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Clinical Findings and Electrodiagnostic Testing in Ulnar Neuropathy at the Elbow and Differences According to Site and Type of Nerve Damage

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ABSTRACT

Objective To evaluate the clinical and electrodiagnostic testing (EDX) in ulnar neuropathy at the elbow (UNE) and differences according to site (humeroulnar arcade, HUA, vs. retroepicondylar groove, REG) and injury physiopathology (axonal vs. demyelinating), through prospective multicenter case-control study. **Design** Cases and controls were matched by age and sex. UNE diagnosis was made on symptoms. Statistical analysis was performed using Mann-Whitney, Chi-square and ANOVA tests. **Results** 144 cases and 144 controls were enrolled. Sensory loss in the fifth finger (U5) had the highest sensitivity (70.8%) compared to clinical findings. Motor conduction velocity across-elbow (MCV-AE) reached the highest sensitivity (84.7%) in localizing UNE recording from at least one of two hand muscles (first interosseous-FDI and abductor digit minimi-ADM). Abnormal sensory action potential amplitude from U5 occurred more frequently in axonal than in demyelinating forms. Differences between REG and HUA regarded conduction block (CB) and job type. **Conclusions** Clinical findings have less usefulness than EDX in UNE diagnosis. MCV-AE recorded from both ADM and FDI increases diagnostic accuracy. Axonal forms have greater clinical and EDX severity than demyelinating forms, that are more frequent in REG. Manual workers prevailed in HUA. These findings may be helpful in prognostic and therapeutic approaches.

Keywords: electrodiagnosis, peripheral neuropathy, ulnar neuropathy, ulnar nerve entrapment, ulnar nerve physiopathology.

What is known: Electrodiagnostic testing (EDX) compared to clinical findings, remains the most sensitive tool for the diagnosis of Ulnar Neuropathy at the Elbow (UNE).

What is new: Delayed Motor Conduction Velocity (MCV)-across-elbow achieves higher sensitivity in localizing UNE than MCV drop and increases the diagnostic accuracy when recorded from both abductor digiti minimi (ADM) and first dorsal interosseous (FDI).

Identifying both the site and physiopathology of injury, can be useful for prognosis and treatment of UNE.

Introduction

Ulnar neuropathy at the elbow (UNE) is the second most common focal neuropathy following carpal tunnel carpal syndrome (CTS).[1]

Patients with symptoms suggesting UNE (numbness, tingling, other sensory symptoms in the fourth and fifth digits, weakness and wasting of the hand muscles) are referred for electrodiagnostic testing (EDX) to confirm the diagnosis. In the last decades, ultrasonography (US) of the ulnar nerve and surrounding structures has joined EDX for correct UNE diagnosis.[2,3] The most frequently involved sites are at the retroepicondylar groove (REG) (80-85% of UNE), and beneath humeroulnar arcade (HUA) (15-20%).[4] Since these two UNE localizations are clinically indistinguishable, motor neurography with inching test and US may identify the site of injury.[5-8] A correct identification of the location and type of damage (axonal or demyelinating) appears useful to formulate the prognosis and address the best therapy.[9]

Many studies on EDX in UNE were published in literature until now, but few studies reported the clinical findings and EDX in a large sample of UNE.[2,3,9-11] The two major limitations of previous studies were: small sample size and lack of a control group.

We aimed to report through a prospective multicenter case-control study: (1) clinical and EDX findings in a consecutive series of patients affected by idiopathic UNE compared to a control group, (2) relations of EDX and clinical findings in UNE cases, (3) differences of EDX and clinical outcomes between the two UNE locations (REG vs. HUA) and two physiopathological mechanisms of nerve damage (axonal vs. demyelinating).

2. Materials and methods

Enrollment criteria of cases and controls

Cases and controls were consecutively and prospectively enrolled among the subjects admitted from May 2014 to September 2016 to three primary public outpatient electromyography (EMG) labs.

All cases and controls were sent to our EMG labs by the referring doctors (general practitioners or medical specialists) with a request of EDX because they referred upper limb complaints.

Cases were subjects with UNE diagnosis based on clinical history and sensory symptoms (numbness, tingling, burning or pain) along the sensory distribution of the ulnar nerve at the hand and might include involvement of the forearm or arm and pain at the elbow. Motor symptoms might be absent or ranged from mild clumsiness to severe weakness of the hand.

Controls were matched by age and sex with a case/control ratio of 1:1. The control subjects were those who complained about upper limb symptoms other than UNE.

We excluded from both cases and controls subjects with age <14 and >70 years, with C8-T1 radiculopathy, brachial plexopathy, polyneuropathies, CTS and other upper limb mononeuropathies, fracture of arm, trauma and arthritis of elbow, motor neuron and central nervous system diseases, diabetes, thyroid and connective disorders, renal failure, cancer in the previous five years and subjects undergone previous ulnar nerve and CTS surgery.

Age, sex, education level, and detailed information on employment were also collected. Education level was ranked in five classes: (1) no formal education, (2) 5 years of primary education, (3) lower secondary education, (4) upper secondary education, and (5) university degree. According to the International Standard Classification of Occupations (ISCO-08),[12] subjects were grouped into two main occupational categories (i.e. manual and non-manual workers) by a physician blinded to case/control status.

Manual workers were those subjects with occupational activities included in groups 5-9 of ISCO, whereas the other subjects were classified as non-manual workers. The retired and unemployed subjects were included among manual workers in the case they experienced heavy manual work when the symptoms started at the time of their employment; otherwise, they were included among non-manual workers.

Clinical examination

Cases and controls filled in a hand diagram to indicate the site of hand sensory symptoms[13] and completed a self-administered questionnaire evaluating the severity of the symptoms complained in the last week (UNEQ).[14]

Physical examination included manual evaluation of the segmental muscle strength with the Medical Research Council (MRC) rating scale, muscle stretch reflex and sensitivity. Touch sensation was evaluated with cotton wool and Semmes-Weinstein monofilaments comparing the affected with the contralateral asymptomatic sides and between the ulnar nerve and median/radial nerve territories. It was enough to find one of these two anomalies in the

comparative sensation tests to include a patient among those with sensory loss.[15]

We graduated the clinical severity of UNE using a 1-4 ordinal scale according to presence/absence of touch sensory loss, motor deficit and muscular atrophy[14] (for details see Table 1).

Electrodiagnostic examination

To confirm UNE diagnosis EDX protocol was performed according to the American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM)[16] including: motor and sensory neurography of the ulnar and median nerves; standard needle EMG of the first dorsal interosseous (FDI), abductor digiti minimi (ADM), flexor carpi ulnaris (FCU), abductor pollicis brevis (APB), biceps brachii muscles, and at least one extensor muscles.

Motor conduction velocity (MCV) of the ulnar nerve, recorded with surface electrodes from ADM and FDI muscles, was calculated in the following segments: (1) from below elbow to wrist, (2) from above elbow to below elbow (MCV across-elbow), (3) from axilla to above elbow. Distal motor latency (DML) was measured with a distance of 7 and 14 cm between the stimulation point of the nerve at the wrist and ADM and FDI muscles. We also calculated the amplitude of compound muscle action potential (CMAP) from baseline to negative peak at each site of stimulation, the difference between MCV across-elbow vs. below elbow-wrist segments (MCV drop) and percent decrease in CMAP amplitude from below elbow to above elbow (conduction block) (CB). During MCV assessment, the elbow was moderately flexed (80°-90°), and the length of segment across-elbow was 10 cm. We have carefully searched the presence of

Martin-Gruber anastomosis, and its existence was not an exclusion criterion of case and control enrollment.

To localize the site of UNE under HUA or at REG, we performed 2 cm short-segment MCV study with six positions of the ulnar nerve stimulation from 4 cm distal to 6 cm proximal to medial epicondyle every 2 cm (inching test). We took into account the differences in latency and percent decreases of CMAP amplitude between two next sites of stimulation.[5,6]

We orthodromically measured sensory conduction velocity (SCV) of the ulnar nerve in the fourth digit-wrist (U4) and in the fifth digit-wrist (U5) segments through surface recording and stimulating ring electrodes. We also antidromically assessed SCV of the dorsal ulnar cutaneous nerve (DUCN) from the ulnar styloid to the hand dorsum in the metacarpal interspace between the fourth and fifth rays. Sensory nerve action potential (SNAP) amplitude was calculated peak-to-peak. Because the ulnar hand dorsum may be innervated partially or entirely by the superficial radial nerve (SRN), we also stimulated SRN 3 cm above radial styloid recording at the same site of ulnar hand dorsum.[17] If we found this variant of innervation, cases and controls were excluded from the study, because this variant may overestimate DUCN neurographic abnormalities.[18]

Sensory and motor neurography of the median nerve was also carried out and neurography from ADM and of U5 in the contralateral side of UNE cases.

We considered abnormal the values of DML, MCV (including drop) and SCV if differed at least 2 SD from the mean of normative data of our labs, and abnormal CMAP (including CB) and

SNAP amplitudes if lower than the fifth percentile of the mean of log-transformed normative data. In our EMG labs we have two different abnormal cut-offs of all neurographic findings according to two age groups obtained from 65 healthy subjects.

We localized UNE under HUA or at REG if at least one 2 cm short-segment motor interlatency was >0.55 ms or CMAP amplitude drop >15% in the corresponding tracts, according to our normative cut-off obtained from 59 healthy subjects.

"Localizing" motor neurographic findings of UNE were one of the following abnormal values: MCV across-elbow, MCV drop, CB.

Standard needle EMG included observation of abnormal spontaneous activity at rest (positive sharp waves, fibrillations and high-frequency repetitive discharges), qualitative evaluation of motor unit action potentials (MUAPs) and recruitment at maximum effort. We considered as EMG abnormalities denervation activity at rest in at least two separate areas of the tested muscle and/or neurogenic recruitment at full effort (reduced MUAPs with increased firing frequency).

We distinguished UNE in primarily axonal damage forms for the presence of MCV slowing across-elbow, neurogenic EMG pattern including denervation activity at rest and/or reduction of CMAP amplitude at the wrist, no CB and in primarily demyelinating forms in the presence of CB and/or MCV slowing across-elbow without abnormalities of CMAP amplitude at the wrist and no denervation activity at rest. The reduction in amplitude or the absence of U5 SNAP were not used to differentiate the two forms.

EDX of the "controls" was performed, as for all patients admitted to our EMG labs, according to the request of the referring physician, complained symptoms and neurological examination. In addition, in all controls we mandatorily carried out electrophysiological examination of the median and ulnar nerves. They included MCV of ulnar nerve across-elbow and below elbow-wrist segments, DML, CMAP amplitudes, MCV drop, CB at least recording from ADM muscle, U5 SCV and SNAP, motor and sensory neurography of the median nerve and FDI EMG.

Skin temperature of the arm was maintained, if necessary, above 32°C with an infrared lamp.

The four neurophysiologists of the three recruitment centers were experienced, received the same neurophysiological training, established the same diagnostic criteria of UNE, and standardized clinical and electrophysiological protocol before the enrollment. The same neurophysiologist, at least one for each center, who performed EDX was blinded to hand diagram and UNEQ, but not to physical examination.

The local Ethics Committee approved the study, and all cases and controls signed informed consent.

Statistical analysis

Descriptive statistics were presented as mean and SD or number and percentage, as appropriate. The number of UNE cases with abnormal clinical and electrophysiological findings were reported along with proportions among controls. The proportion of cases with abnormal tests (i.e. sensitivity) were calculated.

The Kolmogorov-Smirnov test with Lilliefors correction was used to test the normal distribution of values. For non-normal distributions, 2-sample tests were performed using the Mann-Whitney nonparametric U test. Categorical variables were assessed using Pearson's chi-squared test.

We used ANOVA with Tukey's post hoc test to perform multiple comparisons of neurographic continuous variables and UNEQ score according to clinical severity. We calculated the correlations between UNEQ score and age of patients, duration of symptoms, and main neurographic parameters of the ulnar nerve by Spearman coefficient.

The statistical analysis was carried out at the "patient-level" and not at the "elbow/hand level", because including a patient with bilateral UNE as two cases may introduce a source of bias where statistical significance of the results could be overestimated if the correlation between the two sides is not appropriately taken into account.[19] Therefore, subjects with bilateral symptoms were included only once and the results of the worst side were reported or, if there was no difference between sides, the dominant side was chosen.

All analyses were performed using SPSS.23 software package. An alpha error of 0.05 was accepted.

Results

In the enrollment period, 144 cases and 333 controls were selected. After matching, 144 controls were identified with the same age and sex distribution of the cases. The mean age of the study group was 49.6±12.2 years. Males were more represented than females (61.8%, 89/144). All

participants were Caucasian. There were no differences in educational level and occupational activities between cases and controls.

Clinical Findings

All cases were included in "definite" or "possible" categories according to hand diagram.[13] The fifth and fourth fingers, palm and dorsum of the hand were marked in hand diagram by 98.6%, 85.4%, 56.3%, 58.3% of cases and by a low number of controls (14.6%, 16%, 6.2%, 7.6%), respectively. Cases with bilateral UNE symptoms were 19 (13.2%). With respect to handedness, the left side was more affected than the right side among cases (55.6%, 80/144); among controls, the most frequently examined side was the right one (68.1%, 98/144). Cases had a higher score of UNEQ than controls (2.2 ±0.7 vs. 1.3±0.4, Z=11.5, P=0.001). Mean values of UNEQ among cases significantly increased with clinical severity of UNE: stage 1=2.03±0.6; stage 2=2.1±0.6; stage 3=2.38±0.7; stage 4=2.61±0.5 (F=4.15, P=0.007). Post hoc test showed that relevant differences were between stage 4 and the first two stages. When the results of the single nine questions of UNEQ were examined, increased score and significant differences between the clinical severity stages concerned the items no. 1-4 (these regarded the severity and the changes of numbness and tingling in the fourth and fifth fingers with elbow positions) and, especially, the item no. 9 (i.e. "Do you have difficulty leafing through a newspaper, turning a key or using small objects?") (F=21.4, P<0.0001).

There were correlations between UNEQ score and duration of the symptoms, MCV across-elbow, CMAP amplitude recording from ADM and FDI muscles, SNAP amplitudes of U5 and DUC (r_s values between 0.17 and 0.29, P values between 0.046 and <0.0001). There were no

correlations between UNEQ score and age of patients, education level, MCV drop, CB, DML (recording from both muscles).

Table 1 shows the distribution of cases according to the four-stage severity scale. Table 2 reports the distribution of cases and controls with respect to anomalies of objective clinical findings. Sensory loss of the fifth finger had the highest sensitivity (70.8%) and reduced strength of FCU (MRC <5) the lowest (10.4%).

Neurographic findings

Table 3 shows the normative values of neurographic EDX according to the age group and the neurographic EDX findings among cases and controls.

MVC across-elbow and MCV drop had high sensitivity regardless of the recording muscle (usually about 80%). CB and reduced wrist CMAP amplitude had very low sensitivity. U5 SNAP amplitude was abnormal in 70.8% of cases. Reduced U5 SNAP amplitude could be present also in cases with CB in absence of EMG denervation activity at rest or EMG neurogenic pattern. The anomalies of U4 and DUCN SNAPs and especially of SCVs were much less frequent in cases.

There were significant differences in all neurographic parameters of the ulnar nerve between cases and controls (see Supplemental Digital Content 1, http://links.lww.com/PHM/A857).

Some cases had neurographic abnormalities recorded only from one of the two hand muscles. Combining the abnormalities of the two muscles together (FDI+ADM), the sensitivity of motor

neurography increased even slightly (Table 4).

If we considered altogether the six "localizing" neurographic parameters recording from both hand muscles, at least one abnormal neurographic parameters were observed in 130/144 (90.3%) cases.

We found 24 unilateral UNE (16.7%) with delay of MCV across-elbow in the contralateral side without symptoms and signs of UNE. Almost all these 24 cases also had abnormal MCV drop and none CB.

There were significant relations between the clinical severity scale and the values of almost all EDX of the ulnar nerve (F values between 6.9 and 33.8, $P<0.0001$). Most of the EDX values tended to worsen with increasing clinical severity stage. The highest differences were observed when the cases ranged from severity stage 1 to 2 and from 2 to 3 (see Supplemental Digital Content 2, http://links.lww.com/PHM/A858).

EMG findings

EMG abnormalities were more frequent for FDI than ADM, but this difference was not significant (49 vs. 42 cases). EMG abnormalities of FCU were always accompanied by ADM and FDI abnormalities. Abnormalities of ADM always matched with those of FDI except for two cases. Therefore, the overall sensitivity in at least one muscle was 35.4% (51/144) (Table 4). When we compared cases showing EMG abnormalities with those having reduced manual strength (MRC<5), the former was more frequent than the latter (35.4% vs. 28.4%).

There were no cases with abnormal EMG and/or SNAP and normal "localizing" neurographic parameters.

Differences of clinical and EDX findings according to the site of UNE

We did not perform inching test in 29 cases (20.1%), and we were unable to localize the site in 12 (8.3%). In the remained 103 cases, we localized the site of UNE at REG in 71 cases (68.9%), under HUA in 32 (31.1%). The left side was more frequently involved in REG than in HUA cases (40.6% vs. 62%, chi-square=4.1, P=0.04). There were more heavy manual workers in HUA than in REG cases (65.6% vs. 42.3%, chi-square=4.8, P=0.028). There were no other differences in terms of demographic, clinical and EDX findings except for CB. There were more cases with CB in REG than in HUA recording from ADM (3.1% vs. 26.8%, chi-square=6.4, P=0.011), but the difference of CB recording from FDI was relevant but not significant (15.6% vs. 31%, chi-square=2.7, P=0.1).

Differences of clinical and EDX findings between primarily axonal vs. primarily demyelinating forms

Cases with all normal EDX were 14 (9.7%). Among the other 130 cases, primarily demyelinating forms were 72 (55.4%) and primarily axonal 58 (44.6%). The cases with primarily axonal form were older than those with primarily demyelinating form (53.2±12.1 vs. 47.7±11.5 years, Z=-2.8, P=0.006). There were no other differences with respect to demographic findings, side and localization of UNE. Axonal forms were clinically more severe than demyelinating according to symptom severity (UNEQ score 2.41±0.6 vs. 2±0.6, Z=-4, P<0.001), clinical

severity scale (chi-square=61.8, P<0.001) and number of cases with abnormal single items of clinical findings (touch sensory loss, reduced muscular strength and atrophy; chi-square between 64.4 and 14.9, P<0.0001). The values of all motor neurographic parameters (excluding MCV drop), and U4, U5 and DUCN SNAPs were lower in axonal forms (Z values between -6.5 and -2.7, P between 0.004 and <0.001). Cases with abnormal sensory neurographic findings were more frequent for axonal than demyelinating forms (all values of chi-square>16, and P<0.001).

Discussion

This study estimated clinical and EDX findings in idiopathic UNE. Suspected UNE diagnosis was based on symptoms, excluding, through appropriate tests, other alternative diagnoses.

Male prevalence was confirmed.[1,20,21] The left side was more frequently affected regardless of dominance.[10,21,22] The real cause is unknown. Some authors hypothesized more frequent misplacement of the non-dominant limb during some work activities and inappropriate prolonged elbow positions, especially in UNE at REG.[9]

Sensory symptoms without subjective or objective weakness were complained by 72.2% of the cases; other studies reported lower percentages, about 35%.[23] Almost all cases complained of sensory symptoms in the fifth finger (98.6%) and 70.8% showed touch sensory loss in the fifth finger. Only about half cases complained about sensory symptoms and sensory loss in the ulnar palm and dorsum of the hand. Motor clinical signs (atrophy and weakness) had low utility in UNE diagnosis. Cases with purely clinical motor UNE have been reported[23,24], but according to other evidences[2], patients with isolated motor deficit were not identified.

EDX protocol of this study was developed in agreement with AANEM.[16] Although new proposals of EDX protocol were recently published[25,26], there is not a real international consensus yet.

Cut-off values separated in two age groups were used; it is well known that the values of SCV, MCV, SNAP and CMAP amplitudes decrease with age. During motor neurography across-elbow, to minimize the technical errors, we took care of Landau's suggestions. They included the elbow position, length of the across-elbow, supramaximal nerve stimulation especially at below elbow, temperature control of the skin across-elbow, small progressive movements of the stimulator along the nerve course to seek sudden drop of CMAP amplitude or configuration change, accurate measure around the flexed elbow especially in subjects with high BMI to avoid false negative results.[27,28,29]

Short segment incremental stimulation is useful to identify the location of ulnar nerve injury. Regarding this neurographic technique, we prefer to perform the stimulation over the 2-cm interval of consecutive segments and not at 1-cm as previously suggested.[1,3,5,8,30-37] The measurement of motor latency and amplitude of CMAP across the flexed elbow is more difficult than along a straight line (as occurs in the median nerve for CTS). The intensity of electric current sufficient to obtain supramaximal focal stimulation at 1-cm of interval along the ulnar nerve may cause spread especially during the stimulation below medial epicondyle where the nerve is beneath the humeroulnar arcade more than stimulation at 2-cm interval segment. Besides, 2-cm interval offers some other technical advantages.[37] The literature data on the cut-off values of motor inching test and how they were obtained varied from authors to authors. In our

EMG lab the cut-off value of 2-cm interval segment latency is 0.55 ms and it is very similar to that used in other labs.[5,6,8,31] However, as for any neurographic parameters, any EMG lab should have its own normative values.

According to inching test, in the study of differences between the two sites of injury, we included 103 out of 144 enrolled cases (71.5%) because the test was not performed in 29 cases and the results were inconclusive in the other 12. In 10 of these 12 we were unable to demonstrate a significant change in latency of CMAP or block in one or two consecutive 2-cm interval segments. This occurred because technical problems or because there were no significant changes in any segments. We also excluded the remaining two cases because they demonstrated a delay in four consecutive segments two below and two above point 0 (i.e. the line drawn from the tip of medial epicondyle to the olecranon) without significant block. In these two cases we were unable to localize the electrophysiological changes under HUA or at REG. It is possible that these cases had double sites of damage as in case series reported by Campbell et al.[32]

Delayed MCV across-elbow reached the highest sensitivity between localizing EDX and was more sensitive in detecting conduction abnormality than MCV drop. CB, often coupled with different configuration and temporal dispersion of CMAP across-elbow, had the lowest sensitivity but, if present, reinforced UNE diagnosis. In almost all cases, slowed MCV across-elbow from ADM was accompanied by a similar delay from FDI. Shakir et al., by using ROC curves, already found that MCV across-elbow recording from ADM and FDI was more sensitive than MCV drop especially if CMAP amplitude was much reduced. The authors hypothesized that if the injury of the nerve at elbow causes axonal loss of the faster fibers, also MCV in below-

elbow segment decreases. This results in the normalization of MCV difference between the two segments.[38] Other studies showed the highest sensitivity in detecting motor slowing across-elbow recording from FDI than ADM[39], and others found similar sensitivity[2,38]. Using the "intra nerve-ratio", higher FDI susceptibility to damage than ADM was reported, explained by somatotopic organization of ulnar nerve fibers.[40] EMG abnormalities of FDI and ADM always matched with delayed MCV across-elbow and had low sensitivity, but higher than that of motor clinical signs. Contrarily to AANEM remarks[16], we recommend performing EMG and neurography recording from both ADM and FDI, in order to increase the diagnostic sensitivity.

In our study, we did not find cases with EMG and sensory neurography abnormalities without abnormal localizing EDX. Usually in EDX protocol of UNE, the neurography of sensory branches of ulnar nerve is carried out distally to the site of injury, and for this reason U4, U5 and DUCN SNAP may be normal, reduced in amplitude or absent according to the severity of nerve damage and SCV almost always normal or slightly delayed. Sensory neurography and EMG abnormalities when present alone have low sensitivity in detecting UNE than the localizing EDX (abnormal MCV across elbow, MCV drop and CB). Nevertheless, when present and in association with one or more localizing EDX, can strength UNE diagnosis.

Otherwise, DUCN neurography and FCU EMG are poorly helpful in UNE diagnosis because they are frequently normal and sensory symptoms and signs in ulnar hand dorsum and palm are often absent. FCU and DUCN are less frequently damaged because of the different anatomical arrangement of nerve bundles at the elbow.[41] Conversely, fascicles from terminal digital sensory branches and to small hand muscles, running deeply at the elbow, are more prone to damage.

Moreover, ulnar hand dorsum can be partially or fully supplied by the sensory radial nerve (SRN), and anastomoses between SRN dorsal branches and DUCN were described.[42]

We observed high relation between symptoms, clinical severity and all neurographic parameters, especially in more advanced stages. Consequently, EDX well reflected the clinical worsening in UNE.

Bilateral UNE is not frequent (13.2%). However, 16.7% of unilateral cases showed an asymptomatic delay of MCV across-elbow in the contralateral side, suggesting similar risk factors in both arms.

Comparing the two sites of injury, there were more heavy manual workers in HUA than in REG UNE and prevalence of left side in REG that seems to be due to a different type of occupational activity and to a prolonged flexed position of the non-dominant arm in REG form.[4] There were no other differences, except for the CB, mostly observed in REG, reinforcing the hypothesis that demyelinating change might be more frequent in this form.[4]

When the two injury types were compared, cases with primarily axonal forms were older; contrarily to the previous report,[43] any other differences in demographic and handedness were not found. Abnormal muscle bulk and severe weakness of ulnar hand muscles were more frequent in axonal forms. This result was obvious because there were relations between motor clinical findings and CMAP and EMG abnormalities and these EDX were used to separate the two forms according to physiopathology.

This study has some limitations. The major flaw is the lack of US that could help to identify ulnar damage in cases with non-localizing or normal EDX. However, about less than 10% of the cases of this study had normal EDX. EDX offers an advantage over US because EDX is less operator-dependent than US.

Another problem is the classification according to physiopathology of UNE. Our classification is similar but not the same as those already reported[3,42,44,45] The classification made by these authors substantially follows the physiopathology of polyneuropathies.[46] We considered axonal form of UNE in presence of denervation activity at rest and/or CMAP amplitude reduction, in absence of CB, but these cases had MCV delay across-elbow and might be affected by mixed damage (i.e. combination of primarily axonal and demyelinating) or primarily demyelinating form with secondary axonal loss. In addition, with respect to previous studies, we decided to exclude the absence or reduced SNAP (measured in the fifth digit-wrist tract) from the criteria of axonal damage. A reduction of the amplitudes of SNAP may occur from the dispersion of the afferent volley, CB or axonal loss; the last two mechanisms could be present in UNE patients.[47] Severe axonal injury can cause absent SNAP due to Wallerian degeneration. Occasionally also demyelinating damage may cause absence of SNAP due to dispersion and phase cancellation.

In addition, study timing may play an important role to assign patients to one or another group. Our case-control study analyzed findings collected at a specific point in time. Demyelinating form may transform into primarily axonal across time. However, in our series, primarily axonal forms were more severe than demyelinating, taking into account clinical and EDX findings, and the duration of symptoms was not different between the two forms.

In our study the specificity and likelihood ratios of EDX and clinical findings cannot be fully calculated, because of the selection criteria of the control group. We used the same exclusion criteria in the enrollment of cases and controls and consequently we excluded from the control group subjects with competing diagnosis with UNE. If we had calculated the specificity and likelihood ratios using this type of controls (i.e. without the subjects who had disorders that could mimic UNE), we erroneously increased the specificity, especially for the clinical findings, and incorrectly calculated the values of likelihood ratios.

Another limit was that the neurophysiologist who performed EDX was blinded to hand diagram and UNEQ, but not to physical examination.

Finally, we grouped the cases in two main categories (heavy manual and non-manual workers) according to occupational classification as provided by ISCO-08[12], and we did not explore the occupational biomechanical overload of the different job titles, including repetitive and forceful tasks, prolonged non-neutral elbow posture, and hand-arm vibration exposure that may be considered as risk factors.[48]

Furthermore, it should be taken into account that in this field, the integration between clinical and instrumental data is always fundamental for diagnostic accuracy.[49]

Conclusion

Clinical findings are not very sensitive for the diagnosis of UNE; only touch sensory loss of the fifth finger has relatively high sensitivity. EDX remains the primary diagnostic tool to identify

the site, severity and physiopathology of the neuropathy.

EDX, identifying the site of injury, may be useful for prognosis and therapeutic approach[9] (surgical decompression in HUA or conservative treatment including physical medicine and rehabilitation techniques in RTC). This observation requires further controlled trials.

Abnormal FCU EMG and DUCN neurography and the presence of symptoms and sensory loss in ulnar palm and dorsum are poorly helpful in confirm UNE diagnosis.

EMG and motor neurography recording from the two hand ulnar intrinsic muscles increase the internal consistency of EDX abnormalities. The detection of more than one localizing abnormality increases the EDX sensitivity in UNE and reduces the diagnostic error (inclusions of false positive cases).

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Table 1

Distribution of 144 cases of suspected UNE according to the clinical severity scale[14]

Stage	Description	Cases (N=144) n (%)
1	Only sensory symptoms, also intermittent, in ulnar nerve territory, with normal touch sensation and normal muscular strength and bulk	40 (27.8)
2	Sensory symptoms in ulnar nerve territory and sensory loss by comparison of the fifth and third digits with monofilaments or cotton, and normal muscular strength and bulk	64 (44.4)
3	Sensory loss and MRC 3-4 in ulnar hand intrinsic muscles with or without atrophy	25 (17.4)
4	Sensory loss and MRC 1-2 and atrophy of ulnar intrinsic hand muscles	15 (10.4)

MRC: Medical Research Council rating scale

Table 2

Distribution of anomalies of clinical findings among cases and controls

Clinical variables	**Proportion of UNE cases with anomalies n/N (%)**	**Proportion of controls with anomalies n/N (%)**
Sensory loss of the fifth digit	102/144 (70.8)	0/144 (0)
FDI MRC <5	42/144 (29.2)	0/144 (0)
ADM MRC <5	40/144 (27.8)	0/144 (0)
FCU MRC <5	15/144 (10.4)	0/144 (0)
FDI hypotrophy/atrophy	29/144 (20.1)	1/144 (0.7)
Hypothenar hypotrophy/atrophy	21/144 (14.6)	1/144 (0.7)

Strength of FCU muscle was evaluated with the flexion and adduction of the wrist against a resistance (the examiner's hand).

Table 3

Normative values of neurographic EDX according to age group and EDX neurographic findings among cases and controls

Variables	Normative data, subjects <60 years (lower/upper limits)	Normative data, subjects ≥60 years (lower/upper limits)	Proportion of UNE cases with anomalies n/N (%)	Proportion of controls with anomalies n/N (%)
1. Motor neurography				
a. ADM recording				
MCV across- elbow (m/s)	49.5	47.1	118/144 (81.9)	23/144 (16.0)
MCV drop (m/s)	9.2	12.5	103/144 (71.5)	21/144 (14.6)
Conduction block (%)	-15.2	-23.2	21/144 (14.6)	1/144 (0.7)
CMAP wrist (mV)	6.4	4.5	16/144 (11.1)	3/144 (2.1)
b. FDI recording				
MCV across- elbow (m/s)	49.2	46.8	115/144 (79.9)	n.a.
MCV drop (m/s)	9.6	13	90/144 (62.5)	n.a.
Conduction block (%)	-14.9	-23.8	28/144 (19.4)	n.a.
CMAPa wrist (mV)	7.9	5.6	31/144 (21.5)	n.a.
Sensory neurography				
U4 SCV (m/s)	43.2	40.7	21/144 (14.6)	1/144 (0.7)
U4 SNAP (µV)	3.8	2.0	80/144 (55.6)	19/144 (13.2)
U5 SCV (m/s)	45.1	42.6	30/144 (20.8)	1/144 (0.7)
U5 SNAP (µV)	8.2	4.0	102/144 (70.8)	38/144 (26.4)
DUCN SCV (m/s)	47.9	45.2	42/144 (29.2)	5/144 (3.5)
DUCN SNAP (µV)	11.9	6.1	74/144 (51.4)	11/144 (7.6)

ADM: abductor digiti minimi muscle; FDI: first dorsal interosseous muscle; MCV: motor conduction velocity; MCV drop: difference between MCV across-elbow vs. below elbow-wrist segments; CMAPa wrist: compound muscle action potential amplitude stimulating at wrist; Conduction block: percent decrease of CMAP amplitude from below elbow to above elbow; SCV: sensory conduction velocity; SNAPa: sensory nerve action potential amplitude; U4: from fourth digit to wrist segment; U5: from fifth digit to wrist segment; DUCN: dorsal ulnar cutaneous nerve. n.a.: not available by protocol design (see methods section).

Table 4

Abnormalities of motor neurography (upper) and electromyography (lower) findings among 144 UNE cases.

1. Motor Neurography					
Variables	**Both normal from ADM and FDI n (%)**	**Abnormal only from ADM n (%)**	**Abnormal only from FDI n (%)**	**Both abnormal from ADM and FDI n (%)**	**Abnormal at least from one muscle =overall sensitivity n (%)**
MCV across-elbow (m/s)	22 (15.3)	7 (4.9)	4 (2.8)	111 (77.1)	122 (84.7)
MCV drop (m/s)	30 (20.8)	24 (16.7)	11 (7.6)	79 (54.9)	114 (79.2)
Conduction block (%)	111 (77.1)	5 (3.5)	16 (11.1)	12 (8.3)	33 (22.9)
CMAPa wrist (mV)	112 (77.8)	1 (0.7)	16 (11.1)	15 (10.4)	32 (22.2)

2. Electromyography			
Recording muscle	**Spontaneous activity at rest n (%)**	**Neurogenic recruitment at full effort n (%)**	**At least one abnormal parameters n (%)**
FDI	36 (25)	46 (31.9)	49 (34.0)
ADM	30 (20.8)	41 (28.5)	42 (29.2)
FCU	9 (6.3)	18 (12.5)	19 (13.2)

ADM: abductor digiti minimi muscle; FDI: first dorsal interosseous muscle; FCU: flexor carpi ulnaris muscle; MCV: motor conduction velocity; MCV drop: difference between MCV across-elbow vs. below elbow-wrist segments; CMAPa wrist: compound muscle action potential amplitude stimulating at wrist; Conduction block: percentage decrease of CMAP amplitude from below elbow to above elbow.