GROWTH PATTERN AND FINAL HEIGHT OUTCOME IN CHILDREN WITH SEPTO-OPTIC DYSPLASIA AND ISOLATED HYPOPITUITARISM TREATED WITH rhGH IN A SINGLE CENTRE

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BACKGROUND

Septo-optic dysplasia (SOD) is defined by the presence of two or more features of the "classic SOD triad" that consists of 1) optic nerve hypoplasia, 2) pituitary deficits, and 3) midline brain defects. Due to its rarity (estimated incidence: 5.5 in 100,000 live births), there is limited evidence in relation to the phenotypic spectrum of children with this condition.

AIM

To identify the distinctive features of GH Deficiency (GHD) and to assess the response to GH treatment (rhGH) in children with SOD compared to those with Multiple Pituitary Hormone Deficiencies (MPHD) (without optic nerve and midline brain abnormalities).

PATIENTS, DESIGN AND METHODS

PATIENTS

- 171 children with SOD
- 53 children with MPHD

DESIGN

- Retrospective longitudinal single centre study

METHODS

- GHD was diagnosed in patients with growth failure by an insufficient GH response (≤6.7 µg/l) to provocation (Insulin Induced Hypoglycaemia or Glucagon) combined with low IGF1/IGFBP3.
- Neurosecretory GH dysfunction was diagnosed in children with low IGF1/IGFBP3, poor growth velocity (GV), structural Hypothalamo-Pituitary (H-P) abnormalities and abnormal nocturnal GH production characterised by fewer than 3 GH peaks > 6.7 ng/L on overnight profile (20' sampling for 12 hours).

RESULTS

1) GENERAL FEATURES (TABLE 1)

- Within the SOD cohort, 132/171 (77.2%) had some degree of hypopituitarism.

TABLE 1 (WHOLE COHORT)	SOD (n:171)	MPHD (n:53)	p
Gender (M/F)	96/75	30/23	ns
Age at diagnosis (years) mean ± SD (range)	2.45±2.89 (0.01-14.36)	1.78±2.15 (0.01-6.53)	0.010
Age at last appointment (years) mean ± SD (range)	9.24±4.64 (0.52-21.00)	9.00±4.66 (0.46-21.48)	ns
Follow-up duration (years) mean ± SD (range)	7.81±4.15 (0.40-17.50)	7.07±3.76 (0.45-16.70)	ns

2) GHD CHARACTERISTICS (TABLE 2)

- Only 11/132 (8.3%) SOD (age range: 0.52-15.46 years) and 2/53 (3.8%) MPHD (ages: 0.57, 0.62 years) had preserved GH function.

TABLE 2 (PATIENTS WITH GHD)	SOD (n:121)	MPHD (n:51)	p
SGA n (%)	9/121 (7.4)	3/51 (5.9)	ns
Age at GHD diagnosis (years) mean±SD (range)	3.45 ± 2.93 (0.1-14.36)	2.67 ± 2.22 (0.06-10.60)	ns
GH peak (ug/L) mean±SD (range)	2.94 ± 2.10 (0.05-6.70)	2.32 ± 1.90 (0.10-6.50)	ns
GH peak ≤ 3 ug/L % (n)	51.2 (43/84)	68.4 (26/38)	ns

3) NEUROSECRETORY GH DYSFUNCTION

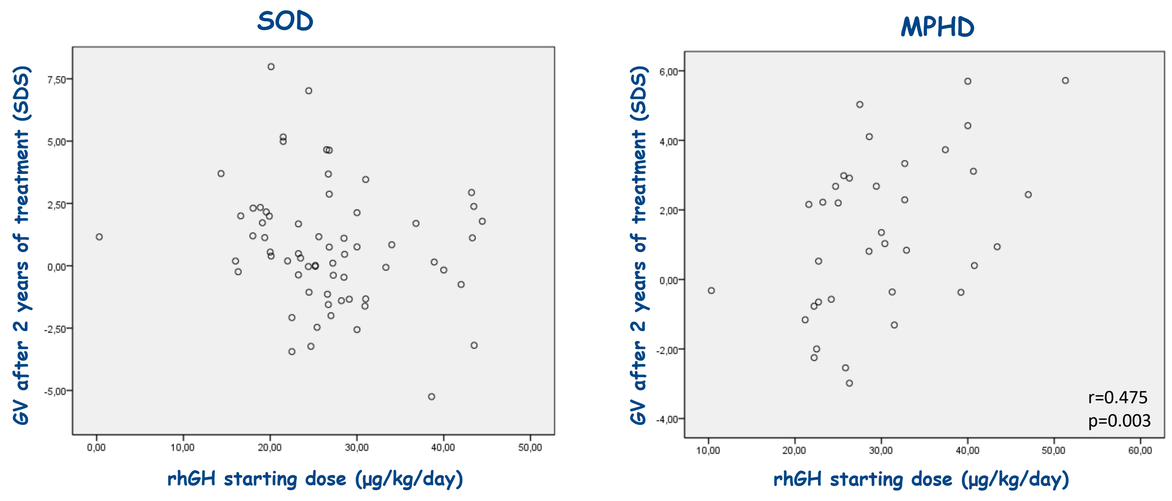
- Neurosecretory GH dysfunction was diagnosed in 5/121 (4.1%) SOD (but none of MPHD) (age at diagnosis: 2.55-14.64 years). All 5 SOD children with neurosecretory GH dysfunction had small anterior pituitary, two had posterior pituitary absence, and one had pituitary stalk interruption syndrome.

4) RESPONSE TO rhGH (TABLE 3 AND FIGURE 1)

- Despite being started on lower rhGH doses (Table 3), SOD patients had similar GV and IGF1 SDS after one and two years of treatment *(data not shown)* and similar delta between mid-parental height and height at the onset of puberty (Table 3), as compared with MPHD.

TABLE 3 (PATIENTS WITH GHD)	SOD (n:122)	MPHD (n:51)	p
GH starting dose (µg/Kg/day) mean±SD (range)	25.61 ± 7.61 (10.00-44.44)	29.12 ± 9.29 (8.10-51.30)	0.012
GH dose at last appointment (µg/kg/day) mean±SD (range)	24.56 ± 11.22 (5.00-60.90)	26.26 ± 9.62 (7.90-58.10)	ns
Height at onset of puberty (SDS) mean±SD (range)	-0.54 ± 1.61 (-3.51-3.73) *(n:44)*	-0.06 ± 1.77 (-2.39-3.95) *(n:11)*	ns
Delta mid-parental height – height at onset of puberty (SDS) mean±SD (range)	0.55 ± 1.67 (-2.84-3.67) *(n:39)*	0.13 ± 1.80 (-3.78-2.29) *(n:9)*	ns

FIGURE 1 Correlation between the starting rhGH dose and GV SDS after 2 years of treatment in SOD and MPHD



- In MPHD only, there was a direct correlation between the starting rhGH dose and GV SDS after 2 years of treatment (Figure 1).

5) FINAL HEIGHT DATA IN SOD AND MPHD TREATED FOR GH DEFICIENCY (TABLE 4)

- Although not reaching statistical significance due to the small numbers, the final height SDS was lower in MPHD compared to SOD, whilst the delta between mid-parental height and final height was similar between groups.

TABLE 4 (PATIENTS WITH GHD ACHIEVING THE FINAL HEIGHT)	SOD (n:18)	MPHD (n:6)	p
Age at GHD diagnosis (years) mean±SD (range)	6.03 ± 3.82 (0.88-14.36)	4.78 ± 0.92 (3.50-6.09)	ns
GH starting dose (µg/Kg/day) mean±SD (range)	27.84 ± 8.26 (16.60-43.30)	38.42 ± 11.18 (31.25-51.30)	ns
GH dose at last appointment (µg/Kg/day) mean±SD (range)	18.79 ± 10.16 (5.00-35.78)	20.81 ± 9.06 (8.80-27.70)	ns
Final height (SDS) mean±SD (range)	-0.82 ± 1.66 (-3.55-1.18)	-1.73 ± 1.80 (-3.40-1.33)	ns
Delta Mid-parental height - Final height (SDS) mean±SD (range)	0.77 ± 1.90 (-3.03-3.76)	1.12 ± 1.74 (-1.28-2.95)	ns

CONCLUSIONS

Although GHD is the most frequent hormone deficiency in children with SOD and MPHD, it may not always be present at diagnosis. When compared with MPHD, SOD patients with GHD display similar growth responses and final height outcomes, despite the use of lower GH doses. In SOD with structural H-P abnormalities and normal GH responses to provocation, but with low growth rates and growth factor concentrations, an abnormality of the GH secretory pattern should be considered.

Disclosure statement: the authors have nothing to declare