (LS) including the head-face subtype, *en coup de sabre* (ECDS), and deep morphea (DM). Extracutaneous manifestations were also recorded. The serum autoantibody profile included antinuclear antibodies (ANA), anti-SCL-70 (DNA-topoisomerase1), anticentromere (ACA), anticardiolipin antibodies (ACL), and rheumatoid factor (RF). Abnormal values were referred to the normal range of laboratory standards. ANA titer was tested on Hep2 cell line, Scl-70, anticentromere (ACA) and anticardiolipin antibodies (ACL) were tested by ELISA, rheumatoid factor (RF) was tested by nephelometry.

Esophageal manometry

Esophageal manometry was performed using an 8-hole catheter (Ø 3 mm), with 4 radial holes (oriented at 90° from each other) for the lower esophageal sphincter (LES) study. LES function and esophageal motility study, evaluated after wet swallows, included: basal LES pressure (mmHg), LES post-swallowing relaxation (%), amplitude (mmHg) and duration (seconds) of esophageal body contractions and esophageal body

peristaltic contractions (%). Data have been compared with our laboratory normal values obtained from 30 healthy subjects (age 6-18 yrs).

24-hour pH-monitoring of the distal esophagus

Esophageal pH-monitoring was performed according to the guidelines of the European and North American Societies of Pediatric Gastroenterology and Nutrition (4).

Data were collected using a portable device with a 1-point antimony electrode (Digitrapper II, Medtronic, Milan, Italy). Acid reflux was defined as the presence of an esophageal pH lower than 4, in accordance with international criteria. The pH test was used to assess: reflux index (RI, as percentage of the total registration time in which the esophageal pH is < 4) (%), esophageal clearance (reflux time/number of reflux episodes; min/refl), number of refluxes > 5 min, number of reflux episodes. pH-monitoring parameters were compared with normal values from the literature (4).

Upper gastrointestinal endoscopy

This procedure was performed using a PENTAX video-endoscope (EG-2470 K, EG-1870 K) under deep sedation and biopsies were collected at proximal and distal esophagus, gastric body, antrum and duodenum.

Endoscopic features of the esophagus were classified according to the Los Angeles classification criteria. These criteria focus on the extent of visible mucosal breaks with a grading ranging from grade A (one or more mucosal break no longer than 5 mm, that does not extend between the tops of two mucosal folds) to grade D (one or more mucosal break which involves at least 75% of the esophageal mucosa) (5). Since reflux esophagitis is a patchy lesion, histological criteria for gastroesophageal reflux disease were not used (6, 7).

Ethical considerations

The study was approved by the Ethical Committee of the Pediatrics Department at the University of Padua. Parents and/or patients signed to give their informed consent.

Results

Study subjects

Fourteen patients entered the study and their clinical features are sumarized in Table I. Ten were female and four male. Ten had a linear scleroderma subtype, three generalized morphea and one deep morphea.

Four patients had other extracutaneous manifestations such as: 2 episcleritis, 1 Raynaud phenomenon, 1 EEG alterations and 1 aortic insufficiency. Five patients were ANA positive (pts. no. 2, 3, 4, 6, 8), and in three, RF was present (pts. no. 2, 8, 13). None was Scl-70, ACA or ACL positive. Five patients had gastrointestinal symptoms such as upper abdominal pain, regurgitation, dysphagia and nausea. None had been previously treated with NSAIDs or corticosteroids, nor with proton pump inhibitors or calcium channel blockers. All patients underwent esophageal 24-hour pH-monitoring, esophageal manometry and upper gastrointestinal endoscopy.

Table I. Clinical characteristics of the patients.

Gender (F: M)	2.5:1
Age at GI evaluation (yrs)	
Mean (range)	13.3 (6-18)
Disease duration at GI evaluation (yrs)	
Mean (range)	4.7 (0.2-13.2)
Clinical subtypes (no. patients)	
Linear	10 (71%)
Generalized	3 (21%)
Deep	1 (7%)
Autoantibodies (no. patients)	
Antinuclear (ANA)	5 (35%)
AntiDNA-topoisomerase1 (Scl-70)	0
Anticentromere (ACA)	0
Anti cardiolipin (ACL)	0
Rheumatoid factor	3 (21%)
Extracutaneous involvement (no. patients)	
Episcleritis	2 (14%)
Raynaud phenomenon	1 (7%)
Aortic valve insufficiency	1 (7%)
Abnormal EEG	1 (7%)

Esophageal manometry

Abnormalities were recorded in five subjects (35%) (Table II). In case no. 1, LES relaxation after swallowing was lower than normal (70.2%). During the test, 20% of the contractions recorded were of lower than normal amplitude.

Case no. 2 showed a low percentage of peristaltic waves (69%), and decreased LES basal pressure (9.3 mmHg). In case no. 3, we found increased amplitude of contractions in the distal esophagus (188.5 mmHg). Case no. 4 had an increased LES basal pressure (34.8 mmHg) and increased contractions amplitude of the distal esophagus (204 mmHg). In case no. 5, increased LES basal tone (mean basal pressure 38.2 mmHg) was found.

24-hour esophageal pH monitoring

A pathological acid exposure of the distal esophagus was detected in 7 patients (50%), with a mean RI of 15.7 ± 6.7 (range 11.4-27.4). One patient had a longer esophageal clearance time (14.5 min/refl) associated with a pathological RI.

Upper GI endoscopy

Five patients with pathological findings at esophageal 24-hours pH-monitoring and gastrointestinal symptoms presented esophagitis, which was of grade A in 4 and of grade B in one patient.

No other significant abnormalities were found in gastric and duodenal biopsies and no patient presented eosinophilic esophagitis. Interestingly, four out of five patients with esophagitis presented with positive ANA (pts. no. 3, 4, 6, 8) and one was also RF+ (pt. no. 8).

Table II. Esophageal findings of the patients with juvenile localized scleroderma.

Patients	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Normal value
Clinical subtypes	LS	LS	LS	LS	DM	LS	LS	GM	LS	GM	LS	LS	LS	GM	
Basal LES pressure (mmHg)	27.4	9.3	21.6	34.8	38.2	15	27	22	24	14	13	30	25	21.6	15-25
LES post-swallowing relaxation (%)	70.2	100	80.2	100	100	100	62	100	100	100	100	99.8	100	90	> 80
Amplitude of esophageal body contraction (mmHg)	65.4	89.7	188.5	204	113.7	94.7	106	126.3	179.5	111.6	142.7	141.9	133.3	90	20-180
Esophageal body peristaltic contraction (%)	100	69	100	90	100	100	100	100	100	100	100	80	100	100	> 75
Reflux index (%)	0.7	11.4	14.0	15.1	11.4	13.8	20.7	27.4	0.7	0.4	3.0	**4.1**	2.3	2.5	< 5.4
Esophageal clearance (min/refl)	2.3	14.5	2.7	3.6	1.9	2.3	0.7	1.3	1.1	0.6	1.9	**2**	0.9	1.5	< 4
Refluxes > 5 min (no.)	0	3	4	2	6	5	2	8	0	0	1	**2**	0	1	< 6.8
Reflux episodes (no.)	4	10	105	18	89	195	143	80	10	8	33	**28**	19	24	**< 45**
GI symptoms			upper abdominal pain	nausea, upper abdominal pain		dysphagia	regurgitat., upper abdominal pain	regurgitat., upper abdominal pain							
Endoscopy abnormalities			grade A esophagitis	grade A esophagitis		grade A esophagitis	grade A esophagitis	grade B esophagitis							

LS: linear scleroderma; DM: deep morphea; GM: generalized morphea; ND: not done; ANA: antinuclear antibodies; RF: rheumatoid factor; RP: Raynaud phenomenon.

Discussion

It is well known that patients with JSS may develop esophageal involvement in approximately 75-90% of the cases with the typical pattern consisting in low amplitude contractions of the distal esophagus and low basal LES pressure (2).

It has been recently reported that JLS may also affect extracutaneous sites, which may be neurological (8-10), cardiac (11, 12) and even respiratory (13), albeit at lesser extent in comparison with JSS.

In the present study, we evaluated esophageal motor function and acid exposure, independently on the presence of specific symptoms, in 14 consecutive patients referred to our Department in one year for JLS. We observed esophageal involvement in 8 out of 14 patients (57%) with JLS: 7 had pathological pH-test findings, and in four of them, concomitant esophageal dysmotility was also present.

Interestingly, 5 out of 8 patients with esophageal abnormalities were found to be ANA positive, 2 also RF positive. None of those without esophageal abnormalities were ANA+ and only one RF+. No other correlations were found between esophageal abnormalities and any demographic and clinical characteristics of the patients including disease duration and autoantibodies pattern. However, because of the limited number of patients evaluated, we did not consider it appropriate to make any statistical comparisons.

Since no patient with plaque morphea (PM) was included in the present study, we cannot extended the results obtained to all the JLS subtypes. However, since data from the literature show that the frequency of extracutaneous manifestations is not significantly different among the various subtypes of JLS (14), it is reasonable to speculate that, probably, GI involvement could be present also in the sub-group of patients with PM.

In localized scleroderma, gastrointestinal abnormalities, mainly represented by asymptomatic sclerotic changes of the esophagus or abnormal esophageal motility have been previously described in single case reports (15, 16). Dehen *et al*. found esophageal abnormalities in 7 out of 41 patients with morphea (17%), in some cases associated with the linear subtype. Most of them were asymptomatic patients and some were children. One patient with morphea, who later developed systemic sclerosis, had total dilatation of the esophagus with hypotonia of the LES. In the other 6 patients, decreased esophageal peristalsis and/or hypotonia of the LES were found (13). Weber *et al*. found esophageal abnormalities on 24-hour esophageal pH-monitoring in 4 out of 5 pediatric patients with JLS (17). Other Authors reported gastroesophageal reflux in 3 out of 16 adult patients (18%) with clinical and histological diagnosis of localized scleroderma (18).

In our study, the percentage of patients who had pathological RI is 50% and this result can be considered very important.

The pressure abnormalities that we recorded contrast with those commonly

found in JSS. In fact, in our patients we found an increased basal LES pressure and a wide contractions amplitude of the distal esophagus. Conversely, esophageal involvement in JSS consists of lower LES basal pressure and small amplitude of contractions in the distal esophagus. Only one patient in our series had esophageal motility abnormalities comparable to those reported in JSS, associated with pathological reflux. This patient (No. 2) presented clear features of GER associated with LES hypotonia and low percentage of peristaltic contractions after swallowing. Nevertheless, no signs or symptoms of JSS were present in this patient.

We may speculate that, in our group of patients, GER may be due to a mechanism different from ineffective esophageal motility (as in systemic sclerosis), such as transient lower esophageal sphincter relaxations. In our study, esophageal motility was evaluated using esophageal stationary manometry, which allows a short-time study of esophageal contractility. Therefore, it could be possible that these patients present transient/intermittent motor abnormalities, which in turn could cause reflux. This hypothesis should be confirmed in a larger group of patients by using 24 hour-esophageal manometry.

Interestingly, four out of five patients with symptomatic GER and esophagitis at endoscopy were ANA positive. One of these cases (no. 3), in addition to having esophagitis, pathological RI and manometry abnormalities, also suffered from episcleritis and aortic valve insufficiency. These observations seem to confirm the results of a recent multicenter survey that reported a significantly higher frequency of ANA in JLS patients with extra-cutaneous manifestations (51.6%) in comparison to those without them (39.5%) (14).

Conclusion

Although carried out on a relatively small cohort of patients, this study shows that esophageal involvement can be present in children and adolescents with JLS, either asymptomatic or with evident symptoms of esophageal dysfunction. Thus, these findings highlight the possible risk of extracutaneous involvement in JLS. Once confirmed in a larger cohort of patients, these findings might support the indication for an extensive GI evaluation in patients with JLS, especially in the presence of positive autoantibodies or specific GI symptoms.

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