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Original article

Relationship between nailfold capillary abnormalities and vestibular dysfunction in systemic sclerosis

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ABSTRACT

Objective: To investigate the vestibular dysfunction in a cohort of patients with systemic sclerosis (SSc) and to correlate the findings with disease parameters and microvascular involvement.
Methods: Vestibular affection was assessed in 30 female SSc patients and 29 age-matched healthy females subjects by using the computerized dynamic platform posturography (CDP). Assessment of microvasculature was done by nailfold videocapillaroscopy (NVC). The main clinical correlates of disease, such as renal function, skin, articular and lung involvement, were evaluated by clinical and instrumental investigations.
Results: Subtle vestibular dysfunction was detected in 33% of SSc patients. They exhibited significant decrease in their vestibular ratio values compared to controls ($P = 0.01$). There was a statistical significant association of vestibular affection with both Rodnan's skin score and vascular severity score. Moreover a significant association was found between vestibular dysfunction and NVC patterns. On the other hand, no correlation was observed between vestibular impairment with age, disease duration, disease subsets, autoantibodies and the other clinical disease parameters.
Conclusion: Our results showed an evidence of vestibular impairment in patients with SSc. Vestibular dysfunction positively correlates with vascular severity score as assessed by NVC.

1. Introduction

Systemic sclerosis (SSc) is a diffuse connective tissue disease, characterized by proliferation of the vascular tissue, obliterative microvascular lesions, and immune dysregulation [1]. The pathogenesis of SSc is very complex and still largely unknown, but vascular perturbation is supposed to be a primary event, which may trigger and drive the fibrotic process [2]. Peripheral microangiopathy can be easily recognized by wide-field nailfold videocapillaroscopy (NVC), a non-invasive and safe method that is well established in the investigation of patients with Raynaud's phenomena (RP) and SSc [3]. Most important is that scleroderma microangiopathy correlates with disease subset and severity of peripheral vascular, skin, heart and lung involvement. Moreover in scleroderma patients with late pattern may have an increased risk to experience active disease and to show a moderate/severe skin or visceral involvement compared to patients with early and active patterns. Therefore NVC is a simple, non-invasive and non-expensive investigation, and is useful in staging of scleroderma patients and also can provide prognostic information [4].

Vestibular impairment in autoimmune illnesses, including scleroderma, is one of the least written-about topics in medical journals. Although rare, the impact and potential disability of vestibular affection can be profound for those experiencing it, especially if not recognized and treated early. Vestibular disorders could be assessed using computerized dynamic posturography (CDP), a reliable and valid technology that provides an objective assessment of vestibular involvement [5]. The aim of this case-controlled study is to investigate the vestibular affection in patients with SSc and to correlate the findings with disease parameters and microvascular involvement.

2. Methods

This study comprised 30 female patients with SSc, who met the ACR preliminary criteria for diagnosis and classification of SSc [6] and the LeRoy et al. [7], criteria for subclassification of SSc into limited or diffuse disease pattern. All patients were recruited from the Rheumatology and Rehabilitation Department, Faculty of Medicine, Cairo University. In addition 29 normal healthy age-matched female volunteers served as the control group. In all SSc patients and normal controls could walk independently without ataxia, had no significant lower extremity peripheral neuropathies, and with no history of otologic or confounding neurologic disorders. In all

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patients group antinuclear antibodies (ANA) and anti-centromere antibodies were determined by indirect immunofluorescence using Hep-2 cells as substrates, anti-topoisomerase I antibodies were identified using enzyme-linked immunosorbent assay (ELISA). The study was approved by our institutional ethics committee and informed consent was obtained from all patients.

Skin and visceral organs assessment: skin thickness was scored according to the modified Rodnan's score [8]. Organ system involvement was determined according to Steen et al. [9] with the following visceral involvement assessment: (1) interstitial lung disease (ILD) (bibasilar fibrosis observed on chest radiography and high-resolution computed tomography); (2) pulmonary hypertension (pulmonary artery systolic pressure > 35 mmHg on Doppler echocardiogram; (3) oesophageal involvement (hypomotility shown by barium radiography); (4) joint involvement (inflammatory polyarthralgias or arthritis or tendon friction rub); (5) cardiac involvement (pericarditis, congestive heart failure or arrhythmias requiring treatment); (6) renal involvement (malignant hypertension and rapidly progressive renal failure without any other explanation).

Vascular assessment: vascular involvement was evaluated based on a severity scale classification proposed by Medsger et al. [10]. Briefly, peripheral vascular involvement was judged absent (stage 0) in the case of absence of RP or RP not requiring vasodilators, mild (stage 1) for RP requiring vasodilators, moderate (stage 2) for digital pitting scars, severe (stage 3) for digital tip ulcerations or end stage (stage 4) for digital gangrene. Assessment of microvasculature using nailfold videocapillaroscopy (NVC) was performed by the same operator in all patients. NVC was performed using an optical probe videocapillaroscope connected to image analysis software (KK-Technology, Bridleways Hollyford, and Devon, England). The microvascular alterations were classified into three different patterns according to Cutolo et al. [11]. These include 'early' pattern of few enlarged/giant capillaries, few capillary hemorrhages, relatively well-preserved capillary distribution, and no evident loss of capillaries; the 'active' pattern of frequent giant capillaries, frequent capillary hemorrhages, moderate loss of capillaries, mild disorganization of the capillary architecture, absent or mild ramified capillaries and the presence of edema; the 'late' pattern of irregular enlargement of the capillaries, few or no giant capillaries and hemorrhages, severe loss of capillaries with extensive avascular areas, disorganization of the normal capillary array and the presence of ramified/bushy capillaries.

Vestibular assessment: vestibular affection was assessed using sensory organization test of the CDP on the EquiTest (Neurocom International, Clackamas, Oregon, USA). Vestibular affection was detected by measuring the ratio of the vestibular challenging condition (sway referenced force platform motion and eyes closed) to the control condition (standing quietly with eyes open). Three trials of each of the two conditions were used. The dependent measures for the condition were the average equilibrium score from all three trials.

3. Statistics

The statistical package for social sciences (SPSS) version 10 (LEAD Technology Inc., Charlotle, NC, USA) was used to analyze data. Continuous variables were summarized as median (range) and categorical variables as frequency (percentage). Nonparametric Mann-Whitney U test compared two independent groups and Kruskal-Wallis test compared more than two groups. Associations between categorical groups were tested using the Chi square test (χ^2) with Yates correction or Fisher's exact test as appropriate. Spearman's rank correlation test was used as a measure of association of quantitative variables. In all tests P values < 0.05 were inferred as statistically significant.

4. Results

This study was conducted on 30 female patients with SSc and 29 normal control subjects. No statistical significant differences of the median age between SSc patients and healthy control subjects (49 years, range 19–68 vs. 47 years; range 20–63 respectively; $P = 0.227$). The median disease duration was 7 years ranging from 1–17 years. Seven patients had diffuse SSc and 23 patients had limited SSc. Regarding the autoantibodies found in our patients, ANA was found in 26 patients, anti-topoisomerase I in seven SSc patients (23%) and anti-centromere antibodies in 12 patients (40%). Detailed demographic and clinical features of the SSc patients are presented in Table 1.

Vestibular Score in SSc patients and healthy controls: SSc patients showed significant decrease in the median vestibular ratio than the healthy controls (66.5, range 19–78 vs. 71, range 55–94; $P = 0.010$). There was no statistically significant difference of the median vestibular ratio between patients with diffuse versus those with

Table 1
Demographic and clinical characteristics of whole group of patients ($n = 30$), in patients with vestibular dysfunction (group I), and in patients without vestibular dysfunction (group II).

Parameter	All patients ($n = 30$)	Group I ($n = 10$)	Group II ($n = 20$)	P value significance
Age (years)[a]	48.17 ± 9.36	49.90 ± 10.52	47.30 ± 8.88	0.502
Range (years)	(19–68)	(35–68)	(19–62)	NS
Disease duration (years)[a]	6.78 ± 4.20	5.70 ± 4.83	7.32 ± 3.86	0.267
Range (years)	(1–17)	(3–15)	(1–17)	NS
Rodnan's skin score[a]	25.56 ± 9.41	32.10 ± 8.07	22.30 ± 8.40	0.003
Range	(4–40)	(13–40)	(4–39)	HS
Limited	23 (76.7)	9 (30)	14 (46.7)	0.372
Diffuse	7 (23.3)	3 (10)	4 (13.3)	NS
Acroosteolysis	17 (56.6)	5 (50)	12 (60)	0.705
				NS
Articular	14 (46.6)	5 (50)	9 (45)	1
				NS
Oesophageal dysmotility	24 (80)	8 (80)	16 (80)	1
				NS
Pulmonary Fibrosis	11 (36.6)	4 (40)	7 (35)	1
				NS
Pulmonary hypertension	11 (36.6)	2 (20)	9 (45)	0.246
				NS

[a] Data are the mean ± standard deviation (SD), other data are percentage; Mann-Whitney U test was used to compare continuous variables, while Fisher exact test (χ^2) was used to compare frequencies; HS: highly significant ($P < 0.001$); NS: none significant ($P > 0.05$).

Table 2
The NVC patterns and vascular severity score of SSc patients based on the presence of vestibular dysfunction.

Parameter	All patients ($n=30$)	Group I ($n=10$)	Group II ($n=20$)
Mild vascular score	7 (23.3)	1 (10)	6 (30)
Moderate vascular score	7 (23.3)	1 (10)	6 (30)
Severe vascular score	13 (43.3)	6 (60)	7 (35)
End stage vascular score	3 (10)	2 (20)	1 (5)
Early NVC pattern	9 (30)	1 (10)	8 (40)
Active NVC pattern	12 (40)	4 (40)	8 (40)
Late NVC pattern	9 (30)	5 (50)	4 (20)

All data are percentages; NVC: nailfold videocapillaroscopy.

limited subtype ($P>0.05$). Ten out of our 30 SSc patients (33%) had diminished vestibular ratio (i.e., vestibular dysfunction) (Table 1). A statistical significant difference was found on comparing the median of Rodnan's total skin score in patients with vestibular dysfunction to those patients without ($P=0.004$). Further, Rodnan's skin score was inversely correlated with vestibular ratio ($r=-0.492$, $P=0.006$). No statistical significant differences were found between other organ system involvement, demographic data, and the prevalence of antoantibodies in patients with vestibular dysfunction versus those without ($P>0.05$). In addition, no significant correlations were found between the median age and disease duration with vestibular ratio (data not shown).

Relation of the vestibular dysfunction with the vascular severity score and NVC patterns: nine patients (30%) had an early, 12 (40%) an active and nine (30%) a late NVC pattern. Table 2 shows the NVC patterns and vascular severity score of SSc patients based on the presence of vestibular dysfunction. Patients with vestibular dysfunction was significantly associated with both NVC patterns and vascular severity score (χ^2 for linear trend = 0.135, $P=0.049$ and χ^2 for linear trend = 0.191, $P=0.046$, respectively). In addition, a statistical significant difference was found between median vestibular ratio values and the pattern of NVC with a progressive decrease from early to active, and above all, to late pattern (72, 66.5 and 46, respectively; $P=0.042$ by Kruskal-Wallis test; Fig. 1A). Similarly, the median vestibular ratio values were progressively diminished by increasing vascular severity score from mild to end stage (72, 72, 56, and 45 respectively; $P=0.048$, by Kruskal-Wallis test; Fig. 1B).

5. Discussion

The current case-controlled study showed that 33% of SSc patients have vestibular impairment. This impairment was more frequent in patients with active and late patterns of NVC. Moreover SSc Patients with vestibular dysfunction showed significant association with both NVC patterns and vascular severity score

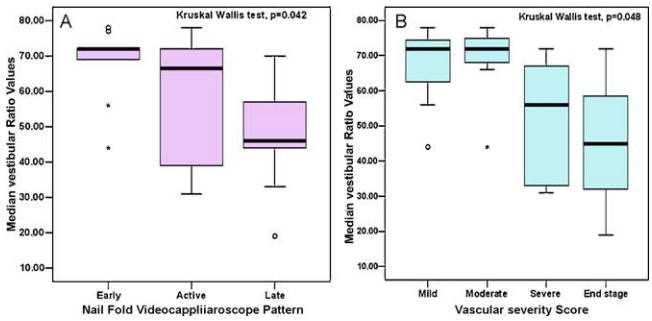

Fig. 1. Vestibular ratio in SSc patients in relation to (A) nailfold videocapillaroscope patterns; (B) vascular severity score. The lines inside the boxes indicate the median; the outer borders of the boxes indicate 25th and 75th percentiles; the bars extending from the boxes indicate the 10th and 90th percentiles.

($P=0.049$ and $P=0.046$, respectively). Inner ear involvement has been reported in many autoimmune connective tissue diseases, including RA, SLE, mixed cryoglobulinaemia, and vasculitic syndromes [12–19]. Similarly to other autoimmune diseases, SSc is likely to trigger vestibulospinal reflex malfunctioning, however the number of the studies that examined vestibular dysfunction and inner ear abnormalities in SSc are scanty [20–22]. Giacomini et al. [20] evaluated the orthostatic postural control in 36 SSc patients and in 10 healthy age-matched females as a control group. In their study postural stability was assessed by means of a static computerized posturography technique. Consistent with our findings, Giacomini et al. [20] observed that posturography results showed relevant differences in body sway between patients and control subjects and SSc patients exhibit a higher level of low/middle frequency oscillations .The authors ending that subtle neurophysiological dysfunctions in the orthostatic postural control exist in their cohort. More recently increased frequency of benign paroxysmal positional vertigo and vestibular pattern in clinical test of sensory interaction and balance have been recently reported in SSc patients [21,22]. Amor-Dorado et al. [21] assessed the frequency and characteristics of benign paroxysmal positional vertigo (BPPV) and clinical test of sensory interaction and balance (CTSIB) abnormalities in 42 patients with SSc and 74 controls. Their results showed that seven patients (17%) fulfilled the diagnostic criteria for BPPV compared with none of the controls ($P<0.001$). A significantly increased frequency of abnormal CTSIB was also observed in SSc patients (48%) compared to controls (10%) ($P<0.0001$). It was caused by a vestibular pattern in most patients ($P<0.0001$). The same group of investigators [22] reported typical pattern of hearing impairment in a series of 35 patients with limited SSc, which was a bilateral and symmetrical sensorineural hearing loss with a flat pattern in the audiogram. Finally, a significantly increased frequency of abnormal caloric test and clinical test of sensory integration and balance were observed in the patients' group ($P<0.001$ for both comparisons); given that these findings demonstrate strong evidence for inner ear compromise in patients with SSc.

The exact mechanism of the vestibular impairment in SSc is not fully understood and remains speculative. In theory immunological features of SSc such as aberrant autoimmune response, collagen hyperproduction, fibrosis and vasculopathy changes in the microvascular tissues could be implicated in vestibular dysfunction [1]. In previous work Arbusow and coworkers [23] have found IgG antibodies against membranous labyrinth in 8/12 patients with idiopathic bilateral vestibulopathies. Vestibular alteration in our study could result from abnormal collagen deposition of the vestibular hair cells. In our study we had found more impairment of vestibular function among patients with increased skin thickness as assessed by Rodnan's scoring system. It was documented that fibrosis in the skin and internal organs in the course of SSc is caused by the accumulation of an excessive quantity of collagen and other components of the extracellular matrix (ECM), in which fibroblasts play an important role in the metabolism of ECM and connective tissue within the skin and internal organs [24]. The vestibular system comprises a series of interconnected fluid-filled membranous canals inside bony channels at the base of the skull. Extensive tissue network, formed by connective tissue cells secreting collagen fibres within the ECM in the membranous labyrinth, helps to control interstitial fluid pressure by restraining the intrinsic swelling tendency of the ground substance [25]. Disorganization of this network structure, probably by affecting the cell–cell and cell–ECM contacts may affect the interstitial fluid pressure with subsequent impaired endolymph outflow and eventually vestibular impairment might occur [26].

In theory microvascular involvement of the labyrinthine vessels may be also responsible for inner ear damage based on our finding

of the association of vestibular impairment with NVC patterns and with the vascular severity score in SSc patients.

Vestibular dysfunction has been previously reported in both patients with primary systemic vasculitis [16], and obliterative vasculitis of the labyrinthic artery orits branches has been previously implicated in the pathogenesis of deafness among patients with relapsing polychondritis [12]. Moreover vasculitic and autoimmune mechanisms have been considered to play a role in the pathogenesis of the frequently subclinical audiovestibular dysfunction that has been previously reported in patients with RA and SLE [13,14], in patients with polyarteritis nodosa [27], and in some cases presenting with sudden deafness and vertigo as early manifestations of the disease [28]. Further more vestibular manifestations, such as vertigo and nystagmus, have been described in patients with giant cell arteritis [17], and in Behcet's disease [18]. Taken together direct vascular involvement in these clinical settings could be implicated. Several studies have addressed a possible relationship between NFC alterations and the extent of visceral involvement in SSc [4,29,30]. NFC abnormalities have been previously correlated positively with the severity of skin, lung, heart involvement and the diffuse form of SSc [4,29]. Bredemeier and coworkers found a positive correlation between the vascular deletion score in NFC and higher Rodnan's skin score, presence of anti-Scl-70 antibodies, signs of peripheral ischemia, esophageal dysfunction and pulmonary disease [30].

The aging process, of our SSc patients, should not have influenced the vestibular ratio since an age-matched control group was preselected for the statistical comparison and no significant difference between age of SSc patients with impaired vestibular function and those with normal function was found. We also examined the influence of disease duration on the development of vestibular abnormalities; however, we found no association between disease duration and the development of vestibular abnormalities.

Finally a diminished vestibular ratio may reflect an ongoing uncompensated vestibulo-spinal deficit in SSc. The correlation between low vestibular ratio scores and vascular severity score suggest that vascular lesions in scleroderma might be behind the delay in central compensation of the vestibular dysfunction.

6. Conclusion

The current study provides an evidence of the presence of vestibular abnormalities in patients with SSc; the later positively correlate with vascular severity score and skin thickness score. Our data suggest that vascular disease in the setting of this connective tissue disease may be responsible for this abnormality. This group of patients needs rehabilitative balance therapy and monitoring their recovery.

Conflict of interest statement

All the authors responsible for this work declare no conflict of interest of any kind.

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