Clinical Neurophysiology 130 (2019) 1091–1097

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Facing the challenges of electrodiagnostic studies in the very elderly (>80 years) population

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ARTICLE INFO

Article history:
Accepted 17 March 2019
Available online 13 April 2019

Keywords:
EDX
Very old
E-norms
EMG
Nerve conduction study
Aging

HIGHLIGHTS

- Electrodiagnostic findings are presented for 1966 very elderly individuals.
- EMG normative data from e-norms were similar to those of lab reference values.
- E-norms provided a wider normality window when applied to nerve conduction data.

ABSTRACT

Objective: Studies on electrodiagnostic (EDX) methods usually exclude the very elderly. This also holds true for studies of normal EDX values. We analyzed the outcome and diagnostic value of EDX and collected reference data in a large cohort of patients ≥80 years of age.
Methods: Referral information, ICD-10 diagnoses and EDX data were retrieved from all patients ≥80 years of age referred for EDX studies at our department in 1995–2015. Normative data, including reference ranges, were obtained using the extrapolated norms (e-norms) method.
Results: 1966 unique patients (2335 examinations) were included. Only 11% were considered to have normal findings. 66% had pathological EDX findings in accordance with the indication for referral. Carpal tunnel syndrome was by far the most common diagnosis. Normative data retrieved using e-norms were similar to those of reference values from healthy subjects regarding EMG multiMUP data, but typically provided a wider normality window when applied to nerve conduction parameters.
Conclusions: EDX studies are valuable in the diagnostic work-up of very elderly patients. Using the e-norms method may be a useful alternative when obtaining reference values in this age group.
Significance: Our findings provide additional insights to the challenges of evaluating very elderly patients with neuromuscular disease and underline the importance of including this growing part of the patient population in EDX research.

1. Introduction

Studies on electrodiagnostic (EDX) techniques in the peripheral nervous system, such as nerve conduction studies (NCS) and needle electromyography (EMG), usually exclude the very elderly, i.e. people over the age of 80. This also holds true for studies on normal values in EDX or studies focusing on the relation between for example age and nerve conduction attributes (Stetson et al., 1992; Tong et al., 2004; Chen et al., 2016). The lack of studies in this age group poses difficulties to interpret EDX data in patients above 80 years and more studies specifically focusing on this growing patient group are warranted. With this in mind, we analyzed the outcome and diagnostic value of EDX in a large cohort consisting of all patients ≥80 years of age referred for EDX at our department between 1995 and 2015. We also collected normative data using e-norms (a method by which reference ranges are retrieved from a patient population, as described below) and compared these data to our own healthy individuals reference values.

2. Methods

2.1. Patient cohort, diagnostic classification and neurophysiological evaluation

All patients aged ≥80.0 years at the time of examination at the Department of Clinical Neurophysiology, Uppsala University

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https://doi.org/10.1016/j.clinph.2019.03.029
1388-2457/

Hospital, between September 1995 and December 2015 were included retrospectively. 1966 unique patients (2335 visits) were included (59% female). The patients were born in 1900–1935 with an age span of 80.0–101.1 (median 83.2) years at the time of their EDX evaluation. The age distribution is shown in Fig. 1a. All patients had received an ICD-10 diagnosis before ('In'; based on the referral and the indication for examination) and immediately after ('Out'; the diagnosis based on the electrodiagnostic findings) the examination and these codes were retrieved from the referral system. ICD-9 codes (used 1995–1996) were converted to the equivalent ICD-10 code. Some patients had several diagnostic codes; e.g. patients referred for carpal tunnel syndrome (CTS) who turned out to have both CTS and polyneuropathy (PNP) received two 'Out' diagnoses. The same equipment (Dantec Keypoint, Alpine Biomedical Aps, Skovlunde, Denmark) was used for all studies. NCS were performed by laboratory technicians using surface electrodes according to standardized techniques and strategies (Stålberg and Falck, 1993; Falck et al., 1994). Concentric needle EMG with quantitative multiMUP analysis was performed by physicians. The reference values that were used when evaluating the patients are given as multiple linear regression equations and SD based on studies of healthy subjects in our lab (Falck et al., 1991; Stålberg and Falck, 1993; Bischoff et al., 1994; Falck et al., 1994). By utilizing the Cross Neuro Database software (Stefan Stalberg Software AB, Helsingborg, Sweden), EDX data were extracted from studies of nerve conduction (amplitudes, conduction velocities, distal latencies, decrement) and EMG (quantitative multiMUP data). Parameters such as age, gender and height were also collected. All data were exported to Excel 2016 for further analysis. A subgroup analysis was performed on the sensory amplitudes of the sural and superficial peroneal nerve obtained from patients with normal electrodiagnostic findings and no symptoms from the leg (according to the referral and the symptom chart drawing made by the patient at the time of NCS) and from patients

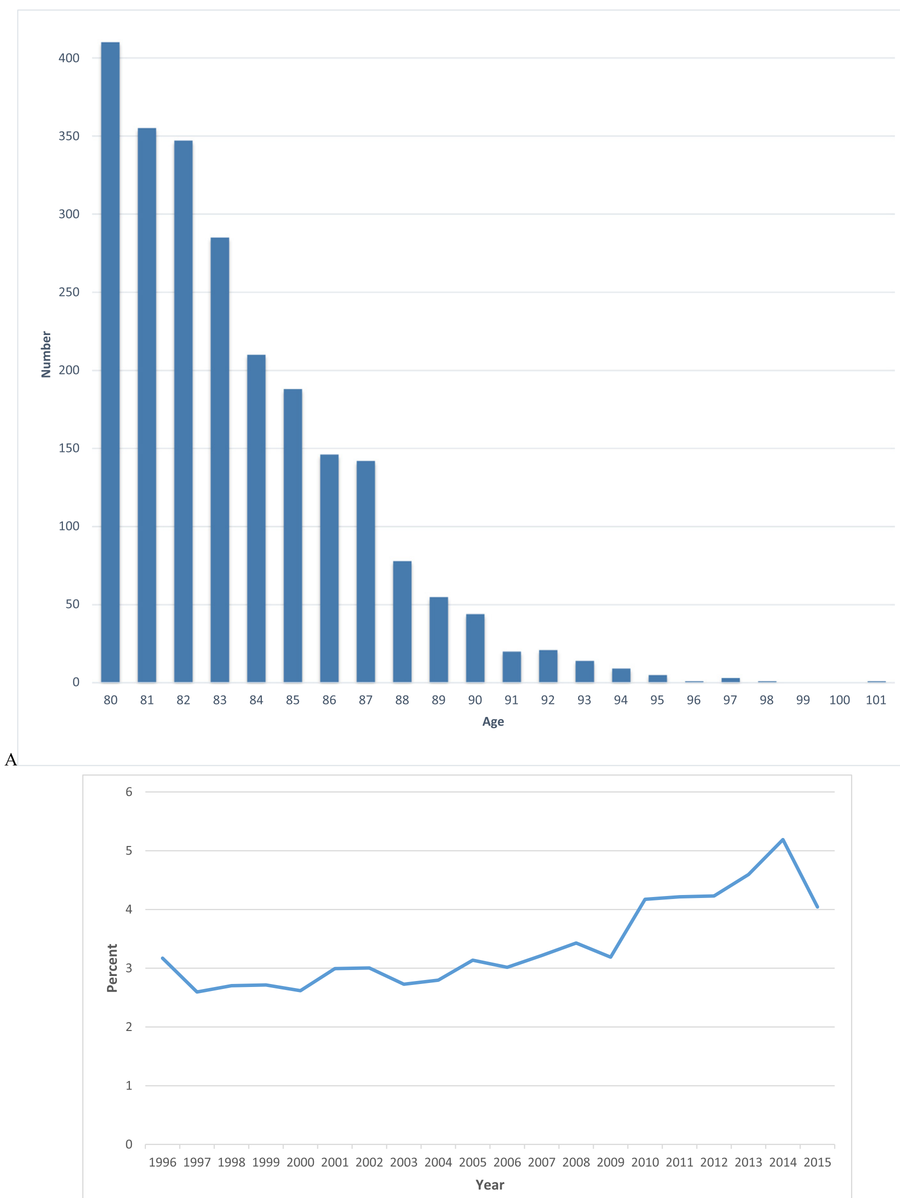

Fig. 1. (A) Number of examinations (y-axis) per year of age (x-axis) in the cohort studied. (B) Percentage (y-axis) of studies performed on patients ≥80 years of age at the Department of Clinical Neurophysiology, Uppsala University Hospital per year (x-axis).

who were examined for isolated upper limb symptoms without any symptoms from the legs. The study was approved by the Uppsala Ethical Review Board (case no 2015/105) and conforms to the Declaration of Helsinki.

2.2. E-norms modeling and analysis of EDX data

Normative data, including reference ranges, were obtained using the extrapolated norms (e-norms) method, described in detail elsewhere (Jabre et al., 2015; Pitt and Jabre, 2017; Nandedkar et al., 2018). In short, the e-norms method derives reference values from data collected from a laboratory population that includes both normal and abnormal studies. The values obtained for a certain parameter (e.g. the motor conduction velocity of the median nerve along with its corresponding variable such as the subject's age or height) are sorted in ascending order and plotted against rank order. Next, the first-order derivatives (the consecutive difference between parameter one and two, two and three, three and four, etc.) are plotted in the same graph. By identifying the tangential inflection points that mark the beginning and end of the "plateau", the parameter's e-norms reference values (mean, standard deviation, minimum and maximum values) can be retrieved. For one parameter, the motor amplitude of the tibial nerve, data were log-transformed using the natural log formula in Excel before obtaining e-norms values. Natural log transformation was performed when the e-norms plateau could not be easily identified. This was usually encountered with data that had a coefficient of variance (SD/Mean expressed in percent) that exceeded 20%. The identification of inflection points was performed blinded to parts of the data, i.e. it was not known which nerve or parameter that was analyzed, to limit preconceived bias. When comparing to healthy individuals reference values, e-norms values were considered normal if the value was within the e-norms derived mean value ± 2SD.

3. Results

3.1. Performed examinations and classification according to EDX findings

The percentage of studies performed on patients older than 80 has gradually increased during the time period studied and at present constitute 4–5% of the total amount of EDX-studies in our department (Fig. 1b).

Among the examinations, 2078 were routine NCS, 1048 EMG, 81 repetitive nerve stimulations, 85 single-fiber EMG, 44 muscle biopsies, 44 sensory evoked potentials, 27 motor evoked potentials, 35 sympathetic skin response, 81 RR-intervals, 14 quantitative sensory testing, 46 incontinence/obstipation evaluations and 38 EMG-guided botulinum toxin injections. There were also occasional needle neurography examinations (N = 10), blink reflexes (N = 3), macro EMG (N = 3), BAEP (N = 1) and intraoperative monitoring (N = 8). Many patients had more than one examination performed during the same visit (e.g. NCS and EMG or repetitive nerve stimulation and SFEMG). Only 255 examinations (11%) had been considered to have normal findings. Sixty-six percent of the patients had pathological EDX findings in accordance with the indication for referral [data covering all main indications (2013 out of 2355 examinations) are presented in Table 1]. In 216 patients the diagnostic code 'Out' was "abnormal examination findings" without any specific diagnosis (e.g. if there were some abnormal findings but not sufficient to fulfill the criteria for a certain diagnosis). In 55 patients, no diagnostic codes had been provided and these patients were thus excluded from further study.

3.2. Lower limb sensory responses in patients without sensory symptoms from the legs

Out of the 289 examined sural nerves in this subgroup, 16 (6%) had no response. In 16 out of 100 (16%) examinations there was no sensory response from the superficial peroneal nerve (in 14 of these there was a sural response).

3.3. Findings in specific diagnoses

3.3.1. Carpal tunnel syndrome (CTS)

As could be expected, CTS was by far the most common diagnosis both for referral and after the EDX evaluation in all age groups (Table 1, Fig. 2). Out of 846 patients referred with the question of CTS, 689 (81%) had EDX findings supporting this diagnosis (of these, 58 also had ulnar neuropathy and 65 also had polyneuropathy (PNP)). The patients referred for CTS that turned out to have other specific pathological EDX findings suffered from e.g. ulnar neuropathy (N = 26), polyneuropathy (N = 22) or cervical radiculopathy (N = 4).

3.3.2. Ulnar neuropathy

Of the 103 patients referred with the question of ulnar neuropathy, 60 had also got that 'Out' diagnosis (16 of those also had CTS). Of those not found to have an ulnar neuropathy, the majority had PNP (13).

Table 1
Findings at EDX in relation to the indication of referral. NB: not all diagnoses are included in the table. *N* = number of examinations.

Indication	*N*	Normal findings	Pathological findings in accordance with indication	Other pathological findings
Peripheral nerve disease upper extremity				
–Carpal tunnel syndrome	846	58 (7%)	689 (81%)	99 (12%)
–Ulnar nerve	103	10 (10%)	60 (58%)	33 (32%)
–Radial nerve	21	0 (0%)	15 (71%)	6 (29%)
Peripheral nerve disease lower extremity				
–Sciatic nerve	16	1 (6%)	10 (63%)	5 (31%)
–Peroneal nerve	45	1 (2%)	23 (51%)	21 (47%)
Radiculopathy				
–Cervical	28	6 (21%)	11 (39%)	11 (39%)
–Lumbosacral	112	9 (8%)	78 (70%)	25 (22%)
Plexopathy	27	0 (0%)	19 (70%)	8 (30%)
Motor neuron disease	90	3 (3%)	35 (39%)	52 (58%)
Polyneuropathy	529	90 (17%)	264 (50%)	175 (33%)
Myasthenia gravis	60	13 (22%)	36 (60%)	11 (18%)
Myopathy/myositis	77	12 (16%)	34 (44%)	31 (40%)
Total	2013	203 (10%)	1331 (66%)	479 (24%)

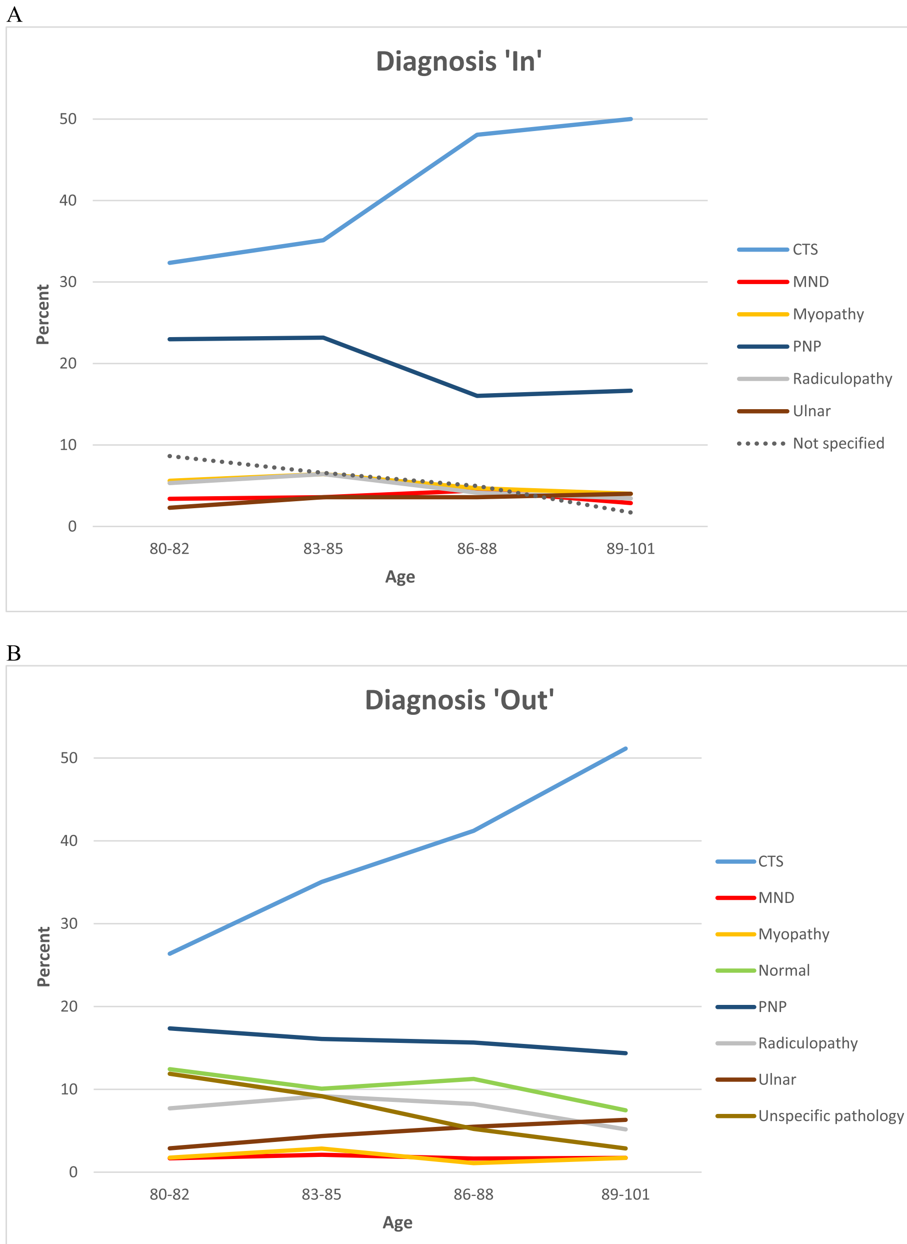

Fig. 2. Percental distribution (y-axis) of diagnoses per age group (x-axis). (A) Diagnosis according to referral ('In'). (B) Diagnosis after electrodiagnostic evaluation ('Out').

3.3.3. Polyneuropathy (PNP)

Suspected PNP was the referral diagnosis in 529 patients and in only 264 of those patients (50%) a final diagnosis of PNP could be confirmed. Ninety patients had normal findings and the other patients had received other diagnoses such as lumbosacral radiculopathy (N = 47), CTS (N = 27), motor neuron disease (MND; N = 3) or peroneal entrapment at the fibular head (N = 3).

3.3.4. Amyotrophic lateral sclerosis (ALS)

Eighty patients had been referred with the question of ALS (10 patients were referred for other specified MND types). The diagnosis of ALS/MND was confirmed in 35 patients, whereas the other patients got the following diagnoses: PNP (N = 13), CTS (N = 1), myasthenia gravis (N = 1), myopathy/myositis (N = 5), lumbosacral radiculopathy (N = 5) and normal findings (N = 3). The remaining patients had been classified as "abnormal examination findings" without any specific EDX diagnosis. In addition, five patients who were initially referred for other disease types (radiculopathy, peripheral nerve entrapment and myositis) had EDX findings in support of ALS.

3.4. E-norms

E-norms values (mean ± 2SD) for NCS and EMG data are presented in Tables 2 and 3 respectively. Compared to our own laboratory reference values derived from healthy subjects, the results obtained using e-norms reference values for mean MUP amplitudes were very similar to ours for all muscles. For nerve conduction studies, however, there were considerable differences for several of the parameters with the e-norms method generally exhibiting a higher percentage of patient data within the normal

Table 2
E-norms reference data calculated from parameters obtained by nerve conduction studies. Both sides are included if nothing else is noted. Zero values (no response) have been excluded. *N*; number of nerves examined, SD, standard deviation. "%abnormal using E-norms" and "%abnormal using lab ref values"; the percentage (out of N) of observations with values lower or higher (depending on the parameter) than the normal range of the respective reference values. CMAP; compound motor action potential, MCV; motor nerve conduction velocity, SCV; sensory nerve conduction velocity, ADM; abductor digiti minimi muscle, APB; abductor pollicis brevis muscle, AHB; abductor hallucis brevis muscle, EDB; extensor digitorum brevis muscle. N/A = data not available.

Nerve	Parameter	*N*	Mean	Mean −2SD	Mean + 2SD	%abnormal using E-norms	%abnormal using lab ref values
Median	distal latency left (ms)	1248	4.1	3.3	4.8	35	55
	distal latency right (ms)	1548	3.9	3.4	4.4	45	54
	CMAP amplitude APB (mV)	2798	4.4	2.7	6.1	25	27
	MCV (m/s)	2732	52	50	55	35	39
	SCV dig III (m/s)	1688	49	40	57	18	33
	sensory amplitude dig III (μV)	1691	3.3	0.7	5.8	3	54
Ulnar	distal latency	2854	3.1	2.7	3.6	12	17
	MCV	2682	55	49	60	16	19
	CMAP amplitude ADM	2855	6.2	4.3	8.2	14	9
	SCV dig V	2130	51	44	57	13	19
	sensory amplitude dig V	2138	2.9	0.8	4.9	3	25
Radial	SCV	936	58	51	65	22	15
	sensory amplitude	937	7.7	2.4	13	6	30
Tibial	CMAP amplitude AHB[a]	1317[a]/1780	1.9	1.5	2.4	32	12
	MCV	1730	40	34	47	12	12
Peroneal	CMAP amplitude EDB	1504	1.8	0.5	3.0	26	39
	MCV	1438	41	37	45	23	20
Sural	SCV	1040	47	39	55	12	4
	sensory amplitude	1040	2.3	0.7	3.9	2	13
Superf peroneal	SCV	326	46	40	52	18	6
	sensory amplitude	328	2.1	0.6	3.6	2	5

[a] E-norms log transformed data.

Table 3
E-norms reference data calculated from the mean MUP amplitude (μV) obtained by quantitative multi-MUP analysis from each subject. *N*; number of muscles examined, SD; standard deviation, %normal using E-norms; the percentage of mean MUP amplitudes within the mean ± 2SD range using E-norm values, %normal using lab ref values; the percentage of mean MUP amplitudes within the normal range using laboratory reference values from healthy subjects, EDC; extensor digitorum communis muscle, FDI; first dorsal interosseous muscle, TA; anterior tibial muscle.

Muscle	*N*	Mean	Mean −2SD	Mean + 2SD	%normal using E-norms	%normal using lab ref values
Biceps	334	550	333	766	68	72
Deltoid	215	634	359	908	70	71
EDC	232	774	343	1205	73	73
FDI	551	955	403	1507	68	78
Gastrocnemius	479	1038	415	1661	64	61
Sphincter ani	103	440	204	677	68	75
TA	941	1245	423	2067	67	72
Vastus lat	739	1161	553	1770	67	65

range than results obtained using our healthy subjects reference values, particularly in sensory studies.

4. Discussion

This retrospective study provides an overview of the electrodiagnostic spectrum in a very large cohort of patients older than 80 years of age, a patient group that is either heavily underrepresented or nonexistent in most studies. Previous studies, even those focusing on normal values or the effects of aging on EDX, have included very few subjects above 80 (Bouche et al., 1993; Rivner et al., 2001; Tong et al., 2004; Chen et al., 2016) or have been limited to specific conditions (Vrancken et al., 2002; Blumenthal et al., 2006).

The remaining life expectancy at old age is increasing steadily. In this study, the number of patients referred who were ≥80 years almost doubled between 1996 and 2015 (Fig. 1b), indicating an increasing demand. Still, the fact that people ≥80 years currently constitute only 4–5% of all patients referred suggests that EDX evaluations might be either under-used or considered redundant in this patient group.

The effects of aging pose challenges to the clinician when evaluating neurological symptoms and findings. Transient neurological symptoms are common in individuals over 65 years of age (Mavaddat et al., 2013) and there are more comorbidities and adverse effects of prescription drugs that result in neurological symptoms the older one gets (Budnitz et al., 2011; Schott, 2017). Even in very elderly people without neurological symptoms or comorbidities, neurological variance from younger individuals are common (Kaye et al., 1994; Vrancken et al., 2002). This makes diagnosing neurological disease by clinical examination alone in this age group challenging, a fact supported by the present study since only 66% of the patients were diagnosed in accordance with the indication for referral while merely 11% turned out normal. EDX evaluation thus resulted in an alternative diagnosis in nearly a quarter of the patients. Among patients referred with the question of polyneuropathy, only 50% had EDX findings supporting that diagnosis. EDX is thus of great value when it comes to delineate pathology in this age group, particularly in diseases that may be mimicked by normal aging, such as polyneuropathy. This is further supported by a recent study on the utility of EDX studies where it was concluded that EDX was more likely to alter the diagnosis and management plan in older patients than in younger ones (Lindstrom and Ashworth, 2018).

Nevertheless, similar diagnostic difficulties are encountered in EDX, since several EDX parameters change with normal aging.

The experimental setups and results from such studies are somewhat diverse and beyond the topic of this study. It should be noted, however, that an absent sural nerve SNAP is rare (0–9%) in healthy older controls (Vrancken et al., 2002), even when specifically looking at the very elderly (Falco et al., 1994). In the present study, sensory responses from the sural and superficial peroneal nerve were absent in 6% and 16% respectively in patients without sensory symptoms from the legs. Since they were referred with the suspicion of a neurological disease these patients cannot be considered healthy, but our findings underline the fact that absent sensory responses from the legs are an uncommon finding even after 80 years of age if sensory leg symptoms are not present, a fact that should be taken into consideration when interpreting NCS.

Not only are many EDX parameters affected by normal aging, the risk of measurement errors also increases with age as older subjects more often have e.g. cold limbs due to circulatory disturbances. In addition, self-reported height is over-estimated in 70% of those older than 80 as compared to 30–40% of those aged 60–69 (Sahyoun et al., 2008), suggesting that the effect of a body height factor in NCS may be miscalculated. It thus becomes clear from what has been mentioned above that applying reference values derived from linear algorithms based on values obtained from younger subjects when evaluating the very elderly patients may in fact be incorrect. In a normative data task force driven meta-analysis (Chen et al., 2016), only very few studies on routine NCS were considered of good methodology overall and these only include subjects up to the age of 79. There is thus an apparent lack of reference data for the very elderly regarding most clinical neurophysiological methods. To try a different approach, we applied the e-norms methodology to our data set. Instead of using healthy asymptomatic individuals, e-norms extract reference data from a laboratory population and thus make use of a cohort of subjects with both presumed abnormal and normal values, which might be particularly useful in this age group. E-norm values correspond to reference values obtained from healthy subjects regarding e.g. single-fiber EMG in infants, another patient group where the possibility to obtain normal values from healthy subjects is limited (Pitt and Jabre, 2017). The e-norms method has also been applied successfully to H-reflex latency (Zaccarini et al., 2016) and median and ulnar nerve NCS parameters (Jabre et al., 2017; Zhu et al., 2017).

In the present study, applying e-norms values obtained from our laboratory population of very elderly patients was compared to our preexisting laboratory reference values from healthy subjects. The results obtained when using EMG data were very similar (Table 3). Data obtained from NCS (Table 2) varied much more – specifically considering the SNAPs where applying the e-norms values resulted in a considerably lower number of nerves with abnormal findings. It was also noted that when using the healthy subjects reference values, almost all patients ended up either within the normal range or as pathological with very few patients being on the "supranormal" side. Using e-norms, in general more patients ended up within the normal range and the rest was often more evenly distributed between pathological and "supranormal". Some of these differences can be explained by the different methodology applied with e-norms, which uses mean and standard deviation to determine normal versus abnormal, whereas our method uses multiple linear regression equations and SD to do so. There are thus certain differences in the way the two different methods pick up presumed pathology where e-norms reference data for NCS generally exhibit less degree of abnormality than healthy subjects' reference values. Exactly how these differences affect the sensitivity and specificity to detect a specific condition would be a subject for future studies. The large difference between using healthy objects reference values and e-norms reference values on SNAPs in the present study may be due to the high variance accounted for by age in this parameter (Falck et al., 1991) and it is plausible that e-norms data would benefit from subgrouping into e.g. more restricted age-groups. A further limitation of the current study is its retrospective nature, relying on the diagnoses made by each attending physician at the time of the EDX study.

5. Conclusion

With age, the clinical picture of patients with neurological symptoms is often clouded by the normal consequences of aging, comorbidities, inactivity and adverse effects of drugs. Even though challenging to perform and interpret, electrodiagnostic evaluation is of great value in the very elderly patient group and is probably under-used. There is a lack of sufficient data regarding e.g. reference values and methodology in this growing part of the population and methods such as e-norms could play an important role in this context.

Acknowledgements

The authors are grateful to the technicians and physicians at the Department of Clinical Neurophysiology, Uppsala University Hospital.

Funding

This work was supported by ALF funding to Clinical Neurophysiology.

Conflict of interest statement

None of the authors have potential conflicts of interest to be disclosed.

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