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Autonomic Symptom Burden and Neuroendocrine Stress Signatures in Chronic Cerebral Ischemia: A Retrospective Study

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A B S T R A C T

Background: Autonomic symptoms and affective distress often accompany chronic cerebrovascular pathology, yet their connection with hypothalamic-pituitary-adrenal and endogenous opioid systems is poorly understood. We compared the burden of autonomic symptoms, perception of stress, anxiety levels, morning cortisol and β-endorphin levels between patients with Chronic Cerebral Ischemia (CCI) with and without somatoform autonomic dysfunction and healthy controls.

Methods: This retrospective, single-centre, three-group study involved 118 subjects: CCI with somatoform autonomic dysfunction (n=48), CCI without somatoform autonomic dysfunction (n=40) and healthy controls (n=30). Autonomic symptoms were assessed by the Composite Autonomic Symptom Score-31 (COMPASS-31). The PSS-10 and HADS-A scales were used to evaluate perceived stress and anxiety. Morning serum cortisol and plasma β-endorphin levels were determined by means of chemiluminescence immunoassay and enzyme-linked immunosorbent assay, respectively. Differences between all groups were assessed by analysis of variance for a general linear model. Welch t test was applied for pairwise comparisons with Holm adjustment for all outcomes.

Results: Group effects were observed for COMPASS-31 ($F=82.42$; $\eta^2=0.589$), PSS-10 ($F=37.51$; $\eta^2=0.395$), β-endorphin ($F=22.65$; $\eta^2=0.283$), age ($F=13.85$; $\eta^2=0.194$), cortisol ($F=13.23$; $\eta^2=0.187$) and HADS-A ($F=11.86$; $\eta^2=0.171$; all omnibus $p<0.001$). Compared with CCI without somatoform autonomic dysfunction, the comorbid group had higher COMPASS-31 (mean difference 15.34), PSS-10 (8.96), HADS-A (1.90) and cortisol (216.52 nmol/L), but lower β-endorphin (−53.89 pg/mL; all Holm-adjusted $p\leq0.0031$). Compared with controls, the comorbid group showed the same directional pattern. CCI without somatoform autonomic dysfunction had higher PSS-10, COMPASS-31 and β-endorphin than controls after within-outcome Holm adjustment, whereas cortisol and HADS-A did not differ.

Conclusion: The presence of CCI together with somatoform autonomic dysfunction is marked by greater psychological and autonomic symptoms, higher cortisol levels in the morning and lower β-endorphins. These unadjusted associations indicate a distinct clinical picture, yet causation cannot be determined from the associations alone.

Keywords: Autonomic symptoms, β-Endorphin, Chronic cerebral ischemia, COMPASS-31, Cortisol, Perceived stress, Somatoform autonomic dysfunction

1. Introduction

Impaired cerebral perfusion and microvascular disease have been suggested to play a role in the development of cognitive, affective and functional impairment via interaction of vascular, metabolic and neuroinflammatory processes[1-3]. The term 'Chronic Cerebral Ischemia' (CCI) or 'dyscirculatory encephalopathy,' has been applied inconsistently in different healthcare settings. For that reason, research applying this concept must operationalize it and distinguish between CCI, which should not be equated to acute ischemic stroke or to vascular cognitive impairment.

Autonomic control is tightly linked to cerebrovascular function. Blood-pressure fluctuations, disturbed baroreceptor control orthostatic intolerance and abnormal heart rate variability may affect cerebral perfusion; cerebrovascular lesions in the autonomic centers can themselves impair cardiac and visceral autonomic regulation[4,5]. However, autonomic symptoms are not characteristic of autonomic disease only, since they can be provoked by anxiety, interoceptive attention and somatic distress. Such a combination leads to an attribution issue of clinical significance, when patients with vascular disease, autonomic dysfunction, medications, comorbidities or all of them suffer from autonomic symptoms.

Somatoform autonomic dysfunction, coded as F45.3 in the International Classification of Diseases, 10th Revision, describes persistent symptoms attributed by the patient to an autonomically innervated organ system in the absence of an adequate organic explanation. Contemporary diagnostic frameworks increasingly conceptualize such presentations through positive cognitive, affective and behavioural features rather than through the mere absence of disease. In patients already carrying a cerebrovascular diagnosis, careful phenotyping is particularly important because organic and functional contributors may coexist.

In terms of biological mechanisms, there is the possibility of a relationship between the cerebrovascular disease and somatic-autonomic symptoms via the stress response system. Cortisol can be regarded as a marker of the activity of the Hypothalamic-Pituitary-Adrenals Axis (HPA axis) and is affected by time of day, acute stress, sleep, medication, metabolic disorders and the severity of the disease state. In the case of an acute stroke, an association of high levels of cortisol with the severity of the disease and poor outcome has been observed, but the extrapolation of this observation to chronic cerebrovascular diseases is problematic[6,7]. β-Endorphin, which is a derivative of proopiomelanocortin, is involved in pain, stress reaction, behavior and energy metabolism[8]. Concentration of β-endorphins is preanalytically unstable and has no well-defined role in the clinic unlike cortisol.

In most previous studies, either autonomic symptoms, psychological distress or neuroendocrine markers were examined separately. The co-occurrence of these variables in CCI in presence and absence of somatoform autonomic dysfunction has been rarely investigated. In this study, we compared (i) the load of autonomic symptoms, (ii) perceived stress and anxiety and (iii) morning cortisol and β-endorphins in patients with CCI with somatoform autonomic dysfunction, in patients with CCI without this condition and in healthy controls. It was expected that the comorbidity group would demonstrate the highest values of both the parameters of autonomic and psychological distress and neuroendocrine biomarkers.

In recent observational studies performed in Uzbekistan, ischemic stroke features have once again been demonstrated to be highly heterogeneous. Stroke severity and functional recovery have been studied in association with the length of hospitalization stay[9], ischemic territory of cerebral arteries[10] and structural abnormalities on MRI and cognitive disorders[11]. Even though all these conference supplement articles focus on acute ischemic stroke rather than CCI, this example underlines the need for consideration of clinical severity, vascular anatomical features, imaging, cognition and functional recovery in the characterization of cerebrovascular disease populations.

2. Materials and Methods

2.1. Study design and setting

This retrospective comparative study used medical records from a tertiary neurology clinic in Tashkent, Uzbekistan, between January 2024 and June 2025. Health-check records provided the control group. Reporting was structured according to the STROBE principles for observational studies[12].

2.2. Participants

The study comprised three prespecified groups: CCI stage I-II with somatoform autonomic dysfunction (group 1; n=48), CCI stage I-II without somatoform autonomic dysfunction (group 2; n=40) and healthy controls (group 3; n=30). CCI eligibility was defined in the source protocol as age 40 to 95 years and a stage I or II diagnosis supported by neurological assessment and neuroimaging. For group 1, somatoform autonomic dysfunction had to be documented according to ICD-10 F45.3 by a neurologist or psychiatrist. Group 2 had no documented somatoform autonomic dysfunction.

Exclusion criteria were acute stroke or acute coronary syndrome during the preceding six months, severe heart failure, active infection or inflammatory disease at assessment, Cushing disease, Addison disease and exposure to systemic glucocorticoids or opioids. Controls had no documented chronic neurological, cardiovascular or psychiatric disease and no medication known to materially affect HPA-axis or autonomic function.

2.3. Clinical measures

The COMPASS-31 is a 31-item self-report instrument covering orthostatic, vasomotor, secretomotor, gastrointestinal, bladder and pupillomotor domains. Weighted scores range from 0 to 100, with higher scores indicating greater autonomic symptom burden[13,14].

Perceived stress was assessed with the 10-item Perceived Stress Scale (PSS-10; range 0-40), with higher scores indicating greater appraisal of life as unpredictable, uncontrollable or overwhelming[15]. Anxiety symptoms were measured using the seven-item HADS-A (range 0-21), which limits emphasis on somatic symptoms; scores of 8-10 are commonly considered borderline and scores ≥11 clinically elevated, although interpretation depends on setting[16-18].

2.4. Biomarker measurement

Fasting blood was collected between 08:00 and 09:00. Serum cortisol was measured by chemiluminescence immunoassay in the hospital laboratory. Plasma β-Endorphin was measured by

enzyme-linked immunosorbent assay after collection into EDTA tubes, centrifugation and storage at -80°C. β-Endorphin samples were assayed in duplicate and averaged; the reported inter-assay coefficient of variation was <8%.

2.5. Statistical analysis

Descriptive data are reported as mean ± Standard Deviation (SD). Overall differences were evaluated using one-way analysis of variance (ANOVA) and eta squared (η^2) quantified the proportion of total variance associated with group membership. Following the omnibus analysis, all three pairwise contrasts were calculated from the reported group sizes, means and SDs using two-sided Welch t tests with Satterthwaite degrees of freedom and 95% Confidence Intervals (CIs). To control multiplicity, p values were adjusted using the Holm procedure separately within each outcome. Analyses were performed using SPSS version 26; pairwise estimates were independently recalculated and verified from the summary statistics. Statistical significance was defined as two-sided adjusted $p<0.05$.

2.6. Ethics

The study was approved by the institutional ethics committee. Because this was a retrospective analysis of existing clinical records using de-identified data, the requirement to obtain individual informed consent was waived by the committee. The study was conducted in accordance with the Declaration of Helsinki and applicable institutional requirements.

3. Results

3.1. Participant characteristics and outcome distributions

The analysis included 118 participants: 48 in group 1, 40 in group 2 and 30 controls. Group 1 was older than both group 2 (adjusted $p=0.0030$) and controls (adjusted $p<0.0001$); group 2 and controls did not differ significantly in age. Because group 1 was significantly older than both comparison groups, subsequent between-group differences may be partly attributable to age. The control cortisol distribution showed substantial dispersion, which was retained in the analysis rather than modified post hoc. Descriptive data are summarized in (Table 1).

Table 1: Descriptive characteristics by study group.

Variable	CCI + somatoform autonomic dysfunction (n=48)	CCI without somatoform autonomic dysfunction (n=40)	Healthy controls (n=30)
Age, years	61.83±7.82	55.40±10.08	52.53±4.88
Cortisol, nmol/L	662.63±238.74	446.11±161.52	398.65±343.21
β-Endorphin, pg/mL	84.00±33.81	137.88±48.29	105.63±23.94
COMPASS-31	37.01±6.83	21.68±7.52	17.95±7.11
PSS-10	23.58±8.39	14.63±7.03	10.23±3.71
HADS-A	9.90±2.90	8.00±2.33	7.17±2.29

Values are mean ± SD, CCI: Chronic Cerebral Ischemia; COMPASS-31: Composite Autonomic Symptom Score-31; HADS-A: Hospital Anxiety and Depression Scale-Anxiety; PSS-10: Perceived Stress Scale-10.

3.2. Overall group differences

All six analyzed variables differed across the three groups in omnibus analyses (all $p<0.001$). The largest effect was observed for COMPASS-31 ($\eta^2=0.589$), followed by PSS-10 ($\eta^2=0.395$) and β-endorphin ($\eta^2=0.283$). Age, cortisol and HADS-A showed smaller but still substantial group effects (Table 2). These unadjusted effect sizes describe separation among the observed groups and should not be interpreted as independent effects of somatoform autonomic dysfunction.

Table 2: One-way analysis of variance across the three groups.

Variable	F (df=2,115)	p value	η^2
Age	13.85	<0.001	0.194
Cortisol	13.23	<0.001	0.187
β-Endorphin	22.65	<0.001	0.283
COMPASS-31	82.42	<0.001	0.589
PSS-10	37.51	<0.001	0.395
HADS-A	11.86	<0.001	0.171

3.3. Pairwise group comparisons

Compared with group 2, group 1 had higher COMPASS-31, PSS-10, HADS-A and cortisol and lower β-endorphin; every contrast remained significant after Holm adjustment within the relevant outcome. Compared with controls, group 1 showed the same directional profile. Group 2 had higher β-endorphin, COMPASS-31 and PSS-10 than controls, whereas cortisol and HADS-A did not differ (Table 3).

Table 3: Welch pairwise comparisons with within-outcome Holm adjustment.

Outcome	Comparison	Mean difference	95% CI	t (df)	Holm-adjusted p
Age, years	Group 1 vs group 2	6.43	2.54 to 10.33	3.29 (72.79)	0.0030
	Group 1 vs control	9.30	6.44 to 12.16	6.47 (76.00)	<0.0001
	Group 2 vs control	2.87	−0.78 to 6.52	1.57 (59.37)	0.1216
Cortisol, nmol/L	Group 1 vs group 2	216.52	131.21 to 301.83	5.05 (82.73)	<0.0001
	Group 1 vs control	263.98	120.09 to 407.88	3.69 (46.56)	0.0012
	Group 2 vs control	47.47	−89.44 to 184.37	0.70 (38.64)	0.4872
β-Endorphin, pg/mL	Group 1 vs group 2	−53.89	−71.97 to −35.80	−5.95 (67.96)	<0.0001
	Group 1 vs control	−21.64	−34.69 to −8.58	−3.30 (74.72)	0.0015
	Group 2 vs control	32.25	14.65 to 49.85	3.67 (60.08)	0.0010

COMPASS-31	Group 1 vs group 2	15.34	12.26 to 18.41	9.93 (79.75)	<0.0001
	Group 1 vs control	19.06	15.80 to 22.32	11.70 (59.80)	<0.0001
	Group 2 vs control	3.73	0.21 to 7.24	2.12 (64.39)	0.0382
PSS-10	Group 1 vs group 2	8.96	5.69 to 12.23	5.45 (86.00)	<0.0001
	Group 1 vs control	13.35	10.58 to 16.12	9.62 (69.91)	<0.0001
	Group 2 vs control	4.39	1.79 to 6.99	3.38 (61.89)	0.0013
HADS-A	Group 1 vs group 2	1.90	0.79 to 3.00	3.40 (85.91)	0.0020
	Group 1 vs control	2.73	1.55 to 3.91	4.61 (71.73)	<0.0001
	Group 2 vs control	0.83	−0.28 to 1.95	1.49 (63.20)	0.1399

Mean differences are calculated as the first-listed group minus the second-listed group. Holm adjustment was performed separately across the three pairwise contrasts for each outcome.

4. Discussion

4.1. Principal findings

In the current retrospective analysis with three groups, patients with CCI and somatoform autonomic dysfunction had the greatest burden on measures of autonomic symptoms, perceived stress, anxiety and morning cortisol. They had a lower level of β-endorphins compared to healthy controls. For patients with CCI but no somatoform autonomic dysfunction, the pattern was somewhat more limited. They had a higher level of perceived stress and β-endorphins but not cortisol and anxiety. The two greatest omnibus effects involved COMPASS-31 and PSS-10, which suggests that patient separation was greatest on the basis of self-reported autonomic symptoms and stress measures.

The results suggest an association between the two conditions and a greater psychophysiological burden. They do not prove that one condition causes the other, that cortisol or β-endorphin is indicative of a biological subtype or that either biomarker has any diagnostic value. All such conclusions would require evidence from other studies with appropriate design and analysis, confounder-adjusted models, internally validated discrimination and calibration analyses and independent external validation.

4.2. Autonomic and psychological burden

The marked elevation of the COMPASS-31 score in group 1 is clinically sensible since autonomic symptoms play a part in the definition of the comorbid condition. However, such a similarity between the exposure and the outcome introduces potential incorporation bias. Hence, the large COMPASS-31 effect should be interpreted as an indication of construct-consistent symptom separation rather than objective autonomic failure. For that, one would have to apply physiological autonomic testing such as orthostatic blood pressure, heart-rate variability, Valsalva responses, sudomotor testing or composite autonomic severity score.

PSS-10 and HADS-A were also higher in group 1. HADS-A was chosen wisely in a medically ill population for its lack of somatic symptoms. However, the group mean of 9.90 is in the common range of borderline cases, not of an anxiety disorder in a group. Psychological findings can be explained by illness burden, symptom vigilance, sleep disturbance, socioeconomic stress or psychiatric comorbidity. Such factors were not evaluated sufficiently to elucidate a pathway.

4.3. Cortisol and β-Endorphin

Higher morning cortisol in group 1 is in line with HPA-axis activation, but a single serum measurement is insufficient for differentiating persistent hyperactivity from day-to-day variations or an acute reaction to venepuncture, sleep, pain and medications. Multiple measurements, saliva-based diurnal profiles, dexamethasone suppression tests or hair cortisol would be more informative about sustained HPA-axis activation.

The β-Endorphin profile was non-monotonic: group 2 had higher concentrations than controls and group 1 had lower concentrations. It is a potentially interesting finding, but it does not alone suggest “adaptive” and “exhausted” phenotypes of β-endorphin action. β-Endorphin depends on physical activity, pain perception, mood, circadian time, assay system, sample preparation and storage conditions. To make any conclusions, one should replicate the results with proper pre-analytical control and simultaneously measure adrenocorticotropic hormone.

4.4. Clinical and research implications

The findings support a multidimensional approach in assessing patients complaining of autonomic symptoms in the presence of chronic cerebrovascular disease. An evaluation of patients should separate the symptom burden from the actual evidence of autonomic dysfunction and rule out anxiety, somatic complaints, pharmacological factors, endocrine and cardiovascular causes. The current evidence does not support a specific treatment approach based on cortisol or β-Endorphin levels and thus cannot be used to advocate any drug therapy for either HPA or opioid axes.

The future research studies should include standardized definitions of cerebrovascular pathology, criteria for neuroimaging, quantify the load of lesions and use appropriate control groups that match the subjects by age and gender. A hypothesis-driven approach to choosing covariates should be used. Repeated measurements of biomarkers and autonomic function can show whether psychological stress is a mediator, an effect modifier or just a concurrent factor in the association between cerebrovascular abnormalities and autonomic symptoms. In case any diagnostic or prognostic value is claimed, TRIPOD standards should be adhered to.

5. Strengths and Limitations

The strengths include concurrent assessment of autonomic, psychological and neuroendocrine systems; standardized morning blood draws; duplicate β-endorphin assays; inclusion of all pairwise contrasts; multiplicity correction; and provision of effect sizes and confidence intervals. Several major limitations severely restrict any inferences from the findings. First, the study had the retrospective, single-centre design, which is prone to selection and measurement biases. Second, groups differed in age

and individual data were not available to correct for covariates; therefore, age, gender, vascular risk, disease stage, medication, sleep, pain, depression and other possible sources of bias are expected. Third, the local CCI classification and partially known imaging criteria may impede generalization across countries. Fourth, the COMPASS-31 scale is conceptually overlapping with the grouping variable, creating the incorporation bias. Fifth, cortisol measured once is subject to error; the control group was widely spread and analytical metadata were unavailable at kit level. Sixth, sex-stratified results, detailed information on missing values and complete diagnostics of models were lacking from the archival summary data. Seventh, the sample was not designed and powered for validation of biomarkers.

6. Conclusion

Patients with CCI and somatoform autonomic dysfunction reported higher burden of symptoms from both systems, elevated morning cortisol levels and reduced β-Endorphins compared to both CCI patients without the additional diagnosis and healthy controls. The CCI without somatoform autonomic dysfunction was related to increased perceived stress, autonomic complaints and β-Endorphins and did not have elevated cortisol levels or anxiety compared to controls. While these results suggest the distinct profile of psychophysiology, they are still unadjusted observational associations. The prospective study with covariate adjustment, objective measurements of autonomic symptoms and repeated biomarker samples is required before any practical application.

7. Ethics Approval

The study was approved by the Institutional Ethics Committee and was conducted in accordance with the Declaration of Helsinki and applicable institutional requirements.

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