

GROWTH PATTERN, RESPONSE TO GH TREATMENT AND THE EFFECTS OF PUBERTAL SPURT ON FINAL HEIGHT IN PATIENTS AFFECTED BY RASOPATHIES

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OBJECTIVES

Reduced growth is a common feature in RASopathies. Several studies generated data on growth, final height (FH), and height velocity (HV) after growth hormone (GH) treatment. However, these studies refer to heterogeneous cohorts. Poor data are available about pubertal spurt and the effect on FH in these patients.

We analyzed growth trend and body proportions in 88 patients affected by RASopathies with molecularly confirmed diagnosis, pubertal pattern in 44 of them and FH reached in 33, including 16 treated with GH therapy for proven GH deficiency.

METHODS

The study cohort includes patients with clinical features fulfilling criteria for RASopathies. The *clinical diagnosis was molecularly confirmed*. Molecular analyses were performed by Sanger sequencing the entire coding sequences of the PTPN11, SOS1, KRAS, NRAS, HRAS, RIT1, SHOC2, SPRED1, BRAF, RAF1, MAP2K1, and MAP2K2, on the basis of the clinical diagnosis.

Anthropometric measurements were compared with the standard growth curves for the general Italian population and for NS and were expressed as SD scores. Growth velocity SDS were calculated on Tanner charts.

Patients were screened for thyroid function and markers of malabsorption, such as celiac disease. Patients with H lower than -3 SDS, or H <-2 SDS and GV <-1 SDS, or severe reduction in GV (lower than -2 SDS/year) were tested for GH deficiency by pharmacological stimulation.

Table 1 Biometrical and clinical features at the main time-points for GH-treated patients with RASopathies

	Beginning of therapy (n=33)	After first year (n=26)	At Final Height (n=16)
Age (yrs)	6.9 ± 3.6	7.7 ± 3.5	18.4 ± 2.2
Height (SDS Cacciari)	-2.8 ± 0.8	-2.3 ± 0.7	-2.2 ± 0.7
Height (SDS Ranke)	-0.7 ± 0.9	-0.3 ± 0.8	-0.03 ± 0.7
Growth Velocity (SDS)	-2.6 ± 1.2	1.9 ± 1.5	
IGF1 (SDS)	-1.9 ± 1.1	-0.1 ± 1.3	-0.2 ± 1.1
BMI (SDS Cacciari)	-0.3 ± 1.3	-0.7 ± 1.2	-0.5 ± 1.2
HOMA-R (SDS)	1.2 ± 0.9	1.2 ± 0.6	1.6 ± 0.9

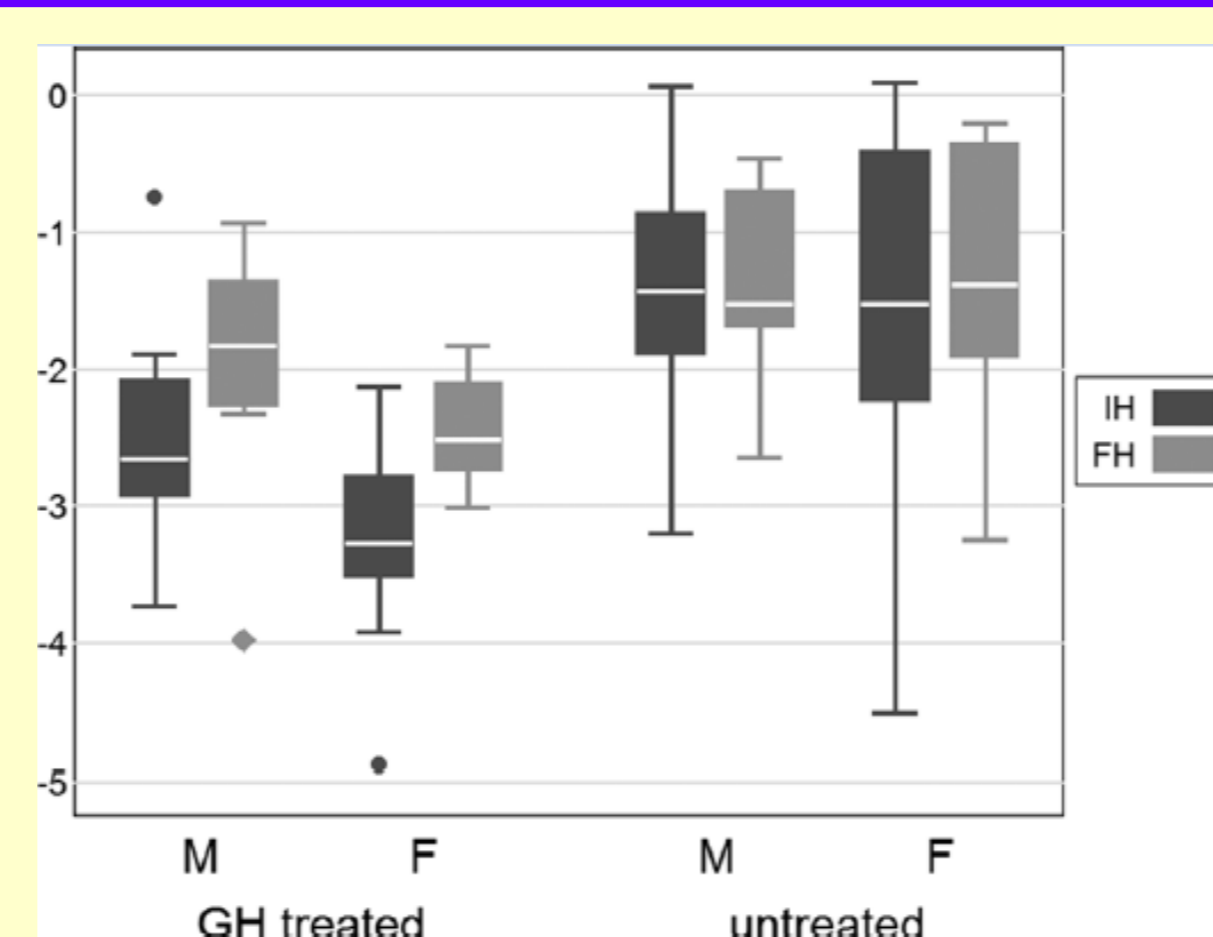


Fig. 1. IH and FH comparison by GH treatment and sex

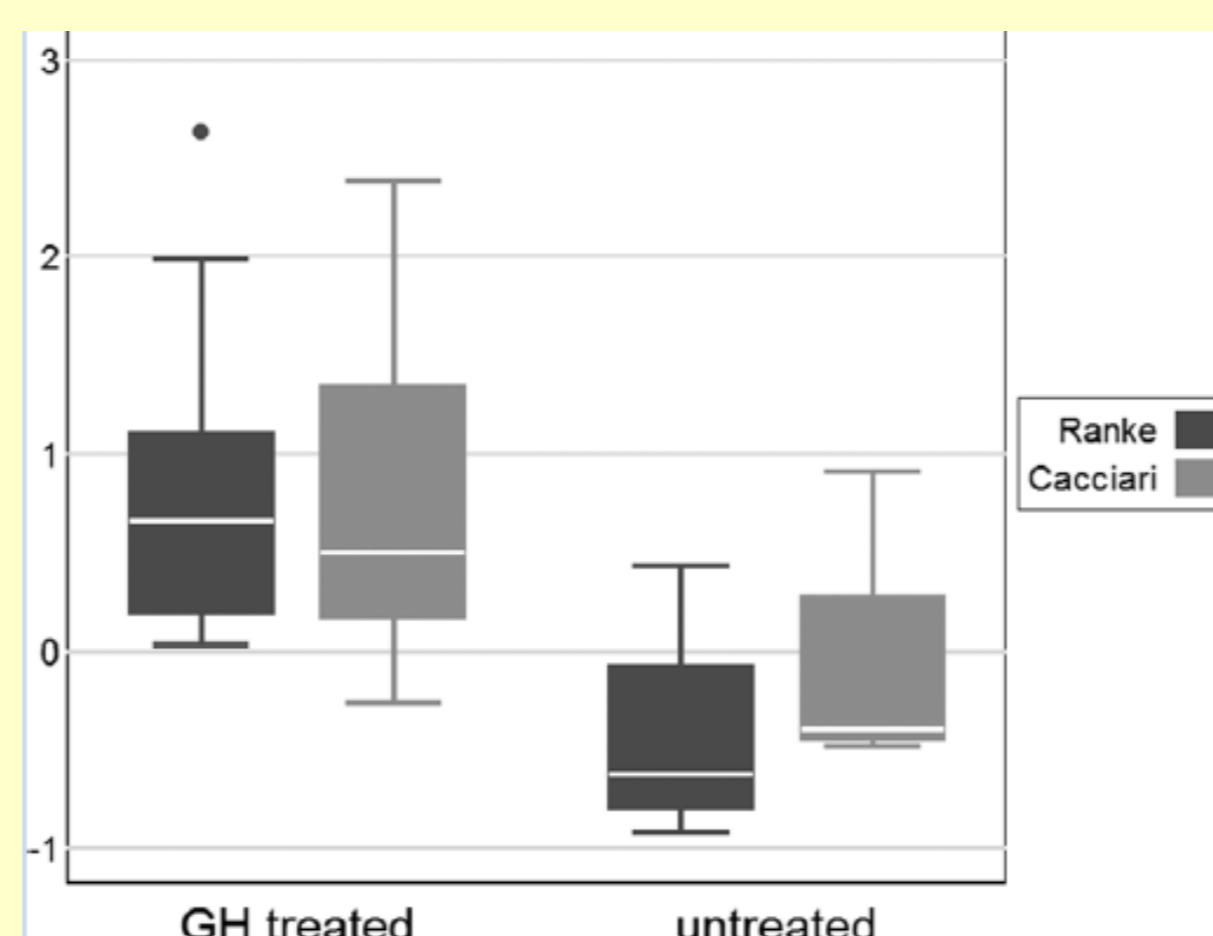


Fig. 2 Height Gain comparison by GH treatment;

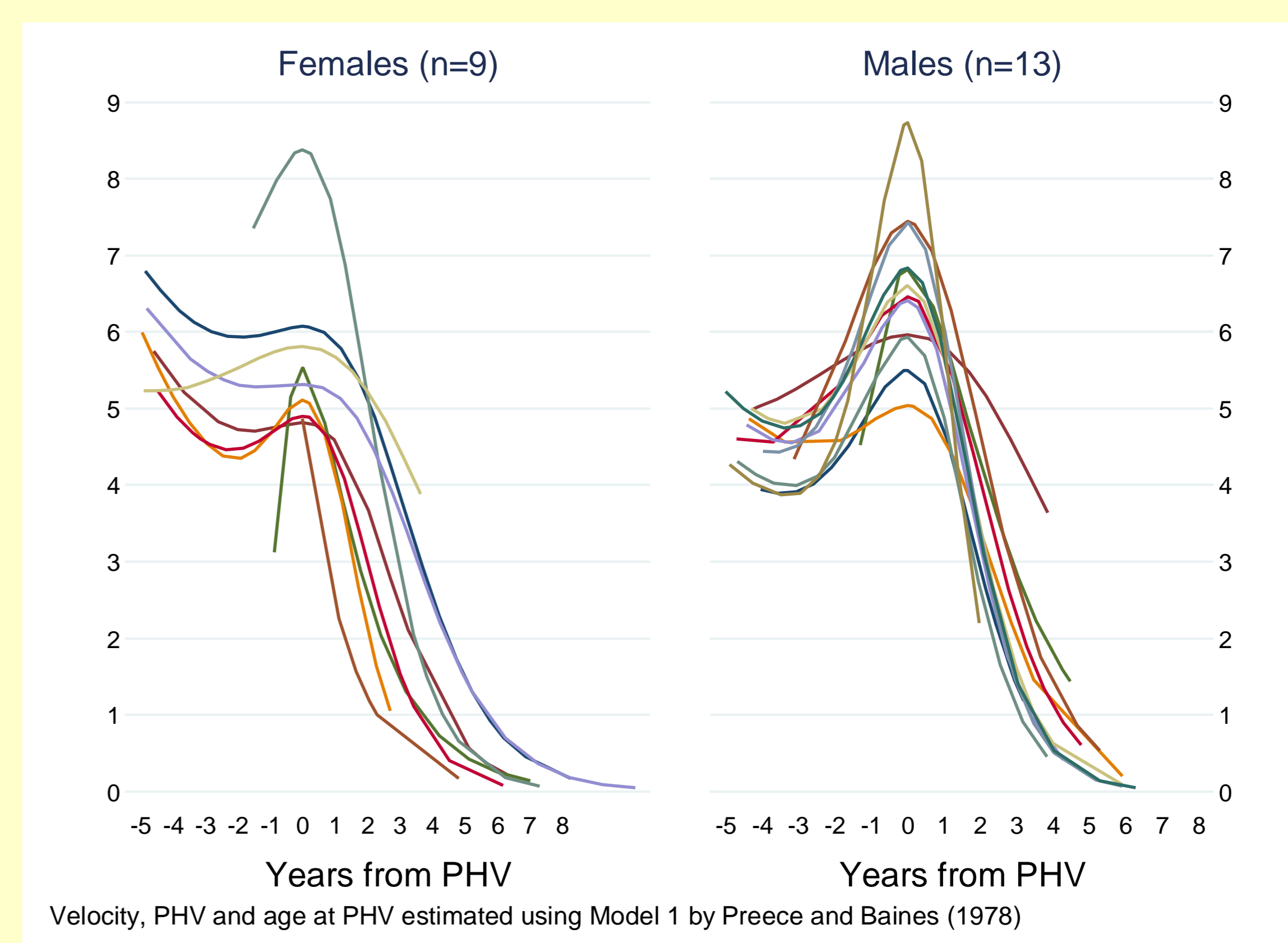


Fig.3 Individuals HV curves for F and M plotted according to their peak height velocity (PHV).

RESULTS

Thirty-three patients showed GH deficiency after pharmacological tests, and were GH-treated for an average period of 6.8±4.8 years.

Before starting therapy, HV was -2.6±1.3 SDS, and mean basal IGF1 levels were -2.0±1.1 SDS.

Long-term GH therapy, starting early during childhood, resulted in a positive height response compared with untreated patients (1.3 SDS in terms of height-gain), normalizing FH for Ranke standards but not for general population and Target Height [Table 1 - Fig.1, Fig2].

First **pubertal clinical signs** were observed at age of 11.8 ±1.9 yrs in female and 12.1±1.3 yrs in males. Pubertal growth showed a lowered peak (6.2±1.5 cm/yrs in female and 6.8 cm/yrs in males), and a delay in onset by about 6 months, compared to the general population. Pubertal spurt length resulted 5.3±1.1 yrs in female and 4.7±0.6 yrs in males [Fig. 3].

The delayed pubertal development and the inadequate pubertal catch-up growth could explain the impaired FH.

CONCLUSIONS

Our patients on GH-therapy benefitted from the pharmacological treatment if started in pre-puberty and given for a long time. Probably, the prepubertal start of GH-treatment could compensate the lack of a pubertal growth spurt. During GH treatment, no significant change in bone age velocity, body proportions, or cardiovascular function was observed.

References

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