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ORIGINAL ARTICLE

Autonomic Dysfunction in Cluster Headache Patients in Remission

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Abstract

Background: Cluster headache (CH) is a primary, trigeminal autonomic headache consisting of unilateral attacks of facial pain lasting 15-180 minutes, recurring up to eight times a day, with ipsilateral autonomic features and restlessness. Autonomic symptoms occur as a result of both sympathetic and parasympathetic system involvement. In this study, we aimed to investigate the presence of autonomic involvement in patients with CH interictal period.

Methods: The Composite Autonomic Symptom Score-31 (COMPASS-31) was administered to 19 patients with CH during remission and to 19 healthy controls of similar age and sex, and the responses of the two groups were compared.

Results: Patients with CH showed orthostatic intolerance, increased secretomotor and pupillomotor complaints and increased COMPASS-31 total score during remission.

Conclusions: Patients with CH showed increased orthostatic intolerance, secretomotor and pupillomotor complaints. This suggests that there may be not only cranial autonomic involvement but also systemic autonomic involvement and that this involvement is not only during attacks. Our study will shed light on further studies including objective and advanced investigations that should be performed to show that these complaints are increased in the group with CH.

Keywords: Cluster headache, orthostatic intolerance, secretomotor, pupillomotor, COMPASS-31

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INTRODUCTION

Cluster headache (CH) is a primary, trigeminal autonomic headache lasting weeks to months, consisting of unilateral orbital, periorbital, temporal facial pain attacks lasting 15-180 minutes, recurring up to eight times a day, with autonomic features and restlessness in the ipsilateral facial half (1, 2). The combined lifetime prevalence of CH is 0.12% (3). While a male predominance in CH has been reported, with a male-to-female ratio of 4:1 (3), newer studies suggest a smaller difference than previously reported (4). The most common age of onset is between 20-29 years (4). The diagnosis is made according to The International Classification of Headache Disorders, 3rd edition (ICHD-3) (5). CH is divided into two different forms as episodic and chronic. This distinction is defined according to the duration of painless intervals between attacks, and this interval between attacks should be shorter than 3 months for chronic CH (5). Approximately 10-15% of patients have chronic CH (3). Presence of family history, smoking, alcohol consumption, male gender and head trauma are thought to be related with CH (6).

The pathophysiology of CH involves complex alterations in the central and peripheral nervous system, including activation of the hypothalamus, trigeminovascular system and autonomic nervous system (6). The pattern of attacks synchronised with the circadian rhythm appears to be related to hypothalamic involvement. Melatonin secretion and related autonomic dysfunction also play a role in the chronobiology of CH (6).

Lacrimation, conjunctival injection, nasal congestion and rhinorrhoea during the attack are thought to be symptoms of parasympathetic hyperactivity which occurs with activation of the trigemino-parasympathetic reflex (7). Myosis and ptosis also occur due to sympathetic defect (8). Autonomic symptoms appear to have both sympathetic and parasympathetic origin.

Treatment of CH is typically divided into three categories: acute, transitional (bridging), and prophylactic. Acute treatment options include 100% oxygen, triptans, and non-invasive vagal nerve stimulation. Bridging therapies such as corticosteroids (e.g., prednisolone) and greater occipital nerve block are used to manage symptoms. Prophylactic treatments include verapamil, lithium, galcanezumab, topiramate, and melatonin (2, 9).

A significant proportion (around 94%) of individuals with chronic CH report that they experience limitations in their personal and/or professional lives during attack periods. Moreover, 15% of these patients still reported limitations in their general daily activities despite being in remission (10). Since the number of studies investigating the presence of autonomic involvement in remission and systemic autonomic involvement in CH, whose effects continue even during remission, is limited, this study aimed to reduce these gaps in the literature and to demonstrate the presence of autonomic involvement during remission.

MATERIALS AND METHODS

Patients who were admitted to the Neurology outpatient clinic of Niğde Training and Research Hospital and diagnosed with CH were included in the study if they did not have active complaints at the time of presentation to the outpatient clinic or patients who had a CH diagnosis recorded in the hospital system were contacted by a neurologist via telephone, and those who fulfilled the ICHD-3 diagnostic criteria and were not in an active attack period were also included. This study was approved by the Niğde Ömer Halisdemir University Ethical Committee (Approval Date:17.01.2025 Approval Number:2024/98). All participants were given detailed information before the study and then their written or verbal consent was obtained.

Study Design

This cross-sectional observational study included 19 patients diagnosed with CH using the ICHD-3 diagnostic criteria and none of the patients were in an attack period; patients with at least 1 month since their last CH were included. Patients with diseases that may cause autonomic involvement and any medication use were not included in the study. The control group consisted of 19 healthy adults of similar age and gender to the patient group, without any psychiatric disorder, migraine, CH or other primary headache, without any disease that may cause autonomic involvement and without any medication, selected among hospital visitors and relatives of patients. After both groups were identified, The Composite Autonomic Symptom Score-31 (COMPASS-31) was completed by a neurologist for each group either face-to-face or by telephone.

The Composite Autonomic Symptom Score-31 (COMPASS-31)

COMPASS-31 is an easily applicable, noninvasive scoring system used for the documentation of autonomic symptoms associated with neurodegenerative diseases (11). The Turkish version was validated by İş et al. (12).

The assessment is made over six different domains: orthostatic intolerance (10 points); vasomotor (6 points); secretomotor (7 points); gastrointestinal (28 points); bladder (9 points) and pupillomotor (15 points). The first four questions were related to orthostatic intolerance, questions 5-7 to vasomotor, 8-11 to secretomotor, 12-23 to gastrointestinal, 24-26 to bladder, and 27-31 to pupillomotor complaints. A higher score indicates worse autonomic dysfunction. Simple yes or no questions are scored 0 points for no and 1 point for yes. Questions about a specific symptom zone are scored 0 points if not present and 1 point for each zone or condition if present. All questions about the frequency of symptoms are scored 0 points for rarely or never, 1 point for occasionally or sometimes, 2 points for often or "most of the time" and 3 points for almost always or constantly. All questions about the severity of symptoms are scored 1 point for mild, 2 points for moderate and 3 points for severe. When evaluating the time course of a symptom, 0 points are given for responses such as "it got a little better", "it got much better", "it completely passed" and "I did not experience any of these symptoms", 1 point for "it remained almost the same", 2 points for "it got a little worse" and 3 points for "it got much worse" (11).

Statistical Analysis

Statistical evaluation was performed with IBM SPSS 26.0 (SPSS Inc., Chicago, IL, USA) package program. The test for conformity to normal distribution was evaluated by Shapiro-Wilk test. Numerical variables showing normal distribution were expressed as mean ± standard deviation, numerical variables that are not normal distribution were expressed as median and categorical variables were expressed as frequency (percentages). Differences between groups were determined by Student-t test for numerical variables with normal distribution and Mann Whitney U Test for numerical variables without normal distribution. The relationships between categorical variables were evaluated by Fisher Exact Chi-square analysis. Statistical significance was set at $p<0.05$.

RESULTS

Demographic characteristics, habits and course of the disease of the participants are shown in Table 1.

Table 1. Demographic characteristics of the participants

	Patient Group (n: 19)	*Control Group (n: 19)*	*P value*
Age[1]	34 ± 8.38	40.42 ± 6.19	0.33
Male[2]	89.5 % (n: 17)	89.5 % (n: 17)	1.00
Female[2]	10.5 % (n: 2)	10.5 % (n: 2)	1.00
Smokers[2]	63.2 % (n: 12)	36.8 % (n: 7)	0.105
Alcol users[2]	26.3 % (n: 5)	15.8 % (n: 3)	0.426
Episodic CH	94.7 % (n: 18)		
Chronic CH	5.3 % (n: 1)		

n : Number CH: Cluster headache Independent samples

[1]t-test was used for normally distributed continuous variables (age)

[2]Chi-square test was used for categorical variables (sex, smoking, alcohol use)

As shown in Table 2, orthostatic intolerance, secretomotor and pupillomotor parameters of the 6 sub-parameters of the COMPASS-31 scale were significantly affected in the patient group, while the patient group was significantly more affected by autonomic symptoms in the total scale. Orthostatic intolerance was reported by 11 patients and 4 control group members, and dry mouth was reported by 9 patients and 3 control group members.

Table 2. Comparison of the total and subgroups of Compass-31 scores in two groups

Variables	Patient group (n:19)		Control group (n:19)		*P value*
	Mean±SD	Median (IQR)	Mean±SD	Median (IQR)	
Orthostatic Intolerance[1]	2.37±2.29	2 (4)	0.84±1.92	0 (0)	***0.015***
Vasomotor[1]	0.47±1.02	0 (0)	0.32±1.00	0 (0)	0.421
Secretomotor[1]	1.95±1.22	2 (2)	0.89±1.21	1 (2)	***0.008***
Gastrointestinal[1]	7.11±4.04	8 (8)	5.21±3.77	4 (7)	0.139
Bladder[1]	0.89±1.37	0 (1)	0.26±0.45	0 (1)	0.119
Pupillomotor[2]	6.05±0.84	6 (6)	3.79±0.64	4 (5)	***0.038***
Total[2]	18.84±2.18	19 (15)	11.32±1.53	12 (14)	***0.008***

n: Number, SD: Standard Deviationö IQR: Interquartile Range

[1]Mann–Whitney U test was used for non-normally distributed variables (Orthostatic intolerance, Vasomotor, Secretomotor, Gastrointestinal, Bladder).

[2]Independent samples t-test was used for normally distributed variables (Pupillomotor, Total score).

DISCUSSION

Our study demonstrated that autonomic involvement is present in patients with CH even without an attack, and this autonomic involvement may not only cause cranial symptoms but also lead to systemic effects.

In the literature, cranial autonomic symptoms observed during the attack period, which are also included in the diagnostic criteria of the disease, have been focused on. In a study conducted in 1988 in 27 patients with CH in the remission period, ocular sympathetic dysfunction on the symptomatic side and parasympathetic overactivity provoked by the greater superficial petrosal nerve were found (13). In a study in which cranial autonomic function was evaluated by light reflex pupillometry, temporal artery ultrasound and retinal vascular imaging in 30 patients with CH during the remission period, it was reported that the parasympathetic response decreased significantly in both eyes, especially on the symptomatic side, the retinal veins on the symptomatic side were narrower and this may be related to decreased cranial parasympathetic tone (14). In a study

including 19 patients with CH, prolongation was found in the mean latency of sympathetic skin response on the symptomatic side (15).

Although studies on autonomic symptoms in CH have focused on cranial symptoms, accompaniment of systemic autonomic symptoms is an expected finding because of the undeniable role of the hypothalamus in systemic autonomic response. In an analysis of 22 studies including patients in the pain-free period, subclinical parasympathetic hyperactivation and sympathetic dysfunction were found (16).

In a 1996 study conducted in Germany, patients diagnosed with CH were evaluated during the attack period through four daily measurements of plasma catecholamines (norepinephrine and epinephrine), and cerebrospinal fluid (CSF) levels of norepinephrine, epinephrine, dopamine, and the metabolites homovanillic acid (HVA), vanillylmandelic acid (VMA), and 5-hydroxyindoleacetic acid (5-HIAA). Compared to the control group, plasma norepinephrine levels in the CH group were significantly reduced. Additionally, CSF concentrations of norepinephrine, HVA, and 5-HIAA were notably decreased. A progressive reduction in CSF levels of HVA and 5-HIAA was observed with increasing disease duration. Moreover, plasma norepinephrine levels were significantly correlated with attack duration, severity, and frequency. These findings indicate a reduction in sympathetic nervous system activity during the attack period. The observed decrease in CSF neurotransmitter levels underscores the involvement of the central autonomic system and circadian mechanisms in the pathophysiology of CH (17).

In a study evaluating heart rate variability using 24-hour Holter ECG monitoring in patients during both headache and headache-free periods, autonomic dysfunction was detected in both phases (18). Furthermore, spectral analysis of heart rate variability performed before, during, and after CH attacks revealed a primary activation of both sympathetic and parasympathetic functions. It was indicated that the sympathetic component plays a role in the development of the attack, whereas parasympathetic activation is triggered after the onset of pain and appears to occur independently of the pain itself (19). In another study utilizing 24-hour Holter monitoring to assess heart rate variability across both daytime and nighttime periods, as well as during headache and headache-free phases, autonomic dysfunction was also identified in CH patients even in the absence of pain (20).

In a study conducted using videolaryngoscopy during the CH attack period, the presence of creaky voice was identified in affected individuals. Furthermore, mild to moderate vocal cord edema and signs of laryngopharyngeal reflux were found to be significantly more prevalent compared to healthy controls. These findings have been interpreted as indicators of autonomic dysfunction, likely related to increased parasympathetic tone during the active bout period (21).

Although clinical studies to understand the pathophysiology of CH are limited due to its rarity compared to other primary headaches and short duration of attacks, three important mechanisms including the trigeminovascular system, the trigeminal-autonomic reflex and the hypothalamic system are thought to be effective. According to a published review, it was stated that the hypothalamus and central connections play a central role in triggering attacks, the suprachiasmatic nucleus of the hypothalamus leads to periodicity, but more studies are needed on the nuclei of the hypothalamus that trigger autonomic symptoms (8).

The limitations of the study were that it was performed in a single center with a small number of patients, only COMPASS-31 was used, objective tests were not performed, and evaluation according to circadian rhythm was not performed.

In conclusion, increased orthostatic intolerance, secretomotor and pupillomotor complaints have been shown in patients with CH. It is recommended to investigate not only cranial but also systemic autonomic involvement in remission by performing objective tests considering circadian rhythm in these patients compared to the normal population.

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Abbreviations list

CH: Cluster headache
COMPASS-31: The Composite Autonomic Symptom Score-31
ICHD-3: The international classification of headache disorders, 3rd edition
HVA: Homovanillic acid
VMA: Vanillylmandelic acid
5-HIAA: 5-Hydroxyindoleacetic acid

Ethics approval and consent to participate.

This study was approved by the Niğde Ömer Halisdemir University Ethical Committee (Approval Date:17.01.2025 Approval Number:2024/98)

Consent for publication

ll participants provided informed consent prior to their inclusion in the study. The data were collected and analyzed anonymously. Consent for publication of the anonymized findings was obtained in accordance with institutional and ethical guidelines.

Availability of data and materials

Not available.

Competing interests

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Authors' contributions

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