www.jmscr.igmpublication.org Impact Factor 3.79
ISSN (e)-2347-176x

IGM Publication Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Electrophysiological Changes in Uncontrolled Type-2 Diabetic People with Peripheral Neuropathy

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ABSTRACT

Introduction: *Diabetes mellitus the incidence of which is very high in our nation and presenting as a serious health problem. Some of its serious complications are retinopathy, neuropathy, nephropathy and vascular problems. Among these peripheral neuropathy is reaching 60-70% of the diabetic population especially if it is uncontrolled and of longer duration. Majority of cases of neuropathy can be delayed with judicious control of hyperglycemia and early diagnosis of neuropathy. Nerve conduction studies are of great help in the diagnosis and treatment of neuropathy.*

Materials And Methods: *After the judicious elimination of possible other types of neuropathies, the study group consists of 30 subjects with uncontrolled diabetes mellitus type -2 between the age groups of 40-55yrs, of both sexes. Study period is from June 2014 to June 2015.All the cases are from an endocrinology center present in Visakhapatnam. All these patients were subjected to electrophysiological studies in the neurophysiolology laboratory at Visakhapatnam. Instrument used is NeuroPerfect. The nerves selected for the study are:*

- Motor- *median nerve, ulnar nerve in the upper limb, lateral poplitial and posterior tibial in lower limb.*
- Sensory- *median nerve, ulnar nerve in upper limb and sural nerve in the lower limb.*

Results:

Motor Changes: *The distal latencies are increased in ulnar of the upper limb and lateral popliteal in the lower limb. Amplitude is decreased in ulnar and posterior tibial nerves. Slowing of (NCV) was prominent in all the cases."F" wave was normal.*

Sensory Changes: *The Amplitude was extremely low in the sural nerve. Amplitude and NCV were moderately decreased in median and ulnar nerves.*

Conclusion: *In our study diabetic neuropathy most commonly manifests as symmetrical peripheral polyneuropathy, the most common manifestation being symmetrical sensory loss in the distal lower extremities and motor deficits. Upper extremity involvement is less common progressing in the duration of the disease.*

Key Words: *Diabetes type 2, Diabetic neuropathy, distal latency, NCV,"F" wave, Amplitude.*

INTRODUCTION

The incidence of diabetes with its complications is increasing to staggering proportions. Presently the world health organization estimates an overall prevalence of more than 130 million, but by 2025 there will be 300 million individuals with diabetes mellitus. The incidence of diabetic neuropathy approaches 50% in most diabetic populations [1]. The development of new treatment to slow or arrest the progression of diabetic polyneuropathy has increased the importance of the early and accurate identification of this complication. It is likely that effective intervention will be possible only during the sub-clinical or early phase of dysfunction. Accurate diagnosis of diabetic polyneuropathy is a formidable task because of diversity of presentations, involvement of different nerve fiber types and the common dissociation of symptoms from objective measures of neural function. Several diagnostic tools are available, each with its strengths and limitations. Among these electrophysiology is a sensitive objective and targeted measure of diabetic polyneuropathy. The existing diagnostic tool and newly emerging methods provide a battery of tests that can be used to assess multiple aspects of neural function and increased sensitivity to detect the onset and progression of diabetic neuropathy. Diabetic neuropathy which affects 60-70% of those with diabetes mellitus is one of the most troubling complications. Often neuropathy leads to foot ulcers and lower limb amputations, both of which are preventable.

Classification of Diabetes mellitus

Diabetes mellitus can be divided into two major types:

1. The insulin dependent diabetes mellitus (IDDM) in which exogenous insulin is required to prevent diabetic keto acidosis. Term type 1 was applied only to diabetes resulting from autoimmune destruction of beta cells.
2. Non-insulin dependent diabetes mellitus (NIDDM) is applied to any form of diabetes, regardless of etiology in which, endogenous production of insulin is sufficient to prevent diabetic keto acidosis. Type 2 do not have any beta cell destruction, it is not autoimmune.

Type 2 diabetes mellitus etiology, genetics, and pathophysiology:

Familiar aggregation of type 2 (NIDDM) is very common.38% of siblings and 1/3rd of off springs of individuals with diabetes (NIDDM) exhibit diabetes. The glucagon producing islet cell mass is increased while beta cell mass is normal with amyloid deposits are seen between the endocrine cells and capillaries. Peripheral insulin resistance is present in type 2 diabetes mellitus. Increased adiposity and obesity increase in diabetes. In chronic stage of diabetes retinopathy, nephropathy and neuropathy are severe complications. Among the three chronic complications diabetic neuropathy which is associated with the nervous system have long been recognized [2, 3] most of the neurological complications associated with diabetes mellitus involve the peripheral nervous system. Symptoms of diabetic neuropathy are: patients can't feel properly in their legs, feet are numb, legs are too heavy, lightening pains of skin with great pain worsening at night [4]. There are many classifications for diabetic neuropathy [5-9]. Fauserberg suggested the presence of a material positive for periodic acid Schiff staining stenosis and hyalinization of intraneural vessels [10]. Chopra and colleagues held that segmental demyelination, presumably the result of a metabolic disturbance of Schwann cell function, was the primary abnormality [11]. reduction in number of myelinated fibers is the characteristic finding in the diabetic peripheral nerve [12], duck suggested that dorsal roots were more effected than ventral roots in his study [13].

Methodology of nerve conduction study

Motor and sensory nerves are stimulated as described

Principles of motor nerve conduction: The moor nerve is stimulated at least at two points along its course. The pulse is adjusted to record a compound muscle action potential. Ground electrode is placed between stimulating and recording electrode. Surface stimulation of a healthy nerve requires a square wave pulse of 0.1ms duration with an intensity of 5-40ma.filter setting at hz-10kHz and sweep speed 2-5mts/division.

The measurements for motor nerve conduction include:

1. Onset latency
2. Duration
3. Amplitude of compound muscle action potential (CMAP)

The onset latency is a measure of conduction in the fastest conducting motor fibers. Duration correlates with the density of small fibers. The amplitude of CAMP is measured from base line to the negative peak between negative and positive peaks. The nerve conduction velocity is expressed as meters per second.

Conduction velocity=

$$\frac{\text{Distance between proximal and distal stimulation points in mm}}{\text{Latency difference in milliseconds}}$$

$$= \frac{D}{PL-DL}$$

PL= proximal latency in ms

DL=distal latency in ms

D=distance between proximal and distal stimulation points in mm.

For accurate motor nerve conduction velocity measurements, the distance between two points of stimulation should be at least 10cm to reduce the error.

Principles of sensory nerve conduction:

The sensory nerve conduction can be measured orthodromically or antidromically.In orthodromic conduction a distal portion of the nerve is stimulated and sensory nerve action potential is recorded (SNAP).in antidromic sensory nerve conduction measurement the action potential may be obscured by super imposed muscle action potential which is elicited due to stimulation of motor nerve axon in the mixed nerve. For orthodromic conduction ring electrodes are preferred to stimulate the digital nerve. Whereas surface electrodes are used for antidromic stimulation .the recommended filter setting for sensory conduction is 10 Hz-2khz.sweep speed 1-2 ms/division and gain 1-5µV/division. The signal enhancement with averaging is generally required for the sensory conduction study. Similar to motor nerve conduction measurements include onset latency, amplitude, duration of SNAP and nerve conduction velocity. The latency of orthodromic potential is measured from the stimulus artifact to the initial positive or subsequent negative peak. The initial positive peak in SNAP giving it a triphasic appearance is a feature of orthodromic potential. In antidromic potential the initial positivity in SNAP is lacking. The SNAP amplitude is measured from base line to negative peak or from positive to negative peak. The amplitude of SNAP suggest the density of nerve fiber where as the duration suggests the number of slow conducting fibers. The duration of SNAP is measured from the initial positive peak to the intersection between the descending phase and the base line or to the negative or subsequent positive peak or return to the base line. Sensory nerve conduction velocity, unlike motor nerve conduction velocity can be measured by stimulating at a single stimulation site, because the residual latency, which comprises of neuromuscular propagation time is not applicable in sensory nerve conduction. Thus the sensory nerve conduction velocity is calculated by dividing the distance (mm) between stimulating and recording site by the latency (ms).

AIMS AND OBJECTIVES:

Aims of the study are:

1. To establish the incidence and extent of diabetic neuropathy in uncontrolled type 2 people with diabetes mellitus.
2. Comparison between motor and sensory involvement in general
3. Comparison between upper limb motor vs. lower limb motor and upper limb sensory vs. lower limb sensory.
4. Relation to the duration of diabetes for each case.

MATERIALS AND METHODS

The study group consisted of 30 subjects of confirmed cases of uncontrolled type2 diabetes. All are selected from an endocrinology center near Visakhapatnam and are compared with normal subjects of similar age group selected from the general population whose blood sugar levels are normal and not having any other diseases both the groups are between 40-55yrs of age. The instrument used was NEUROCARE EMG MACHINE provided by BIO-TECH (INDIA) Ltd. The nerves selected for study are:

- (motor)-median nerve, ulnar nerve in the upper limb, lateral poplitial and posterior tibial in lower limb.
- (Sensory)-median nerve, ulnar nerve in upper limb and sural nerve in the lower limb.

Criteria of exclusion:

1. Above 55 yrs age group and below 40 age groups were excluded.
2. People with history of other neuropathies like congenital or other causes were excluded.
3. People diagnosed as diabetic for a minimum of one year duration and who are having high blood glucose levels.
4. People taking any medicines which can cause neuropathy are also excluded.

Screening tests:

Before under taking the electrophysiological investigation, the following investigations were done:

1. Urine for the presence of glucose
2. Fasting blood sugar,
3. Post prandial blood sugar HBA_1C

Reports & Discussion

Thirty patients of both sexes aged 40-55yrs with duration of diabetes from 1 to 20 yrs with uncontrolled type 2 diabetes mellitus, with or without signs and symptoms of peripheral nerve diseases were studied to assess the objectivity of neurophysiologic al study in relation to diabetic neuropathy and to ascertain the prevalence of diabetic neuropathy. In a total of 30 diabetics 29 had manifestations of neuropathy of different stages. Majority of patients presented with numbness or insensitivity to pain, tingling, burning, and pricking, rarely muscle cramps and extreme sensitivity to touch and other sensibilities. A few complained of loss of balance and coordination. One case presented with foot ulcer. In most of the cases, sense of vibration was lost. Ankle jerk was sluggish in all and lost in 4 cases. Only two cases had sluggish or absent knee jerk. These findings reflect the loss of distal myelinated nerve fibers and agree with the findings of [14] but disagree with the findings of [15] who suggest that patient age or duration of disease do not correlate with motor conduction velocity. The reflexes in the upper limb were rarely effected. The fasting blood glucose ranged between 150mg/dl to 460mg/dl with mean of 250.90 and post prandial blood glucose ranged from 220mg/dl to 600mg/dl with a mean of 347.50mg/dl. In all the cases HbA1C is more than 7.5.Nerve conduction studies were conducted by recording the compound motor action potential in the median and ulnar nerves in the upper limb and lateral poplitial and posterior tibial nerves in the lower limb. Sensory nerve action potentials were recorded from the sensory median and ulnar nerves in the upper limb and purely sensory sural nerve in the lower limb. The distal latency, amplitude, nerve conduction

velocity (NCV) and (F) wave were measured in the CMAP and Amplitude and NCV was measured in the SNAP and the results were tabulated and analyzed as shown.

1. Comparison between motor and sensory nerve involvement in general
2. Comparison between upper limb motor vs. lower limb motor and upper limb sensory vs. lower limb sensory.
3. Relation to the duration of diabetes for each case.

The fasting and post prandial blood glucose levels were estimated and the patients were instructed to come to the electrophysiological laboratory next day. The patients were made to relax in a comfortable position, the test procedure was explained and consent was taken. The (CMAP) & (SNAP) were recorded

1. **Comparison of sensory and motor nerve involvement in general**: Distal latency increased in all the motor nerves effecting median, ulnar, nerves to a greater extent compared to lateral poplitial and posterior tibial. Absence of "F" wave was more in the lateral poplitial and posterior tibial as compared to median ulnar nerves. Deviation and amplitude of F wave depend on the number and size of motor units. F wave absence and variations are highly suggestive of peripheral neuropathies and proximal nerve injury due to hyperglycemic state. Absence of (SNAP) suggests axonopathy and proximal neuronal involvement as seen in the study groups. Distal sensory involvement is greater in the lower limbs as compared to upper limbs. (TABLE: 1)
2. **Comparison between upper limb motor vs. lower limb motor and upper limb sensory vs. lower limb sensory.** : Total absence of (CMAP) either in the upper or lower limbs was compared to total absence of SNAP. Mean amplitudes were normal in upper and lower limbs but there is decreased amplitude in the type 2 diabetes with a longer duration of the disease in motor nerves. Mean ulnar amplitudes were 7.50 mv and 8.13 mv compared to sural nerve amplitude of 3.43mv.NCV was slower both in the median &ulnar nerve suggestive of segmental demyelination. (TABLE 2a & TABLE 2b)
3. **Relation to the duration of diabetes for each case:** Deterioration in sensory and motor nerves was seen with increase in duration of diabetes type 2. These findings reflect the loss of distal myelinated nerve fibers. From the above findings we observed that sensory neuropathy progressively increasing with duration of the disease, effecting distal nerves initially followed by proximal nerves. Tthus we agree with the work of [16] Marchal decalvi in 1864 was the first to suggest that diabetes mellitus type 2 might be the cause rather than the effect of neuropathy. A progressive decrease in amplitude and (NCV) was prominent in the sural nerve followed by median and ulnar nerves with least changes in the motor nerves of the upper limb. Motor nerves of lower limb are effected later followed by motor nerves of upper limb F wave changes suggest disease progression in the proximal segments and roots.

TABLE:1 Comparison Of Sensory And Motor Nerve Involvement In Study And Control Groups

MOTOR FUNCTION						SENSORY FUNCTION					
MEDIAN NERVE	CONTROL GROUP	MEAN	SD	NO.OF CASES EFFECTED	PERCENT EFFECTED %	MEDIAN NERVE	CONTROL GROUP	MEAN	SD	NO.OF CASES EFFECTED	PERCENT EFFECTED %
DISTAL LATENCY(ms)	3.1 -3.8	3.46	0.9	11	36.7						
AMPLITUDE (mv)	4 - 10	7.52	3.08	4	13.3	AMPLITUDE (mv)	23.5-53.5	21.53	17.76	20	66.7
NCV (mts/sec)	52-61	44.07	9.17	26	86.7	NCV (mts/sec)	49-62	45.1	18.65	11	36.7
F.WAVE (ms)	22-31	25.97	9.33	12	40						
ULNAR NERVE	CONTROL GROUP	MEAN	SD	NO.OF CASES EFFECTED	PERCENT EFFECTED %	ULNAR NERVE	CONTROL GROUP	MEAN	SD	NO.OF CASES EFFECTED	PERCENT EFFECTED %
DISTAL LATENCY (ms)	2.2-2.8	2.92	0.68	19	63.3						
AMPLITUDE (mv)	3.7-7.7	7.34	2.84	2	6.7	AMPLITUDE (mv)	15-50	23.71	16.11	5	5
NCV (mts/sec)	56-61	44.43	11.32	23	76.7	NCV (mts/sec)	49.5-60.1	42.32	18.48	16	16
F.WAVE (ms)	21-32	27.4	7.95	10	33.3						
LATERAL POPLITEAL	CONTROL GROUP	MEAN	SD	NO.OF CASES EFFECTED	PERCENT EFFECTED %	SURAL NERVE	CONTROL GROUP	MEAN	SD	NO.OF CASES EFFECTED	PERCENT EFFECTED %
DISTAL LATENCY (ms)	3-4.5	4.01	1.36	9	30						
AMPLITUDE (mv)	3.4-7.4	4.45	2.78	12	40	AMPLITUDE (mv)	9.5-28.5	4.46	6.8	23	23
NCV (mts/sec)	44-52	34.59	12.36	23	76.7	NCV (mts/sec)	45.5-63.3	15.03	23.57	23	23
F.WAVE (ms)	38-57	36.36	20.83	10	6.7						
POST TIBIAL NERVE	CONTROL GROUP	MEAN	SD	NO.OF CASES EFFECTED	PERCENT EFFECTED %						
DISTAL LATENCY (ms)	3.2-4.5	4.22	1.33	9	56.7						
AMPLITUDE (mv)	12-26	9.22	5.9	12	63.3						
NCV (mts/sec)	44-53	36.54	10.34	23	76.7						
F.WAVE (ms)	41-57	46.46	17.05	8	26.7						

TABLE: 2(A) COMPARISON OF MOTOR FUNCTIONS BETWEEN UPPER LIMB AND LOWER LIMB

UPPER LIMB						LOWER LIMB					
MEDIAN	CONTROL GROUP	MEAN	SD	NO.OF CASES EFFECTED	PERCENT EFFECTED	LAT.POPLETEAL	CONTROL GROUP	MEAN	SD	NO.OF CASES EFFECTED	% EFFECTED
DIS-LAT (ms)	3.1-3.8	3.74	0.821	11	36.7	DIS-LAT (ms)	3-4.5	4.12	1.505	9	30
AMPLITUDE (mv)	4-10	7.50	3.301	4	13.3	AMPLITUDE (mv)	3.4-7.4	4.39	2.927	12	40
NCV (mts/sec)	52-61	45.96	6.575	26	86.7	NCV (mts/sec)	44-52	35.06	13.7	23	76.7
F.WAVE (ms)	22-31	25.68	11.258	12	40	F.WAVE (ms)	38-57	35.36	22.828	2	6.7
ULNAR NERVE						POS. TIBIAL					
DISTAL LATENCY (ms)	2.2-2.8	3.19	0.582	19	63.3	DISTAL LATENCY (ms)	3.2-4.5	4.66	1.457	17	56.7
AMPLITUDE (mv)	3.7-77	8.13	3.051	2	6.7	AMPLITUDE (mv)	12-26	9.18	6.151	19	63.3
NCV (mts/sec)	56-61	46.58	9.284	23	76.7	NCV (mts/sec)	44-53	38.11	9.298	23	76.7
F.WAVE (ms)	30	27.16	10.284	10	33.3	F.WAVE (ms)	41-57	46.14	20.542	8	26.7

TABLE:2(B) COMPARISON OF SENSORY FUNCTIONS BETWEEN UPPER LIMB AND LOWER LIMB

UPPER LIMB						LOWER LIMB					
MEDIAN	CONTROL GROUP	MEAN	SD	NO.OF CASES EFFECTED	PERCENT EFFECTED %	SURAL	CONTROL GROUP	MEAN	SD	NO.OF CASES EFFECTED	% EFFECTED
AMPLITUDE	23.5-53.5	21.87	18.27	20	66.7	AMPLITUDE (mv)	9.5-28.5	3.43	6.279	23	76.7
NCV (mts/sec)	49-62	45.97	19.93	11	36.7	NCV (mts/sec)	45.5-63.3	13.79	23.976	23	76.7
ULNAR											
AMPLITUDE (mv)	15-50	22.33	17.75	5	16.7						
NCV (mts/sec)	49.5-60.1	40.24	22.58	16	53.3						

Summary and Conclusion

The present study revealed the following conclusions:

1. Reduction of CMAP and SNAP amplitude were more marked in the lower limb than the upper limb and in the distal records compared to proximal.
2. CMAP was unrecordable in 2 cases out of the 30 in the lateral popliteal nerve and SNAP was unrecordable in 6 cases of the ulnar, 4 cases of the median and 23 cases of the sural nerve showing severity of axonopathy and neuronal degeneration in the lower limb sensory nerves is more as compared to upper limb.
3. Nerve conduction velocity (NCV) slowing was mild to moderate in the motor nerves of the upper limb compared to lower limbs. The NCVs being 45.96 mts/sec and 46.58 mts/sec with ulnar nerve and 35.06 mts/sec and 38.11 mts /sec in lateral popliteal.
4. NCV slowing was maximal in the sural nerve i.e.; lower limb (3.43mts/sec) in comparison to upper limb (45.97 mts/sec and 40.24 mts /sec) respectively in the median and ulnar nerves.
5. NCV slowing is more in symptomatic than asymptomatic and also it is more pronounced temporal dispersion of CMAP due to axonal loss along with demyelination. Routine NCV studies do not evaluate the small and unmyelinated nerve fibers. F wave was absent in 8/22 and 4/22 cases in lateral [popliteal and posterior tibial respectively. In 4/22 and 3/22 cases in median and ulnar nerves respectively. Slowing of F wave with normal distal motor conduction points to a proximal nerve or root lesion.
6. The results are statistically significant where the value of P is less than 0.001.

Electrophysiological study proves to be contributory as a diagnostic tool in asymptomatic cases, evaluating in symptomatic cases and useful assessment of effective therapeutic intervention in diabetes mellitus cases.

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