Mapping the journey of transition - A single center study of 170 childhood onset GH deficiency patients

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Abstract

Objective: To analyze metabolic parameters, body composition (BC) and bone mineral density (BMD) in childhood onset GH deficiency (COGHD) patients during transition period (TP).

Design: Single center, retrospective study was performed on 170 consecutive COGHD patients (age 19.2±2.0 years, range 16-25) transferred after growth completion from two pediatric clinics to adult endocrine unit. Two separate analyses were performed: 1) cross-sectional analysis of hormonal status, metabolic parameters, BC and BMD at first evaluation after transfer from pediatrics to adult department; 2) longitudinal analysis of BC and BMD dynamics after 3 years of GH replacement therapy (rhGH) in TP.

Results: COGHD was of a congenital cause (CONG) in 50.6% subjects, tumor related (TUMC) in 23.5% and idiopathic (IDOP) in 25.9%. TUMC patients had increased insulin and lipids levels ($p<0.01$) and lower Z score at L-spine ($p< 0.05$) compared to CONG and IDOP groups. Patients treated with rhGH in childhood demonstrated lower fat mass and increased BMD compared to rhGH-untreated group ($p<0.01$). Three years of rhGH after growth completion resulted in significant increase in lean body mass (12.1%) and BMD at L-spine (6.9%), parallel with decrease in FM (5.2%).

Conclusion: The effect of rhGH in childhood is invaluable for metabolic status, BC and BMD in transition to adulthood. Tumor related COGHD subjects are at higher risk for metabolic abnormalities, alteration of body composition and decreased BMD, compared to those with COGHD of other causes. Continuation of rhGH in transition is important for improving BD and BMD in patients with persistent COGHD.
Introduction

Patients with childhood onset GH deficiency (COGHD) represent a heterogeneous group in terms of etiology of growth hormone deficiency (GHD), time of GHD onset and recombinant human GH (rhGH) replacement commencement, duration, length of gap in rhGH between pediatric and adult endocrine care or in comorbidities. Reported studies are inconsistent regarding the anthropometric characteristics, metabolic profile alteration, body composition (BC) deterioration, bone mineral density (BMD) impairment in different COGHD subgroups (1). Observations are particularly contradictory concerning BC and BMD in respect of the role of rhGH continuation in transition period (TP). Several studies have demonstrated improvement of these parameters, while some others have reported no change (2-4).

Almost all published studies related to COGHD in transition with sizable number of patients are multicentric. Monocentric studies on this topic involved a smaller number of subjects (5-8). We focused on investigating BC and BMD alterations in COGHD patients on rhGH during TP. Our framework consisted of assessment of hormonal and metabolic parameters, BC and BMD in different etiology-dependent subgroups of patients with COGHD, in relation to rhGH replacement in childhood and to the GHD persistence at retesting after growth completion. To our knowledge, this is the largest single center study addressing different aspects of COGHD patients and the effects of rhGH treatment during TP.

Patients and methods

We conducted a single center observational, retrospective study on 170 consecutive COGHD patients in TP transferred after growth completion from two pediatric clinics to adult endocrine care. The study was conducted at the Neuroendocrine Department at the Clinic for Endocrinology, Diabetes and Metabolic Diseases, University Clinical Center of Serbia from December 2006 to March 2021. In this study two separate analyses were performed: 1) cross-sectional analysis of auxological data, etiology of
COGHD, start and duration of rhGH treatment in childhood, duration of rhGH pause after pediatric care termination, hormonal status, metabolic parameters, bone turnover markers, BC, BMD and associated comorbidities at first evaluation after transfer from pediatrics to adult endocrine care; 2) longitudinal analysis of BC and BMD alterations after 3 years of rhGH replacement in TP. Metabolic profile was assessed by analyzing fasting glycemia, fasting insulin, peak and AUC glycaemia and peak and AUC insulin in OGGT, HOMA index, HbA1c, lipid profile - total cholesterol, HDL, LDL and triglycerides. BMD at lumbar spine (BMD LS) and femoral neck (BMD FN) presented as BMD- \( \text{g/cm}^2 \) and Z score, and BC (percentage of fat-Fat\%, fat mass-FM, lean body mass-LBM, total bone mineral content- TBMC) were examined by dual-energy x-ray absorptiometry (DXA; Discovery W-QDR, Software Apex 2.3.2; Hologic Inc., Waltham, Mass., USA). Subjects were analyzed by comparison of following subgroups: i) according to etiology (congenital vs tumor related vs idiopathic COGHD); ii) COGHD treated in childhood with rhGH vs COGHD untreated with rhGH before TP; iii) persistent vs transient GHD group after retesting in TP.

At first evaluation upon transfer to adult care all enrolled patients were reassessed regarding GHD etiology and retested for GHD persistence. One or two tests were performed (insulin tolerance test - ITT and glucagon test) depending on the presence of isolated GHD or multiple pituitary hormone deficiency (MPHD) during childhood. Stimulated peak GH of less than 15 mU/l was considered confirmatory for GHD in both tests (9-11). Prior to retesting, rhGH therapy was discontinued for at least one month. Subjects with three or more pituitary hormones deficiencies were exempt from further testing of GH secretion. All patients who continued rhGH in transition were on adequate replacement for other hormonal deficiencies.

The study was approved by Ethical Committee of University Clinical Center of Serbia. Written consent has been obtained from each subject after full explanation of the purpose and nature of all procedures used.
Statistics

Results were presented as count (%), means ± standard deviation (range) or median (25\textsuperscript{th}-75\textsuperscript{th} Percentile) depending on data type and distribution. Groups were compared using parametric tests (t test, ANOVA). To assess correlation between variables Pearson and Spearman correlation were used. All p values less than 0.05 were considered significant. Integrated areas of serum glucose and insulin levels during OGTT (AUC\textsubscript{0-120min}) were calculated using the trapezoidal method. All data were analyzed using SPSS 20.0 (IBM Corp.).

Results

We enrolled 170 COGHD patients (mean age 19.2 ± 2.0 years, range 16-25), 123 males (72.4%) and 47 females (27.6%) referred by two pediatric centers to our adult neuroendocrine unit. Patients with pituitary and midline axial structural abnormalities or genetic syndromes were classified as congenital (CONG) COGHD accounting for more than half of all included patients (86/170; 50.6%), Figure 1. Patients with history of cranial tumor, hematological malignancies or pituitary TSH hyperplasia (non-tumoral TSH-cell hyperplasia occurring in primary hypothyroidism) were marked as tumoral cause (TUMC) of COGHD; TUMC included 40/170 patients, (23.5%). Patients with normal cranial/pituitary MRI and unknown cause were assigned to group of idiopathic (IDOP) COGHD which included 44/170 patients (25.9%). Detailed distribution according to the etiology of all 170 patients is presented in Table 1. In TUMC group cranial surgery was performed in 87.5% patients (35/40), while 40.0% (16/40) of TUMC subjects were treated with chemotherapy and 61.0% (25/40) received cranial radiotherapy. Concomitant comorbidities observed in the investigated COGHD cohort in TP are presented in Table 2.

Upon first assessment after transfer from pediatric care, isolated GHD was detected in 40/170 (23.5%) of patients. MPHD were detected in 88/170 (51.8%) (Table 3). Diabetes insipidus was observed in 21 patients (12.3%) - out of which 3 from the CONG group and remaining 18 from the TUMC group.
MPHD was confirmed in 80% (20/25) subjects treated with cranial irradiation and in 62.5% (10/16) treated with chemotherapy. After first evaluation of our patients thyroxine replacement was continued in 46.4%, hydrocortisone in 35.8%, testosterone in 36.5% of males and estradiol in 55.3% of females.

**Growth hormone replacement**

One hundred and forty-two patients (142/170; 83.5%) received rhGH during childhood for average duration of 6.7±3.7 years (range 2.5-17yrs). The mean age at the start of childhood rhGH was 10.7 ± 3.5 years (range 2-16). rhGH replacement was discontinued prior to transfer to adult care at an average age of 17.4 ± 1.8 (11-25) yrs. Duration of rhGH gap between pediatric and adult care evaluation was 1.7±2.4 yrs (range 0.1 -14 yrs) (Table 4). Majority of subjects had an interval without rhGH of 1 to 3 months before retesting in TP (88/142; 62.0%). Recovery of GH/IGF-I axis was confirmed in 28.2% of all patients in this cohort (40/142). The prevalence of GH/IGF-I axis recovery was greatest in the IDIOP subgroup (31/43; 72%). TUMC and CONG groups demonstrated significantly lower prevalence of transient GHD (3/28; 10.7% and 6/71; 8.4%, respectively). Patients with persistent COGHD had lower IGF-I than transient GHD group after cessation of rhGH at retesting in adult care unit (77.5 vs 373.5 ng/ml, p< 0.01). Beside etiology, the number of missing pituitary hormones was associated with persistency of GHD in transition (p <0.01). Of the 102 patients with persistent COGHD treated during childhood, 10 have declined the advice to continue rhGH and were subsequently lost to follow-up (Figure 1). In the remaining 92 patients rhGH was reintroduced at age 19.3 ± 2.0 yrs (15-25).

Twenty-eight patients (28/170;16.5%) were not treated with rhGH during childhood and 24 of them started with rhGH in TP at the average age of 18.8 ± 1.7 years (16-22 yrs). Thus, a total of 116 patients have been on rhGH in TP, receiving the average daily rhGH dose of 0.5±0.3 mg (Figure 1).

**Glucose and lipids metabolism**

Metabolic profiles of 142 patients rhGH-replaced in childhood were analyzed according to their COGHD etiology (Table 5). TUMC subjects had increased peak insulin and insulin-AUC in OGTT, total
cholesterol, LDL cholesterol and triglycerides, compared to CONG and IDOP groups (significant at 0.001 level), (Table 5).

Comparison of metabolic parameters in childhood-GH-treated and untreated patients revealed significantly higher fasting insulin, insulin peak, insulin AUC, and glucose AUC in OGTT, HOMA index and triglycerides (Table 4).

Subjects who recovered GH/IGF-I axis in transition (majority belonging to the IDOP group) demonstrated significantly higher fasting glucose (p=0.05), glucose peak and glucose AUC in OGTT (p<0.001), but lower total cholesterol and LDL cholesterol (p<0.001) compared to those with persistent GHD after growth completion (p<0.001) (Table 4). Insulin levels and HOMA index did not differ between persistent and transient GHD groups.

We found that the length of rhGH-treatment gap between pediatric and adult care (rho=-0.23; p=0.013) correlated negatively with HDL levels after transfer to adult care. Figure 2.

**Body composition**

BC analysis in 142 patients on rhGH in childhood revealed that body weight, BMI, and waist circumference were significantly increased in TUMC compared to CONG and IDOP groups (p<0.05). IDOP subjects had significantly higher LBM compared to CONG group (p<0.05) and lower Fat% and FM compared to TUMC and CONG group (p<0.01), Table 5.

Increased TBMC (p=0.05), lower Fat% (p=0.03) and tendency to LBM increase (p =0.08) were demonstrated in childhood-GH-treated compared to GH-untreated group (n=28), Table 4.

Patients who recovered GH/IGF-I axis were taller (p=0.01), with lower Fat% and FM compared to persistent GHD subjects (p<0.001), Table 4.

In search for predictors of BC outcomes we observed that final body height correlated significantly negatively with Fat% and positively with LBM and TBMC (data not shown). BMI was predictive of higher Fat%, FM, LBM and TBMC at first evaluation in adult endocrine unit (data not
shown). Number of missing pituitary hormones was associated with Fat% increase (rho= 0.49, p <0.001) and FM (rho= 0.41, p <0.001) of investigated COGHD patients. Duration of rhGH was positive predictor of Fat% (rho= 0.23; p=0.019) and FM (rho=0.26; p= 0.01).

**Bone mass**

Densitometric (DXA) analysis at first evaluation after transfer from pediatric care, on 142 COGHD patients treated with rhGH during childhood revealed BMD Z-scores of < -2 in 31.4% at lumbar spine (LS) and in 8% at the femoral neck level (FN). TUMC subjects had significantly lower Z-sc LS (p<0.05) and bone turnover markers compared to CONG and IDOP groups, Table 5.

By comparing patients receiving rhGH in childhood and those deprived of rhGH before TP (n=28) lower BMD LS, Z-sc LS and Z-sc FN were demonstrated in untreated group (p<0.01), Table 4. Subjects from the untreated group had Z-sc LS < -2 in 45.8% and Z-sc FN < -2 in 22.7% at first evaluation.

BMD at LS and FN did not differ statistically between transient and persistent COGHD patients (p =0.75 and p=0.31, respectively). However, osteocalcin (OC) and beta cross laps (BCL) levels were significantly higher in patients who have recovered GH/IGF-I axis (Table 4).

The final body height and BMI correlated significantly positively with BMD and Z-sc at LS and FN (data not shown). Duration of rhGH in pediatric age predicted higher bone mass according to BMD LS (rho =0.20, p =0.040), BMD FN (rho=0.19, p=0.053). Duration of pause in rhGH between pediatric and adult care did not predict values of bone parameters. However, age at rhGH treatment cessation before transfer to adult endocrine care correlated negatively with BMD LS and Z-sc LS (r= -0.18, p = 0.05; r= -0.19, p=0.03, respectively), Figure 3.

**Changes in body composition and BMD during follow-up on rhGH in transition period**

Out of 116 subjects on rhGH in TP, we evaluated BC and BMD in 40 (34.4%) of them (32 patients continuing rhGH and 8 patients starting rhGH in TP) after 3 years of treatment. Significant improvement in BC was observed, manifesting as Fat% decrease by 5.2% and LBM increase of 12.1% during three-year
follow-up (Table 6). Changes in bone mass indicated significant increment of BMD LS by 6.9%. BMD increment was additionally demonstrated by Z-sc LS and Z-sc FN improvement. (Table 6).

Of these 40 patients, we followed up 15 subjects after 6 years of rhGH in TP (some outgrowing 25 years as the end-age for transition period). We detected further trend of increase in LBM and BMD LS. Fat mass and Fat% did not change over this extended follow-up, but BMD FN had tendency of decreasing (data not shown).

**Discussion**

In this study we analyzed 170 patients with COGHD recruited over the last 15 years and referred to single adult neuroendocrine unit from two pediatric centers after completion of linear growth. More than a half of enrolled patients had congenital etiology of GHD, while tumor caused and idiopathic COGHD were represented about one-fourth each. The observed distribution is in agreement with results of our earlier study relating to the etiology of hypopituitarism in Serbia (12). In monocentric French study on 112 COGHD patients in transition, acquired GHD was recorded in 56% of subjects, congenital in 33% and idiopathic in 11% (6). In KIMS database study involving 314 young adult COGHD patients, the most common single cause of GHD was idiopathic (in 33%) followed by craniopharyngioma (in 20%) (13). A Scottish multicentric study focusing on management of COGHD in 130 young adults, structural abnormalities were detected in 30%, tumor related COGHD in 40% while GHD cause was unknown in 11%. (5).

Cranial tumor and ALL were behind COGHD in 23.5% of patients in our study. Cranial surgery and/or radiotherapy, experienced by majority of these patients, made them prone to develop hypothalamic damage presenting as a higher prevalence of MPH and metabolic deterioration. We demonstrated that TUMC had notably more pituitary hormone deficits and higher incidence of diabetes insipidus compared to other two etiological groups. Subjects belonging to TUMC demonstrated worse
metabolic outcomes according to higher values insulin in OGTT and worse lipid profile than CONG and IDIOP groups. They had increased Fat% and FM compared to IDIOP, but similar to CONG group. Most numerous patients in the TUMC group were those treated for craniopharyngioma in childhood. Yuen et al. analyzed 260 adults with COGHD caused by craniopharyngioma and showed that they had higher prevalence MPH and greater BC alterations but comparable fasting glucose, HbA1c, cholesterol levels as the patients with other causes of COGHD (14). Subjects with history of medulloblastoma tend to develop MPH dependent on the received craniospinal radiation dose (15). Metabolic syndrome was reported in 23% as a late effect in childhood ALL survivors treated with cranial irradiation (16). Our tumor related group included 5 patients who experienced medulloblastoma and 2 subjects who underwent chemotherapy and cranial irradiation due to ALL. These underlying diseases probably contributed to the poorer metabolic profile of this group. Hoybye et al. observed that patients with organic pituitary disease are commonly overweight with adverse lipid profile (17). Survivors of childhood brain tumor are recognized as a high-risk population for decreased BMD due to the neoplasia itself, treatments and their sequelae, hypopituitarism, malnutrition, and lifestyle - all likely to negatively affect bone metabolism (18). Results of our study support this, as TUMC patients had lower Z-sc LS and bone turnover compared to two other etiology-dependent groups. We enrolled 4 patients with history of intracranial germinoma, who contributed the reduced BMD in TUMC group. Low BMD was reported as prevalent in patients with a history of intracranial germinoma (19, 20).

Comparison of COGHD patients treated with rhGH in childhood (before age of 16, for at least 2.5 years) with those deprived of rhGH demonstrated worse metabolic profile in untreated group regarding adverse lipid profile and higher insulin resistance. Benefits of rhGH in childhood were manifested by increased TBMC, BMD LS, Z-sc LS and Z-sc FN, tendency to increased LBM and parallel Fat% reduction in TP. Upon reaching the final height, approximately 20% of GHD children treated with rhGH had a BMD LS between -1 and -2SD of the normal mean (21). Kaufman et al. indicated that COGHD presents with a
low bone mass despite prior rhGH in childhood (22). Cohen et al. analyzed BMD in 36 post-pubertal adolescents with cranial tumor related COGHD on rhGH in childhood had a higher BMD Z sc LS and Z-sc FN than untreated subjects (18). Similarly, we detected Z-sc LS < -2 in 31.4% patients adequately replaced with rhGH in childhood, contrary to 45.8% in GH-untreated COGHD group. We observed that longer duration of rhGH replacement correlated positively with BMD in both investigated skeletal sites. On the other hand, older age at rhGH cessation before transfer to adult endocrine care was associated with lower BMD LS and Z-sc LS. Tritos et al. showed that a longer gap between pediatric and adult age rhGH replacement was negatively associated with BMD at FN in adults (13). Conversely, we did not find any influence of duration of interval between stopping and recommencement of rhGH on bone parameters. However, we detected a negative correlation of the length of that interval (1.7 years) with HDL levels in transition. The similar was observed in the KIMS study in which the duration of rhGH discontinuation between childhood and adulthood (4.4 years) was associated with significantly more detrimental lipid profiles (23).

Clinical studies of bone density in COGHD adolescents reported conflicting findings related to the effect of continuation of rhGH after final height achievement (24, 25). Our results demonstrated significant increase of BMD LS (6.9%), Z-sc LS and Z-sc FN in 40 COGHD subjects on rhGH treatment after 3 years during TP. Also, other studies have confirmed that continuation of rhGH is associated with increasing of BMD LS by 2% to 6% after 1-2 years of follow-up (2, 3, 7, 26). In addition, study of Hyldstrup et al. showed that 24 months of continuation of rhGH after achievement of final height in young COGHD adults resulted in increased cortical bone thickness (27). However, some studies observed no change in BMD after 6-24 months of rhGH discontinuation after growth completion compared to control subjects (4, 28, 29). Many factors such as gender, height, age at onset, body composition, gonadal status or GHD severity may contribute to conflicting data on bone mass in patients with COGHD (25).
Similar to the contradictory reports related to bone mass, there are inconsistent findings on the effect of continuing rhGH on body composition in TP. Our study showed the favorable effect of the resumption of rhGH in 40 COGHD subjects after 3 years in TP. We observed significant decrease of Fat% (5.2%) and increase of LBM (12.1%). In accordance to our results, other studies demonstrated that recommencement of rhGH in TP with duration of 1-2 years manifested a significant LBM increase (6-14%) and FM reduction (7-12%). Discontinuation of rhGH treatment for 6-24 months in COGHD adolescents after final height achievement resulted in FM increase (10-17%) and LBM decrease by up to 8% (3, 8, 30-35). By contrast, a few studies reported no difference in BC parameters after 6-24 months period off rhGH after growth completion (4, 36). At first evaluation after transfer from pediatric care we showed that final body height correlated negatively with Fat% and positively with LBM and TBMC. However, BMI was predictive of not only higher Fat% and FM, but increased LBM and TBMC. In addition, number of missing pituitary hormones was associated with higher Fat% and FM.

Previous studies reported prevalence of persistent GHD upon retesting in adulthood ranging from 52 to 94% (5, 6, 37). After retesting we detected 28.2% of patients who recovered GH/IGF-I axis and showed that predictors of persistent GHD included tumor etiology and number of missing pituitary hormones, similarly as reported previously (13). Quigley et al. reported that in idiopathic GHD patients the best predictor of persistent GHD is IGF-I below -5.3 SD measured after 6 weeks from rhGH termination (38). In line with that, our transient-GHD group had significantly higher IGF-I compared to persistent-GHD subjects at retesting. In accordance to reports of Bechtold et al., we detected better BC in transient GHD compared to those with persistent GHD (39). However, their fasting glucose, peak and AUC glucose in OGTT were higher than in persistent GHD. Observed glucose impairments could have a possible explanation in predominant origin of these subjects in idiopathic COGHD. Early retesting in idiopathic GHD children before TP was reported to reveal complete GH-secretion normalization in 84%
These patients may experience endogenous GH normalization by the time adult height is achieved and possible over-treatment with prolonged rhGH leading to risk of glucose metabolism impairment.

The advantages of this comprehensive study are a large number of enrolled patients who have been evaluated at the same adult department after transfer from two pediatric centers which resulted in uniform recruitment and evaluation protocol, thus presenting well organized “transition unit care” (41). The limitation of our study may lay in focusing the follow up of BMD to the patients with worse baseline values at first evaluation possibly creating some bias in obtained results. Reaching the accepted cut-off response of GH excludes severe GHD, but not a possible lesser degree of GH deficiency. This is an inherent limitation of every assessment of GH-secretion by stimulation tests, and a possible source of discrepancies between different studies, in addition to occasional divergence in selected cut-off points.

In conclusion, the effect of growth hormone replacement in childhood is invaluable for metabolism, body composition and skeletal system during transition period. Patients with COGHD caused by a cranial tumor are at greatest risk for metabolic abnormalities, altered body composition and lower BMD. Continuation of rhGH in transition is important for improving body composition and increasing bone mass in patient with persistent GHD.
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Figure Legends:

Figure 1. Study cohort flow chart

Figure 2. Gap duration between rhGH in childhood and transition correlated negatively with HDL levels (n=142)
Figure 3. Z-sc at lumbar spine correlated negatively with age in the year of discontinuation of rhGH therapy before retesting in transition (n=142)
Figure 1. Study cohort flow chart

165x92mm (96 x 96 DPI)
Figure 2. Gap duration between rhGH in childhood and transition correlated negatively with HDL levels (n=142)
Figure 3. Z-sc at lumbar spine correlated negatively with age in the year of discontinuation of rhGH therapy before retesting in transition (n=142)
### Table 1. Distribution of patients according to the etiology of CO-GHD in all included patients (n=170)

| Etiology                                      | No  | %    |
|----------------------------------------------|-----|------|
| **Congenital COGHD**                         |     |      |
| Pituitary/midline structural abnormalities   |     |      |
| Anterior pituitary hypoplasia                | 25  | 14.7 |
| PSIS                                         | 6   | 3.5  |
| Anterior pituitary hypoplasia + EP           | 5   | 2.9  |
| Anterior pituitary hypoplasia + PSIS         | 8   | 4.7  |
| Anterior pituitary hypoplasia + EP + PSIS    | 13  | 7.6  |
| Empty sella                                  | 5   | 2.9  |
| Rathke cleft cyst                            | 6   | 3.5  |
| Arachnoid cyst                               | 2   | 1.1  |
| SOD                                          | 12  | 7.0  |
| Genetic syndromes                            |     |      |
| Charge Sy                                    | 1   | 0.5  |
| Prader Willi Sy                              | 1   | 0.5  |
| Noonan Sy                                    | 1   | 0.5  |
| Tuberous sclerosis                           | 1   | 0.5  |
| **Tumor related COGHD**                      |     |      |
| Cranial tumor                                |     |      |
| Craniopharyngioma                            | 15  | 8.8  |
| Germinoma                                    | 4   | 2.3  |
| Histiocytosis X                              | 6   | 3.5  |
| Meduloblastoma                               | 5   | 2.9  |
| PNET                                         | 1   | 0.5  |
| Hamartoma                                    | 1   | 0.5  |
| Ganglioglioma                                | 1   | 0.5  |
| Astrocytoma                                  | 2   | 1.1  |
| Pituitary pseudotumor (TSH hyperplasia)      | 2   | 1.1  |
| Hematological malignancies                   |     |      |
| ALL                                          | 2   | 1.1  |
| **Other malignancies**                       |     |      |
| Malignant triton tumor                       | 1   | 0.5  |
| **Idiopathic COGHD**                         |     |      |
|                                              | 44  | 25.9 |

COGHD - childhood onset growth hormone deficiency; PSIS- pituitary stalk interruption syndrome; EP- ectopic posterior pituitary; SOD- septo-optic dysplasia; ALL-acute lymphoblastic leukemia; PNET-primitive neuroectodermal tumor
**Table 2. Comorbidities in enrolled patients (n=170)**

| Condition                              | No  | %    |
|----------------------------------------|-----|------|
| No comorbidities                       | 89  | 54.0 |
| Visual field defect                    | 15  | 8.8  |
| Mental retardation                     | 10  | 5.8  |
| Epilepsy                               | 10  | 5.8  |
| Primary hypothyroidism                 | 9   | 5.2  |
| Undescended testis                     | 8   | 4.7  |
| Inguinal hernia                        | 6   | 3.5  |
| Heart defects                          | 6   | 3.5  |
| Benign tumors/cyst                     | 6   | 3.5  |
| (kidney 2, adrenal 1, mediastinum 1, skin 2) |     |      |
| Skeletal deformities                   | 5   | 2.9  |
| Thyroid nodule                         | 3   | 1.7  |
| Schizophrenia                          | 2   | 1.1  |
| Gallbladder calculus                   | 2   | 1.1  |
| Bronchial asthma                       | 2   | 1.1  |
| Atopic dermatitis                      | 2   | 1.1  |
| Eyelid defect                          | 2   | 1.1  |
| Hepatic steatosis                      | 2   | 1.1  |
| Hyperthyroidism                        | 1   | 0.5  |
| Pyloric stenosis                       | 1   | 0.5  |
| Celiac Disease                         | 1   | 0.5  |
| Renal calculus                         | 1   | 0.5  |
| Acute pancreatitis                     | 1   | 0.5  |
| Bacterial meningitis                   | 1   | 0.5  |
| Sleep apnea                            | 1   | 0.5  |
Table 3. Review of the literature regarding *HRAS* and *BRAF* mutations in ordinary PCC/PGL

| Year | HRAS Mutation rate | Mutation sites | BRAF Mutation rate | Mutation sites | Ref |
|------|--------------------|----------------|--------------------|----------------|-----|
| 2004 | N/A | - | 0 (0/34) | - | (15) |
| 2013 | 6.9% (4/58) | Q61R, Q61K, G13R | 0 (0/58) | - | (16) |
| 2014 | 5.2% (14/271) | Q61R, Q61K, G13R | N/A | - | (13) |
| 2015 | 7.1% (6/85) | Q61R, G13R | 1.2% (1/85) | V600E | (17) |
| 2016 | 7.1% (11/156) | Q61R, Q61K, Q61L, G13R | N/A | - | (18) |
| 2016 | N/A | - | 0 (0/110) | - | (19) |
| 2017 | N/A | - | 0 (0/64) | - | (14) |
| 2017 | 9.8% (17/173) | Q61R, Q61K, G13R, Q61L | 0.6% (1/173) | G469A | (9) |
| 2019 | 5.7% (13/227) | Q61R, Q61K, G13R, G12R | N/A | - | (20) |
| 2020 | 6.7% (2/30) | Q61R, G12D | N/A | - | (21) |
| 2020 | 16.5% (107/650) in Chinese; 9.8% (68/692) in European | Q61R, Q61K, G13R | N/A | - | (4) |

Ref, reference. N/A, not reported.
Table 4. Comparison of COGHD patients according to rhGH replacement during childhood and persistency of GHD at first evaluation after transfer from pediatric care

| Variable                       | Treated with GH in childhood (n=142) | Untreated with GH in childhood (n=28) | Persistent GHD (n=102) treated with GH in childhood | Transient GHD (n=40) treated with GH in childhood |
|--------------------------------|-------------------------------------|-------------------------------------|----------------------------------------------------|--------------------------------------------------|
|                                | n                                  | n                                  | n                                                  | n                                                |
| Body weight (kg)               | 66.7 ± 16.8                        | 63.5 ± 24.8                        | 67.3 ± 17.7                                        | 65.3 ± 14.8                                      |
| Body height (cm)               | 171.0 ± 9.9                        | 160.0 ± 11.8**                     | 169.2 ± 10.8**                                    | 173.8 ± 6.6**                                    |
| BMI (kg/m²)                    | 22.6 ± 4.8                         | 24.4 ± 7.6                         | 23.1 ± 5.0                                        | 21.4 ± 4.0                                       |
| Waist circumference (cm)       | 82.0 ± 11.9                        | 85.8 ± 13.9                        | 85.0 ± 12.8                                       | 76.1 ± 6.8**                                     |
| Age at start of rhGH           | 10.7 ± 3.5                         | /                                  | 9.8 ± 3.6                                         | 10.3 ± 2.1**                                     |
| Duration of rhGH               | 6.7 ± 3.7                          | /                                  | 7.6 ± 3.8                                         | 4.4 ± 1.9**                                      |
| Duration of rhGH treatment gap | 1.7 ± 2.4                          | /                                  | 2.1 ± 2.7                                         | 0.8 ± 0.9                                        |
| Body weight (kg)               | 66.7 ± 16.8                        | 63.5 ± 24.8                        | 67.3 ± 17.7                                        | 65.3 ± 14.8                                      |
| Body height (cm)               | 171.0 ± 9.9                        | 160.0 ± 11.8**                     | 169.2 ± 10.8**                                    | 173.8 ± 6.6**                                    |
| BMI (kg/m²)                    | 22.6 ± 4.8                         | 24.4 ± 7.6                         | 23.1 ± 5.0                                        | 21.4 ± 4.0                                       |
| Waist circumference (cm)       | 82.0 ± 11.9                        | 85.8 ± 13.9                        | 85.0 ± 12.8                                       | 76.1 ± 6.8**                                     |
| Age at start of rhGH           | 10.7 ± 3.5                         | /                                  | 9.8 ± 3.6                                         | 10.3 ± 2.1**                                     |
| Duration of rhGH               | 6.7 ± 3.7                          | /                                  | 7.6 ± 3.8                                         | 4.4 ± 1.9**                                      |
| Duration of rhGH treatment gap | 1.7 ± 2.4                          | /                                  | 2.1 ± 2.7                                         | 0.8 ± 0.9                                        |
| Fasting glucose (mmol/l)       | 4.5 ± 0.6                          | 4.7 ± 0.5                          | 4.4 ± 0.6                                         | 4.7 ± 0.5**                                      |
| Fasting insulin (mU/l)         | 16.6 ± 13.3                        | 20.3 ± 10.3**                      | 17.3 ± 15.4                                       | 15.4 ± 10.4                                      |
| Peak glucose in OGTT (mmol/l)  | 7.5 ± 1.8                          | 8.0 ± 1.6                          | 7.0 ± 1.5                                         | 8.4 ± 1.9**                                      |
| Peak insulin in OGTT (mU/l)    | 91.8 ± 57.3                        | 116.3 ± 56.9**                     | 89.9 ± 58.8                                       | 95.5 ± 55.1                                      |
| AUC glucose in OGTT (mmol/l/120min) | 24.3 ± 5.0 | 27.3 ± 5.1**                     | 23.3 ± 4.6                                        | 26.7 ± 5.1**                                    |
| HbA1c (%)                      | 5.1 ± 0.3                          | 5.2 ± 0.3                          | 5.0 ± 0.4                                         | 5.1 ± 0.3                                        |
| HOMA index                     | 3.2 ± 2.6                          | 4.3 ± 2.2**                        | 3.3 ± 2.8                                         | 3.1 ± 2.4                                        |
| Total cholesterol (mmol/l)     | 4.6 ± 1.2                          | 4.7 ± 1.2                          | 4.8 ± 1.3                                         | 3.9 ± 0.6**                                      |
| HDL cholesterol (mmol/l)       | 1.3 ± 0.3                          | 1.1 ± 0.3**                        | 1.3 ± 0.3                                         | 1.4 ± 0.4                                        |
| LDL cholesterol (mmol/l)       | 2.6 ± 1.0                          | 2.7 ± 0.9                          | 2.9 ± 1.1                                         | 2.0 ± 0.6**                                      |
| Triglycerides (mmol/l)         | 1.3 ± 1.0                          | 1.7 ± 0.9**                        | 1.3 ± 1.1                                         | 1.1 ± 0.9                                        |
| OCL (ng/ml)                    | 54.8 ± 38.4                        | 48.4 ± 31.1                        | 41.2 ± 24.0                                       | 80.3 ± 47.4**                                    |
| BCL (pg/ml)                    | 1197.2 ± 871.1                     | 1112.8 ± 687.5                     | 1011.8 ± 634.1                                    | 1558.4 ± 1145.2**                                |
| Fat%                           | 27.5 ± 9.4                         | 32.4 ± 9.4**                       | 30.7 ± 8.3                                        | 18.9 ± 6.7**                                     |
| Fat%                           | 19.4 ± 9.8                         | 23.7 ± 12.5                        | 21.6 ± 9.3                                        | 13.2 ± 8.8**                                     |
| Fat%                           | 45.1 ± 10.4                        | 40.2 ± 13.7                        | 44.3 ± 11.2                                       | 47.0 ± 7.8                                       |
| Fat%                           | 2.2 ± 0.5                          | 2.0 ± 0.7**                        | 2.2 ± 0.4                                         | 2.3 ± 0.4                                        |
| Fat%                           | 0.90 ± 0.1                         | 0.80 ± 0.1**                       | 0.89 ± 0.1                                       | 0.90 ± 0.1                                       |
| Fat%                           | -1.3 ± 1.3                         | -2.3 ± 1.8**                       | -1.4 ± 1.4                                        | -1.1 ± 1.2                                       |
| Fat%                           | 0.87 ± 0.1                         | 0.80 ± 0.2                         | 0.86 ± 0.1                                       | 0.89 ± 0.1                                       |
| Fat%                           | -0.6 ± 1.0                         | -1.1 ± 1.4**                       | -0.6 ± 0.9                                        | -0.4 ± 0.9                                       |

Data shown as mean ± SD

*a* p <0.05, treated vs untreated with GH in childhood;

*a** p <0.01, treated vs untreated with GH in childhood;

*b* p <0.05, persistent GHD vs transient GHD in patients treated with GH in childhood;

*b** p <0.01, persistent GHD vs transient GHD in patients treated with GH in childhood
Table 5. Characteristic of patients treated with rhGH during childhood (n=142) and difference according to etiology of COGHD

| Variable                                | Congenital COGHD (n=71) | Tumor related COGHD (n= 28) | Idiopathic COGHD (n= 43) |
|-----------------------------------------|-------------------------|----------------------------|--------------------------|
|                                        | n                       | n                          | n                        |
| Body weight (kg)*                       | 64.9 ± 18.4             | 72.7 ± 14.0                 | 65.5 ± 15.0               |
| Body height (cm)                        | 169.3 ± 10.8            | 172.3 ± 10.2                | 173.5 ± 7.2               |
| BMI (kg/m^2) *                          | 22.4 ± 5.3              | 24.4 ± 4.0                  | 21.5 ± 4.1                |
| Waist circumference (cm) *              | 83.9 ± 15.1             | 87.2 ± 5.8                  | 75.7 ± 5.9                |
| Age at start of rhGH**                  | 9.3 ± 3.8               | 10.8 ± 2.9                  | 12.8 ± 2.2                |
| Duration of rhGH *                      | 7.9 ± 4.7               | 6.5 ± 4.2                   | 5.7 ± 2.0                 |
| Duration of rhGH treatment gap         | 2.3 ± 2.8               | 2.0 ± 2.5                   | 0.8 ± 1.2                 |
| Age at cessation of rhGH before transfer to adult care | 17.1 ± 2.0             | 18.0 ± 1.8                  | 17.4 ± 1.2                |
| Fasting glucose (mmol/l) *             | 4.4 ± 0.6               | 4.5 ± 0.5                   | 4.7 ± 0.3                 |
| Fasting insulin (mU/l)                 | 16.4 ± 14.6             | 23.1 ± 19.1                 | 13.4 ± 6.1                |
| Peak glucose in OGTT (mmol/l) **       | 7.0 ± 1.6               | 7.4 ± 1.6                   | 8.3 ± 1.9                 |
| Peak insulin in OGTT (mU/l)**          | 78.0 ± 42.8             | 137.4 ± 84.5                | 83.8 ± 40.8               |
| AUC glucose in OGTT (mmol/l/120min)    | 23.1 ± 5.0              | 25.0 ± 5.1                  | 25.5 ± 4.7                |
| AUC insulin in OGTT (mU/l/120min)      | 215.6 ± 122.9           | 390.1 ± 274.0               | 220.2 ± 115.6             |
| HbA1c (%)                               | 5.0 ± 0.3               | 5.2 ± 0.4                   | 5.1 ± 0.2                 |
| HOMA index                              | 2.9 ± 2.2               | 4.8 ± 4.3                   | 2.7 ± 1.3                 |
| Total cholesterol (mmol/l)**           | 4.6 ± 1.0               | 5.3 ± 1.7                   | 3.9 ± 0.6                 |
| HDL cholesterol (mmol/l)               | 1.3 ± 0.4               | 1.2 ± 0.3                   | 1.4 ± 0.3                 |
| LDL cholesterol (mmol/l) **            | 2.7 ± 1.0               | 3.1 ± 1.3                   | 2.0 ± 0.5                 |
| Triglycerides (mmol/l) **              | 1.0 ± 0.6               | 1.9 ± 1.4                   | 1.0 ± 0.8                 |
| OCL (ng/ml) **                          | 45.5 ± 35.6             | 38.1 ± 20.0                 | 73.3 ± 42.0               |
| BCL (pg/ml) *                           | 1133.9 ± 737.2          | 771.5 ± 473.3               | 1472.2 ± 1076.3           |
| Fat% **                                 | 30.4 ± 9.2              | 29.8 ± 7.7                  | 19.3 ± 6.3                |
| FM (kg) **                              | 21.4 ± 10.3             | 21.3 ± 7.8                  | 13.7 ± 8.9                |
| LBM (kg) *                              | 42.8 ± 11.5             | 46.7 ± 8.8                  | 48.4 ± 8.3                |
| TBMC (kg)                               | 2.1 ± 0.5               | 2.2 ± 0.4                   | 2.3 ± 0.2                 |
| BMD lumbar spine (g/cm^2)              | 0.90 ± 0.1              | 0.86 ± 0.1                  | 0.90 ± 0.1                |
| Z-sc lumbar spine *                     | -1.31 ± 1.4             | -1.72 ± 1.3                 | -0.95 ± 1.3               |
| BMD femoral neck (g/cm^2)              | 0.85 ± 0.1              | 0.86 ± 0.1                  | 0.90 ± 0.1                |
| Z-sc femoral neck                       | -0.67 ± 1.1             | -0.65 ± 1.1                 | -0.39 ± 1.0               |

Data shown as mean ± SD
* p <0.05, difference between three etiologies of COGHD
** p <0.01, difference between three etiologies of COGHD
Table 6. Effects of 3 years of rhGH replacement in transition period on body composition and BMD (n=40)

| Parameter                        | Visit 0  | Visit 1  | Absolute change | Percent of change | P value |
|----------------------------------|----------|----------|------------------|-------------------|---------|
| %Fat                             | 30.7 ± 8.9| 29.1 ± 9.1| -1.62           | 5.2               | 0.043   |
| FM (kg)                          | 20.7 ± 9.5| 21.1 ± 9.1| 0.40            | 1.9               | 0.571 (NS) |
| LBM (kg)                         | 42.9 ± 10.5| 47.3 ± 10.9| 4.38            | 12.1              | 0.001   |
| TBMC (kg)                        | 2.14 ± 0.5| 2.33 ± 0.5| 0.19            | 8.8               | 0.001   |
| BMD lumbar spine (g/cm²)         | 0.87 ± 0.2| 0.93 ± 0.2| 0.06            | 6.9               | 0.001   |
| BMD femoral neck (g/cm²)         | 0.85 ± 0.2| 0.86 ± 0.2| 0.01            | 1.2               | 0.456 (NS) |
| Z-sc lumbar spine                | -1.58 ± 1.7| -1.25 ± 1.5| 0.33            |                   | 0.005   |
| Z-sc femoral neck                | -0.77 ± 1.3| -0.50 ± 1.3| 0.27            |                   | 0.007   |

Visit 0- first DXA evaluation at admission on adult care unit
Visit 1-second DXA evaluation after 3 years of rhGH replacement in transition period