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Neurology

"CLINICAL AND ELECTROPHYSIOLOGICAL EVALUATION OF PATIENTS WITH DIABETIC NEUROPATHY"

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KEYWORDS :

INTRODUCTION

Peripheral neuropathy caused by Diabetes (DM) was recognised only in 1864 by Marchel de Calvi.(1) Till then it was assumed that diabetes was caused by disease of the nervous system. However, once the relationship was rightly recognised, much documentary evidence soon emerged regarding the various clinical manifestations occurring in diabetic peripheral neuropathy. Thus, the loss of tendon reflexes in the legs was described by Bouchard (1887),(2) similarities to tabes stressed by Althaus (1885)(3), spontaneous pain and hyperesthesia by Pavy (1885)(1904)(6) and motor manifestations by Bruns (1890)(6) and Charcot (1890) and cranial nerve involvement by Ogle (1896).(8) While Leyden (1893)(9) and Pryce (1893)(10) set out a classification of the different manifestations of the disease, is was Rundles11 who in 1945 first drew attention to the autonomic nerve involvement in diabetes. Later, scientists turned their interest to the etiopathogenetic mechanisms resulting in peripheral neuropathy. This in turn gave impetus to the experimental production of diabetic neuropathy (DN) in order to understand the evolution of the disease. Though a large volume of work has been carried out in this regard and many problems solved, many questions still remain unanswered. There is a need, therefore, for more comprehensive studies of the prevalence, severity, natural history, and cause of specific types of diabetic neuropathy.

Clinical classifications of diabetic neuropathies*

Symmetric
- Diabetic polyneuropathy
- Painful autonomic neuropathy
- Painful distal neuropathy with weight loss "diabetic cachexia"
- Insulin neuritis
- Polyneuropathy after ketoacidosis
- Polyneuropathy with glucose impairment
- Chronic inflammatory demyelinating polyneuropathy with diabetes mellitus

Asymmetric
- Radiculoplexoneuropathies
  - Lumbosacral
  - Thoracic
  - Cervical
- Mononeuropathies
- Median neuropathy at wrist
- Ulnar neuropathy at the elbow
- Peroneal neuropathy at the fibular head
- Cranial neuropathy

Aims and Objectives:

1. To assess the incidence of various types of Diabetic Neuropathies
2. To examine the Clinical Profile of each type of Diabetic Neuropathy
3. To study the Neurophysiologic patterns in each type of Diabetic Neuropathy and the extent of their clinical correlation.

Materials and Methods:

Inclusion criteria:

1. Diabetic patients referred to Neurology O.P.D for symptoms of peripheral neuropathy were assessed and those with clinically demonstrable Peripheral Neuropathy (DPN) were screened.
2. Patients who were admitted in General Medical and Neurology ward with symptoms related to diabetic neuropathy were also selected for this study.

Exclusion Criteria:

1. Patients with a family history of inherited neuropathies, occupational or environmental history of heavy metal exposure, history of lumbar or cervical radiculopathy as well as patients using medications which could cause polyneuropathy were excluded.
2. Patients with nutritional deficiencies, collagen vascular disease, malignancies, tabes dorsalis, toxin exposure (e.g., alcohol, occupational toxins, vitamin B6, and medications known to be associated with peripheral neuropathy), hypothyroidism, pernicious anemia, dysproteinemias, amyloidosis, AIDS, spinal cord disease, and cauda-equina syndrome were excluded.

Methodology:

This study was done over a period of two years - between March 2007 and February 2009. 156 patients were selected for study, out of the 207 patients screened. The study protocol was approved by the Ethics Committee of the Government General Hospital and all subjects gave their informed consent prior to the study.

Assessment of neuropathy:

Determination of whether a patient had neuropathy was based on review of the medical record, neurologic tests including bed side autonomic function tests, nerve conduction (NC) abnormalities. Three approaches were used to determine whether a neurologic abnormality was due to diabetes mellitus or to another cause: (1) the patient's history and the medical record were searched (2) additional tests were performed if needed; and (3) judgments were made as to whether the findings were typical of diabetic neuropathy. Systematic questioning, including family history of nondiabetic peripheral nerve disease and the presence of toxic, metabolic, mechanical, and vascular causes of nerve disease, was conducted. All patients underwent tests for complete blood count and routine serum chemistry including lipid profiles as well as tests for thyroid hormones, HbA1C and E.C.G.

Standardization of examining methods.

History and physical examination were included. In the sensory examination ambiguous findings were considered negative. The response to each test were considered normal, decreased, or absent. The instruments used were **1)** a disposable pin for pain evaluation, **2)** a cotton tip for light touch, **3)** a 128 Hz tuning fork for vibration sensation, and **4)** finger and toe movements with immobilization of the proximal joint to evaluate joint position. The sites examined included the distal toe and distal finger. The motor system was examined manually for individual muscles with a previously used validated grading system. Mechanical devices to evaluate strength may not add precision because they emphasize groups of muscles and because the condition of the joints and periarticular tissues frequently are abnormal

in diabetes. Muscle testing is of limited value in assessing mild diabetic neuropathy. Weakness appears late and usually only involves intrinsic foot muscles and ankle dorsiflexors; more proximal muscles are only involved in more severe cases of diabetic polyneuropathy. Reflexes were classified as **1)** present and active, **2)** present and hypoactive, and **3)** absent. Autonomic function tests were done for symptomatic patients. More specific staging of diabetic polyneuropathy (DPN) described by Dyck and Dyck **(27)**: (NO, no neuropathy; N1, asymptomatic neuropathy without (N1a) or with (N1b) findings on neurological examination; N2, symptomatic; N3, disabling) were applied to all patients.

Electrodiagnostic Measures-Standardization

The RMS system was used. Recommended filter settings (approximate values) were 20-3,000 Hz bandpass for sensory studies, 2-10,000 Hz bandpass for motor studies, and 20-10,000 Hz bandpass for needle electromyography.

Protocol for electrodiagnostic test

A. Motor nerve conduction studies

1. Unilateral studies of ulnar and median nerve including F waves in the upper limb
2. Unilateral studies of peroneal and posterior tibial nerve including F wave in the lower limb 3. Measurement of muscle action potential amplitude and latency at each site of stimulation and calculation of segmental conduction velocity

B. Sensory nerve conduction studies

1. Unilateral studies of ulnar and median nerve in the upper limb
2. Unilateral studies of either sural or medial plantar nerve in the lower limb
3. Measurement of nerve action potential amplitude and latency at each site of stimulation and calculation of segmental conduction velocity

C. Studies of additional nerves were undertaken to characterize abnormalities based on the distribution of clinical symptoms or signs.

D. Facial nerve conduction was done in all patients (even those without clinial involvement)

E. The normal values for representative nerve conduction values at various sites of stimulation were derived at after analyzing the NC of 30 age matched patients who came to Neurology OPD for complaints other than neuropathy.

Motor Nerve Conduction

Nerve	Distal Latency (ms)	Amplitude (mv)	CV (m/s)	F-Wave Latency (ms)
Median	<4.2	>4	>49	<31
Ulnar	<3.4	>4.5	>49	<32
Tibial	<6.0	>3.5	<40	<56
Peroneal	<6.0	>2.2	<40	<56
Facial	<1.1	>1.4	-	-

Sensory Nerve Conduction

Nerve	Amplitude (uV)	CV (m/s)
Median	>5	-
Ulnar	>5	-
Sural	>6	>40

RESULTS:

The mean age of the diabetics was 53.0 ± 12.4 years. Their ages ranged from 31–67years. The duration of diabetes varied from newly detected to more than 20 years with a mean duration of 8.4 ± 6.9 years. Of the 156 patients 92 were males (59.3%) and 64 females (41.2%). Males predominated in all age groups. Around two thirds of males (85%) were in the age group between 40 and 70 years and two-third of females (84%) were in the age group between 40 and 70 years. The highest proportion among the diabetics was in the age group of 50–59 years with a frequency of 34.2%.

Characteristics	Diabetics (N=156)
Number (male/female)	92/64
Age (years) (mean, SD)	53.0 ± 12.4
Duration of diabetes mellitus (years)	8.4 ± 6.9
Mode of treatment (%)	
OHA	82.5
Insulin	12.5

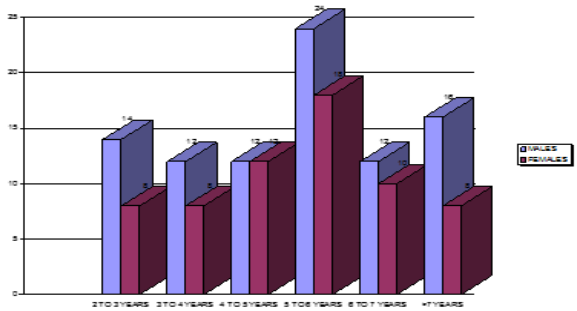
Sensorimotor polyneuropathy was the most common form of peripheral neuropathy, with a frequency of 47.4%, followed by mixed type peripheral neuropathy (26.7%) and Autonomic Neuropathy(AN) (15.6%). The different stages of neuropathy using the Dyck grading system was analyzed based on gender among the diabetics. Fifteen subjects—8 male diabetics and 7 female diabetics (9.6%)—had stage-0 neuropathy, while 39—21 male and 18 female—diabetics (25%) had stage 1.

Grades of diabetic-peripheral neuropathy by gender(27)

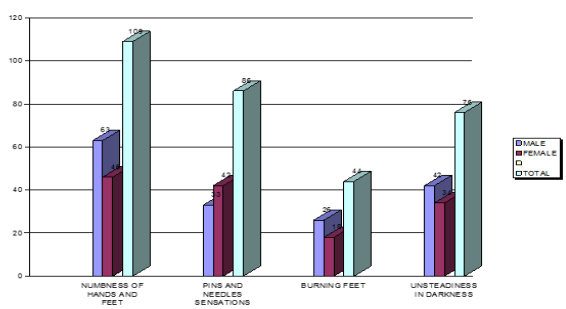
Grades	Male Diabetics	Female Diabetics
Stage N 0	8	7
Stage N 1	21	18
Stage N2	41	32
Stage N 3	12	7

There was no significant difference between males and females with severity of peripheral neuropathy. Most of the patients were type II, (88.2%) while 16 were type I (11.8%). The mean duration of DM was 7.5 ± 4.2 1 years. Oral hypoglycemic agents (OHG) were the treatment used by 81 patients (59.6%), followed by insulin 46 (33.8%), diet 5 (3.7%) and combined OHG and insulin in 4 (2.9%). Among the patients studied about two thirds (78% of males and 57% females) had diabetic neuropathic symptoms in the duration of 6 months to more than 2 years.Poor glycemic control was found in 87 patients (64%) while 49 (36%) were well controlled. In this study 84 patients had autonomic symptoms, most common autonomic symptom is postural hypotension 27 patients (17%). Eigty-nine (57.3%) patients were hypertensive while hyperlipidemia was found in 48 (30.7%) and a history of smoking in 43 (27.3%). Normal NCS were found in 28 patients (18%). Abnormal NCS were found in 124 patients (80%).

DURATION OF DIABETES		
	MALES	FEMALES
2 TO 3 YEARS	14(15%)	8(13%)
3 TO 4 YEARS	12(13%)	8(13%)
4 TO 5 YEARS	12(13%)	12(19%)
5 TO 6 YEARS	24(26%)	18(28%)
6 TO 7 YEARS	12(13%)	10(16%)
>7 YEARS	16(17%)	8(13%)



CLINICAL SYMPTOMS	MALE	FEMALE	TOTAL
NUMBNESS OF HANDS AND FEET	63(63%)	46(72%)	109(70%)
PINS AND NEEDLES SENSATIONS	33(36%)	42(66%)	86(55%)
BURNING FEET	26(28%)	18(28%)	44(28%)
UNSTEADINESS IN DARKNESS	42(46%)	34(53%)	76(49%)



Nerve conduction abnormalities in symptomatic patients were significantly related to poor glycemic control. Seventy-one (81.6%) poorly controlled patients had abnormal NCS as compared to 16 (18.4%) well controlled patients (P <0.001). Long duration of DM was also strongly related to abnormalities in NCS, the mean duration of DM in patients with NCS abnormalities was 7.4 years as compared to 3.1 years in those with normal NCS (P <0.001). Abnormal NCS were also significantly associated with insulin use, 32 (69.6%) of those on insulin showed abnormal NCS compared to 14 (30.4%) who showed normal NCS. There was no significant relation between abnormal NCS and patients age (p0.4), sex (p0.7), type of DM (p0.1), hypertension (p0. 5), hyperlipidemia (p0.23) or smoking (p0.13). in this study 84 patients had autonomic symptoms, most common autonomic symptom is postural hypotension 27 patients (17%)

Summary of NCS Study:

Distal Motor Latency

	Total No. Of Patients	Normal	Increased	No response	Mean ± SD	Range
Median	156	94	46 (4†)	16	4.0 ± 1.8	3.1- 12.8
Ulnar	156	108	32 (2†)	16	3.8 ± 1.0	2.6-9
Tibial	148	82	47	19	5.6 ± 1.5	3.6-13.7
Peroneal	152	86	46	20	5.5± 1.2	3.9-9.5
Facial	156	147	9 (5†)	-		

Distal Motor Amplitude

	Total No. Of Patients	Normal	Decreased	No response	Mean ± SD	Range
Median	156	38	102 (32†)	16	2.6 ± 1.8	0.2- 8.8
Ulnar	156	42	98 (30†)	16	3.0 ± 2.1	0.5-9.1
Tibial	148	37	92	19	2.3 ± 1.5	0.3-6.5
Peroneal	152	37	95	20	1.8 ± 1.3	0.3-7.4
Facial	156	151	5 (1†)	-		

Motor Conduction Velocity

	Total No. Of Patients	Normal	Decreased	No response	Mean ± SD	Range
Median	156	104	36 (3†)	16	48.8 ± 7.1	19.0-59.0
Ulnar	156	108	32 (2†)	16	48.3 ± 8.8	8.9-54.2
Tibial	148	90	39	19	38.4 ±4.0	20.4-43.0
Peroneal	152	89	43	20	39.9 ± 2.1	23.0-42.0

F Waves Latency

	Total No. Of Patients	Normal	Increased	No response	Mean ± SD	Range
Median	156	88	52 (10†)	16	33.5 ± 3.9	25.0-75.0
Ulnar	156	98	42 (12†)	16	33.8 ± 2.3	20-66
Tibial	148	53	76	19	62.5 ± 4.5	34.0-45.2
Peroneal	152	66	40	46	63.2 ± 4.9	50.0-137.0

Sensory Amplitude

	Total No. Of Patients	Normal	Decreased	No response	Mean ± SD	Range
Median	156	75	66 (11†)	4	12.0 ± 4.2	1.8-20.0
Ulnar	156	86	58 (8†)	4	11.4 ± 3.1	1-15.0
Lower Limb	137	37	84	16	4.5 ± 2.6	1.3-15.7

Sensory Conduction Velocity (Sural)

	Total No. Of Patients	Normal	Increased	No response	Mean ± SD	Range
Lower Limb	137	74	47	16	35.7 ± 4.4	26.0-49.0

† Patients with no upper limb symptoms

Nerve	No. of nerves studied	No.(%) of patients with findings of focal demyelination	Conduction Block	Temporal Dispersion
Median	156	46	5	2
Ulnar	156	32	3	1
Peroneal	152	46	3	21
Tibial	148	47	1	8

TYPES OF NEUROPATHIES			
	MALES	FEMALES	TOTAL
SYMMETRIC SENSORIMOTOR	52(26.9%) 26(†) 2(††)	42(21.1%) 23(†) 4(††)	94 (48.0%) 49 (31.4%) 6 (3.8%)
PAINFUL DISTAL SESORY	20(12.8%) 19(†)	17(10.8 %) 15(†)	37(23.6%) 34(21.9%)
DIABETES WITH AIDP	4(2.5%)	1(0.6%)	5(3%)
DIABETES WITH CIDP	6(3.8%)		6(3.8%)
LUMBOSACRAL RALICULO	2(1.3%)	3(2%)	
MONONEURITIS MULTIPLEX	3(2%)		3(2%)
CRANIAL NEUROPATHIES	5(3%)	3(2%)	8(5%)

† With Autonomic Involvement
†† With Carpal tunnel Syndrome

Discussion:

DN is a common complication of DM and it is encountered in more than one third of diabetic patients(81). Pirar et al(82) had found a five fold increase in the incidence of DN after 25 years of follow up. Although methods of assessing peripheral nerve function are improving, no single test is indicative of nerve disease.(68) The San Antonio conference on diabetic neuropathy(69) recommended obtaining ≥1 measure from each of the following categories to better define and classify diabetic neuropathy: clinical symptoms, clinical examination, electrodiagnostic studies, quantitative sensory testing and autonomic function testing. Likewise we in our study have used NCS as an extension of clinical examination.

Discordance between nerve conduction velocity and symptoms and signs of DN has been reported before.(83,84) We found that 36% of our patients with symptomatic DN had normal NCS, which is higher than that reported by Sangiorgio et al(83) and Fedele et al(84). Also nearly 30% of patients who did not have symptoms related to upper limbs showed some abnormality in NCS. This discordance between symptoms and NCS means that we can not rely on patient's symptoms for the diagnosis of DN and we need NCS for better assessment and diagnosis of DN.

The various clinical types of PN in this study correlate well with most studies all over the world, with sensorimotor polyneuropathy — diagnosed in 48%—being the most common.(71) Symptoms of PN manifested at a significantly lower age in our study. This is in agreement with Vondrova and coworkers in Czech, who found that diabetic polyneuropathy manifested at a younger age.(74) The average age of onset was 40 years in males and 42.3 in females.

There were no significant relation between Diabetic neuropathy and sex, BMI, hypertension or hyperlipidemia which is in agreement with the findings of Hillson et al(88) and Maser et al(89). The relation between smoking and DN is conflicting, some reports showed significant relation(85) while others(16) didn't find any relation. We found no significant relation between Diabetic neuropathy and smoking.

The overall high frequency of diabetic AN in this study (54%) was in keeping with what has been seen by other workers. Fernandez-Castaner and colleagues(76) had reported that 53% of an unselected series of diabetics had symptoms suggestive of autonomic dysfunction, while Thi and coworkers(77) documented that 67.6% of Vietnamese diabetics have cardiac AN. Most studies suggest a fairly close association between AN and sensory neuropathy. This was again true in our case, were all diabetics with AN had an associated somatic neuropathy that precedes abnormalities of autonomic function (78).

While no significant relation has been found between age and abnormal NCS, a strong relation was found with poor glycemic

control, this means that even young patients can develop alteration in Nerve Conduction Study if they are not well controlled. As the pathogenic mechanisms of Diabetic neuropathy are not fully understood, there is no satisfactory and fundamental therapy for Diabetic neuropathy. Therefore, further researches are needed especially into pathogenic mechanisms in order that satisfactory treatment is achieved. Good glycemic control is essential if the risk of diabetic complications is to be minimized(90).

There was a strong relation between baseline glycated hemoglobin and the loss of tactile sensation and temperature sensation (91). Intensive diabetic control had been shown to reduce the occurrence of clinical neuropathy by 60% (92,93). Several prospective randomized clinical trials have shown the beneficial effect of tight glycemic control on the progression of chronic microvascular complications of DM (94,95). This means that strenuous control of blood glucose is the key in the ultimate prevention of diabetic neuropathy

In our study too prolonged and poorly controlled DM were the most significant factors associated with Diabetic neuropathy as has been reported by others (83,84,85,86). A significant proportion of patients in our study who were on insulin had severe PN. This relationship may have more to do with poor control of diabetes in these patient, rather than insulin usage by itself. Similar to our report Cheng et al(87) had also shown a significant relation between insulin use and Diabetic neuropathy.

Cranial neuropathies are known to occur commonly in diabetics. There are only few studies on the frequency of clinically apparent cranial nerve lesions associated with diabetes mellitus. Large retrospective series revealed 0.97% incidence of oculomotor and facial nerve palsies in diabetic patients over a 25-year period which was 7.5 fold more frequent than in the nondiabetic control group (Urban *et al.*, 1999)(96). Urban *et al.* (l999)(96) reported that 77.5% of their diabetic patients demonstrated a significant prolongation of distal motor latency of VIIth nerve. Johnson and Waylonis (1964) (97) stressed the fact that, even though the conduction of limb nerves were unaffected, subclinical involvement of the facial nerve was present in a group of known diabetics (Johnson *et al.,* 1964 ; Waylonis *et al.,*\1964) (97). In our study a total of 8(5%) patients had clinical evidence of cranial nerve involvement, among which 6 patients had facial nerve involvement,2 patients had painful oculomotor palsy. But on nerve conduction studies 14(9%) patients had abnormality in the form of prolonged Distal Motor Latency (9patients) and axonal changes(5 patients). Although a few symptomatic patients in our study did show some NC abnormalities, this was not statistically significant. This may be due to the fact that most of the polyneuropathy in diabetes being length-related, facial nerve conduction may be less impaired than limb nerve conduction.

Several workers have demonstrated subclinical involvement of nerve fibres in patients with diabetes by comparing conduction between patients and normal subjects. These studies concerned patients with or without diabetic neuropathy (Lawrence and Locke, 1961; Mulder et al., 1961; Skillman et al., 1961;

Fagerberg et al., 1963; Mayer, 1963; Gamstorp, 1964; Eeg-Olofsson and Petersen, 1966)(101,102,103,104) and mixed groups (Gregersen, 1964, 1967). In the individual patient, slowing in motor conduction was often borderline in the non-affected nerves of patients with isolated peripheral nerve lesions (Gilliatt and Willison, 1962). (105,106,107). In our study, although we did not include asymptomatic diabetics, we were able to analyze the conduction in clinically unaffected limb (mostly upperlimb). Out of 56 patients who did not have upperlimb symptoms 32 patients showed abnormalities in motor conduction while 15 patients had additional sensory disturbance.

Many patients with sensorymotor neuropathy (76 patients) showed a prolongation in distal motor latency in addition to more than 50% reduction in amplitude, this we assume to be due to the loss of myelinated fibres. Also 5 patients with sensorymotor neuropathy, in addition to prolongation in latency and reduction in amplitude, showed a significant slowing in conduction velocity pointing to the possibility of additional focal abnormalities.

The slowing in the common peroneal nerve was the electro physiological parameter most closely related to the severity of the neuropathy ($P < 0\text{-}001$). In previous studies, the average slowing in motor conduction along the median and ulnar nerves has been reported to be as severe as in the common peroneal nerve, both in patients with and without clinical signs of neuropathy (Mulder et al., 1961; Lawrence and Locke, 1962; Mayer, 1963; Gamstorp, 1964;Gregersen, 1967). (116,117,118,101)

In our patients, distal slowing as measured by DML was as pronounced in the upper as in the lower extremities, but in the more proximal segments of the nerves (as measured by F wave latency) slowing was 1.5 times greater in the lowerlimb nerves than in the upper. This is consistent with the findings of Skillman et al. (1961) (119) and of Johnson (1962) (124) and with the more pronounced clinical involvement of the legs than of the arms.

The 2 main pathophysiologic mechanisms proposed for diabetic neuropathy are nerve ischemia (microangiopathy) and metabolic derangement of nerves. However, DM is one of the group of autoimmune disorders, [126,127] and there is growing evidence that immune and inflammatory processes play a role in some of the neuropathies occurring in DM, including demyelinating polyneuropathy.[128,129] Mitchell et al 7 reported finding major histocompatibility class II antigen expression on Schwann cells, similar to that found in I-CIDP, in the nerves of patients with diabetic amyotrophy. Younger et al 8 found that upto 60% of sural nerve biopsy specimens from 20 diabetic patients with various types of neuropathy had lymphocyticmicrovasculitis or perivasculitis, and endoneurial T-cell infiltrates, with increased expression of tumor necrosis factor α cytokines, and components of themembrane attack complex. Several studies have suggested that autoantibodies directed against phospholipid, 130,131 gangliosides, sulphatide, nerve growth factor, and advanced glycation end products may play a role in the pathogenesis of diabetic neuropathy. This probably explains the large number of patients in our study showing focal changes in NCS.

Limitation of our study:

1. Potential bias of patient referral. Most of the patients referred to our OPD had a severe neuropathy
2. Lack of biopsy correlation.

Conclusions:

Among the different types of Diabetic neuropathy, chronic sensorimotor neuropathy was the commonest, with a prevalence of 48%. Autonomic neuropathy had a prevalence of 31.4%. AN was almost always associated with sensory neuropathy. Among the focal neuropathies CIDP was the commonest . 65% of patients with clinical neuropathy showed abnormalities on nerve conduction studies. Nearly 30% of patients with no upper limb symptoms showed abnormalities in NCS. Showing a discordance between symptoms and nerve conduction studies. Longer duration of DM strongly correlated to abnormalities in NCS, the mean duration of DM in patients with both upper and lower limb NCS abnormalities was 7.4 years as compared to 3.1 years in those with only lowerlimb changes. It merely reflect the increased probability of finding more severe manifestations of a neuropathy when the diabetes has lasted longer. There was no relation between abnormal NCS and patients age, sex, type of Diabetes mellitus, hypertension, hyperlipidemia or smoking. Prolonged poorly controlled diabetes was an important risk factors associated with diabetic neuropathy. Aggressive/strict control of blood glucose is the key in the ultimate prevention of diabetic neuropathy. Lowerlimb F wave latency prolongation may correlate well with severity of the neuropathy. Presence of focal abnormalities in NC in addition to diffuse changes indicates that immune mediated mechanisms may play an additional role in development of diabetic neuropathy.

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