Electrophysiological changes in sensorimotor nerves in diabetes mellitus & usefulness of nerve conduction studies for early diagnosis of diabetic neuropathy

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Abstract

Background: Diabetes Mellitus (DM) a metabolic disorder is the most common cause of peripheral neuropathy. Nerve conduction studies (NCS) are commonly employed to detect the neuropathy. The present study was undertaken to find out the utility of NCS as an early indicator of neuropathy in diabetic patients.

Materials & methods: Study was carried out in 50 diagnosed DM patients attending OPD in Medicine, Civil Hospital, Ahmedabad. Diabetic subjects were selected having FBS >110 mg/dL with duration of DM > 5 years. Their HbA1c levels were measured for glycaemic control. Diabetic patients with good glycaemic control were grouped in group A & that with poor glycaemic control in group B. 25 age matched non-diabetic & healthy subjects were selected for control group C. NCS was performed at Institute of Spine, Civil Hospital Campus, Ahmedabad. Nerve conduction parameters like compound muscle action potential (CMAP), sensory nerve action potential (SNAP), nerve conduction velocity (NCV) & distal latency (DL) were studied.

Results: In our study there is increase in DL of peroneal, sural; median & ulnar sensory nerves in group B subjects. NCV of sensorimotor nerves is significantly decreased in group B subjects. SNAP of all nerves is reduced in group A & B. CMAP is reduced significantly in all nerves in group B.

Conclusion: As DM progress further, it increases risk of neuronal involvement which can be accelerated by poor glycaemic control. Our result indicates demyelinating type of neuropathy with some changes of axonopathy. Therefore NCS is done for early detection of neuropathy in DM patients.

Keywords: Diabetes Mellitus (DM), hyperglycaemia, Nerve conduction studies (NCS), Diabetic neuropathy (DN)

1. Introduction

DM is an endocrine disorder that is characterized by defect in insulin secretion &/or insulin action resulting in hyperglycaemia. Diabetic neuropathies (DN) are neuropathic disorders that are thought to result from diabetic microvascular injury involving small blood vessels that supply nerves (vasa nervosum) in addition to macrovascular conditions that can culminate in DN cause significant morbidity & mortality¹,².
Symptoms of DN include a sensation of pain, numbness, tingling, burning or prickling that begins in the feet. In later stages of DN, the hands can be affected as well. In some cases of DN, the abnormal sensations can extend to the arms, legs, & trunk (truncal neuropathy). There are three general types of diabetic neuropathy that affect the nerves of the nervous system. They include sensory neuropathy, also called peripheral neuropathy (PN), in which the nerves that carry messages about sensation to the brain are damaged. Motor neuropathy occurs when the nerves that carry messages about movement from the brain to the muscles are damaged. Autonomic neuropathy occurs when the nerves that control involuntary activities of the body, such as digestion & sweating, are affected.

Evaluation of neuropathy is undertaken by electrophysiological measurements. Electrophysiologic assessments are sensitive, specific & reproducible measures of the presence & severity of peripheral neuropathy & they define quantitative nerve dysfunction. NCS are used for the assessment of DN not only to evaluate the degree of abnormality but also to document serial changes in the clinical course of the disease.

The present study was designed to observe the effects of long duration of DM on electrophysiological study of peripheral nerves that can help for the better management of the patients suffering from DN.

2. Methods & Materials

This study was carried out at Civil Hospital, Ahmedabad in DM patients attending OPD of Medicine. 50 diabetic patients were selected on basis of following criteria: (1) DM patients with complains of tingling, numbness, burning & prickling sensations in the limbs, (2) FBS > 110 mg/dL, (3) History of DM for more than 5 years. Diabetic subjects having acute diabetic complications, pregnancy & other acute or chronic illness were excluded from the study. Their detailed family history & medical history was taken with physical & clinical examination. Fasting blood sample (FBS) was taken on the day of NCS test. Percentage of HbA1c was measured as a marker of glycaemic control. 25 age matched non-diabetic & healthy males were selected for control group.

The HbA1c levels were determined by the borate affinity assay. This method measures total glycosylated Hb, including HbA1c & Hb glycosylated at other sites & tends to demonstrate the least interference from the presence of Hb variants & derivatives.

22 subjects having good glycaemic control were grouped in Group A, 28 subjects with poor glycaemic control were grouped in Group B & 25 non-diabetic apparently healthy controls were included in the study in Group C.

Neurological parameters of median, ulnar, peroneal & sural nerves were measured by standard Nerve Conduction Velocity- Electromyography (NCS-EMG) equipment at Institute of Spine, Civil Hospital Campus.

Motor NCS are performed by electrical stimulation of a peripheral nerve & recording from a muscle supplied by this nerve. Sensory NCS are performed by electrical stimulation of a peripheral nerve & recording from a purely sensory portion of the nerve, such as on a finger. Neurological parameters studied were: nerve conduction velocity (NCV) expressed in meter/second (m/S), distal latency (DL) expressed in millisecond (ms), compound muscle action potential (CMAP).

For median motor NCS, the recording electrode is placed close to the motor point of abductor pollicis brevis & stimulating electrode at flexor carpi radialis near wrist joint. For median sensory NCS by orthodromic stimulation the recording electrode is placed 3 cm proximal to the distal wrist crease & stimulating electrodes are placed at the second or third digits. Ulnar motor NCS is performed by placing stimulating electrode at 3 cm proximal from wrist joint & recording electrode over abductor digiti minimi. Ulnar sensory NCS by orthodromic conduction is recorded by stimulating digital nerve at interphalangeal joint of the little finger & recording electrode 3 cm proximal from wrist joint along course of ulnar nerve. Peroneal NCS is performed by placing stimulating electrode at ankle, 2 cm distal to fibular neck & recording electrode over extensor digitorum brevis. For sural NCS by antidromic conduction recording electrode is placed between lateral malleolus & tendoachilles; stimulating electrode is placed 10-16 cm proximal to recording electrode, distal to lower border of gastrocnemius at the junction of middle & lower third of leg. The DL, NCV, SNAP & CMAP are recorded following stimulation.

2.1 Statistical Method

Data were summarized with unpaired ‘t’ test, p-value < 0.05 were considered as significant (S), < 0.001 as highly significant (HS) & > 0.05 as not significant (NS). Level of significance used was 95%. All parameters are expressed in Mean ± SD.
3. Results

In our present study 50 DM patients were selected with chief complains of paresthesia, tingling, numbness & burning sensations in limbs. All patients FBS & glycosylated Hb(HbA1c) was measured for their glycaemic status.

### Table 1: Glycaemic status of subjects

| Parameters    | Group A: DM with normal HbA1c (n=22) | Group B: DM with high HbA1c (n=28) | Group C: control group |
|---------------|--------------------------------------|------------------------------------|------------------------|
| HbA1c(%)      | 5.3±0.5                              | 7.2±1.3                            | 4.5±0.5                |
| FBS(mg/dL)    | 118.7±7.4                            | 143.3±12.6                         | 80.5±5.7               |

The table shows in group A HbA1c & FBS levels were lower than that of group B. The values are given in Mean ± SD (Table 1).

### Table 2: Conduction velocity of upper & lower limb nerves in group A, B & C.

| Conduction velocity(m/S) | Group A | Group B | Group C | p-value  |
|--------------------------|---------|---------|---------|----------|
|                          |         |         |         | Group A vs C | Group B vs C |
| Median motor             | 57.3±2.3| 49.3±1.6| 61.73±3.4| 0.09<sup>SS</sup> | 0.0012<sup>S</sup> |
| Ulnar motor              | 59.65±2.7| 52.23±2.4| 67.42±2.8| 0.02<sup>S</sup> | 0.002<sup>S</sup> |
| Peroneal nerve           | 43.45±3.2| 26.33±2.4| 50.6±2.7 | 0.02<sup>S</sup> | 0.0003<sup>SS</sup> |
| Sural nerve              | 48.35±2.4| 30.05±3.8| 53.32±3.3| 0.053<sup>SS</sup> | 0.0017<sup>S</sup> |
| Median sensory           | 51.67±3.2| 32.44±2.5| 58.54±3.8| 0.049<sup>S</sup> | 0.0012<sup>S</sup> |
| Ulnar sensory            | 55.4±2.6| 42.6±1.8| 63.5±3.3 | 0.01<sup>S</sup> | 0.0012<sup>S</sup> |

This table shows that the NCV is significantly decreased in group A(except in median motor & sural & B subjects in all nerves when compared with control group.(Table 2).

### Table 3: Distal latency in upper & lower limb nerves in group A, B & C.

| Distal latency(ms) | Group A | Group B | Group C | p-value  |
|--------------------|---------|---------|---------|----------|
|                    |         |         |         | Group A vs C | Group B vs C |
| Median motor       | 4.1±0.4 | 5.2±0.7 | 3.43±0.2| 0.1<sup>NS</sup> | 0.06<sup>NS</sup> |
| Ulnar motor        | 3.32±0.6| 3.85±0.3| 2.75±0.5| 0.55<sup>NS</sup> | 0.056<sup>NS</sup> |
| Peroneal nerve     | 4.86±0.3| 13.5±0.6| 4.35±0.4| 0.33<sup>NS</sup> | 0.0003<sup>SS</sup> |
| Sural nerve        | 2.67±0.3| 10.2±0.8| 2.04±0.3| 0.15<sup>NS</sup> | 0.0006<sup>SS</sup> |
| Median sensory     | 3.22±0.6| 4.13±0.6| 2.33±0.4| 0.2<sup>NS</sup> | 0.037<sup>S</sup> |
| Ulnar sensory      | 2.87±0.8| 3.73±0.7| 1.67±0.6| 0.07<sup>NS</sup> | 0.009<sup>S</sup> |

DL of peroneal, sural, median sensory & ulnar sensory nerves is significantly increased in group B subjects.(Table 3).

### Table 4: Compound muscle action potential (CMAP) of motor nerves:

| Motor amplitude (mV) | Group A | Group B | Group C | p-value  |
|---------------------|---------|---------|---------|----------|
|                     |         |         |         | Group A vs C | Group B vs C |
| Median motor        | 5.8±1.3 | 5.2±1.4 | 11.6±2  | 0.01<sup>S</sup> | 0.009<sup>S</sup> |
| Ulnar motor         | 10.4±1.7| 9.05±1.3| 13.7±1.8| 0.06<sup>SS</sup> | 0.02<sup>S</sup> |
| Peroneal nerve      | 5.3±0.9 | 4.32±0.7| 6.7±1.5 | 0.09<sup>SS</sup> | 0.03<sup>S</sup> |

CMAP of all motor nerves is significantly reduced in group B & in group A CMAP of median motor nerve is reduced.(Table 4.)
4. Discussion

The detection of DN is an area of ongoing interest for the researchers & clinicians, not only for diagnosing & managing it earlier but also for understanding the disease which is still under exploration. Mostly NCS have been accepted as an essential part of diagnosis for DN as it has many benefits. Hyperglycaemia is now well established risk factor in both patients with type I & type II diabetes. Other correlates & associations include age, duration of DM, quality of metabolic control, height, presence or absence of background or proliferative diabetic retinopathy, cigarette smoking, high density lipoprotein, cholesterol & presence of cardiovascular disease.

Most recognized neurologic complications associated with diabetes involve the peripheral nervous system. Disorders of the nervous system associated with DM were first recognized by Rollo in 1798. It was Marchal de Calvi in 1864 who first suggested that DM might be the cause rather than the effect of neuropathy.

Predominately sensory or sensorimotor distal polyneuropathy is the most common of the DN. Both lightly myelinated & unmyelinated small nerve fibers & the myelinated large nerve fibers are affected. Earliest deficits involve the small nerve fibers characterized by deficit in pain & temperature perception, paresthesias, dysesthesias & predisposition to develop foot ulceration. Involvement of large myelinated nerve fibers is characterized by loss of position & vibration sense & loss of deep tendon reflexes.

4.1 Pathophysiology of DN

Hyperglycaemia cause a non-enzymatic covalent bonding of glucose with proteins that alters their structure & inhibits their functions. These glycosylated proteins can lead DN. Hyperglycaemia also increases intracellular diacylglycerol, which activates protein kinase C(PKC); that causes increased vascular permeability, impaired nitric oxide(NO) synthesis & compromise nerve regeneration. Elevated levels of glucose results in activation of Polyol or Aldose reductase pathway. Excessive activation of polyol pathway leads to increased levels of sorbitol & increased activity of oxygen free radicals. It decreases dihydronicotinamide adenine dinucleotide phosphate(NADPH), NO & glutathione, as well as increases osmotic stress on the cell membrane. By impairing Na⁺-K⁺ ATPase activity it causes nodal swelling & other structural changes. Oxidative stress causes breaking of DNA strand; leads activation of poly(ADP-Ribose) polymerase(PARP) that further mediate pathways of hyperglycaemia induced damage. One cause of microangiopathy is long term hyperglycaemia. In DN there is thickening of basement membrane & endothelial cell hyperplasia as entry of glucose in cells remain unchecked by insulin. Necrotizing vasculitis & microsphere embolization leads to ischaemia which play an important role in development of DN.

Cho & colleagues reported that in clinically diagnosed DN subjects NCS led to an alternative diagnosis in about 30% of cases. Kothari & colleagues reported 42.9% among referrals for all polyneuropathy types. Kanavi Roopa Shekharappa concluded decrease in NCV & amplitude with increase in duration & poor glycaemic control of DM. Bansal & Kalita suggested slowing of NCV associated with demyelinating neuropathy.

PN is a major complication of DM & marked differences can be observed in sensorimotor nerves. Significant decrease in NCV along with increase in DL indicate damage to the myelin sheath. Reduced CMAP & SNAP indicates onset of axonopathy. If DN is not diagnosed earlier then foot ulceration & neuropathic arthropathy (Charcot joint) are two major neurological complications of DN. Symptoms of DN are also observed in newly diagnosed & poorly controlled diabetic patients & that rapidly improves with control of hyperglycaemia.
5. Summary & Conclusion

The physiological properties of nerve & muscle are modified due to pathophysiological changes resulting from DM. Distal sensorimotor polyneuropathy, the most common complication of DM may cause severe morbidity. In our study results conclude that the changes of DN affected sensorimotor nerves in both limbs. NCS not only used to diagnose the DM but also monitor the effect of treatment of DN. By regular NCS & good glycaemic control, symptoms of DN can be reversed & further complications like foot ulceration, Charcot’s joint & amputation can be prevented.

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