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ORIGINAL ARTICLE

Neurosonological and cognitive screening for evaluation of systemic sclerosis patients

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Abstract

Objective Assessment of cerebrovascular hemodynamics, third ventricle diameter (as a proxy of brain atrophy) by transcranial sonography (TCS), and screening of cognitive performance by the Symbol Digit Modalities Test (SDMT) in systemic sclerosis (SSc) patients.

Methods A total of 38 SSc patients recruited from the outpatient clinic of the Rheumatology Department, Kasr Alainy Hospital, Cairo University, and 51, age- and sex-matched, healthy controls were included in the study. TCS was used to assess the mean flow velocity (MFV), pulsatility index (PI) of the anterior, middle, and posterior cerebral arteries bilaterally, and to measure the third ventricle diameter as a proxy of brain atrophy. Cognitive impairment was screened using the SDMT. p values < 0.05 were considered statistically significant.

Results There was no significant difference between SSc patients and controls regarding either PI or MFV of the anterior, middle, and posterior cerebral arteries; also, there was no difference regarding the third ventricle diameter; however, limited SSc patients showed a significant increase in the PI of PCA and MFV of ACA as compared with diffuse SSc patients ($p = 0.005$, 0.004). There was a significant difference between SSc patients and controls regarding the SDMT ($p = 0.016$).

Conclusion There is an evidence of increased cerebral vascular tone and resistance in limited SSc patients compared with diffuse SSc subgroup, without evidence of cerebral atrophy, suggesting early cerebrovascular affection even in asymptomatic limited SSc patients. There was also an evidence of cognitive impairment in SSc patients.

Keywords Mean flow velocity · Pulsatility index · Systemic sclerosis · Transcranial sonography

Introduction

Systemic sclerosis (SSc) is a systemic autoimmune disease characterized by fibroblast activation and excessive collagen deposition in the skin and internal organs, mainly the lung, heart, and gastrointestinal system [1].

SSc-associated inflammatory processes lead to peripheral endothelial dysfunction [2], arterial vasoconstriction [3], and increased arterial stiffness; this process occurs also in the intracerebral circulation, leading to direct effect on cerebral perfusion; however, the intracerebral arterial hemodynamics in SSc have not been well estimated [4]. On the other hand, the central nervous system may be affected by microvascular damage as a complication of systemic involvement [5].

Transcranial sonography (TCS) allows portable, non-invasive measurement of blood velocity in the accessible cerebral vessels, e.g., the anterior cerebral artery (ACA), middle cerebral artery (MCA), and posterior cerebral artery (PCA), and permits calculation of pulsatility index (PI) and mean flow velocity (MFV) [6], where increased PI signifies increased cerebrovascular tone, and resistance [7, 8], while decreased MFV indicates decreased cerebral blood flow [8]. Analysis of the third ventricular diameter is used for the determination of brain atrophy. In addition to MRI, the ventricular system can be accurately evaluated using TCS [9].

SSc is known to cause widespread microvascular damage, which may be a possible mechanism for the neuropsychiatric symptoms of mood, anxiety, and cognitive disorders that have

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been documented in SSc patients [10]. Symbol Digit Modalities Test (SDMT) is a test directed to assess attention and cognitive processing speed [11, 12], which is the speed at which information can be maintained and manipulated in the brain [13]. Deficit in the information processing speed is reported in autoimmune diseases like systemic lupus erythematosus (SLE) [14]. The SDMT has been used in many neurological disorders, including multiple sclerosis, Alzheimer's disease, and Parkinson's disease [15, 16]. This test consists of a sheet of paper; at its top, there is a sequence of nine symbols and nine corresponding numbers (key). This test requires a person to substitute geometric symbols for numbers within a 90-s time. The test can be administered in both written and oral modalities [17]. Recent findings suggest that compared to other measures of cognitive performance, the SDMT reflects cognitive impairment more accurately [18], leading some researchers to conclude that the SDMT is the most sensitive cognitive screening tool in both clinical and research settings [19, 20].

The SDMT is a brief test that can be translated into different languages with good reliability observed across multiple languages [21–24]. Moreover, many studies used this test in non-English-speaking populations for cognitive assessment [25–27]. The SDMT stimuli are deemed adequate for international use, at least for cultures where Arabic numerals are in common use [28].

The aims of this study are the assessment of cerebrovascular hemodynamics, third ventricle diameter (as a proxy of brain atrophy) by TCS, and screening of cognitive performance by the SDMT in SSc patients.

Patients and methods

Study design This is a case-control, single-center study. SSc patients and controls were selected consecutively.

Patients and controls A total of 38 SSc patients aged ≥ 16 years who fulfilled the American Rheumatism Association diagnostic and therapeutic criteria for systemic sclerosis [29] were recruited from the outpatient clinic of the Rheumatology Department, Kasr Alainy Hospital, Cairo University. Fifty-one, age- and sex-matched, healthy subjects were included as the control group. Exclusion criteria for SSc patients and controls included moderate-to-severe arterial hypertension (≥ 160/100 mmHg); uncontrolled diabetes mellitus (fasting blood sugar > 130 mg/dl and 2 h postprandial > 180 mg/dl according to the American Diabetes Association); cardiovascular disease; neurologic diseases; renal, respiratory, or hepatic failure; and those with previous history of cerebrovascular accidents or depression.

Data collection

- Demographic characteristics: age, age of onset, sex, and smoking status were recorded.
- Clinical data included: disease duration, type of skin involvement (diffuse or limited scleroderma), sclerodactyly, digital pitting scars, Raynaud's phenomenon, lung involvement (pneumonitis, fibrosis), esophageal dysmotility, presence of gastro-esophageal reflux, and cardiac disease. Skin thickness was quantified using the modified Rodnan skin thickness scoring technique [30], in which skin thickness was assessed in each of 17 body surface areas on a 0–3 scale: 0: normal, 1: mild thickness, 2: moderate thickness, 3: severe thickness (maximum score of 51).
- History of drug intake: calcium channel blockers, sildenafil, corticosteroids, methotrexate, azathioprine, cyclophosphamide, mycophenolate mofitel, baby aspirin and proton pump inhibitors
- History of comorbidities, e.g., hypertension and diabetes mellitus

All participant patients and controls were subjected to the following

- Laboratory investigations: complete blood picture, serum aspartate transaminase (AST), serum alanine transaminase (ALT), serum creatinine, blood urea, blood cholesterol, serum triglycerides. Dyslipidemia included those with hypercholesterolemia > 200 mg/dl, or hypertriglyceridemia> 150, or both. Cutoff value for anemia was hemoglobin (HB) < 11.

- Neurosonological assessment: The transcranial sonography (TCS) studies took place in Cairo University neurosonology unit at the Neurology Department, Kasr Alainy Hospital, Cairo University, and were performed by experienced certified neurosonographers (European Society of Neurosonology and Cerebral Hemodynamics "ENSCH"), who were blinded to the subjects' clinical data throughout the entire study. The studies were carried out using a high-resolution ultrasonography instrument (PHILIPS IU22 xMATRIX, CA, USA, L 1-5 transducer, equipped with a 2.5-MHz-phased array transducer. The subjects were investigated in supine position, via the transtemporal window, the sonographic assessment was carried out in two ventricular planes, plane of the thalamus and mesencephalic brainstem plane.

First plane: (to evaluate third ventricle diameter) the system was adjusted according to recommended ultrasound system settings [31] for brain parenchyma assessment using TCS and applied tissue harmonic imaging to increase the tissue contrast and therefore enable an easier delineation of the third ventricle with the landmark appear as double track of the third ventricle with hyper echoic edges that is normally at depth about 50–60 mm in the diencephalic plan (plane of the thalamus) and as a confirmatory landmark structure of this plane is represented by the highly echogenic pineal gland, due to its calcification, and structures assessed are the bilateral thalami and the third ventricle diameter in between (mm).

Second plane: (to evaluate intracranial vessels) the mesencephalic brainstem is displayed in an axial section as the central orientation structure. It appears as a butterfly-shaped structure with low echogenicity surrounded by echogenic basal cisterns. Super imposing the color-coded image with the B-mode gray scale at the mesencephalic axial level which the arteries of the circle of Willis can be identified by their anatomical location to the brain stem structures and by the determination of their flow direction based on specific color coding of the blood flow velocity.

The Doppler gate was adjusted to the size of the vessel without angle correction in the ACA, MCA, and the PCA.

We registered in each of these vessel segments the mean flow velocity (MFV) (cm/s) and the PI which was defined according to Gosling and King [32] and calculated as (PSV − EDV)/MFV bilaterally. The mean value of the three measurements from the right and left sides of ACAs, MCAs, and PCAs was used for statistical evaluation.

- **-**Attention and information processing speed assessment using the Symbol Digit Modalities Test (SDMT): The SDMT was conducted on only 15 cases of the studied SSc patients who were educated and compared with 30 controls. The SDMT (oral version) [33] presents a series of nine symbols, each paired with a single digit in a key at the top of a standard sheet of paper. The test was performed in Arabic language where the English numbers were replaced by Arabic numbers and instructions were translated and back translated to and from Arabic language in Cairo University translation unit. (The translated form is shown in Supplementary Fig. 1). Participants were asked to voice the digit associated with each symbol as rapidly as possible for 90 s. The number of correct responses in 90 s was recorded.

Statistical methods Data were coded and entered using the statistical package SPSS (Statistical Package for the Social Sciences) version 24. Data was summarized using mean, standard deviation, median, minimum, and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were done using the non-parametric Mann-Whitney test. For comparison of paired measurements within the same patient, the non-parametric, Wilcoxon signed-rank test was used [34]. For comparing categorical data, chi-square (χ^2) test was performed. Exact test was used instead when the expected frequency is less than 5 [35]. Correlations between quantitative variables were done using Spearman correlation coefficient [36]. ROC curve was constructed with area under curve analysis performed to detect best cutoff value of the third ventricle for detection of cases. p values < 0.05 were considered as statistically significant.

Results

The mean age of the SSc patients was 42.08 ± 12.6 years and the mean age of controls was 40.18 ± 9.6 years (p = 0.916). Disease duration ranged from 1 to 21 years with a mean of 9 ± 6.1 years. Table 1 demonstrates disease characteristics of the studied SSc patients. Laboratory investigations of the patients and controls are shown in Table 2. There was no significant difference between patients and controls regarding dyslipidemia or diabetes mellitus (Table 2).

Table 1 Disease characteristics of the studied SSc patients

Range, mean± SD N (%)	SSc patients (n=38)
Age (years)	22-75 (42.08±12.6)
Age of disease onset (years)	9-64 (33.37±12.4)
Sex (Females)	32 (84.2%)
Smokers	1 (2.6%)
Co-morbidities	
Hypertension (mild)	5 (13.2%)
Diabetes mellitus	3 (7.9%)
Skin tightness	
Diffuse	27 (71.1%)
Limited	11 (28.9%)
Rodnan scoring	2-27 (11.21±6.34)
Raynaud's phenomenon	38 (100 %)
Sclerodactyly	38 (100%)
Digital pitting scars	28 (73.7%)
Lung affection	22 (57.9%)
Pneumonitis	12 (31.6%)
Fibrosis	10 (26.3%)
Pulmonary hypertension	8 (21.1%)
Esophageal dysmotility	29 (76.3%)
Gastro-esophageal reflux	31(81.6%)
Cardiac (2 patients with tricuspid regurge, 1 with hypertrophic cardiomyopathy, 1 with restrictive cardiomyopathy)	4 (10.5%)

Table 2 Demographic characteristics and laboratory findings of the SSc patients and controls

Mean ± SD, range	SSc patients ($n = 38$)	Controls ($n = 51$)	p
Age (years)	42.08 ± 12.6	40.18 ± 9.6	0.916
Sex (females %)	84.2%	87.3%	0.675
Smokers (%)	2.6%	3.6%	1
Diabetes mellitus	3 (7.9%)	0 (0%)	0.065
Hypertension(mild)	5 (13.2%)	0 (0%)	0.010
Hb (g/dl)	12.3 ± 1.5 8.4–16.2	12.9 ± 1.06 12.8–10.7	0.021
TLC (×10^3/mm^3)	7.15 ± 1.75 4.1–10.9	7.1 ± 1.7 4–11.2	0.088
Platelet (×10^3/mm^3)	233.9 ± 69.2 119–377	251.8 ± 58 133–438	0.113
ESR (mm/1st hour)	38.5 ± 21.8 10–90	22.8 ± 11.18 3–45	<0.001
Blood urea (mg/dl)	24.2 ± 7.1 11–40	22.8 ± 5.7 11–40	0.581
Creatinine (mg/dl)	0.6 ± 0.15 0.3–0.9	0.6 ± 0.18 0.3–1	0.859
AST (IU/L)	24.3 ± 14.8 11–94	20.1 ± 6.8 4–40	0.289
ALT (IU/L)	22.1 ± 13.8 7–64	19 ± 8.5 6–47	0.503
Total cholesterol (mg/dl)	182.24 ± 36 93–288	183.25 ± 40.6 114–348	0.922
Serum triglycerides (mg/dl)	123.34 ± 58.9 47–309	111.5 ± 68.13 50–418	0.153
Dyslipidemia (n, %)	8 (21.1%)	7 (12.7%)	0.283
Anemic (n, %)	5 (13.2%)	1(1.8%)	0.040

SSc, systemic sclerosis; *Hb*, hemoglobin; *TLC*, total leucocytic count; *ESR*, erythrocyte sedimentation rate; *AST*, aspartate transaminase; ALT, alanine transaminase. p values are significant at $p < 0.05$

Drug intake by the studied SSc patients Calcium channel blockers were received by 32 patients (84.2%) either to treat Raynaud's phenomenon or to control hypertension (in 3 hypertensive patients), sildenafil by 15 patients (39.5%), corticosteroids by 31 patients (83.8%), mean corticosteroid dose was 10.24 ± 7.3 mg/day, baby aspirin was received by 17 patients (45.9%), methotrexate by 8 patients (21.1%), azathioprine by 25 patients (65.8%), cyclophosphamide by 18 patients (47.4%), mycophenolate mofitel by 2 patients (5.3%), and proton pump inhibitors by 31 patients (81.6%).

There was no significant difference between SSc patients and the controls regarding MFV or PI of the anterior, middle, and posterior cerebral arteries; also, there was no difference between both groups regarding the third ventricle diameter (Table 3); however, limited SSc patients showed a significant increase in the PI of the PCA and MFV of the ACA compared with diffuse SSc patients ($p = 0.005$, 0.004, respectively) (Table 4).

The MFV, and the PI of the middle, anterior, and posterior cerebral arteries together with the third ventricle diameter, did not show any significant difference between SSc patients who manifested with digital pitting scars or lung fibrosis and those who did not (Tables 5 and 6).

The influence of comorbidities on our results was studied revealing that there was no significant difference in the MFV or the PI of the studied cerebral arteries or the third ventricle diameter between anemic and non-anemic SSc patients (Table 7); also, there was no significant difference in the studied parameters between hypertensive and normotensive SSc patients (Table 8).

There was a significant difference between limited and diffuse SSc patients regarding age and disease duration; however, there was no significant difference regarding dyslipidemia, anemia, hypertension, diabetes mellitus, vasodilator intake, or mean corticosteroid dose (Table 9). In order to study the impact of age on the MFV and PI, SSc patients of different age groups (20–40, 41–60, > 60 years) were compared according to the MFV; PI of the ACA, MCA, and PCA; and the third ventricle diameter, revealing no significant difference in the studied parameters between different age groups (Table 10).

Table 3 Comparison between SSc patients and controls regarding mean flow velocity; pulsatility index of the middle, anterior, and posterior cerebral arteries; and 3rd ventricle diameter

Mean ± SD range	SSc patients ($n = 38$)	Controls ($n = 51$)	p value
MCA MFV (cm/s)	57.20 ± 14.34 30–83	61.15 ± 11.09 40–83	0.172
MCA PI	0.96 ± 0.24 0.36–1.51	0.94 ± 0.15 0.43–1.4	0.650
PCA MFV (cm/s)	40.50 ± 9.20 22–65.5	39.89 ± 8.52 16.5–64	0.707
PCA PI	1.02 ± 0.24 0.52–1.56	1.05 ± 0.23 0.73–2	0.617
ACA MFV (cm/s)	45.66 ± 11.21 23–69.5	44.80 ± 10.81 27–77	0.863
ACA PI	0.99 ± 0.22 0.32–1.4	0.96 ± 0.19 0.66–1.6	0.167
3rd ventricle (mm)	0.30 ± 0.19 0.07–0.99	0.28 ± 0.12 0.11–0.53	0.957

SSc, systemic sclerosis; *MCA*, middle cerebral artery; *ACA*, anterior cerebral artery; *PCA*, posterior cerebral artery; MFV, mean flow velocity; *PI*, pulsatility index. p values are significant at $p < 0.05$

There was no association between disease duration, cholesterol level, triglyceride level, and either PI or MFV (Table 11).

Regarding the SDMT, in SSc patients, it ranged from 7 to 46 with a median of 23, while in the controls, it ranged from14–72 with a median of 32.5, with a statistically significant difference ($p = 0.016$) (Fig. 1).

Discussion

Systemic sclerosis represents a complex autoimmune collagen disorder with evidence of multisystem affection. Few studies have investigated the incidence of cerebrovascular disease in SSc. To our knowledge, this is the first study evaluating the MFV; PI of the ACA, MCA, and PCA; and the third ventricle diameter along with screening the cognitive performance in SSc patients.

In the present study, there was no difference in the MFV and PI values of the ACA, MCA, and PCA between SSc patients and controls, yet comparing the subsets of SSc disease (the limited and the diffuse subgroups) revealed significantly higher PI of the PCA, and significantly lower MFV of the ACA in the limited SSc subset, denoting increased cerebral vascular tone and resistance in the limited SSc subset where impaired vascular tone denotes the earliest sign of vascular dysfunction [37].

Our results are in accordance with earlier reports declaring that the vascular component of SSc is much more prominent in the limited SSc subset than in the diffuse SSc subgroup and is responsible for many of the vascular complications that characterize limited SSc such as pulmonary artery hypertension [38, 39], while diffuse SSc is characterized more by visceral complications [38].

Peripheral vascular involvement was reported to be more pronounced in the limited SSc patients; in this context, Timár et al. [40] reported that arterial stiffness in the brachial artery measured by pulse wave velocity using an arteriography was significantly higher in patients with limited SSc compared to those with diffuse SSc ($p = 0.034$) indicating more severe macro-vascular involvement in this subgroup. Furthermore, Veale et al. [41] stated that the prevalence of symptomatic macrovascular disease in SSc patients, as defined by the World Health Organization questionnaire for intermittent claudication, was predominantly increased in the limited subtype. Moreover, Youssef et al. [42] found that the prevalence of peripheral large

Table 4 Comparison between SSc patients with diffuse and limited skin sclerosis regarding mean flow velocity; pulsatility index of the middle, anterior, and posterior cerebral arteries; and 3rd ventricle diameter

Mean ± SD Range	Limited SSc patients ($n = 11$)	Diffuse SSc patients ($n = 27$)	p value
MCA MFV (cm/s)	55.1 ± 18.09 30–77	58.00 ± 13.00 33–83	0.625
MCA PI	1.01 ± 0.30 0.49–1.5	0.94 ± 0.22 0.36–1.3	0.511
PCA MFV (cm/s)	38.4 ± 9.24 25–55	41.37 ± 9.21 22–65	0.390
PCA PI	1.18 ± 0.22 0.95–1.5	0.95–0.23 0.52–1.4	0.005
ACA MFV (cm/s)	36.95 ± 8.96 23–52	49.14 ± 10.18 33–69	0.004
ACA PI	0.97 ± 0.33 0.32–1.4	0.99 ± 0.17 0.61–1.3	0.815
3rd ventricle (mm)	0.31 ± 0.20 0.09–0.75	0.29 ± 0.20 0.07–0.99	0.849

SSc, systemic sclerosis; *MCA*, middle cerebral artery; *ACA*, anterior cerebral artery; *PCA*, posterior cerebral artery; *MFV*, mean flow velocity; *PI*, pulsatility index. p values are significant at $p < 0.05$

Table 5 Comparison between SSc patients with and without digital pitting scars regarding mean flow velocity; pulsatility index of the middle, anterior, and posterior cerebral arteries; and 3rd ventricle diameter

Mean ± SD range	SSc patients ($N = 38$)		p value
	SSc patients with digital pitting scars ($n = 28$)	SSc patients without digital pitting scars ($n = 10$)	
MCA MFV (cm/s)	56.19 ± 13.59 30–77	59.95 ± 16.66 33–83	0.533
MCA PI	0.94 ± 0.24 0.36–1.5	1.02 ± 0.23 0.72–1.3	0.533
PCA MFV (cm/s)	40.73 ± 10.17 22–65	39.85 ± 6.07 30–50	0.807
PCA PI	0.97 ± 0.23 0.52–1.5	1.15 ± 0.26 0.82–1.5	0.082
ACA MFV (cm/s)	46.04 ± 10.56 23–69	44.38 ± 13.93 27–64	0.743
ACA PI	0.96 ± 0.23 0.32–1.4	1.07 ± 0.17 0.86–1.3	0.428
3rd ventricle (mm)	0.31 ± 0.19 0.09–0.99	0.26 ± 0.19 0.07–0.75	0.214

SSc, systemic sclerosis; *MCA*, middle cerebral artery; *ACA*, anterior cerebral artery; *PCA*, posterior cerebral artery; *MFV*, mean flow velocity; *PI*, pulsatility index. p values are significant at $p < 0.05$

vascular disease is significantly increased in limited SSc in comparison to controls.

Our hypothesis is that increased vascular tone and relative vasoconstriction affecting peripheral vessels similarly affect cerebral vasculature, as the underlying mechanism of peripheral [43, 44] and cerebral hypoperfusion [2] is similar where increased collagen deposition leads to narrowing of the intravascular lumen hindering the blood flow; moreover, endothelial cells are activated, possibly through ischemia-reperfusion injury, leading to an increased production of vasoconstrictors such as endothelin together with an underproduction of vasodilators such as prostacyclin [45]. These microvascular abnormalities contribute to the pathogenesis of pulmonary arterial hypertension, Raynaud's phenomenon, and digital ulceration [46].

SSc is a systemic autoimmune disease [1], causing widespread microvascular damage [10]; consequently, limited SSc patients showed higher PI and lower MFV in the three cerebral arteries (ACA, PCA, and MCA); however, their values reached a statistical significant difference only in the PCA, ACA mostly due to the small sample size, which was a confounder in our study.

Table 6 Comparison between SSc patients with and without lung fibrosis regarding mean flow velocity; pulsatility index of the middle, anterior, and posterior cerebral arteries; and 3rd ventricle diameter

Mean ± SD range	SSc patients ($n = 38$)		p value
	SSc patients with lung fibrosis ($n = 10$)	SSc patients without lung fibrosis ($n = 28$)	
MCA MFV (cm/s)	57.83 ± 13.01 30–78	57.00 ± 14.96 33–83	0.821
MCA PI	1.01 ± 0.18 0.49–1.3	0.95 ± 0.26 0.36–1.5	0.542
PCA MFV (cm/s)	39.95 ± 11.06 25–56	40.70 ± 8.66 22–65	0.832
PCA PI	1.02 ± 0.29 0.52–1.5	1.02 ± 0.23 0.82–1.5	0.909
ACA MFV (cm/s)	50.44 ± 10.62 27–69	44.24 ± 11.17 23–64	0.206
ACA PI	1.04 ± 0.12 0.61–1.3	0.97 ± 0.25 0.32–1.4	0.451
3rd ventricle (mm)	0.40 ± 0.27 0.11–0.99	0.26 ± 0.14 0.07–0.75	0.087

SSc, systemic sclerosis; *MCA*, middle cerebral artery; *ACA*, anterior cerebral artery; *PCA*, posterior cerebral artery; *MFV*, mean flow velocity; *PI*, pulsatility index. p values are significant at $p < 0.05$

Table 7 Comparison between anemic and non-anemic SSc patients regarding mean flow velocity; pulsatility index of the middle, anterior, and posterior cerebral arteries; and 3rd ventricle diameter

Mean ± SD range	SSc patients(38)		*p* value
	Anemic ($n = 5$)	Non-anemic ($n = 33$)	
MCA MFV (cm/s)	59.8 ± 11.27 42–73	56.8 ± 14.87 30–83	0.620
MCA PI	0.9 ± 0.15 0.79–1.19	0.96 ± 0.25 0.36–1.51	0.846
PCA MFV (cm/s)	41.5 ± 10.07 27–55	40.35 ± 9.21 22–65.5	0.769
PCA PI	1.02 ± 0.11 0.91–1.20	1.02 ± 0.26 0.52–1.56	0.802
ACA MFV (cm/s)	46.6 ± 15.32 31.5–69.5	45.5 ± 10.72 23–67.5	0.802
ACA PI	0.91 ± 0.26 0.62–1.27	1.00 ± 0.22 0.32–1.4	0.421
3rd ventricle (mm)	0.28 ± 0.17 0.09–0.54	0.30 ± 0.20 0.07–0.99	0.965

SSc, systemic sclerosis; *RT*, right; *LT*, left; *MV*, mean velocity; *MCA*, middle cerebral artery; *ACA*, anterior cerebral artery; *PCA*, posterior cerebral artery; *MFV*, mean flow velocity; *PI*, pulsatility index. *p* values are significant at $p < 0.05$

In comparison to SLE, Greene et al. [47] reported an evidence of reduced PI values in the MCA using TCS in SLE patients, suggesting a relatively decreased vascular tone and cerebral hyperperfusion mostly due to increased production of nitric oxide and nitric oxide derivatives with consequent vasodilation which has been demonstrated in patients with SLE [48], while the underlying etiology of increased cerebral vascular tone in the limited SSc patients is attributed to a disturbance in the balance between vasodilation and vasoconstriction in favor of reduced vasodilation (as a result of a relative deficiency of nitric oxide or of vasodilatory neuropeptides such as calcitonin-gene-related peptide) and increased vasoconstriction (as a result of increased release of endothelin-1) [49, 50].

In the current study, the limited SSc patients were older than the diffuse SSc patients, yet upon comparing the PI and the MFV values among different age groups, there was no significant difference in the studied parameters; in addition, there was no association between age and either PI or MFV of the PCA and the ACA; therefore, the changes in the PI of PCA, MFV of ACA could not be attributed to the age difference between limited and diffuse SSc. This is in agreement with Hennerici et al. who found only a subtle decrease in cerebral flow velocity with age in the middle cerebral artery but not in the anterior and posterior cerebral arteries [51]. Also, Macchi et al. and Bartels et al. did not find any age dependency of flow parameters [52, 53]. Furthermore, Farhoudi et al. [54] reported that there was no relation between age and either PI or MFV.

Despite the longer disease duration in the limited SSc patients than in the diffuse subset, there was no association between disease duration and either PI or MFV; accordingly, hemodynamic changes are suggested to be related to the disease process.

Intake of vasodilator drugs (calcium channel blockers and sildenafil) in SSc patients could potentially influence cerebral vascular tone; however, comparison between limited and diffuse SSc patients revealed no difference in the percentage of patients receiving calcium channel blockers or sildenafil in either groups; therefore, their effect on PI or MFV was negligible.

Table 8 Comparison between hypertensive and normotensive SSc patients regarding mean flow velocity; pulsatility index of the middle, anterior, and posterior cerebral arteries; and 3rd ventricle diameter

Mean ± SD range	SSc patients ($n = 38$)		*p* value
	Patients with mild hypertension ($n = 5$)	Normotensive patients ($n = 33$)	
MCA MV (cm/s)	57.00 ± 15.56 40.5–75.5	57.23 ± 14.41 30–83	1.000
MCA PI	1.19 ± 0.23 0.96–1.5	0.93 ± 0.22 0.36–1.34	0.05
PCA MV (cm/s)	36.40 ± 9.42 27.5–51	41.12 ± 9.15 22–65.5	0.290
PCA PI	1.23 ± 0.34 0.82–1.5	0.98 ± 0.22 0.52–1.4	0.172
ACA MV (cm/s)	45.70 ± 14.96 29–69.5	45.65 ± 10.79 23–67.5	0.909
ACA PI	1.13 ± 0.16 1.00–1.4	0.96 ± 0.22 0.32–1.3	0.141
3rd ventricle (mm)	0.28 ± 0.17 0.09–0.54	0.30 ± 0.20 0.07–0.99	0.965

SSc, systemic sclerosis; *MCA*, middle cerebral artery; *ACA*, anterior cerebral artery; *PCA*, posterior cerebral artery; *MFV*, mean flow velocity; *PI*, pulsatility index. *p* values are significant at $p < 0.05$

Table 9 Comparison between limited and diffuse SSc patients

Mean ± SD, range (*N*, %)	Limited SSc patients ($n = 11$)	Diffuse SSc patients ($n = 27$)	*p* value
Age	49.18 ± 7.0 39–58	39.19 ± 13.42 22–75	0.010
Age of disease onset	37.00 ± 12.35 17–53	31.89 ± 12.35 14–64	0.251
Disease duration	12.36 ± 6.05 3–21	7.67 ± 5.77 1–20	0.032
Total cholesterol	182.00 ± 26.82 147–226	179.7 ± 37.63 93–288	0.704
Serum triglycerides	134.45 ± 55.37 66–225	118.8 ± 60.70 47–309	0.264
Mean steroid dose	9.55 ± 11.06 0–40	7.87 ± 6.07 0–20	0.899
Females (*n*, %)	10 (90.9%)	22 (81.5%)	0.650
Diabetics (*n*, %)	1 (9.1%)	2 (7.4%)	1
Dyslipidemia (*n*, %)	4 (36.4%)	4 (14.8%)	0.195
Hypertensive (*n*, %)	3 (27.3%)	2 (7.4%)	0.134
Smokers (*n*, %)	0 (0%)	1 (3.7%)	1
Anemic (*n*, %)	2 (18.2%)	3 (11.1%)	0.615
Intake of calcium channel blockers (*n*, %)	8 (72.7%)	24 (88.9%)	0.329
Intake of sildenafil (*n*, %)	6 (54.5%)	9 (33.3%)	0.285

SSc, systemic sclerosis. *p* values are significant at $p < 0.05$

Regarding comorbidities, neither anemia nor hypertension had an impact on our results, as there was no significant difference in PI and MFV values between anemic and non-anemic patients; also, there was no difference in the studied parameters between hypertensive and normotensive SSc patients; moreover, there was no difference regarding dyslipidemia or diabetes mellitus between patients and controls.

Furthermore, there was no difference regarding comorbidities between limited and diffuse SSc patients; also, there was no association between cholesterol, triglyceride level, and both PI and MFV; consequently, PI and MFV changes in the limited subgroup could not be attributed to changes in the HB level, diabetes mellitus, hypertension, or dyslipidemia.

Table 10 Comparison between different age groups in SSc patients regarding mean flow velocity; pulsatility index of the anterior, middle, and posterior cerebral arteries; and 3rd ventricle diameter

Mean ± SD range	Age of SSc patients (N = 38)			*p* value
	20–40 years	41–60 years	> 60 years	
MCA MFV (cm/s)	59.14 ± 14.40 33.5–83	56.00 ± 14.71 30–76.5	50.00 ± 14.85 39.5–60.5	0.585
MCA PI	0.91 ± 0.24 0.36–1.34	1.00 ± 0.24 0.48–1.51	1.14 ± 0.02 1.12–1.15	0.205
PCA MFV (cm/s)	41.28 ± 9.55 22–65.5	39.17 ± 8.63 25–55	45.50 ± 14.85 35–56	0.619
PCA PI	0.99 ± 0.22 0.60–1.46	1.04 ± 0.27 0.52–1.56	1.06 ± 0.30 0.85–1.28	0.601
ACA MFV (cm/s)	47.38 ± 10.59 33–69.5	42.50 ± 10.93 23–61	56.25 ± 15.91 45–67.5	0.336
ACA PI	0.99 ± 0.16 0.70–1.30	0.98 ± 0.29 0.32–01.40	1.08 ± 0.10 1.02–1.15	0.675
3rd ventricle	0.31 ± 0.19 0.09–0.99	0.26 ± 0.19 0.07–0.75	0.31 ± 0.20 0.09–0.75	0.214

SSc, systemic sclerosis; *MCA*, middle cerebral artery; *ACA*, anterior cerebral artery; *PCA*, posterior cerebral artery; *MFV*, mean flow velocity; *PI*, pulsatility index. *p* values are significant at $p < 0.05$

Table 11 Correlation of the mean flow velocity and pulsatility index with the demographic features, HB level, cholesterol, serum triglycerides level, and mean steroid dose in SSc patients

(*r*) (*p* value)	MCA MFV (cm/s)	MCA PI	PCA MFV (cm/s)	PCA PI	ACA MFV (cm/s)	ACA PI
Age	− 0.245	3990.	− 0.166	1330.	0.108	0.217
	(0.144)	(0.015)	(0.319)	(0.426)	0.536	(0.212)
Rodnan score	− 0.042	− 0.006	0.203	− 0.266	0.367	0.063
	(0.804)	(0.970)	(0.221)	(0.107)	0.030	(0.719)
Disease duration	0.187	0.113	− 0.030	− 0.054	0.013	− 0.047
	(0.269)	(0.507)	(0.856)	(0.748)	0.941	(0.790)
Hb	− 0.439	0.008	− 0.027	− 0.09	− 0.159	0.089
	(0.007)	(0.960)	(0.874)	(0.586)	0.360	(0.610)
Cholesterol	0.096	0.159	− 0.121	− 0.200	− 0.239	− 0.256
	(0.573)	(0.346)	(0.468)	(0.228)	0.167	(0.138)
Triglycerides	− 0.141	− 0.028	− 0.250	0.065	− 0.007	0.128
	(0.404)	(0.867)	(0.130)	(0.696)	0.968	(0.463)
Mean steroid dose	− 0.073	− 0.073	− 0.169	0.075	− 0.178	0.241
	(0.667)	(0.668)	(0.310)	(0.655)	0.306	(0.162)

SSc, systemic sclerosis; *MCA*, middle cerebral artery; *ACA*, anterior cerebral artery; *PCA*, posterior cerebral artery; *MFV*, mean flow velocity; *PI*, pulsatility index; *HB*, hemoglobin. *p* values are significant at $p < 0.05$

Indeed, without concurrent MRI images of brain morphology and perfusion analysis, we can only speculate about possible cerebral hypoperfusion by the significant decreased MFV of ACA. Nevertheless, the result obtained in the present study using TCS is supported by previous reports of decreased cerebral blood flow in SSc using other methodologies [55–57].

In contrast to previous reports using MRI or SPECT to assess cerebral vascular involvement in SSc [55–57], Transcranial Doppler ultrasonography was used in this study, which is a cost-effective, simple, robust, bed-side, non-invasive technique, does not use ionizing radiation which the patient has to be faced with during the evaluation by

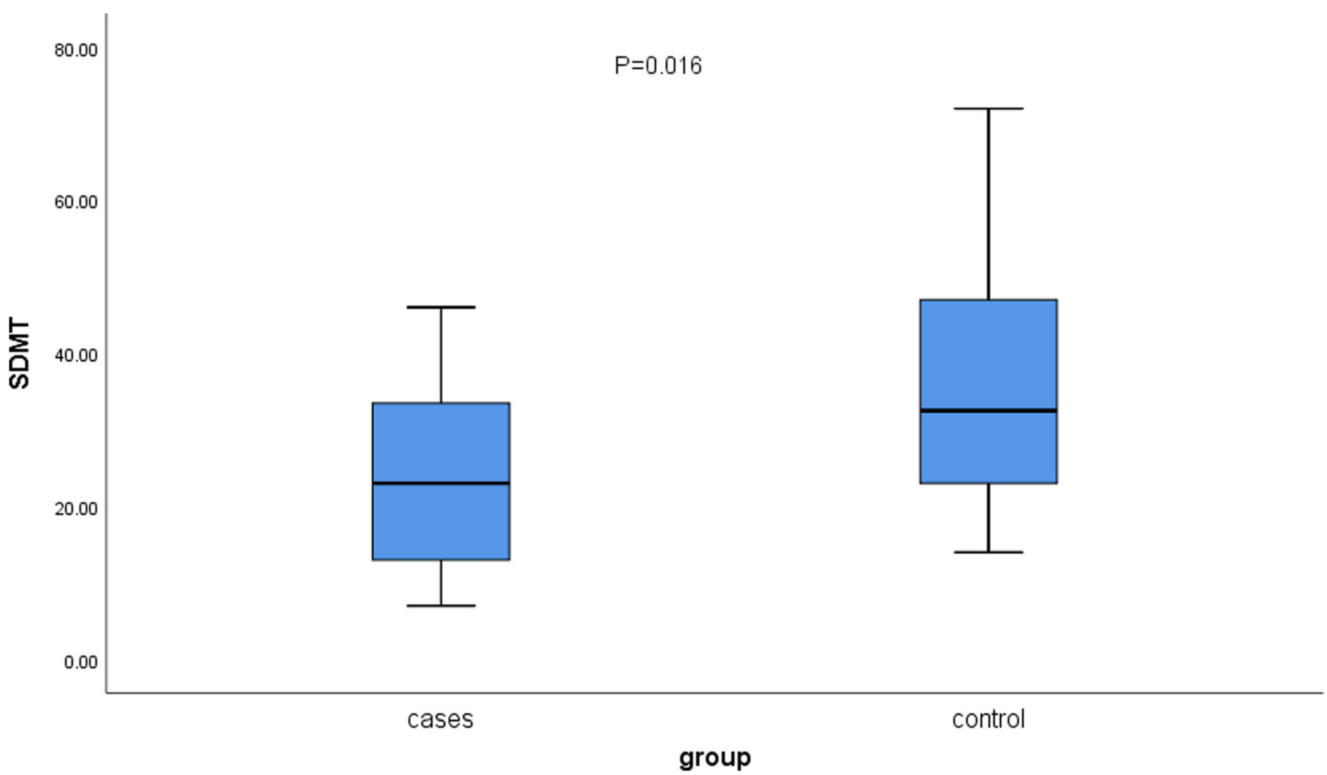

Fig. 1 Symbol Digit Modalities Test

SPECT, which make us propose transcranial color-coded ultrasonography as a quick and easy surrogate marker for evaluating and following up cerebral hemodynamics of SSc patients throughout the disease course.

There was no significant statistical difference in the diameter of the third ventricle (which is a marker of brain atrophy) [58, 59] either between SSc patients and controls, or between limited and diffuse SSc, denoting no evidence of cerebral atrophy in SSc patients, which is in line with previous studies, where Nobili et al. [55] and Sardanelli et al. [56] reported that only white matter with no evidence of ventricular dilatation was observed in SSc.

Regarding cognitive performance, the SDMT was significantly lower in SSc patients compared with controls denoting cognitive impairment in SSc patients, which is in accordance with McNair et al. [10], Giuliodori et al. [60], and Yilmaz et al. [61], who stated that SSc patients could suffer from cognitive dysfunction. Cognitive impairment is reported in other rheumatic diseases; however, the underlying mechanism is different among various rheumatic disorders, while cognitive impairment in antiphospholipid syndrome is related to thrombotic mechanisms [62]; in SLE, it is due to autoantibodies directed towards the nervous system or small-vessel vasculitis [63], and in rheumatoid arthritis, it is due to accelerated atherosclerosis [64]; cognitive impairment in SSc is attributed to microvascular damage and cerebral vascular compromise leading to cognitive disorders, and it could be considered as a systemic cause of vascular cognitive impairment [10, 60, 61].

In summary, in sight of our results, there is an evidence of increased PI of PCA, decreased MFV of ACA in limited SSc patients detected by TCS, denoting increased cerebral vascular tone, and resistance in limited SSc patients compared with diffuse SSc subgroup, along with cognitive impairment in SSc patients, with no evidence of cerebral atrophy; the relevant aspect of this study is that even in asymptomatic SSc patients, early cerebrovascular affection was detected, suggesting that early detection of such condition may provide an opportunity for targeting mediators of vascular injury to modify the course of the disease.

Limitations

Our study has several limitations. Firstly, this is a single-center study; secondly, the sample size is small; and consequently, these results need to be confirmed in a larger cohort. Also, the SDMT was only conducted on 15 cases as they were the only cases who were educated, while the rest were illiterate, which was a major confounder in our study.

Conclusion

There is an evidence of increased cerebral vascular tone, and resistance in limited SSc patients compared with diffuse SSc subgroup, with no evidence of cerebral atrophy, suggesting early cerebrovascular affection even in asymptomatic limited SSc patients. There was also an evidence of cognitive impairment in SSc patients.

Recommendations

The implication of this study is that TCS can be used as a tool for radiological assessment in SSc patients especially limited SSc patients for early detection of cerebrovascular sequelae of the disease. Also, assessment of the whole battery of cognitive functions is recommended in further studies especially on big sample size.

Compliance with ethical standards

Disclosures None.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

Abbreviations *SSc,* systemic sclerosis; *MCA,* middle cerebral artery; *ACA,* anterior cerebral artery; *PCA,* posterior cerebral artery; *MFV,* mean flow velocity; *PI,* pulsatility index; *TCS,* transcranial sonography; *MRI,* magnetic resonance imaging; *SPECT,* single-photon emission computed tomography; *SDMT,* Symbol Digit Modalities Test; *SLE,* systemic lupus erythematosus

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