Electrophysiological assessment of Chronic Inflammatory Demyelinating Peripheral Polyradiculoneuropathy (CIDP) in Patients with Diabetes Mellitus

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Summary:

Background: Peripheral neuropathy is a common complication of diabetes mellitus. However, patients with diabetes are more vulnerable to develop chronic inflammatory demyelinating peripheral polyradiculoneuropathy (CIDP) which is an acquired immune-mediated disorder.

Objectives: Assess the role of electrophysiological study (NCS and EMG) in the diagnosis of CIDP in diabetic patients and differentiate between diabetic CIDP and diabetic peripheral polyneuropathy (PNP).

Subjects and methods: Three groups of subjects of either sex involved in this study; forty-six (46) patients with diabetic CIDP, forty-six (46) patients with diabetic peripheral polyneuropathy and forty-six (46) control subjects. Sensory and motor nerve conduction study (NCS) and electromyography (EMG) of both upper and lower limbs were performed for each subject. This study was conducted at the unit of neurophysiology in Neuroscience Hospital and Al-Yarmouk Teaching Hospital, in a period from November 2012 to May 2013.

Results: Prolonged distal sensory latency distal (DSL), decreased sensory nerve action potential (SNAP) amplitude and slowing of sensory nerve conduction velocity (SNCV). Sensory NCS was significantly changed in both groups. While the presence of abnormal median-normal sural (AMNS) and abnormal radial—normal sural (ARNS) pattern of sensory involvement were detected only in diabetic CIDP patients. Concerning motor nerve conduction study, prolonged distal motor latency (DML), slowing of conduction velocity and prolonged mean F-wave latency were detected in both patients group, but these abnormalities were more in diabetic CIDP patients. Conduction block CB% and abnormal temporal dispersion TD% were observed only in diabetic patients with CIDP. Whereas needle EMG of diabetic CIDP revealed that there are mixed axonal and demyelinating neuropathy.

Conclusion: This study conclude that the abnormal sensory and motor NCS in the lower limbs were higher when compared with that of upper limbs. However, the changes in motor parameters are more in diabetic patients with CIDP than that of diabetic PNP. In addition, the proximal nerve segments are more vulnerable to be affected by demyelinating process rather than the other segments. Moreover, most of diabetic patients with CIDP have mixed axonal and demyelinating changes in respect to those who had only demyelinating neuropathy.

Keywords: CIDP (chronic inflammatory demyelinating peripheral polyradiculoneuropathy), DM (diabetes mellitus).

Introduction:

Peripheral neuropathy is a non-traumatic generalized disorder of peripheral nerves, Diabetic neuropathy (DN) has been defined as presence of sings and/or symptoms of peripheral nerve dysfunction in diabetic after exclusion of other causes (1).

Chronic inflammatory demyelinating peripheral polyradiculoneuropathy (CIDP) is an acquired neuropathy that commonly has heterogeneous, symmetric, proximal, distal limb weakness and distal sensory loss that progresses over more than 2 CIDP is one of the most common chronic autoimmune neuropathy. It is treatable condition for relatively long periods of time (months to years) in the majority of patients (3). Although CIDP can occur in patients with diabetes, alcoholism, uremia, HIV infection, cancer or an autoimmune disease, the other types of neuropathies that are more commonly encountered in these conditions should be excluded before concluding that the primary neuropathy is CIDP (4). CIDP can affect all ages but is most commonly presents in adults with a peak incidence at about 40–60 years; there is a slightly increased prevalence in men. It is thought that the disease is more likely to be progressive in the older age group with relapsing-remitting fashion in younger patients (5). The electrophysiological evaluation of patients with peripheral neuropathy provides data that are critical to both diagnosis and treatment. Analysis of the wave forms of evoked

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sensory and motor action potentials provide information that permit determination of presence or absence of neuropathy, and provide information concerning severity, pathology and prognosis. However, electrodiagnostic techniques are extremely valuable in helping to define the underlying pathophysiologic process; whether axonal or demyelinating, distribution (focal, multifocal or generalized) and the functional subtypes of the nerves involved (motor, sensory, large-fiber sensory, small-fiber sensory or autonomic)(6). This study is designed to assess the role of electrophysiological study (NCS and EMG) in the diagnosis of CIDP in diabetic patients and to differentiate between diabetic CIDP which is treatable condition and diabetic peripheral polyneuropathy (PNP).

Subjects and methods:
Three groups of subjects of either sex involved in this study; forty one control group (21 males and 20 females) with a mean age of (50.09±13.17 years), forty one patients with diabetic CIDP (22 males and 19 females) with a mean age of (50.61±15.04 years) and forty six patients with diabetic peripheral polyneuropathy (25 males and 21 females) with a mean age of (54.91±14.54 years).

Electrophysiological tests of both upper and lower limbs were performed which include: sensory nerve conducting study (SNCS) for median, ulnar, radial, and sural nerves, in which distal sensory latency, sensory nerve action potential (SNAP) amplitude and sensory nerve conduction velocity (SNCV) are performed. However, motor nerve conducting study (MNCS) For median, ulnar, fibular (Common peroneal), and tibial nerves, which includes measurement of distal motor latency (DML), compound muscle action potential (CMAP) amplitude, motor nerve conduction velocity (MNCV), mean F-wave latency, terminal latency index (TLI), temporal dispersion (TD) and conduction block (CB)%. In addition, needle EMG for proximal and distal muscles which include: biceps, and 1st dorsal interosseous muscles for upper limb and vastus medialis, tibialis anterior and Extensor digitorum brevis for lower limb, in which insertional activity, spontaneous activity, motor unit action potential (duration, amplitude and polyphasia%) and recruitment pattern are considered and assessed.

Statistical analysis: Statistical Package for Social Sciences, version 16 was used. Numeric variables were presented as mean ±SD (standard deviation). Nominal variables were presented as frequency and percent. Independent samples t-test, one way ANOVA, post hoc LSD test, chi-square test were performed. The level of P<0.05 was considered to be significant.

Results:
The results of this study revealed that sensory NCS was significantly changed in both diabetic patients when compared with healthy control subjects in the form of prolonged distal sensory latency, decreased SNAP amplitude and slowing of SNCV. However, the differences are not statistically significant (P>0.05) between diabetic CIDP and those of diabetic PNP except the distal sensory latency and sensory conduction velocity (CV) of ulnar nerve and in all sensory parameters of sural nerve, in which the differences are significant (P<0.05). In addition, the percentage of presence of abnormal median-normal sural and abnormal radial – normal sural pattern of sensory involvement was (21.95%) and (12.19%) respectively, which reflect the demyelinating neuropathy, while such pattern was not detected in diabetic patients with PNP. Concerning motor nerve conduction study, prolonged DML, slowing of conduction velocity and prolonged mean F-wave latency were detected in both groups of patients when compared with those of healthy control subjects. However, the differences were also statistically significant within the patients groups (P<0.05) except in the terminal latency index (TLI) of median and ulnar nerve and CMAP amplitude of median, ulnar and common peroneal nerves. Moreover, in diabetic patients with CIDP, (CB) and abnormal (TD%) were observed in 38.18% and 26.81% of the total examined nerves respectively. However, the higher percentage of CB% was detected in the ulnar nerve when compared to the lower percentage of the tibial nerve in which higher percentage of abnormal TD% was recorded. As demonstrated in table (1), the higher percentage of CB% in the intermediate segment involves right ulnar nerve (73.17%), while, the higher percentage of proximal segment block involves right common peroneal nerve (8.57%).

Table (1): Distribution of conduction block in diabetic CIDP patients.

<table>
<thead>
<tr>
<th>Number of nerves</th>
<th>Nerve</th>
<th>Intermediate segment</th>
<th>Proximal segment</th>
</tr>
</thead>
<tbody>
<tr>
<td>41</td>
<td>Right median</td>
<td>22 (53.65 %)</td>
<td>1 (2.43 %)</td>
</tr>
<tr>
<td>41</td>
<td>Left median</td>
<td>13 (31.70 %)</td>
<td>2 (4.87 %)</td>
</tr>
<tr>
<td>41</td>
<td>Right ulnar</td>
<td>30 (73.17 %)</td>
<td>2 (4.87 %)</td>
</tr>
<tr>
<td>35</td>
<td>Right common peroneal</td>
<td>6 (17.14 %)</td>
<td>3 (8.57 %)</td>
</tr>
<tr>
<td>33</td>
<td>Left common peroneal</td>
<td>11 (33.33 %)</td>
<td>2 (6.06 %)</td>
</tr>
<tr>
<td>29</td>
<td>Right tibial</td>
<td>2 (6.89 %)</td>
<td>1 (3.44 %)</td>
</tr>
</tbody>
</table>

Total= 220 84 (38.18%) 11 (5.0%)

Analysis of involvement of various nerve segments whether terminal (distal), main nerve trunk (intermediate) and proximal segment of different nerves was considered in this study to detect which segment is affected by demyelination more than other of the peripheral nerve. However, this analysis was performed by studying the DML, MNCV and F-wave latency as shown in table (2). A noticed in this table that the lower percentage of abnormality involves distal nerve segment; by prolongation of DML (83.63%), while the higher percentage of abnormality is in the proximal nerve segment; by prolongation of F wave latency (97.72%).
Table (2): Involvement of different nerve segments in diabetic CIDP.

<table>
<thead>
<tr>
<th>Number of nerves</th>
<th>Nerve</th>
<th>Distal part of the nerve (DML)*</th>
<th>Main nerve trunk (MNCV)**</th>
<th>Proximal part of the nerve (F-wave latency)</th>
</tr>
</thead>
<tbody>
<tr>
<td>41</td>
<td>Right median</td>
<td>36 (87.80 %)</td>
<td>39 (95.12 %)</td>
<td>41 (100%)</td>
</tr>
<tr>
<td>41</td>
<td>Left median</td>
<td>35 (85.36 %)</td>
<td>36 (87.80%)</td>
<td>40 (97.56%)</td>
</tr>
<tr>
<td>41</td>
<td>Right ulnar</td>
<td>29 (70.73%)</td>
<td>39 (95.12%)</td>
<td>41 (100%)</td>
</tr>
<tr>
<td>35</td>
<td>Right common peroneal</td>
<td>28 (80 %)</td>
<td>27 (77.14%)</td>
<td>32 (91.42%)</td>
</tr>
<tr>
<td>33</td>
<td>Left common peroneal</td>
<td>28 (84.84%)</td>
<td>27 (81.81%)</td>
<td>32 (94.94%)</td>
</tr>
<tr>
<td>29</td>
<td>Right tibial</td>
<td>28 (96.55%)</td>
<td>29 (100%)</td>
<td>29 (100%)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>184 (83.63 %)</td>
<td>197 (89.54%)</td>
<td>215 (97.72 %)</td>
</tr>
</tbody>
</table>

Median and ulnar nerve terminal latency index was considered to compare the distal segment (distal to the wrist) with intermediate segment (wrist to elbow). It is calculated according to the formula developed by Shahani et al., 1979. As shown in table (3), there are 25 out of 123 nerves developed abnormal TLI (20.32%), in which the higher abnormal percentage involved the right median nerve (31.70%).

Table (3): Distribution of abnormal terminal latency index (TLI) in diabetic CIDP.

<table>
<thead>
<tr>
<th>No. of nerve</th>
<th>Nerves</th>
<th>Abnormal TLI</th>
</tr>
</thead>
<tbody>
<tr>
<td>41</td>
<td>Right median</td>
<td>13 (31.70%)</td>
</tr>
<tr>
<td>41</td>
<td>Left median</td>
<td>8 (19.51%)</td>
</tr>
<tr>
<td>41</td>
<td>Right ulnar</td>
<td>4 (9.75%)</td>
</tr>
<tr>
<td>Total=123</td>
<td></td>
<td>25 (20.32%)</td>
</tr>
</tbody>
</table>

In this study, sensory motor discrepancy was present in only 5 patients out of total 41 diabetic CIDP (12.19 %), while, there are 6 nerves out of total 220 examined nerves (2.72%) with sensory-motor discrepancy. Concerning EMG findings, there are nearly similar between both patients groups in form of increased duration, amplitude and polyphasia% of motor unit action potential (MUAP). While, percentage of spontaneous activity in diabetic PNP patients is higher than that of diabetic CIDP, specifically at distal muscles more than proximal and in lower limbs more than upper limbs. In contrast, diabetic CIDP patients have higher percentage of decreased interference pattern than diabetic PNP patients.

Discussion:
The prolonged distal sensory and/or motor latency and slowing of nerve conduction velocities are seen when the largest and fastest conducting fibers are conducting slowly due to demyelination. Whereas, reducing amplitude of the sensory nerve action potential (SNAP) or compound muscle action potential (CMAP) reflects the amount of axonal degeneration and indicates drop in some of the sensory fibers in the nerve since the potential represents the summed potential of all active fibers under the recording electrode (7). The main reason for the difficulty in discriminating primary demyelination from primary axonal loss is the conduction slowing, in addition to involvement of myelin or Schwann cells in demyelinating neuropathy, can also be caused by secondary loss of fast conducting, large-diameter fibres in axonal neuropathy. Moreover, SNAP or CMAP amplitude reduction in addition to axonal degeneration and loss of fibres in fibrous neuropathy can also be due to temporal dispersion or secondary axonal degeneration in demyelinating neuropathy (8).

The pattern of an abnormal median-normal sural (AMNS) sensory response is associated with acute and chronic inflammatory demyelinating polyradiculoneuropathy (AIDP and CIDP) (9). Another type of sensory involvement patterns associated with demyelinating peripheral neuropathy, is an abnormal radial-normal sural (ARNS), which reflect the involvement of more proximal sensory nerve in CIDP, as opposed to dying-back degeneration in a length-dependent manner in axonopathies (10).

The significant differences in motor parameters (distal motor latency, conduction velocity, F-wave latency, conduction block and temporal dispersion) between patients with diabetic PNP and those with diabetic CIDP are in agreement with those reported by Fuglsang-Frederiksen, 2011(11). Although these motor parameter are affected in both neuropathic groups but the abnormalities in diabetic CIDP are within demyelinating range.

TLI was used to confirm the electrophysiological classification. Patients with the distal pattern of demyelination have significantly smaller TLI, so when the distal latencies are prolonged to a greater degree than proximal latencies, a small TLI describes this relationship (disproportionately prolonged distal latencies were consistent with a smaller terminal latency index). This means, when TLI is normal, not necessary indicate normal NCS, but when it is abnormal, it indicates slowing at the distal nerve segment (12). The percentage of abnormal TLI in diabetic CIDP patients are (20.32%) of the examined nerves, these findings are lower than that reported by Stewart, 1996 (13) and Sharma, 2002 (14) who reported
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The percentage of prolonged DML was (83.63%) of the examined nerves which is similar to that reported by Barohn, et al., 1989 (15) but higher than that reported by Sharma, 2002 (14), who reported 46.3%. This prolongation of the DML is believed to be due to demyelination of the motor axons distally.

To detect proximal nerve involvement, mean F-wave latencies were recorded. F-wave was absent or prolonged latency in 97.72% of the examined nerves, these findings are similar to that reported by other study (16). Whereas, the affection of main nerve trunk indicated by the slowing of motor conduction velocity (89.54%) of the examined nerves is higher than that detected by Sharma, 2002 (14) who reported (59.5%). In this study, the distal segment is the least affected by demyelination as compared with the middle and proximal segment, this finding could be explained by the fact that, thick myelinated fibers are more liable to be affected by this disorder than thin myelinated fibers (17). These results are in complete agreement with other study (18) that conclude, in segmental demyelination, the process of impulse conduction along the nerve is transformed from saltatory conduction to a continuous smooth type of conduction similar to that in type C fibers. So the terminal segment may be particularly less susceptible because of its distance from the cell body. The proximal segments are more vulnerable to demyelination due to increased permeability of the spinal root blood-nerve barrier owing to the lack of well-formed perineurium (19).

Abnormal temporal dispersion (TD%) in diabetic patients with CIDP can be explained by multifocal demyelination of individual axons, resulting in some fibers having little or no demyelination and other fibers having multiple areas of demyelination, so there is marked difference in the range of conduction velocity and block of conduction in some fibers (18).

Duration of the CMAP is generally longer with more proximal stimulation because the range of conduction time among the individual fibers increases with longer distance between stimulation and recording sites, the increased range of conduction velocities results in the initial component of the CMAP (representing the fastest fibers) being greatly separated from the trailing portion of the CMAP (representing the slowest conduction in the most demyelinated fibers) (20).

A partial conduction block is the abnormality in which only a few fibers are affected. The nerve can still be stimulated above the lesion, but since only a few fibers conduct, a low amplitude response is obtained (18). In the present research there were multiple motor partial CB% predominantly located in the forearm. Among the arm nerves, most abnormalities are found in the right ulnar nerve (73.17%). While the lowest percentage of CB is in the tibial nerve (6.89%), however, the total percentage of CB is (38.18%) of the examined nerves. Whereas, there were only one out of 41 patients with diabetic CIDP without CB at any nerve (2.4%), these results are in harmony with that reported by Stewart, 1996 (13) and Sharma, 2002 (14).

A sensory -motor discrepancy was noted in individual nerves, in which motor study was abnormal while sensory study was normal. Several possibilities exist that explain the sensory discrepancy as well as motor sensory discrepancy. The size of the myelinated fiber and the amount of myelin were somehow protective in acquired demyelinating neuropathies.

In the present study, sensory -motor discrepancy was detected in 12.19% of diabetic CIDP patients. This finding is less than that reported by other author (20) who conducted on idiopathic CIDP. This is because of overlapping of axonal neuropathy on demyelinating change in patients with diabetic CIDP in which the sensory nerves might be already affected by axonal degeneration rather than demyelination. So the suspicion of sensory -motor discrepancy has little value in diabetic CIDP. Since that this study was conducted with diabetic CIDP not with idiopathic CIDP, no typical EMG finding of demyelinating neuropathy was reported. This is due to the presence of mixed pathological process (axonal and demyelinating neuropathies). In this study, needle EMG abnormalities in distal leg muscles precede those abnormalities in distal upper extremity muscles of both patients group. However, diabetic CIDP patients had a features of axon loss on needle EMG study especially in the lower limb muscles, this finding is similar with that of other study (14).

Conclusion:
This study concluded that most of diabetic patients with CIDP have mixed axonal and demyelinating changes in respect to those who had only demyelinating neuropathy. In diabetic CIDP patients, proximal (radicular) nerve segments were more vulnerable to be affected by demyelination than other segments (distal or intermediate). Moreover, higher percentage of CB% is detected in the ulnar motor nerve, when compared to the tibial motor nerve which had the higher percentage of abnormal TD%. However, AMNS and/or ARNS pattern of sensory nerve involvement and sensory- motor discrepancy which reflect demyelination were reported in lower percentage in comparison with other disorders of pure demyelinating neuropathy.

Authors’ Contributors:
Marwa Saheb Suhail: MSc. Student who perform the study project including selection of the sample, examination and doing concerned tests in addition to writing the thesis. Najeeb Hassan Mohammed: Supervisor who design the protocol of the study and support in writing the thesis. Safaa Hussien Ali: Supervisor who help student in performing the electrophysiological tests and data collection.

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