ELECTRODIAGNOSIS OF ULNAR NEUROPATHY AT THE ELBOW (UNE): ROC CURVE AND ACCURACY OF A CASE-CONTROL STUDY AND COMPARISON WITH AANEM GUIDELINES

Mondelli M [1], Farioli A [2], Ciaramitaro P [3], Aretini A [1], Giorgi S [3], Greco G [4], Sicurelli F [5], Vinciguerra C [5], Mattioli S [2]

1 EMG Service, Local Health Unit 7, Siena; 2 Dpt. Medical and Surgical Sciences, University of Bologna; 3 Clinical Neurophysiology, CTO, Dpt. Neuroscience, AO "Città della Salute e della Scienza", Torino; 4 EMG Service, Local Health Unit 7, "Nottola" Hospital, Montepulciano (Siena); 5 Dpt. Medical, Surgical and Neurosciences, University of Siena

BACKGROUND

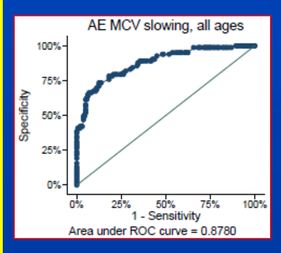
The electrodiagnosis of ulnar neuropathy at the elbow (UNE) is not easy as that of carpal tunnel syndrome. In 1999 the American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM) suggested electrodiagnostic usefulness of four electrophysiological parameters of the ulnar nerve (listed in ascending order by strength of evidence): 1) reduction of MCV in across-elbow segment <50 m/s ("AE MCV slowing"); 2) drop of MCV across-elbow vs. forearm MCV >10 m/s ("MCV drop"); 3) drop of CMAP amplitude across the elbow ("conduction block"-CB) >20%, 4) significant change in CMAP configuration at the above elbow site compared with the below elbow site [1]. They are considered "UNE localizing" electrodiagnostic parameters.

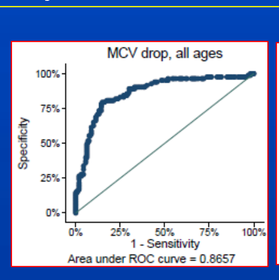
Subjects

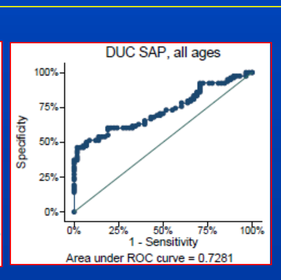
"Case" and "controls" were consecutively recruited among all patients referred to 4 outpatient EMG labs to perform electrodiagnosting testing at the upper limbs from June 2014 to April 2015.
UNE diagnosis ("cases") was made according to clinical findings. Mandatory symptoms included numbness, tingling, or burning sensation in the fifth digit of the hand or weakness in an ulnar distribution. "Hand diagram protocol" proposed by Werner et al. was also used [3]. Guyon's canal syndrome, C8-T1 radiculopathy, brachial plexopathy, thoracic outlet syndrome were excluded with adequate instrumental tests if necessary.
"Controls" were all the other subjects admitted to the same EMG labs without symptoms and neurological findings of peripheral nervous system and muscular diseases. "Case" and "controls" with age <14 and >70 years, polyneuropathy, multifocal motor neuropathy, amyotrophic lateral sclerosis, diabetes, connective and thyroid diseases, renal failure, history of alcoholism and malignancy in the previous 5 years were excluded. Because the "controls" were "symptom-free individuals", their neurographic values were called "REFERENCE VALUES" [4].

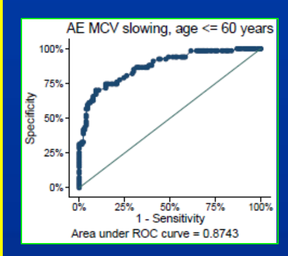
Results

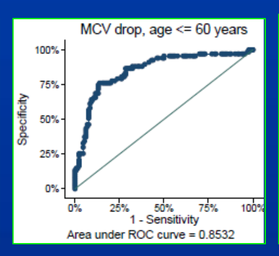
We prospectively enrolled 83 consecutive UNE "cases" (mean age 49.2 years, 45.8% females, 45.8% blue collars) and 160 consecutive controls (mean age 47.3 years, 51.3% females, 45% blue collars). There were no significant differences of age, sex and job titles between two groups.
All parameters had moderate accuracy (AUC>0.6) in the whole sample. The largest AUC were 0.88 (AE MCV slowing) and 0.87 (MCV drop). The cut-offs of AE MCV slowing (49.7 m/s) and drop (8.6 m/s) provided sensitivity of 73.5% and 79.5% and specificity of 87.5% and 85%, respectively. Between "non-localizing" parameters DUC SAP cut-off (12.8 μV) provided the highest sensitivity and specificity (60.3% and 80%). If we separated the sample in two age groups, the sensitivity and specificity further slightly increased (see figures).
If we considered the cut-offs of AANEM MCV slowing and drop, they had high similar sensitivity and specificity, while the "normative values" had high specificity (>92%) but low sensitivity. CB had moderate accuracy only if "reference values" were used.

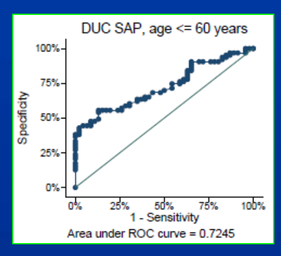


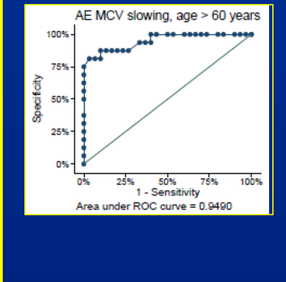


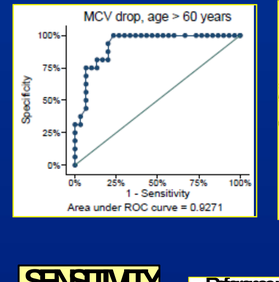


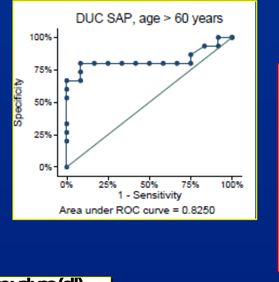










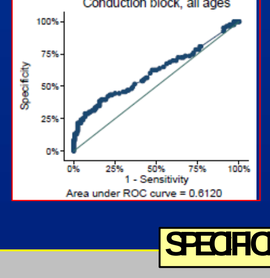


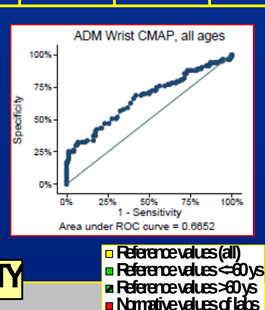
Area under the ROC curve (AUC) with confidence interval (CI) and optimal cut-off

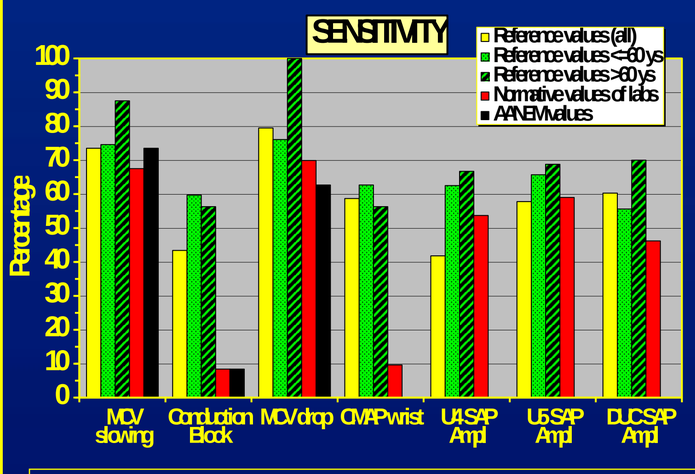
Neurographic parameters	All subjects		Subjects <60 years		Subjects >60 years	
	AUC (95% CI)	Cut-off	AUC (95% CI)	Cut-off	AUC (95% CI)	Cut-off
AE MCV slowing	0.88 (0.83-0.92)	48.7 m/s	0.87 (0.82-0.93)	50.8 m/s	0.95 (0.88-1)	47.3 m/s
Conduction block	0.61 (0.53-0.68)	4.8%	0.61 (0.52-0.69)	2.75%	0.68 (0.48-0.87)	6.6%
MCV drop	0.86 (0.82-0.90)	8.5 m/s	0.85 (0.79-0.91)	8.6 m/s	0.93 (0.86-1)	8.1 m/s
CMAP Wrist ampl.	0.68 (0.59-0.73)	10.75 mV	0.65 (0.56-0.73)	10.85 mV	0.75 (0.60-0.91)	8.4 mV
U4SAP ampl.	0.62 (0.54-0.71)	3.45 μV	0.61 (0.51-0.7)	6.65 μV	0.75 (0.56-0.94)	1.75 μV
U5SAP ampl.	0.67 (0.59-0.75)	8.15 μV	0.67 (0.59-0.76)	9.55 μV	0.75 (0.55-0.94)	3.05 μV
DUCSAP ampl.	0.73 (0.64-0.81)	12.75 μV	0.72 (0.63-0.82)	12.95 μV	0.83 (0.65-1)	8 μV

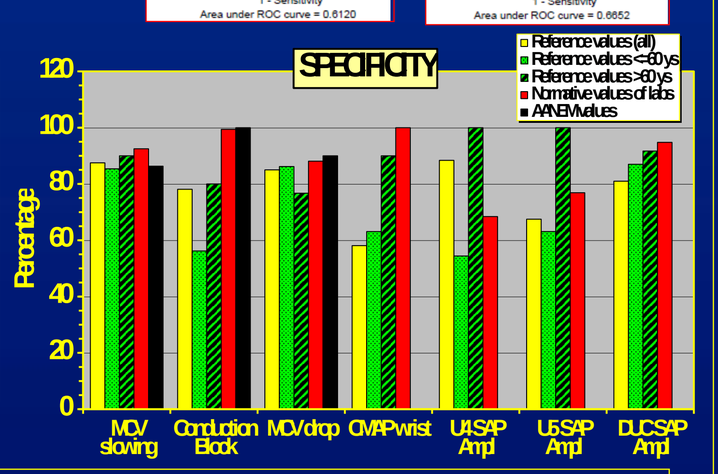
Neurographic cut-offs of the ulnar nerve

Neurographic parameters	Normative values			AAEMN values
	Siena Labs (<60 ys)	Siena Labs (>60 years)	Torino Lab	
AE MCV slowing (m/s)	49	46.8	48	50
Conduction block AE (%)	15.2	23.2	20	20
MCV drop (m/s)	8.7	12.7	10	10
CMAP Wrist ampl. (mV)	6.44	3.49	4	
U4SAP ampl. (μV)	3.83	1.92	–	
U5SAP ampl. (μV)	8.19	3.55	13	
DUCSAP ampl. (μV)	11.9	6.1	10	









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AIMS OF THE STUDY

1) To check optimal cut-off values of the first three AANEM "localizing" and other "non-localizing" neurographic parameters of the ulnar nerve (see statistical methods) to identify patients with UNE using receiver-operating characteristic (ROC) curves. The neurographic values were obtained from consecutive subjects enrolled in four EMG labs by a "case-control" study designed for another aim [2].
2) To compare the sensitivity and specificity of the cut-offs obtained with ROC curve with those of AAENM and those of "normative values" of each EMG lab.

Statistical and electrophysiological methods

The neurographic values of "cases" and "controls" were utilized to construct non-parametric ROC curves. We estimated the area under the curve (AUC) and calculated sensitivity, specificity and positive and negative predictive values of the following neurographic parameters: AE MCV slowing, drop and CB of the ulnar nerve, ulnar nerve CMAP amplitude at the wrist and SAP amplitudes of the fourth finger and fifth finger-wrist segment (U4, U5) and of dorsal ulnar cutaneous nerve (DUC). Significant change of CMAP configuration was not analyzed because this variable is dichotomous and all the cases with change of CMAP configuration had also CB. We carried out ulnar nerve motor neurography with the elbow flexed at 90° that provides the greatest correlation between surface skin measurement and true nerve length and the across elbow interstimulus distance was 10 cm with distal stimulation at 2 cm distally to the medial epicondyle.
We chose optimal cut-off points based on the Liu method (maximization of the sensitivity and specificity product) [5]. In addition we separated the results according to the age of subjects (<60 ys and > 60 ys).
For comparison we also calculated the sensitivity and specificity of AANEM cut-offs and those of "normative values" of each EMG labs.
The "NORMATIVE VALUES" of each lab derived from "disease-free individuals" [4] selected among administrative and sanitary personnel, students and relatives of patients (3 labs of Siena) and Kimura's values (1 lab of Torino).
We performed electrodiagnostic testing according to common standardized protocol inspired by AANEM, based upon recommendations by Werner et al. and reported elsewhere in details [1,6,7]. In particular, the position for ulnar MCVs is moderate flexion (90° from horizontal).

DISCUSSION

Many studies of "normative values" used convenience or feasibility samples composed of hospital personnel, students, and friends. This type of sample has limitation for generalization and might produce results of questionable validity for comparison of the general population [8]. In this study we used an appropriate "reference" cohort belonging to the same cohort of the patients, and theoretically the patients and controls might come from the same population even if they might not represent the general population. In addition our samples are sufficient in size to obtain reliable results.

A normal range may be defined in different ways, the most known were to calculate the percentile values or values within 2 SD of the mean. The latter method depends on a Gaussian distribution. Few electrodiagnostic parameters show a Gaussian distribution. The number of type I errors ("normal" mistakenly considered "abnormal") can be reduced by using a critical values of 2 SD from the mean but it would increase the number of type II errors ("abnormal" considered to be "normal"). The relationship between the true and false positive subjects can best demonstrate using ROC curves [9]. ROC methods were rarely used to obtain the optimal cut-offs of neurographic values not only in the ulnar nerve but in all the nerves. Only a recent paper used ROC curve and Bayesian analyses [10].

CONCLUSIONS

Using ROC analysis the discriminative ability of two "localizing" parameters (MCV slowing and drop) to detect UNE patients has high accuracy. The optimal cut-offs of "reference values" with the highest sensitivity and specificity are 49.7 m/s and 8.5 m/s, respectively. The specificity and especially sensitivity increase if we separate the optimal cut-offs in two age groups.

If we use the cut-offs of AAEMN the sensitivity and specificity are similar but slightly lower than our "reference values". The "normative values" have high specificity but low sensitivity.

Our "reference values" and "normative values" of MCV slowing across elbow are very similar to those of AAEMN and higher than many "normative" ranges of some papers (i.e. about 40 m/s) even if the electrodiagnostic methods are very like to ours [11]. The problem of this difference is the choice of "reference" population and the type of the job of the selected subjects because asymptomatic delay of MCV across the elbow is relatively frequent in subjects with certain jobs.

"Non-localizing" neurographic factors may be useful to confirm UNE diagnosis, especially DUC SAP, they have lower accuracy, but they may help to document axonal degeneration.