Pituitary Stalk Interruption: A sequential manner to gain pituitary hormone deficiencies with a still unknown molecular basis

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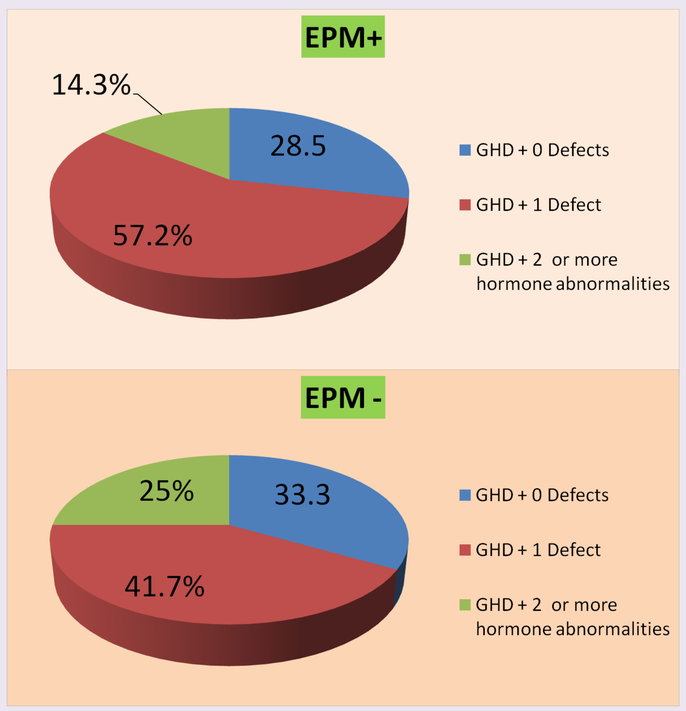
Background: Pituitary stalk interruption syndrome (PSIS) is characterized by the absence of the pituitary stalk, pituitary hypoplasia and an ectopic posterior pituitary. This anatomical abnormality can be associated with other midline defects and variable endocrine disorders, ranging from isolated growth hormone deficiency (IGHD) to multiple hormone deficiency. Although the exact etiopathogenesis of PSIS is still poorly understood, there is evidence of antenatal malformation or acquired origin due to perinatal trauma and/or hypoxic-ischemic encephalopathy.

Objective: We aimed to retrospectively analyze the clinical, auxological, biochemical and radiological findings in Spanish patients with PSIS.

Material and methods: We retrospectively studied 27 patients with PSIS according to the results of MRI. We studied the perinatal characteristics (gestational age, delivery, neonatal hypoxemia and associated malformations). Auxological data (growth velocity, height, weight, BMI and bone age) and the evolution of endocrine parameter (the percentage of pituitary hormone deficits and the age of onset thereof), before the initiation of GH therapy and after 1, 2 and 3 years of treatment were analyzed. Genomic DNA was screened for HESX1, PROP1, POU1F1, LHX3 and LHX4 mutations. Statistical analysis was performed with the statistical package SPPS 20. A paired Student's T test was used to compare growth velocity in the 1st and 3rd year of growth. A "p" of <0.01 was considered significant. We compared the differences in hormonal deficits between 2 groups of patients with PSIS and extra-pituitary malformations associated or not and differences were considered significant at p <0.05.

FIGURE 1. COMPARISON BETWEEN HORMONE DEFICIENCY GROUP WITH EXTRA-PITUITARY MALFORMATIONS (EPM+) GROUPS AND WITHOUT MALFORMATIONS (EPM -).



The EPM + group comprises 14 patients and the EPM – comprises 12 patients. GHD + 1 hormone abnormality was significantly more common in the EPMC group than in the EPMK group (57.2% vs 41.7%; P = 0.035); Although we found no significant differences when there are 2 or more hormonal deficits associated with GHD (71.5% vs 66.7% p = 0.06).

Patients & Results: Of 27 patients, 7 were female and 20 male. The mean age at diagnosis was 3.98 ± 3.47 SDS. Perinatal features: Six patients (23%) had intrauterine growth restriction (most symmetric), 38.5% were delivered by Cesarean section and 46.2% suffered dystocia. Associated malformations (microphallus, cryptorchidism and midline abnormalitiies) were present in 57.7% of the patients. Auxological results at diagnosis and during the first three years of follow-up are shown in Table 1. Age at diagnosis for GH, TSH, ACTH, FSH/LH deficiency and hyperprolactinemia was 3.9 years ± 3.5 SDS (range: 0.05-11.64), 3.7 ± 4.6, 4.1 ± 5.4, 12.3 ± 5.1 and 3.4 ± 4.8, respectively. Among these, 18.5% had isolated GH deficiency, 51.9% had combined pituitary hormone deficiencies, 25.9% had three, and 4.9% had four (Figure 1). rGH treatment was started at 4.1 ± 3.6 yrs. Mean height before rGH therapy was -3.2 ± 1.4 SDS. Mean IGF-I and growth velocity before therapy, during the first, second and third year are shown in Figure 2. Adult height was available for eleven patients (42.3%), seven (63.6%) reaching or surpassing target height. No molecular abnormalities were found in the genes analyzed.

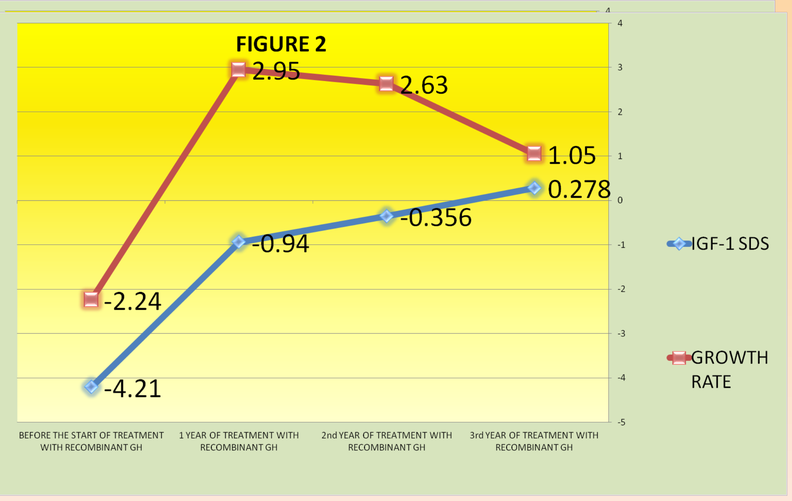


Table 1: Auxological results at diagnosis and after starting rGH.

The auxological data at diagnosis and after treatment with GH, expressed as mean ± SDS for age and sex, are shown. The mean age at onset of treatment table was 4.1 ± 3.6 years.

	Diagnosis	1st year of rGH treatment	2nd year of treatment with rGH	3rd year of treatment with rGH
Height (SDS)	-3.2±1.4	-2.36 ±1.35	-1.44 ±1.02	-1.16±1.17
BMI (SDS)	-0.15±0.99	-0.45±0.84	-0.24±0.76	-0.07±0.86
Growth velocity (SDS)	-2.24±1.33	2.95 ±3.09	2.63±2.11	1.05±1.17
Δ CA-BA (SDS)	2.68±1.1	2.44±1.32	1.92±1.1	1.62±1
Δ TH-H (SDS)	2.16 ±2.23	1.48±1.47	0.61±1.37	0,52±1,50
CA: chronological age. BA: Bone age (Greulich-Pyle method) H: height, TH target height				

Conclusions: Children with PSIS develop pituitary hormone deficiencies in a sequential manner, starting with GH deficiency. Good response to rGH therapy is seen with the highest growth velocity observed during the first year of treatment.