Structural, Functional and Autonomic Changes in the Cardiovascular System in Growth Hormone Deficient Patients

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Background: Growth hormone deficiency (GHD) is known to cause higher rates of cardiovascular mortality. The purpose of the study was to analyze the structural and functional changes in the heart and investigate their relation to autonomic function as assessed with heart rate variability (HRV).

Methods: Eleven untreated GHD patients (mean age 50.4 ± 10.7 years, M/F: 3/8) and 15 age- and sex-matched healthy persons (mean age 45.3 ± 10.4 years, M/F: 5/10) were compared. Both groups were examined with echocardiography, HRV, and exercise testing and findings were analyzed.

Results: The groups were similar in height, weight, body mass index, body surface area, systolic and diastolic blood pressure, heart rate. The GHD patients had lower exercise duration and metabolic equivalent (MET) compared to controls (7.94 ± 1.26 vs. 9.8 ± 1.9 min, $P < 0.001$, for MET 8.85 ± 0.86 vs. 10.7 ± 2.23 , $P = 0.03$). On echocardiography, GHD patients had lower interventricular septum diastolic diameter (9 ± 0.89 vs. 10.7 ± 0.88 mm, $P < 0.001$) and posterior wall thickness (8.4 ± 0.93 vs. 9.8 ± 0.91 mm, $P = 0.002$), and lower left ventricle mass index (90.9 ± 20 vs. 112 ± 8 g/m², $P = 0.01$). Left ventricular ejection fraction was lower in the GHD patients ($57.4 \pm 5.12\%$ vs. $65.5 \pm 4.1\%$, $P < 0.001$). Time and frequency domain heart rate variability parameters, SDNN, SDANN, VLF, LF ve LF/HF were lower in GHD patients compared to controls. There was a significant correlation between left ventricle diastolic diameter and LF ($r = 0.62$, $P = 0.02$).

Conclusion: GHD seemed to cause decreased left ventricle mass and decreases in the sympathetic components of HRV that may have a bearing on the increased cardiovascular risk seen in these patients.

A.N.E. 2004;9(1):19–23

growth hormone deficiency; heart rate variability; autonomic dysfunction

Increased mortality observed in growth hormone deficient (GHD) patients is mainly attributed to cardiovascular reasons.^{1–4} Though the cardiovascular reasons are not entirely elucidated, different studies reported structural and functional defects in the cardiovascular system of GHD patients.^{2,5–7}

In recent years, the autonomic functions in some diseases that predispose victims to sudden death were investigated with heart rate variability (HRV), and serious derangements were uncovered.^{8,9} Disturbance in sympathovagal tone was implicated in

the development of arrhythmia and sudden death in different patient groups.¹⁰

Therefore, it was tempting to speculate that early cardiovascular death observed in GHD patients was due to autonomic dysfunction.¹¹ Autonomic function assessed using different methods to verify this hypothesis revealed some abnormalities in GHD patients.^{11,12}

The purpose of the study was to assess the cardiac structure and function in adult GHD patients and relate these to autonomic function as assessed with the time and frequency domain HRV.

METHOD

Patients

There were 11 GHD study patients followed up in the Department of Internal Medicine, Division of Endocrinology, Istanbul Faculty of Medicine, University of Istanbul, and 15 age- and sex-matched normal controls. Patients with hypertension, ischemic heart disease, heart failure, diabetes mellitus, nephropathy, atrial fibrillation, interventricular conduction defect, or patients using drugs that could influence autonomic function were excluded from the study. All patients were informed of the scope of the study and gave written consent.

The etiology of hypopituitarism in GHD patients was tumor excision or irradiation (six patients), Scheehan syndrome (three patients), and primary empty sella (two patients). Mean duration of known hypopituitarism was 12.4 ± 7.7 years.

The criterion for GHD was deficiency in at least three pituitary hormone and insulin-like growth factor (IGF-1) <86 ng/ml or GH response to glucagon stimulation of <3 ng/ml at peak values.

All patients were on hormone replacement therapy for thyroid and adrenal gland and were on sex hormone (except postmenopausal women). All patients were given optimal doses as assessed with biochemical and hormonal parameters. Two patients in the control group were postmenopausal and were not on hormone replacement therapy. None of the patients were on GH replacement therapy. All patients had been on treatment for more than 6 months.

Physical examination and hormone samples were drawn in the morning between 8.00 AM and 12.00 PM. Patients refrained from smoking and stopped intake of alcohol and caffeinated beverages for 24 hours before blood samples were drawn. Twelve-lead ECG and echocardiography was done after the physical examination, and the recorder for 24-hour ECG Holter monitoring was applied.

Echocardiographic Examination

The M Mode and 2D echocardiographic examination was done on left lateral decubitus position according to the criteria of the American Society of Echocardiography with Vingmed System Five echocardiographic system using a 2.5 MHz linear array probe. Interventricular septum thickness (IVS), left ventricle posterior wall thickness (LVPW), and left ventricle end-systolic and end-

diastolic diameters were measured and ejection fraction (EF) and left ventricle mass index (LVMI) were calculated.

Twenty-Four-Hour ECG Recordings and HRV Analysis

Marquette SEER solid-state recorder was used to record the 24-hour ambulatory ECG recordings. The recordings were downloaded to Marquette Laser SXP Holter system (Marquette Electronics, Inc., Wisconsin). The recordings were reviewed to confirm 18 hours of clear recording. The beats were classified, manually checked, and corrected.

Long-term time domain versus frequency domain HRV were automatically calculated by the software "Marquette Electronics Series 8000 Holter Analysis System Version 5.8." The standard output obtained included the following parameters: in time domain analysis; SDNN (the standard deviation of all the RR intervals), SDANN (the standard deviation of the 5-minute RR interval means), SD (the mean of the 5-minute RR interval standard deviations), rMSSD (the square root of the mean of the squared differences of two consecutive RR intervals), pNN50 (the percentage of the beats with consecutive RR interval difference of more than 50 ms) were calculated. In frequency domain analysis; total power (TP) (the area under the spectral curve from 0.01 to 1.0 Hz), very low-frequency power (VLF), low frequency power (LF) (The area under the spectral curve from 0.04 to 0.15 Hz), high-frequency power (HF) (the area under the spectral curve from 0.15 to 0.40 Hz), and the LF/HF ratio were calculated.

In time domain analysis SDNN and SD were accepted as equivalent of TP, SDANN to ultra-low frequency, and rMSSD and pNN50 to HF. In frequency domain analysis, LF was accepted as equivalent to the sympathetic plus parasympathetic components of autonomic function, HF was accepted as representing the parasympathetic component of autonomic function, and LF/HF as depicting the sympathovagal balance of the autonomic function.⁸

Exercise Testing

All patients enrolled in the study were examined with symptoms of limited exercise testing with Bruce protocol. ECG monitoring was done during testing and 12-lead ECG was taken at the end of

each stage and at 2-minute intervals at recovery. Blood pressure was recorded at the same periods.

Statistical Analysis

Statistical analyses were performed with Statistical Package Program for Social Sciences (SPSS for Windows 10.0, Chicago, IL). Values were given mean $\pm$ SD. The comparison of the means of two numerical parameters was done with Student's *t*-test and Wilcoxon rank when appropriate. The correlation between two numerical variables with non-normal distribution was done with Spearman's bivariate nonparametric correlation test. *P* values less than 0.05 were accepted as significant.

RESULTS

The GHD patients and controls were similar for height, weight, body mass index, systolic and diastolic blood pressure, and heart rate (Table 1). The duration of exercise and metabolic equivalent (MET) in the GHD patients was shorter compared to controls (7.94 ± 1.26 vs. 9.8 ± 1.9 min, $P < 0.001$, for MET 8.85 ± 0.86 vs. 10.7 ± 2.23 , $P = 0.03$). On echocardiography IVS (9 ± 0.89 vs. 10.7 ± 0.88 mm, $P < 0.001$), PWD (8.4 ± 0.93 vs. 9.8 ± 0.91 mm, $P = 0.002$) and LVMI (90.9 ± 20 vs. 111.8 ± 18 g/m², $P = 0.01$) were lower in GHD patients compared to controls. Left ventricle EF was lower in the GHD patients ($57.4 \pm 5.12\%$ vs. $65.5 \pm 4.1\%$, $P < 0.001$) (Table 2). The GHD patients had lower SDNN (104.5 ± 18.7 vs. 138.8 ± 33.7 ms, $P = 0.004$), SDANN (89.5 ± 16.3 vs. 117.4 ± 25 ms, $P = 0.002$), VLF (36 ± 10.3 vs. $49.7 \pm$

14.2 ms, $P = 0.01$), LF (19.7 ± 5.7 vs. 28.1 ± 8.6 ms, $P = 0.008$) and LF/HF ratio (1.13 ± 0.26 vs. 1.6 ± 0.36 , $P = 0.002$) compared to controls (Table 3). RMSSD, PNN50, HF were similar between groups. On correlation tests there was significant correlation between left ventricular end-diastolic diameter and LF ($r = 0.62$, $P = 0.02$, Fig 1). A negative correlation was found between left ventricular end diastolic diameter, MET, and GHD duration ($r = -0.53$, $P < 0.05$, $r = -0.55$, $P < 0.05$).

DISCUSSION

Sudden death due to cardiovascular cause is known to be increased in GHD patients. It is not surprising due to the fact that one of the target organs of the growth hormone is the heart and its deficiency is bound to cause certain anomalies. In our study we found that GHD patients had thinner IVS, LVPW, and smaller left ventricle internal diameters hence smaller hearts with lower LVMI. The EF was also lower compared to controls though it was within normal limits. On exercise testing, duration of exercise and the MET achieved were lower in GHD patients. We can say from these data that the hearts of the GHD patients are smaller and weaker than a comparatively sized control.

It is known that growth hormone and insulin-like growth factor receptors are expressed on cardiac myocytes. The stimulation of these receptors directly or indirectly increases mRNA expression that codes for contractile proteins and increases myocyte size.² The growth hormone also has positive inotropic effect on the heart.¹³ Therefore, its utility in heart failure patients was reported in several articles.^{14,15}

Table 1. Demographic Data of the GHD Patients and Controls

	GHD Patients	Controls	P Value
Age (years)	50.4 ± 10.7	45.3 ± 10.4	NS
Sex (male/female)	3/8	5/10	NS
Duration of GHD (years)	12.4 ± 7.7		
Height (cm)	163 ± 7.4	162 ± 6.5	NS
Weight (kg)	64.5 ± 6.5	65 ± 5.9	NS
Body mass index (kg/m ²)	25.09 ± 3.01	24.4 ± 2.3	NS
Systolic blood pressure (mmHg)	122 ± 11	120.6 ± 8.8	NS
Diastolic blood pressure (mmHg)	73.6 ± 6.7	74.6 ± 7.4	NS
Heart rate	77 ± 7	75 ± 5	NS
Exercise duration (min)	7.94 ± 1.26	9.8 ± 1.9	< 0.01
MET	8.85 ± 0.86	10.7 ± 2.23	0.03

GHD: growth hormone deficiency; MET: metabolic equivalent; NS: not significant.

Table 2. Echocardiographic Findings in the GHD Patients and Controls

	GHD Patients	Controls	P Value
LVED (mm)	46.3 ± 5.1	45.5 ± 4.4	0.6
LVES (mm)	32.2 ± 3.3	29.2 ± 3	0.06
IVS(mm)	9 ± 0.89	10.7 ± 0.88	<0.001
PWD (mm)	8.4 ± 0.93	9.8 ± 0.91	0.002
LVEF (%)	57.4 ± 5.1	65.5 ± 4.1	<0.001
LVMI (g/m ²)	90.9 ± 20	111.8 ± 18	0.01

GHD: growth hormone deficiency; IVS: interventricular septum diastolic diameter; LVED: left ventricular enddiastolic diameter; LVEF: left ventricular ejection fraction; LVES: left ventricular endsystolic diameter; LVMI: left ventricular mass index; PWD: Posterior wall diastolic diameter.

Children with GHD are known to have stunted growth of the target organs and especially the heart.^{6,15} In studies with small sample size, certain cardiac anomalies persist in GHD patients after the linear growth phase has ended.^{2,6} Different studies described decreased left ventricle internal diameter,¹⁶ and decreased systolic⁶ and diastolic performance.^{17,18}

Longobardi et al.⁴ reported that GHD children and patients with GHD developing in adulthood had lower left ventricle EF, lower exercise duration compared to matched controls, and pointed out the importance of growth hormone in sustaining normal cardiac function way into adult life.

In studies that growth hormone replacement therapy was given to GHD patients, structural

Table 3. Heart Rate Variability Parameters in the GHD Patients and Controls

	GHD Patients	Controls	P Value
SDNN (ms)	104.5 ± 18.7	138.8 ± 33.7	0.004
SD (ms)	49 ± 15	62.4 ± 18.5	0.06
SDANN (ms)	89.5 ± 16.3	117.4 ± 25	0.002
RMSSD (ms)	41.2 ± 16.6	48.8 ± 27.9	0.6
PNN50 (ms)	8 ± 7.95	9.07 ± 7.17	0.5
VLF (ms)	36 ± 10.3	49.7 ± 14.2	0.01
LF (ms)	19.7 ± 5.7	28.1 ± 8.6	0.008
HF (ms)	18.9 ± 8.3	18 ± 5.6	0.8
LF/HF	1.13 ± 0.26	1.6 ± 0.36	0.002

GHD = Growth hormone deficiency, HF = High frequency, LF = Low frequency, pNN50 = The percentage of the beats with consecutive RR interval difference of more than 50 milliseconds, rMSSD = The square root of the mean of the squared differences of two consecutive RR intervals, SDANN = The standard deviation of the 5-minute RR interval means, SDNN = The standard deviation of all the RR intervals, VLF = Very low frequency.

Figure 1. The correlation of left ventricular diastolic diameter and LF power in patients group.

changes in the heart were reversed and left ventricle systolic function improved.^{7,19,20} The patients who rejected treatment but were followed for a year had deterioration in both exercise capacity and exercise and rest left ventricle EF.²⁰ The authors speculated that the growth hormone was a somatic maturation hormone for the heart.

It should not be surprising that GHD can cause structural changes in the heart. The contradictory results in the literature can be explained by the small sample size of the studies, inhomogeneity of the study groups, shortness of the duration of GHD, and the presence of confounding factors that may influence cardiac morphology. This limiting factor, the small sample size, and wide distribution of age also beset this study, which was unavoidable because of the rarity of the condition. The decrease in the duration of exercise can be explained by lower heart and skeletal-striated muscle performance in GHD patients. As the patients were on hormone replacement therapy for other deficient hormones in optimal doses, we do not believe that this deficiency had any influence on our results. In previous studies on isolated GHD patients decreased exercise capacity was observed.⁵ Growth hormone replacement was shown to reverse this decrease.^{7,21}

Anomalies observed in HRV parameters may contribute to the cardiovascular mortality observed in these patients. In our study, HRV parameters that reflect sympathetic autonomic function, SD, SDNN, SDANN, LF were significantly decreased in GHD patients compared to controls. Additionally, left ventricle diastolic diameter and LF were

strongly correlated. These findings may indicate that changes in the left ventricle structure are reflected in the HRV parameters. Decreased sympathetic components of HRV may either indicate autonomic nervous system dysfunction or impaired end-organ response. In our study, structural changes in the heart were related to HRV changes, which may imply failure of activation of the heart in response to sympathetic activation. It was previously reported that HRV is significantly reduced in essential hypertension and myocardial infarction patients and is also closely connected with cardiac structure and function. This finding supports our view that structural impairment in heart may cause impaired HRV, which is interpreted as impaired response to sympathetic activation.

Leong et al.¹¹ showed a decrease in sympathetic tonus with standard autonomic function tests in GHD patients and postulated that this may be either due to central sympathetic tonus decrease or decrease in sympathetic control of cardiac function. In this study changes in the cardiac morphology were not studied and studies in the literature on changes in cardiac structure were cited to explain the changes in autonomic function. Leong et al.¹² in another study examined GHD patients with short-term frequency domain HRV and found no difference between controls and growth hormone treated GHD patients, whereas found decreased VLF, LF ve LF/HF ratio in untreated GHD patients compared to controls. Six months of growth hormone replacement therapy significantly increased VLF. The postgrowth hormone treatment amelioration of HRV parameters was explained with the improvements in cardiac structure and function.

It was concluded that in GHD patients, certain abnormalities in cardiac structure, function, and autonomic control are present and may contribute to the observed increase in sudden death due to cardiovascular causes.

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