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Entrapment neuropathies and polyneuropathies in joint hypermobility syndrome/Ehlers–Danlos syndrome

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HIGHLIGHTS

- This study aims to investigate the involvement of the peripheral nervous system, with particular attention to entrapment syndromes, in JHS/EDS-HT patients by performing an extensive clinical, neurophysiological and ultrasonographic (US) examination.
- The study shows an inconsistency between symptoms and neurophysiological and ultrasound evidences of focal or diffuse nerve involvement.
- The high prevalence of ulnar nerve subluxation/luxation at elbow in Ehlers–Danlos syndromes/hypermobility type patients could be explained by the presence of Osborne ligament laxity.

ABSTRACT

Objective: This study aims to investigate the involvement of the peripheral nervous system in Ehlers–Danlos syndromes/hypermobility type patients with particular attention to entrapment syndromes.
Methods: We consecutively enrolled Ehlers–Danlos syndromes/hypermobility type patients. Patients underwent clinical, neurophysiological and ultrasound evaluations. Dynamic ultrasound evaluation was also performed in healthy subjects as control group.
Results: Fifteen Ehlers–Danlos syndromes/hypermobility type patients and fifteen healthy subjects were enrolled. Most of patients presented tingling, numbness, cramps in their hands or feet. Clinical evaluation was normal in all patients. One patient was affected with carpal tunnel syndrome and one with ulnar nerve entrapment at elbow. One patient had an increased and hypoechoic ulnar nerve at elbow at ultrasound evaluation. Dynamic ultrasound evaluation of ulnar nerve at elbow showed, in patients, twelve subluxations and three luxations. In the control group dynamic evaluation showed one case of ulnar nerve luxation.
Conclusion: Statistical analysis showed a significant difference in the occurrence of ulnar nerve subluxation and luxation between patients and control subjects.
Significance: The study shows an inconsistency between symptoms and neurophysiological and ultrasound evidences of focal or diffuse nerve involvement. The high prevalence of ulnar nerve subluxation/luxation at elbow in Ehlers–Danlos syndromes/hypermobility type patients could be explained by the presence of Osborne ligament laxity.

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1. Introduction

Joint hypermobility (JHM) is a common heritable trait referring to the ability to extend one or more synovial joints beyond their normal limits (Hakim and Grahame, 2003). Though usually considered a clinically unremarkable trait, generalized JHM is the hallmark of various heritable connective tissue disorders (HCTDs), mainly the Ehlers–Danlos syndromes (EDSs). Among the various forms of EDS, the hypermobility type (EDS-HT) is probably the most common (Hakim and Sahota, 2006). However, it is often underdiagnosed due to the lack of clear-cut clinical features other than generalized JHM

Abbreviations: 1M, first digit to wrist for median nerve; 1R, first digit to wrist for radial nerve; 3M, third digit to wrist for median nerve; 5U, fifth digit to wrist for ulnar nerve; BCTQ, Boston Carpal Tunnel Questionnaire; CMAP, compound motor action potential; CSA, cross sectional area; CTS, carpal tunnel syndrome; DML, distal motor latency; EDSs, Ehlers–Danlos syndromes; EDS-HT, EDS hypermobility type; FUNCT, functional status of CTS; HCTDs, heritable connective tissue disorders; JHM, joint hypermobility; JHS, joint hypermobility syndrome; MNCV, motor nerve conduction velocity; SAP, sensory action potential; SNCV, sensory nerve conduction velocity; SYMPT, symptoms of CTS; UNE, ulnar nerve entrapment at elbow; US, ultrasonographic.

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and reliable molecular tests. EDS-HT it is now considered undistinguishable from the joint hypermobility syndrome (JHS), an emerging rheumatologic condition associating generalized JHM with a wide variety of musculoskeletal and extra-musculoskeletal features, including arthralgias, pelvic dysfunction and minor eye and skin anomalies (Grahame, 2000; Tinkle et al., 2009).

For decades, medical literature neglected the neurological aspects of EDSs and, in particular, of JHS/EDS-HT. However, in the clinical practice neurological features are common and accurate nervous system assessment is mandatory in JHS/EDS-HT. Accordingly, Voermans and colleagues (Voermans et al., 2009) first reported an extensive neurological survey on 40 patients with various forms of EDSs and showed that EDSs often displays myopathic or mixed neuropathic-myopathic pattern at electromyography, sometimes coupled with reduced muscle diameter and echo intensity by ultrasound examination and unspecific myopathic changes at biopsy. At the same time, chronic pain is now considered a common cause of disability in JHS/EDS-HT (Voermans et al., 2010, 2011a) and the link with a possible primary impairment of the nervous system is a prolific field for further investigations. In line with this, a questionnaire study suggested a neuropathic component for chronic pain in about 2/3 JHS/EDS-HT patients (Camerota et al., 2010), a finding that may be partly explained by a higher rate of compression and peripheral neuropathies in EDSs (Voermans et al., 2011b).

This study aims to investigate entrapment syndromes and polyneuropathies in JHS/EDS-HT patients by performing an extensive clinical, neurophysiological and ultrasonographic (US) examination.

2. Materials and method

2.1. Clinical examination

From September 2010 to October 2011, we consecutively enrolled patients with EDS-HT followed in the "Joint Hypermobility" outpatient clinic at the Department of Physical Medicine and Rehabilitation of the Umberto I University Hospital in Rome (Italy). Assessment of the patients was always supported by a clinical genetic evaluation. Diagnosis was based on published criteria including the Brighton criteria for JHS (Grahame et al., 2000) and the Villefranche criteria for EDS-HT (Beighton et al., 1998). Patients were included if they met at least one of these two sets. In our clinical practice, the Brighton criteria are the most stringent for young-adult, adult and elder patients, while the Villefranche criteria are the best for individuals in the pediatric age. For this study, JHM was mainly assessed applying the Beighton score (Beighton et al., 1973). Further, joints or group of joints were equally evaluated although, at the moment, their status does not influence diagnosis establishment. Beighton score is a 9-point evaluation with attribution of one point in the presence of any of the following: (a) passive apposition of the thumb to the flexor aspect of the forearm (one point for each hand), (b) passive dorsiflexion of the V finger beyond 90° (one point for each hand), (c) hyperextension of the elbow beyond 10° (one point for each arm), (d) hyperextension of the knees beyond 10° (one point for each leg), (e) forward flexion of the trunk with the knees extended and the palms resting flat on the floor. Skin/superficial connective tissue features were qualitatively assessed, on the basis of accumulated experience, by palpation and gentle stretching of the skin at the volar aspect of the palm (at the IV metacarpus) and/or forearm. Individuals with incomplete diagnosis were excluded. This implied that those patients with features of JHS/EDS-HT still insufficient for a firm clinical diagnosis based on available diagnostic criteria, but likely destined to develop full-blown JHS/EDS-HT, were not included in this study. Each patient underwent clinical, neurophysiological and US evaluations, all performed by the same neurophysiologist. Patient history was recorded to exclude the presence of diseases that could cause or contribute to carpal tunnel syndrome (CTS) or other peripheral nerve disease, such as diabetes, hypothyroidism or acromegaly.

Clinical examination included the evaluation of tendon reflex, Phalen test at wrist, Tinel and provocative test at elbow, sensory and motor functions evaluation. Segmental muscle strength of the four limbs main muscles (tibialis anterior, extensor hallucis longus, peroneus longus, gastrocnemius, quadriceps, abductor digit minimi, first interosseous, abductor pollicis brevis, common fingers extensor, brachial biceps, deltoid) was assessed and scored through MRC score. Superficial sensibility of the four limbs was evaluated trough cotton-wool test. Particular attention was paid to sensory evaluation of hands and feet.

2.2. Neurophysiological study

Neurophysiological examination was performed by using an Oxford Synergy (Surrey, England) equipment. Skin temperature was controlled during neurographic study and maintained always at 32 °C or above. Nerve conduction studies of the following nerves were performed: median (motor and sensory), ulnar (motor and sensory), peroneal (only motor), radial and sural (sensory) nerves. All these nerves were studied on both sides. Nerve conduction studies were performed using surface recording electrodes according to conventional procedures. The following segments of upper limb sensory nerves were studied orthodromically: from first digit to wrist for radial nerve (1R), from first and third digit to wrist for median nerve (1M and 3M) and from fifth digit to wrist for ulnar nerve (5U) (Padua et al., 1996). Sural nerves were studied antidromically from sura to calf (Padua et al., 2011). The following segments of upper and lower limb motor nerves were studied: peroneal nerve neurography was performed stimulating the nerve at the ankle, at the fibular head and at the lateral popliteal fossa recording from the extensor digitorum brevis muscle (Padua et al., 2011), median nerve was stimulated at wrist and at elbow recording from the abductor pollicis brevis muscle while ulnar nerve was stimulated at wrist, below and above elbow recording from the abductor digit minimi muscle. Neurophysiologic findings where compared to our laboratory reference values. Median nerve: distal motor latency (DML) <4.0 ms, motor nerve conduction velocity (MNCV) wrist–elbow tract >45 m/s, compound motor action potential (CMAP) >4 mV, 1M sensory nerve conduction velocity (SNCV) >42 m/s, 3M SNCV >44 m/s, 1M and 3M sensory action potential (SAP) >4 μV. Ulnar nerve: DML <4.0 ms, MNCV below elbow–wrist tract >45 m/s, MNCV above–below elbow tract >40 m/s, 5U SNCV >42 m/s, CMAP >4 mV, 5U SAP >4 μV. Peroneal nerve: DML <6.0 ms, MNCV fibular head–ankle tract >40 m/s, MNCV popliteal fossa-fibular head tract >40 m/s, CMAP >1 mV. Sural nerve: SNCV >42 m/s, SAP >4 μV (Padua et al., 1996). CTS diagnosis was based on established criteria and recommendations of the American Academy of Neurology according to standardized protocols described elsewhere (American Academy of Neurology, 1993; Padua et al., 1999). The diagnosis of ulnar nerve entrapment at elbow (UNE) was based on the presence of a reduced MNCV of the nerve in the below–above elbow tract. According to AANEM recommendations also a >10 m/s relative reduction in this tract compared to the below elbow–wrist tract was considered pathological (AAEM, 1999). A sensory axonal polyneuropathy diagnosis was performed when there was at least a bilateral reduction of sural nerve SAP (associated or not with upper limb sensory nerve SAP reduction).

2.3. Ultrasound investigations

US evaluation was performed with the patient in supine position for upper limbs nerves and in prone position for lower limbs

nerves. Median, ulnar, peroneal, tibial and sural nerves were studied. Each nerve was followed along its whole course from the origin to the most distal visible point or to its terminal division point. US evaluation was performed through both quantitative (cross sectional area) and qualitative measures (echogenicity and echotexture). For each nerve cross sectional area (CSA), echogenicity and echotexture was evaluated along the entire studied tract. Moreover CSA, echogenicity and echotexture were recorded at several standardized sites. We planned to make additional measurements only if the operator found nerve alterations outside the standard established recording site. We considered the nerve to be pathological only if CSA was abnormal. To avoid measurements errors due to incorrect inclination of the probe, isolated alteration of echogenicity and echotexture was considered as normal. Median nerve was measured at wrist, middle third of the forearm, elbow, middle third of the arm and axilla. Ulnar nerve was measured at wrist, middle third of the forearm, elbow (inside epitrochlear groove), middle third of the arm and axilla. Sural nerve was measured at ankle level. Peroneal nerve was measured at fibular head and popliteal fossa while tibial nerve at ankle and popliteal fossa. All nerves were assessed bilaterally. CSA was automatically calculated with ellipse method where the nerve was bigger according to the operator opinion.

A dynamic evaluation of ulnar nerve at elbow was also performed on both sides in order to evaluate the presence of nerve luxation or subluxation. This examination was performed with the patient seated with upper limb abducted to ninety degree. The dynamic assessment was performed scanning the ulnar nerve with the probe fixed at the epitrochlear groove as the patients flexed the forearm until he/she touched the shoulder with the hand. In order to leave the nerve free to move outside the groove during flexion, the operator used a generous amount of gel in order not to press the probe too firmly against the elbow. Dynamic US evaluation was also performed in fifteen healthy subjects as control group. According to the classification proposed by Okamoto et al., ulnar nerve was classified in three categories: normal, subluxation and luxation (Okamoto et al., 2000). We used CSA normal values obtained by our laboratory calculated as mean ± 2SD. Median nerve: wrist <12 mm^2, at forearm <9 mm^2, at arm <11 mm^2, and at axilla <12 mm^2. Ulnar nerve: wrist <9 mm^2, forearm <8 mm^2, elbow <10 mm^2, arm <8 mm^2, axilla <9 mm^2. Peroneal nerve: fibular head <13 mm^2, popliteal fossa <8 mm^2. Sural nerve <3.5 mm^2. Tibial nerve ankle <15 mm^2, popliteal fossa <25 mm^2.

2.4. Patient-oriented measures

Finally, each patient was asked to fill in the Italian version of the Boston Carpal Tunnel Questionnaire (BCTQ) in order to obtain information from the patient's point of view on sensitive hand symptoms and function (Levine et al., 1993; Padua et al., 1998). The BCTQ evaluates two domains of CTS, namely "symptoms" (SYMPT), assessed with an 11-item scale and "functional status" (FUNCT) assessed with an 8-item scale (each item has five possible responses). Each score (SYMPT and FUNCT) is calculated as the mean of the responses of the individual items. Although BCTQ was developed for CTS, it is not specific and sensory symptoms and function of the hand are well assessed and quantified.

Moreover we asked the patients if they experienced cramps, numbness, paresthesias and hypoesthesia in the limbs and, if present, we investigated the distribution of the symptoms.

2.5. Statistical analysis

Descriptive statistic describes the population and the occurrence of neurophysiological, clinical and US signs of entrapments and neuropathy. Non-parametric statistical analysis through 2×2 table chi square test (Statsoft Oklaoma, USA) was performed to compare the occurrence of ulnar nerve luxation and subluxation in EDS patients and control group.

3. Results

Fifteen EDS-HT patients were enrolled (1 male and 14 females; mean age of patients 35.4, range 15–58). Fifteen healthy subjects were enrolled as control group (3 male and 12 female; mean age 30,2, range 24–55).

3.1. Symptoms and patient-oriented measures

Twelve EDS-HT patients reported paresthesias and/or numbness of the whole hand. Eight patients reported paresthesias and/or numbness mainly in the fourth and fifth digits (the same patients sometimes complained of sensory symptoms at the whole palm and sometimes at fourth and fifth digits). Two EDS-HT patients had unilateral paresthesias at fourth and fifth digits on right side. Two EDS-HT patients reported bilateral numbness and/or paresthesias at feet soles. One EDS-HT patient complained of numbness and/or paresthesias only at right foot sole. Eleven EDS-HT patients reported frequent cramps at both lower limbs while 3 EDS-HT patients reported unilateral lower limb cramps (2 on right and 1 on left side) (Table 1).

Mean BCTQ SYMPT score was 2.8, mean FUNCT score was 2.5.

3.2. Clinical examination

No EDS-HT patients had sensory or motor deficits at clinical examination and all had normal tendon reflexes except for one patient on whom we were not able to elicit the ankle jerk reflex on the right side.

3.3. Neurophysiological findings

No one of the patients was affected with polyneuropathy. One EDS-HT patient was affected with "mild" CTS graded according to classification of Padua et al. (Padua et al., 1997). One patient was affected with a "mild" ulnar nerve entrapment at elbow according to AANEM recommendations (AAEM, 1999).

3.4. Ultrasound findings

All patients had normal nerve CSA and echotexture outside entrapment sites. One patient had an increased and hypoechoic ulnar nerve at elbow (CSA 11 mm^2). In all other EDS-HT patients US showed normal nerves.

Dynamic US evaluation of ulnar nerve at elbow in EDS patients showed six subluxations and two luxations on the right side, six subluxations and one luxation on the left side. Other ulnar nerves were normal at dynamic evaluation. In the control group dynamic evaluation of the ulnar nerve showed normal findings in all but one

Table 1
Summary of the occurrence of sensory symptoms and in EDS-HT patients.

Referred symptoms	Number of EDS-HT patients	
	Right	Left
Paresthesias and/or numbness mainly in the fourth and fifth digits	10	8
Paresthesias and/or numbness at whole hand	12	12
Numbness and/or paresthesias at soles of feet	3	2
Cramps at lower limbs	13	12

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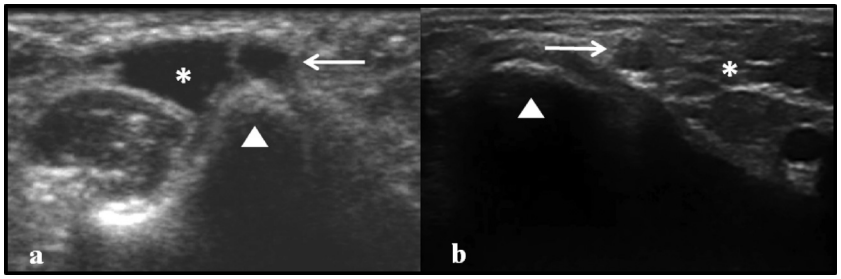

Fig. 1. (a) Ulnar nerve subluxation at elbow. (b) Ulnar nerve luxation at elbow. The narrows indicate the ulnar nerve at elbow. Asterisks indicate the triceps muscle. Triangles indicate the medial humeral epicondyle.

Table 2
Summary of the dynamic US findings and statistical significance.

Dynamic US evaluation of ulnar nerve at elbow	EDS-HT patients		Control group		Statistical analysis (p value)	
	Right	Left	Right	Left	Right	Left
Normal	7	8	14	15	NS	NS
Subluxation	6	6	0	0	$p = 0.01$	$p = 0.01$
Luxation	2	1	1	0	NS	NS
Luxation + subluxation	8	7	1	0	$p = 0.002$	$p = 0.005$

NS = not significant.

case (luxation on the right side). Fig. 1 shows an example of ulnar nerve luxation and subluxation at elbow.

Statistical analysis showed a significant difference in the occurrence of ulnar nerve subluxation and luxation (considered together) between EDS patients and symptoms free subjects both on right and left side (respectively $p = 0.002$ and $p = 0.005$). A statistic significant difference between EDS-HT patients and symptom free subjects was also evident in the occurrence of ulnar nerve subluxation on both side ($p = 0.01$ for both side). No statistic significant difference between EDS-HT patients and symptoms free subjects was present in the prevalence of luxation ($p > 0.5$) (Table 2).

The patient with abnormal ulnar nerve CSA (MM) had nerve luxation and normal NCV in the above–below elbow tract. The patient with reduction of ulnar nerve conduction velocity across the elbow (CC) had a normal CSA at elbow and a luxation. The patient with focal median nerve entrapment at wrist (GM) showed normal nerve ultrasound findings at the same level.

The main US and neurophysiologic findings are summarized in Table 3.

4. Discussion

In the year 2009 Voermans et al. published the first systematic study focused on neuromuscular involvement in well-defined EDS types patients demonstrating mild-to moderate neuromuscular involvement in a large proportion of patients (Voermans et al., 2009). They found some cases of axonal sensory-motor polyneuropathy, predominantly in the TNX-deficient type, whereas some patients of all EDS types had mixed myopathic-neurogenic or myopathic features on electromyography. In their work the authors did not systematically screen for entrapment neuropathies (March et al., 1988; Francis et al., 1987; Aktas et al., 2008). Our work is the first prospective study assessing the occurrence of entrapment neuropathy in EDS patients. We evaluated a homogeneous group of 15 EDS-HT patients. Our findings suggest that the prevalence of carpal tunnel syndrome in EDS-HT patients is not higher than that reported in general population (Atroshi et al., 1999). More difficult is assessing whether occurrence of UNE in EDS is higher than in general population: no prevalence data were previously reported while incidence in a region of Italy was reported in one article (24.7 cases per 100,000 person-years: Mondelli et al., 2005).

In their paper Voermans et al. performed muscular ultrasound in order to find echotexture alterations due to myopatic or neuropatic alterations. To our knowledge there are no studies in literature evaluating the sonographic appearance of nerves in EDS patients. In our study we evaluated through US the main nerves of upper and lower limbs both inside and outside entrapment sites. We demonstrated that all EDS-HT patients had normal nerve CSA and echotexture outside entrapment sites and we found only one patient with mild abnormality of ulnar nerve at elbow.

The only patient with abnormal ulnar nerve CSA at the elbow had nerve luxation and a normal NCV in the above–below elbow tract. The presence of ulnar nerve luxation in this patient might have caused an overestimation of ulnar nerve motor conduction velocity during neurophysiological evaluation (because of measurement error). The patient with a reduction of nerve conduction velocity across the elbow had a normal CSA at elbow and a luxation. Although normal, the CSA of ulnar nerve at elbow on the side with slowed motor conduction velocity was almost twice the CSA on the other side. This might be interpreted as pathological. The patient with reduced conduction velocity of the median nerve at wrist had normal ultrasound findings at the same level. This is sometimes seen in CTS and in a previous paper we demonstrated that, in CTS, US has a lower sensitivity than neurography, especially in mild cases (Padua et al., 2008).

US dynamic evaluation of ulnar nerve at elbow showed, although the small sample of patients, a significant difference in the prevalence of ulnar nerve subluxation and luxation at elbow between EDS-HT patients and control group. In our opinion these findings are highly consistent with the disease features and could be explained by the presence of Osborne ligament laxity. It is difficult to understand the effects of the possible Osborne ligament laxity: this could enhance the frequency of ulnar nerve luxation–subluxation, but it might decrease the incidence of ulnar nerve entrapment neuropathy at elbow as well, as the tunnels may not be as narrow in patients compared to controls. However it is possible that a luxation or subluxation over the long term may increase the ulnar nerve CSA due to the recurrent friction between the nerve and the bone. At the moment we are not able to hypothesize the complex relationships of the effects of altered connective

Table 3
Summary of the US and neurophysiological findings.

Patients	Side	1M SNCV (m/s)	1M SAP amplitude (μV)	3M SNCV (m/s)	3M SAP amplitude (μV)	5U SAP amplitude dito (μV)	Sural nerve SAP amplitude (μ/s)	Median nerve DML	Ulnar nerve MNCV above–below elbow tract	CSA ulnar nerve elbow (mm^2)	CSA median nerve wrist (mm^2)	Luxation/ subluxation
MV	Right	47	19	49	20	15	33	2.7	76	4	8	Subluxation
MV	Left	49	31	51	41	15	23	2.6	65	7	8	Subluxation
MP	Right	50	10	53	10	7	13	2.7	70	6	7	Subluxation
MP	Left	52	13	52	13	6	14	2.5	63	5	7	Subluxation
CG	Right	56	13	58	15	9	10	3.2	77	6	6	Subluxation
CG	Left	45	25	53	18	11	45	3.5	56	8	Bifid	Subluxation
VV	Right	48	25	54	20	9	24	2.9	63	5	5	Normal
VV	Left	50	26	57	22	10	22	2.5	74	4	5	Normal
GM	Right	37	10	45	10	6	20	3.5	71	6	10	Normal
GM	Left	41	16	42	17	5	17	3.4	54	6	9	Normal
CC	Right	49	18	48	14	19	17	3	55	4	5	Subluxation
CC	Left	45	15	49	15	7	16	3.2	39	7	7	Luxation
SA	Right	42	25	47	27	20	10	2.4	58	6	8	Normal
SA	Left	44	30	53	40	15	10	2.9	62	5	6	Normal
GA	Right	53	10	48	14	16	13	2.9	52	7	8	Normal
GA	Left	50	11	48	15	16	14	2.5	69	9	7	Normal
CS	Right	43	12	49	12	9	13	3.3	55	5	7	Normal
CS	Left	47	14	54	21	8	10	3	62	6	10	Normal
TMA	Right	43	13	52	24	11	6	2.9	70	6	9	Normal
TMA	Left	46	14	46	17	9	7	3.4	47	6	7	Normal
BC	Right	43	12	51	13	7	20	2.9	60	7	8	Subluxation
BC	Left	44	16	52	18	13	21	3.15	63	6	8	Subluxation
MM	Right	45	9	53	7	6	14	2.6	58	9	Bifid	Normal
MM	Left	50	8	53	7	5	14	2.8	45	11	Bifid	Luxation
CG	Right	47	35	50	26	11	50	2.65	73	8	7	Subluxation
CG	Left	46	30	46	28	25	51	2.55	59	8	6	Normal
SF	Right	44	17	52	30	15	25	2.5	67	9	8	Normal
SF	Left	54	25	54	27	17	30	2.7	62	7	7	Normal
PG	Right	45	21	50	22	9	13	2.9	65	8	10	Luxation
PG	Left	47	37	56	26	10	14	2.9	71	8	8	Subluxation

tissues (on the nerve tension due to possible altered nerve stroma, on the ligaments that should fix the nerves, on tendon etc.).

Note that no definite data in literature are available on symptoms in luxation/subluxation condition and, in our experience, luxation/subluxation can be occasional findings in non symptomatic patients. At the moment we suggest to perform US in all patients with ulnar sensory symptoms, regardless neurophysiological results, because we previously demonstrated that US is more sensitive than neurophysiology and it can provide dynamic evaluation of Ulnar nerve. In EDS patients US can be more useful to demonstrate the presence/absence of luxation/subluxation in order to monitor (neurophysiologically and ultrasonographycally) this condition that is likely to predispose ulnar neuropathy at elbow.

The joint laxity could not be a direct cause of the sensory symptoms but at least joint pain may be due to stretching of the joint capsule with involvement of the fine sensory capsular/joint terminations.

Finally we want to underline that the presence of ulnar nerve displacement at elbow (luxation/subluxation) may be important to avoid overestimation of ulnar nerve conduction velocity during neurophysiological evaluation (Won et al., 2011).

In our study we did not find any cases of polyneuropathy. Although our patients were not genetically screened to exclude a tenascin-deficent type, it is possible to affirm that our data are compatible, at least partially, with those found by Voermans et al. Indeed in their study no patients classified as EDS hypermobility type had an axonal sensory-motor polyneuropathy (Voermans et al., 2006).

The most interesting result of the study is the inconsistency between symptoms and neurophysiological and US evidences of focal or diffuse nerve involvement. In fact, although the majority of EDS-HT patients enrolled in our study reported paresthesias/numbness in hands and/or feet, only a minority had clearly neurophysiologically demonstrable nerve alterations.

This inconsistency could be due to the absence of nerve disease or to the presence of very mild and transient nerve involvement that cannot be demonstrated with standard neurophysiological test and ultrasound evaluation. Further studies are ongoing to assess the most distal nerve segments and the sensory fibers function that cannot be assessed through standard nerve conduction studies. However we cannot exclude that, at least partly, the symptoms reported by patients may be due to cervical and/or lumbosacral radiculopathy. The electromyographic study was not planned at the beginning of the study for several reasons: (1) needle EMG is not well tolerated by many patients (in some cases we should have examined many muscles) and the risk of having partial data was high; (2) the study protocol was already very long and time consuming (for patients and physicians); (3) the clinical picture of a typical EDS-HT patient is very often characterized by the presence of pure sensory symptoms, almost always normal tendon jerks, no clear motor deficits and, based on our clinical and neurophysiologic experience, it is very common to find normal needle EMG findings in patients with only sensory symptoms and normal tendons jerks, also if radiculopathy is strongly suspected. To our knowledge systematic studies focused on this topic are not currently available in literature.

Disclosure

Authors declare no conflicts of interest.

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