Pituitary (2023) 26:115–123
https://doi.org/10.1007/s11102-022-01295-z

Evaluation of cardiac structure, exercise capacity and electrocardiography parameters in children with partial and complete growth hormone deficiency and their changes with short term growth hormone replacement therapy

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Accepted: 27 November 2022 / Published online: 4 December 2022

Abstract

Purpose To evaluate cardiac structure, exercise capacity and electrocardiography (ECG) parameters of children with complete and partial growth hormone (GH) deficiency (GHD) and the effect of 12 months GH treatment on these.

Methods M-mode echocardiography, ECG and exercise test expressed as metabolic equivalent (MET) were performed in children with GHD, aged 9–14 years, divided into those with a peak GH response < 7 µg/L (complete GHD; n = 30) and 7–10 µg/L (partial GHD; n = 17) after two GH stimulation tests, at baseline and 12 months after GH initiation. Forty-eight healthy peers underwent the same tests once.

Results Left ventricular mass (LVM) was significantly lower before treatment in both groups with GHD compared to healthy peers ($p = 0.015$ and $p = 0.032$) but LVM in the GHD groups was similar to controls after 12 months of treatment. The increase in LVM in the complete GHD group was significant ($p = 0.044$). LVM index was significantly reduced with treatment in children with partial GHD ($p = 0.035$). Max METs, VO_{2max} and exercise duration were significantly increased in children with complete GHD after treatment ($p = 0.022$, $p = 0.015$ and $p = 0.002$, respectively). Significant changes in P wave and QTc dispersion on ECG between groups were within physiological limits.

Conclusion This study showed that children with both partial and complete GHD had smaller cardiac structures and less exercise capacity compared to their healthy peers prior to GH treatment but this improved with 12 months of treatment. The cardiac trophic effect of GH, as well as the effect of increasing exercise capacity, is greater in those with complete GHD than in those with partial GHD.

Keywords Growth hormone deficiency · Left ventricular mass · Electrocardiography · Children

Introduction

Growth hormone (GH) has a profound effect on the structural and functional maintenance of a normal adult heart. For normal cardiac function in adults, there should be neither a deficiency nor an excess of GH [1]. It has been shown in previous studies that childhood-onset GH deficiency (GHD) lead to cardiac functional impairment in adulthood if not treated [2, 3]. In our recent study, we demonstrated that cardiac systolic and diastolic functions are impaired, even in childhood, in children with GHD and begin to improve after 12 months of GH treatment [4].

It has been reported that not only cardiac functional impairment, but also cardiac structural impairments are present in both children and adults with GHD. Studies have revealed that cardiac structural impairment improve with GH treatment [3, 5–7]. We hypothesized that cardiac impairment seen in GHD may also cause electrocardiographic changes. There are limited studies evaluating electrocardiography (ECG) in patients with GHD. In previous

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studies, heart rate variability in 24-hour ECG was evaluated in adults with GHD [8–10]. To date, there is only one study evaluating ECG in children with GHD, which also reported evaluations before and after GH treatment [11].

In adults with GHD, impairment in exercise capacity, as well as impairment of cardiac structure and function, has been described and it has been reported that exercise capacity improves with GH replacement therapy [12]. Only one study evaluating exercise capacity in children with GHD was found in the literature. This study demonstrated that the impaired cardiopulmonary capacity in children with GHD improved with GH replacement therapy [13].

In the present study, we divided children receiving GH treatment into two groups according to their GH stimulation test responses; those with a GH response of 7–10 µg/L were defined as partial GHD, and those with < 7 µg/L were defined as isolated GHD. We compared GH deficient groups with their healthy peers in terms of cardiac structure, exercise capacity and ECG parameters before and 12 months after GH treatment. The aim of the study was to evaluate the cardiac structure, exercise capacity and ECG parameters of children and adolescents with complete and partial GHD and to investigate the effect of 12 months GH treatment on these parameters.

Participants and methods

Selection of participants

Children and adolescents, aged 9–14 years, with isolated and partial GHD and their healthy peers were included in the study. GHD was diagnosed according to clinical and auxological criteria. In a child with short stature, if severe, defined as a height more than three standard deviations (SD) below the mean, if their height was below 2 SD of the population mean and the annual height velocity was below 2 SD, if other causes of growth failure (hypothyroidism, small for gestational age, chronic systemic disease, Turner syndrome or skeletal system disorders) were excluded, a diagnosis of GHD was considered and GH stimulation tests were performed (L-Dopa and insulin tolerance test). GHD was defined as peak GH <10 µg/L after two separate GH stimulation tests, according to the GH Research Society's Consensus guidelines in 2000 [14]. However, as a result of the workshop held in 2019, this value was reduced to below 7 µg/L [15]. We divided the participating children with GHD into two groups; those with a peak GH level of < 7 µg/L (complete GHD) and those with peak GH 7–10 µg/L after two stimulation tests (partial GHD). None of the children with GHD had other pituitary hormone deficiency and all GHD patients underwent magnetic resonance imaging (MRI) to confirm isolated GHD. GH treatment was initiated at 30 µg/kg/day and patients received GH therapy throughout the study period.

Forty-eight children in the same age group, who were admitted to the pediatric cardiology outpatient clinic with complaints, such as chest pain, dizziness, and syncope, and in whom no pathological cause was found, participated in the study as the control group.

Ethical considerations

This study was approved by the local Ethics Committee for Clinical Investigation. In addition, informed consent was obtained from the parents of both the children with GHD and control children who participated in the study. The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice.

Study design

Height and body weight of all participants were measured. Weight was measured using digital scales with a precision of 0.1 kg, and height was measured to the nearest 0.1 cm with a stadiometer. M Mode echocardiography, ECG and treadmill exercise stress test were performed on all children and adolescents participating in the study. These tests were performed in the children and adolescents with GHD before starting GH treatment and 12 months after starting treatment. Tests in the control group were only performed once, while pretreatment tests were administered to children with GHD .

Pulse-wave Doppler echocardiography and tissue Doppler imaging (TDI) were also performed in the patient and control groups. Echocardiographic parameters in our previous article were evaluated at the 6th and 12th months of the treatment. Data on pulse-wave Doppler echocardiography and tissue Doppler imaging (TDI) are published in a separate article, so it is not appropriate to re-include this data here [4]. Two children, one from the control group and one with partial GHD, were excluded from this study because they were not cooperative with the exercise tests.

Auxological evaluation

Weight was measured to the nearest 0.1 kg using a balance beam scale, with outer clothes and shoes off, and height was measured to the nearest 0.1 cm with a stadiometer in bare feet. The body mass index (BMI; reported in kg/m^2) was used as an index of relative weight. Comparison of weight, height and BMI among children requires the use of standard deviation scores (SDS). SDS for height, BMI, and weight were calculated, based on national growth charts, to

compare weight, height and BMI status of the participating children [16].

Cardiological examination

Echocardiography

All cases and controls had echocardiographic studies performed at the time of diagnosis and in the children with GHD, at 12 months of GH treatment, using M-mode conventional transthoracic echocardiography with the GE-Vingmed Vivid S6 system ultrasound device and a M4S-RS probe. Left ventricular mass (LVM) and left ventricular mass index (LVMI) were obtained using a LVMI calculator. LVM was calculated by using Devereux's formula according to ASE convention and accounting for this discrepancy (formula): Formula: LVM (ASE): 0.8 (1.04 ([LVIDD + PWTD + IVSTD]^3- [LVIDD]^3)) + 0.6 g [17]. LVM was indexed for body surface (calculated by the Dubois formula) [18], and for height elevated to the 2.7 power, as recommended by De Simone et al. [19].

Exercise test and determination of effort capacity

Exercise duration and maximum work done were evaluated with the test performed by applying the Bruce protocol. [20], The work done was expressed as metabolic equivalent (MET). One MET is defined as the amount of oxygen consumed while sitting at rest and is equal to 3.5 mL O_2 per kg body weight x min. Functional classification according to MET values is: 7 METs and above were defined as I, 5 to 7 METs II, 2 to 5 METs III, and below 2 METs IV. Classification was made according to the recommendations of the American Heart Association [21].

During the test, neurological symptoms (ataxia-darkening), symptoms due to peripheral circulatory disorders (cyanosis-paleness), severe arrhythmias, deterioration of blood pressure, technical reasons, the patient's desire to stop, new and severe angina, despite increased workload decrease in systolic blood pressure, heart rate 200/min even if asymptomatic, severe hypertension (systolic BP above 250 mmHg, diastolic BP above 125 mmHg), ST depression or elevation more than 3 mm on ECG were indications for termination of the test [22].

Electrocardiographic (ECG) evaluation

ECG recordings were made with a Kardiopet 600 (PETAŞ; Turkey) ECG device at a speed of 25 mm/sec, 1 mV amplitude and standard 12 leads, including at least 6 QRS complexes for each derivation. During the recording, the patients breathed easily, but they were not allowed to speak. P wave times in all leads were measured manually with an electronic digital caliper (KNMASTER Model No: KM-150 K) with a resolution of 0.1 mm/0.01 inch. The beginning of the P wave was taken as the intersection of the isoelectric line and the P wave. The end point was taken as the intersection of the isoelectric line and the end point of the P wave. The longest P wave and the longest atrial conduction time were accepted as the maximal P wave duration. The difference between the longest P wave (Pmax) and the shortest P wave (Pmin) was accepted as the P dispersion (Pd = Pmax-Pmin). The QT interval between the beginning of the QRS complex and the point where the descending branch of the T wave cuts the isoelectric TP segment was taken as the QT interval and calculated by the same cardiologist. Derivations in which the T wave could not be detected were excluded. QT dispersion was defined as the difference between the longest QT interval and the shortest QT interval (QTd = QTmax-QTmin). Bazett's formula (QTc = QT/√R-R) was used for QTc and QTc dispersion was similarly determined as the difference between the longest QTc interval and the shortest QTc interval. QT, QTc, QTd, Tp-e values of all participants were reported in milliseconds while Pmax, Pmin, and Pd were calculated in seconds.

Statistical analysis

All data were tested for normality using the Kolmogorov-Smirnov test or Shapiro-Wilks test. Since there were variables that were non-normally distributed, the comparison of the GH-deficient groups before, after treatment and the control group was performed using the nonparametric Kruskal-Wallis test (Pairwise comparisons were made with the Mann-Whitney test and Bonferroni correction was applied). Paired sample test and Wilcoxon signed rank test were used for comparisons before and after treatment in groups with GHD. Statistical analyses were performed using Statistical Package for Social Sciences, version 15.0 (IBM Inc., Chicago, IL, USA). A $p < 0.05$ was considered statistically significant.

Results

In total, 47 children with some degree of GHD and 48 children in the control group participated. Amongst the children with GHD, the mean age of the 30 children with complete GHD (63.8%) was 11.6 ± 2.4 years and the mean age of 17 children (36.2%) with partial GHD was 11.9 ± 2.3 years. The mean age of the 48 children in the control group was 11.6 ± 2.6 years. There was no significant age difference between the groups ($p = 0.879$). Age and anthropometric data of the groups are shown in Table 1. Although the

Table 1 Mean age and anthropometric parameters of the GHD and control groups before treatment

Parameters	Complete GHD (n = 30)		Partial GHD (n = 17)	Control group (n = 48)	*p* value*
Age (years)	11.6 ± 2.44	11.9 ± 2.32	11.6 ± 2.63		0.599
Height SDS	-2.54 ± 0.64[a]	-2.59 ± 0.68[a]	0.53 ± 0.65[b]		< 0.001*
BMI SDS	0.13 ± 1.61[a]	-0.90 ± 0.94[b]	0.25 ± 0.74[a]		0.001*
Weight for height (%)	104.2 ± 21.08[a]	91.5 ± 9.98[b]	97.0 ± 10.45[a,b]		0.04*

*Kruskal-Wallis, $p < 0.05$ is significant; ** The groups with the same letters within a column are not significantly different according to pairwise comparisons; SDS: Standard Deviation Score, BMI: Body Mass Index; GHD: Growth Hormone Deficiency

Table 2 Cardiac structure, effort and ECG parameters in GH deficient groups and control group before treatment

Parameters	Complete GHD (n = 30)	Partial GHD (n = 17)	Control group (n = 48)	*p* value*
Cardiac structure parameters				
LVM (g)	58.5 ± 21.9[a]	57.8 ± 15.6[a]	71.0 ± 22.0[b**]	0.019*
LVM/Index($g/m^{2.7}$)	33.5 ± 32.4	26.6 ± 4.5	25.2 ± 6.8	0.081
LVM/BSA (g/m^2)	53.5 ± 12.6	56.4 ± 10.4	55.3 ± 15.0	0.777
Effort parameters				
Target HR	202.4 ± 9.7	200.3 ± 9.3	199.9 ± 9.2	0.122
Max HR	180.5 ± 12.3[a]	178.7 ± 19.0[a]	186.4 ± 13.9[b]	0.047*
Max SBP (mmHg)	138.2 ± 19.8	138.5 ± 20.7	144.2 ± 16.7	0.199
Max DBP (mmHg)	74.6 ± 12.2[a,b]	69.8 ± 9.9[a]	79.1 ± 9.8[b]	0.002*
HRR	60.71 ± 6.0	66.2 ± 23.8	61.3 ± 27.5	0.561
VO_{2max}	43.8 ± 14.7	45.51 ± 1.1	49.8 ± 7.9	0.136
Exercise duration (minutes)	8.7 ± 3.3[a]	9.1 ± 2.0[a]	10.8 ± 1.9[b]	0.001*
Max METs	12.5 ± 4.2	13.0 ± 3.1	14.2 ± 2.2	0.166
Maximum stage n (%)				
-Stage I	25 (83.3)	14 (82.4)	48 (100)	0.001*
-Stage II	1 (3.3)	3 (17.6)	-	
-Stage III	4 (13.3)	-	-	
ECG Parameters				
Heart rate (beat/minute)	97.3 ± 17.8	86.7 ± 12.8	98.1 ± 19.9	0.110
P wave (s)	0.065 ± 0.01[a]	0.057 ± 0.01[b]	0.064 ± 0.010[a]	0.022*
PR interval (s)	0.118 ± 0.019	0.112 ± 0.024	0.114 ± 0.016	0.650
Pwd (s)	0.014 ± 0.009	0.010 ± 0.004	0.0127 ± 0.00	0.337
QT (ms)	300 ± 30.0[a]	320 ± 20.0[b]	290 ± 20.0[a]	0.018*
QTC (ms)	386.4 ± 20.3	388.5 ± 23.1	377.3 ± 20.7	0.076
QTCd (ms)	28.1 ± 19.7	30.7 ± 19.2	26.5 ± 10.6	0.839
Tp-e (ms)	57 ± 11.0	57 ± 9.0	54 ± 8.0	0.251
Tp-e/QT max	0.18 ± 0.03	0.17 ± 0.02	0.18 ± 0.03	0.570

*Kruskal-Wallis, $p < 0.05$ is significant; **The groups with the same letters within a column are not significantly different according to pairwise comparisons. LVM, Left ventricle mass; g, Gram; ECG, Electrocardiogram; BSA, body surface area; HR, target heart rate; HRmax, maximum heart rate; SBP-max, maximum systolic blood pressure; DBPmax, maximum diastolic blood pressure; HRR, heart rate reserve; METS, metabolic equivalents; VO_{2max}, maximal oxygen uptake; Pwd (s), P wave dispersion (second); QT(s), QT interval (millisecond); QTC, corrected QT interval; QTCd, corrected QT interval dispersion

BMI-SDS of both children and adolescents with complete GHD and the control group were significantly higher than those with partial GHD, weight for height was significantly higher in those with complete GHD than in those with partial GHD ($p < 0.05$). Height SDS of children and adolescents with partial and complete GHD were similar before treatment and after treatment (Table 1). Height SDS increased significantly in both groups ($p < 0.01$) (-2.54 ± 0.64 before treatment, -2.11 ± 0.68 after 12 months GH treatment in complete GHD, -2.59 ± 0.68 before treatment, -1.93 ± 0.64 after 12 months GH treatment in partial GHD).

Cardiac structure

LVM was significantly lower before treatment in both groups with GH compared to the control group ($p = 0.015$ and $p = 0.032$). There was no significant difference between the groups in LVMI and LVM/BSA ratios ($p = 0.081$, $p = 0.777$, respectively) (Table 2).

At twelve months of GH treatment there was no significant difference in LVM between the group of patients with GHD and the control group ($p > 0.05$) (Table 3). Although LVM increased after 12 months of GH treatment in both GHD groups, the increase in patients with complete GHD was statistically significant ($p = 0.044$). LVMI value

Table 3 Cardiac structure, effort and ECG parameters in GH deficient groups and control group after treatment

Parameters	Complete GHD (n = 30)	Partial GHD (n = 17)	Control group (n = 48)	*p* value*
Cardiac structure parameters				
LVM(g)	65.1 ± 23.2	62.1 ± 20.7	71.0 ± 22.0	0.281
LVM/ Index ($g/m^{2.7}$)	25.9 ± 6.8	24.2 ± 6.7	25.2 ± 6.8	0.890
LVM/BSA (g/m^2)	54.3 ± 13.0	53.9 ± 15.0	55.3 ± 15.0	0.945
Effort parameters				
Target HR	202.1 ± 9.7	199.3 ± 12.2	199.9 ± 9.2	0.277
Max HR	176.1 ± 17.1[a]	175.7 ± 14.9[a]	186.4 ± 13.9[b**]	0.007*
Max SBP (mmHg)	138.9 ± 17.2	143.3 ± 18.4	144.2 ± 16.7	0.415
Max DBP (mmHg)	72.8 ± 12.8[a]	76.7 ± 19.3[a]	79.1 ± 9.8[b]	0.024*
HRR	57.6 ± 15.8	56.4 ± 14.2	61.3 ± 27.5	0.996
VO_{2max}	50.8 ± 7.9	46.0 ± 11.4	49.8 ± 7.9	0.337
Exercise duration (minutes)	10.8 ± 1.8	10.7 ± 1.7	10.8 ± 1.9	0.921
Max METs	14.4 ± 2.5	13.5 ± 2.1	14.2 ± 2.2	0.397
Maximum stage n (%)				
-Stage I	30 (100)	17 (100)	48 (100)	
-Stage II	-	-	-	
-Stage III	-	-	-	
ECG Parameters				
Heart rate (beat/ minute)	88.3 ± 16.0	91.9 ± 10.3	98.1 ± 19.9	0.066
P wave (s)	0.068 ± 0.01[a]	0.060 ± 0.007[b]	0.064 ± 0.01[b]	0.05*
PR interval (s)	0.114 ± 0.014[a]	0.111 ± 0.016[b]	0.114 ± 0.017[a]	< 0.01*
Pwd (s)	0.027 ± 0.06	0.017 ± 0.02	0.0127 ± 0.00	0.775
QT (ms)	310 ± 20.0	300 ± 20.0	290 ± 20.0	0.023
QTC (ms)	384.8 ± 31.4	382.5 ± 26.3	377.3 ± 20.7	0.864
QTCd (ms)	24.1 ± 11.5	21.8 ± 16.2	26.5 ± 10.6	0.041*
Tp-e (ms)	60 ± 10.0[a]	54 ± 12.0[b]	54 ± 8.0[b]	0.022*
Tp-e/QT max	0.20 ± 0.05	0.17 ± 0.03	0.18 ± 0.03	0.070

*Kruskal-wallis, p < 0.05 is significant; **The groups with the same letters within a column are not significantly different according to pairwise comparisons; LVM, Left ventricle mass; gr, Gram; ECG, Electrocardiogram; BSA, body surface area; HR, target heart rate; HRmax, maximum heart rate; SBPmax: maximum systolic blood pressure; DBPmax, maximum diastolic blood pressure; HRR, heart rate reserve; METS, metabolic equivalents; VO2 max, maximal oxygen uptake; Pwd (s), P wave dispersion (seconds); QT (ms): QT interval (millisecond); QTC: corrected QT Interval; QTCd, corrected QT interval dispersion

decreased with treatment in both groups. This decrease was statistically significant in patients with partial GHD ($p = 0.035$) (Table 4).

Effort parameters

Before treatment, maximum heart rate (max HR), exercise duration and maximum diastolic blood pressure (DBP), which are the parameters of effort, differed significantly among the control group and the groups with GHD ($p < 0.05$). Max DBP in the control group was significantly higher compared to that of the children with partial GHD ($p < 0.01$), and the duration of exercise was significantly longer than both in the children with partial and complete GHD ($p = 0.015$ and $p = 0.001$ respectively). Max HR was found to be significantly higher in the control group than in the children with both complete and partial GHD ($p = 0.04$ and $p = 0.05$, respectively). The METs levels, in which functional capacities were evaluated, were significantly higher in the control group than in children with GHD, since all children in the control group were in Stage I ($p = 0.001$) (Table 2).

After 12 months of GH treatment, Max HR and Max DBP were significantly lower in children with both partial and complete GHD compared to the control group ($p = 0.006$, $p = 0.021$, and $p = 0.015$, $p = 0.05$, respectively). The exercise duration of the three groups was similar. The METs of both groups with GHD reached stage I, similar to the control group. There was no transition to stages II and III (Table 3).

Maximal oxygen uptake (VO_{2max}), an indicator of exercise capacity, was not different before and after treatment in children with GHD compared to their healthy peers ($p > 0.05$). Max METs, VO_{2max} and exercise duration were significantly increased in children and adolescents with complete GHD after treatment. Although there was a slight increase in these effort parameters in children and adolescents with partial GHD, this increase was not statistically significant (Table 4).

ECG parameters

Before treatment, the P wave, one of the ECG parameters, was found to be significantly shorter in children with partial GHD than in the control group and in children with complete GHD ($p = 0.011$). The QT interval in ECG was found to be significantly longer in children with partial GHD compared to children with complete GHD and the control group ($p = 0.018$ and $p = 0.005$, respectively). Although QTc and QT dispersion were longer in GHD children compared to the control group, they were not statistically significant ($p > 0.05$) (Table 2).

At the first year of treatment, the P wave was significantly different among the three groups ($p = 0.018$). The longest was in those with complete GHD and the shortest in those with partial GHD. In those with complete GHD, the P wave duration was closer to the control group (Table 3).

Table 4 Cardiac structure, effort and ECG parameters in children with complete and partial GHD before and after treatment

Parameters	Complete GHD (n = 30)		*p** value	Partial GHD (n = 17)		*p*** value
	Before treatment	**After treatment**		**Before treatment**	**After treatment**	
Cardiac structure parameters						
LVM (g)	58.5 ± 21.9	65.1 ± 23.2	0.044*	57.8 ± 15.6	62.1 ± 20.7	0.379
LVM/Index ($g/m^{2.7}$)	33.5 ± 32.4	25.9 ± 6.8	0.174	26.6 ± 4.5	24.2 ± 6.7	0.035*
LVM/BSA (g/m^2)	53.5 ± 12.6	54.3 ± 13.0	0.766	56.4 ± 10.4	53.9 ± 15.0	0.142
Effort parameters						
Target HR	202.4 ± 9.7	202.1 ± 9.7	0.900	200.3 ± 9.3	199.3 ± 12.2	0.609
Max HR	180.5 ± 12.3	176.1 ± 17.1	0.221	178.7 ± 19.0	175.7 ± 14.9	0.777
Max SBP (mmHg)	138.2 ± 19.8	138.9 ± 17.2	0.881	138.5 ± 20.7	143.3 ± 18.4	0.433
Max DBP (mmHg)	74.6 ± 12.2	72.8 ± 12.8	0.547	69.8 ± 9.9	76.7 ± 19.3	0.307
HRR	60.71 ± 6.0	57.6 ± 15.8	0.358	66.2 ± 23.8	56.4 ± 14.2	0.126
VO_{2max}	43.8 ± 14.7	50.8 ± 7.9	0.015*	45.51 ± 1.1	46.0 ± 11.4	0.765
Exercise duration (minutes)	8.7 ± 3.3	10.8 ± 1.8	0.002*	9.1 ± 2.0	10.7 ± 1.7	0.017*
Max METs	12.5 ± 4.2	14.4 ± 2.5	0.022*	13.0 ± 3.1	13.5 ± 2.1	0.370
ECG parameters						
Heart rate ((beat/minute)	97.3 ± 17.8	88.3 ± 16.0	0.001*	86.7 ± 12.8	91.9 ± 10.3	0,126
P wave (s)	0.065 ± 0.01	0.068 ± 0.01	0.214	0.057 ± 0.01	0.060 ± 0.007	0.254
PR interval (s)	0.118 ± 0.019	0.114 ± 0.014	0.281	0.112 ± 0.024	0.111 ± 0.016	0.928
Pwd (s)	0.014 ± 0.009	0.027 ± 0.06	0.251	0.010 ± 0.004	0.017 ± 0.02	0.107
QT (ms)	300 ± 30.0	310 ± 20.0	0.069	320 ± 20.0	300 ± 20.0	0.024
QTC (ms)	386.4 ± 20.3	384.8 ± 31.4	0.824	388.5 ± 23.1	382.5 ± 26.3	0.162
QTCd (ms)	28.1 ± 19.7	24.1 ± 11.5	0.300	30.7 ± 19.2	21.8 ± 16.2	0.081
Tp-e (ms)	57 ± 11.0	60 ± 10.0	0.022	57 ± 9.0	54 ± 12.0	0.301
Tpe/QT max	0.18 ± 0.03	0.20 ± 0.05	0.207	0.17 ± 0.02	0.17 ± 0.03	0.834

*Paired sample test, ** Wilcoxon signed rank test $p < 0.05$ is significant; LVM, left ventricular mass; g, Gram; ECG, Electrocardiogram; BSA, body surface area; HR, target heart rate; HRmax, maximum heart rate; SBPmax: maximum systolic blood pressure; DBPmax, maximum diastolic blood pressure; HRR, heart rate reserve; METS, metabolic equivalents; VO2 max, maximal oxygen uptake; Pwd (s), P wave dispersion (seconds); QT (ms): QT interval (millisecond); QTC: corrected QT Interval; QTCd, corrected QT interval dispersion

Except for the significant decrease in HR observed after treatment in those with complete GHD, the ECG parameters before and after treatment did not change significantly after 12 months of GH treatment in those with either complete or partial GHD (Table 4).

Discussion

To our knowledge this is the first study to examine in cardiac structure, exercise capacity and electrocardiographic parameters and their changes after short-term GH treatment in children and adolescents with partial and complete GHD. In this study, it was shown that children and adolescents with both complete GHD and partial GHD have impairment in cardiac structure and exercise parameters when compared to their healthy peers. Although these parameters improved after 12 months of GH treatment, they did not reach the level of their healthy peers. In addition, while there were significant changes in children and adolescents with complete GHD after GH treatment, the absence of significant changes in those with partial GHD was notable. Furthermore, there were differences in the ECG parameters of children and adolescents with both complete and partial GHD both before and after treatment when compared to their healthy peers. However, when we compared before and after GH treatment in both groups with GH deficiency, no significant change was detected in the ECG parameters.

GH significantly affects cardiac structure in adults with childhood-onset and acquired GHD [23, 24]. Especially in adults with childhood-onset GHD, marked impairment in cardiac structure has been detected. In these patients, it was reported that the cardiac structure improved within six months with GH treatment, but it did not completely normalize [25]. In our study, we showed that children and adolescents with both complete and partial GHD have a smaller LVM compared to their healthy peers. This indicates that the effect of GHD on LVM does not differ much, even if the degree of GHD is different. After 12 months of GH treatment, the increase in LVM was greater in those with complete GHD compared to those with partial deficiency, but the difference was not statistically significant. There was significant difference in LVM in both groups compared to their healthy peers. These results suggest that GH has a

similar effect in both groups. However, when we evaluated the groups according to the change in LVM after GH treatment, a significant increase was found in those with complete GHD, while the increase was not significant in those with partial deficiency. This suggests that GH therapy may be more effective in those with GH response < 7 µg/L in GH stimulation tests. Capalbo et al. reported that there was a significant reduction in cardiac size in children with both partial and complete GHD compared to the control group, and GH therapy normalized in both group in children with GHD [7]. No other studies were found comparing partial and complete GHD.

In previous studies, LVM was found to be lower in children with GHD compared to non-GHD controls, as in our study [7, 13, 26–29]. In these studies, it was reported that after GH treatment the LVM of GHD children approached or reached the LVM of the control group. In our study, we calculated the LVM in grams, similar to the study of Gupta et al. [27]. The increase in LVM with GH therapy also raises the concern that cardiac enlargement may continue as the treatment period is prolonged. For this reason, more accurate values can be obtained by dividing the ventricular mass by the body surface area (BSA), especially in adults. In previous studies with children with GH deficiency, LVM was evaluated by dividing by square meters or BSA and compared with the control group. In these studies, it was observed that the selected control groups were younger than the patients and had the same body surface area [7, 13, 25–27]. Since the control group in our study was the same age as the patients, their BSA was larger than that of the GHD patients. Therefore, we did not find that the LVMI before and after treatment were different from the control. When we compared the LVMI values before the treatment and at 12 months of the treatment in the groups, a decrease was found due to the increase of height of the children in the group with partial deficiency. This shows that despite an increase in LVM in grams, this increase is consistent with BSA. Thus, prolonged GH treatment does not appear to cause cardiac hypertrophy. Shulman et al. reported an increase in LVM indices as well as an increase in LV mass in grams in the first year of GH treatment. They explained this result by suggesting that the rate of increase of LVM was greater than the increase in BSA during GH treatment [30]. Esen et al. reported similar results [31].

In our study, while exercise duration was shorter in children with complete and partial GHD before treatment than in their healthy peers, a similar exercise duration was evident after 12 months of GH treatment. The shortness of exercise duration was more pronounced in those with complete GHD. There are no studies on exercise duration in children with GHD. Only one study evaluated exercise time in adult GHD, and the reported results are consistent with our study [32]. There are studies showing that exercise capacity is impaired in adults with GHD and improves with GH treatment. The parameters measured in these studies are VO_{2max}, maximal power output, max HR, and ventilatory threshold [12]. In our study, we evaluated VO_{2max} and max HR. VO_{2max} indicates functional capacity of the cardiorespiratory and skeletal muscle systems. Due to the wide variation in body size and composition in children and adolescents, it is recommended to use an allometrically scaled $VO_{2\ peak}$ for lean body mass (LBM) [33]. In our study, we evaluated exercise capacity with VO_{2max}. VO_{2max} was non-significantly lower before treatment in children with both complete and partial GHD compared to healthy peers and VO_{2max} improved after one year of treatment. However, a significant increase was detected after treatment only in children with complete GHD. This indicates that exercise capacity is significantly reduced, especially in children with complete GHD. Capalbo et al. reported similar results to our study with the exercise capacity they evaluated with VO_{2peak} [13]. Similar results were obtained in a meta-analysis of 11 studies investigating exercise capacity in adult GHD patients [12]. In another meta-analysis consisting of 15 studies, it was concluded that an increase of approximately 10% in aerobic exercise capacity was achieved with GH treatment in adults [34].

We investigated whether there were changes in ECG due to changes in cardiac structure and functions in children with GHD. In our study, children with partial GHD had a significant shortening of the P wave before treatment compared to their healthy peers, and this did not change after treatment. Although it was not statistically significant in both GH deficient groups, they had prolonged QTc dispersion compared to their healthy peers. A decrease was observed with GH treatment. Prolonged QTc dispersion may be an important indicator of ventricular arrhythmias [35]. Only one study in the literature has addressed this issue and it has been shown that QTc values do not change before and after GH treatment [11]. In keeping with this, we found there was no difference in ECG parameters before and after treatment in either GH deficient group. Although the changes in some ECG parameters were statistically significant, they do not indicate any pathology as they are within physiological limits [36, 37]. However, we suggest that it would be advisable to monitor long-term changes with annual ECG control throughout GH treatment.

Our study has some limitation. The measurements of healthy children included in the control group were only made once. Although healthy children were recalled for second measurements at the end of the first year, since most of them did not come, both the pre-treatment and post-treatment measurements of the patients were compared with the only available measurements of their healthy peers.

A second limitation was the short-term evaluation of the effects of GH therapy. In our opinion it would be informative to evaluate the cardiac effects of GH in each patient between baseline and after the end of treatment.

In summary, this study showed that LVM assessed in grams in both complete and partial GH-deficient children was smaller than in their healthy peers, but LVM approached that of controls after 12 months of GH treatment. However, in those with complete GHD, the gram LVM increase was more pronounced with GH treatment. While there was no difference in LVMI compared to their healthy peers, there was a decrease due to greater height growth in those with partial deficiency. Exercise capacity, as assessed by VO_{2max}, METs and exercise duration, increased with treatment, especially in children with complete GHD. Children with GH deficiency had a non-significant but prolonged QTc dispersion, which could be the cause of ventricular arrhythmias, compared to healthy peers but this normalized with a significant decrease after GH treatment.

In conclusion, this study revealed that children with both partial and complete GHD had smaller cardiac structures and less exercise capacity compared to their healthy peers. These deficiencies improved with 12 months of GH treatment. The cardiac trophic effect of GH, as well as the effect of increasing exercise capacity, was greater in those with complete GHD than in those with partial GHD. Although within physiological limits, ECG parameters may change in children with GHD undergoing GH treatment and should be monitored.

Acknowledgements We thank Mr Jeremy Jones for his contribution to the English grammar used in this article.

Author contributions Fatos Alkan: Study concept, study design, material acquisition, data collection, literature search, writing, critical reviewing. Betul Ersoy: Study design, supervision, critical reviewing, literature search, data analysis and interpretation, writing. Deniz Ozalp Kızılay: Material acquisition, data collection. Beyhan Cengiz Ozyurt: The statistical analysis of the study. Senol Coskun: Study concept.

Funding This research did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sector.

Ethics declarations

Ethics approval The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Ethics in Research Committee of the School of Medicine of the Celal Bayar University of Manisa.Informed consent: Informed consent was obtained from all individual participants included in the study.

Consent to participate All participants provided written informed consent.

Disclosure statement The authors declare that they have no competing interests.

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