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ORIGINAL ARTICLE

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아칼라지아 환자의 자율신경계 기능 이상

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Autonomic Nervous System Dysfunction in Achalasia

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Background/Aims: Achalasia is an esophageal motility disorder characterized by dysphagia and noncardiac chest pain. Impairment of vagal function has been reported in achalasia. This study evaluated autonomic nervous system (ANS) dysfunctions in patients with achalasia to establish a correlation between an ANS dysfunction and the clinical symptoms of achalasia.
Methods: Nineteen patients with achalasia (six males/13 females; mean age, 47.1±16.3 years) and 10 healthy controls (four males/six females; 34.8±10.7 years) were enrolled prospectively at Gangnam Severance Hospital between June 2013 and June 2014. All patients completed a questionnaire on ANS dysfunction symptoms and underwent a heart rate variability (HRV) test.
Results: ANS dysfunction symptoms were present in 13 patients with achalasia (69%) and three controls (30%). The ANS dysfunction score was significantly higher in patients with achalasia than in the controls (p=0.035). There were no significant differences in the standard deviation of all normal R-R intervals, high frequency (HF), low frequency (LF), and LF/HF ratio in the HRV test. In subgroup analysis comparing female achalasia patients with controls, the cardiac activity was significantly higher in the female achalasia patients than in the controls (p=0.036). The cardiac activity (p=0.004) and endurance to stress (p=0.004) were significantly higher in the achalasia patients with ANS dysfunction symptoms than the achalasia patients without ANS dysfunction symptoms.
Conclusions: ANS dysfunction symptoms are common in patients with achalasia. Female achalasia patients and those with ANS dysfunction symptoms showed increased cardiac activity. Hence, more attention should be paid to cardiac overload in achalasia patients who are female or have ANS dysfunction symptoms. **(Korean J Gastroenterol 2024;83:54-60)**

Key Words: Esophageal achalasia; Autonomic nervous system; Heart rate

INTRODUCTION

Achalasia is a primary motor disorder of the esophagus caused by autonomic denervation.[1] Achalasia is associated with extraesophageal sympathetic and parasympathetic dysfunction. An impaired vagal function has also been reported in achalasia, and the parasympathetic nervous system is coordinated via the cervical vagus nerve. Therefore, patients with achalasia have autonomic nerve dysfunction in the vagal nerve outside the esophagus.[1-3] The pathological findings in patients with achalasia included the following: loss of ganglion cells within the myenteric plexus, degeneration of vagal fibers, reduction and depigmentation of cells in the dorsal motor nucleus of the vagus, and disturbance of esophageal adrenergic innervation.[4-7] Achalasia is characterized by a loss of peristalsis in the smooth muscle part of the esoph-

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ageal body and inadequate relaxation of the lower esophageal sphincter (LES) in response to swallowing.[8] Some studies have suggested that achalasia is associated with extra-esophageal dysmotility disorders, such as delayed emptying of the stomach and dysfunctions of the small intestine and sphincter of Oddi.[9-12] Histological studies have reported that approximately 50% of patients with achalasia also showed the denervation of ganglion cells in the stomach.[13]

Disorders of the extrinsic nerve supply to the gut are associated with clinical manifestations indicating gastrointestinal dysmotility.[14] These disturbances can affect all levels of the pathways (sympathetic and parasympathetic) supplying the digestive tract. Autonomic function abnormalities have also been documented in patients with functional gastrointestinal disorders.[15] Experimental models of the gut motor function suggest that the extrinsic nervous system has a predominant modulatory role, with the enteric nervous system exerting primary control.[16] The enteric nervous system is considered the third division of the autonomic nervous system (ANS).[17] These studies suggest that changes in the ANS extend beyond the esophagus. Therefore, it is unclear how significantly autonomic dysfunction affects gastrointestinal dysmotility and the development of functional gut disorders. ANS dysfunction testing for achalasia patients would be a useful alternative to the current invasive tests used to assess motility disturbances of the digestive tract. In addition, some patients with achalasia have microvascular angina, of which an ANS dysfunction may be one cause.[18,19] Therefore, this study evaluated the ANS dysfunction in patients with achalasia to determine the correlation of an ANS dysfunction with the clinical symptoms of achalasia.

SUBJECTS AND METHODS

Nineteen patients diagnosed with achalasia and 10 healthy age- and sex-matched controls were included in the study. The patients' history was taken, and a physical examination, including routine laboratory testing, conventional abdominal ultrasonography, electrocardiography, and blood pressure measurements, was performed. Patients with cardiac arrhythmia, diabetes mellitus, or neurological and ophthalmologic diseases were excluded. The results were compared with those of the healthy controls.

All patients completed a questionnaire for ANS dysfunction symptoms (Table 1) and underwent a heart rate variability (HRV) test.[20] The ANS tests consisted of detailed HRV analysis, as described by Olk et al.[7] The computerized electrocardiogram system ProSciCard (MediSyst; Medical Research and Diagnostic Computer Systems GmbH, Linden, Germany) was used to investigate the HRV. The HRV was characterized using power spectral

Table 1. Autonomic Nervous System Dysfunction Symptom Score Questionnaire[18]

	None	Sometimes	Always
Symptoms when you take the supine position			
Is your heart beating fast?			
Is your vision blurred?			
Do you feel dizzy?			
Does your skin become sticky?			
Does your stomach feel uncomfortable?			
Symptoms when you are sweating			
Has your sweating increased in certain areas?			
Has your sweating decreased in certain areas?			
Do you sweat during or after eating?			
Symptoms in the stomach and intestines			
Do you have diarrhea?			
If you have diarrhea, does it get worse at night?			
Are your bowel movements less smooth than before?			
Do you easily feel full before you finish eating?			
Total score:			

Scoring: none, 0; sometimes, 1; always, 2.

analysis after a fast Fourier transformation. This allowed the differentiation of three main sinusoidal functions of different frequencies that represent the modulation of the HRV according to the vasomotor tone (low frequency [LF]: 0.001-0.05 Hz,

Table 2. Clinical Baseline Characteristics

Parameter	Control (n=10)	Patient (n=19)
Age (yr)	39.8±10.6	47.1±16.3
Sex, male:female	4:6	6:13
Duration of dysphagia (months)		43.57±92.9
Types of achalasia		
Type I		1 (5.2)
Type II		10 (52.6)
Type III		1 (5.2)
Undifferentiated		1 (5.2)
Not performed		6 (31.8)
ANS dysfunction symptom, absence: presence	7:3	5:13[a]
ANS dysfunction score	0.50±0.77	2.11±2.47[b]

Values are presented as mean±standard deviation or number (%) unless otherwise indicated.
ANS, autonomic nervous system.
[a]One patient was not assessed using the scoring system; [b]p=0.035.

Table 3. Power Spectral Analysis of the Heart Rate Variability in Achalasia Patients and Controls

Variability	Control (n=10)	Patient (n=19)	p-value
Mean R-R interval	793.50	781.00	0.750
Mean HR (beats/min)	75.50	75.00	0.962
SDNN (ms)	33.50	33.00	0.198
Complexity	0.55	0.50	0.801
TP (ms^2)	7.00	7.20	0.369
LF (nu)	53.10	53.40	0.850
HF (nu)	46.95	46.60	0.925
LF/HF ratio	1.13	1.15	0.814
HRV index	10.15	10.20	0.524
RMSSD (ms)	18.00	19.00	0.571
SDSD (ms)	23.00	24.00	0.671
pNN50 (%)	71.85	66.00	0.175
PNS activity (%)	47.35	51.70	0.524
Stress endurance (%)	46.40	50.70	0.097
Cardiac activity (%)	45.50	48.10	0.253
Physical arousal (%)	52.35	51.70	0.981
Cardiac aging (%)	52.80	48.90	0.316
SNS activity (%)	53.25	58.50	0.220
ANS balance (%)	51.20	51.90	0.906
Heart load (%)	51.90	48.90	0.328
ANS dysfunction score	0	2	0.014[a]

HR, heart rate; SDNN, standard deviation of all R-R intervals; TP, total power; LF, low frequency; nu, normal units; HF, high frequency; HRV, heart rate variability; RMSSD, root-mean square of successive differences; SDSD, standard deviation of successive differences; pNN50, the percentage of adjacent R-R intervals that differ from each other by more than 50 ms; PNS, parasympathetic nervous system; SNS, sympathetic nervous system; ANS, autonomic nervous system.
[a]$p<0.05$.

mediated by sympathetic and parasympathetic nervous activity) or baroreceptor activity (middle frequency: 0.05-0.15 Hz, predominantly representing parasympathetic nervous activity).[6]

The total variance (total power) can be divided into three spectral components (fractions of total variance) centered at different frequencies.[21] A high frequency (HF), a respiratory-linked component centered at approximately 0.25 Hz was considered to reflect mostly vagal activity and a LF component centered at approximately 0.1 Hz, reflected mostly sympathetic activity and its changes. The oscillatory components between 0 and 0.03 Hz were considered DC noise. Each spectral component was presented in a normalized form by dividing it by the total powerless status of the DC component, if present. The LF/HF ratio was used to index the sympathovagal balance. The Local Ethics Committee at Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea, approved this study (IRB number: 3-2021-0017). Informed consent was obtained from all patients, and the study fulfilled the criteria of the declaration of Helsinki.

Statistical analysis was performed using a Student's t-test for matched pairs of patients and controls. The data are expressed as the means and standard deviations. The level of significance was set to $p<0.05$.

RESULTS

ANS dysfunction symptoms were present in 13 patients with achalasia (69%) and three controls (30%). The ANS dysfunction score was significantly higher in patients with achalasia than in the controls (2.11 vs. 0.50, p=0.035). Table 2 lists the clinical baseline characteristics of the patients with achalasia and controls. The standard deviations of the normal R-R intervals, HF component, LF component, and LF/HF ratio in the HRV test were similar in the patient and control groups (Table 3). Subgroup analysis of female achalasia patients and controls revealed the cardiac activity to be significantly higher

Table 4. Power Spectral Analysis of the Heart Rate Variability in Female Achalasia Patients and Controls

Variability	Control (n=6)	Patient (n=13)	p-value
mean R-R interval	747.00	768.00	0.416
mean HR (beats/min)	80.00	78.00	0.467
SDNN (ms)	36.00	38.50	0.323
Complexity	0.55	0.50	0.898
TP (ms^2)	7.15	7.20	0.639
LF (nu)	50.15	53.95	0.416
HF (nu)	49.80	45.80	0.152
LF/HF ratio	1.01	1.14	0.467
HRV index	8.95	12.45	0.152
RMSSD (ms)	16.50	21.00	0.416
SDSD (ms)	23.00	26.50	0.701
pNN50 (%)	79.20	54.35	0.058
PNS activity (%)	52.80	52.00	0.765
Stress endurance (%)	52.00	51.35	0.072
Cardiac activity (%)	41.40	50.90	0.036[a]
Physical arousal (%)	57.65	55.15	0.416
Cardiac aging (%)	57.65	46.35	0.106
SNS activity (%)	54.15	58.90	0.579
ANS balance (%)	46.30	53.30	0.152
Heart load (%)	48.90	48.90	0.368
ANS dysfunction score	0.5	2	0.083

HR, heart rate; SDNN, standard deviation of all R-R intervals; TP, total power; LF, low frequency; nu, normal units; HF, high frequency; HRV, heart rate variability; RMSSD, root-mean square of successive differences; SDSD, standard deviation of successive differences; pNN50, the percentage of adjacent R-R intervals that differ from each other by more than 50 ms; PNS, parasympathetic nervous system; SNS, sympathetic nervous system; ANS, autonomic nervous system.
[a]$p<0.05$.

Table 5. Power Spectral Analysis of the Heart Rate Variability in Achalasia Patients and Controls Who Had ANS Dysfunction Symptoms

Variability	Control (n=3)	Patient (n=13)	p-value
mean R-R interval	802.50	746.50	0.779
mean HR (beats/min)	75.00	80.00	0.779
SDNN (ms)	25.00	38.5	0.076
Complexity	0.45	0.55	0.353
TP (ms^2)	6.70	7.20	0.179
LF (nu)	53.10	52.75	0.968
HF (nu)	46.90	47.15	0.718
LF/HF ratio	1.13	1.10	0.968
HRV index	7.65	12.35	0.041[a]
RMSSD (ms)	15.00	19.50	0.239
SDSD (ms)	19.00	24.50	0.207
pNN50 (%)	84.80	62.20	0.051
PNS activity (%)	44.40	51.10	0.239
Stress endurance (%)	36.50	51.05	0.009[b]
Cardiac activity (%)	40.95	50.65	0.002[b]
Physical arousal (%)	51.45	57.65	0.779
Cardiac aging (%)	61.40	47.15	0.076
SNS activity (%)	39.75	58.90	0.109
ANS balance (%)	51.40	50.80	0.718
Heart load (%)	54.55	49.20	0.130

ANS, autonomic nervous system; HR, heart rate; SDNN, standard deviation of all R-R intervals; TP, total power; LF, low frequency; nu, normal units; HF, high frequency; HRV, heart rate variability; RMSSD, root-mean square of successive differences; SDSD, standard deviation of successive differences; pNN50, the percentage of adjacent R-R intervals that differ from each other by more than 50 ms; PNS, parasympathetic nervous system; SNS, sympathetic nervous system.
[a]$p<0.05$; [b]$p<0.01$.

in the female achalasia patients (p=0.036) than in the female controls (Table 4). The pNN50 (the percentage of adjacent R-R intervals that differ from each other by more than 50 ms) of the female patients with achalasia showed a decreasing trend compared to that of the female controls (p=0.058).

The cardiac activity (p=0.002) and endurance to stress (p=0.009) were significantly higher in the achalasia patients with ANS dysfunction symptoms compared to the controls with symptoms (Table 5).

DISCUSSION

To the best of the authors' knowledge, this study is the first to confirm a relationship between achalasia and ANS dysfunction using the ANS dysfunction score and HRV test findings. The results showed that achalasia may be associated with an extraesophageal alteration of the ANS.[9] This conclusion was based on von Herbay et al.,[2] who reported that patients with achalasia exhibit abnormalities in various standardized autonomic function tests, such as the Valsalva maneuver during deep respiration. Several other studies also reported an ANS dysfunction in achalasia patients; the strongest evidence relates to an altered pupillary function in achalasia patients compared to the healthy control.[1,2,8] von Herbay et al.[2] also reported changes in postprandial blood flow regulation in the superior mesenteric artery in achalasia patients. Another important observation in several studies was that patients with achalasia and controls showed significant postprandial decreases in PI and RI of the superior mesenteric artery.[22-24] In addition, increased mesenteric blood vessel resistance is mediated by the sympathetic and parasympathetic nerve function, which may have the opposite effect.[2] On the other hand, Ohlsson et al.[1] found no evidence of sympathetic nervous system involvement in achalasia. In the present study, achalasia patients with ANS dysfunction symptoms, particularly female patients, showed increased cardiac

activity. Moreover, not all HRV test findings were abnormal in patients with achalasia. An indicator of the sympathetic activity, the HF respiratory-linked band, and the ratio between LF and HF were similar in achalasia patients and controls.[25] Previous studies indicated a normal vagal function in these patients.[26] By contrast, Rinaldi et al.[21] contradicted the reports on normal sympathetic function in achalasia patients and reported that these patients have impaired sympathetic autonomic control, as indicated by the smaller increase in diastolic pressure during sustained handgrip. Most studies indicated a LES dysfunction caused by vagal damage.[5,6,13,27]

The exact cause of the elevated cardiac activity in female achalasia patients compared to the control group is unknown. On the other hand, there are interesting reports from previous studies. A study of achalasia patients analyzed gender differences and revealed a significantly higher rate of chest pain in the female group.[28] In addition, a study involving noncardiac chest pain patients identified increased sensitivity to esophageal acid reflux in individuals with an ANS dysfunction.[29] These findings suggest a potential association between the symptom complaints and ANS dysfunction in female achalasia patients. Nevertheless, further studies will be needed to confirm any causal relationship.

This study had several limitations. First, securing sufficient statistical significance and performing a multilateral correlation analysis was difficult because the sample size was small. This research was a single-center study; therefore, there is a limit to ensuring sufficient numbers of patients because of the small number of patients visiting the center owing to the low prevalence of achalasia. The sample size of the control group was also limited because the aim was to include only healthy controls, excluding other factors that might affect the results. Furthermore, some rate differences still existed due to the limited pool of eligible patients, even with the best efforts to match for gender and age between the two groups. Second, the study used a questionnaire method relying on the patient's personal experiences to measure the degree of ANS dysfunction. More objective results could have been obtained if tests, such as pupillometry or head-up-tilt test, had been performed. Third, additional factors, such as the treatment of achalasia, should have been considered when determining the impact on ANS function. Nevertheless, considering additional factors influencing ANS was challenging because of the limited size of the patient sample and the absence of additional tests to assess the ANS function. Given these limitations, future studies must consider these factors in more detail to supplement the results.

The achalasia patients with ANS dysfunction symptoms in this study were characterized by significantly higher cardiac activity and stress endurance. Moreover, some patients with achalasia had microvascular angina; an ANS dysfunction is one of the probable causes of microvascular angina.[18,19] Therefore, monitoring of the cardiovascular dynamics is necessary for safety when patients with achalasia who also have an ANS dysfunction require invasive procedures, such as per-oral endoscopic myotomy. In the present study, not all HRV test findings were abnormal for patients with achalasia. Further studies will be needed to evaluate sympathetic-parasympathetic interactions that modulate the cardiac function in patients with primary achalasia.

ANS dysfunction symptoms are relatively common in achalasia patients. In this study, achalasia patients with ANS dysfunction symptoms and female patients showed increased cardiac activity. Therefore, more attention should be paid to cardiac overload in achalasia patients who are female or have ANS dysfunction symptoms.

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