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Evaluation of puberty in patients with Noonan syndrome and mutations in the RAS/MAPK genes.

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INTRODUCTION

Noonan syndrome (NS) is a rare genetic disease characterized by facial dysmorphism, short stature, heart defects, chest deformities, and variable developmental delay/learning disabilities. Almost 80% of patients have a mutation in the genes encoding components of the RAS/MAPK pathway.

Puberty was described as delayed in NS patients, but only a few studies have focused on this subject and genotype-phenotype correlations so far (1-3).

In order to address this issue, we evaluated puberty in patients clinically and molecularly diagnosed with NS.

METHODS

This study was a retrospective analysis of 84 NS patients (39 females) with mutations in the RAS/MAPK pathway genes (55 *PTPN11*, 5 *RAF1*, 5 *SOS1/2*, 4 *BRAF*, 4 *LZTR1*, 3 *RIT1*, 3 *KRAS*, 2 *SHOC2*, 2 *MAP2K1/2*, 1 *NRAS*).

Genotype-phenotype correlations were analyzed between patients with *PTPN11* mutations (n=55) and patients with mutations in other NS related genes (n=29).

RESULTS

Age at puberty onset and menarche in girls was 11.9±2.0 years and 14.7±1.9 years (n=20), respectively. Nine out of 39 girls (23%) had delayed puberty. Age at puberty onset was 12.9±2.1 years in boys, and 16 out of 45 boys had delayed puberty (36%). Frequency of delayed puberty was similar in boys and girls.

Table 1 shows the clinical characteristics of 59 patients with normal puberty and 25 patients with delayed puberty. Figure 1 shows height and BMI SDS in patients with normal and delayed puberty.

Height-SDS ($p<0.001$) and BMI-SDS ($p=0.049$) can negatively predict age at puberty onset in a multiple linear regression model ($R2=0.40$). No difference was observed concerning the frequency of delayed puberty, puberty onset, age at menarche, height-SDS, and BMI-SDS between patients with or without mutations in the PTPN11 gene.

Table 1: Clinical characteristics of 84 NS patients with mutations in the RAS/MAPK pathway regarding age at puberty onset.

	Normal Puberty	Delayed Puberty	p
N (M:F)	59 (29:30)	25 (16:9)	
Chronological Age (yr)	11.3 ± 1.3	15.0 ± 1.0	<0.001
Height SDS	-2.0 ± 1.0	-3.8 ± 0.9	<0.001
BMI SDS	-0.6 ± 1.1	-1.7 ± 1.3	<0.001
% BMI SDS < -2	10	20	N.S.
Age at menarche (yr)	14 ± 1.6	16.6 ± 1.4	0.002
% *PTPN11*+	68	60	N.S.

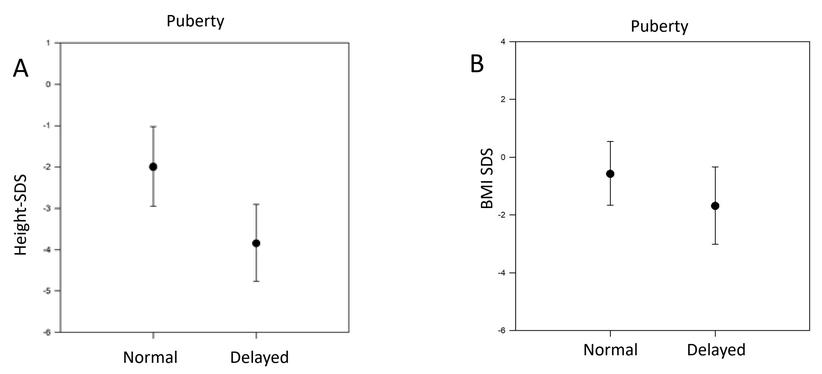

Figure 1: Height SDS (A) and BMI SDS (B) in patients with normal and delayed puberty .

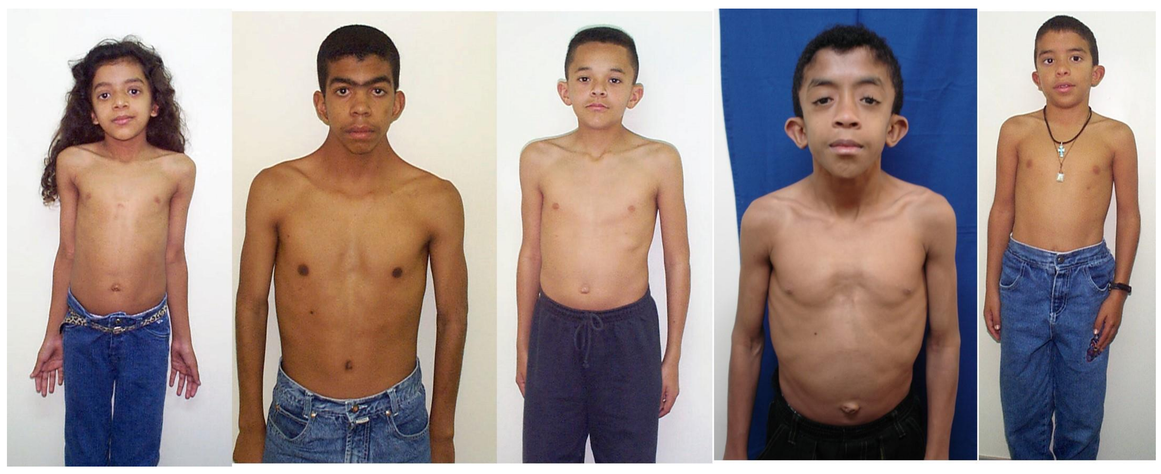

Figure 2: Five patients with *PTPN11* mutations and a lean phenotype.

CONCLUSIONS

Delayed puberty was observed in 30% of NS patients. Patients with delayed puberty were shorter and thinner than patients with normal puberty resembling constitutional delay of growth and puberty (Figure 2). Prospective studies are required to further investigate the link between metabolism and puberty in NS patients.

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