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THE IMPACT OF GROWTH HORMONE THERAPY IN NOONAN SYNDROME CHILDREN WITH IDENTIFIED MUTATIONS IN RAS/MAPK PATHWAY

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OBJECTIVES

To evaluate the response to recombinant human GH (rhGH) treatment in NS children with short stature and previously identified mutations in the RAS/MAPK pathway genes.

METHODS

Twenty-three patients with NS (17 males; 19 *PTPN11*, 3 *RAF1* e 1 *SHOC2*) were daily treated with rhGH (mean rhGH dose of 47µg/kg.d). The main outcome measures were 1st year growth velocity, change in height SDS (Noonan syndrome specific), change in IGF-1 levels and adult height SDS.

RESULTS

At the start of rhGH treatment, the mean age was 10.7 ± 3.7 yr, bone age was 8.6 ± 3.2 yr and 18 children were prepubertal. All subjects presented a height SDS < -2 for reference population (H-SDS = -3.4 ± 0.8) and appropriate BMI-SDS. Noonan syndrome specific height SDS (HNS-SDS) was -0.8 ± 0.7. Growth velocity (GV) during the 1st year of therapy was 7.0 ± 2.0 cm/y, an increment of 2.9 ± 3.2 in baseline GV. Height SDS significantly improved after 1 year of rhGH therapy (mean change in HNS-SDS of 0.5 ± 0.4, p<0.001). IGF-1 levels also increases during the first year of therapy (99.7 ± 56 µg/L to 237 ± 104 µg/L, p<0.001). Adult height was achieved in 8 patients (6 *PTPN11*, 1 *RAF1*, 1 *SHOC2*) after 3.5 years of treatment. The total height SDS gain in relation to Noonan syndrome specific growth chart was 1.0 ± 1.3, equivalent of 6 cm. No clear genotype influences on treatment outcomes were observed.

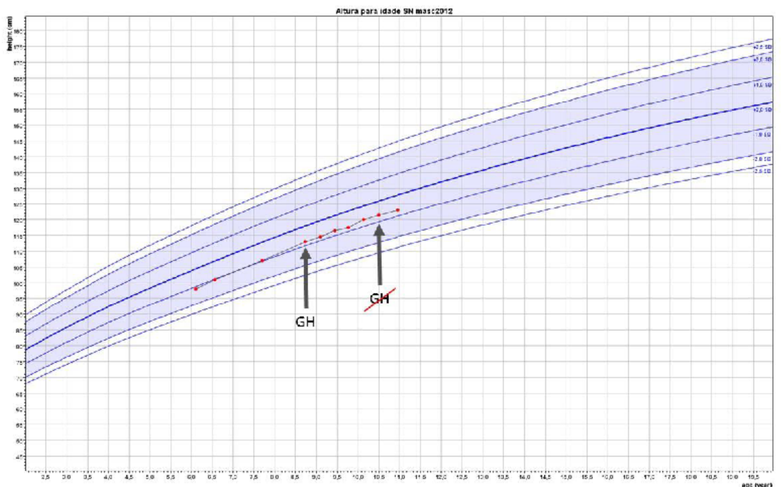

Figure 1: L.E.C.S., 11 year-old boy, *RAF1*-mutation positive. Age at the start was 8.7 years old. rhGH dose was 35 µg/kg.d because of our concerns about mild left ventricular hypertrophic cardiomyopathy. NS specific height SDS increment at the first year was 0.0. Treatment was discontinued after 1.7 year. Total gain in height SDS was 0.1 at the end of rhGH treatment.

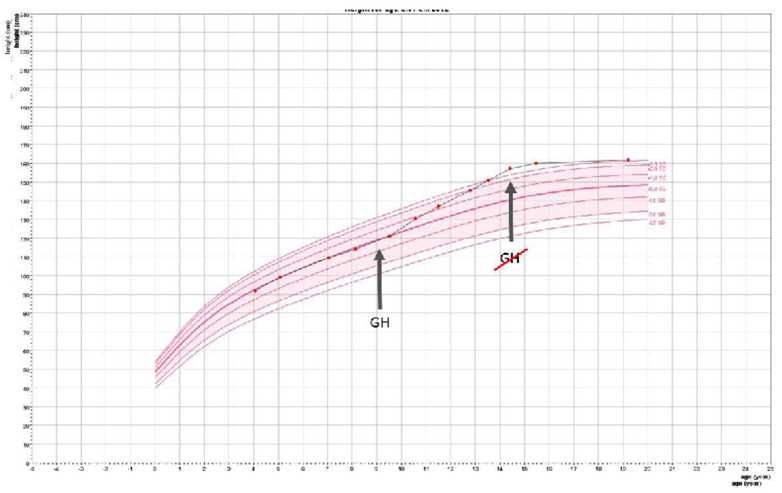

Figure 2: P.S.F., 24 year-old female, *PTPN11*-mutation positive. Age at the start was 9.5 years old. rhGH dose was 50 µg/kg.d. NS specific height SDS increment at the first year was 0.8. Age at start of puberty was 14.9 years. Treatment was discontinued after 4.9 years. Total gain in height SDS was 3.3 at the end of rhGH treatment.

	At start	1th year	At the end	Adult Height
CA (years)	10.7 ± 3.7	11.7 ± 3.8	16.3 ± 1.4	20.8 ± 0.4
BA (years)	8.6 ± 3.2	10.7 ± 2.7	13.9 ± 2.4	N.A.
Growth velocity (cm/y)	4.1 ± 1.2	7.0 ± 2.0	4.2 ± 2.2	N.A.
Height SDS (CDC)	-3.4 ± 0.8	-2.9 ± 1.1	-2.6 ± 0.8	-2.4 ± 1.3
Height SDS (NS specific)	-0.8 ± 0.7	-0.3 ± 0.9	0.3 ± 1.0	0.1 ± 1.5
ΔHeight-SDS	N.A.	0.5 ± 0.4	1.0 ± 0.9	1.0 ± 1.3

CA: chronological age; BA: bone age

CONCLUSIONS

The use of rhGH to promote linear growth in short children with NS is still controversial. The increment of height SDS in relation to population matched Noonan syndrome specific growth chart supports a benefit of this therapy to improve the adult height.

REFERENCES

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