Original Article

The Prevalence and Severity of Autonomic Dysfunction in Chronic Inflammatory Demyelinating Polyneuropathy

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Abstract

Introduction: In chronic inflammatory demyelinating polyneuropathy (CIDP), emphasis has been on motor disabilities, and autonomic dysfunction in these patients has not been addressed systematically. **Materials and Methods:** Autonomic function was prospectively analyzed in 38 patients with CIDP. Quantitative autonomic function testing was done using Finometer® PRO and severity of adrenergic and cardiovagal dysfunction graded according to composite autonomic severity score and sudomotor dysfunction assessed using sympathetic skin response. **Results:** Thirty-four (89%) patients had features of autonomic dysfunction. Thirty-three (86%) patients had cardiovagal dysfunction, 21 (55%) had adrenergic dysfunction, and 24 (63%) had sudomotor dysfunction. Autonomic dysfunction was mild to moderate in the majority (86%). **Conclusions:** Autonomic dysfunction in CIDP is underreported and potentially amenable to therapy. Our cohort had a high proportion of adrenergic dysfunction compared to previous studies.

Keywords: Autonomic dysfunction, chronic inflammatory demyelinating polyneuropathy, orthostatic hypotension, postural orthostatic tachycardia syndrome, valsalva maneuver

Introduction

Chronic inflammatory demyelinating polyneuropathy (CIDP) is a common cause of chronic neuropathy, first described in 1958 by James Austin as a steroid-responsive relapsing polyneuropathy.[1,2] In view of the profound motor weakness, emphasis has always been on the motor disabilities in this condition. Abnormalities of the small myelinated and unmyelinated fibers could lead to autonomic dysfunction,[3] and the autonomic dysfunction in these patients has not been systematically addressed in the clinical setting. Identifying the domains of autonomic involvement is important and will help in planning targeted treatment strategies.

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 a cohort of patients with CIDP and to quantify the degree of dysfunction.

The objective of the present study was to assess the frequency of occurrence, spectrum, severity, and effect of the treatment of autonomic dysfunction in patients with CIDP.

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Materials and Methods

The study was conducted in the Department of Neurology, Christian Medical College and Hospital, a 2500 bedded tertiary hospital in South India. Eligible participants were recruited from the neurology outpatient clinics or wards (study period: January 2013 to December 2015). The study design was a prospective cross-sectional study. The study design and methods were approved by the Institutional Review Board. Patients diagnosed to have CIDP by European Federation of Neurological Societies/Peripheral Nerve Society 2010 criteria[4] were included in the study after obtaining informed consent. Only patients with "typical CIDP"[5] were included in the study. The patients with "clinical variants of CIDP"[5] and coexistent diabetes mellitus, paraproteinemia, lymphomas, inherited neuropathies, or amyloidosis were excluded from the study.

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Baseline demographic data were recorded and a detailed neurological examination was done in all patients. Total neuropathy score (TNS)[6] was used as a standardized measurement of severity of motor, sensory, and autonomic deficits. The total score is expressed as a composite score ranging from 0 (no impairment) to 40 (maximal impairment). Composite autonomic symptom score-31 (COMPASS-31) scoring system[7] (minimum 0, maximum 75) was used to score severity of autonomic symptoms.

Quantitative autonomic function tests (AFTs) used for assessment included valsalva ratio and heart rate response to deep breathing, the beat-to-beat blood pressure measurements in response to head-up tilt test (HUT) and valsalva maneuver, and sympathetic skin response (SSR).[8-13] Composite autonomic scoring scale (CASS) is a ten-point scale for autonomic function based on autonomic reflex screen.[14] CASS allots four points for adrenergic function and three points each for cardiovagal and sudomotor function. The severity of adrenergic and cardiovagal dysfunction was graded according to the CASS system. In view of lack of facilities for quantitative sudomotor axonal reflex test (QSART), SSR was used to assess sudomotor functions.[15,16]

Data were acquired from Finometer PRO™ which provided a noninvasive beat-to-beat blood pressure measurement and provided accurate measurements through return-to-flow calibration using an inflatable arm cuff and direct graphic parameter visualization on a built-in flat screen. All the tests were performed in a silent room with a temperature of 22°C–25°C.

Statistical analysis was done using SPSS software (Version 16). Chi-square test was used to compare categorical variables. Student's *t*-test and ANOVA were used for comparison of continuous variables. $P < 0.05$ was considered statistically significant

Results

Thirty-eight patients were included in the study. The study population comprised 84% of males and 16% of females. The mean age at the time of autonomic testing was 46.55 (standard deviation [SD] 12.9 years) and duration of illness was 3.76 (SD 3.59 years). The baseline and demographic variables are as presented in Table 1. The distribution according to severity based on TNS score included: severe (TNS >20) 21 (55.3%), moderate (TNS 10–19) 15 (39.5%), and mild (TNS <10) 1 (5.3%).

In our study, 30 of 38 had autonomic symptoms; distribution was as follows: sicca symptoms in 24/38 (91%), orthostatic intolerance in 14/38 (58%), gastrointestinal and sudomotor in 20/38 (52%), sexual dysfunction in 9/38 (23%), vasomotor in 7/38 (18%), and genitourinary symptoms in 6/38 (15%) patients.

On quantitative autonomic function testing, 33 of 38 (86%) patients had features of autonomic dysfunction. Twenty-four of 38 (63%) patients had sudomotor dysfunction, 33 of 38 (86%) had cardiovagal dysfunction, and 21 of 38 (55%) had adrenergic dysfunction. The severity of the adrenergic and cardiovagal dysfunction was graded according to the CASS system as represented in Table 2.

During HUT, 9 of 38 (23%) patients had orthostatic hypotension and 5 of 38 (13%) had postural orthostatic tachycardia syndrome (POTS). Abnormal heart rate variability with deep breathing was detected in 29 of 38 (76%) patients. Valsalva ratio was abnormal in 18 of 38 (47%) patients, and blood pressure changes in valsalva maneuver showed abnormal responses in 17/38 (44%) patients. These abnormalities have been depicted in detail in Table 3. Sample recordings showing orthostatic hypotension, POTS, and abnormal responses to valsalva have been shown in Figure 1. SSR was absent in 22 of 38 (58%) patients. It was absent in 16 of 38 (42%) patients in lower limbs and 6 of 38 (16%) in both upper limbs and lower limbs.

The predictors of severity of autonomic dysfunction in the cohort assessed included age at onset more than 40 years ($P = 0.05$), duration of disease more than 4 years ($P = 0.16$), baseline TNS score more than 20 ($P = 0.48$), COMPASS 31 score ($P = 0.04$), female sex ($P = 0.048$), and course of disease ($P = 0.79$).

Discussion

This prospective cohort with CIDP revealed a relatively high prevalence of autonomic symptoms and abnormalities in

Table 1: Demographic and disease characteristics of patients with chronic inflammatory demyelinating polyneuropathy

Characteristics	Values
Age at onset, years (mean±SD)	46.55±12.9
Male, *n* (%)	32 (84.21)
Disease duration, years (mean±SD)	3.76±3.59
Acute onset CIDP, *n* (%)	3 (7.8)
Progressive course, *n* (%)	20 (52.6)
Relapsing and remitting, *n* (%)	15 (39.4)
CSF nucleated cells (cells/dL), mean±SD (*n*=32)	7.09±11.08
COMPASS 31 score (mean±SD)	9.0±5.16
TNS (mean±SD)	19.47±5.34

TNS = Total neuropathy score, CIDP = Chronic inflammatory demyelinating polyneuropathy, COMPASS = Composite autonomic symptom score, CSF = Cerebrospinal fluid, SD = Standard deviation

Table 2: Severity of adrenergic and cardiovagal score according to composite autonomic scoring scale in patients with chronic inflammatory demyelinating polyneuropathy

Score	Adrenergic, *n/t* (%)	Cardiovagal, *n/t* (%)
0	17/38 (45)	3/38 (13)
1	5/38 (13)	19/38 (50)
2	6/38 (16)	14/38 (37)
3	4/38 (10)	0/38
4	6/38 (16)	N/A

N/A = Not applicable

quantitative AFTs. The prevalence of autonomic dysfunction in patients with CIDP based on previous studies varies from 21% to 76%.[3,17,18] However, most of these studies were retrospective, and factors such as selection and recall bias could account for the high variability in prevalence of autonomic dysfunction. The difference in prevalence of quantitative autonomic dysfunction could be explained by the study setting, methodology of AFTs, and temporal profile of disease (acute versus chronic).

The prevalence of clinical symptoms of autonomic dysfunction in our study using the COMPASS 31 score was about 78%. This is much higher than previously reported in literature.[17,19,20] 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 again emphasizes the need for a systematic questionnaire-based approach at initial presentation for exact documentation of the profile of autonomic symptoms.

Table 3: Heart rate variability with deep breathing and valsalva responses in patients with chronic inflammatory demyelinating polyneuropathy

	n (%)
Heart rate variation with deep breathing	
Decreased ≥50% of minimum	14 (37)
Decreased ≤50% of minimum	15 (39)
Valsalva ratio	
Decreased ≥50% of minimum	17 (45)
Decreased ≤50% of minimum	1 (2)
Blood pressure response to valsalva	
Exaggerated early blood pressure Phase 2 fall (mmHg)	
20-40	4 (10)
≥40	6 (15)
Blunted late Phase 2 response	17 (44)
Absent Phase 4 blood pressures over shoot	11 (28)

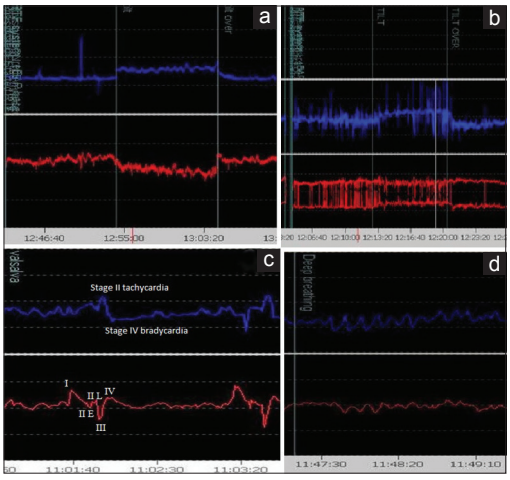

Figure 1: X-axis indicates the time and Y-axis in upper trace indicates pulse rate and lower trace indicates blood pressure. During head-up tilt test (a and b): (a) Drop in blood pressure more than 40 mm Hg (OH) with appropriate rise in pulse rate (b) Rise in pulse rate greater than 120/min without change in blood pressure (postural orthostatic tachycardia syndrome). (c) Stages of valsalva maneuver (d) heart rate variation with deep breathing

In this study, we found that 33 of 38 (86%) of CIDP patients had quantitative autonomic dysfunction. In comparison, Stamboulis *et al*.(*n* = 17) reported autonomic dysfunction in 76% of CIDP patients.[17] Figueroa *et al*.(*n* = 47) reported autonomic dysfunction in 47% of CIDP patients.[19] Among 86% of our patients with abnormal AFTs, 78% had clinical symptoms suggestive of autonomic system involvement. These observations were comparable to previously published data. Stamboulis *et al*. reported (*n* = 17) AFT abnormalities in 13 patients, among them ten had clinical symptoms indicative of autonomic involvement. Overall, these observations support the fact that there is a substantial subset of patients with subclinical autonomic dysfunction in CIDP.

In our study, both parasympathetic and sympathetic systems were affected, cholinergic (86%) being more involved than adrenergic system (55%). One important observation of our study was that 9 of 38 (23%) patients had orthostatic hypotension and 5 of 38 (13%) had POTS.[21] Stamboulis *et al*. (*n* = 17) reported that both arms of autonomic systems were affected equally. Figueroa *et al*. (*n* = 47) reported that cholinergic systems (40%) were involved predominantly with relative sparing of adrenergic system. Lyu *et al*. reported autonomic dysfunction in CIDP patients (*n* = 12), which involved both arms of autonomic system equally. An interesting observation in our cohort was the fact that there were a substantial proportion of patients with moderate to severe adrenergic dysfunction (10, 26%) in comparison with cholinergic dysfunction which though common was mild in majority.

Meticulous documentation of symptoms using standardized questionnaire and quantitative autonomic function testing is essential in providing holistic care in patients with CIDP.

In the acute setting, plasmapheresis may worsen autonomic symptoms in patients with autonomic dysfunction and could therefore be avoided. Recognizing and management of autonomic symptoms would result in improvement of the quality of life of patients with CIDP. Serial testing of autonomic functions could also help in assessing response to therapy and predicting relapse.

The limitations of the study included a relatively small sample size. QSART was not done as a result of which sudomotor dysfunction could not be quantitatively assessed as mentioned earlier.

Conclusions

Autonomic dysfunction in CIDP is an underdiagnosed entity with a high prevalence. There is involvement of both the sympathetic (55%) and parasympathetic arms (86%), with more severe involvement of the sympathetic arm. The severity of involvement is greater than previously reported literature.

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Conflicts of interest

There are no conflicts of interest.

References

1. Austin JH. Recurrent polyneuropathies and their corticosteroid treatment; with five-year observations of a placebo-controlled case treated with corticotrophin, cortisone, and prednisone. Brain 1958;81:157-92.
2. Dyck PJ, Lais AC, Ohta M, Bastron JA, Okazaki H, Groover RV. Chronic inflammatory polyradiculoneuropathy. Mayo Clin Proc 1975;50:621-37.
3. Ingall TJ, McLeod JG, Tamura N. Autonomic function and unmyelinated fibers in chronic inflammatory demyelinating polyradiculoneuropathy. Muscle Nerve 1990;13:70-6.
4. Joint Task Force of the EFNS and the PNS. European Federation of Neurological Societies/Peripheral Nerve Society Guideline on management of paraproteinemic demyelinating neuropathies. Report of a Joint Task Force of the European Federation of Neurological Societies and the Peripheral Nerve Society – First revision. J Peripher Nerv Syst 2010;15:185-95.
5. Gorson KC, Katz J. Chronic inflammatory demyelinating polyneuropathy. Neurol Clin 2013;31:511-32.
6. Cornblath DR, Chaudhry V, Carter K, Lee D, Seysedadr M, Miernicki M, *et al.* Total neuropathy score: Validation and reliability study. Neurology 1999;53:1660-4.
7. Sletten DM, Suarez GA, Low PA, Mandrekar J, Singer W. COMPASS 31: A refined and abbreviated Composite Autonomic Symptom Score. Mayo Clin Proc 2012;87:1196-201.
8. Baldwa VS, Ewing DJ. Heart rate response to Valsalva manoeuvre. Reproducibility in normals, and relation to variation in resting heart rate in diabetics. Br Heart J 1977;39:641-4.
9. Kapoor WN, Smith MA, Miller NL. Upright tilt testing in evaluating syncope: A comprehensive literature review. Am J Med 1994;97:78-88.
10. Samoil D, Grubb BP. Head-upright tilt table testing for recurrent, unexplained syncope. Clin Cardiol 1993;16:763-6.
11. Ravits JM. AAEM minimonograph #48: Autonomic nervous system testing. Muscle Nerve 1997;20:919-37.
12. Consensus statement on the definition of orthostatic hypotension, pure autonomic failure, and multiple system atrophy. The Consensus Committee of the American Autonomic Society and the American Academy of Neurology. Neurology 1996;46:1470.
13. Benarroch EE. Postural tachycardia syndrome: A heterogeneous and multifactorial disorder. Mayo Clin Proc 2012;87:1214-25.
14. Low PA. Composite autonomic scoring scale for laboratory quantification of generalized autonomic failure. Mayo Clin Proc 1993;68:748-52.
15. Gutrecht JA. Sympathetic skin response. J Clin Neurophysiol 1994;11:519-24.
16. Hoeldtke RD, Davis KM, Hshieh PB, Gaspar SR, Dworkin GE. Autonomic surface potential analysis: Assessment of reproducibility and sensitivity. Muscle Nerve 1992;15:926-31.
17. Stamboulis E, Katsaros N, Koutsis G, Iakovidou H, Giannakopoulou A, Simintzi I. Clinical and subclinical autonomic dysfunction in chronic inflammatory demyelinating polyradiculoneuropathy. Muscle Nerve 2006;33:78-84.
18. Lyu RK, Tang LM, Wu YR, Chen ST. Cardiovascular autonomic function and sympathetic skin response in chronic inflammatory demyelinating polyradiculoneuropathy. Muscle Nerve 2002;26:669-72.
19. Figueroa JJ, Dyck PJ, Laughlin RS, Mercado JA, Massie R, Sandroni P, *et al.* Autonomic dysfunction in chronic inflammatory demyelinating polyradiculoneuropathy. Neurology 2012;78:702-8.
20. Chiang MC, Lin YH, Pan CL, Tseng TJ, Lin WM, Hsieh ST. Cutaneous innervation in chronic inflammatory demyelinating polyneuropathy. Neurology 2002;59:1094-8.
21. Adamec I, Bilic E, Lovric M, Habek M. Postural orthostatic tachycardia syndrome (POTS) as presenting symptom of CIDP. Neurol Sci 2016;37:1163-6.