Clinical Outcomes in Primary Empty Sella (ES) Syndrome in Childhood-Onset Growth Hormone Deficiency: Data from KIGS (Pfizer International Growth Database).

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BACKGROUND and AIMS

The incidence of ES in children varies greatly depending on the population surveyed, ranging from 1.2%-9% to 68% (children without and with known endocrinopathies, respectively). MRI is the main diagnostic tool for screening pituitary and in a previous KIGS study, 3.0% of patients with GHD were identified with ES and 7.8% with pituitary hypoplasia (Maghnie et al, EJE (2013).

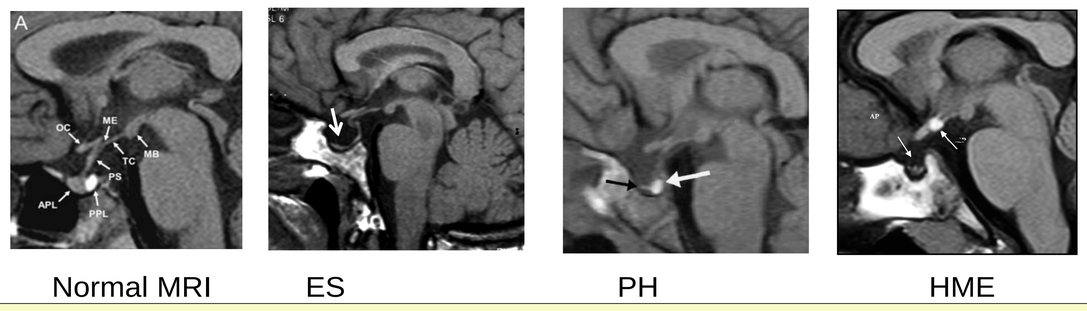
Empty sella was reported mostly in children with isolated GHD, multiple pituitary hormone deficiency (MPHD), hypoplastic/missing/ectopic pituitary deficiency, in obese children or in those who presented pseudotumor cerebri. Thus, somatotrophs are probably vulnerable component of the pituitary in ES but significant data in a large group and their long-term outcomes based on detailed characteristics have not been reported.

The Aims of the study were : 1) To evaluate the clinical outcomes ~~to~~ of GH treatment in patients with ES and 2) compare the clinical response in patients with pituitary hypoplasia (PH), hypoplastic anterior pituitary, missing pituitary stalk and ectopic posterior pituitary (HME) and other central malformation (OCM).

SUBJECTS and METHODS

- All patients diagnosed with GHD and neuroimaging findings of ES, PH, HME and OCM in KIGS were included in this study.

MRI Pictures



Normal MRI ES PH HME

- Near" adult height (NAH) was defined as:
  1. Stopped growing (HV < 2 cm/y)
  2. Or Age >16 (girls) / 18 (boys) if HV is not available
  3. GH therapy > 4 years where > 1 year pre-puberty

Statistical Analyses

Descriptive statistics
Compare growth response between diagnoses/groups at year 1, 5 and NAH
Compare growth response within each diagnoses/groups at year 1, 5 and NAH
Compare growth response between diagnoses/groups at year 1, 5 and NAH
Compare growth response within each diagnoses/groups at year 1, 5 and NAH

- Delta height SDS (ΔHt SDS) among the other cohorts were compared at yr 1. Wilcoxon signed rank and Kruskal–Wallis tests were applied. Significance level=5%.

RESULTS

Clinical characteristics and outcomes in patients with ES.

At visit	Baseline	Yr 1	Yr 5	NAH	P-value**
Variable	Mean (SD)	Mean SD)	Mean SD)	Mean(SD)	
N (boys %)	702 (69)	702 (69)	370 (69)	89 (61)	
Age at diagnosis (yr)	7.7 (5.0)				
Chronological age	8.0 (4.9)	9.0 (4.9)	11.3 (4.1)	17.6 (1.4)	<.001
Mid-parental Ht SDS Prader	-0.8 (1.2)				
Height (SDS) Prader	-3.5 (1.6)	-2.5 (1.5)	-1.1 (1.4)	-0.8 (1.3)	<.001
ΔHt SDS Prader		1.0 (0.8)	2.5 (1.4)	3.1 (1.5)	<.001
Ht - MPH (SDS) Prader	-2.6 (1.6)	-1.6 (1.4)	-0.3 (1.4)	0.1 (1.1)	<.001
Weight (SDS)	-2.4 (2.0)	-1.7 (1.7)	-0.4 (1.6)	-0.3 (1.9)	<.001
In puberty	11%	20%	37%	100%	
Bone Age (yr)	6.2 (4.1)	7.3 (4.3)	10.0 (3.6)	15.8 (1.4)*	0.031
Max GH peak (µg/L)	4.6 (5.7)				
Dose (mg/kg/week)	0.22 (0.08)	0.21 (0.06)	0.20 (0.06)	0.15 (0.09)	<.001
Years on GH treatment				10.6 (3.6)	

*N=13 at NAH; **Comparing NAH vs baseline

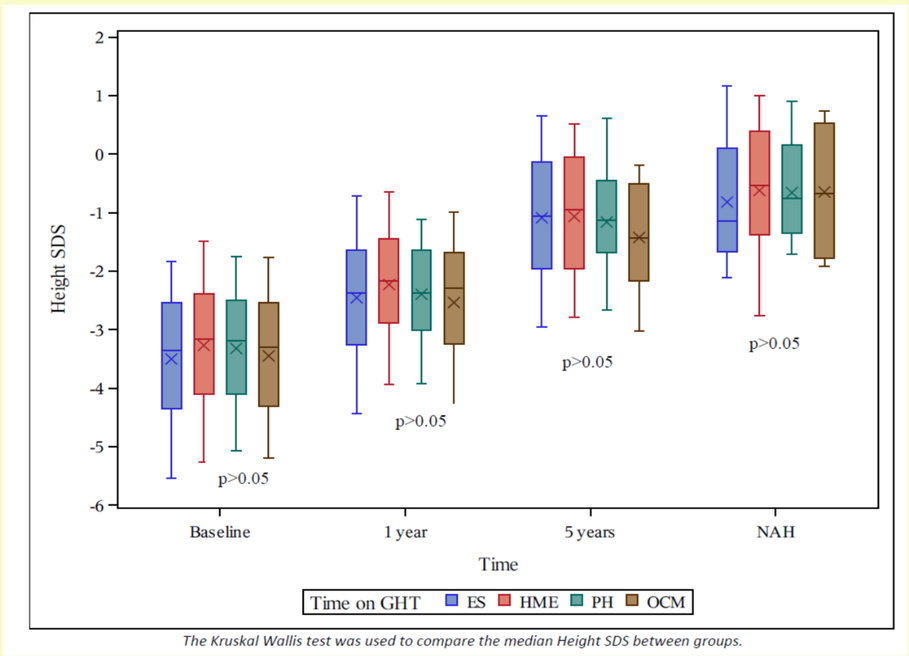
Summary results for other cohorts included height SDS at baseline and year 1 ΔHt SDS: PH (n=180; -3.4(1.6); 0.9(0.7), HME (n=485; -3.3(1.7);1.1 (1.0) and OCM (n=121; -3.5(1.6); 1.0(1.0). P-values=0.09, 0.134.

Safety/Adverse Events; Overall, there were adverse events (AEs) reported in 321(21.6%) patients, with considered as serious (SAE) in 79 (5.3%) patients. None of the AEs were unexpected. 4 deaths were reported not related to treatment.

Table 2. Clinical characteristics of all cohorts

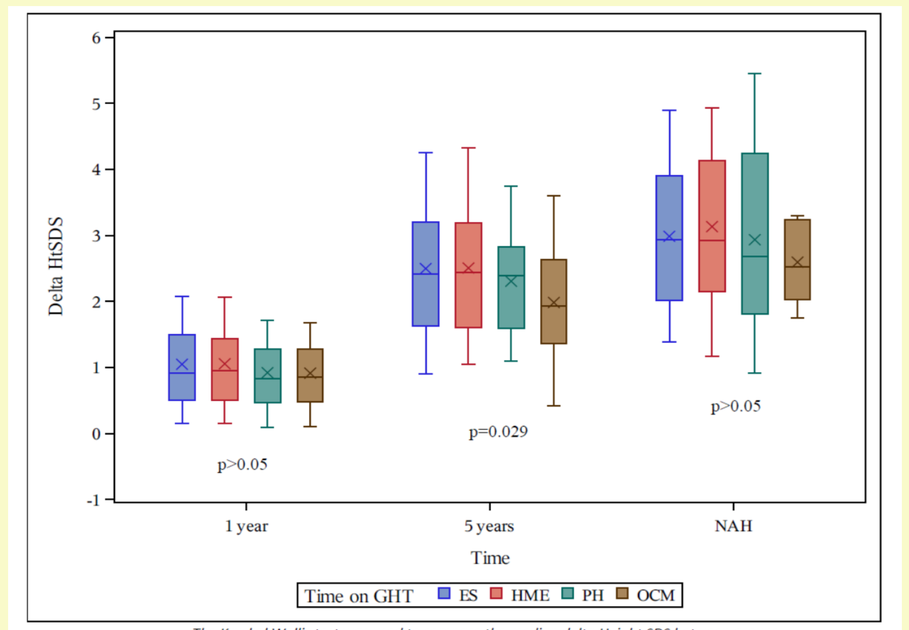
		N	Mean	SD	p-value
Chronological age	ES	702	7.96	4.92	<0.001
	HME	485	6.54	4.78	
	PH	180	8.30	4.87	
	OCM	121	7.42	4.60	
Age at diagnosis (Yr)	ES	620	7.69	5.01	<0.001
	HME	361	6.45	4.99	
	PH	143	7.99	4.91	
	OCM	100	6.19	4.87	
Gender (Boys)	ES	69%			0.047
	HME	65%			
	PH	71%			
	OCM	59%			
Height (SDS) Prader	ES	702	-3.51	1.58	0.093
	HME	485	-3.33	1.69	
	PH	180	-3.36	1.65	
	OCM	121	-3.49	1.60	
Mid parental Ht SDS Prader	ES	631	-0.85	1.25	0.007
	HME	442	-0.67	1.09	
	PH	157	-1.03	1.12	
	OCM	104	-0.95	1.25	
Dose (mg/kg/week)	ES	702	0.22	0.08	<0.001
	HME	485	0.24	0.08	
	PH	180	0.23	0.07	
	OCM	121	0.22	0.07	
Max GH peak ug/L	ES	623	4.57	5.69	0.002
	HME	401	4.93	5.18	
	PH	153	5.32	4.83	
	OCM	112	5.39	4.91	
Bone age	ES	211	6.20	4.13	0.097
	HME	143	6.08	4.23	
	PH	67	7.03	4.01	
	OCM	30	7.64	4.23	

Figure 1: Height SDS for each group from baseline, year 1 and 5 of GH treatment and at near adult height (NAH)



The Kruskal Wallis test was used to compare the median Height SDS between groups.

Figure 2: Delta height SDS for each group from baseline, year 1 and 5 of GH treatment and at near adult height (NAH)



The Kruskal Wallis test was used to compare the median delta Height SDS between groups.

CONCLUSIONS

A significant clinical response to GH treatment in ES patients was observed at all treatment time points.
Patients with other diagnosis also demonstrated a positive response to treatment at year 1.

References

[1]. Maghnie M, Lindberg A, Koltowska-Häggström M, Ranke MB. Magnetic resonance imaging of CNS in 15,043 children with GH deficiency in KIGS (Pfizer International Growth Database). Eur J Endocrinol. 2013 Jan 17;168(2):211-7. doi: 10.1530/EJE-12-0801.

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Growth and syndromes (to include Turner syndrome)

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