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Characteristics and Outcomes of the Italian Subpopulation Enrolled in the Observational, Multicenter, Hypopituitary Control and Complications Study (HypoCCS)

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ABSTRACT

Aim: To describe characteristics and outcomes of Italian patients with hypopituitarism participating in HypoCCS.
Methods: Study population was stratified by max GH peak (mGHp) and body mass index (BMI). Baseline variables included demographic characteristics, type of deficit, smoking habits; variables analyzed over time included weight, Framingham Cardiovascular Disease (CVD) risk, lipids, GH dose.
Results: Italian subpopulation included 342 patients with mGHp ≤33 (group A); 345 with 33< mGHp ≤66 (group B); and 337 with mGHp >66 percentile (group C) with mean age [years(SD)] of 44.2 (16.2), 44.6 (16.0), 42.6 (15.1), respectively, and adult onset GHD [(%): 75.8, 77.1 and 78.4%, respectively]. GHD was diagnosed mainly with GHRH + Arginine test (roughly 66% of diagnoses) and % of multiple pituitary hormone deficits was higher (p<0.001) in subgroup A (92.7) than in B (85.2) or C (69.5). Patients were equally distributed across normal-, under- and over-weight with average BMI of 28. No differences were detected in smoking habits or in Framingham CVD risk at baseline. More patients in group A than in B or C had hyperlipidemia [N (%): 92 (35.1), 86 (31.1), 69 (24.7) respectively; p=0.029]. Mean GH dose at baseline was significantly lower in group A than in B, C [dose/kg (SD): 311.0 (162.5), 356.3 (217.9), 391.7 (323.1); p=0.0009] and with a longer treatment duration [years (SD): 7.2 (9.2), 5.5 (8.2), 5.0 (7.6); p=0.0014]. Analyses over time showed group differences only at certain single time-points. Overall, no significant differences in treatment emergent adverse events (TEAEs) were detected across subgroups, while among the serious TEAEs, only “infections and infestations” were significantly different [N (%): 6 (1.8), 5 (1.5), 0 (0.00); p=0.0406].
Conclusions: Italian patients with mGHp ≤33 percentile had the worst lipid profile and were given the lower GH treatment dose. The highest % of multiple deficits in this group suggests the more severe GHD.

INTRODUCTION

Adult patients with hypopituitarism and growth hormone deficiency (GHD) suffer from increased abdominal fat, decreased lean body mass, dyslipidemia and premature mortality, often due to cardiovascular disease (CVD).[1,2] The indication of growth hormone (GH) therapy for adults with GHD was approved in Europe in 1995 and the Hypopituitary Control and Complication Study (HypoCCS) was started at that time. HypoCCS is an international, observational study designed to examine efficacy and safety of GH replacement in adults. Analyses of the HypoCCS database have focused primarily on epidemiological aspects, and have shown how the adult GHD indication has gained increasing acceptance in all countries involved. From the very beginning of HypoCCS, Italy has been a major contributing country to the database, with the number of enrolled patients second only to the US among the participating countries.

OBJECTIVE

The aim of the present analysis was to describe the characteristics and outcomes of the Italian adult patients with hypopituitarism/GHD who are participating in HypoCCS.

PATIENTS and METHODS

Patients entered into the HypoCCS database meet the criteria for the adult indication for Humatrope®, according to the approved package insert. The onset of GHD could have been either during childhood (CO) or during adulthood (AO). As an observational study, diagnosis and treatment were at the discretion of the investigating physician. Data were assessed for Italian patients in the HypoCCS database for the data lock of July 2010. Patients with evaluable data were grouped according to tertiles (Group A ≤33%, Group B >33–≤66%, Group C >66%) of maximum GH peak concentration reported from stimulation testing at the time of entry to the study. Patients were also assessed according to body mass index (BMI) category (≤25, >25–≤30, >30 kg/m^2). Baseline demographic and other patient characteristics were analyzed. GH dose, BMI, serum lipid concentrations, smoking status and CVD risk according to the Framingham index were analyzed at baseline and over time of GH treatment, at yearly intervals.

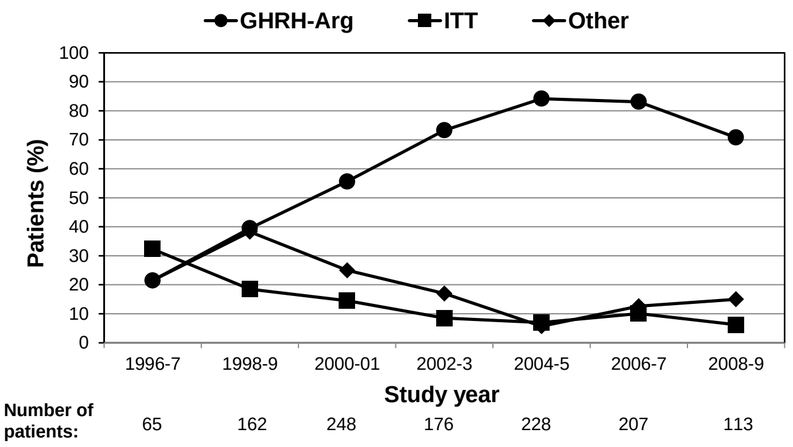
Statistics

Differences between groups for baseline parameters were examined by analysis of variance (ANOVA). Between-group differences during follow-up were examined by analysis of covariance (ANCOVA), including treatment group and baseline value as factors.

RESULTS

- The HypoCCS database included 1025 patients in Italy with data available for analysis. The most frequent cause of hypopituitarism/GHD was pituitary adenoma reported for 40% of patients, with craniopharyngiomas reported for 14% and idiopathic GHD reported for 13% (34% in CO and 6% in AO patients).
- The overall median (quartiles) GH peak concentration reported from GH releasing hormone (GHRH)-arginine stimulation tests was 1.5 (0.5–3.4) µg/L.
- The median (quartiles) GH peak concentration from all other stimulation tests was 0.6 (0.2–1.5) µg/L.
- The GHRH-arginine test became the most frequent GH stimulation test used in Italian adult patients entered into HypoCCS (Figure 1).

Figure 1. Proportion of patients with each type of GH stimulation test administered at 2-year intervals of HypoCCS in Italy



GHRH-Arg=GH releasing hormone-arginine; ITT=insulin tolerance test

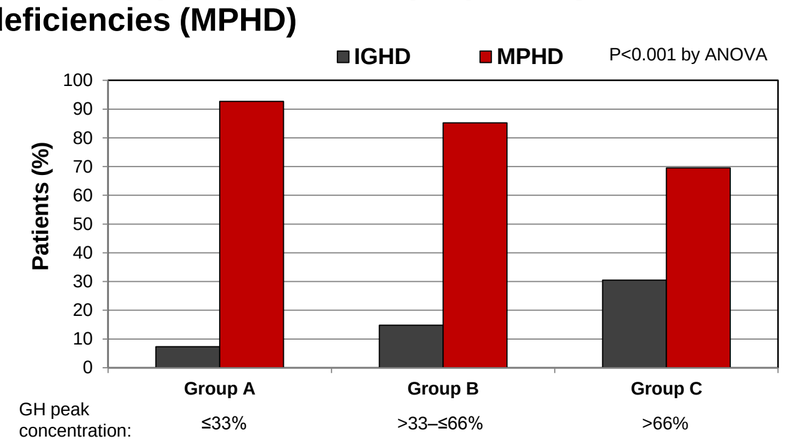
Table 1. Baseline demographics, GH dose and duration of follow-up, by tertiles of maximum GH peak concentration in stimulation tests

	Group A N=342	Group B N=345	Group C N=338	P
Age, years[a]	44 ± 16	45 ± 16	43 ± 15	0.231
Female, n (%)	148 (43.3)	132 (38.3)	144 (42.6)	0.350
Male, n (%)	194 (56.7)	213 (61.7)	194 (57.4)	
Adult onset, n (%)	258 (75.9)	266 (77.1)	265 (78.4)	0.737
Childhood onset, n (%)	82 (24.1)	79 (22.9)	73 (21.6)	
Serum IGF-I, µg/L[b]	78.0 (61.0-95.0)	101.6 (85.2-118.0)	139.3 (119.5-159.1)	<0.001
Starting GH dose, µg/day[b]	311 (291-331)	356 (330-383)	392 (351-433)	<0.001
GH treatment duration, years[b]	7.2 (6.2-8.2)	5.5 (4.6-6.3)	5.0 (4.1-5.8)	0.001

[a]mean ± SD; [b]mean (95% confidence interval); P-values are from ANOVA; tertiles: group A ≤33%, group B >33–≤66%, group C >66% of stimulated peak GH concentration; IGF-I=insulin-like growth factor-I

Patients with the lowest stimulated peak GH concentration had a lower mean IGF-I concentration and mean starting dose of GH and were treated for significantly longer (Table 1). There were no significant between-group differences for maximum GH dose at later times.

Figure 2. Proportions of patients with isolated GH deficiency (IGHD) and multiple pituitary hormone deficiencies (MPHD)



MPHD was reported more frequently by patients with the lowest stimulated GH peak concentration (Figure 2).

Table 2. Body mass index (BMI) and factors associated with cardiovascular risk, at baseline

	Group A N=342	Group B N=345	Group C N=338	P
BMI, kg/m^2, mean ± SD	28.1 ± 6.3	28.2 ± 6.0	28.4 ± 7.3	0.790
BMI ≤25 kg/m^2, n (%)	118 (34.5)	113 (33.0)	106 (32.0)	0.879
BMI >25-≤30 kg/m^2, n (%)	113 (33.0)	115 (33.6)	121 (26.6)	
BMI >30 kg/m^2, n (%)	111 (32.5)	114 (33.3)	104 (31.4)	
Never smoked, n (%)	167 (78.8)	169 (75.5)	143 (69.1)	0.179
Total cholesterol, mg/dL, mean ± SD	211.8 ± 48.7	213.9 ± 49.2	208.2 ± 42.9	0.370
HDL cholesterol, mg/dL, mean ± SD	50.7 ± 15.5	49.5 ± 14.5	51.5 ± 17.1	0.373
Triglycerides, mg/dL, mean ± SD	156.9 ± 100.5	154.7 ± 103.7	137.9 ± 82.8	0.058
Framingham CVD risk, mean ± SD	7.59 ± 7.45	8.37 ± 6.90	7.45 ± 7.51	0.358

P-values are from ANOVA; tertiles: group A ≤33%, group B >33–≤66%, group C >66% of stimulated peak GH concentration

BMI and other factors associated with cardiovascular risk did not differ between the groups categorized by stimulated GH peak concentration, at baseline (Table 2) or during follow-up (not shown).

Table 3. Proportions of patients reporting co-morbidities at baseline

	Group A N=342[a]	Group B N=345[a]	Group C N=338[a]	P
Hyperlipidemia	92 (35.1%)	86 (31.1%)	69 (24.7%)	0.029
Hypertension	71 (26.0%)	62 (21.8%)	69 (23.7%)	0.498
Diabetes mellitus	10 (3.7%)	15 (5.2%)	11 (3.8%)	0.581
Cerebrovascular disease	15 (5.5%)	14 (4.9%)	6 (2.1%)	0.087
Coronary artery disease	6 (2.2%)	12 (4.2%)	4 (1.4%)	0.090

[a]Number of patients with available data could vary; P-values are from ANOVA; tertiles: group A ≤33%, group B >33–≤66%, group C >66% of stimulated peak GH concentration

Among co-morbidities specified by the investigators, hyperlipidemia was reported more frequently for patients with the lowest stimulated peak GH concentration (Table 3). Other co-morbidities did not differ significantly between the groups.

Table 4. Treatment-emergent adverse events (TEAE) reported by Italian patients during GH treatment in HypoCCS

	Group A N=342	Group B N=345	Group C N=338	P
Any TEAE	89 (26.0%)	77 (22.3%)	84 (24.9%)	0.513
Any serious TEAE[a]	25 (7.3%)	19 (5.5%)	7 (2.1%)	0.006
Infections and infestations	6 (1.8%)	5 (1.5%)	0 (0%)	0.041
Neoplasms	6 (1.8%)	4 (1.2%)	5 (1.5%)	0.811

[a]There were no significant difference for any system organ classes not shown; P-values are from ANOVA; tertile: group A ≤33%, group B >33–≤66%, group C >66% of stimulated peak GH concentration

More patients in the lowest stimulated GH peak category reported serious adverse events during follow-up (Table 4). The only system organ class that differed significantly between the categories was infections and infestations.

SUMMARY

- In adult patients treated with GH in HypoCCS in Italy, the most frequent GH stimulation test used for diagnosis was GHRH-arginine and the majority of patients had stimulated GH peak below standard cut-off levels for GHD (GHRH-Arg <4.1 µg/L; all other tests <3 µg/L).
- Patients in the lowest GH peak concentration group started on a lower GH dose than the other groups (Table 1), although there were no between-group differences at later times.
- Patients with the lowest stimulated GH peak concentration had lower IGF-I (Table 1) suggesting more severe GHD, and were more likely to have multiple pituitary hormone deficiencies (Figure 2).
- Baseline means for BMI, serum lipids, smoking status and Framingham CVD risk did not differ between the categories of stimulated GH peak concentration (Table 2). Mean BMI, serum lipid values and Framingham CVD risk during follow-up did not differ between the GH peak concentration groups.
- More patients in the lowest GH peak concentration group reported hyperlipidemia (Table 3).
- Treatment-emergent adverse events were reported by similar numbers of patients in each GH peak concentration group. Serious adverse events were reported more frequently in the patients with the lowest stimulated GH peak concentration, but the only system organ class that differed significantly between groups was infections and infestations (Table 4).

CONCLUSIONS

In adult GH-deficient patients in HypoCCS in Italy, those with stimulated peak GH concentration in the lowest 33rd percentile:

- were more likely to have multiple pituitary hormone deficiencies, indicating more severe GH deficiency
- had the lowest mean starting dose of GH
- had hyperlipidemia reported more frequently
- reported serious adverse events more frequently.

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