ELECTROPHYSIOLOGICAL EVALUATION OF PERIPHERAL AND AUTONOMIC NEUROPATHY IN PATIENTS WITH NEWLY DIAGNOSED DIABETES

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ABSTRACT

BACKGROUND

India has one of the highest prevalence of T2DM in the world. It is estimated that by the year 2030 there are will be nearly 80 million Indians with T2DM in the country. Although neuropathy is an extensively studied complication in patients with DM; however, the neuropathy risk in pre-diabetes and in newly diagnosed diabetes has not been well characterized.

The aim and objective of the study is assess and characterize the early electrophysiological signs of peripheral neuropathy and to evaluate the prevalence autonomic neuropathy in diabetic patients at diagnosis in comparison with controls.

MATERIALS AND METHODS

The study was conducted on 38 subjects and 28 age-matched Controls. Diabetes was defined using WHO Criteria. Neuropathy was evaluated by nerve conduction studies performed on bilateral medial ulnar, peroneal, tibial, dorsal sural and medial Planter nerve conductions using conventional techniques. Neuropathy was also evaluated by autonomic function tests for both parasympathetic (testing heart rate variation with deep breathing, standing 15:30 ratio and Valsalva manoeuvre) and sympathetic (testing postural hypotension and blood pressure variation after sustained hand grip) using automated CAN system analyser.

RESULTS

Neuropathy present in 16 (42.1%) cases and in 2 (7.1%) controls, and 21 (55.3%) cases when medial plantar and dorsal sural are considered. Total 25 members (65%) showed alteration in some form of NCS parameter. Dorsal sural (16 subjects (42.1%)) and medial plantar (15 subjects (39.5)) are two most commonly involved nerves among cases, followed by medial motor (13 subjects (34.2%)). Means of both sensory and motor distal latencies are higher and CMAPs, SNAPs and CVs are lower in subjects with neuropathy than without neuropathy among all tested, though only some parameters are statistically significant. Early and definite autonomic neuropathy is present in 8 (21.1%) and 2 (5.3%) cases respectively.

CONCLUSION

Electrophysiological evaluation of diabetics in the early stage of disease can detect abnormalities of peripheral and autonomic nerves system. Assessment of medial plantar and dorsal sural NCS increases the sensitivity in the detection of neuropathy. Early and definite autonomic dysfunction can be seen in newly diagnosed diabetic patients.

KEYWORDS

Electrophysiology, Peripheral, Autonomic Neuropathy, New Diabetes.

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BACKGROUND

The number of people with diabetes has risen from 108 million in 1980 to 422 million in 2014.[1] In 2000, India (31.7 million) topped the world with the highest number of people with DM and number raised to 69.2 million (8.7%) in 2015.[1,2] It is predicted that by 2030 DM may afflict up to 79.4 million individuals in India.[3]

Studies in USA reported that neuropathic pain syndromes have affected up to 70% population with DM.[4] and painful symptoms had occurred in 26% in patients without neuropathy and 60% of patients with severe neuropathy.[5]

In India there had been a small number of trials to screen the current status for DPN, among them a study estimated an overall prevalence of neuropathy as 19.1% in south Indian Type 2 diabetic patients.[6]

Aim and Objectives-

- To assess and characterize the early electrophysiological signs of peripheral neuropathy in diabetic patients at diagnosis and those with impaired GTT.
- To compare electrophysiological studies in non-neuropathic and neuropathic patients.
- To find the association between biochemical parameters like FBS, PPBS and BMI in neuropathic and non-neuropathic patients.

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- To assess and compare electrophysiological studies in right side and left side in newly diagnosed diabetes patients.
- To evaluate the prevalence autonomic neuropathy in non-diabetic controls and newly diagnosed diabetes cases and those with impaired GTT using Ewing's criteria.

MATERIALS AND METHODS

Study period- April 2015 to Feb 2017.

Subjects are those who are diagnosed to have impaired glucose tolerance or to have new onset diabetes attending to outpatient departments of endocrinology and medicine, KGH, Visakhapatnam; during the study period.

Age matched subjects with normal GTT are taken as controls.

Informed consent is taken.

Definitions-

Diabetes and impaired glucose tolerance are defined according to WHO criteria and as follows:

Impaired GTT-

Two-hour glucose levels of 140 to 199 mg per dL on the 75-g oral glucose tolerance test.

Diabetes-

During a 75-g oral glucose tolerance test-

Fasting plasma glucose ≥ 126 mg/dL (Fasting is defined as no caloric intake for at least 8 h).

OR

Two-hour plasma glucose ≥ 200 mg/dL.

Defining New Onset Diabetes-

Having diagnosed to having diabetes for the first time or diagnosed in last six months duration.

Inclusion Criteria-

Patients between 18 years to 60 years with new onset diabetes or impaired GTT as described above.

Exclusion Criteria-

Above and below the specified age limit.

Pregnant woman.

Patients with any abnormal clinical presentation that known to produce neuropathy.

Patients with using drugs that known to produce neuropathy.

After taking subjects into study detailed history is taken regarding neuropathic symptoms and any chronic drug usage, toxin exposure and history suggestive of hypothyroidism and vitamin B12 deficiency.

A detailed general and neurological examination is performed.

Routine investigations: Haemogram, urine routine examination, serum creatinine, chest X- ray and serum B12 and thyroid profile was done in whom electrophysiology is suggestive of neuropathy. Conventional NCS are done in both upper and both lower limbs: Bilateral median, ulnar, common peroneal, posterior tibial and sural nerves as per our laboratory standards, and medial dorsal and lateral plantar nerves are also studied as these nerves could increase the sensitivity of neuropathy in diabetics.

Neuropathy is considered when abnormal NCS present in ≥2 nerves.

NCS is considered abnormal if there is any reduction of CMAP/SNAP amplitudes, reduction in CV, increased DL more than two standard deviations.

NCS testing procedure that followed: NCS tests done by Nicolet Viking.

Normal Values for Representative Nerve Conduction Values at Various Sites of Stimulation
Motor Nerve Conduction Studies

Nerve	Distal Stimulation Site	Other Stimulation Sites	Recording Site	Onset Latency (ms)	AMP (mv)	CV (m/s)	Distance (cm)	F-latency (ms)
Median	Wrist	Elbow	APB	<4.2	>4.4	>49	6- 8	<31
Ulnar	Wrist	BG, AG	ADM	<3.4	>6.0	>49	5.5-7.5	<32
Peroneal	Ankle	BFH, AFH	EDB	<5.8	>2.0	>42	6-11	<58
Tibial	Ankle	PF	AH	<6.5	>3.0	>41	6.8	<59

Sensory Nerve Conduction Studies

Nerve	Distal Stimulation Site	Recording Site	Onset Latency (m s)	AMP (µv)	CV (m/s)	Distance (c m)
Median	Wrist	Digit 2	<2.5	>20	>52	13
Ulnar	Wrist	Digit 5	<2.1	>15	>52	11
Sural	Calf	Ankle	<2.5	>6	>42	14

Tests for Evaluation of Autonomic Function Tests are- Assessment of CAN was done using Automated CAN system analyser.

Data Entry and Statistical Analysis-

- Data was entered into Microsoft Excel sheet and analyzed using IBM SPSS Statistics for Windows, Version 22.0.
- Descriptive statistics were expressed as Means and percentages.

- Inferential statistical analysis was done using chi-square tests for nominal and ordinal variables, and ANOVA tests for interval variables.
- P-value of <0.05 will be considered statistically significant.

RESULTS

NCS are done in total 68 subjects of which 38 are new onset diabetics, 2 are with impaired GTT and 28 are controls.

Only two cases had impaired GTT (one male and one female) and their electrophysiological and CAN study is normal.

		Cases	Controls	Total	P- Value
Sex	F	19 (50.00%)	13 (46.40%)	32 (48.50%)	0.485
	M	19 (50.00%)	15 (53.60%)	34 (51.50%)	
Total		**38 100.00%**	**28 100.00%**	**66 100.00%**	

Table 1. Gender Comparison in Cases and Controls

Variable	Cases		Controls		p-value
	Mean	Std. Deviation	Mean	Std. Deviation	
Age	47.95	7.551	46.93	7.911	.597
BMI	26.3929	4.71023	26.7143	3.33175	.759
FBS	205.58	47.849	77.5	11.097	.000
PPBS	298.53	63.431	101.43	20.766	.000

Table 2. Different Variables Distribution in Cases and Controls

Motor Nerve		Case		Control		p-value
		Mean	Std. Deviation	Mean	Std. Deviation	
Median	Latency	4.013158	0.969932	3.560714	0.388577	0.023
	CMAP	12.26316	3.791129	13.64643	2.046177	0.085
	CV	53.3289	4.18698	54.8893	3.09998	0.101
	F latency	27.76351	2.819467	26.11429	1.871811	0.009
Ulnar	Latency	2.752632	0.433238	2.455357	0.389525	0.006
	CMAP	14.35921	3.027729	15.03036	2.535757	0.345
	CV	51.382	4.6534	59.875	5.2416	<0.001
	F latency	27.72432	2.644823	26.10893	1.572569	0.006
Peroneal	Latency	4.256579	0.654833	3.892857	0.440058	0.013
	CMAP	7.444737	3.27011	9.623214	3.005504	0.007
	CV	45.921	4.3004	46.196	3.2698	0.778
	F latency	48.5375	5.355763	47.15357	2.988618	0.225
Tibial	Latency	4.498684	0.740388	4.039286	0.540123	0.007
	CMAP	14.67368	7.126101	15.3625	6.088812	0.682
	CV	44.487	4.0495	45.429	3.1261	0.309
	F latency	51.32838	5.611985	49.17679	3.724008	0.084

Table 3. Motor Nerves Electrophysiology in Cases and Controls

Means of latencies, CMAPs, CVs and F latencies of tested motor nerves of cases are compared against means of controls. In all tested nerves distal latencies and F latencies are higher and CMAPs and CVs are lower in cases than those of controls. Differences in means are statistically significant in median distal latency and F latency; ulnar distal latency, CV & F latency in upper limbs; distal latency and CMAP of peroneal nerve; distal latency of tibial nerves in lower limbs.

Sensory Nerve		Case		Control		p-value
		Mean	Std. Deviation	Mean	Std. Deviation	
Median	Latency	2.476316	0.552113	2.207143	0.14827	0.015
	SNAP	49.263	16.6201	59.125	11.4363	0.009
	CV	54.363	5.8859	55.786	2.9232	0.244
Ulnar	Latency	1.934211	0.297309	1.921429	0.056811	0.823
	SNAP	62.671	12.1685	63.625	7.4494	0.715
	CV	57.395	5.2879	57.804	3.1866	0.601
Sural	Latency	2.554054	0.300319	2.353571	0.412743	0.027
	SNAP	14.392	7.4313	20.125	7.712	0.004
	CV	47.622	4.3484	49.589	4.2667	0.073
Dorsal Sural	Latency	2.048649	0.397996	2.021429	0.263674	0.755
	SNAP	6.703	3.4206	7.679	2.5211	0.209
	CV	51.176	12.5909	51.214	7.7846	0.989
Median Plantar	Latency	2.369737	0.437521	2.210714	0.152362	0.07
	SNAP	9.184	4.3827	16.536	7.8951	<0.001
	CV	53.743	11.0815	57.161	4.5726	0.13

Table 4. Sensory Nerves Electrophysiology in Cases and Controls

Means of latencies SNAPs and CVs of tested sensory nerves of cases are compared against means of controls. In all tested nerves distal latencies and F latencies are higher and SNAPs and CVs are lower in cases than those of controls. Difference in mean statistically significant in median latencies and SNAPS in upper limbs distal latency and SNAP of sural nerve and SNAP of medial plantar nerves in lower limbs.

		Neuropathy	
	Absent	Present	P- Value
Case	17 (44.7%)	21 (55.3%)	<0.001
Control	26 (92.9%)	2 (7.1%)	

Table 5. Neuropathy in Cases and Controls

		Neuropathy	
	Absent	Present	P- Value
Case	22 (57.9%)	16 (42.1%)	0.001
Control	26 (92.9%)	2 (7.1%)	

Table 6. Neuropathy in Cases and Controls without DS and MP Nerves

When medial plantar and dorsal sural are excluded, then neuropathy present in 16 (42.1%) cases and in 2 (7.1%) controls, which is also statistically significant.

Metabolic Indices in Neuropathic and Non-Neuropathic Cases-

Mean ages of neuropathic & non-neuropathic groups are 48.48 (±7.897) and 47.29 (±7.28) respectively but statistically not significant (p value- 0.638)

Mean BMI is higher, (28.25 (±5.27)) for neuropathic group than that of non-neuropathic group (25.16 (±2.64)) and is statistically significant (p value-0.034)

There is statistically significant difference between means of both FBS and PPBS of neuropathic and non-neuropathic groups. Mean FBS of neuropathic group is higher 221.19 (± 41.66), than that of non-neuropathic group 178.35 (± 43.88) with a p value of 0.004.

Means of PPBS of neuropathic group is 320.71 (± 53.288) of non-neuropathic group is 257.29 (± 46.143) with a p value of <0.001.

Neuropathy		Absent		Present		p-value
		Mean	Std. Deviation	Mean	Std. Deviation	
Median	Latency	3.547059	0.386681	4.390476	1.134308	0.006
	CMAP	12.32353	3.403864	12.21429	4.161104	0.931
	CV	55.147	3.8069	51.857	3.9691	0.014
	F latency	26.21875	1.776783	28.94048	2.928763	0.002
Ulnar	Latency	2.579412	0.377102	2.892857	0.432806	0.024
	CMAP	14.69706	3.337686	14.08571	2.805626	0.543
	CV	54.059	3.557	49.214	4.3491	0.001
	F latency	26.5875	2.484921	28.59048	2.47758	0.02
Peroneal	Latency	3.938235	0.443188	4.514286	0.693026	0.005
	CMAP	8.197059	3.758427	6.835714	2.758992	0.206
	CV	47.882	3.209	44.333	4.4787	0.009
	F latency	45.65312	3.647075	50.845	5.452303	0.003
Tibial	Latency	4.147059	0.442461	4.783333	0.816905	0.007
	CMAP	15.41471	5.988003	14.07381	8.025952	0.571
	CV	46.941	3.7578	42.5	3.1265	<0.001
	F latency	48.32188	4.034062	53.61905	5.63417	0.003

Table 7. Motor Neurons Electrophysiology in Neuropathic and Non-neuropathic Patients

Means of Distal latencies, F latencies are higher and CMAPs, CVs are lower in subjects with neuropathy than without neuropathy in all tested motor nerves among cases. Among these statistically significant ones are Means of Median distal latency, CV, F latency; Ulnar distal latency, CV and F latency; peroneal distal latency, CV and F latency; tibial distal latency, CV and F latency.

Neuropathy		Absent		Present		p-value
		Mean	Std. Deviation	Mean	Std. Deviation	
Median	Latency	2.191176	0.187279	2.707143	0.640954	0.003
	SNAP	54.882	14.0951	44.714	17.4217	0.06
	CV	56.941	2.157	52.276	7.0814	0.013
Ulnar	Latency	1.817647	0.148893	2.028571	0.353402	0.028
	SNAP	68	9.1686	58.357	12.7673	0.013
	CV	58.912	4.1467	56.167	5.868	0.113
Sural	Latency	2.4125	0.223979	2.661905	0.310606	0.01
	SNAP	19.125	8.5274	10.786	3.6454	<0.001
	CV	49.188	4.0285	46.429	4.2904	0.055
Dorsal	Latency	1.990625	0.338732	2.092857	0.440819	0.447
Sural	SNAP	7.656	3.4531	5.976	3.2919	0.141
	CV	52.5	11.8926	50.167	13.2969	0.584
Median	Latency	2.232353	0.255527	2.480952	0.522369	0.081
Plantar	SNAP	11.265	4.7766	7.5	3.2596	0.007
	CV	54.031	6.9485	53.524	13.5909	0.893

Table 8. Sensory Nerve Electrophysiology in Neuropathic and Non-neuropathic Patients

Means of Distal latencies, F latencies are higher whereas SNAPs, CVs are lower in subjects with neuropathy than without neuropathy in all tested sensory nerves among cases. Among these statistically significant ones are median distal latency and CV; Ulnar distal latency and SNAP; sural distal latency and SNAP; medial plantar SNAP.

RESULTS –

Autonomic Neuropathy-

	Case	Control	p-value
Normal	28	27	0.048
	73.70%	96.40%	
Early	8	1	
	21.10%	11.10%	
Definite	2	0	
	5.30%	0.00%	
Total	**38**	**28**	
	100.00%	**100.00%**	

Table 9. Autonomic Neuropathy in Cases and Controls

Of total 38 cases, early and definite autonomic neuropathy is present in 8 (21.1%) and 2 (5.3%) cases respectively. No cases of severe autonomic neuropathy are detected. Among 28 controls only 1 (3.57%) subject with early autonomic neuropathy found.

Difference is statistically significant.

Borderline and abnormal HR variation with deep breathing is seen in 27 (71.1%), 8 (21.1%) and 3 (7.9%) patients respectively.

Borderline and abnormal heart rate variation with standing is seen in 23 (60.5%), 11 (28.9%) and 4 (10.5%) patients respectively.

Borderline and abnormal heart rate variation with Valsalva is noted in 30 (79%), 7 (18.4%) and 1 (2.6%) patients respectively.

Borderline postural hypotension is noted among 2 (5.3%) cases and abnormal among none.

Borderline blood pressure variation with sustained hand grip noted in 3 (7.9%) and abnormal variation in none.

DISCUSSION

Compared with previous studies on newly diagnosed diabetic patients, in which alterations were detected, in NCS, in a smaller proportion of subjects, 15.2% by Lehtinen et al., 15.7% by Ratzmann et al., and 4.5% by Partanen et al. These differences could be due to different methods were used, in particular, the criteria adopted to define electrophysiological neuropathy, making a true comparison appears difficult. In Eugenia et al, inclusion criteria were intentionally less strict so as to detect even the smallest electrophysiological signs of neuropathy resulted in 72% of neuropathy.

Ashok et al used a biothesiometer 8 which is less sensitive than NCS studies in detecting neuropathy; Aarindam Datta et al;[7] and HK Gill et al; used Neuropathy Symptom Score, Neuropathy Disability Score and Nerve Conduction Studies and in NCS studies, tested fewer nerves than present study.

In current study total 18 nerves (8 motor, 10 sensory) and 62 parameters are studied per individual and that could be reason behind high prevalence and adding dorsal sural and medial plantar nerve increased the prevalence as expected.[8]

In fact, frank DM may be the final stage of a deranged glucose regulation, preceded by a sustained impaired glucose tolerance; in this sort of a pathophysiological continuum, nerve function may be damaged early on, above all in small fibres (Ratzmann et al., 1991; Novella et al., 2001; Singleton et al., 2001; Sumner et al., 2003). Then, the progression of the neuropathy seems to be quite slow as suggested by Lehtinen et al.'s (1993) 5-year follow-up study. Therefore, it is not surprising that the prevalence of nerve conduction abnormalities in our group, at diagnosis, is having high prevalence.

Study	Number of Patients	Percentage
Present Study	21	55%
Eugenia Rota et, al.	28	72%
Abhay Kumar Pandey et, al.	24	33%
Abhijeet A et, al.	21	42%
Ratzman et.al	95	6.3%
Dipika Bansal et, al	369	9.2%
HK Gill	195	29.2%
Lehtinen et, al.	132	2.3%
Arindam Dutta et, al.	32	32%

Table 10. Prevalence of Peripheral Neuropathy in Various Studies

Of total 38 cases when either only left side and only right-side nerves are considered, neuropathy present 17 (right)and 13 (left) cases only, but there is no statistically significant difference (p value 0.241) between sides. As diabetes is a systemic condition symmetrical involvement is expected and symmetrical distal neuropathy is common in diabetes.[9]

Predominant lower limb involvement than upper limb is consistent with previous studies like S. Kersidag el al;[10] Dyck et al**;**[11] and Rambabu Singh et al; who also found predominant lower limb involvement although actual nerves involved may vary from study to study.

Raised fasting and post prandial blood sugar levels among the neuropathy group is suggesting that chronic elevated blood sugar levels could be the reason behind pathology of neuropathy. Blood sugar levels alter the nerve conduction parameters. The main responsible cause for changing conduction of impulse in nerve is degree of hyperglycaemic hypoxia.[12] Dysfunction of ion conductance, especially voltage gated ion channels could contribute to abnormalities in the generation and conduction of action potential**.**[13] In hyperglycaemic environment, oxidative stress leads to endothelial dysfunction and decreased capillary blood flow which in turn leads to endoneural hypoxia causing death of nerve cells and so nerve conduction parameters are altered.[14]

Studies	No Neuropathy	With Neuropathy	
Present Study	178.3 ± 43.9	221.2	± 41.7
Abhay Kumar Pandey et, al.	197.7 ± 61.2	224.2	± 76.3
Ratzman et.al	210	216	
Arindam Dutta et, al.	197.2 ± 57.6	220.9	± 84

Table 11. FBS Distribution among Neuropathic and Non Neuropathic Patients

Studies	No Neuropathy	With Neuropathy
Present Study	257.3 ± 46.1	320.7 ± 53.29
Abhay Kumar Pandey et al.	302.6 ± 63.8	336.6 ± 78.4
Arindam Dutta et al.	296.44 ± 60.75	333.3 ± 84.01

Table 12. PPBS Distribution among Neuropathic & Non Neuropathic Patients

Present study used Ewing's criteria like Giacomo et al; and results are comparable to it. Giacomo Zoppini et al; using Ewing's criteria in a cohort of 557 patients with newly diagnosed type 2 diabetes reported prevalence of confirmed CAN was 1.8%, whereas that of early CAN was 15.3%. Prevalence did not differ between men and women.[15]

CONCLUSION

Abnormalities of nerve conduction studies and are frequent in patients with both sexes of newly diagnosed diabetes.

- Electrophysiological feature of neuropathy is significantly associated with BMI and both FBS & PPBS.
- Assessment of medial plantar and dorsal sural NCS increases the sensitivity in the detection of neuropathy.
- Early and definite but not severe autonomic dysfunction can be seen in newly diagnosed diabetic patients.
- Electrophysiological evaluation of diabetics in the early stage of disease can detect abnormalities of peripheral and autonomic nerves system.

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