의학석사 학위논문

Autonomic dysfunction is associated with the extent of hypothalamic involvement and increased risk of being metabolically unhealthy in patients with childhood onset craniopharyngioma

소아기에 발병한 두개인두종 환자에서 시상하부 손상 정도에 따른 자율신경계 기능 이상과 대사성 합병증의 위험도 증가에 관한 연구

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Abstract

Introduction: Autonomic nervous system (ANS) dysfunction is implicated in the development of hypothalamic obesity. In patients treated for childhood onset craniopharyngioma, we investigated changes in ANS activity according to the extent of HI and presence of obesity, using measures of heart rate variability (HRV). Changes in HRV and the risk of being metabolically unhealthy were analyzed.

Methods: From March 2014 to January 2016, HRV indices of overall variability [standard deviation NN interval (SDNN) and total power (TP)], parasympathetic modulation [root mean square of successive RR interval differences (RMSSD) and high frequency (HF)], and sympathetic or sympathovagal modulation [low frequency (LF) and LF/HF ratio] were measured in 48 patients (28 males, 10-30 years of age) with HI after craniopharyngioma treatment at Seoul National University Children's Hospital. The extent of HI was graded on magnetic resonance imaging. Anthropometric measurements, fasting glucose, insulin, lipid panel, and blood pressure were obtained.

Results: Patients with extensive HI showed increased BMI z-scores (P = 0.008), waist circumference (P = 0.037) and insulin resistance (homeostasis model assessment of insulin resistance, HOMA-IR, P = 0.043). There was a general decrease in overall variability, parasympathetic modulation and sympathetic/sympathovagal modulation with extensive HI. There was no difference in HRV indices between obese and non-obese subjects. Obese patients with concomitantly reduced overall variability (by SDNN or TP) showed increased HOMA-IR ($P < 0.05$, for both), triglycerides ($P < 0.05$, for both), blood pressure ($P < 0.05$, for both), and decreased HDL cholesterol ($P < 0.05$, for both). Risk of

being metabolically unhealthy was increased in patients with both obesity and reduced overall variability ($P < 0.05$, for both).

Conclusion: Extensive HI is associated with obesity as well as decreases in overall variability and parasympathetic modulation. Obese patients with concomitant reduced HRV had higher risk of being metabolically unhealthy.

Keywords : Autonomic dysfunction, Heart rate variability, Hypothalamic involvement, Craniopharyngioma, Metabolically unhealthy

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Table of Contents

List of Tables

List of Figures

List of Abbreviations

ANS, autonomic nervous system

HI, hypothalamic involvement

HRV, heart rate variability

SDNN, standard deviation NN interval

TP, total power

RMSSD, root mean square of successive RR interval differences

HF, high frequency

LF, low frequency

BMI, body mass index

HOMA-IR, homeostasis model assessment of insulin resistance

HDL, high density lipoprotein

LDL, low density lipoprotein

BP, blood pressure

MRI, magnetic resonance imaging

HbA1c, hemoglobin A1c

INTRODUCTION

Craniopharyngiomas are rare, histologically benign tumors of the sellar and parasellar area that arise from the remnants of Rathke's pouch. Approximately 30-50% of craniopharyngiomas develop in childhood and adolescence and represent 1.2-5% of all intracranial tumors in children (1, 2). Even though overall survival rates are high, excess mortality and morbidity have been reported to be marked in childhood onset craniopharyngiomas (3). Damage to the optic tract, pituitary gland, and hypothalamus by tumor invasion and ensuing treatments results in visual defects, neurocognitive deficits, pituitary hormone deficiencies, hypothalamic dysfunction, and morbid obesity.

Hypothalamic obesity is of especial concern as it affects nearly 50% of patients after initial treatment and is associated with poor quality of life in long-term studies (4, 5). Pathophysiologic mechanisms of hypothalamic obesity are complex with implications of disturbances in orexigenic and anorexigenic pathways as well as dysfunction of sympathetic and parasympathetic components of the autonomic nervous system (ANS) (6).

In this study, we aimed to evaluate the function of the ANS in patients treated for childhood onset craniopharyngioma through measures of heart rate variability (HRV). We evaluated whether there were differences in HRV parameters according to the presence of obesity and the extent of hypothalamic involvement (HI). Furthermore, the importance of changes in HRV on the status of metabolic health was assessed.

MATERIALS AND METHODS

Subjects

Of 113 patients followed up for childhood onset craniopharyngioma, 76 patients who were between 10 to 30 years of age and at least 6 months past initial surgery were screened for enrollment. Twenty patients were not enrolled due to comorbid diseases (n = 6), medications affecting the ANS (n = 3), or lack of consent (n = 11). Of the enrolled patients, 8 patients were further excluded due to lack of recent magnetic resonance imaging (MRI; n = 1), lack of HI on MRI (n = 5) or artifacts on cardiac autonomic function testing (n = 1). A total of 48 patients (28 males) were included in the final analysis. The study was approved by the Institutional Review Board at Seoul National University Children's Hospital (IRB No. 1311-079-535).

Clinical and anthropometric data

A detailed medical history of the patients including previous operations, medications and family history was obtained by a retrospective review of the electronic medical records. The extent of HI was classified according to Puget's grading system (7) by two individual radiologists who were unaware of the clinical status of the patients. Grade 1 patients showed minimal hypothalamic damage or residual tumor displacing the hypothalamus while grade 2 patients had extensive hypothalamic damage with an unidentifiable floor of the third ventricle.

On the day of the cardiac ANS testing, height was measured by a Harpenden stadiometer (Holtain Ltd., Crymmych, Wales, UK) and weight by a digital scale scale (150 A; Cas Co. Ltd., Seoul, Korea). The body mass index (BMI) was calculated accordingly. Measures of height, weight and BMI were expressed as

age- and sex-specific z-scores according to the 2007 national growth charts of Korean children and young adults (8). Waist circumference was measured and body composition analyzed by bioimpedance (InBody 770, InBody Co., Seoul, Korea). Obesity was defined as a BMI ≥ 95th percentile (BMI z-score ≥ 1.645) for children and absolute BMI ≥ 25 kg/m^2 for adults (9). Central obesity was defined as a waist circumference ≥ 90th percentile for age- and sex-specific references (8) in children and an absolute waist circumference ≥ 90 cm (in adult males) and ≥ 80 cm (in adult females) (9).

Assessment of insulin resistance and metabolic health status

Samples of plasma glucose, insulin, hemoglobin A1c (HbA1c), total cholesterol, triglycerides, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, and uric acid levels were obtained after a 12-hour fast. The homeostatic model assessment of insulin resistance (HOMA-IR) was calculated by the following formula: [fasting plasma glucose (mmol/l) x fasting serum insulin (μIU/mL)]/22.5. Blood pressure (BP) was taken by an automated device (Vital Signs monitor 53N00-E1, Welch Allyn Inc., New York, United States) at the time of ANS testing after a ten minute rest.

The metabolic status of patients was assessed according to criteria for the metabolic syndrome proposed by the revised National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III) (10). Furthermore, patients who were positive for one or more of the following criteria (disregarding the presence of central obesity) were classified as being metabolically unhealthy: 1) fasting glucose ≥ 100 mg/dL, 2) triglycerides ≥ 150 mg/dL, 3) HDL cholesterol < 40 mg/dL (males) or <50 mg/dL (females), and/or 4) systolic BP ≥ 135 mmHg and/or diastolic BP ≥ 85 mmHg (11).

Questionnaires regarding physical activity (International Physical Activity Questionnaire short form; IPAQ-SF) (12), symptoms of autonomic dysfunction (Abbreviated Composite Autonomic Symptom Score; COMPASS 31) (13) and dietary intake (three day food diary) were completed. Physical activity was scored by Metabolic Equivalents (METs) minutes as well as categorized into groups with or without regular physical activity according to definitions established by the US Department of Health and Human Services (14). The three day food diary was analyzed by a nutritionist with calculation of the total caloric intake as well as intake of proteins, fats and carbohydrates.

Cardiac Autonomic function testing

Patients arrived for cardiac ANS testing after having avoided caffeinated beverages and heavy physical exercise in the preceding 24 hours. HRV indices were measured using a computer based system: DiCan (Medicore, Seoul, South Korea). Measurements were performed over a five minute period in the supine position after a 10 minute period of rest and heart rate stabilization. Time domain indices including the standard deviation of all normal R-R intervals (SDNN) and the root-mean square of the difference of successive R-R intervals (RMSSD) were obtained. Frequency domain parameters were analyzed by power spectral analysis of intervals between sequential R waves with resultant calculations of total power (TP), high frequency (HF; 0.15-0.4 Hz), low frequency (LF; 0.04-0.15 Hz), and the LF to HF ratio (LF/HF). The SDNN and TP in their respective time and frequency domains reflect the overall variability. The parasympathetic modulation is reflected by RMSSD and HF (ms^2 and normalized units, nu). The physiological interpretation of LF is not as clear as it may reflect the sympathetic component (especially when expressed in nu) or both sympathetic and vagal components.

(Table 1).

Statistical Analysis

SPSS for Windows (version 22.0, SPSS Inc., Chicago, IL) was used for statistical analyses. Variables were tested for normal distribution. The fasting insulin, HOMA-IR, triglyceride and the LF/HF ratio were log-transformed while the total power, LF (m^2) and HF (m^2) were square root transformed to approximate normal distributions. Continuous variables with normal distributions are described as mean ± standard deviation. The Student t-test and the Mann-Whitney U test were used to compare means of continuous variables with normal and non-normal distribution between two groups, respectively. Categorical variables were compared with chi-square tests. According to central obesity and overall HRV, patients were classified into four groups: Group 1: no central obesity and overall HRV above the median, Group 2: no central obesity and overall HRV below the median, Group 3: central obesity and overall HRV above the median, Group 4: central obesity and overall HRV below the median. The proportion of patients who were metabolically unhealthy were analyzed by chi-test for trend and analysis of variance (ANOVA) with post hoc Bonferroni testing. Multivariate logistic regression analysis was performed to evaluate the independent relationship of central obesity and overall HRV with metabolically unhealthy status. In addition, univariate and multiple linear regression analyses were used to identify factors associated with overall HRV and parameters of metabolic health. Statistical significance was defined as $P \leq 0.05$.

RESULTS

Baseline characteristics

Baseline characteristics of the 48 patients (28 males) and comparisons according to extent of HI are shown in Table 2. The mean age at the time of study was 18.5±4.8 years (range 10.1-30.8). Initial operations of the patients were undertaken between November, 1993 and November, 2012 at a mean age of 8.0±3.8 years (range 1.7-18.1). The extent of tumor removal by the operations were gross total removal (n = 34), near total removal (n = 5), or subtotal removal (n = 9). The surgical approach was transcranial (n = 42) or transsphenoidal (n = 6). The mean postoperative follow up duration was 10.5±5.5 (range 1.7-21.1) years. All patients were regularly followed at the outpatient clinic and receiving pituitary hormone replacements (hydrocortisone, n = 45; levothyroxine, n = 47; growth hormone, n = 43; desmopressin, n = 46). Out of 43 patients of pubertal age, 41 patients were receiving sex hormone replacement therapy.

The respective mean z-scores of height and BMI were 0.13±1.34 (range -2.47 to 2.87) and 0.95±1.37 (-1.85 to 3.14). Obesity was present in 20 (42%) of patients while central obesity was present in 25 (52%). Twelve (25%) patients met the criteria for the metabolic syndrome. A metabolically unhealthy phenotype was present in 34 (71%) of patients (21 with central obesity). The remaining 14 (29%) were metabolically healthy (4 with central obesity).

Obesity, IR, and metabolic risk factors according to the extent of hypothalamic damage

According to the extent of hypothalamic damage, patients were classified into minimal HI (grade 1, n= 19) and severe HI (grade 2, n = 29) groups. Severe HI

group had significantly higher BMI z-scores (0.32±1.40 vs. 1.37±1.20, $P = 0.008$), WC (82.6±13.3 vs. 91.5±15.5, $P = 0.040$), and fat mass (%) (28.3±7.0 vs. 32.6±6.3, $P = 0.031$) than minimal HI group, although there were significant differences in caloric intake and physical activity between the two groups. Systolic BP (100±10 vs. 109±12, $P = 0.007$), and measures of IR (fasting insulin 11.5±6.7 vs. 17.3±9.3, $P = 0.052$; HOMA-IR 2.5±1.5 vs. 3.9±2.0, $P = 0.043$) were significantly higher in severe HI than in the minimal HI group with no differences in fasting glucose, triglycerides, and HDL cholesterol. There were no differences in the prevalence of the metabolic syndrome or in the proportion of patients with a metabolically unhealthy phenotype between the two groups (data not shown).

Is cardiac autonomic modulation reduced in patients with greater hypothalamic damage?

Table 3 shows results of overall HRV (SDNN, TP), parasympathetic modulation (RMSSD, HF) and sympathetic modulation (LF). First, indices of HRV were compared according to the presence of obesity as defined by BMI z-scores and/or presence of central obesity. There were no differences in any of the HRV indices according to BMI z-scores. Also, there were no significant differences in HRV indices between the centrally obese and non-obese groups (data not shown). Next, HRV was compared according to the extent of HI (Table 3). Overall HRV parameters (both SDNN and TP) were significantly reduced in the severe HI group (46.3±16.7 vs. 33.1±17.8, $P = 0.014$ for SDNN; TP 1863.0±1146.7 vs. 1010.3±1103.8 for TP, $P = 0.004$). Parasympathetic modulation reflected by RMSSD was decreased significantly in the severe HI group (41.5±20.1 vs. 29.5±17.9, $P = 0.035$), while HF (m^2) showed a marginal difference between the two groups (436.9±315.6 vs. 292.7±238.4, $P = 0.055$). Furthermore, LF (m^2) was

also significantly decreased in the severe HI group (434.3±365.9 vs. 264.6±503.6, P = 0.031) without significant differences in LF (n.u). There were also no differences in HF (nu) and the LF/HF ratio between the two groups. Few patients complained symptoms of autonomic dysfunction (orthostatic intolerance, vasomotor, secretomotor, gastrointestinal, urinary, and pupillomotor symptoms) without significant difference between the two groups.

The negative association between the extent of HI and overall HRV parameters was significant, after adjusting for central obesity (P = 0.022 for SDNN; P = 0.005 for TP). The negative relationship of the extent of HI with parasympathetic modulation was marginally significant (P = 0.058 for RMSSD; P = 0.054 for HF (m^2)).

Does reduced HRV with coexisting central obesity contribute to a metabolically unhealthy status?

The importance of changes in HRV on metabolic health was analyzed by categorizing the patients into groups according to the presence of central obesity and whether overall HRV (assessed by SDNN and/or TP) was above or below the median. Group 1 had no central obesity and overall HRV above the median (n = 14 by SDNN, n = 13 by TP). Group 2 had no central obesity but had overall HRV below the median (n = 9 by SDNN, n = 10 by TP). Group 3 had central obesity and overall HRV above the median (n = 10 by SDNN, n = 11 by TP) while Group 4 had central obesity and overall HRV below the median (n = 15 by SDNN, n = 14 by TP). The percentage of patients who were metabolically unhealthy, showed an increasing trend from group 1 through to group 4 for assessments by both indices of overall variability (SDNN, P = 0.048; TP, P = 0.042; Figure 1).

There were no differences in fasting glucose levels between the four groups.

However, when levels of insulin resistance (HOMA-IR), hypertriglyceridemia, hypertension, and HDL were each analyzed for comparison between the four groups, there was a significant increasing trend (for HOMA-IR, triglyceride, and systolic blood pressure) and a significant decreasing trend (for HDL) consecutively from group 1 to group 4. Results of post hoc Bonferroni testing are shown in Figure 2.

Multiple logistic regression analysis for predictors of metabolically unhealthy status showed that central obesity in the presence of lower HRV (group 4) was the only significant predictor of being metabolically unhealthy (Table 4). Such risk was significantly increased only in those patients with central obesity and concomitant measures of decreased overall variability by SDNN (OR 8.03, 95% CI 1.0-65.4, $P = 0.05$) and TP (OR 9.80, 95% CI 1.0-91.3, $P = 0.045$) below the median after adjusting for gender, age, and family history of cardiovascular disease.

Table 1. Descriptions of heart rate variability indices and clinical implications.

Indices	Description	Implications
Time domain		
SDNN (ms)	Standard deviation of all normal R-R intervals	Overall variability
RMSSD (ms)	Root mean square of the difference of successive R-R intervals	Parasympathetic modulation
Frequency domain		
TP (ms^2)	Variance of NN intervals over the temporal segment	Overall variability
HF (ms^2 or n.u)	Power in high frequency range (0.15-0.4 Hz)	Parasympathetic modulation
LF (ms^2 or n.u)	Power in low frequency range (0.04-0.15 Hz)	Sympathetic modulation or both components
LF/HF ratio	Ratio of low frequency to high frequency	Sympathetic modulation or both components

Abbreviations: SDNN, standard deviation of all normal R-R intervals; RMSSD, root mean square of the difference of successive R-R intervals; HF, high frequency; LH, low frequency; ms, milliseconds; n.u, normalized units.

Table 2. Baseline characteristics

	Total (n=48)	Puget Grade 1 (n=19)	Puget Grade 2 (n=29)
Clinical Characteristics			
Age [years]	18.5±4.8 (10.1-30.8)	17.9±4.1	18.9±5.3
Male (%)	28 (58%)	9 (47%)	10 (35%)
Age at initial operation [years]	8.0±3.8 (1.7-18.1)	7.1±4.8	8.6±3.0
Postoperative years	10.5±5.5 (1.7-21.1)	10.8±5.5	10.4±5.6
Radiation therapy history (%)	10 (21%)	5 (26%)	5 (17%)
Recur history (%)	15 (31%)	6 (32%)	9 (31%)
Family history of cardiovascular disease (%)*	14 (29%)	2 (11%)	12 (41%)
Visual defect (%)	29 (60%)	12 (63%)	17 (59%)
Measures of physical activity, autonomic symptoms and dietary intake			
Regular physical activity (%)	9 (19%)	2 (11%)	7 (24%)
IPAQ score	1762±1682 (0-7824)	1812±1742	2108±2652
COMPASS 31 survey score	14.2±12.0 (0-53.0)	14.2±12.7	14.2±11.7
Total caloric intake [kcal]	1925±727 (1043-5416)	1874±394	1952±859
Anthropometry and obesity measures			
Height z-score	0.13±1.34 (-2.47 to 2.87)	-0.25±1.49	0.38±1.20
Weight z-score*	0.92±1.53 (-2.7 to 3.4)	0.19±1.60	1.40±1.29
BMI z-score*	0.95±1.37 (-1.85 to 3.14)	0.32±1.40	1.37±1.20
Obesity [%]	20 (42%)	6 (32%)	14 (48%)
Fat mass [%]*	30.9±6.8 (18.4-50.4)	28.3±7.0	32.6±6.3
Waist circumference [cm]*	88.0-15.2 (60-133)	82.6±13.3	91.5±15.5
Central obesity [%]	25 (52%)	8 (42%)	17 (59%)
Risk factors of the metabolic syndrome (excluding central obesity)			
Fasting glucose [mg/dL]	90±7 (76-106)	89±6	91±8
Fasting insulin [uIU/mL]	15±9 (2-41)	11.5±6.7	17.3±9.3
HOMA-IR*	3.4±2.0 (0.4-8.7)	2.5±1.5	3.9±2.0
Triglycerides [mg/dL]	140±75 (41-425)	143±88	137±66
HDL [mg/dL]	43±12 (22-63)	45±12	42±12
Resting systolic blood pressure*	105±12 (83-135)	100±10	109±12
Resting diastolic blood pressure	68±10 (50-91)	65±7	70±11
Metabolic syndrome† (%)	12 (25%)	4 (21%)	8 (28%)
Metabolically unhealthy phenotype‡ (%)	34 (71%)	13 (68%)	21 (72%)

†According to the revised NCEP-ATP III criteria.

‡Presence of more than one of the following: fasting glucose ≥100 mg/dL, triglycerides ≥150 mg/dL, HDL <40 mg/dL (males) or <50 mg/dL (females), systolic BP ≥135 mmHg and/or diastolic BP ≥85 mmHg

Abbreviations: IPAQ, international physical activity questionnaire; COMPASS 31, composite autonomic symptom score; BMI, body mass index; HOMA-IR, homeostatic model assessment of insulin resistance.

*$P < 0.05$

Table 3. Comparison of heart rate variability indices according to obesity and hypothalamic involvement

	Total (n=48)	**Puget Grade 1 (n=19)**	**Puget Grade 2 (n=29)**
Overall variability			
SDNN [ms] *	38.3±18.4	46.3±16.7	33.1±17.8
Total power† [ms^2] **	1347.8±1186.2	1863.0±1146.7	1010.3±1103.8
Parasympathetic modulation			
RMSSD [ms] *	34.3±19.5	41.5±20.1	29.5±17.9
HF† [ms^2]	331.7±281.1	436.9±315.6	292.7±238.4
HF [nu]	48.3±18.4	50.2±4.0	47.0±3.6
Sympathetic modulation			
LF† [ms^2] *	349.8±455.4	434.3±365.9	264.6±503.6
LH [nu]	51.8±18.6	49.8±4.0	53.0±3.6
Sympathetic-parasympathetic ratio			
LF/HF ratio†	1.75±2.34	1.4±1.7	2.0±2.7

†Log or square root transformed

‡Central obesity: waist circumference >80 cm (for females) or >90cm (for males) or >90^{th} percentile for age and sex matched reference (in children).

Abbreviations: SDNN, standard deviation of all normal R-R intervals; RMSSD, root mean square of the difference of successive R-R intervals; HF, high frequency; LH, low frequency; ms, milliseconds.

* $P < 0.05$,

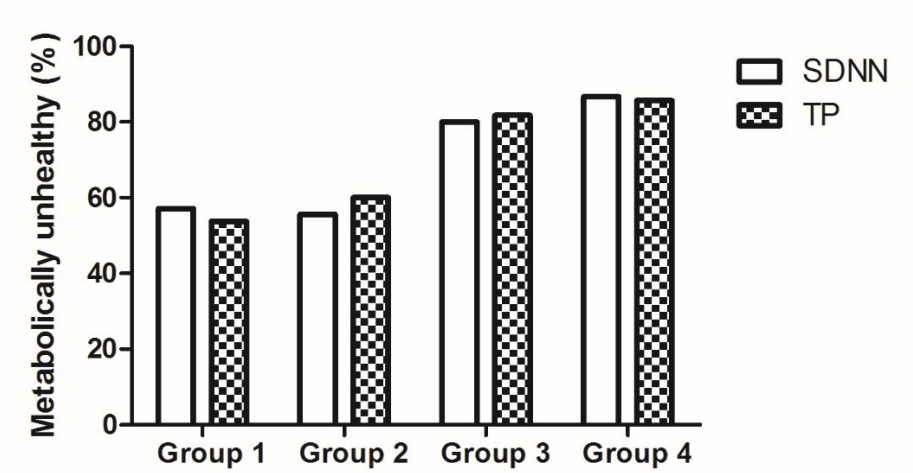
** $P < 0.01$

Table 4. Predictors of the metabolically unhealthy phenotype

Risk factors	OR (95% CI)	p-value
Gender		
Female	1.00	
Male	1.62 (0.37-7.23)	0.525
Testing Age	0.93 (0.73-1.09)	0.351
Family history of cardiovascular disease		
No	1.00	
Yes	1.84 (0.36-9.50)	0.468
Central obesity and overall HRV		
Group 1 (reference)	1.00	
Group 2	1.18 (0.21-6.58)	0.850
Group 3	5.77 (0.73-45.74)	0.097
Group 4	9.80 (1.05-91.31)	0.045

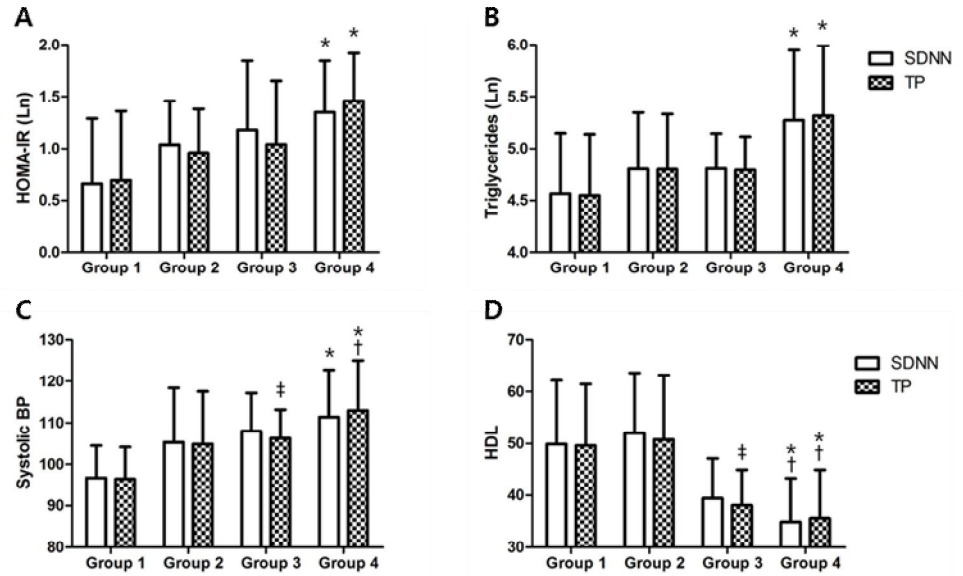
Abbreviations: HRV, heart rate variability; OR, odds ratio; CI, confidence interval.

Figure 1. Trends in the percentage of the metabolically unhealthy phenotype according to the presence of central obesity and whether overall HRV (by SDNN and TP) is above or below the median.



Group 1: no central obesity and overall variability above the median, Group 2: no central obesity and overall variability below the median, Group 3: central obesity and overall variability above the median, Group 4: central obesity and overall variability below the median.
Abbreviations: SDNN, standard deviation of all normal R-R intervals; TP, total power.

Figure 2. Comparisons of insulin resistance by HOMA-IR (A), triglyceride (B), systolic blood pressure (C) and HDL cholesterol (D) levels according to the presence of central obesity and whether overall HRV (by SDNN and TP) is above or below the median.



Group 1: no central obesity and overall variability above the median, Group 2: no central obesity and overall variability below the median, Group 3: central obesity and overall variability above the median, Group 4: central obesity and overall variability below the median.

Abbreviations: SDNN, standard deviation of all normal R-R intervals; TP, total power; HOMA-IR, homeostatic model assessment of insulin resistance; BP, blood pressure; HDL, high density lipoprotein.

*p<0.05 (vs. group 1)

†p<0.05 (vs. group 2)

‡p<0.05 (vs. group 2)

DISCUSSION

ANS dysfunction and obesity according to hypothalamic damage, and their contribution to the risk of being metabolically unhealthy were evaluated in patients with childhood onset craniopharyngioma. Patients with more extensive HI had a greater degree of obesity. Interestingly, the degree of HI rather than the degree of obesity was associated with reduced HRV and decreased parasympathetic activity. A metabolically unhealthy phenotype was present in 71% of the patients, with the risk of being metabolically unhealthy being significantly increased only in those patients with concomitant central obesity and overall HRV below the median. Decreased overall HRV in combination with central obesity may be an independent predictor for the risk of being metabolically unhealthy in patients treated for childhood onset craniopharyngioma.

In our patient group, extensive HI was associated with increased obesity parameters. The first postoperative year as the critical period for rapid increases in BMI z-scores and its association with pre- and post-operative HI has been studied and reported for this group of patients (15). Other studies have quantified the extent of postoperative HI on MRI and demonstrated its positive correlation with postoperative weight gain (7, 16-18) as well as longitudinal studies demonstrating that hypothalamic obesity after craniopharyngioma treatment was associated with hypothalamic location, damage or dysfunction (19). Nuclei that are responsible for regulating body weight are dispersed throughout the hypothalamus, with important centers located in the anterior (paraventricular nucleus, PVN), medial (arcuate nucleus, ARC, and ventromedial nucleus, VMN) posterior (dorsomedial nucleus, DMN, dorsal hypothalamic area, DHA) and lateral (lateral hypothalamic area,

LHA) regions (20). A study which assessed post-operative MRI damage according to the locations of specific hypothalamic nuclei demonstrated that lesions of the dorsal hypothalamic area (DHA) and dorsomedial nucleus (DMN) in the posterior hypothalamus induced especially high risk for rapid gains in BMI during the first year following surgery (21). Disruption in the integrity of the hypothalamus leads to the complex clinical picture of hypothalamic obesity, which is pathophysiologically characterized by central leptin resistance and autonomic dysfunction in the respective afferent and efferent arms of the hypothalamic-energy balance pathway (22).

Changes in the sympathetic and parasympathetic modulation of the ANS with resultant autonomic dysfunction are thought to contribute to the development of hypothalamic obesity. Rats with lesions of the ventromedial hypothalamus (VMH) have been shown to have increased parasympathetic activity and decreased sympathetic activity. Increased parasympathetic activity stimulates pancreatic β-cells to increase insulin secretion and promote lipogenesis in response to glycemic loads (22-24). Decreased sympathetic activity has been previously reported in studies of craniopharyngioma patients with impaired epinephrine response to hypoglycemia (25) and decreased urinary excretion of homovanillic acid and vanillylmandelic acid (26). Such changes, associated with reduced resting energy expenditure, fatigue and lack of physical activity, can contribute to obesity.

Despite what is known about the pathophysiologic changes of the ANS in the development of hypothalamic obesity, a previous study of HRV indices in craniopharyngioma patients reported a negative correlation between HRV parasympathetic indices with the waist-to-height ratio (27). In that study, findings of decreased parasympathetic modulation in obese craniopharyngioma patients

were more consistent with reports of decreased parasympathetic activity in patients with simple obesity (28-31). In our assessment of the modulatory tone of the different arms of the ANS, we could not demonstrate a definite association between the degree of obesity and HRV indices. Rather, HRV indices were clearly associated with the degree of HI and not with the presence of obesity, with evidence of decreased parasympathetic modulation in patients with more extensive HI. When factors affecting changes in HRV were analyzed, HI was associated with changes in HRV even after adjusting for obesity. This is the first study to find a possibly direct association between the degree of HI and changes in HRV in craniopharyngioma patients. A previous study of brain correlates of autonomic modulation found that the functional MRI signal of the hypothalamus was positively correlated with HF in healthy subjects (32). The associations between the hypothalamus and the ANS can be attributed to the central regulatory role of the hypothalamus in controlling efferent sympathetic and parasympathetic branches of the ANS through the locus ceruleus, ventral lateral medulla and dorsal vagal complex (DVC) (33). Changes in sympathetic modulation were more difficult to elucidate in our study, as there is no definite HRV index which solely reflects sympathetic modulation. Although the absolute value of LF (m^2) was significantly decreased in our patients with extensive HI, cautious interpretation is warranted as the LF in absolute values can tend to decrease due to the decreased variance and TP. There was no significant change in LF (nu) according to extent of HI in our study.

Although there was no definite association between obesity and HRV indices in our study, there was a significant increase in metabolic consequences in the presence of both obesity and reduced HRV. While central obesity presents the greatest risk to developing metabolic syndrome (34,35), the concepts of

metabolically healthy obesity and metabolically unhealthy normal-weight individuals takes into consideration other factors that play a role in the development of a metabolically unhealthy phenotype. To assess the importance of HRV derangements on metabolic health, the patients were grouped according to the presence of abdominal obesity and overall HRV above or below the median due to the lack of specified reference cutoff values of overall HRV in children and adolescents. Analyses demonstrated that decreased HRV which coexists with central obesity significantly increases the risk of being metabolically unhealthy. Evidence for decreased parasympathetic and increased sympathetic activity in the metabolic syndrome has been previously reported (36, 37). Also, a a decrease in overall variability was shown to be an independent risk factor for increased blood pressure and glucose (38), important components of metabolic health. Furthermore, decreases in overall variability have also been associated with poor cardiovascular prognosis in acute coronary events (39-42) and diabetes. Mechanisms for such changes are not clear however, the hypothalamus centrally controls efferent ANS pathways that in turn innervate peripheral tissues involved in metabolism. The sympathetic innervation of brown adipose tissue and white adipose tissue regulates thermogenesis and lipolysis respectively. Hepatic glucose production and pancreatic insulin production is regulated by splanchnic sympathetic and vagal parasympathetic nerves. Glucose utilization in the skeletal muscle is also controlled by sympathetic and parasympathetic innervation (33). By way of its effects on adipose tissues, liver, pancreas and skeletal muscle, the branches of the autonomic system clearly play an important role in control of energy expenditure and metabolism. Findings from our study suggest that not only obesity but changes in the ANS itself may additionally add to the risk of developing the metabolic

syndrome in craniopharyngioma patients. Further studies in this regard are warranted as standardized incidence ratios of type 2 diabetes mellitus and cerebral infarction are increased in patients with childhood onset craniopharyngioma (5).

Our study is limited in that only a group of craniopharyngioma patients was studied, without a control group matched for age and obesity, to which the changes in HRV indices could be put in better perspective. However, the study included craniopharyngioma patients who were of normal weight, overweight and obese, allowing for various comparisons within the patient group regarding the relationship between obesity, HI, ANS function and the metabolic syndrome. Secondly, the study included patients who had more than 6 months follow up after initial treatment in order to assess for long term changes in obesity, HRV and metabolic syndrome after a period of stabilization. However, changes in BMI usually occur within the first three years after the initial surgery. Thus, dynamic changes of the ANS function and its relationship to the development or progression of obesity could possibly be better explored if conducted during this time of active weight gain for a better understanding of the pathophysiologic changes of hypothalamic obesity. Thirdly, the number of patients included was rather small, with certain trends being seen that could not be deemed statistically significant. This is the first study to demonstrate differences in autonomic function according to the grade of hypothalamic involvement. Also, the evaluation of autonomic dysfunction in the context of central obesity on the metabolic health of craniopharyngioma patients has not been previously reported to the best of our knowledge.

In conclusion, there is a decrease in overall HRV and parasympathetic modulation of craniopharyngioma patients with more extensive postoperative HI.

Coexistence of autonomic dysfunction and central obesity in craniopharyngioma patients is associated with increased risk for being metabolically unhealthy.

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국문 초록

서론: 자율 신경계의 이상은 시상하부성 비만 발생에 기여한다. 소아기에 발병한 두개인두종 환자에서 자율신경계 균형의 이상을 심박 변이도를 측정하여 평가하고자 하였다. 시상하부의 손상 정도와 비만 여부에 따른 심박 변이도의 변화를 평가하고 심박 변이도의 변화와 대사성 합병증의 위험도에 대해서도 분석을 하고자 하였다.

방법: 2014년 3월부터 2016년 1월까지 소아청소년기에 두개인두종으로 진단 및 치료를 받고 6개월 이상이 지난 48명의 환자 (나이 10-30세)를 대상으로 심박 변이도 검사를 하였다. 전반적인 심박 변이도를 반영하는 지표로 전체 NN 간격의 표준편차 (standard deviation NN interval, SDNN) 및 전체 주파수 강도 (total power, TP)를 측정하였다. 부교감신경의 조절 능력을 반영하는 인접 NN 간격의 차이에 대한 제곱의 평균합의 제곱근 (root mean square of successive differences, RMSSD) 및 고주파대 (high frequency, HF)를 측정하고 교감신경 또는 교감/부교감 조절 능력을 반영하는 저주파대 (low frequency) 및 고주파 대 저주파 비 (LF/HF)도 측정하였다. 시상하부의 손상 정도는 뇌자기공명영상에서 평가하였으며 신체 계측 지표와 공복 상태에서의 혈당, 인슐린, 및 지질 농도를 검사하였다.

결과: 시상하부 손상 정도가 심한 환자들에서 체질량 지수 z-score (P = 0.008), 허리둘레 (P = 0.037), 및 인슐린 저항성 (HOMA-IR, P = 0.043)이 모두 증가되어 있었다. 심박 변이도 지표들은 시상하부 손상 정도가 심한 환자들에서 감소 되어 있었으며 비만 여부에 따른 심박 변이도 지표들의 차이는 없었다. SDNN (46.3±16.7 ms vs. 33.1±17.8 ms, P = 0.014), (1863.0±1146.7 ms^2 vs. 1010.3±1103.8 ms^2, P = 0.004), RMSSD (41.5±20.1 ms vs. 29.5±17.9 ms, P = 0.035), 및 LF (434.3±365.9 ms^2 vs. 264.6±503.6 ms^2, P = 0.031) 는 모두 유의하게 시상하부 손상 정도가 심한 군에서 감소되어 있었다. 복부 비만이 있는 환자에서 전반적인 심박 변이의 지표인 SDNN 또는 TP의 감소

가 동반되어 있을 경우 HOMA-IR ($P < 0.05$), 중성지방 ($P < 0.05$), 및 혈압 ($P<0.05$)이 증가되어 있었으며 HDL 콜레스테롤 ($P<0.05$)은 감소되어 있었다. 복부 비만과 심박 변이도의 감소가 같이 있을 경우 대사성 합병증의 위험도가 증가하였다 ($P <0.05$).

결론: 두개인두종 환자에서 시상하부의 손상 정도가 심할수록 비만하였으며 전반적인 심박 변이도 및 부교감신경계의 조절 능력이 감소하였다. 특히 복부 비만과 전반적인 심박 변이도의 감소가 동시에 있을 경우 대사성 합병증의 위험이 증가하였다.

Keywords : 자율신경계 기능 이상, 심박 변이도, 시상하부 손상, 두개인두종, 시상하부성 비만, 대사성 합병증

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