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 predominately 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). Conductive 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 neuropathies.
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 TLI. 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

| Variable                          | Response                  | Idiopathic         | DM                | p-value |
|----------------------------------|---------------------------|--------------------|-------------------|---------|
| Age                              | Mean ± S.D.               | 54.1 ± 18.8        | 55.6 ± 12.7       | 0.767   |
| Sex                              | F                         | 20 (50%)           | 6 (33%)           | 0.238   |
| 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    | 131.06 ± 75.97    | 0.340   |
| Median TLI                       | Mean ± S.E.\(^1\)         | 0.283 ± 0.018      | 0.298 ± 0.027     | 0.639   |
| Ulnar TLI                        | Mean ± S.E.\(^1\)         | 0.406 ± 0.026      | 0.452 ± 0.037     | 0.290   |
| Fibular TLI                      | Mean ± S.E.\(^1\)         | 0.527 ± 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.
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; 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).

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 investiga-

| 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 |
| Tibial | Right | 15 (37.5%) | 9 (50%) |
| | Both | 8 (20%) | 7 (38.9%) |
| | Left | 8 (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 |
| Tibial | 100% (65/65) | 100% (26/26) | NA |
| Ulnar | 94% (61/65) | 90% (27/30) | 0.551 |

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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