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Research paper

Value of terminal latency index and sensory electrophysiology in idiopathic and diabetic chronic inflammatory demyelinating polyradiculoneuropathy

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ABSTRACT

Objectives: To evaluate sensory electrophysiology, terminal latency index (TLI), and treatment response in idiopathic and diabetic chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).
Methods: We performed a retrospective review of 147 patients with CIDP who underwent electrodiagnostic evaluation (January 2000–December 2015). Eighty-nine patients fulfilled electrophysiological criteria described by the Ad hoc Subcommittee of the American Academy of Neurology and Albers et al. Fifty-eight patients were divided into idiopathic (N = 40) and diabetic (N = 18) groups. These groups were compared for age, sex, cerebrospinal fluid protein, response to treatment, sensory response abnormalities, and TLI measurements using chi-square tests for binary and categorical variables and using t-tests and mixed-effects models for continuous variables.
Results: The difference in abnormal rates of sensory responses was significant for the sural nerve, with the idiopathic group having a lower rate than the diabetic group (80% vs. 100%, $p < 0.001$). No group differences in the TLI measurements were significant.
Conclusions: Sural sensory responses may have some value in differentiating idiopathic CIDP from diabetic CIDP. Larger prospective studies are needed to confirm our findings.
Significance: Our study suggests that abnormal sural sensory potentials may have some significance in differentiating idiopathic CIDP from diabetic CIDP.

1. Introduction

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an immune-mediated neuropathy. The history of CIDP dates to 1958 when it was first described by Austin (1958). Its clinical, electrophysiological, and pathological features were delineated in 1975 (Dyck et al., 1975). Clinically, CIDP predominantly presents with symmetric motor weakness affecting both proximal and distal muscles of both upper and lower extremities with absent and reduced deep tendon reflexes (Ramchandren and Lewis, 2009). Large myelinated fibers are more affected than small unmyelinated fibers (Ramchandren and Lewis, 2009). Electrodiagnostic studies show evidence of segmental demyelination such as conduction block, temporal dispersion of the compound muscle action potential on proximal stimulation, prolonged distal motor latencies, prolonged duration of the distal compound muscle action potential, and prolonged F wave and H reflex latencies (Ramchandren and Lewis, 2009).

The relationship between CIDP and diabetes is controversial (Jann et al, 2009; Ramchandren and Lewis, 2009; Stewart et al., 1996). Conduction velocity slowing can be seen in patients with diabetes, which is an important demyelinating criterion for CIDP (Miyasaki et al., 1999). Patients with diabetes can also have an elevated level of cerebrospinal fluid (CSF) protein (Miyasaki et al., 1999). CIDP should be suspected in patients with diabetes who have a rapidly progressive course of disease with both proximal and distal weakness and very high CSF protein, i.e., >150 mg/dl (Ramchandren and Lewis, 2009).

A low value of terminal latency index (TLI) has been described as a useful electrophysiological marker for CIDP associated with myelin-associated glycoprotein (MAG) antibody (Kaku et al., 1994). The usefulness of sensory nerve conduction studies has been demonstrated in demyelinating and axonal peripheral

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neuropathies (Bromberg and Albers, 1993; Rajabally and Narasimhan, 2007). This retrospective study aimed to evaluate the value of sensory electrophysiology and TLI to differentiate idiopathic CIDP (I-CIDP) from CIDP associated with diabetes mellitus (DM-CIDP).

2. Methods

2.1. Patient selection

We performed a retrospective chart review of patients with the diagnosis of CIDP (n = 147) who underwent electrodiagnostic evaluation at Henry Ford Health System between January 2000 and December 2015. This study was approved by the hospital's institutional review board. Patients (n = 89) who fulfilled the electrophysiological criteria described by the Ad hoc Subcommittee of the American Academy of Neurology and Albers et al. were included in the study. We excluded patients with acute inflammatory demyelinating neuropathy, hereditary sensorimotor neuropathy, vasculitis, and polyneuropathy with paraproteinemia (n = 31). Fifty-eight patients were included in the study and divided into I-CIDP (n = 40) and DM-CIDP (n = 18) groups.

Patients' age at the time of diagnosis, gender, and clinical features were recorded. Data of initial electrophysiological studies, diagnostic evaluation including CSF analysis, and treatment were collected.

2.2. Electrophysiological assessment

The sensory nerve action potential (SNAP) amplitudes of the two groups, I-CIDP (n = 40) and DM-CIDP (n = 18), were reviewed. Patients in both groups had undergone assessment of at least one in each of sural, radial, median, and ulnar nerve. We compared the SNAP amplitude of the I-CIDP group with that of the DM-CIDP group. Absence of SNAP amplitudes was recorded as undetectable, while reduced SNAP amplitudes were recorded as abnormal. Because of the poor reliability of sensory distal latency and velocity abnormalities (Kimura et al.,1988), only SNAP amplitude was utilized.

Motor nerve conduction studies of the median, ulnar, fibular, and tibial nerves were performed using the surface stimulating and recording technique, with skin temperature maintained above 32 °C according to the standards of the American Association of Neuromuscular and Electrodiagnostic Medicine (2004). Median, ulnar, fibular, and tibial motor amplitudes were measured as a baseline to peak for the compound muscle action potentials and from the positive to the negative peak for sural, radial, median, and ulnar SNAPs.

TLI was calculated for median, ulnar, fibular, and tibial nerves that could be measured. One person, blinded to the study hypothesis, measured all TLIs. TLI was calculated as distal conduction distance (mm)/conduction velocity (m/s) × distal motor latency (ms) (Bromberg and Albers, 1993; Rajabally and Narasimhan, 2007). Distal conduction distance (distance between the recording and the stimulating electrode at the most distal site) was 60 mm for median and ulnar nerves, 80 mm for the fibular nerve while recorded from extensor digitorum brevis, and 85 mm for the tibial nerve.

2.3. Statistical analysis

The two groups were compared for age, sex, response to treatment, and available CSF protein measurements using chi-square tests for binary and categorical variables and using t-tests for continuous variables. For TLI measurements, both left- and right-sided responses were included, and the two groups were compared using mixed-effects modeling. For these models, group and side were considered as fixed effects and the patient was considered as a random effect. The undetectable TLI measurements were defined as a value of 0 and included in all analyses.

Additionally, the number and percentage of SNAP amplitudes with abnormal results for each group were computed. Rao-Scott chi-square tests were performed to compare the percent of abnormal results between the two groups. This method takes into account multiple measurements (i.e., right and left) on the same patient and does not consider the right and left sides as independent measurements. If this test did not converge (i.e., zero cells), the data were smoothed by adding a case that was given a weight substantially less than the weights of the observed data when computing the chi-square test. The data gathered were compiled into Microsoft Excel (Microsoft Inc., Redmond, WA). SAS 9.4 (SAS Institute Inc., Cary, NC) was used to perform statistical analysis. All testing was done at the alpha = 0.05 level.

3. Results

Table 1 lists descriptive statistics and group comparisons. The differences between the two groups for age and sex were not significant. The differences in response to treatment and CSF

Table 1
Comparison of I-CIDP and DM-CIDP groups.

Variable	Response	Idiopathic (N = 40)	DM (N = 18)	p-value
Age	Mean ± S.D.	54.1 ± 18.8	55.6 ± 12.7	0.767
Sex	F	20 (50%)	6 (33%)	0.238
	M	20 (50%)	12 (67%)	
All Rx responses	No follow-up	8 (20%)	7 (39%)	0.051
	Monotherapy	18 (45%)	5 (28%)	
	Combination	14 (35%)	4 (22%)	
	No tx offered	0 (0%)	2 (11%)	
Rx response for patients with follow-up	Monotherapy	19 (59%)	5 (45%)	0.092
	Combination	12 (38%)	4 (36%)	
	No tx offered	0 (0%)	2 (18%)	
	Refractory to tx	1 (3%)	0 (0%)	
CSF protein	Mean ± S.D.	162.12 ± 106.26 (N = 26)	131.06 ± 75.97 (N = 14)	0.340
Median TLI	Mean ± S.E.[1]	0.283 ± 0.018	0.298 ± 0.278	0.639
Ulnar TLI	Mean ± S.E.[1]	0406 ± 0.026	0.452 ± 0.037	0.290
Fibular TLI	Mean ± S.E.[1]	0.237 ± 0.033	0.199 ± 0.049	0.524
Tibial TLI	Mean ± S.E.[1]	0.190 ± 0.031	0.206 ± 0.047	0.773

[1] Mean and standard error computed from mixed-effects model adjusted for side.

Table 2
Distribution of undetectable motor responses.

Nerve	Side	Idiopathic No. of patients (%)	DM No. of patients (%)
Median	Right	0	0
	Left	0	0
	Both	0	0
Ulnar	Right	1 (2.5%)	0
	Left	1 (2.5%)	0
	Both	1 (2.5%)	0
Fibular	Right	15 (37.5%)	9 (50%)
	Left	9 (22.5%)	9 (50%)
	Both	8 (20%)	7 (38.9%)
Tibial	Right	16 (40%)	7 (38.9%)
	Left	9 (22.5%)	8 (44.4%)
	Both	9 (22.5%)	6 (33.3%)

Table 3
Comparison of the rate of abnormal sensory responses in the nerves tested.

Nerve	Idiopathic % (No. abnormal/total no. tested)	DM % (No. abnormal/total no. tested)	p-value
Sural	80% (51/64)	100% (29/29)	<0.001
Radial	85% (46/54)	81% (22/27)	0.702
Median	100% (65/65)	100% (26/26)	NA
Ulnar	94% (61/65)	90% (27/30)	0.551

protein were also not significant. Differences between the two groups for TLI measurements were not significant.

There were several instances where responses could not be recorded for the fibular and tibial nerves. Table 2 shows the distribution of the number of undetectable responses for each nerve by the group. For example, in the I-CIDP group, undetectable responses were recorded for the fibular nerve on the right side in 15 patients, on the left side in 9 patients, and on both right and left sides in 8 patients.

The difference in abnormal SNAP rates was significant for the sural nerve, with the I-CIDP group having a lower rate than the DM-CIDP group (80% vs. 100%, $p < 0.001$, Table 3). Using the information given in Table 3, the sensitivity and specificity of an abnormal sural SNAP for DM-CIDP vs. I-CIDP were 100% and 20%. No differences were detected for the ulnar and radial nerves. For the medial nerves, all results were abnormal.

We found no statistically significant differences in the treatment responses of the two groups ($p = 0.092$). In the I-CIDP group, 18/32 (56%) received monotherapy (IVIG = 13, steroids = 4, PLEX = 1), 14/32 (43%) received combination therapy (IVIG + steroids = 8, steroid + CellCept = 1, steroid + methotrexate 1, steroid + PLEX = 2, steroid + IVIG + cyclosporine = 1), and 8/40 (20%) patients were lost to follow-up after initial diagnosis was established. In the DM-CIDP group, monotherapy (IVIG = 3, PLEX = 1, steroid = 1) was offered to 5/9 (55%) patients, 4/9 (44%) patients were treated with combination therapy (IVIG + steroid + Imuran = 1, IVIG + steroid + PLEX = 1, and steroid + CellCept, IVIG + steroid = 1), and 2 received no treatment. In this group, 7/18 (38%) patients were lost to follow-up.

4. Discussion

Sensory nerve conduction abnormalities are not included in any electrodiagnostic demyelinating criteria for CIDP except the Ad hoc Subcommittee of the American Academy of Neurology criteria, which recognizes sensory conduction velocity reduction below 80% of the lower limit of normal as supportive of CIDP (Gorson et al., 2000). Abnormal sural and normal radial pattern was supportive of CIDP in patients without diabetes (n = 20) in the correct clinical setting (Rajabally and Narasimhan, 2007); these investigators excluded patients with diabetes in view of mixed demyelinating and axonal features reported in this subgroup (Rajabally and Narasimhan, 2007; Gorson et al., 2000). In our evaluation of the sensory electrophysiological differences between I-CIDP and DM-CIDP, we found that abnormal sural SNAP rates were significantly higher in DM-CIDP than in I-CIDP. Others have reported more abnormal nerve conduction studies, with lower sural SNAPs recorded in DM-CIDP subjects (Dunnigan et al., 2014). Our study showed an equal number of abnormal median SNAP response rates in I-CIDP and DM-CIDP. A pattern of abnormal median and normal sural responses has been reported in patients with acute inflammatory demyelinating polyradiculoneuropathy (AIDP), CIDP, and diabetic polyneuropathy, and this was supportive of a diagnosis of primary demyelinating polyneuropathy (Bromberg and Albers, 1993). Abnormal median and abnormal sural patterns are more common in long-standing polyneuropathies such as AIDP, CIDP, and diabetic peripheral neuropathy (Bromberg and Albers, 1993).

Our study assessed TLI, as others have reported significantly lower TLI values in CIDP associated with immunoglobulin M paraproteinemia and anti-MAG antibody (MAG-CIDP) (Kaku et al., 1994; Cocito et al., 2001; Maisonobe et al., 1996; Trojaborg et al., 1995). We found that TLI has no value in differentiating I-CIDP from DM-CIDP. One explanation for this finding is that the CIDP pattern of demyelination in diabetes may be diffuse, which could be due to blood–nerve barrier disruption as well as hypoxia in the endoneural space component (Kanda, 2013).

The high percentages of absent fibular and tibial motor responses in the DM-CIDP group favor the length-dependent neuropathy pattern commonly observed in diabetic polyneuropathies.

Whether the demyelination of DM-CIDP is due to diabetes or CIDP remains unknown. The odds of the occurrence of CIDP were 11 times higher in subjects with diabetes than in those without diabetes (Ellie et al., 1996). Patients with DM-CIDP have shown similar clinical features but more axonal loss and less improvement with treatment than those with I-CIDP (Gorson et al., 2000). Ongoing research assesses whether diabetes and CIDP may share a causative contributing factor such as neurotoxic sphingolipids (Dohrn et al., 2015).

5. Conclusion

To the best of our knowledge, no previous study has reported sensory electrophysiological differences between the I-CIDP and DM-CIDP groups. Our study suggests that abnormal sural sensory potentials may have some significance in differentiating I-CIDP from DM-CIDP with 100% sensitivity but only 20% specificity. As our study was limited by small sample size and its retrospective design, a larger prospective study may help delineate this distinction.

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.

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