Title: Pre-clinical cardiac involvement in adulthood growth hormone deficiency: role for left ventricular remodeling. A single-centre case-control study

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Author's response to reviews: see over
COMMENTS TO REVIEWERS

Reviewer n 1 (Salerno)

Major Compulsory Revisions required

1) The aim of the study is not completely clear; left ventricular resting morphology and function, by echocardiography, have been already been studied in subjects with adult-onset GHD, what is new in the aim of this study? The aim of the study has been clarified in the “introduction” as the reviewer indicates.

2) The definition of the study population is confused and unclear. On page 4, line 10 the authors refer to 2 groups of patients who are not defined until page 5. The control group (group C) is described before groups A and B are defined. The paragraph concerning the study population and the diagnosis of GHD should be merged and shortened. The definition of the study population and the 3 groups of patients should also be more clear. The definition of the study population (group A, group B and controls) has been provided in the “methods” section. The correct order of the 3 groups has been also given. The paragraphs “study population” and “diagnosis of GHD” have been merged in a single paragraph, named “study population”, as the reviewer indicates.

3) Did the patients have other additional hormonal deficiency and were they on replacement therapy? Are only TSH and GH deficiency found in all 50 patients? All these information have been included in the new paragraph “study population”, as the reviewer indicates.

4) What is the rational for evaluating basal serum GH levels? When the authors stated that basal GH was measured in all the 70 enrolled patients did they mean 50 GHD and 20 controls? Why was basal GH also evaluated in controls, and why weren’t IGF-I levels evaluated? We do agree with the reviewer that provide basal GH serum levels is unnecessary and may be confusing. Thus, this information has been cancelled, as the reviewer indicates.

5) What was the source of the control subjects - were they from the same social class and geographic region? This piece of information has been provided (please, look at the last line of the “methods” section), as the reviewer indicates.

4) Statistical analysis should be more detailed, in particular concerning student t-test and the linear correlation. Statistical analysis has been reviewed. Of note, multivariate analysis has been also performed in order to examine the main determinants of LVMi, as the reviewer indicates.

5) Differences with other studies showing a decrease in LVM in GHD or other cardiac results different from this study patients are not adequately discussed. Data about previous studies that have demonstrated reduced LVM in GHD have been included both in the “background” and “discussion” sections. Moreover, a new figure 1 describing the distribution of the LVM/LVMi in the study population has been built, as the reviewer indicates.

Minor Essential Revisions

Not required
Reviewer n 2 (Marzullo)

Major Compulsory Revisions required

English should be reviewed throughout the whole manuscript. English has been deeply reviewed throughout the whole manuscript, as the reviewer indicates.

Abstract: The conclusion remarks, on the statistical significance of the Authors' findings, are unclear and should be reviewed. The abstract has been completely rewritten, as the reviewer indicates.

Background: Few introductory hints on the (debated) cardiac alterations of GHD should be mentioned, i.e. wall hypotrophy, diastolic dysfunction, scant systolic performance under exercise. Previous data on normotensive GHD differ from those seen in obesity and hypertension, where LV hypertrophy is expectedly more common. This statement and the study rationale (lines 11-14) should be reviewed. This part of the manuscript has been reviewed, taking into account all these suggestions. Thus the study rationale has been also clarified in the “background” section, as the reviewer indicates.

Methods: The Authors should define just once (page 4, line 11 or ahead) how patients grouping was carried out. Do patients with pituitary tumors differ from those with adenomas? The Authors should state if any patient was previously operated for GH-secreting tumor, irradiated, treated with antihypertensive compounds, or substituted for adrenal, gonadal or vasopressin deficiency. Was GH measured only randomly in controls? All these information have been quoted. In agreement with 2/3 of the reviewer, measurements of basal GH serum levels appear to be unnecessary, as the reviewer indicates. Thus, they have been cancelled in the new version.

Results: The upper figure 1 (LVM vs. IGF-I) should be omitted and would include one with LVMi vs. GH peak, even if this is nonsignificant. Figure 1 should differentiate patients with partial or complete GHD, for example with close and open circles. Figures 1 and 2 now changed in Figures 3 and 4, respectively. In these new figures, the reviewer’s suggestions have been considered. In fact, the relationship between LVM and IGF-1 has been omitted, while the correlations between LVMi and GH-peak / IGF-1 have been displayed. Figures also differentiate severe (= complete) and mild (= partial) GHD patients, as the reviewer indicates.

Results: Was age or disease duration related to RWT, LVMi or E/A? Was RWT related to systolic or diastolic indices or blood pressure? The role of the age in patients’ discrimination for systolic and diastolic function have been investigated and a new picture (Figure 2) has been provided, as the reviewer indicates.

Results: How many patients with abnormal LV were hypertensive? This piece of information has been provided at pg 8, lines 9-11, as the reviewer indicates.

Discussion: The Authors should also attempt to provide an explanation for their findings on eccentric hypertrophy in the GHD setting and comment on the greater prevalence of hypertension in their GHDs compared to controls. Further explanation of the prevalence of eccentric hypertrophy in our whole GHD population (22%) vs controls (15%), has been quoted. We believe that in the previous version of the manuscript, such misinterpretation occurs with regard to the prevalence of hypertension.
In fact, we did not find significant between-group difference in patients with high LVMi (pg 8, line 1-2, previous version), and we can confirm this result even in the revised manuscript. We are sorry for misunderstanding.

Minor Essential Revisions

Names/location of drugs or assays producers should be mentioned. Measure units for GH and IGF-I should be reviewed. Table 2: measure units of pericardial adiposity, DT, A velocity should be defined. LVEF should be expressed as percentage as indicated (i.e. 63%, etc.). Patients distribution in subgroups in table of Fig. 2 should be detailed in the legend. All these changes have been done, as the reviewer indicates.
Reviewer 3 (Di Bello)

Major Compulsory Revisions

The study population is sufficient but the methods might be expanded:
a) midwall fractional shortening might be calculated
b) Isovolumic relaxation time and Tei Index should be showed.
If also these variables in the three groups are not statistically significant, then the Authors’ conclusions could be more strong.
As indicated by the reviewer, midwall fractional shortening (MFS) has been integrated with the LV functional indexes, as the reviewer indicates. Unfortunately, IVRT and TEI index were available only from 65% of the patients, thus we decided not to include these latter parameters.

Minor Essential Revisions

The discussion and the conclusion should be more short and the English improved.
Both these paragraphs have been shortened. English has been improved throughout the whole manuscript, as the reviewer indicates.

GENERAL COMMENTS

The number of the enrolled patients with GHD has increased (4 more cases). Thus, the study group now includes 54 patients.
Two new figures have been provided, on the basis of such reviewers’ suggestions.
The definitions “complete/partial” GHD have been changed in “severe/mild” GHD.