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RELATIVE FREQUENCY OF DYSAUTONOMIA IN PARKINSONS DISEASE : A SINGLE CENTRE URBAN STUDY IN INDIA

Neurology

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ABSTRACT

Background: Autonomic failure is an integral component of Parkinson's disease (PD), and orthostatic hypotension (OH) can be an important clue to the underlying cardiovascular autonomic failure. Symptoms of autonomic dysfunction impact quality of life more than motor symptoms. Patients may be asymptomatic during the early stage of disease but may have underlying cardiovascular dysautonomia which becomes obvious on stress and as disease advances. Most of the earlier studies used morphological and functional methods to evaluate autonomic control but were unable to evaluate during dynamic conditions.

Aims and Objectives: The aim of the study was to study autonomic dysfunctions in patients with PD under dynamic conditions using head-up tilt table test (HUTT). The objective of the study was to document the spectral profile of heart rate variability (HRV) and blood pressure (BP) to orthostatic challenges using HUTT, Valsalva and Heart rate deep breathing (HRDB) in patients with PD. Secondary end point was to document the spectrum of autonomic dysfunction based on age, sex and duration of illness of the patients.

Materials and Methods: This was a hospital based descriptive cross-sectional study in cohort of patients and a sample size of N=162 patients was taken. Sample size was calculated to estimate 95% confidence interval for AD in PD with 5% absolute error of margin and finite correction. (N=162) sample size works out to be 85 patients assuming that prevalence to be 52%. A continuous lead II ECG was recorded along with BP every 2 min in patients with PD during HUTT for 10 min in supine, 45 min in 70° tilt and again 10 min in supine position which were later analyzed using BIOPAC software for HRV and HRDB.

Results: This study revealed that Autonomic nervous system dysfunction (AD) was present in 85.9% (73) patients with PD. It was analysed that 24 (32.9%), 27 (36.9%) and 22 (30.2%) patients had mild, moderate and severe autonomic dysfunction respectively. Spectrum analysis of data concluded that 11 (15.06%), 16 (21.91%) and 46 (63.03%) patients had sympathetic nervous system (SNS), parasympathetic dysfunction (PSNS) and mixed autonomic nervous system dysfunction (MANS) respectively. The severity of autonomic dysfunction increased with duration of disease and this association was found to be statistically significant as per Chi-Square test ($p<0.05$).

Conclusions: Patients with PD suffered from symptoms of autonomic dysfunction and had predominantly cardiovascular autonomic dysfunction that becomes more obvious as age advances. There is a significant association between the age, duration of illness and the spectrum of ANS dysfunction. As the age and duration of disease advances the severity of AD also worsens. Patient with lesser disease duration had mild dysfunction whereas patients with disease duration more than ten years had predominantly moderate to severe ANS dysfunction.

KEYWORDS

Parkinson Disease (PD); Autonomic Dysfunction (AD); Heart Rate Variability (HRV); Head up Tilt-table Test (HUTT); Valsalva test ; Heart rate deep breathing (HRDB)

INTRODUCTION

Parkinson's disease (PD) is a long-term degenerative disorder of the central nervous system that mainly affects the motor system.[1] Early in the disease, the most obvious symptoms are tremors, rigidity, bradykinesia, and postural instability. Dementia, cognitive and behavioral problems are also common in the advanced stages of the PD.[2] Apart from classical motor symptoms major non-motor symptoms are olfactory loss, psychiatric disturbances of depression and anxiety, sleep disorders (frequent waking, rapid eye movement sleep behavior disorder (RBD), and day time somnolence), sexual dysfunction and chiefly the Autonomic Dysfunction (AD).[3-5] As the disease worsens, non-motor symptoms become more common. These symptoms usually emerge slowly. The main motor symptoms are collectively called "parkinsonism", or a "Parkinsonian syndrome".

Overall worldwide prevalence of PD is estimated to be 160 per 1 lakh of the population. The incidence and prevalence of PD increases with advancing age, being present in 1% of people over the age of 65 years.[6] Early-onset Parkinson's disease (EOPD) is defined as the onset of parkinsonian features before the age of 40 years. It accounts for 3-5% of all PD cases. It is classified into the 'juvenile' (occurring before the age of 21 years) and 'young-onset' PD (YOPD, occurring in the age range of 21- 40 years). Autonomic dysfunction in PD patients is being recognized since the original description by James Parkinson in 1817. Although severe ANS dysfunction is mostly seen with advanced PD, it is present in PD patients even in the early stages of the disease.

Orthostatic hypotension (OH) is the most common symptom of cardiovascular autonomic dysfunction in PD[7,8] which can affect both patients with Parkinson's disease (PD) and atypical parkinsonism (AP). In general, OH refers to a fall in systolic blood pressure of at least 20mmHg and diastolic blood pressure of at least 10mmHg on standing or head-up tilt; its prevalence in PD varies between 9.6% and 58%.[9,10] Other cardiovascular autonomic dysfunctions commonly observed in Parkinson's disease (PD), includes supine hypertension (SH), nocturnal hypertension (NH), labile blood pressure (BP), absence of decrease in BP during the night ("non-dipping"), and heart rate variability (HRV).These abnormalities are interrelated in patients with PD.

Autonomic testing has been widely used in clinical practice for past 50 years, with decades of extensive experience and thousands of studies published on its use. Autonomic testing is an umbrella term that covers testing of the various branches of the nervous system: the sympathetic, parasympathetic, and enteric. It should be noted that the ANS extends to nearly every organ system in the body; so many organ specific tests are in fact tests of autonomic function (such as urodynamic studies, gastric motility testing, pupillometry, tests of lacrimal and salivary gland production etc.). Autonomic Disorders is an established subspecialty recognized by the United Council on Neurologic Subspecialties (UCNS), which certifies physicians and laboratories with training and expertise in this discipline.

Presently there were no comprehensive studies addressing spectrum of autonomic dysfunction in the early and late stage of disease. Hence, the present study was done at our tertiary care centre to assess the autonomic dysfunction in PD, their prevalence, early identification and clinical testing, to diagnose early autonomic dysfunction, in order that suitable treatment may be initiated early to prevent falls due to dysautonomia in addition to a movement disorder, measures can significantly improve the quality of life.

METHODOLOGY

1. INCLUSION CRITERIA

This study was approved by the Institutional Review Board and ethical committee of Armed Forces Medical College, Pune, India. The study

was a cross sectional descriptive study in a cohort of patients and a sample size of N=162 patients was taken. Sample size was calculated to estimate 95% confidence interval for AD in PD with 5% absolute error of margin and finite correction. (N=162) sample size works out to be 85 patients assuming that prevalence to be 52%[11]. This was calculated by Survey System (http:// www.surveysystem.com/ sscalc.htm#one). The clinical diagnosis of PD was made according to the UK Brain Bank criteria. Clinical information included age, sex, symptom duration, history of arterial hypertension, diabetes mellitus, cigarette smoking, and current medication. All patients were evaluated by the Unified Parkinson's Disease Rating Scale (UPDRS) part I–III and classified by modified Hoehn and Yahr (H&Y) stage. An informed written consent was taken from patients for the purpose of the study.

2. Exclusion criteria:

a) History of diabetic neuropathy or other peripheral/autonomic neuropathy
b) History of previous relevant cardiac disease detected on electrocardiography
c) Patients on medications known to influence autonomic functions except anti-parkinsonian medications.

TESTS OF ASSESSMENT OF AD

There are a wide variety of tests for testing the ANS.[12-15]Hence standardization before performing the tests is required. Caffeine and nicotine should be withheld for at least 3-4 hours before testing, alcohol for 8 hours. Anticholinergics should be withheld 48 hours before testing and sympathomimetic drugs 24-48 hours before testing. All BP and heart rate tests were performed after discontinuing any antihypertensive medications for more than 7 days (7.4 ± 0.3 days). During this period, no serious clinical problems were observed. Based on the wide distribution of the ANS a wide range of tests are required.

1 Head up tilt test (HUTT)- The test should be performed after overnight fasting or several hours after a meal in the morning. A provocative tilt test is performed on an automated tilt test table, which allows a consistent slow tilt to 60-80 degrees. In subjects with a positive tilt test result the syncope generally takes place between the 10th and 30th min of examination. Continuous electrocardiographic and noninvasive BP monitoring leads were connected for each patient (YM6000, Mediana Tech, Redmond, WA, USA). After 30 min of supine rest, the head-up tilt test (20 min at 60°) was performed using the Manumed Special Tilt 1-section (ENRAF NONIUS, Rotterdam, the Netherlands). BP was obtained every 5 minutes before and 1, 3, 5, 10, 15, and 20 minutes during tilt, 1 minute post-tilt, and as indicated for patient safety. The mean supine baseline and lowest tilt values for BP were then recorded. For statistical analyses, the lowest values recorded between 3 and 5 minutes were selected.

2 Valsalva manoeuvre- It is a autonomic testing maneuver in which the patient exhales against resistance and the BP and HR are recorded, typically on a beatto-beat basis. This test evaluates the complex sympathetic adrenergic and parasympathetic responses to the transient reduction in cardiac preload caused by an increase in intrathoracic pressure. The subject is allowed to rest for 15-20 minutes and then the test is performed in seating position. He or she is then asked to blow into the mouth piece of a manometer to maintain a column of mercury at 40 mmHg for 15 s with a clamp placed on the nose which is suddenly released after 15 s. ECG is recorded during resting period and during subsequent 40 heart beats after releasing the clamp. Test is repeated three times and an average is thus taken. It is used to assess the function of baroreceptors. In phase I there is increased intrathoracic and intra-abdominal pressure causing activation of baroreceptors in the aorta and a brief rise in blood pressure. Phase II begins with a drop of blood pressure secondary to reduced venous return and cardiac output with concomitant compensatory tachycardia. In phase III the expiration is stopped and a further transient fall in blood pressure is observed because of pulmonary vasculature expansion, while heart rate increases. In phase IV, probably due to baroreceptors' activation, an abrupt rise in blood pressure with concomitant bradycardia occurs. Valsalva ratio is derived from the longest RR interval in phase IV divided by the shortest RR interval in phase II and at the very beginning of phase III. Its value below 1.21 is considered abnormal .Valsalva ratio reflects parasympathetic activity.

3 Heart rate variability (HRV) spectral analysis- It has been widely used in the study of AD. There are assumptions that the neurodegenerative characteristics of PD may be associated with indices of HRV. Two major types of frequencies components are observed: Low frequency (LF) (0.04–0.15Hz) and high frequency (HF) (0.15–0.4Hz) components. HF fluctuations are modulated primarily by parasympathetic tone, whereas LF bands are affected by the sympathetic and parasympathetic activity.[16.]

4 Heart rate deep breathing (HRDB)- The subject is asked to breathe at 6 breaths per minute. (inspiratory and expiratory cycles of 5 second each), and then the difference between the average of the largest accelerations during inspiration and the average of the largest decelerations during expiration is calculated. It should not be lower than 10–15 beats per minute. The expiratory-inspiratory ratio (E: I ratio), which is the ratio of the longest RR interval during expiration and the shortest RR interval during inspiration from 5 cycles, can also be determined. The E: I ratio in young persons should be higher than 1.2

STATISTICAL ANALYSIS

Patients were initially stratified to a mild motor symptom group (modified H&Y stage score 1 and 1.5), a moderate motor symptom group (modified H&Y stage score 2 and 2.5), or a severe motor symptom group (modified H&Y stage score ≥ 3). Quantitative data is presented with the help of Mean and Standard deviation. Comparison among the study groups is done with the help of unpaired t test as per results of normality test. Qualitative data is presented with the help of frequency and percentage table. Association among the study groups is assessed with the help of Fisher test, student 't' test and Chi-Square test. 'p' value less than 0.05 is taken as statistical significant**.**

Pearson's chi-squared tes

$$X^2 = \sum_{i=1}^{n} \frac{(O_i - E_i)^2}{E_i}$$

Where X2 = Pearson's cumulative test statistic.
Oi = an observed frequency;
Ei = an expected frequency, asserted by the null hypothesis;
n = the number of cells in the table.
Results were graphically represented where deemed necessary.
Appropriate statistical software, including but not restricted to MS Excel, SPSS ver. 20 will be used for statistical analysis. Graphical representation will be done in MS Excel 2010.

RESULTS

1. Of the 85 patients, 68 (80%) were men. The mean age (± standard deviation) was 60.21 ± 10.66 years, and the mean disease duration was 5.4 ± 3.7 years. Majority of the patients (37.8%) were from the age group of 51-60 years followed by 23.4% from the age group of 61-70 years, 21.2% from the age group of 71-80 years and 17.6% from the age group of 41-50 years.Total UPDRS and H&Y stage scores were 27.2 ± 25.2 and 1.8 ± 0.9, respectively. (Graph 1,2 and 3)

2. Study revealed 12 (16.4%) patients in the age group of 41-50 years, 29 (39.7%) and 17 (23.3%), 15 (20.6%) patients in the age group of 51-60 years ,61-70 years and 71-80 years respectively had autonomic dysfunction. There was significant association of autonomic dysfunction and age of patients as per Chi-Square test (**p<0.05**).(Table 1)

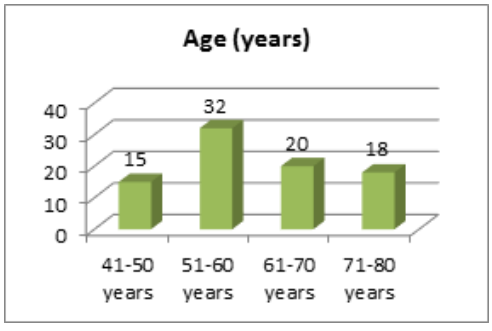
3. In this study, 60 (82.2%) male and 13 (17.8%) female patients had autonomic dysfunction. There was no significant association of autonomic dysfunction and gender of patients as per Chi-Square test (p>0.05). Spectrum analysis revealed that 7 (9.7%) patients in the age group of 40-55 years had SNS and PSNS, 22 (29.9%) patients in the age group of 56-70 years had mixed autonomic dysfunction. Majority of the male patients (23.3%) in the age group of 56-70 years had mixed dysfunction while 7 (9.7%) male patients in the age group of 40-55 years had PSNS. 6 (8.1%) male patients in the age group of 40-55 years had SNS dysfunction. Majority of the female patients (6.8%) in the age group of 56-70 years had mixed dysfunction. There was no significant association of spectrum of autonomic dysfunction and gender of patients and Age and autonomic dysfunction (p>0.05).(Table 2 and graph 4)

4. It was also observed that 19 (26.1%) male patients had mild autonomic dysfunction while 24 (32.8%) and 17 (23.4%) male patients had moderate and severe autonomic dysfunction respectively. 5 (6.8%) female patients had mild autonomic dysfunction while 3 (4.1%) and 5 (6.8%) female patients had moderate and severe

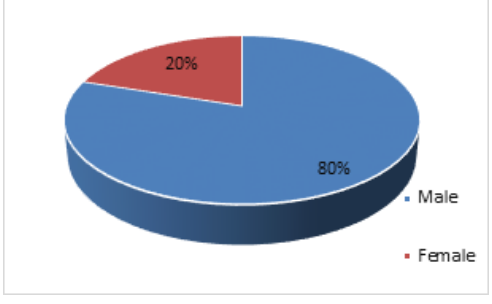
autonomic dysfunction respectively. There was no significant association of severity of autonomic dysfunction and gender of patients as per Chi-Square test (p>0.05).

5. In the age group of 41-50 years, 9 (12.3%) patients had mild autonomic dysfunction while 2 (2.8%) and 1 (1.4%) patient had moderate and severe autonomic dysfunction respectively. In the age group of 51-60 years, 9 (12.3%) patients had mild autonomic dysfunction while 15 (20.4%) and 5 (6.9%) patients had moderate and severe autonomic dysfunction respectively. Age group of 61-70 years, 5 (6.9%) patients had mild autonomic dysfunction while 8 (10.9%) and 4 (5.6%) patients had moderate and severe autonomic dysfunction respectively. In the age group of 71-80 years, 1 (1.4%) patient had mild autonomic dysfunction while 2 (2.8%) and 12 (16.3%) patients had moderate and severe autonomic dysfunction respectively. There was significant association of severity of autonomic dysfunction and age of patients as per Chi-Square test (**p<0.05**). (Table 2 and graph 5, 6)

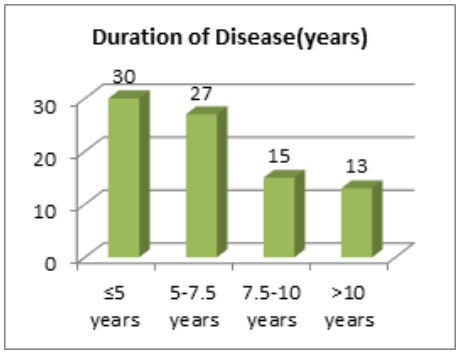
6. In the present study, patients with disease duration of ≤5 years, 17 (23.4%) patients had mild autonomic dysfunction while 6 (8.2%) and 5 (6.7%) patients had moderate and severe autonomic dysfunction respectively. In patients with duration of disease 5-7.5 years, 2 (2.8%) patients had mild autonomic dysfunction while 16 (21.9%) and 3 (4.2%) patients had moderate and severe autonomic dysfunction respectively. In more prolonged illness of duration 7.5-10 years, 5 (6.7%) patients had mild autonomic dysfunction while 3 (4.2%) and 5 (6.7%) patients had moderate and severe autonomic dysfunction respectively. In group with disease duration >10 years, 2 (2.8%) patients had moderate autonomic dysfunction while 9 (12.3%) patients had severe autonomic dysfunction. The severity of autonomic dysfunction worsened with increase in duration of disease and this association is statistically significant as per Chi-Square test (**p<0.05**).(Table 3 and graph 7)



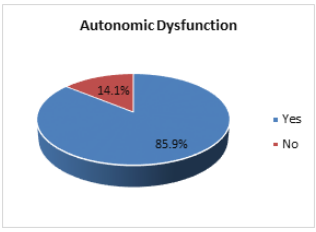
Graph 1: Distribution of patients according to Age



Graph 2: Distribution of patients according to Gender



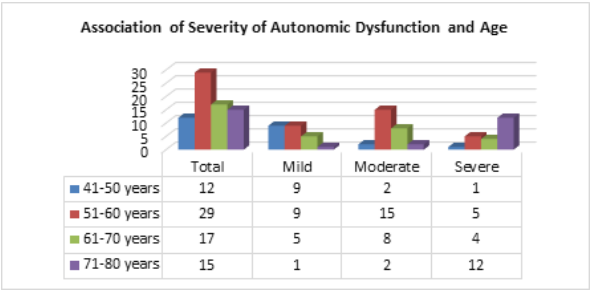
Graph 3: Distribution according to Duration of Disease



Graph 4: Distribution according to Incidence of AD

Table 1: Association of Severity of Autonomic Dysfunction and Age of patients

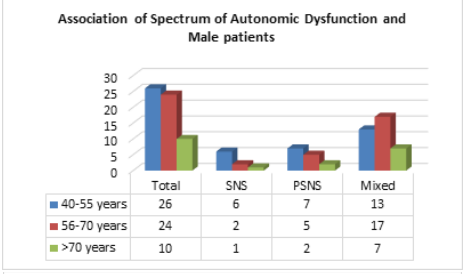
Age (years)	Total	Mild		Moderate		Severe		p Value
		N	%	N	%	N	%	
41-50 years	12	9	12.3%	2	2.8%	1	1.4%	**<0.05**
51-60 years	29	9	12.3%	15	20.4%	5	6.9%	
61-70 years	17	5	6.9%	8	10.9%	4	5.6%	
71-80 years	15	1	1.4%	2	2.8%	12	16.3%	
Total	73	24	32.9%	27	36.9%	22	30.2%	

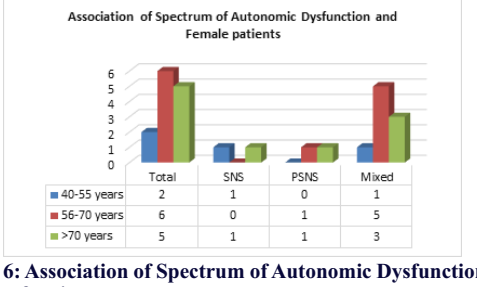


Graph 5 : Association of Severity of Autonomic Dysfunction and Age of patients

Table 2: Association of Spectrum of Autonomic Dysfunction and Gender of patients

Male	Total	SNS		PSNS		Mixed		p Value
		N	%	N	%	N	%	
40-55 years	26	6	8.1%	7	9.7%	13	17.8%	>0.05
56-70 years	24	2	2.7%	5	6.8%	17	23.3%	
>70 years	10	1	1.4%	2	2.7%	7	9.7%	
Total	60	9	12.2%	14	19.2%	37	50.8%	
Female	**Total**	**SNS**		**PSNS**		**Mixed**		**p Value**
		N	%	N	%	N	%	
40-55 years	2	1	1.4%	0	-	1	1.4%	>0.05
56-70 years	6	0	-	1	1.4%	5	6.8%	
>70 years	5	1	1.4%	1	1.4%	3	4.1%	
Total	13	2	2.8%	2	2.8%	9	12.3%	

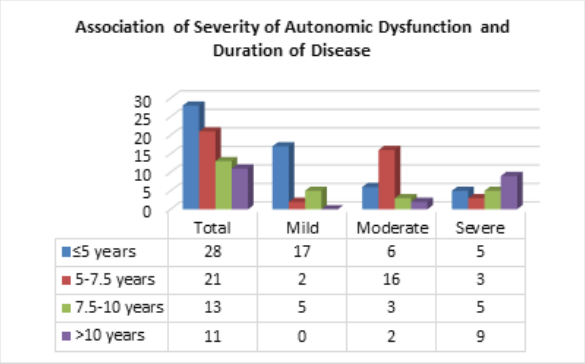




Graph 6: Association of Spectrum of Autonomic Dysfunction and Gender of patients

Table 3: Association of Severity of Autonomic Dysfunction and Duration of Disease of patients

Duration	Total	Mild		Moderate		Severe		p Value
		N	%	N	%	N	%	
≤5 years	28	17	23.4%	6	8.2%	5	6.7%	<0.05
5-7.5 years	21	2	2.8%	16	21.9%	3	4.2%	
7.5-10 years	13	5	6.7%	3	4.2%	5	6.7%	
>10 years	11	0	-	2	2.8%	9	12.3%	
Total	73	24	32.9%	27	36.9%	22	30.2%	



Graph 7: Association of Severity of Autonomic Dysfunction and Duration of Disease of patients

DISCUSSION

1. This hospital based cross sectional descriptive study was conducted with 85 patients to study the prevalence of autonomic dysfunction in patients of PD and to document the spectrum of autonomic dysfunction based on age, sex and duration of illness. Patients may be clinically asymptomatic during the early stage of disease but may have underlying cardiovascular dysautonomia. It would be clinically relevant to identify such patient which will help the physician to modify the treatment accordingly to prevent falls due to dysautonomia.

2.There is a significant association between the age and ANS dysfunction, as the age advances the severity of dysfunction also worsens. There is no significant correlation between the sex and severity of ANS dysfunction. As the disease duration advances the severity of dysfunction increases. Patient with lesser disease duration do not have ANS dysfunction or only mild dysfunction whereas with patients having disease duration more than 10 years have predominantly moderate to severe ANS dysfunction in all patients. The severity of autonomic dysfunction increased with increase in duration of disease.

3.There appears to be an exciting future ahead in both our understanding and management of Idiopathic Parkinson disease. Despite the many new developments in therapy, many aspects of management remain controversial. Future studies will hopefully provide empirical evidence to rationalize current treatment and management strategies.

CONCLUSION

Patients with PD suffered from symptoms of autonomic dysfunction and had predominantly cardiovascular autonomic dysfunction that becomes more obvious as age advances. There is a significant association between the age, duration of illness and the spectrum of ANS dysfunction. As the age and duration of disease advances the severity of AD also worsens. Patient with lesser disease duration had mild dysfunction whereas patients with disease duration more than ten years had predominantly moderate to severe ANS dysfunction. There is no significant correlation between the sex and severity of AD. The outcomes of this study will help the clinicians to identify the patients of PD with autonomic nervous system dysfunction at an early stage and modify treatment accordingly. It also help patient to be more aware about their AD symptom and to take apt precautionary measures and preventing frequent falls related to dysautonomia responsible for significant morbidity in elderly and henceforth enhancing the quality of life.

LIMITATIONS

The study was conducted in a relatively small group of patient and henceforth rationalization of results needs study to be conducted on a larger population group. This study involved mainly cardiovascular autonomic dysfunction however a patient with PD had other non motor autonomic dysfunction including GI disturbances, sexual dysfunction and sweating abnormality. Specific tests are designed for these AD like QSART (quantitative sudomotor axon reflex test), sweat imprint test, TST (thermoregulatory sweat test), SSR (sympathetic skin response), Hand grip, cold presser test. These tests for AD were not included in our study.

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