Med. J. Cairo Univ., Vol. 86, No. 7, December: 3705-3713, 2018
www.medicaljournalofcairouniversity.net

The Predictive Factors of Abnormal Esophageal Motility in Systemic Sclerosis Patients by High Resolution Manometry

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Abstract

Background: Esophageal motility changes occur in about 80% of systemic sclerosis (SSc) patients with decreasing the motility of the lower two-thirds of the esophagus and lower esophageal sphincter (LES) pressure.

Aim of Study: Using high resolution manometry (HRM) to study the esophageal motility disorder in patients with systemic sclerosis to evaluate the predictive factors associated with esophageal affection.

Patients and Methods: A prospective study was done on twenty female patients with SSc. Demographic data and esophageal symptoms including Gastroesophageal Reflux disease (GERD) and dysphagia were evaluated. All patients underwent HRM and High Resolution Computed Tomography (HRCT), Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), Hemoglobin level (Hgb), Forced Vital Capacity (FVC).

Results: High resolution manometry showed normal upper esophageal contraction in 100% of patients. Middle and lower esophageal contraction were normal in 30%, hypoperestalsis in 5%, and aperestalsis in 65% of patients. Regarding the lower esophageal sphincter pressure, it showed normal pressure in 30%, hypotensive in 65% and hypertensive in 5% of patients. The esophageal involvement was GERD in 70% and dysphagia in 45% of patients. The pulmonary involvement was dyspnea in 70% and cough in 40% of patients. All patients had skin involvement. Abnormal motility was present in 14 out of 20 patients (70%) which was significantly related to Interstitial Lung Disease (SSc-ILD) (p= 0.001), SSc subtypes (p=0.03), dyspnea (p=0.01) and FVC (p=0.046). A significant relation between GERD and ILD (p<0.05) was found.

Conclusion: This study confirmed an increased prevalence of esophageal motility disorders in SSc patients with and without esophageal symptoms.

Key Words: *HRM – Systemic sclerosis – HRCT – Esophageal motility.*

Introduction

SYSTEMIC sclerosis (SSc) is a generalized disease affecting the connective tissue of skin, gastrointestinal tract, lungs, kidneys and heart. There is massive deposition of the collagen, alterations of the microvasculature and disturbances of the immune system [1]. Pulmonary hypertension, progressive pulmonary fibrosis, severe gastrointestinal involvement, and heart disease related to systemic sclerosis are the main causes of death. Limited disease has a relatively better prognosis except when pulmonary hypertension develops as a late complication [2]. The annual incidence of systemic sclerosis is estimated to be 10 to 20 cases per 1 million persons [3].

Its aetiology is unknown, occurring most frequently in females, aged 35-65 years. It is classified as diffuse cutaneous systemic sclerosis (dcSSc) or limited cutaneous systemic sclerosis (lcSSc) based on the extent of cutaneous involvement [4]. The lcSSc patients may have skin thickening which involves the extremities distal to the knees and elbows. In contrast, dcSSc have skin thickening involving the trunk and/or limbs proximal to the knees and elbows [5].The collaboration of the American College of Rheumatology and the European League Against Rheumatism (EULAR) proposed a new set of criteria in 2013. Further items are given a weighted score, a score of 9 or more is diagnostic of systemic sclerosis. A score of 9 is given for the major criterion of skin thickening extending proximal to the metacarpophalangeal (MCP) joints, therefore is sufficient to make a diagnosis on its own [6].

Gastrointestinal tract involvement is very common, affecting about 90% of the systemic sclerosis patients [7]. It is commonly affecting the esophagus. The incidence of subjective esophageal symptoms (reflux and/or dysphagia) ranges from 42-80%, and as many as 50-90% of patients with SSc have abnormalities on esophageal motility. Thus, the esophagus is second to the skin as the most commonly affected organ in SSc [8-10]. The gastroesophageal reflux (GER) is suggested to be an important cause of interstitial lung disease (SSc-ILD) and idiopathic pulmonary fibrosis [11].

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An esophageal motility pattern consisting of distal aperistalsis and a hypotensive lower esophageal sphincter (LES) is often termed scleroderma esophagus; however, this pattern can be identified in other systemic diseases [12]. Despite its prevalence, the understanding of the pathogenesis of esophageal dysfunction in SSc remains relatively poor; mechanisms involving neurodegeneration, vascular injury, ischemia and collagen deposition causing muscular atrophy and fibrosis are considered [13].

Late manifestation of SSc-related lung disease is dyspnea; however, lung involvement is common and is the leading cause of death in patients with systemic sclerosis [14]. Systemic sclerosis can cause affection of the lung parenchyma in the form of interstitial lung disease and the pulmonary blood vessels in the form of pulmonary arterial hypertension. Thus, for the early detection of interstitial lung disease and pulmonary arterial hypertension, a routine screening in all patients using pulmonary function tests and Doppler echocardiography is necessary [15,16].

Symptoms are poorly correlated with objective findings of esophageal disease in patients with SSc [17]. So this study was conducted to detect the relation between the esophageal symptoms and the findings of esophageal motility to accomplish early and effective management.

Patients and Methods

This study included 20 patients with a definite diagnosis of SSc. Patients attended the Department of Internal Medicine, Assiut University Hospital (Motility Unit), during the period from March 2014 to October 2015. Full history, clinical evaluation, laboratory investigations; Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and Hemoglobin level (Hgb), high resolution CT chest and pulmonary function test were done. The patients were all females and their age ranged 19-60 years with mean age 39.7± 14.4 and their disease duration range was considered from the onset of Raynaud's phenomena. The criteria for diagnosis of SSc were based on the American college of rheumatology and EULAR new classification criteria for SSc [6]. Patients were grouped according to LeRoy and Medsger (2001) Criteria for SSc [5]. They were grouped into 2 groups; 7 patients (35%) had diffuse SSc (dcSSc) and 13 patients (65%) had limited cutaneous SSc (lcSSc). Modified Rodnan Skin Score (MRSS), to measure dermal skin thickness based on 17 body parts, scored 0-51 [18].

They underwent high resolution manometry assessment to the esophageal motility to evaluate if there was difference between the two groups. The data of the swallows were recorded and evaluated for each patient and compared to the other parameters. The exclusion criteria were patients who couldn't withstand the procedure, patients with overlap syndrome, localized form of scleroderma, diabetes or thyroid diseases.

Detailed history was taken from each patient including age, sex, smoking, disease duration, skin manifestation (Raynaud's phenomena, skin tightness), gastrointestinal manifestations in the form of dysphagia, GERD (heart burn and/or regurgitation) and pulmonary manifestations as cough and dyspnea according to New York Heart Association (NYHA) classification.

High resolution manometry was done by a 32-channel solid-state catheter with 1cm intervals pressure sensors (Medical Measurement Systems, MMS Enschede, Netherlands). The catheter was put in water for zeroing before use. The maneuver was done with the patient in a sitting position. A local anesthetic spray was introduced in the nostril before passing the catheter trans-nasally and the patient was asked to swallow water during its pass then fixed to the nose after correct positioning by the appearance of the LES (lower esophageal sphincter) and UES (upper esophageal sphincter) pressure waves.

The resting pressure of the upper esophageal sphincter and lower esophageal sphincter were recorded first. Then ten swallows of water each 5ml was taken with 30 seconds apart. All data was stored and analyzed using MMS Database software (MMS, Enschede, Netherlands). The amplitude (mmHg), duration (seconds) and velocity of each contraction were measured, the esophageal body contractions were divided into the proximal third contraction; between the upper esophageal sphincter and the transition zone, the middle one; between the transition zone and the distal trough and the distal one; between the distal trough and the upper border of the LES [19].

Esophageal body motility was classified according to Chicago Classification as normal contraction when 20mmHg isobaric contour without large or small break, weak contraction as shown in Fig. (1) when large break more than 5cm length in the 20mmHg isobaric contour in more than 20% of swallows or more than 30% of swallows with 2-5cm break length in the 20mmHg isobaric contour of the esophagus and aperistalsis as shown in Fig.

(2) when the esophageal contraction in the smooth muscle part of the esophagus (distal two thirds) were absent. The resting basal pressure of the LES was measured (normally 10-45mmHg), when the LES resting pressure was below 1 0mmHg a hypotensive LES was considered, and hypertensive LES when the resting LES pressure was more than 45mmHg. The integrated relaxation pressure 4-seconds (IRP4s) was measured (normally less than 15mmHg) [20]. The proximal and distal contractile integral (PCI and DCI), the contractile front velocity were assessed for the distal two thirds of the esophagus [19,21].

The pulmonary function test was performed. Forced Vital Capacity (FVC) was done by spirometry according to standard technique and patients were classified into normal FVC ≥ 80% of predicted and abnormal FVC as <80% of predicted. The High-Resolution Computed Tomography (HRCT) scans were evaluated for the absence or presence of the interstitial lung disease (ILD) according to Goh et al., [22].

This study was approved by the Ethical Committee of Faculty of Medicine, Assiut University. All patients in this study were informed in a written consent containing the detailed description of the study.

Statistical analysis:

Statistical analysis of the data was performed using the SPSS software (version 16). Descriptive statistics: Mean, standard deviation and percentages were calculated. Student *t*-test was used to compare the mean difference between the two groups and Chi-square test was used to compare the difference in proportion between the two groups. A significant *p*-value was considered when it is <0.05.

Results

Twenty non-smoker female patients (mean ± SD 39.7± 14.4, range 19-60) were included in this study. The range of the disease duration was 2-18 years (7.4±4.6). The patients were divided into 2 subtypes; limited SSc (13 patients, 65%) and diffuse SSc (7 patients, 35%). Esophageal abnormal motility was present in 14 patients (70%). Patients' parameters were described in Table (1).

All patients included in this study had skin involvement. The esophageal involvement was GERD 70% and dysphagia 45%. The pulmonary involvement was dyspnea 70% and cough 40% as shown in Table (2).

Table (1): Distribution of patients' parameters.

Patients' Parameters	No.	%
Age:		
Range	19–60 year	
Mean ± SD	39.7± 14.4	
Sex:		
Male	0	0
Female	20	100
Smoking:		
Yes	0	0
No	20	100
Disease duration:		
Range	2–18 year	
Mean ± SD	7.4±4.6	
Subtype:		
Limited	13	65
Diffuse	7	35
FVC (% of predicted):		
Mean ± SD		
Normal ≥80% (90.70±8.30)	8	40
Abnormal <80% (67.66±5.44)	12	60
CRP:		
Positive	14	70
Negative	6	30
ESR:		
Range (women)	0–29	
Mean ± SD	42.3 ± 14.7	
Normal	2	10
Abormal	18	90
Hgb:		
Range (women)	12–15.5g/dl	
Mean ± SD	11.4± 1.6	
Normal	8	40
Abormal	12	60
Esophageal motility:		
Normal	6	30
Abnormal	14	70

Table (2): Distribution of diseases manifestation.

Diseases manifestation	No.	%
Skin involvement:		
Raynaud's phenomena	20	100
Skin tightness	20	100
MRS S/51		
Range	9–29	
Mean ± SD	19±5.8	
Esophageal involvement:		
Dysphagia	9	45
GERD	14	70
Pulmonary involvement:		
Cough	8	40
Dyspnea	14	70

MRSS: Modified Rodnan Skin Score

Esophageal motility pattern by high resolution manometry:

Upper esophageal contraction was normal in 100% of the patients. Middle and lower esophageal contraction were normal (30%), hypoperestalsis (5%), and aperestalsis (65%). High resolution manometry regarding the lower esophageal sphincter pressure showed normal pressure (30%), hypotensive (65%) and hypertensive (5%) as in Table (3).

There was a significant statistical result that esophageal motility is affected by SSc subtypes with $p<0.05$ as shown in Table (4). There was a significant relation ($p<0.01$) between abnormal esophageal motility disorders and LES pressure abnormalities as described in Table (5).

There was a significant relation between GERD and ILD ($p<0.05$) as shown in Table (6). Abnormal motility was found in patients with ILD ($p=0.001$), dSSc ($p<0.05$), abnormal FVC ($p<0.05$), dyspnea ($p<0.01$) and dysphagia ($p<0.01$). While no significant relation was found regarding GERD, cough, CRP, ESR and Hgb level as summarized in Table ([7]).

Table (3): Patterns of esophageal motility by High Resolution Manometry in SSc patients.

Motility patterns	LES pressure				Body peristalsis			
	Normal	Hypotensive	Hypertensive	*p*-value	Normal	Hypoperistalsis	Aperistalsis	*p*-value
Normal	6 (30%)	0	0	0.003	6 (30%)	0	0	<0.01
Abnormal	0	13 (65%)	1 (5%)		0	1 (5%)	13 (65%)	

Significant *p*-value <0.05

Table (4): HRM findings in SSc patients with and without esophageal symptoms.

	LES pressure				Body peristalsis			
	Normal	Hypotensive	Hypertensive	*p*-value	Normal	Hypoperistalsis	Aperistalsis	*p*-value
Systemic Sclerosis:								
Limited	6	6	1	<0.05	6	1	6	<0.05
Diffuse	0	7	0		0	0	7	
Dysphagia:								
Yes	0	8	1	0.022	0	1	8	0.022
No	6	5	0		6	0	5	
GERD:								
Yes	3	11	0	0.09	3	0	11	0.09
No	3	2	1		3	1	2	

Significant *p*-value <0.05 LES: Lower Esophageal Sphincter.

Table (5): Relation between LES pressure and esophageal body contraction in SSc patients.

Middle and lower esophageal contraction	Lower Esophageal Sphincter pressure			*p*-value
	Normal No.	Hypotensive No.	Hypotensive No.	
Normal	6	0	0	
Hypoperistalsis	0	0	1	<0.01
Aperistalsis	0	13	0	

Significant *p*-value <0.05.

Table (6): Relation between ILD and the associated GERD in SSc patients.

GERD	ILD				*p*-value
	Yes		No		
	No.	%	No.	%	
Yes	13	85	1	25	<0.05
No	3	15	3	75	

Significant *p*-value <0.05. ILD: Interstitial lung disease.

Table (7): Predictive parameters for abnormal esophageal motility in SSc patients.

	Abnormal Motility		Normal Motility		*p*-value
	No. 14	%	No. 6	%	
ILD by HRCT:					
Yes	14	100	2	33.33	0.001
No	0	0	4	66.67	
Dysphagia					
Yes	9	64.29	0	0	0.008
No	5	35.71	6	100	
GERD:					
Yes	11	78.57	3	50	0.201
No	3	21.43	3	50	
Cough:					
Yes	6	42.86	2	33.33	0.68
No	8	57.14	4	66.67	
Dyspnea:					
Yes	14	100	0	0	<0.01
No	0	0	6	100	
CRP:					
Positive	10	71.43	4	66.67	0.83
Negative	4	28.57	2	33.33	
ESR:					
Normal	2	14.29	0	0	0.32
Abnormal	12	85.71	6	100	
Hgb:					
Normal	4	28.57	4	66.67	0.11
Abnormal	10	71.43	2	33.33	
FVC:					
Normal	2	14.29	6	100	0.046
Abnormal	12	85.71	0	0	
Systemic Sclerosis:					
Limited	7	50	6	100	<0.05
Diffuse	7	50	0	0	

Significant *p*-value <0.05.

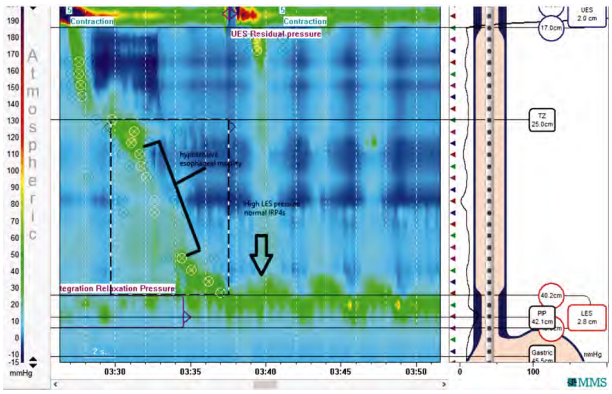

Fig. (1): Hypoperistalsis in the middle and distal esophagus with large break more than 5cm length in the 20mmHg isobaric contour with high LES and normal IRP4s.

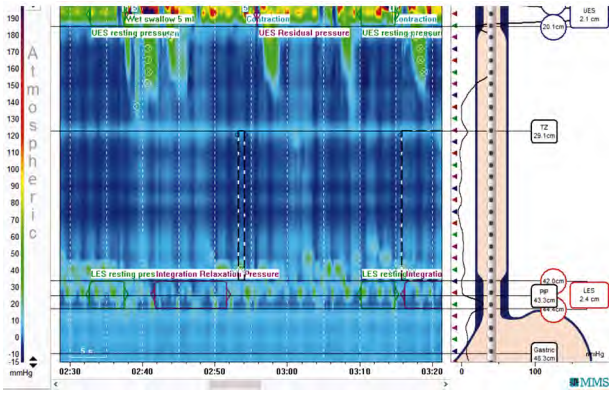

Fig. (2): Aperistalsis in the distal two thirds of the esophagus.

Discussion

Systemic sclerosis is a chronic systemic autoimmune disease causing hardening of the skin, and affecting the internal organs in more severe cases. Gastrointestinal tract involvement is common in patients with systemic sclerosis **[10]**. The esophagus is the most commonly affected organ of the gastrointestinal tract in SSc; dysphagia and heart burn are the most common esophageal symptoms **[23]**.

Normal motility was found in 6 patients (30%) and the prevalence of esophageal motility disorders was 70%; in the form of hypotensive LES and aperistalsis in 13 patients (65%) each, while only one patient showed hypoperistalsis and hypertensive LES resting pressure (5%). It is noticeable that aperistalsis was more prevalent than hypo peristalsis. Other studies found that the prevalence of esophageal motility disorders ranged from 68.1-81.6% of patients **[1,24,25,26]**. Thus our obtained results regarding the prevalence of esophageal motility disorders and LES pressure were more or less similar to the mentioned studies.

It is clear that the most frequent esophageal symptom was GERD, which was present in 70% of patients. No significant statistical positive relation between the lower esophageal sphincter pressure abnormality, abnormal esophageal motility and the presence of GERD was recorded. Agreed with Roman et al., [17] who found that GERD was in 68.6% of patients and hypotensive LES and aperistalsis in SSc are common findings in patients with GERD but without a statistical significant value. On the contrary, Sallam et al. and Gemignani et al., [27,28] explained that GERD in SSc could be due to the reduction or absence of LES pressure and esophageal motility disorders.

Roman et al., [17] recorded that dysphagia was not a predictive factor of esophageal dysmotility, in contrary to our results which revealed that dysphagia was present in 9 out of 14 patients with motility disorders (64.29%) with statistical positive relation (p-value 0.008) between the presence of dysphagia and esophageal dysmotility. While 5 of the tested patients with motility disorders didn't complain of dysphagia which could be due to the preservation of the motility of the upper third of the esophagus, the gravity and decreased LES pressure, which led to the passage of the bolus through the esophagus without much resistance.

It was found that the upper esophageal segment contraction was normal in 100% of the systemic sclerosis patients that have motility disorders. This was in agreement with Yarze et al., [7] who found that normal proximal esophageal contraction pressures were documented in all cases.

Noticeably the lower esophageal sphincter pressure was hypotensive in 65% of SSc patients which was nearly similar to Lahcene et al., [29] who found a hypotensive LES in 60.8% of the SSc patients.

Reflux may lead to pulmonary disease via aspiration of gastric contents, and vagal stimulation by acid in the esophagus that causes bronchoconstriction. Conversely, pulmonary disease may exacerbate reflux by increasing inspiratory force, augmenting negative intrathoracic pressure required for ventilation [30].

ILD may be a complication of esophageal motility disorders and associated GERD. The reduced LES pressure in our patients with SSc. with ILD indicates an incompetent antireflux barrier, leading to aspiration of gastric content into the lungs, as reported by Hershcovici et al., [31]. Although the present study doesn't offer direct evidence that aspiration occurred, it suggests that GERD may be one of the predisposing factors, as our patients with severe esophageal motility disorders had higher prevalence of evidence for ILD (p-0.001), which was in agreement with Savarino et al., [26] who found that the prevalence of ILD was higher in patients with severe esophageal manometric impairment than in patients without esophageal motor disturbances.

Moreover, the relationship between esophageal and lung manifestations may also be due to a concomitant involvement of the internal organs in SSc process, resulting in ILD and fibrosis of esophageal smooth muscle. Confirmed by our results that a significant relation (p-value <0.05) between the presence of ILD and the associated GERD was found. Similarly, Gilson et al., [11] found that GERD was an important cause of both SSc-ILD and idiopathic pulmonary fibrosis (IPF). Additionally, ILD is a major cause of morbidity and mortality in SSc, aggressive acid-reducing therapy is important in treating reflux to improve pulmonary function [13].

A significant relation between the presence of esophageal dysmotility and pulmonary function abnormalities (FVC) with p-value 0.046 was recorded. This was similar to Lock et al., Christmann et al., Airo et al., [32,33,34] who found a reduced lung function as assessed by FVC in patients with absent esophageal contractility, while Marie et al. and Kimmel et al., [1,35] found that FVC tended to be lower in SSc patients with severe esophageal manometric involvement, but of no significant value.

Regarding the relation between esophageal motility disorder and SSc subtypes, a significant statistical relation of p-value<0.05 was found. This was in agreement with Kimmel et al., [35] who found that diffuse skin involvement that correlates with worse prognosis was associated with esophageal dysmotility, in contrary to Savarino et al., [26] who found that disease variant (diffuse vs. limited) were inaccurate predictors of the presence and severity of esophageal involvement.

A significant statistical positive relation between lower esophageal sphincter pressure abnormalities and esophageal body abnormalities in SSc patients was present with p-value <0.01. Similarly, Roman et al., [17] found that LES and esophageal body abnormalities were associated. A shared pathologic mechanism between skin and esophageal wall thickening could provide insight into the method of esophageal dysfunction in SSc, the presence and composition of esophageal thickening has not been identified on SSc-autopsy studies [36,37].

Therefore, additional study of well-characterized esophageal function and histology, skin involvement, and symptoms is required.

In conclusion, esophageal involvement is frequent in SSc patients affecting middle and lower parts of the esophagus than upper part. Esophageal dysmotility was present even in patients without symptoms, thus performing HRM in SSc patients with or without esophageal symptoms may benefit for the early detection of esophageal motility disorders in order to reach appropriate treatment of esophageal involvement which may ameliorates symptoms and prevents complications. The association of GERD with SSc-ILD is common, so early management of GERD could postpone the development of SSc-ILD.

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العوامل التنبؤية لحركية المرئ الغير طبيعية فى مرضى التصلب الجهازى بإستخدام جهاز قياس حركية المرئ عالى الد قة

المقدمة: يحدث الأضطراب الحركى للمرئ فى حوالى ٨٠٪ من مرضى التصلب الجهازى مع ضعف الحركية فى الثلثين السفليين من المرئ مع إنخفاض ضغط العضلة العاصرة السفلية للمرئ.

الأهداف: إستخدام جهاز قياس حركية المرئ فى مرضى التصلب الجهازى لتقييم العوامل التنبؤية المرتبطة بتأثير المرئ.

الطرق: تم إجراء دراسة أستطلاعية على عشرين مريضة من مرضى التصلب الجهازى. تم تقييم البياناتالديموغرافية وأعراض المرئ بما فى ذلك مرض الإرتجاع المعدى المريئى وصعوبة البلع. خضع جميع المرضى لجهاز قياس حركية المرئ عالى الدقة والأشعة المقطعية عالية الدقة، ومعدل ترسيب كريات الدم الحمراء، وبروتين سى التفاعلى، ومستوى الهيموجلوبين، والسعة الحيوية القسرية للرئة.

النتائج: أظهر جهاز قياس حركية المرئ عالى الدقة إنقباضاً لعضلة المرئ العلوية فى ١٠٠٪ من المرضى. وكان إنقباض عضلة المرئ الوسطى والسفلية طبيعياً فى ٣٠٪ ، وضعيفاً فى ٥٪ ومنعدماً فى ٦٥٪من المرضى. وفيما يتعلق بضغط العضلة العاصرة السفلية للمرئ فقد أظهر ضغطاً طبيعياً فى ٣٠٪ وضغطاً ضعيفاً فى ٦٥٪ وضغطاً مرتفعاً فى ٥٪ من المرضى. وكان الإرتجاع المريئى فى ٧٠٪ وصعوبة البلع فى ٤٥٪ من المرضى. وكان ضيق التنفس فى ٧٠٪ والسعال ٤٠٪ من المرضى. وكان جميع المرضى لديهم تأثير بالجلد. وكانت الحركية غير الطبيعية بالمرئ فى ١٤ مريض من أصل ٢٠ مريضاً بنسبة ٧٠٪ وكانت مرتبطة بشكل كبير بمرضى داء الرئة الخلالى (p=٠.٠١) والأنواع الفرعية للتصلب الجهازى (p=٠.٠٣) وضيق التنفس (p=٠.٠١) والسعة الحيوية القسرية للرئة (p=٠.٠٤٦) وأيضاً وجدت علا قة بين الإرتجاع المعدى المريئى وداء الرئة الخلالى (p<٠.٠٥).

الخلاصة: أكدت هذه الدرسة زيادة أنتشار أضطرابات حركية المرئ فى مرضى التصلب الجهازى فى وجود وعدم وجود أعراض المرئ.