



Ulnar neuropathy at the elbow: Reappraisal of the wrist-upper arm latency difference between ulnar and median nerves



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HIGHLIGHTS

- Ulnar neuropathy at the elbow can be diagnosed by comparing ulnar to median nerve motor latency.
- Ulnar-median latency difference >0.69 ms indicates ulnar neuropathy.
- Sensitivity and specificity of this approach is similar to standard nerve conduction studies.

ABSTRACT

Objectives: To evaluate the sensitivity and specificity of the latency difference (DLat) between ulnar and median nerves of the arm after stimulation at the wrist; one of the easiest techniques proposed for recognizing ulnar neuropathy at the elbow (UNE). As latency difference is not a standardized technique, we set up a multicenter study to recruit large numbers of normal subjects and patients with UNE or generalized neuropathy.

Methods: Six centers participated in the study with data obtained from three groups of participants, controls (CTRLs), patients with UNE and patients with generalized neuropathy (GNP).

We first verified the anatomical superposition of the ulnar and median nerves in cadaver examination. The optimal recording site for these two nerves was found to be 10 cm above the medial epicondyle. We then standardized the position of the arm with full extension of the elbow and stimulated first the median and then the ulnar nerves at the wrist. CTRLs were examined on both arms at two consecutive visits.

Results: We recorded 32 idiopathic UNE cases, 44 GNP patients and 62 controls.

We demonstrated that a DLat cut-off value of 0.69 ms brings a sensitivity of 0.86 and specificity of 0.89 to discriminate CTRLs from UNE. We also validated that intra-examiner reproducibility was good.

Conclusion: We report a lower normal value for DLat than reported in several non-standardized studies and CTRL and UNE groups have clearly separated DLat values.

Significance: Due to its high sensitivity, our standardized technique could be used as a first-line diagnostic tool when UNE is suspected.

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Abbreviations: Amp peak, peak amplitude; CNAP, compound nerve action potential; CTRL, healthy control; DLat, difference in latency; GNP, generalized neuropathy; Lat peak, peak latency; NCS, Nerve conduction studies; UNE, ulnar neuropathy at the elbow.

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1. Introduction

Nerve conduction studies (NCS) used for detecting ulnar neuropathy at the elbow (UNE) can be difficult as they depend on accurate determination of ulnar nerve-length across the elbow. Similarly, NCS are challenging in obese subjects, or following transposition of the ulnar nerve (AAEM and Campbell, 1999). In 2000,

Merlevede et al. (2000) published a new approach that used the latency difference (DLat) between mixed or compound nerve action potentials (CNAPs) of the ulnar and median nerves, elicited orthodromically by stimulation at the wrist and recording 10 cm above the elbow. The study was a single-center study and their derived normal DLat upper-limit value of 1.4 ms appears greater than the one currently used in common practice.

With this in mind, we initiated a multicenter study recruiting large numbers of normal subjects and patients with UNE or generalized neuropathy. The aim of the study was to estimate the upper limit of the ulnar-median DLat as well as its sensitivity and specificity to distinguish presence of UNE or not in a more heterogeneous population.

2. Methods

2.1. Participants

Following a joint meeting in May 2017, six European University Hospitals (Lausanne and Geneva, Switzerland; Marseille, Lyon, and Besançon, France and Liège, Belgium) agreed to each recruit 5 normal control subjects, 5 patients with ulnar neuropathy and 5 patients with generalized neuropathy. We recruited patients and healthy controls prospectively for this study between June 2017 and May 2018. All controls were volunteers with no reports of elbow trauma. A certified neurologist examined all controls to ascertain they were healthy. Patients with clinical symptoms and signs of UNE (including pain or positive Tinel sign, sensory or motor disturbances in the ulnar nerve distribution) or with manifestations of generalized polyneuropathy (pain, numbness, tingling, or muscle wasting, weakness and areflexia affecting both sides) were recruited among patients who presented to our EMG laboratories. All participants gave informed, oral consent for the study. The study conformed to the standards set by the latest revision of the Declaration of Helsinki and was approved by the clinical research ethics board of the University of Lausanne.

2.2. Electrodiagnostic protocol

For controls, we collected the following data: body mass index, age and sex. To minimize variability in nerve conduction studies (NCS) associated with different examiners, the same electrophysiologist performed repeat studies on individual subjects. All subjects had bilateral NCS over the course of two successive visits (V1 and V2), separated by at least 2 days. NCS were used to measure ulnar-median DLat only (see below). In cases of DLat > 1 ms, NCS were then completed as recommended in the summary statement of the 'Practice parameter for electrodiagnostic studies in UNE' (AAEM and Campbell, 1999).

For UNE and generalized neuropathy (GNP) patients, we first recorded routine motor and sensory NC in the affected arm as recommended in the summary statement of the 'Practice parameter for electrodiagnostic studies in UNE' (AAEM and Campbell, 1999) or limb using standard laboratory techniques and then measured ulnar-median DLat on one or both sides.

Stimulation of the ulnar and median nerves: Nerves were stimulated at the wrist, about 1 cm above the distal cutaneous folds; the median nerve with the stimulator placed radial to the superficial flexor tendons to avoid co-stimulating the ulnar nerve and for the ulnar nerve, just medial to the superficial flexor tendons. We delivered surface nerve stimulations with an impulse duration of 0.3 ms to record the supra-maximal CNAP following five shocks with averaging method.

Sites of recordings: To avoid 'nerve sliding' phenomenon [action potentials of the two nerves may superimpose at the same latency

with the arm straight but separate from each other with the arm flexed (Leote et al., 2017)], we kept the arm straight, with the forearm and arm aligned using a pillow placed under the elbow. A preliminary anatomical study performed by one of us (LT) verified the best site for arm recording between the biceps brachialis and triceps muscles. We found that placing the active electrode 10 cm above the medial epicondyle corresponded well to the superposition of the ulnar and median nerves (see Fig. 1). The reference electrode was then placed three to 4 cm proximally, with the ground electrode situated at the mid-forearm.

Filters, settings and measurements: Filter settings were 20 Hz to 2–3 kHz for sensory CNAP, sweep speed 2 ms/division and gain at 10 to 20 μ V. For measurements, cursors were placed as follows: latency at the negative peak (Lat peak), amplitude from peak to peak (Amp peak) and duration from baseline departure to final return to baseline (Dur). We then calculated ulnar-median DLat as the difference between the Lat peak of the ulnar nerve and the Lat peak of the median nerve.

2.3. Statistical analysis

We used descriptive statistics (mean, range, standard deviation) to describe patients' demographic and clinical characteristic variables. Comparison between control groups V1 and V2 was performed using t-test and Wilcoxon correlation tests as appropriate.

Finally, we compared the ability of DLat to discriminate between groups using ROC (Receiver Operating Characteristic) curve analysis. Logistic regression was carried out with group membership as the outcome variable and DLat at a specific latency as predictor (procedure logistic, followed by the lroc command in Stata). The area under the ROC curve (AUC) was calculated; AUC can range from 0.5 to 1, with the former value indicating no, and the latter, perfect discriminating ability.

3. Results

3.1. Patient and control populations

At the end of recruitment, we had examined 79 subjects. Their characteristics and the results of diagnostic testing (180 ulnar nerve recordings) are shown in Table 1 and Fig. 1 depicts examples of recordings.

Thirty-two controls (CTRLs) were recruited and 62 ulnar nerves recorded in the first visit (V1 only); out of these, 42 were recorded at a second visit (V2 only) giving a total of 104 healthy ulnar nerve recordings over two visits (V1 and V2). Twenty-one CTRLs were female and the mean age was 43 years (range 20–79).

Twenty-five UNE patients were seen, from which we recorded 32 ulnar neuropathies (seven patients had bilateral UNE). Thirty recordings were available for analysis as two patients lacked motor and sensory ulnar nerve recordings. Seven patients were female and the mean age was 53 years (range 20–91).

Twenty-two patients had clinical and electrophysiological evidence of a generalized neuropathy (GNP) and we recorded 44 ulnar nerves. Seven patients were female and the mean age was 57 years (range 23–83). Among the GNP group, eleven had inflammatory neuropathy (3 Guillain-Barré syndrome, 6 chronic inflammatory demyelinating polyneuropathy and 2 Lewis-Sumner syndrome), six a diabetic neuropathy, one a chemotherapy-induced peripheral neuropathy, one a TTR amyloidosis neuropathy and three were unspecified.

3.2. DLat values for the different groups

Recorded CNAP parameters of ulnar and median nerves are shown in Table 2 for the three groups. In the CTRL group (V1 and

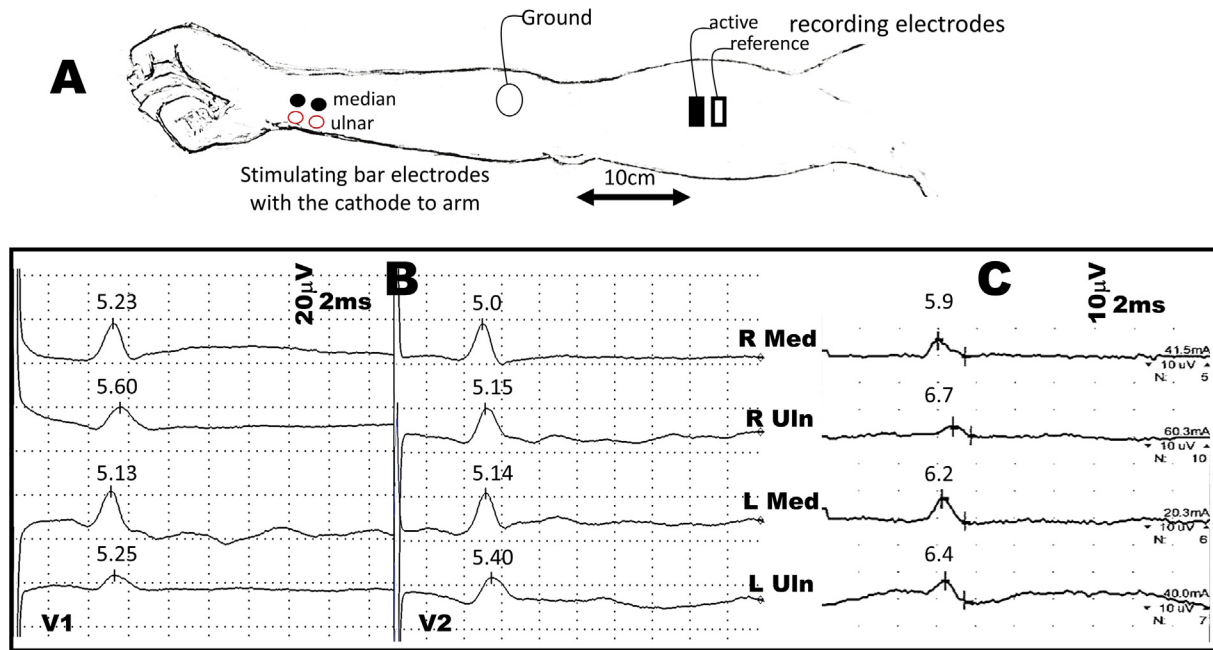


Fig. 1. A. Drawing of the straight arm, depicting the neurophysiological method. As the median and ulnar nerves lie in proximity to each other in the middle part of the arm, the recording electrodes were placed 10 cm above the medial epicondyle of the humerus, between the biceps and triceps brachii muscles. Then, median (Med) and ulnar (Uln) nerves were stimulated in sequence at the wrist (see text) to record the supra-maximal compound nerve action potentials (CNAPs) of the corresponding nerves following 5 shocks with averaging method. We then calculated Uln-Med DLat as the difference between the latency peaks of the ulnar and median nerves. **B.** Med and Uln arm CNAPs in a normal female subject, examined twice (V1 in August and V2 in October). The recorded parameters included peak latencies (shown as numbers in ms), peak to peak amplitude (not shown, between 6.8 and 18.4 μ V), and duration from baseline departure to final return to baseline (not shown, between 2.0 and 2.6 ms). The difference in latency (DLat, in ms) between the ulnar and median CNAPs is 0.37 on the right and 0.12 on the left at V1, and 0.15 on the right and 0.26 on the left at V2. **C:** Bilateral ulnar and median CNAPs in a 63-year-old patient with chronic diabetic polyneuropathy. The patient shows absence of sensory nerve action potentials from the distal upper and lower-limbs, reduced motor conduction velocity (MCV) from the ulnar and median nerves between the elbow and wrist (35 m/s on the right, 45 m/s on the left) and reduced MCV between the segments above and below the elbow (6 m/s on the right and 18 m/s on the left). Note the reduced CNAP amplitudes (minimum 3.3 to maximum 9.1 μ V) and their duration of 1.8 to 2.8 ms. DLat is 0.8 on the right and 0.2 ms on the left. R; right, L; left, V1; first visit, V2; second visit.

Table 1
Characteristics and clinical features of the study population (CTRL, healthy controls; UNE, ulnar neuropathy at the elbow; GNP, generalized neuropathy). V1 and V2 correspond to the two successive visits.

Groups	Patient numbers	Women (%)	Mean age in years, range	Ulnar nerves recorded
CTRL V1	32	21(66)	43, 20 to 79	62
CTRL V2	21	12(57)	44, 27 to 67	42
UNE	25	7(28)	53, 20 to 91	32
GNP	22	7(32)	57, 23 to 83	44

V2 and right and left measurements pooled), DLat was $0.4 \text{ ms} \pm 0.22$ (\pm standard deviation) for 104 records (mean V1 DLat $0.42 \text{ ms} \pm 0.21$, mean V2 DLat, $0.38 \text{ ms} \pm 0.24$; difference in mean DLat between V1 and V2 was $0.17 \text{ ms} \pm 0.13$). The coefficient of correlation between DLat V1 and V2 was good, respectively, 0.85 and 0.81. In the UNE group, DLat value was 1.14 ms and in the GNP group, 0.59 ms.

3.3. Analysis between groups

To determine the best cut-off value of DLat discriminating presence of UNE or not, we plotted V1 plus V2 CTRL DLat values vs. UNE DLat in a ROC curve. This revealed an optimal cut-off at 0.69 ms with a sensitivity of 0.86 and specificity of 0.89 to distinguish presence or absence of UNE (Fig. 2). Recorded values superior to the calculated cut-off were considered abnormal. Similarly, DLat CTRL V1 vs. UNE group gave an optimal cut-off at 0.67 ms, with a sensitivity of 0.86 and specificity of 0.89; and CTRL V2 vs. UNE, a cut-off at 0.69 ms, with a sensitivity of 0.86 and specificity of 0.90.

To estimate the impact of a generalized neuropathy on DLat cut-off values, we plotted pooled V1 and V2 CTRL plus GNP DLat

Table 2
Data of the recorded ulnar compound nerve action potentials (CTRL, healthy controls; UNE, ulnar neuropathy at the elbow; GNP, generalized neuropathy). SD = standard deviation. V1 and V2 correspond to the two successive visits.

Groups	Mean DLat in ms, SD	Mean duration in ms, SD	Mean amplitude in μ V, SD
CTRL V1 + V2	0.40, 0.22	2.12, 0.32	16.49, 8.80
CTRL V1	0.42, 0.21	2.13, 0.34	16.14, 8.59
CTRL V2	0.38, 0.25	2.10, 0.30	17.02, 9.21
UNE	1.14, 1.01	2.37, 0.37	7.09, 5.68
GNP	0.59, 0.52	2.40, 0.56	9.08, 8.41

vs. UNE values and observed that optimal cut-off was the same at 0.69 ms, but with a sensitivity of 0.86 and specificity of 0.80 (Supplementary Fig. S1A). GNP vs. UNE curves gave a cut-off at 0.89 ms with a sensitivity of 0.72 and specificity of 0.80 (Supplementary Fig. S1B).

T-tests showed that DLat differences between the various groups (CTRL V1, V2, V1 + V2, GNP) and UNE were statistically significant (Supplementary Table S1A).

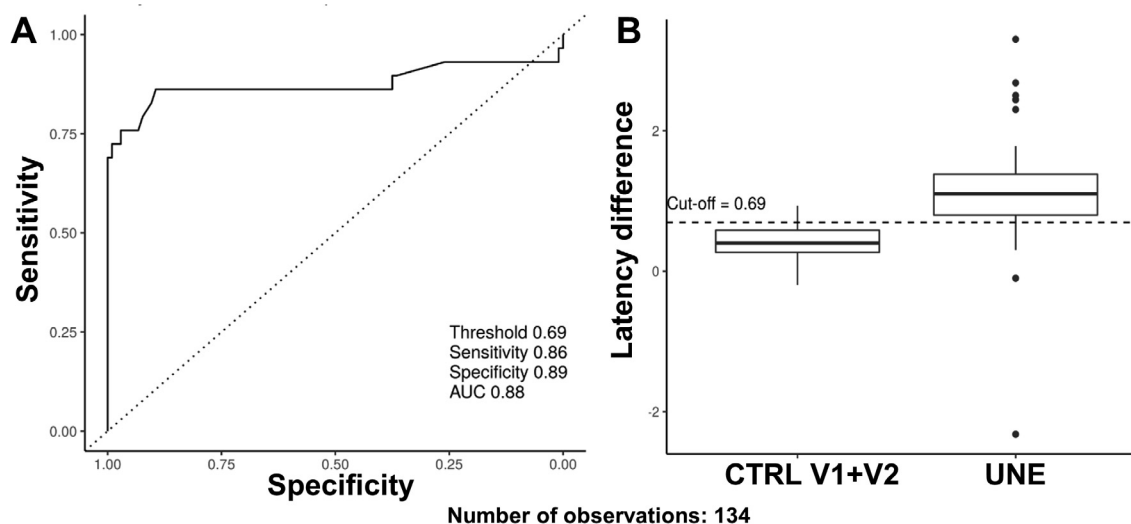


Fig. 2. A: ROC curve: latency difference (DLat) in the UNE group compared to controls V1 and V2 (CTRL V1 + V2). The optimal threshold is 0.69 ms with a sensitivity of 0.86 and specificity of 0.89 to discriminate between the presence and absence of UNE. B: DLat box plot between the two groups with the cut-off of 0.69 ms. V1; first visit, V2; second visit.

3.4. Other parameters

Ulnar nerve CNAP amplitude: The ROC plot of V1 + V2 CTRL vs. UNE data gave a cut-off of 8.4 μ V with a sensitivity of 0.83 and specificity of 0.87 (AUC of 0.86, Supplementary Table S1B). We found an inverse correlation between normal amplitude and body mass index (Supplementary Fig. S1C).

Ulnar nerve CNAP duration: The ROC plot of V1 + V2 CTRL vs. UNE data showed a cut-off of 2.16 ms with a sensitivity of 0.79 and specificity of 0.58 (AUC of 0.70, Supplementary Table S1B).

4. Discussion

NCS are reliable for confirming UNE, but it may be difficult to recognize nerve conduction slowing, necessitating sometimes several approaches to improve diagnostic accuracy (Todnem et al., 2009; Campbell et al., 2015). The measurement of the peak latency difference (DLat) between the ulnar and median mixed nerves of the arm is a simple and accurate technique that can be used for UNE diagnosis. However, since the original study of Merlevede et al. (Merlevede et al., 2000), only a few NCS in UNE have been performed (Heise and Toledo, 2006; Todnem et al., 2009; Omejec and Podnar, 2015; Vazquez do Campo et al., 2019), yet without technical improvement in calculating latency difference. In the experience of our Francophone centers over several years where measurement of ulnar-median DLat was often used in daily practice, we showed that values below 1.4 ms (Merlevede et al., 2000) or even 1.1 (Heise and Toledo, 2006) could correspond to classic cases of UNE. It therefore seemed timely to carry out a multicenter study in order to better evaluate the feasibility and reproducibility of this technique and establish a threshold value having the best sensitivity and specificity to discriminate presence and absence of UNE.

Our study demonstrated that (1) the normal ulnar-median DLat is lower than reported in the non-standardized studies of Merlevede and Heise (Merlevede et al., 2000; Heise and Toledo, 2006) and (2) the CTRL and UNE groups have clearly separated DLat values. Our DLat cut-off value of 0.69 ms allows a sensitivity of 0.86 and a specificity of 0.89 to distinguish between the CTRL and UNE groups; the same cut-off has a sensitivity of 0.86 and specificity of 0.80 discriminating CTRL and GNP groups from the

UNE group. Notably, we also confirmed that intra-examiner reproducibility was good.

Some methodological and statistical distinctions may explain the difference in the DLat cut-off value found in our study. We first verified anatomical superposition of the ulnar and median nerves in cadaver experiments indicating the optimal recording site as 10 cm above the medial epicondyle of the humerus. We then standardized the position of the arm with full extension of the elbow to avoid ulnar nerve sliding phenomenon whereby latency and shape of potentials may change (Leote et al., 2017). With these in mind, we chose to measure the peak latency of the potentials to avoid doubt on precise latency onset. Finally, we selected a ROC curve statistical analysis to determine the best DLat cut-off.

Our study has several limitations. We do not have data comparing the sensitivity and specificity of different electrophysiological methods used to diagnose UNE. Latency difference is measured over a long distance in our method that may reduce sensitivity due to “dilution” of the slow conducting segment in a long normal segment. Despite these limitations, the main advantages of the ulnar-median DLat technique is its high sensitivity and ease to carry out.

Furthermore, due to the high sensitivity in a standardized procedure, particularly by extending the elbow when recording CNAPs, this technique could be used in first intention when UNE is suspected. The method also allows investigating patients in difficult technical conditions, such as elbow trauma, obesity or post-transposition of the ulnar nerve. Ideally, later on in the examination, NCS can be supplemented by motor and sensory conduction measures to improve diagnostic accuracy, to estimate axonal degeneration or to locate better the lesion. UNE localization for example, is well evaluated using inching NCS (Visser et al., 2005; Vazquez do Campo et al., 2019) and axonal degeneration by conventional sensory ulnar NCS and needle electromyography of the first dorsal interosseous muscle (Todnem et al., 2009). Ultrasonography is also a useful tool, especially to delineate the site of compression when NCS reveal important axonal loss (Omejec et al., 2015; Pelosi and Mulroy, 2019).

Overall, our multicentric study allowed us to evaluate the feasibility, reproducibility and diagnostic accuracy of this simple technique as well as to standardize procedures and determine normal values. It will be interesting to further study potential correlations between increased ulnar-median DLat and type and severity of UNE.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.clinph.2019.11.022>.

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