

Early detection of median nerve syndrome at the carpal tunnel with high-resolution 18 MHz ultrasonography in systemic sclerosis patients

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Abbreviations:

EMG: electromyography

MN: median nerve

MNA: median nerve area

MNAP: median nerve antero-posterior diameter

MNT: median nerve transversal diameter

MNFR: median nerve flattening ratio

mRSS: Modified Rodnan Skin Score

RP: Raynaud phenomenon

SSc: systemic sclerosis

CTS: carpal tunnel syndrome

US: ultrasound

Competing interests: none declared.

ABSTRACT

Objectives. To investigate carpal tunnel syndrome (CTS) with ultrasound (US) in asymptomatic SSc patients and to seek out the relationship between CTS and SSc clinical variables

Methods. In 64 SSc patients (55 women and 9 men, mean age 57 ± 14 years) and in 30 healthy controls, area (MNA), transverse (MNT) and anteroposterior (MNAP) diameters of MN at carpal tunnel were studied with US (My Lab 25 XVG US Esaote 18 MHz). MN flattening ratio (MNFR) was calculated. Duration of disease, subset (limited, diffuse), phase of skin involvement (oedematous, atrophic, fibrotic), modified Rodnan skin score (mRSS) and friction tendon rub were also recorded.

Results. MNA ($p < 0.001$), MNT ($p < 0.005$) and MNFR ($p < 0.005$) were significantly higher in the SSc patients than in controls, while no difference in MNAP was found. There was no correlation between median nerve (MN) and SSc clinical features (only lower MNAP correlated inversely with longer disease duration; Spearman coefficient -0.2).

Conclusion. MN involvement is frequently present in all phases of asymptomatic SSc patients, independently to clinical variables.

Introduction

The association of Raynaud's Phenomenon (RP) with carpal-tunnel syndrome (CTS) was first reported at the Mayo Clinic in 1957 (1). Oedema of hand and median nerve (MN) sensory symptoms frequently may precede the onset of RP (2). Blunt demonstrated that CTS is not only owing to mechanical factors, but also to neural ischemia resulting from vasospasm (3). Carpal tunnel tendon friction rub is considered a prognostic negative factor in SSc,

and its relationship with CTS is not still well thought-out in literature (4).

In SSc, early detection of MN involvement is important to prevent functional hand disability (5). Electromyography (EMG) often discloses significant reduction of distal MN sensory and motor conduction rate in SSc (6, 7) also in asymptomatic patients (6). High resolution ultrasound (US) of the carpal tunnel is a feasible and emerging imaging tool for evaluating MN (8, 9), cheaper, faster and less invasive than EMG and more sensitive than clinical examination (10). In SSc, only few issues employed US in joint evaluation (11) and in particular, there are no studies on early diagnosis of CTS. High-frequency 18MHz US offers considerably better resolution than probes that previously estimated MN and, in SSc, was also employed in dermal thickness measurement (12).

The aim of our work was to investigate, with US, MN in asymptomatic SSc patients, and the relationship between CTS and SSc clinical variables (duration of disease, subset, phase of skin involvement, Modified Rodnan Skin Score-mRSS- and tendon friction rub).

Patients and methods

Sixty-four Caucasian patients without motor and sensory symptoms (numbness and muscular weakness) and signs (muscular atrophy) were recruited at the Department of Biomedicine, Division of Rheumatology of the University of Florence and classified as limited or diffuse SSc subsets, according to international consensus criteria (13). Local ethical committee approved the study and an informed consensus was signed by patients and controls.

Thirty healthy volunteers matched for age, sex (same ratio male-female) and

anthropometric values served as the control.

Calcium-channel blockers and vasodilators treatments were discontinued ten days before US.

Patients with previous surgery or trauma or corticosteroid injection in the carpal tunnel, presenting local calcinosis, active wrist synovitis, crystals deposition, abnormal thyroid function and diabetes were excluded.

Ultrasound evaluation

All SSc patients and controls underwent high-resolution real-time US of the carpal tunnel using a My Lab 25 XVG US Esaote 18 MHz linear array transducer, with the fix setting (52% gain, 50% grey scale) of machine and gel lay measured with calibre.

The US examination was performed with the patient seated in a comfortable position in front of the sonographer, with the forearm resting on the table and the palm facing up in the neutral position (8). The temperature of the room was 20°C. The MN cross-sectional area (MNA), the transverse (major axis) (MNT) and anteroposterior (minor axis) (MNAP) diameters were measured, consistently with other studies on CTS (8, 14, 15), at the proximal inlet of carpal tunnel in the transverse plane between the scaphoid tubercle and the pisiform bone. The margin of the nerve was defined using a continuous boundary trace outside the hypoechoic nerve fascicles and inside the hyperechoic nerve sheath (16) (Fig. 1). The flattening ratio (FR) was defined as the ratio of the nerve's major to minor axis (MNFR). We used the cut off proposed for idiopathic CTS by Duncan for MNA >9mm² and MNFR >3.3 (8) and, more recently, by Naranjo for MNA >12mm² (10). The presence of radio carpal effusion (shown by dorsal US evaluation of wrist) and fingers flexor tenosynovitis was noted.

Inter-observer reliability was established in all US independent and consecutive MN measures of patients and controls made by two sonographers (FB. and OK.) unaware of previous examinations. For assessing the intra-observer variability, all patients and controls were examined twice by the first observer.



Fig. 1. MN: Median nerve increased area (15mm²) of a limited SSc patient (oedematous skin) asymptomatic for CTS (with EMG positive for mild CTS), without changes of the anatomical structures: (1) flexor retinaculum, (SC and PIS) scaphoid and pisiform bone, (FT) superficial and deep flexor fingers.

Clinical evaluation

Clinical examination (modified Rodnan skin score -mRSS- (17), friction flexor tendon rub) and features (duration of disease, clinical subset-limited and diffuse-, phase of skin involvement-oedematous, fibrotic and atrophic-) of SSc patients were recorded by two rheumatologists unaware of US results (MLC, IM).

Statistical analysis

MN US parameters differences between SSc and healthy controls were calculated with the Mann-Whitney U-test.

Correlation with clinical variables was estimated by Pearson's parametric and Spearman non-parametric correlation coefficient. *P*-values less than 0.05 were considered significant.

The inter- and intra-observer variability was measured using the intra-class correlation coefficient (ICC).

Results

Demographic and clinical aspects of SSc patients and controls are summarised in Table I.

The ICC intra and inter-observer variability were respectively 0.99 (interval of confidence 0.98-0.99) and 0.92 (interval of confidence 0.86-0.95) for all measures.

MNA, MNT and MNFR were significantly higher in SSc than controls

(Table II), while MNAP values were similar. NMA and NMFR were higher than Duncan cut off respectively in 43/64 (67%) and in 36/64 patients (56.4%); NMA was higher than the Naranjo cut-off in 27/64 (42.2%) subjects.

No radio carpal effusion and fingers flexor tenosynovitis were noted.

Clinical features

Only MNAP inversely correlated with SSc duration of disease (*p*<0.05, correlation not parametric Spearman coefficient -0.2). No significant difference in US values between subsets or phase of skin involvement and no correlation with mRSS were detected. Only 4/64 (6.2%) patients were friction rubs positive, without difference with negative.

Discussion

In our study, all MN SSc measures are higher than controls in all phases of disease independently of duration of SSc, mRSS, subset (limited, diffuse) and phase of skin involvement (oedematous, atrophic, fibrotic). These data clearly show that in SSc patients, the MN involvement at carpal tunnel is more remarkable than previously estimated (18-19), according to Lori that focused a distal mono-neuropathy of MN in 43.7% of asymptomatic SSc patients (6).

Table I. Demographic and clinical features of SSc patients and controls.

	SSc	Controls
Sex (female/male)	55/9	26/4
BMI (*)	23±3 (min 17; max 25)	22±3 (min 18; max 24)
Age (years)	57±14 (min 21; max 78)	53±12 (min 30; max 83)
Duration of disease (years)	6.9±6 (min 1 max. 32)	–
Subset (limited/diffuse)	54/10	–
Phase of skin involvement (oedematous-fibrotic-atrophic)	18/26/20	–
mRSS (**)	8±7 (min 1 max 28)	–
Friction tendon rubs	4 (6.2%)	–

*BMI: body mass index; **mRSS: modified skin score.

Table II. US values of MNA, MNAP, MNT, MNFR in SSc and in healthy controls.

		Mean	Min	Max	SD		Mean	Min	Max	SD	p-value
MNA	SSc	11.1	5.	20	3.6	Healthy	8.2	2	10	1.6	<0.005
MNAP		2.02	1.07	3.2	1.6		1.9	1.4	2.7	0.3	n.s.
MNT		6.8	3.6	11.5	1.8		5.2	4.1	6.4	0.6	<0.001
MNFR		3.4	1.6	4.7	0.85		2.7	1.7	3	0.6	<0.005

p-values are expressed as $p<0.005$, $p<0.001$; n.s. = not significant).

In disagreement to previous issues that ascribed tendon friction rub to fibrous tenosynovitis (20), US did not show abnormalities in flexor tendons in the patients examined, but probably a higher number of subjects with friction rub might be specifically studied in the future, to interpret correctly these data. For the absence of flexor tenosynovitis and radio-carpal synovitis and the low prevalence of friction rub, we may consider the hypothesis, formulated also in previous studies (6, 21), that in these SSc patients, CTS is not a consequence of compression mechanisms and may be raised by ischemia of *vasa nervorum*, following the vasospasm (3).

Blunt showed anatomically that MN epineural, inter- and intrafascicular plexuses communicate among a complex “free vascular network” and that the deeper lying perifascicular plexus is particularly rich of capillars (3), which are the prominent sites of vascular abnormalities in SSc (22). Furthermore, nutrient neural vessels derived from ulnar, common interosseous and anterior interosseous arteries (and inconstantly from radial artery) (3) may also be involved in the disease (22).

Vasodilator treatment, probably washed

out before evaluation with the same method of other studies (6, 21), might have had a protective role on clinical presentation (numbness and muscular atrophy) of CTS in these patients.

Early morphologic changes of MN in SSc resulted in an increasing of area, probably due to axonal regeneration of myelinated and not myelinated fibres after ischemic damage, according to a preceding study on STC in asymptomatic diabetic patients (23).

Probably, only a histological investigation may clearly support this hypothesis and Doppler US of ulnar and radial arteries integrated with MN US evaluation might also be useful in other future studies.

Conclusions

In conclusion, CTS is a frequent sub-clinical disease in SSc, present in all phases and independent of clinical features of disease, which may be diagnosed by US.

References

1. LINSHEID RL, LOWELL PETERSON FA, JUERGENSEN JL, ROCHESTER JL: Carpal tunnel syndrome associated with vasospasm. *J Bone J Surg* 1967; 49: 1141-6.
2. PONCELET AN, CONNOLLY MK: Peripheral

neuropathy in scleroderma. *Muscle Nerve* 2003; 28: 330-5.

3. BLUNT MJ: The vascular anatomy of median nerve in the forearm and hand. *J Anat* 1959; 93: 15-22.
4. STEEN VD, MEDSGER TA: The palpable tendon friction rub. *Arthritis Rheum* 1997; 40: 1146-51.
5. CASALE R, BUONOCORE M, MATUCCI-CERINIC M: Systemic sclerosis (scleroderma): an integrated challenge in rehabilitation. *Arch Phys Med Rehabil* 1997; 78: 767-73.
6. LORI S, MATUCCI-CERINIC M, CASALE R *et al.*: Peripheral nervous system involvement in systemic sclerosis: the median nerve as target structure. *Clin Exp Rheumatol* 1996; 14: 601-5.
7. MONDELLI M, ROMANO C, DE STEFANO R, CIONI R: Nerve conduction velocity study of the upper limb in Raynaud's phenomenon. *Rheumatol Int* 2000; 19: 165-9.
8. DUNCAN I, SULLIVAN P, LOMAS F: Sonography in the diagnosis of carpal tunnel syndrome. *AJR* 1999; 681-4.
9. NARANJO A, OJEDA S, ARAÑA V *et al.*: Usefulness of clinical findings, nerve conduction studies and ultrasonography to predict response to surgical release in idiopathic carpal tunnel syndrome. *Clin Exp Rheumatol* 2009; 27: 786-93.
10. NARANJO A, OJEDA S, MENDOZA D, FRANCISCO F, QUEVEDO JC, ERAUSIN C: What is the diagnostic value of ultrasonography compared to physical evaluation in patients with idiopathic carpal tunnel syndrome? *Clin Exp Rheumatol* 2007; 25: 853-9.
11. RIENTE L, DELLE SEDIE A, FILIPPUCCI E *et al.*: Ultrasound imaging for the rheumatologist XIV. Ultrasound imaging in connective tissue diseases. *Clin Exp Rheumatol* 2008; 26: 230-3.
12. KALOUDI O, BANDINELLI F, FILIPPUCCI E *et al.*: High frequency ultrasound measurement of digital dermal thickness in systemic sclerosis. *Ann Rheum Dis* 2010; 69: 1140-3.
13. LEROY EC, BLACK C, FLEISCHMAIER R *et al.*: Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. *J Rheumatol* 1988; 15: 202-5.
14. BUCHBERGER W, SCHON G, STRASSER K, JUNGWIRTH W: High-resolution ultrasonography of the carpal tunnel. *J Ultrasound Med* 1991; 10: 531-7.
15. BUCHBERGER W, JUDMAIER W, BIRBAMER G, LENER M, SCHMIDAUER C: Carpal tunnel syndrome: diagnosis with high-resolution sonography. *Arthritis Rheum* 1992; 159: 793-8.
16. LEE MT, VAN HOLSBEEK MT, JANEVSKI PK, GANOS DL, DITMARS DM, DARAN VB: Diagnosis of carpal tunnel syndrome: ultrasound versus electromyography. *Radiol Clin North Am* 1999; 36: 859-72.
17. RODNAN GP, LIPINSKI E, LUKSICK J: Skin thickness and collagen content in progressive systemic sclerosis and localized scleroderma. *Arthritis Rheum* 1979; 22: 130-40.
18. SHADY W, SHEARD A, HOSSEL A, HOLT L, JAYSON MIV: Peripheral nerve dysfunction in scleroderma. *Q J Med* 1991; 292: 661-75.
19. HIETARAHARJU A, JAASKELAINEN S, KALIMO H, HIETARINTA M: Peripheral neuro-

- muscular manifestations in systemic sclerosis (scleroderma). *Muscle Nerve* 1993; 16: 1204-12.
20. AKESSON A, FIORI G, KRIEG T, VAN DEN HOOGEN FHJ, SEIBOLD JR: Assessment of skin, joint, tendon and muscle involvement. *Clin Exp Rheumatol* 2003; 21 (Suppl. 29): S5-S8.
 21. MONDELLI M, ROMANO C, DELLA PORTA PD, ROSSI A: Electrophysiological evidence of "nerveentrapment syndrome" and subclinical peripheral neuropathy in progressive systemic sclerosis (scleroderma). *J Neurol* 1995; 242: 185-94.
 22. KAHALEH MB: Vascular involvement in systemic sclerosis (SSc). *Clin Exp Rheumatol* 2004; 22 (Suppl. 33): S19-22.
 23. WATANABE T, ITO H, MORITA A *et al.*: Sonographic evaluation of the median nerve in diabetic patients. *J Ultrasound Med* 2009; 28: 727-34.