Neurology Asia 2026; 31(3) : 1035– 1045

The relationship between autonomic symptoms and quality of life in patients with migraine: A multicenter cross-sectional observational study

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Abstract

Background & Objectives: Migraine is a complex disorder that negatively affects the quality of life. Interictal or ictal cranial autonomic symptoms (CASs) are observed in migraine; however, data regarding extracranial autonomic symptoms (ECASs) are limited. This study aimed to evaluate autonomic symptoms in patients with migraine and to investigate the relationship between these symptoms and the quality of life. *Method:* The study was designed as a cross-sectional observational study. Ictal CASs in migraine were assessed. Participants completed the Composite Autonomic Symptom Scale (COMPASS-31), Migraine Disability Assessment Score (MIDAS), Headache Impact Test (HIT-6) and Migraine-Specific Quality-of-Life Questionnaire (MSQoL). The relationships between autonomic symptoms, headache characteristics and scale scores were analyzed. Patients were categorized as having episodic or chronic migraine, and migraine with or without aura. Data were compared across all patient groups and healthy controls. *Results:* The most common ictal CASs in patients with migraine were lacrimation (38.3%, n = 69) and conjunctival injection (28.3%, n = 51). COMPASS-31 scores were significantly higher in patients with migraine compared with healthy controls (p = 0.001). Higher COMPASS-31 scores were also observed in patients with migraine with aura and in those with greater disability (MIDAS grades 3-4) (p = 0.009, p = 0.001). Additionally, a moderate negative correlation was detected between total COMPASS-31 scores and the MSQoL scores (p = 0.001, r = -0.410).
Conclusions: Autonomic symptoms are common in patients with migraine, especially in migraine patients with aura. These symptoms are associated with lower quality of life and higher disability levels.

Keywords: Migraine, headache, autonomic symptom, quality of life

INTRODUCTION

Migraine is a very common disease that imposes significant health and financial burdens.[1,2] The disease is characterized by recurrent, paroxysmal attacks of moderate-to-severe throbbing, unilateral headaches; in addition to photophobia, phonophobia, nausea or vomiting. Autonomic symptoms associated with migraine are not included in the formal diagnostic criteria. Accordingly, their reported frequency varies across studies, and they are generally perceived as less clinically prominent than headache pain. Cranial autonomic symptoms (CASs) comprise nasal congestion, rhinorrhea, conjunctival injection, ptosis, eyelid edema, lacrimation, and forehead sweating or flushing.[2-6]

Extracranial autonomic symptoms (ECASs) are rare in migraine; however, ongoing research continues to explore this phenomenon. A comprehensive population-based study reported

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Date of Submission: 6 July 2025; Date of Acceptance: 25 February 2026
https://doi.org/10.54029/2026awc

that ECASs were more common among patients with migraine than healthy individuals. Orthostatic hypotension, gastrointestinal symptoms, polyuria and syncope are more common in migraine patients.[7-9] The proposed pathophysiological mechanism underlying ECASs is ictal sympathetic reactivity, characterized by an increase in sympathetic activity from the interictal to the ictal period, referred to as "ictal sympathetic reactivity". This activity activates postsynaptic adrenergic receptors and causes a lasting effect called excitatory postsynaptic potentials (EPSPs).[10,11] However, the pathophysiology of ECASs is not as well determined as CASs.

Scientific data on ECASs in the migraine are limited. In addition, the relationship between ECASs and headache characteristics has not been investigated comprehensively. The first of the three main aims of this study is to evaluate ictal CASs and interictal ECASs in migraine. The second aim is to investigate the relationship between headache characteristics and autonomic symptoms. The final aim is to evaluate the relationship between autonomic symptoms and quality of life.

METHODS

This study had a multicenter, cross-sectional observational study with a control group. Data were collected at 6 different centers by neurologists experienced in headache. All patients were evaluated by these neurologists. The characteristics of the headache were evaluated. Headache duration, frequency, location, aura and the most common associated symptoms (nausea or vomiting, phonophobia, photophobia) were elicited. Migraine was identified by the International Classification of Headache Disease-3 diagnostic criteria.[2] The control group consisted of healthy volunteers who applied to the neurology outpatient clinic, had no exclusion criteria, and were of similar age and gender to the migraine group.

Exclusion criteria for the study were: chronic diseases requiring long-term treatment, psychiatric diseases, chronic neurological diseases (epilepsy, dementia, etc.) and structural organic neurological diseases. The sample size was calculated using the G-power program based on the t-test in independent groups (effect size: 0.744, margin of error: 5%, power ratio: 95%, group ratio: ½).[9] Therefore, 180 patients and 90 healthy volunteers were included in the study. Ethical protocol was approved by Ethics Committee in Selcuk University (Meeting Date: 30.09.2024, Ethics number: 2024/540). The study objectives were thoroughly explained to the participants and informed consent was obtained.

Patients were evaluated regarding ictal CASs and their localization (unilateral or bilateral). Ictal CASs (conjunctival injection, forehead sweating or flushing, nasal congestion, rhinorrhea, lacrimation, ptosis, eyelid edema) features were sought in all participants.

The migraine disability assessment score (MIDAS) scale was employed to evaluate extent of migraine disability. Based on the total score, patients were classified into four MIDAS grades (0–5, 6–10, 11–20, and ≥21), representing minimal, mild, moderate, and severe disability. Subsequently, the groups were reclassified into two categories (grade 1+grade 2) and (grade 3+grade 4). In addition to the scale, "MIDAS-A=total number of headache days in the last three months" and "MIDAS-B=headache intensity from 0 to 10" were determined.[12]

The Headache Impact Test (HIT-6) was applied to evaluate the impact of migraine in subjects. Responses to 6 questions in the HIT-6 are scored on a 5-point Likert scale as never: 6, rarely=8, sometimes=10, very often=11, and always=13, with a total score ranging from 36 to 78. Higher scores are associated with greater negative impact on patients' lives. We categorized our patient scores into four groups based on their scores (≤49, 50–55, 56–59, and ≥60), corresponding to no impact, mild impact, moderate impact, and severe impact, respectively.[13]

Interictal ECASs symptoms were evaluated with the 31-questions according to Composite Autonomic Symptom Scale (COMPASS-31). The scale covers six sub-domains: orthostatic intolerance, vasomotor, secretomotor, gastrointestinal, bladder, and pupillomotor symptoms. The scores from all sub-domains were aggregated to derive a total score. Higher scores indicate greater autonomic symptoms.[14,15] The effect of migraine on quality of life was evaluated using the Migraine-Specific Quality-of-Life Questionnaire (MSQoL). The latter consists of 14 items, questions were scored on a 6-point Likert scale (6=Never, 5=A little bit of the time, 4=Sometimes, 3=A good bit of the time, 2=Most of the time, 1=Always), with the total score ranging from 14 to 84. Higher scores indicate better quality of life. In addition,

the MSQoL has 3 subgroups: role function/restrictive (RFR) = (7 items: limiting daily activities); role function/preventive (RFP) = (4 items: preventing daily activities); and emotional function (EF) = (3 items: about emotions).[16,17]

Data were analyzed using the Statistical Package for Social Sciences (SPSS) 26.0 package program. Data were presented as median (interquartile range (IQR), mean±standard deviation or frequency (%). Categorical data were analyzed using Chi-Square test. Kolmogorov Smirnov or Shapiro Wilk tests were employed to evaluate the distribution of numerical data. For two independent groups, data were analyzed using either Student's T test or Mann Whitney U test according to parametric or nonparametric features. Correlation tests for numerical data were performed using Spearman correlation analysis. A multivariable linear regression analysis was performed to evaluate factors independently associated with MSQoL total score. The following predefined variables were entered simultaneously into the model using the enter method: COMPASS-31 subdomains (orthostatic intolerance, vasomotor, secretomotor, gastrointestinal, bladder, and pupillomotor scores), age, sex, educational level, income level, HIT-6 score, and MIDAS total score. All variables were selected a based on clinical relevance. Log transformation was applied due to non-normal distribution. Regression analyses included a limited number of predefined predictors and were exploratory. P-values were adjusted using the Benjamini–Hochberg false discovery rate (FDR) method, and multicollinearity was assessed before model fitting. p value of <0.05 was considered statistically significant.

RESULTS

In this study, 180 patients with migraine, with a mean age of 33.26±9.58 years, and 90 control participants were included. Among the migraine patients, 159 (88.3%) patients were female and 21 (11.7%) were male. No statistically difference was observed between groups in terms of age and gender (p: 0.111, p: 0.108). The prevalence of smoking among patients was 33.3% while alcohol use was present in 6.1%. Almost half of the patients (n=88, 48.9%) were overweight or obese. In addition, the education level and financial status were lower in migraine group compared to controls (p = 0.001, p = 0.001). Demographic characteristics of patients with migraine and control group are presented in Table 1.

The most prevalent ictal symptoms associated with migraine were nausea or vomiting (76.1%), phonophobia (69.4%), and photophobia (68.9%). In addition, the most frequently observed ictal CASs in patients were lacrimation (38.3%) and conjunctival injection (28.3%). These symptoms were often unilateral.

In the patient group, 151 (83.9%) patients were diagnosed with episodic migraine while 29 (16.1%) were diagnosed with chronic migraine. Based on MIDAS results, 40 (22.2%) patients exhibited mild (Grade 2), 43 (23.9%) patients demonstrated moderate (Grade 3), and 72 (40.0%) patients experienced severe (Grade 4) migraine-related disability. The clinical characteristics, ictal CASs, and MIDAS scores of patients with migraine are presented in Table 2.

Analysis of the COMPASS 31 sub-domain scores revealed that the migraine group exhibited significantly higher scores in orthostatic symptoms, gastrointestinal symptoms, secretomotor symptoms, bladder symptoms and pupillomotor symptoms compared to the control group (all FDR-adjusted $p < 0.05$). No statistically significant difference was observed in vasomotor symptom scores (FDR-adjusted $p = 0.132$). Total COMPASS-31 score was also significantly higher in the migraine group (median (IQR) 34.6 (18.5-48.3) vs. 14.5 (6.0-27.9), FDR-adjusted $p < 0.05$). COMPASS-31 total and sub-domain scores are presented in Table 3.

Patients were categorized as episodic and chronic migraine; the most common ictal CASs in episodic subgroup were lacrimation (n=57, 37.7%) and conjunctival injection (n=46, 30.0%). In chronic migraine, the most common symptom was lacrimation (n=12, 41.4%). The rates of ictal CASs were similar in chronic and episodic migraine groups. Although COMPASS-31 bladder symptom scores were higher in the chronic migraine group compared to the episodic migraine group (p = 0.018), this difference did not remain statistically significant after false discovery rate (FDR) correction. No statistically significant differences were observed between the groups with respect to other autonomic symptoms.

Patients were categorized as ''migraine without aura'' and ''migraine with aura''; the most common ictal CASs in migraine patients without aura were lacrimation (n=44, 31.4%) and conjunctival injection ((n=37, 26.4%). In

Table 1: Demographic characteristics of patients with migraine and control group

	Patient group (n=180) *	Control group (n=90) *	p-value**
Gender			
Female	159 (88.3%)	73 (81.1%)	0.108
Male	21 (11.7%)	17 (18.9%)	
Smoking			
No	120 (66.7%)	68 (75.6%)	0.134
Yes	60 (33.3%)	22 (24.4%)	
Alcohol			
No	169 (93.9%)	86 (95.6%)	0.573
Yes	11 (6.1%)	4 (4.4%)	
Marital status			
Married	122 (67.8%)	54 (60.0%)	0.206
Single	58 (32.2%)	36 (40.0%)	
Residing			
Alone	51 (28.3%)	31 (34.4%)	0.422
Family house	121 (67.2%)	70 (64.5%)	
Other	8 (4.4%)	1 (1.1%)	
Education			
Primary or high school	96 (53.4%)	29 (32.2%)	**0.001**
University	84 (46.6%)	61 (67.8%)	
Financial situation***			
National minimum wage	75 (41.7%)	11 (12.2%)	**0.001**
National minimum wage (x2)	48 (26.7%)	18 (20.0%)	
National minimum wage (x3)	35 (19.4%)	30 (33.3%)	
National minimum wage (x3 more)	22 (12.2%)	31 (34.4%)	
Body mass index			
Underweight	13 (7.2%)	12 (13.3%)	0.263
Normal weight	79 (43.9%)	31 (34.4%)	
Overweight	66 (36.7%)	34 (37.8%)	
Obese	22 (12.2%)	13 (14.4%)	

*Descriptive statistical methods were used to present data as number (n) and percentages (%); **$p < 0.001$ was demonstrated as $p = 0.001$. Bold values signify statistical significance at the $p < 0.05$ level; *** As of January 1, 2025, the minimum wage in Turkey is 26,005.50 Turkish Lira per month. On this date, the exchange rate was 1 Euro = 36.46 Turkish Lira.

migraine patients with aura, the most common symptoms were lacrimation (n=25, 62.5%) and conjunctival injection (n=14, 35.0%). The rates of lacrimation, eyelid edema, nasal congestion, and forehead sweating or flushing were higher in migraine patients with aura ($p = 0.001$, $p = 0.045$, $p = 0.034$, $p = 0.012$), and these associations remained statistically significant after FDR adjustment. Additionally, the number of ictal CASs was greater in migraine patients with aura ($p = 0.003$), remaining significant following FDR correction. Furthermore, vasomotor symptoms, secretomotor symptoms, pupillomotor symptoms and total COMPASS-31 scores were higher in migraine patients with aura ($p = 0.009$, $p = 0.0010$, $p = 0.001$, $p = 0.042$), all of which remained statistically significant after FDR correction.

Differences in MIDAS scores (grade 1+2 vs. grade 3+4) did not show any correlation with ictal CASs. COMPASS-31 scores were higher in the moderate-severe disability group ($p = 0.001$, $p = 0.004$, $p = 0.041$, $p = 0.010$, $p = 0.010$, $p = 0.029$, $p = 0.001$), and these differences remained

Table 2: Clinical characteristics and cranial autonomic symptoms of patients with migraine

Parameters	Total patients (n=180)
Migraine-related symptoms	
Aura	40 (22.2%)
Nausea and vomiting	137 (76.1%)
Phonophobia	125 (69.4%)
Photophobia	124 (68.9%)
Cranial autonomic symptoms	
Conjunctival injection	51/180 (28.3%)
Unilateral	32 (17.8%)
Bilateral	19 (10.6%)
Lacrimation	69/180 (38.3%)
Unilateral	43 (23.9%)
Bilateral	26 (14.4%)
Ptosis	37/180 (20.6%)
Unilateral	21 (11.6%)
Bilateral	16 (8.9%)
Eyelid edema	27/180 (15.0%)
Unilateral	12(6.7%)
Bilateral	15 (8.3%)
Nasal congestion	37/180 (20.6%)
Unilateral	22 (12.2%)
Bilateral	15 (8.3%)
Rhinorrhea	11/180 (6.1%)
Unilateral	6 (3.4%)
Bilateral	5 (2.8%)
Forehead sweating-flushing	27/180 (15.0%)
Unilateral	21 (11.7%)
Bilateral	5 (3.3%)
Migraine type	
Episodic	151 (83.9%)
Chronic	29 (16.1%)
Groups according to MIDAS scores	
Grade 1	25 (13.9%)
Grade 2	40 (22.2%)
Grade 3	43 (23.9%)
Grade 4	72 (40.0%)
Groups according to HITS scores	
Mild	5 (2.8%)
Moderate	15 (8.3%)
Severe	160 (88.9%)

MIDAS=Migraine Disability Assessment Scale, HITS=Headache Impact Test

statistically significant after FDR adjustment. Ictal CASs and COMPASS-31 scores in migraine group are presented in Table 4.

There was a weak positive correlation between migraine duration and gastrointestinal, secretomotor symptom scores ($p = 0.033$, $r = 0.159$; $p = 0.008$, $r = 0.198$). A statistically significant correlation was observed between HITS and COMPASS-31/subdomain scores ($p = 0.001$, $p = 0.002$, $p = 0.001$, $p = 0.001$, $p = 0.001$, $p = 0.001$), with the exception of the vasomotor symptom score ($p = 0.062$). Statistically significant correlations were detected between the MIDAS score and COMPASS-31 total score

Table 3: COMPASS-31 autonomic symptom scores of patients with migraine and control groups

	Patient group (n=180)	Control group (n=90)	p-value
Total weighted score (possible score 0–100)	34.6 (18.5-48.3)	14.5 (6.0-27.9)	**0.001***
COMPASS-31 sub-domain scores			
Sub-domain 1 /// Orthostatic symptoms (possible score 0-40)	20.0 (0.0-28.0)	0.0 (0.0-16.0)	**0.001***
Sub-domain 2 /// Vasomotor symptoms (possible score=0-5)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.132
Sub-domain 3 /// Gastrointestinal symptoms (possible score=0-25)	9.8 (5.3-13.3)	1.2 (4.2-6.2)	**0.001***
Sub-domain 4 /// Secretomotor symptoms (possible score=0-15)	6.4 (0.0-8.5)	0.0 (0.0-6.4)	**0.001***
Sub-domain 5 /// Bladder symptoms (possible score=0-10)	0.0 (0.0-1.9)	0.0 (0.0-0.0)	**0.009***
Sub-domain 6 /// Pupillomotor symptoms (possible score=0-5)	2.3 (1.6-3.2)	1.0 (0.0-2.0)	**0.001***

COMPASS=Composite Autonomic Symptom Scale, n=Number
Values are presented as median (interquartile range). Group comparisons were performed using the Mann–Whitney U test. p-values were adjusted for multiple comparisons using the Benjamini–Hochberg false discovery rate (FDR) method. (*) indicate results that remained statistically significant after FDR correction.

($p = 0.001$, $r = 0.365$). In addition, there were negative correlations between all COMPASS-31 scores and all MSQoL scores. All correlation analyses are presented in Table 5.

In the fully adjusted multivariable regression model including all COMPASS-31 subdomains, sociodemographic variables, MIDAS, and HIT-6 ($R^2 = 0.582$, adjusted $R^2 = 0.551$, $p < 0.001$), higher vasomotor symptom scores remained independently associated with poorer migraine-specific quality of life ($\beta = -0.145$, $p = 0.008$). Among independent variables, higher HIT-6 ($\beta = -0.549$, $p < 0.001$), MIDAS ($\beta = -0.194$, $p = 0.001$), and income level ($\beta = 0.214$, $p = 0.001$) were associated with quality of life (Table 6).

DISCUSSION

Interictal or ictal CASs have been extensively described in migraine; however, data regarding other local or systemic autonomic symptoms remain limited. CASs such as conjunctival injection and lacrimation are characteristic for trigeminal autonomic cephalalgias (TACs).[2] CASs may also be present in patients with migraine; however, these autonomic symptoms are not pathognomonic for migraine.[18] The reported frequency of these symptoms varies widely, ranging from 3.1% to 82%.[19,20] In our study, the frequency of ictal CASs was 42.2% (77/180) among patients with migraine; and two or more CASs were observed in 24.4% (44/180) of the migraine group. These findings are consistent with the existing literature. A recent study suggested that migraine may have endo-phenotypes;[21] however, scientific data regarding a possible autonomic symptom-related endophenotype remain limited.[6]

CASs are frequently observed in TACs, particularly in cluster headache. This is mainly because autonomic symptoms are as severe as headache in trigeminal autonomic cephalgias. However, these symptoms are as prominent as headache in TACs, whereas they are generally less severe than headache in patients with migraine. A study evaluating both migraine and cluster headaches reported that 56% (437/786) of patients with migraine exhibited ictal CASs, compared with 97% (95/98) of patients with

Table 4: Autonomic symptoms according to migraine groups

	Migraine groups-1		Migraine groups-2		Migraine groups-3		p-value		
Parameters	**Episodic migraine [a] (n=151)**	**Chronic migraine [b] (n=29)**	**Migraine without aura [c] (n=140)**	**Migraine with aura [d] (n=40)**	**MIDAS: Grade 1 + Grade 2 [e] (n=65)**	**MIDAS: Grade 3 + Grade 4 [f] (n=115)**	**a-b**	**c-d**	**e-f**
Cranial autonomic symptoms									
Conjunctival injection	46 (30%)	5 (17.2%)	37 (26.4%)	14 (35.0%)	21 (32.3%)	30 (26.1%)	0.148	0.289	0.374
Lacrimation	57 (37.7%)	12 (41.4%)	44 (31.4%)	25 (62.5%)	20 (30.8%)	49 (42.6%)	0.713	**0.001***	0.117
Ptosis	32 (21.2%)	5 (17.2%)	25 (17.9%)	12 (30.0%)	9 (13.8%)	28 (24.3%)	0.630	0.094	0.094
Eyelid edema	25 (16.6%)	2 (6.9%)	17 (12.1%)	10 (25.0%)	10 (15.4%)	17 (14.8%)	0.182	**0.045**	0.913
Nasal congestion	33 (21.9%)	4 (13.8%)	24 (17.1%)	13 (32.5%)	13 (20.0%)	24 (20.9%)	0.325	**0.034**	0.890
Rhinorrhea	10 (6.6%)	1 (3.4%)	8 (5.7%)	3 (7.5%)	4 (6.2%)	7 (6.1%)	0.513	0.678	0.986
Forehead sweating-flushing	22 (14.6%)	5 (17.2%)	16 (11.4%)	11 (27.5%)	6 (9.2%)	21 (18.3%)	0.712	**0.012***	0.103
Total number of cranial autonomic symptoms	0 (0-2)	0 (0-1)	0 (0-1)	1(0-2)	0 (0-1)	0 (0-2)	0.464	**0.003***	0.280
Total weighted COMPASS-31score	34.7 (17.8-48.1)	31.4 (18.7-50.3)	31.4 (16.8-46.7)	44.4 (22.9-54.5)	24.6 (7.0-44.5)	39.5 (23.9-50.7)	0.748	**0.009***	**0.001***
COMPASS-31 sub-domain scores									
Sub-domain 1: Orthostatic symptoms	20.0 (0.0-28.0)	20.0 (0.0-28.0)	20.0 (0.0-28.0)	24.0 (0.0-28.0)	0.0 (0.0-24.0)	20 (0.0-28.0)	0.958	0.099	**0.004***
Sub-domain 2: Vasomotor symptoms	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.412	**0.010***	**0.041**
Sub-domain 3: Gastrointestinal symptoms	9.8 (5.3-13.3)	8.9 (5.3-11.6)	8.9 (5.3-12.5)	11.1 (5.5-14.2)	7.1 (3.5-12.5)	9.8 (6.2-14.2)	0.633	0.078	**0.010***
Sub-domain 4: Secretomotor symptoms	4.2 (0.0-8.5)	6.4 (2.1-9.6)	4.2 (0.0-8.5)	8.5 (2.6-10.7)	2.1 (0.0-8.5)	6.4 (0.0-8.5)	0.145	**0.001***	**0.010***
Sub-domain 5: Bladder symptoms	0.0 (0.0-1.1)	1.1 (0.0-2.2)	0.0 (0.0-1.1)	0.0 (0.0-2.2)	0.0 (0.0-1.1)	0.0 (0.0-2.2)	**0.018**	0.090	**0.029**
Sub-domain 6: Pupillomotor symptoms	2.3 (1.3-3.0)	2.6 (1.8-3.5)	2.3 (1.3-3.0)	2.6 (1.6-3.6)	2.0 (1.0-2.6)	2.6 (1.6-3.6)	0.251	**0.042**	**0.001***

CASs=Cranial autonomic symptoms, COMPASS=Composite Autonomic Symptom Scale; MIDAS=Migraine disability assessment score

Values are presented as n (%) or median (interquartile range). Categorical variables were compared using the Chi-square test. Continuous variables were analyzed using Mann-Whitney U test. For each pairwise comparison set (a–b, c–d, and e–f), p-values were adjusted separately using the Benjamini–Hochberg false discovery rate (FDR) method. All primary significant findings remained statistically significant after FDR correction. (*) indicate results that remained statistically significant after FDR correction

Table 5. Correlation between migraine characteristics, quality of life and autonomic symptoms

Variable	Total number of CAS	COMPASS-31: Sub-domain 1	COMPASS-31: Sub-domain 2	COMPASS-31: Sub-domain 3	COMPASS-31: Sub-domain 4	COMPASS-31: Sub-domain 5	COMPASS-31: Sub-domain 6	COMPASS-31: Total score
Migraine duration	0.464 0.055	0.730 0.026	0.177 0.101	0.033 0.159	0.008 0.198	0.070 0.136	0.939 0.006	0.343 0.071
HITS Score	0.178 0.101	0.001* 0.347	0.062 0.139	0.002 0.231	0.001* 0.250	0.001* 0.251	0.001* 0.362	0.001* 0.394
MIDAS Score	0.033 0.159	0.001* 0.238	0.015 0.182	0.001* 0.272	0.001* 0.328	0.001* 0.276	0.001* 0.371	0.001* 0.365
MIDAS-A	0.142 0.110	0.001* 0.260	0.040 0.153	0.023 0.169	0.001* 0.324	0.002 0.231	0.001* 0.251	0.001* 0.346
MIDAS-B	0.767 0.022	0.011 0.189	0.503 0.050	0.949 0.005	0.884 0.011	0.095 0.125	0.627 0.036	0.073 0.134
MSQoL: RFR	0.071 -0.135	0.001* -0.288	0.008 -0.196	0.010 -0.192	0.001* -0.301	0.001* -0.258	0.001* -0.447	0.001* -0.357
MSQoL: RFP	0.055 -0.144	0.001* -0.333	0.036 -0.157	0.016 -0.180	0.001* -0.282	0.001* -0.269	0.001* -0.395	0.001* -0.367
MSQoL: EF	0.022 -0.171	0.001* 0.326	0.005 -0.209	0.006 -0.202	0.001* -0.311	0.001* -0.327	0.001* -0.417	0.001* -0.389
MSQoL: Total	0.030 -0.162	0.001* -0.346	0.007 -0.201	0.004 -0.211	0.001* -0.326	0.001* -0.306	0.001* -0.475	0.001* -0.410
$p < 0.001$ was demonstrated as 0.001, Above = p value; below = r value.								

COMPASS=Composite Autonomic Symptom Scale, Sub-domain 1=Orthostatic symptoms, Sub-domain 2=Vasomotor symptoms, Sub-domain 3=Gastrointestinal symptoms, Sub-domain 4=Secretomotor symptoms, Sub-domain 5=Bladder symptoms, Sub-domain 6=Pupillomotor symptoms. CAS=Cranial Autonomic Symptom, MIDAS=Migraine Disability Assessment Score, HITS=Headache Impact Test, MSQoL=Migraine-Specific Quality-Of-Life Questionnaire, RFR=Role Function-Restrictive, RFP=Role Function-Preventive, EF=Emotional Function.

Spearman correlation analysis was used. p-values were adjusted for multiple testing using the Benjamini–Hochberg false discovery rate (FDR) method across all correlations presented in the table. Only correlations that remained statistically significant after FDR correction ($q < 0.05$) are marked with an asterisk (*).

Table 6: Multivariable linear regression analysis for migraine-specific quality of life

Variables	B [%95 CI]	Beta	t	p	Zero-order	Partial
Constant	2.699 (2.473-2.919)		23.876	<0.001*		
Age	-0.002 (-0.003-0.000)	-0.108	-1.688	0.093	-0.093	-0.130
Gender	0.025 (-0.019-0.070)	0.058	1.118	0.265	0.038	0.086
Education level	-0.009 (-0.030-0.011)	-0.063	-0.881	0.379	0.139	-0.068
Financial situation	0.028 (0.011-0.045)	0.214	3.299	0.001*	0.316	0.247
MIDAS	-0.001 (-0.001-0.000)	-0.194	-3.399	0.001*	-0.450	-0.254
HITS-6	-0.015 (-0.018- -0.012)	-0.549	-9.415	<0.001*	-0.675	-0.589
Log (COMPASS-1)	0.010 (-0.013-0.034)	0.051	0.883	0.379	-0.192	0.068
Log (COMPASS-2)	-0.104 (-0.180- -0.028)	-0.145	-2.697	0.008*	-0.260	-0.204
Log (COMPASS-3)	0.037 (-0.039-0.114)	0.059	0.957	0.340	-0.192	0.074
Log (COMPASS-4)	-0.003 (-0.041-0.035)	-0.009	-0.146	0.884	-0.266	-0.011
Log (COMPASS-5)	0.013 (-0.054-0.080)	0.022	0.374	0.709	-0.259	0.029
Log (COMPASS-6)	-0.088 (-0.181-0.004)	-0.115	-1.887	0.061	-0.345	-0.144

COMPASS=Composite Autonomic Symptom Scale, Sub-domain 1=Orthostatic symptoms, Sub-domain 2=Vasomotor symptoms, Sub-domain 3=Gastrointestinal symptoms, Sub-domain 4=Secretomotor symptoms, Sub-domain 5=Bladder symptoms, Sub-domain 6=Pupillomotor symptoms. MIDAS=Migraine Disability Assessment Score, HITS=Headache Impact Test, *Statistical significance value

cluster headache. The mean number of CASs was 1.8 in patients with migraine and 3.5 in patients with cluster headache.[22] In our study, CASs were present in 44.2% of patients with migraine, with a mean number of 1.92.

A wide range of CASs has been described in migraine. A recent study reported that the most common CAS in migraine was forehead sweating, observed in 39% of patients, followed by lacrimation (24%), ptosis (14%) and conjunctival injection (13%).[19] Similarly, a population-based study reported red eyes (29.1%), tearing (25.8%), dropped eyelid (22.3%), nose congestion (28.6%), runny nose (12.4%), and eyelid edema (7.5%).[23] In our study, the most common ictal CAS symptoms were lacrimation, conjunctival injection, ptosis and eyelid edema.

The reported rates of these symptoms vary across studies. Since the evaluation of ictal symptoms is based on patient self-reporting, objective assessment is not always possible. Nevertheless, many studies indicate that ocular symptoms are the predominant CASs in patients with migraine. Consistent with this, our study also demonstrated a higher frequency of ocular symptoms. Additionally, lacrimation, eyelid edema, nasal congestion and forehead sweating were more prevalent in patients with migraine with aura than in those without aura. However, no association was found between migraine type (episodic or chronic migraine) and the presence of CASs.

ECASs are observed in patients with migraine and may occur during either ictal or interictal periods; however, visceral symptoms are most commonly present during migraine attacks. The most frequently reported symptoms include nausea, vomiting, constipation, frequent urination, bloating, gastric fullness, eructation, diarrhea and frequent defecation. Approximately half of patients with migraine experience visceral autonomic symptoms before the headache attack.[23] The CAMERA study reported higher rates of orthostatic intolerance (32% vs. 12%) and syncope (13% vs. 5%) in patients with migraine.[24] Other ECASs associated with migraine include nausea, orthostatic intolerance, diarrhea, and polyuria.[25]

Despite the clinical relevance of autonomic symptoms in migraine, studies examining the relationship between ECASs and headaches characteristics remain limited. The first study using the COMPASS-31 questionnaire in migraine was recently published and demonstrated moderate ECASs in the patient population, along with a weak correlation between autonomic symptoms and anxiety-

depression.[26] In our study, both total and sub-domain COMPASS-31 scores were significantly higher in patients with migraine. Moreover, greater severity of autonomic symptoms was associated with lower quality of life (MSQoL) with pupillomotor (e.g. light sensitivity) and vasomotor symptoms showing the strongest association with reduced quality of life. In addition, multivariable regression analysis revealed that vasomotor symptoms (COMPASS subdomain 2), lower financial status, and higher MIDAS and HIT-6 scores were independently associated with poorer quality of life.

Several theories have been proposed to explain the presence of ECASs in migraine. It has been suggested that the underlying pathophysiological mechanism involves desensitization of descending inhibitory nociceptive pathways, leading to increased central sensitization and disruption of the balance between the sympathetic and parasympathetic nervous systems.[27,28] However, there is currently no scientific evidence clearly demonstrating a relationship between headache type or frequency and extracranial autonomic symptoms. In our study, the severity of autonomic symptoms was higher in patients with migraine, particularly in migraine with aura and in patients with higher disability scores. Moreover, ECASs were evaluated during the interictal period and COMPASS-31 scores remained elevated in the migraine group. These results indicate that autonomic symptoms are not limited to the ictal period.

In conclusion, Ictal CASs —particularly ocular symptoms —were observed at higher frequencies in patients with migraine. In addition, interictal ECAS severity was also greater in patients with migraine. Autonomic symptoms were negatively correlated with quality of life, with pupillomotor symptoms demonstrating the strongest association with migraine-related quality of life. Our study underscores the importance of evaluating autonomic parameters in ictal conjunction with headache characteristics in patients with migraine. Further studies are needed to confirm these findings, to identify specific diagnostic and therapeutic approaches, and elucidate the underlying pathophysiological mechanisms.

Limitations of this study are as follows: First, no analysis was performed according to aura subtypes (visual, auditory, sensory, language, etc.); because the number of patients with migraine with aura was insufficient for meaningful statistical analysis of these subgroups. Second, the relationship between CASs and headache location was not evaluated, as was headaches pain was frequently not strictly lateralized, precluding categorization by side. Third, the study population consisted predominantly young women (approximately 88% female, mean age 33). Results may not generalize to men or older populations. Fourth, several important potential confounders were not systematically recorded, including migraine attack frequency, attack severity, and the use of acute or preventive migraine medications. Additionally, education level and financial status differed significantly between the migraine and control groups and may have influenced quality-of-life and autonomic symptom scores. These factors should be considered when interpreting the results. Fifth, the relationship between autonomic symptoms and treatment options (analgesic or prophylactic therapies) was not assessed. Larger, multicenter studies with more diverse patient populations are needed to evaluate the effects different treatment modalities.

ACKNOWLEDGEMENTS

The authors thank to all participants for their valuable support.

DISCLOSURE

Ethics: The study has the permission of Local Ethics Committee (Meeting number: 2024/19, Decision No: 2024/540).

Data availability: The datasets generated and/or analyzed during the current study are not publicly available due to reasons of sensitivity but are available from the corresponding author on reasonable request.

Financial support: None

Conflicts of interest: None

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