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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.

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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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 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