

CONGENITAL HYPOPITUITARISM:

Genotypic-phenotypic-neuroradiological correlation

G. Pozzobon, C. Partenope, C.M. Damia, D. Gallo, M. Lezzi, S. Osimani, G. Weber
Pediatric Department, San Raffaele Hospital, Milan, Italy

Background

Congenital hypopituitarism is a rare cause of pituitary insufficiency, reported with an incidence of 12-42 new cases per million per year and a prevalence of 300 to 455 cases per million. The aetiology remains largely unclear: the most frequently correlated genetic abnormalities are those involving transcription factors implicated in pituitary organogenesis, such as HESX1, PROP1, POU1F1, LHX3, LHX4, PITX2, OTX2, GLI2, SOX2 and SOX3. The phenotype and neuroradiological findings associated with the underlying genotype may be highly variable (from an isolated hypopituitarism to more complex conditions such as septo-optic dysplasia and holoprosencephaly).

Objectives

- 1) Retrospective analysis of a population of pediatric patients with hypopituitarism referred to our center in clinical, diagnostic and therapeutic terms;
- 2) assessment of the phenotypic characteristics in order to highlight common features that, along with other clinical findings, may suggest a diagnosis, a most likely genetic mutation and possible genotypic, phenotypic and neuroradiological correlates;
- 3) evaluation of the therapeutic response to growth hormone replacement.

Methods

Clinical, neuroradiological (brain MRI) and molecular data were collected in 31 patients (M/F=15/16) with congenital hypopituitarism, 15 with neonatal diagnosis and 16 with delayed diagnosis, born from 1989 to 2014.

References

1. K. S. Alatzoglou and M. T. Dattani, "Genetic forms of hypopituitarism and their manifestation in the neonatal period.," *Early Hum. Dev.*, vol. 85, no. 11, pp. 705–12, Nov. 2009.
2. D. Kelberman and M. T. Dattani, "The role of transcription factors implicated in anterior pituitary development in the aetiology of congenital hypopituitarism.," *Ann. Med.*, vol. 38, no. 8, pp. 560–77, Jan. 2006.
3. A. Mehta, P. C. et al., "Congenital hypopituitarism: clinical, molecular and neuroradiological correlates," *Clin. Endocrinol. (Oxf)*, vol. 71, no. 3, pp. 376–82, Sep. 2009.

Results

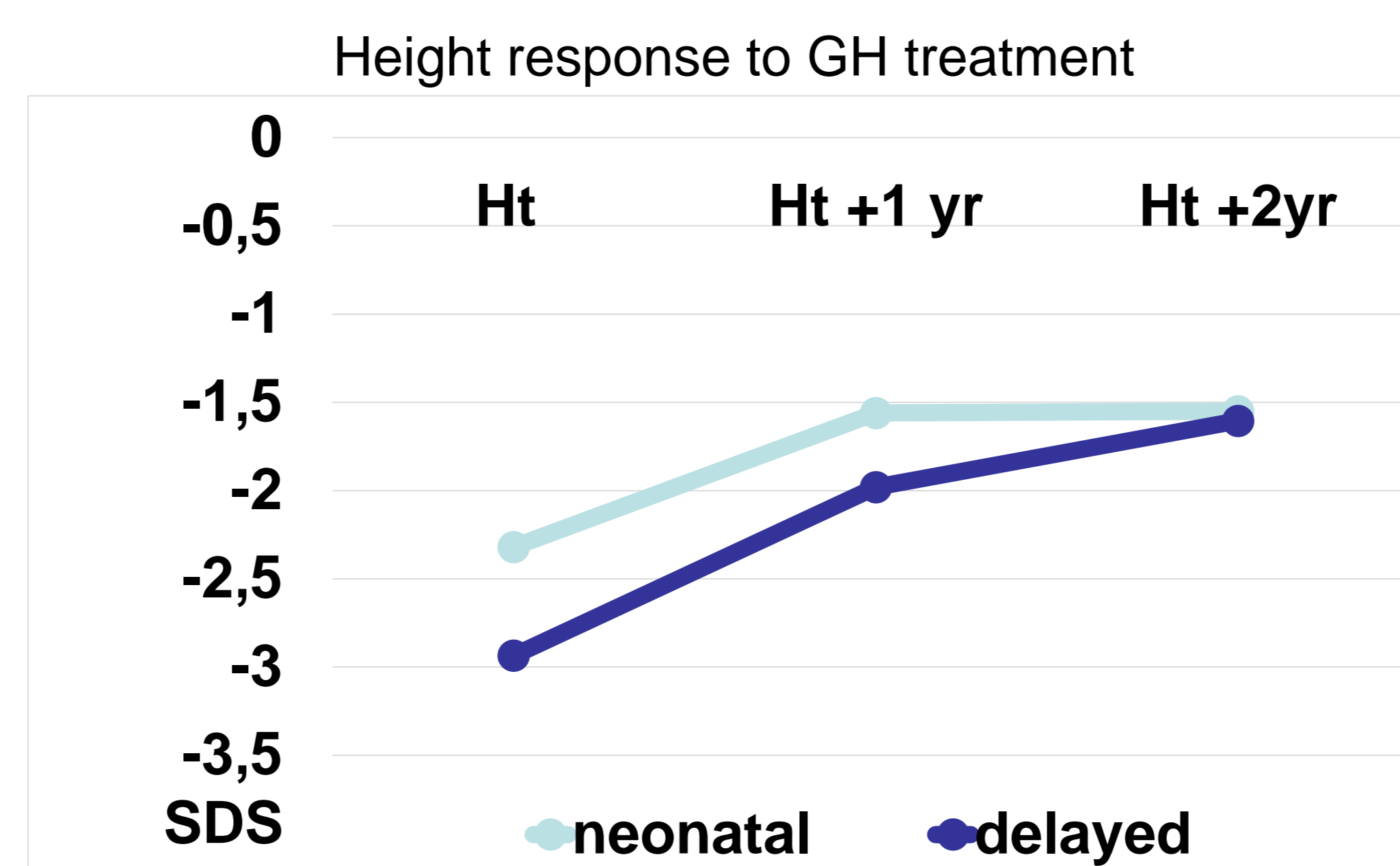
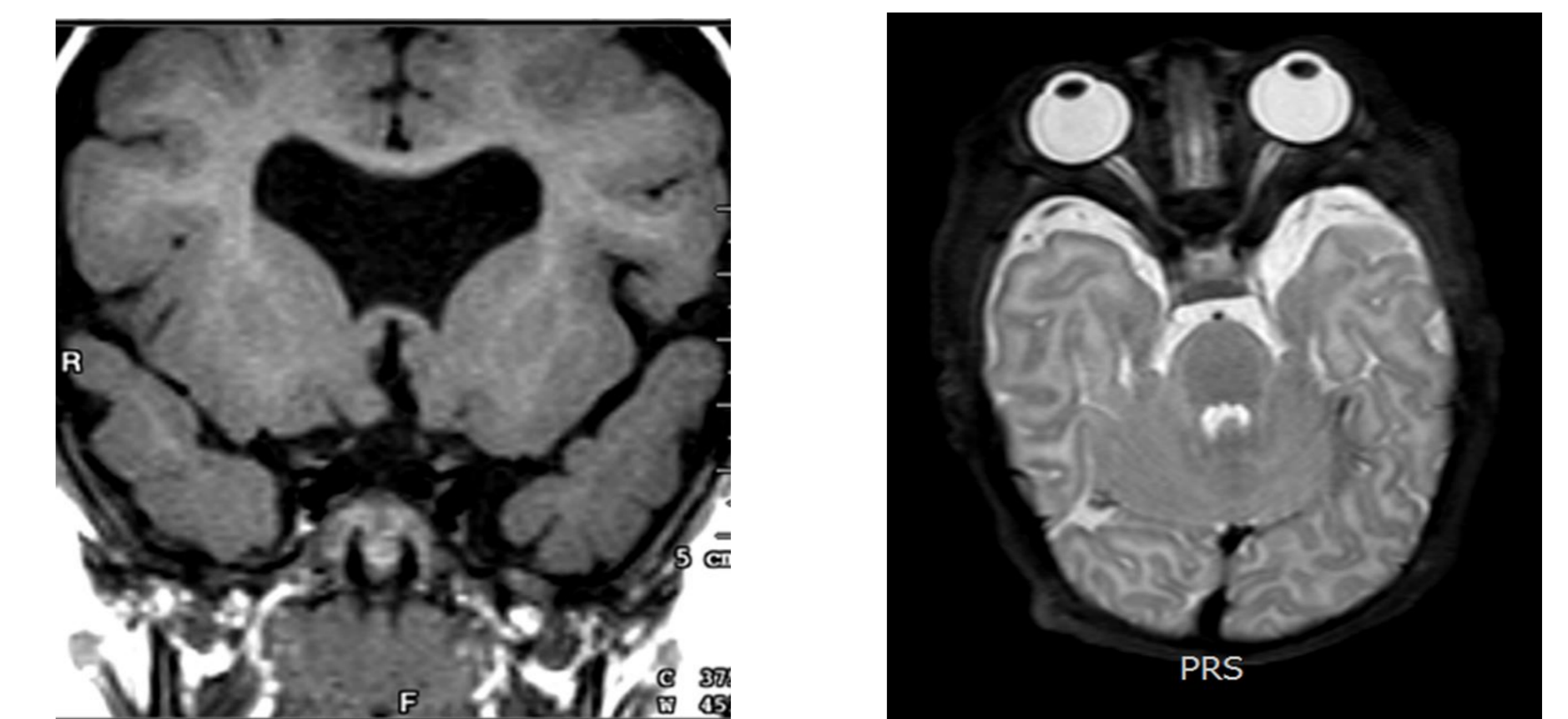
	NEONATAL DIAGNOSIS (48%)	DELAYED DIAGNOSIS (52%)
Median age at diagnosis	0.1 years	3.16 years
Hormones deficiency	GH+TSH+ACTH 97% TSH+GH 3%	GH+TSH+ACTH 90% GH+ACTH 7% TSH+GH 3%
Median cortisol levels (n.v. 50-260 ng/mL)	10 ng/mL	47.5 ng/mL (p <0.0001)
Median fT4 levels (n.v. 0,9-1,9 ng/dL)	0,48 ng/dL	0,7 ng/dL

Peculiar phenotypic traits	%
Depressed nasal bridge	26%
Prominent forehead	23%
Low-set ear	23%
Cleft lip and palate	9%
Polydactyly	9%



SMMCI – Solitary median maxillary central incisor syndrome [Parental consent acquired]

Brain MRI	%
Anterior pituitary hypo-aplasia	84%
Pituitary stalk hypoplasia / interruption / absence	77%
Ectopic neurohypophysis	74%
Septo-optic dysplasia	22%
Midline abnormalities	9%
Normal	3%



Response to GH replacement (mean dose 0.21 mg/kg/wk)	
NEONATAL DIAGNOSIS	DELAYED DIAGNOSIS
ΔHt after 2 years : +1.16 SDS	ΔHt after 2 years: +1.79 SDS
ΔHt final height: +2.61 SDS	ΔHt final height: +3.35 SDS

Genetic analysis showed correlated mutations only in 19% of cases (4 patients: mutation in HESX1, microdeletion in PROP1, mutation in GLI2, deletion 1q24.3q31.1 containing LHX4).

Conclusions

- The clinical suspicion should be placed at birth in those children with characteristic signs and symptoms and/or phenotypic traits..
- MRI evaluation is fundamental in order to predict the endocrinological phenotype and the underlying genotype.
- We reported a very good response to GH treatment, especially in those with delayed diagnosis.
- The evidence of common traits in these patients make the hypothesis of a common genetic alteration more likely. However, the low rate of observed genetic defects suggests that other genes still remain to be identified, but also that other factors (such as environmental) could contribute to the pathogenesis of this complex condition.