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ORIGINAL ARTICLE

Seizures in systemic sclerosis

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Abstract The aim of this study was to evaluate the frequency of seizures in systemic sclerosis (SSc) and to determine the clinical and laboratory features associated with their occurrence. Thirty-four SSc patients (ACR criteria) were analyzed by a standard interview, physical examination, and review of medical charts. Risk factors for seizures, clinical manifestations, associated co-morbidities and current treatment were evaluated. We identified 3 (8.8 %) SSc patients with seizures. A higher median age [61 (35–64) vs. 48 (27–71) years, $p = 0.0005$] and higher activity score [4.75 (4.5–5.0) vs. 2.5 (0–5–5) years, $p = 0.006$] were observed in SSc patients with seizures. No other clinical or laboratory feature was associated with the occurrence of seizure in this cohort. This study demonstrated a higher prevalence of seizures in SSc when compared to general population. Seizures were associated with older age and higher activity score in this cohort.

Keywords Seizures · Epilepsy · Convulsion · Systemic sclerosis · Scleroderma

Introduction

Systemic sclerosis (SSc) is a chronic autoimmune disorder characterized by thickness of skin and visceral involvement. Although the visceral involvements such as esophagus, lungs and heart have been extensively studied, few studies have addressed central nervous system involvement in SSc [1–5].

Neurological involvement has been described to occur in 16 % of SSc; however, the peripheral nervous system is the most frequently involved [2, 3]. Trigeminal neuropathy, polyneuropathy, brachial plexopathy, and lumbosacral radiculopathy have been described [2, 3, 6–8]. Seizures have rarely been reported in SSc [6–12].

However, until this moment, no study has evaluated the frequency and clinical associations of seizures in patients with SSc. Therefore, we sought to determine the frequency and risk factors for seizures in SSc patients. We also analyzed clinical and laboratory features associated with the occurrence of seizures in this cohort.

Methods

This is a retrospective study that screened all patients followed at the Rheumatology Division of the University Hospital Professor Edgard Santos of the Federal University of Bahia. All patients had disease onset after the age of 18 and were diagnosed with SSc following the ACR criteria [13]. Patients with both limited and diffuse forms classified according to Le Roy criteria [14] were screened. Patients with SSc and overlap with other connective tissue diseases, such as dermatomyositis and polymyositis, systemic lupus erythematosus, rheumatoid arthritis, and Sjögren's syndrome, were excluded. In total, 34 patients (6 males and 28 females) were included.

Extensive analysis of the patient's clinical records was performed for all patients. The disease duration was established from the onset of Raynaud's phenomenon. All subjects were evaluated for inner organ involvements.

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Dyspnea was defined as present when patients reported to be limited to extraordinary activity (NYH class II) or worse. High-resolution computer tomography (HRCT) of the lungs and pulmonary function test (PFT) were performed in all patients. Dysphagia and regurgitation symptoms were inquired in all patients, and esophagograms were performed to detect digestive involvement in symptomatic patients.

The modified Rodnan skin score [15] was applied to all patients in a regular basis. Activity and severity scores were applied according to previous descriptions [16, 17].

Diabetes mellitus was defined as fasting blood glucose >126 mg/dL or current use of insulin and/or oral hypoglycemic drugs. Hypertension was defined as systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg or current use of antihypertensive drugs [18].

Neurological evaluation

Seizures were classified according to the International League Against Epilepsy criteria [19, 20]. Electroencephalograms (EEGs) were recorded in the interictal period in a 16-channel analog or 32-channel digital EEG recorder with the International 10–20 System of electrode placement for 20–30 min. We tabulated the presence and localization of interictal epileptiform abnormality and slow wave abnormality. Magnetic resonance imaging (MRI) was performed in all patients who had seizures or other CNS manifestation using a 1.5 Tesla machine and included T1- and T2-weighted imaging and fluid-attenuated inversion recovery (FLAIR) imaging [21].

Statistical analysis

The results of the present study are presented as mean (standard deviations), median (range) or percentages. Statistical analysis was performed using the software GraphPad InStat, version 2.0 (GraphPad Software Inc., San Diego, CA, USA). Nonparametric test was used to compare differences between medians and percentages. Values of $p < 0.05$ were considered statistically significant.

Results

We included 34 patients with SSc and mean age of 49.0 [Standard deviation (SD) ± 10.8 years]. Twenty-eight (82.3 %) patients were female and 6 (17.7 %) and 17 (50 %) of the patients were Caucasian. Mean duration of disease was 13.6 ± 9.1 years. All patients were taking omeprazole and nifedipine for SSc treatment.

Seizures were identified in 3 of 34 (8.8 %) SSc patients. All patients had primarily generalized tonic–clonic seizures, and interictal EEG epileptiform activity (bilateral, synchronous, widespread and most often generalized spike-wave discharges) was seen in all patients. MRI was performed in all patients with seizures, and no abnormalities on visual analysis were observed. All patients have been diagnosed with epilepsy, and their seizures were not obviously provoked in any way. Metabolic conditions and CNS structural alterations were excluded by laboratory tests and by MRI.

Since all patients had recurrent seizures, antiepileptic drugs [phenytoin ($n = 1$), phenobarbital ($n = 3$), valproate ($n = 1$) and lamotrigine ($n = 1$)] were introduced and no recurrence was observed after adequate treatment (Table 1).

A higher median age [61 (35–64) vs. 48 (27–71) years, $p = 0.0005$] and higher activity score [4.75 (4.5–5.0) vs. 2.5 (0–5–5) years, $p = 0.006$] were observed in patients with seizures when compared to those without seizures (Table 2).

No significant differences were observed among groups regarding demographics (age, Caucasian race and disease duration), as well as types (diffuse or limited forms), modified Rodnan scores, prevalence of Raynaud phenomenon,

Table 1 Characteristics of the 3 SSc patients with epileptic seizures

	Age (years) sex, race	Seizure after SSc onset	Age (years) of seizure onset	Diffuse form	Seizure type	>1 seizure	MRI	EEG	Drugs
1	35, F, Mul	+	31	+	Primarily generalized tonic–clonic	+	NL	Bilateral, synchronous, widespread, and generalized spike-wave discharges	PHT, PB
2	64, F, Mul	–	50	+	Primarily generalized tonic–clonic	+	NL	Bilateral, synchronous, widespread, and generalized spike-wave discharges	PB, lamotrigine
3	61, F, Mul	–	45	–	Primarily generalized tonic–clonic	+	NL	ND	PB, valproate

EEG electroencephalogram, *F* female, *MRI* magnetic resonance image, *Mul* mulatto, *ND* not done, *PB* phenobarbital, *PHT* phenytoin, *SSc* systemic sclerosis

Table 2 Comparisons of demographic, clinical and laboratory features, vascular risk factors and medications between the 3 SSc patients with seizures and SSc patients without seizures ($n = 31$)

	SSc with seizures n = 3	SSc without seizures n = 31	*p* values
Age (years)	61 (35–64)	48 (24–71)	0.0005
Female gender, n (%)	3 (100)	25 (80.6)	1.000
Caucasian race, n (%)	0	6 (19.4)	1.000
Duration of disease (years)	21 (4–32)	12 (2–36)	0.113
Diffuse form, n (%)	2 (66.6)	12 (38.7)	0.556
Limited form, n (%)	1 (33.3)	19 (61.3)	0.556
Activity score	4.75 (4.5–5.0)	2.5 (0–5.5)	0.006
Severity score	0 (0–3)	4.5 (0–12)	0.094
Modified Rodnan score	27 (8–32)	20 (0–51)	0.493
Raynaud phenomenon, n (%)	3 (100)	30 (96.8)	1.000
Digital ulcers, n (%)	1 (33.3)	19 (61.3)	0.556
Esophageal impairment, n (%)	3 (100)	24 (77.4)	1.000
Gastric involvement, n (%)	2 (66.6)	14 (45.2)	0.591
Lung fibrosis	1 (33.3)	9 (29.0)	1.000
Arthralgia, n (%)	2 (66.6)	22 (70.9)	1.000
Synovitis, n (%)	0	7 (22.6)	1.000
Myalgia, n (%)	2 (66.6)	11 (35.5)	0.544
Myositis, n (%)	0	5 (16.1)	1.000
Muscle atrophy, n (%)	0	0	1.000
Creatine kinase, IU/mL	54 (50–58)	122 (41.1–692)	0.0002
Renal crisis, n (%)	0	1 (3.10)	1.000
Systemic hypertension, n (%)	1 (33.3)	8 (25.8)	1.000
Glucocorticoid use, n (%)	1 (33.3)	10 (32.3)	1.000
Nifedipine use, n (%)	3 (100)	13 (41.9)	0.094
Erythrocyte sedimentation rate, mm/1st hour	42 (31–53)	41 (4–70)	0.372

Data expressed as median (range) or percentage; *SSc* systemic sclerosis, *n* number of patients

esophageal and gastric involvements, lung fibrosis, arthralgia, synovitis and renal crisis. Also, no differences in treatment strategies, comorbidities and inflammation markers (ESR) were observed among groups ($p > 0.05$) (Table 2).

Discussion

Neurological complications of SSc were considered rare and thought to be coincidental, iatrogenic or secondary to the involvement of inner organs such as the kidney, rather than due to the disease itself [2, 22].

Myopathy is the commonest form of neurological manifestation in scleroderma [23], followed by peripheral neuropathy in 10–20 % of SSc patients [9, 24].

Central nervous system involvement is rarely observed. The paucity of connective tissue, lack of an external elastic lamina with a sparse media and adventitia of cerebral arteries could be a possible explanation. Both seizures [9, 10] and stroke [25–30] have been described, but generally associated with evidence of renal failure or hypertension [2, 22, 31].

We demonstrated a frequency of 8.8 % seizures in patients with SSc and generalized tonic and clonic were the only seizure type observed in this study. This prevalence is higher than observed in the general population, where seizures are observed in 0.5 % [32]. Patients with other connective tissue disease also have a higher prevalence of seizures. In SLE, seizures have been observed in up to 11.6 % [21].

Higher activity score and older age were the only features associated with seizures in our SSc patients, suggesting the role of widespread vasculopathy as possible etiology.

The exact mechanism for seizure generation in SSc is not known. Neuroimaging studies are necessary to determine whether subclinical ischemia or neuronal cell death is involved in this complex CNS manifestation [33]. In localized scleroderma en coup de sabre, seizures have been described more frequently [34]. The "neurovasculitis hypothesis" seems to be widely accepted in this form of scleroderma [35–37]. Localized scleroderma involves the ipsilateral facial tissues and the underlying brain parenchyma, which have a common cell progenitor, leading to the hypothesis of an early malformation affecting one side of the rostral neural tube [38].

Our study has some limitations. The most important is the limited number of participants and the retrospective nature of the study. In fact, future studies with large SSc cohorts need to address specifically the CNS involvement in SSc.

In conclusion, we observed the occurrence of seizures in 8.8 % of patients with SSc. Higher activity score and older age were independently associated with seizure occurrence in SSc.

Key messages

1. About 8.8 % of patients with systemic sclerosis have seizures.
2. Seizures in SSc are associated with higher activity score and older age.

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Conflict of interest The authors declare no conflict of interests.

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