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Autonomic Function Evaluaton in Chronic Polyneuropathies

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Abstract:
Introduction: *Chronic polyneuropathies were most common neuropathies with major emphasis on motor and sensory symptoms with autonomic symptoms overlooked which may be the cause of poor quality of life and mortality.**Aims and Objectives of the Study: 1.**To study the frequency of occurrence of autonomic dysfunction in chronic polyneuropathies.2.To study the pattern of autonomic dysfunction in chronic polyneuropathies.3.To quantitate the severity of autonomic dysfunction using Ewing's criteria.*
Methods: *A sample of 97 chronic polyneuropathycases fulfilling the inclusion and exclusion criteria were taken and autonomic functions were analysed using CAN 504 analyser, sympathetic skin response.*
Results: *Out of 97 cases,DM with polyneuropathy (DPN) were 35 cases (36%, M:F=54:46), CIDP were 26 cases (27%, M:F=69:31) and other polyneuropathies were 36 cases (37%, M:F=67:33). Majority of the cases were having autonomic symptoms (61%).Most common symptomwas orthostatic dizziness. Only mild dysfunction was seen in 48% cases,early diagnosis and treatment may prevent progression to severe dysfunction in majority of chronic polyneuropathies.Definite and severe autonomic dysfunction was more common in CIDP (43%). Among heart rate variable components of autonomic tests highest involvement was seen in standing 30:15 ratio (48%). Both parasympathetic (cardio vagal) and sympathetic (adrenergic) systems were affected, parasympathetic (73%) being more involved than sympathetic system (59%) in the total study population.*
Conclusions: *Autonomic dysfunction in chronic polyneuropathies is common, under diagnosed and potentially treatable disease.Mild autonomic dysfunction is more common than definite and severe dysfunction. Early diagnosis and treatment of underlying cause may prevent further progression. Early treatment would prevent morbidity, mortality and can improve the quality of life.*

Key words: *Chronicpolyneuropathies, Autonomic function, Cardiac Autonomic Function.*

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I. Introduction

Most polyneuropathies produce mixed sensory motor deficits and some degree of autonomic dysfunction. One of the most overlooked of all complications of polyneuropathies is autonomic dysfunction. Autonomic dysfunction can lead to dysfunctional heart-rate control, abnormal vascular dynamics, gastrointestinal symptoms and abnormal sweating.Collectively, these may contribute to an increased risk of morbidity and mortality.

These can be even more troublesome in chronic polyneuropathies which are most common neuropathies[(7)] as major emphasis was only on motor and sensory symptoms, which can lead to poor quality of life because of non-treatment of autonomic dysfunction.

There is a paucity of quantitative studies assessing autonomic dysfunction in both Western and Indian setting. Hence, there is a need for a prospective study to accurately ascertain the actual prevalence of autonomic dysfunction (both clinical and subclinical) in patients with chronic polyneuropathies and to quantify the degree of dysfunction.

Aims and Objectives:

1. To study the frequency of occurrence of autonomic dysfunction in chronic polyneuropathies.
2. To study the pattern of autonomic dysfunction in chronic polyneuropathies.
3. To quantitate the severity of autonomic dysfunction using Ewing's criteria.

II. Materials and Methods

Study Design: Cross sectional observational study**.**
Study period: April 2016 to February2018
Sample size: 97 cases (35 Type 2 DM, 26 CIDP, 36 other neuropathies)
Inclusion criteria: Patients above 15 years and below 70 years of age with features of chronic polyneuropathy (more than 3 months) with Nerve conduction studies (NCS) confirmation presenting to Department of Neurology,Andhra Medical College,Visakhapatnam.

Exclusion criteria:
Acute polyneuropathies,
Subjects with polyneuropathies of more than one etiological possibility,
History of coronary heart disease, myocardial infarction, heart failure (NYHA class III– IV), or cardiac pacemaker
Any medication that may adversely influence autonomic functions
Informed written consent from patient/parent/guardian was taken after explaining in their understandable language. Detailed history and thorough clinical examination was done in all the study subjects.
The study subjects were subdivided based on diagnosis into 3 subgroups:
Diabetes mellitus with polyneuropathy (DPN),
Chronic inflammatory demyelinating polyneuropathy (CIDP),
Other Polyneuropathies (others).
For all study participants routine haematological investigations like hemogram, blood sugar analysis, serum creatinine, serum electrolytes, viral screening, electrocardiography (ECG) and nerve conduction studies were done. Serum protein electrophoresis and nerve biopsy were done if indicated for etiological purposes.
For all the study participants autonomic function tests were evaluated using automated CANS 504 analyser and sympathetic skin response (SSR) was done using Nicolet Viking Machine.**Clinical testing of autonomic neuropathy function:**

Heart rate response to breathing:

The patient lies quietly and breathes deeply at a rate of six breaths per minute (a rate that produces maximum variation in heart rate) while a heart monitor records the difference between the maximum and minimum heart rates.

Heart rate response to standing:

In healthy subjects there is characteristic and rapid increase in heart rate in response to standing that is maximal at approximately the 15^{th} beat after standing. This is followed by a relative bradycardia that is maximal at approximately the 30^{th} beat after standing. In patients with autonomic neuropathy, the maximum and minimum R-R intervals may not always occur at exactly the 15^{th} or 30^{th} beats after standing respectively.

Valsalvamaneuver:

In healthy subjects the reflex response to the Valsalva manoeuvre includes tachycardia and peripheral vasoconstriction during strain, followed by an overshoot in BP and bradycardia after release of strain.

The response is mediated through alternating activation of parasympathetic and sympathetic nerve fibers. In patients with autonomic damage the reflex pathways are damaged. This is seen as a blunted heart rate response and sometimes as a lower than normal decline in blood pressure during strain followed by slow recovery after release.

Technique**:** In the standard Valsalva manoeuvre the supine patient forcibly exhales for15 seconds against a fixed resistance of 40mmHg with an open glottis.

The Valsalva ratio is determined from ECG tracings by calculating the ratio of longest R-R interval after the manoeuvre (reflecting bradycardic response to blood pressure overshoot) to shortest R-R interval during or shortly after the manoeuvre (reflecting tachycardia as a result of strain).

Systolic Blood pressure response to standing:

In healthy subjects, there is an immediate pooling of blood in the dependant circulation resulting in fall in BP that is rapidly corrected by baroreflex mediated peripheral vasoconstriction and tachycardia.. In patients with autonomic neuropathy, baroreflex compensation is impaired. A response is considered abnormal when diastolic BP decrease more than 10mmHg or systolic BP falls by 30mmHg within 2 minutes after standing. A task force of American Academy of Neurology and American Autonomic Society defined orthostatic hypotension as fall in systolic BP of >20mmHg or diastolic BP of >10mmHg accompanied by symptoms.

Diastolic Blood Pressure response to sustained hand grip:

In this test, sustained muscle contraction measured by handgrip dynamometer leads to rise in systolic and diastolic blood pressure and heart rate, caused by a reflex arc from the exercising muscle to central command and back along efferent fibers, innervating the heart and muscle, resulting in increased cardiac output, blood pressure and heart rate. The dynamometer is first squeezed to isometric maximum and then held at 30% maximum for 5 min. The normal response is a rise of diastolic blood pressure >16mmHg whereas a response of <10mmHg is considered abnormal.

Sympathetic skin response:

For the palmar SSR, surface electrodes were used with the active recording electrode placed on the palm of the hand and the reference electrode located at the wrist on the dorsum of the hand. SSR parameter included the latency to the onset of depolarization which was indicated by the first continuous deflection from the baseline. The amplitude was measured from peak to peak. Four successive SSRs were induced by unexpected acoustic stimuli, pinprick, touching and median nerve electrical stimulation at 30 milli ampere stimulus intensity. The stimulating electrodes were placed over the contralateral median nerve. The mean of these four latencies and amplitudes were accepted as the valid value.

The study used an electromyography machine with the filter settings for the low frequency at 0.5 hertz (Hz), and the high frequency at 500 Hz. The sweep speed was set at 300–500 milli seconds per division. Examinations were performed in a quiet room and skin temperature was maintained at >32ºC.

Summary of autonomic function tests done in Cardiac autonomic neuropathy(CAN)

	Normal	Borderline	Abnormal
1. Resting Heart rate	<100bpm	-	>100bpm
2. HR to Valsalva>1.21		1.11-1.20	1.10
3. HR to deep breath	>15bpm	11-14bpm	10bpm
4. HR to standing	>1.04	1.01-103	1.00
5 .Postural BP: Sys fall	<10mmHg	10-20	>30mmHg
6. Sustained handgrip	>16	10-15	<10

First four heart rate tests are parasympathetic and remaining two blood pressure tests are sympathetic in character.

For quantitating autonomic dysfunction (or) cardiac autonomic neuropathy (CAN), Ewing's criteria was used. [(2)]

Ewing's criteria for quantitation of CAN

Normal	All Normal or 1 Borderline
Early	HR tests 1 Grade 2 or 2 Grade 1
Definite	HR tests 2 Grade 2
Severe	HR tests 2 Grade 2+ 1 Grade 2 BP test HR tests 2 Grade 2+ 2 Grade 1 BP test

Descriptive statistics were expressed as means and percentages. Chi-squared test was applied for comparison of variables.For the statistical analysis SPSS software was used.

III. Results

The study included total 97 participants.Males were 61(62.9%) and females were 36(37.1%). DM with polyneuropathy (DPN) were 35 cases (36%, M:F=54:46), CIDP were 26 cases (27%, M:F=69:31) and other polyneuropathies were 36 cases (37%, M:F=67:33) The distribution of the study subjects in other polyneuropathies subgroup is shown as below.

Other polyneuropathies- diagnosis wise

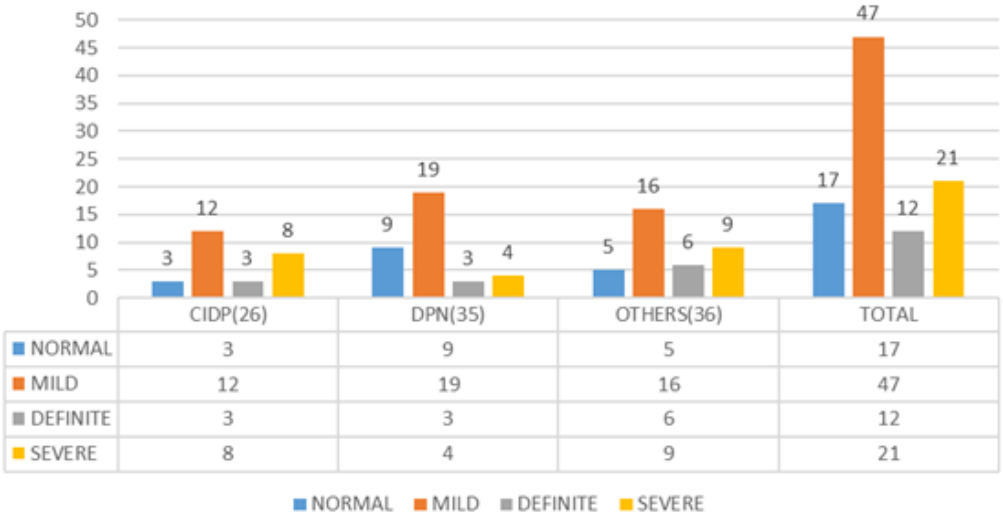
OTHER POLYNEUROPATHIES	MALE	FEMALE	TOTAL
Nutritional & alcohol related	12	1	13
Lepromatous leprosy polyneuropathy	3	2	5
Uremic polyneuropathy	2	1	3
Chemotherapy related	0	3	3
Monoclonal gammopathy	3	0	3
Hereditary polyneuropathy	4	5	9
			36

Mean age of the total study population was 45.3 (± 13.617). In DPN, CIDP and other subgroups the mean ages were 45.6 ± 9.98, 50.11 ± 13.30 and 41.55 ± 15.92 respectively. Average duration of disease was 4.71 ± 3.2.At least one autonomic symptom was reported in 59 cases (61%),with orthostatic dizziness being most common symptom.Sympathetic skin response was abnormal in 17 cases (48.5%) of DPN, 15 cases (57.6%) of CIDP and 20 cases (55.5%) of other polyneuropathies in this study.

Cardiac Autonomic functions: Of the total 97 cases autonomic dysfunction according to Ewing's criteria was present in 80 cases (82.4%), out of which mild dysfunction was seen in 47 cases (48.45%), definite dysfunction in 12 cases (12.3%) and severe dysfunction in 21 cases (21.6%).

In DPN cases out of 35 cases mild autonomic dysfunction was seen in 19 cases (54.28%), definite dysfunction in 3 cases (8.57%) and severe dysfunction in 4 cases (11.43%).In CIDP subjects out of 26 cases mild autonomic involvement was seen in 12 cases (46.15%), definite involvement in 3 cases (11.54%) and severe involvement in 8 cases (30.77%).In other polyneuropathy subjects out of 36 cases mild autonomic involvement was seen in 16 cases (44.4%), definite involvement in 6 cases 16.67%) and severe involvement in 9 cases(25%).

CAN grading in different subgroups



In other polyneuropathies subgroup, autonomic dysfunction according to CAN was seen in 85% of nutritional & alcohol related polyneuropathies. All the three cases each in chemotherapy related and uremic polyneuropathies showed autonomic dysfunction (100%). In each of Hansen's polyneuropathy, monoclonal gammopathy related polyneuropathies, and hereditary polyneuropathies 66% of patients showed evidence of autonomic dysfunction.

Pattern of individual components of CAN:

	DPN	CIDP	OTHERS
Rest Heart rate			
NORMAL	28(80)	18(69)	25(69)
BORDERLINE	0	3(12)	1(3)
ABNORMAL	7(20)	5(19)	10(28)
Deep Breath			
NORMAL	26(74)	10(38)	30(83)
BORDERLINE	3(9)	5(19)	0
ABNORMAL	6(17)	11(43)	6(17)
Standing			
NORMAL	13(37)	9(35)	12(34)
BORDERLINE	7(20)	6(23)	3(8)
ABNORMAL	15(43)	11(42)	21(58)
Valsalva			
NORMAL	30(86)	16(62)	21(58)
BORDERLINE	2(6)	5(19)	7(20)
ABNORMAL	3(8)	5(19)	8(22)
POSTURAL HYPOTENSION			
NORMAL	24(69)	21(81)	33(92)
BORDERLINE	11(31)	5(19)	3(8)
ABNORMAL	0	0	0
ISOMETRICHANDGRIP			
NORMAL	3(9)	2(8)	8(22)

BORDERLINE	11(31)	7(27)	8(22)
ABNORMAL	21(60)	17(65)	20(56)

Both parasympathetic and sympathetic systems were affected. Parasympathetic (73%) being more involved than sympathetic system (59%). Definite parasympathetic involvement was seen in 71.4%, 73% and 75% of cases and the definite sympathetic involvement was seen in 60%, 65.3% and 55.5% of cases in DPN,CIDP and other polyneuropathies respectively each.

Cardiac autonomic dysfunction: Among subjects with autonomic dysfunction advancing age (age>40) and female sex were risk factors for more severe involvement with p values 0.053 and 0.0327 respectively. There was no significant correlation between autonomic dysfunction and disease duration with p value 0.6850. Subjects with autonomic symptoms were associated with more severe cardiac autonomic involvement compared to those without symptoms with p value 0.0340.

CAN grade comparison DPN vs CIDP

DIAGNOSIS	CAN – Grade 0 ,1	CAN – Grade 2,3	
CIDP	15(57.6%)	11(42.3%)	
DPN	28(80%)	7(20%)	P=0.061

When compared to diabetes with polyneuropathy, cases with CIDP had more frequency of definite and severe autonomic dysfunction with p value 0.061.

CAN grade comparison CIDP vs others

DIAGNOSIS	CAN – Grade 0 ,1	CAN – Grade 2,3	
CIDP	15(57.6%)	11(42.3%)	
OTHERS	21(58.3%)	15(41.6%)	P=0.96

Subjects with CIDP and other polyneuropathies had almost similar prevalence of definite and severe autonomic dysfunction with p value 0.96.

CAN grade comparison DPN vs others

DIAGNOSIS	CAN – Grade 0 ,1	CAN – Grade 2,3	
OTHERS	21(58.3%)	15(41.6%)	
DPN	28(80%)	7(20%)	P=0.05

When compared to diabetes with polyneuropathy, cases with other polyneuropathies had more prevalence of definite and severe autonomic dysfunction with p value 0.05.

IV. Discussion

This is one of the first studies done in India evaluating and comparing the pattern of autonomic dysfunction in chronic polyneuropathies.Majority of the cases were having autonomic symptoms (61%). In the present study, most common symptom in DPN was orthostatic dizziness followed by gastrointestinal symptoms. This finding was in accordance with studies by Low et al. [(3)] and Suarez et al. [(4)]Most common symptom in CIDP subgroup was orthostatic dizziness seen in 46% of cases followed by sweat abnormalities. The occurrence of clinical symptoms of autonomic dysfunction in the present study was about 61.5% in CIDP group where as it was higher in Suresh et al.[(5)]study (78%). The variation in frequency of symptoms between studies could be due to less emphasis on autonomic symptoms and due to recall bias in retrospective studies. This emphasizes the need for a systematic questionnaire-based approach at initial presentation for exact documentation of the profile of autonomic symptoms.

In this study subjects with autonomic symptoms were having more severe cardiac autonomic involvement compared to those without symptoms with p value 0.034, similar to Dimitropoulos et al. [(6)]study which showed that autonomic symptoms will develop mostly in advanced stages of the disease.

Autonomic dysfunction was common in chronic polyneuropathies as majority of cases (82%) showed evidence of CAN abnormality in the present study.Even if only definite and severe autonomic dysfunction was considered abnormal then 34% of cases had evidence of autonomic dysfunction. Only mild dysfunction was seen in 48% cases,early diagnosis and treatment may prevent progression to severe dysfunction in majority of chronic polyneuropathies.

Definite and severe autonomic dysfunction was more common in CIDP (43%). Mild autonomic dysfunction was more prominent in DPN cases (55%). Among heart rate variable components of autonomic tests highest involvement was seen in standing 30:15 ratio (48%), followed by heart rate variability with deep breathing (24%). Rest heart rate was abnormal in 22% and Valsalva ratio was abnormal in 17% of cases. These patients with heart rate abnormalities are at higher risk of cardiovascular complications and mortality. [(7)] None

of the cases had definite abnormal blood pressure variables.Isometric handgrip was abnormal in majority of the cases (60%), but it can be false positive as most of the patients with polyneuropathy will have grip difficulty due to weakness of the hand muscles.

In the present study resting heart rate was abnormal in 22% of cases. Similar frequency was seen in study by Lyu et al.[8] Resting heart rate abnormalities may progress later to fixed and unresponsive heart rate to breathing, which indicates more severe denervation and severe CAN.[7,9]. According to Dimitropoulos et al. resting heart rate can be used as a diagnostic and prognostic tool in patients with DM after excluding other causes of tachycardia. [6]

Comparision of various studies CAN in Diabetes mellitus type 2 to present study:

Study	Patients, (n)	E:I ratio	Standing 30:15	Valsalva	Postural Hypo	Frequency of CAN
Low et al. [3]	148	-	-	-	-	73%
Chen et al. [10]	612	61%	76%	19%	32%	60.6%
Eze et al. [11]	79	58%	60%	51%	61%	44.3%
Lerner et al. [12]	384	21%	50%	48%	4%	37%
Mendevil et al.[13]	154	45%	47%	24%	-	68%
Menon et al. [14]	74	66%	28%	-	14%	31%
Tahrani et al. [15]	266	-	-	-	-	40.9%
Present study	35	26%	63%	14%	31%	74%

In the present study, cardiac autonomic dysfunction was present in 74% of cases, which was similar to Low et al.[21] study (73%), Mendevil et al.[13] study (68%) and Menon et al.[14] study (66.2%), but was higher by approximately 20% compared to other studies. This higher prevalence can be due to evaluation of CAN in patients who already had polyneuropathy and also due to the hospital based nature of the present study. Except Menon et al study, standing 30:15 ratio was the most common abnormal component in all the above studies, where it was second most abnormal component following standing E:I ratio.

Comparision of various studies CAN in CIDP to the present study:

Study	Stamboulis et al. [17]	Lyu et al [8]	Ingall et al [18]	Figueroa et al [19]	Suresh et al [5]	Present study
Number	17	12	14	47	38	26
Autonomic involvement	76%	25%	85%	47%	87%	88%
SSR	12%	50%	-	34%	63%	57%
Cardio vagal	53%	-	-	21%	86%	73%
Adrenergic	53%	-	-	9%	55%	65%
E: I	0	9%	28%	-	76%	62%
30:15	29%	20%	21%	-	-	65%
Valsalva	18%	36%	0	-	47%	38%
Postural BP	18%	17%	0	-	23%	19%

Both parasympathetic (cardio vagal) and sympathetic (adrenergic) systems were affected, parasympathetic (73%) being more involved than sympathetic system (59%) in the total study population.Low et al. [3] and Suresh et al,[5] reported similar results in T2DM patients and CIDP cases respetively.Similar level of parasympathetic involvement was seen in all the three subgroups, but sympathetic involvement was higher in CIDP (66%) compared to DPN (60%) and others (56%).

CAN IN OTHER POLYNEUROPATHIES:

OTHER POLYNEUROPATHIES	Patients (n)	CAN prevalence			TOTAL CAN
		Mild	Definite	Severe	
Nutritional & Alcoholic	13	7	2	2	11
Hansen's polyneuropathy	5	3	1	0	4
Uremic polyneuropathy	3	0	1	2	3
Chemotherapy related	3	0	1	2	3
Monoclonal gammopathy	3	1	0	1	2
Hereditary	9	4	0	2	6
Total	36	15	5	9	31

CAN abnormality in other polyneuropathy group was higher when compared to previous other studies[16] may be due to hospital based nature of the study, where patients with more severe disease tendto get admitted to the hospital more frequently.Subgroup of other polyneuropathies was having different cases of nutritional and alcoholic, Hansen's, uremic, chemotherapeutic, paraprotein related polyneuropathies in very small numbers individually to draw conclusions.

Limitations of our study:
Hospital based study.
Observational study.
Subgroups with unequal sample size..
Cases of different diagnoses in other polyneuropathies subgroup.

V. Conclusions

Autonomic dysfunction in chronic polyneuropathies is common, under diagnosed and potentially treatable disease.
Mild autonomic dysfunction is more common than definite and severe dysfunction.
Heart rate variation with standing 30:15 ratio is the most common abnormality in autonomic function tests. These patients are at an increased risk for cardio vascular complications and mortality.
CIDP and other chronic polyneuropathies are more frequently correlated with more severe autonomic dysfunction, when compared to patients with polyneuropathy of T2DM.
There is involvement of both sympathetic and parasympathetic systems with more common involvement of parasympathetic system.
Sympathetic skin response abnormality also correlated with the presence of autonomic dysfunction in chronic polyneuropathies, but it is unreliable compared to other autonomic function tests as it can habituate.

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