Pituitary apoplexy in growth hormone deficient adults treated with GH – a KIMS database retrospective study

Serban Radian[1], Peter J. Jönsson[2], Cecilia Camacho-Hübner[3], Beverly MK Biller[4], Michael Buchfelder[5], Ann-Charlotte Åkerblad[2], Márta Korbonits[1]
[1] Queen Mary University of London, London, UK, [2] Pfizer Endocrine Care, Sollentuna, Sweden, [3]Pfizer Inc., New York City, NY, USA
[4] Massachusetts General Hospital, Boston, MA, USA, [5]Stockholm, Sweden, [5] Department of Neurosurgery, University of Erlangen-Nürnberg, Erlangen, Germany

Background and Aim

- Pituitary apoplexy (PitApo) has significant associated-morbidity and management is not yet standardized. Few large PitApo series exist
- The aim of this study was to describe prevalence, characteristics and response to GH treatment of PitApo patients in growth-hormone deficient (GHD) patients compared with two control populations

Methods

Patients with "Infarction-apoplexy" GHD aetiology code were identified from Pfizer International Metabolic Database (KIMS). Baseline characteristics, GH dosage and 1-year response to GH replacement of PitApo patients were compared with non-functioning pituitary adenoma (NFPA, n=3828) and Sheehan's syndrome (n=495) control groups, using SAS 9.2 software.

Patients

- We identified 151 PitApo patients (0.96% of 15,809 GHD patients)
- 143 patients were diagnosed with PitApo before KIMS start and 8 patients presented PitApo as an adverse event during KIMS (Figure 1)
- 63 PitApo patients (41.7%) had an associated diagnosis of pituitary adenoma (n=60) or other specified tumour (n=3)

- Gender distribution was similar in PitApo and NFPA groups
- Median age of PitApo patients at diagnosis of GHD and at KIMS entry was lower than that of NFPA and higher than that of Sheehan's patients (Table 1)

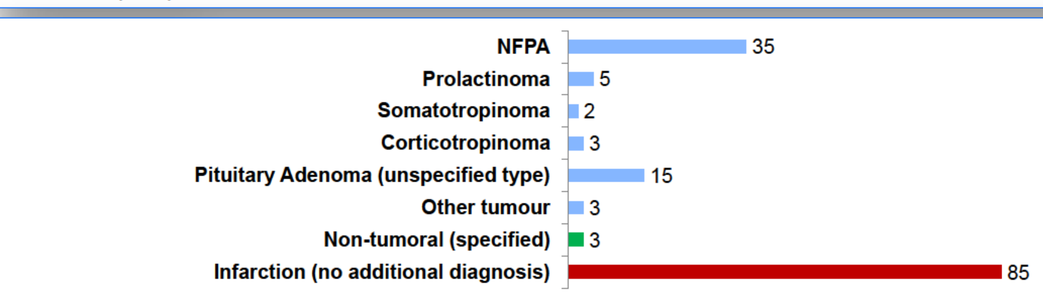

Figure 1. Aetiological classification of pituitary apoplexy patients

Table 1. Baseline characteristics of study groups

	PitApo (n=151)	NFPA (n=3828)	Sheehan's (n=495)
Proportion of male patients	68.2%	60.8%	0
Age at GHD diagnosis [years; median (10th-90th percentile)]	47.8 (29.3-63.2)	51.8 (33.4-66.8)**	42.5 (30.3-57.8)***
Age at KIMS start [years; median (10th-90th percentile)]	51.5 (33.3-65.7)	54.1 (37.1-68.9)**	47 (34.6-61.3)**

** p<0.01; *** p<0.001, vs. PitApo group

Results

- The average GH dose during the 1st year of replacement did not differ between groups, stratified by sex and oestrogen use (Table 2 and Figure 2)

Table 2. Average GH dose between groups (1st year of replacement)

GH dose [mg/day; median (10th-90th percentile)]	PitApo (n=151)	NFPA (n=3828)	Sheehan's (n=495)
Male patients	0.3 (0.13-0.5)	0.28 (0.13-0.53)	na
Female patients not on oestrogen	0.27 (0.2-0.4)	0.27 (0.11-0.53)	0.3 (0.14-0.6)
Female patients on oestrogen	0.38 (0.17-0.49)	0.33 (0.15-0.7)	0.37 (0.2-0.7)

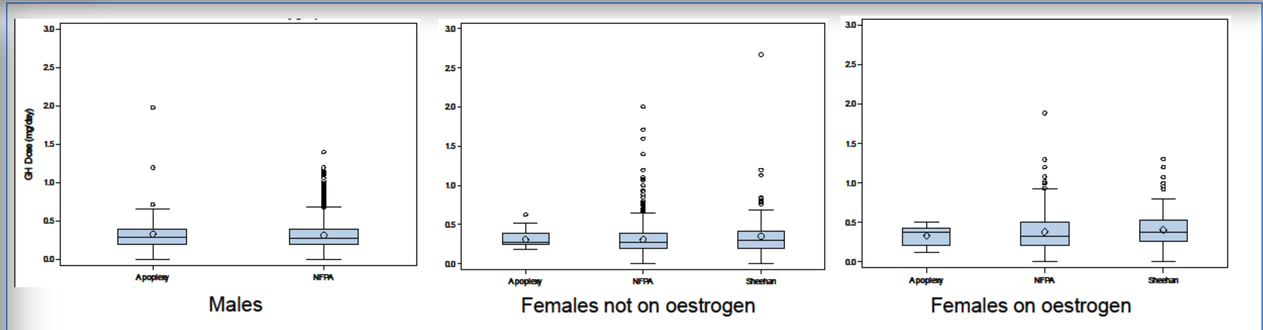

Figure 2. Average GH dose during 1st year of replacement

Effects of GH replacement on IGF-I status

- Baseline IGF-I standard deviation scores (SDS) were similar between PitApo and NFPA groups, but significantly lower in Sheehan's compared to PitApo group (including males) (-2.72 vs. -1.15, p<0.001)
- 1-year IGF-I SDS was also significantly lower in Sheehan's patients than PitApo (including males) (-0.21 vs. 0.33, p<0.001)
- Median IGF-I SDS 1-year change (Δ IGF-1) was similar between PitApo and NFPA groups and higher in Sheehan's compared to PitApo (including males) (2.59 vs. 1.61, p<0.05)
- When stratified by sex, the only remaining difference was for baseline IGF-I SDS, i.e. lower scores in Sheehan's patients vs. female PitApo (Table 3 and Figure 3)

Table 3. Comparison of baseline and 1-year change in sex/age-adjusted IGF-I SDS between groups

Sex and age-adjusted IGF-I SDS [median (10th; 90th percentile)]	PitApo		NFPA		Sheehan's
	Male (n=61)	Female (n=32)	Male (n=1489)	Female (n=1002)	Female (n=312)
Baseline	-0.68 (-3.25; 0.57)	-1.68 (-3.77; -1.06)	-1.22 (-3.02; 0.29)	-1.38 (-3.25; 0.12)	-2.72 (-4.97; -0.88)*
1-year	0.88 (-2.07; 2.27)	-0.03 (-1.64; 1.09)	0.81 (-1.07; 2.23)	0.40 (-1.50; 1.79)	-0.21 (-2.60; 0.86)
1-year increase from baseline	1.61 (0.51; 3.44)	1.76 (1.05; 3.71)	2.03 (0.08; 3.87)	1.71 (-0.08; 3.66)	2.59 (0.14; 4.32)

Only GH-naïve/semi-naïve patients were included in the analysis; * p<0.05 vs. PitApo female patients

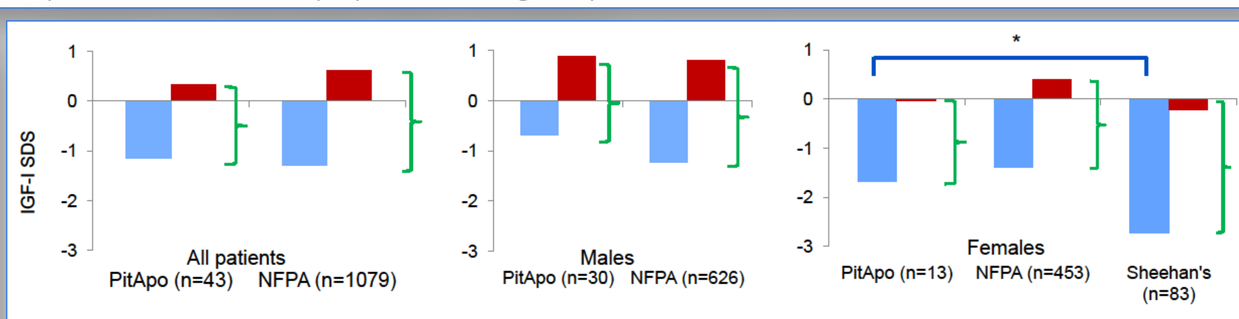

Figure 3. Comparison of median IGF-I standard deviation scores (sex- and age at GHD diagnosis-adjusted) between groups, at baseline (blue columns), 1-year (red columns) and change from baseline after 1 year of GH replacement (Δ IGF-1, green brackets) (* p<0.05).

- The proportion of GH-naïve/semi-naïve patients with normal IGF-I after 1yr of GH replacement was similar between PitApo and NFPA
- The proportion of GH-naïve/semi-naïve patients with normal IGF-I after 1yr of GH was lower in Sheehan's vs. PitApo (including males)
- Following stratification by sex, a significant difference between Sheehan's and female PitApo patients was still observed (Figure 4)

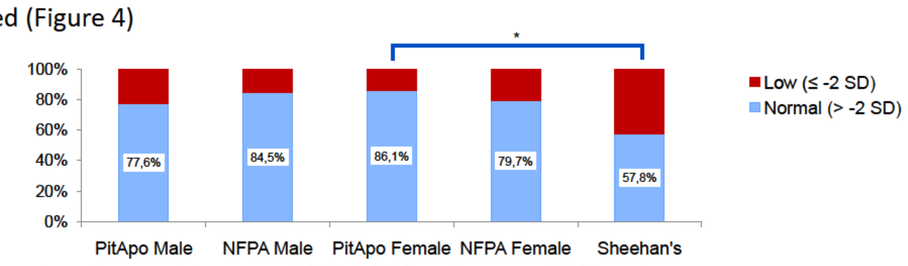

Figure 4. Proportion of patients with normal IGF-I SDS at 1-year of GH replacement (* p<0.0001)

Effects of GH replacement on Quality of Life (QoL)

The 1-year QoL–Assessment of GHD in Adults (QoL–AGHDA) score reduction (indicating improved QoL) was similar in PitApo and NFPA and higher than in Sheehan's patients (Table 5).

Effects of GH replacement on serum lipids

- Mean age/gender-adjusted (general linear model) 1-year serum total cholesterol decrease from baseline was significantly larger in PitApo vs. NFPA and Sheehan's patients
- LDL- and HDL-cholesterol 1-year changes did not differ between groups
- The 1-year decrease in triglyceride levels was significantly larger in PitApo vs. NFPA patients (Table 4)

Table 4. Comparison of 1-year changes in blood lipids levels, using a general linear model to adjust for sex and age at GHD diagnosis (Δ = 1-year – baseline levels)

Least square means	PitApo	NFPA	Sheehan's
Δ total cholesterol (mmol/L)	-0.76*	-0.31	-0.31
Δ HDL-cholesterol (mmol/L)	0.01	0	0
Δ LDL-cholesterol (mmol/L)	-0.27	-0.28	-0.24
Δ triglycerides (mmol/L)	-0.82**	-0.09	-0.31

* p<0.05 vs. NFPA and Sheehan's groups ** p<0.01 vs. NFPA group

Table 5. Comparison of 1-year changes in QoL-AGHDA scores between groups, using a general linear model to adjust for sex and age at GHD diagnosis (Δ AGHDA = 1-year – baseline levels)

Least square means	PitApo	NFPA	Sheehan's
Δ AGHDA	-4.33	-3.76	-1.58*

* p<0.01 vs. PitApo group and p<0.0001 vs. NFPA group

Conclusions

- The prevalence of pituitary apoplexy in this large cohort of GHD patients was ~1%
- GH replacement doses were not different between PitApo patients and NFPA or Sheehan's syndrome controls
- Treatment effects were comparable to NFPA controls, except for greater reductions in serum lipids in PitApo patients
- PitApo patients and NFPA controls attained similar IGF-I SDS and improvement in QoL-AGHDA scores on GH replacement, whereas Sheehan's controls had lower rates of IGF-I normalization and lower improvement in QoL-AGHDA scores

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Disclosures

CCH, PJ, ACA are permanent employees at Pfizer, MB and MK are members of the KIMS Steering Committee. BMKB has been a consultant to NovoNordisk, Pfizer and Versartis and serves as a PI on research grants to Mass General Hospital from NovoNordisk and OPKO. MK has grant support from Pfizer and Novartis and was speaker for Ipsen.

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Serban Radian
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