

Characterization of puberty development in a large cohort of patients with Noonan syndrome with molecular diagnosis

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INTRODUCTION

Noonan Syndrome (NS) is a relatively frequent multisystemic genetic disorder, characterized by typical facial abnormalities, congenital heart disease and short stature [1]. Despite the description of pubertal delay in both sexes, its pathophysiological explanation is still uncertain. The present study aims at characterizing pubertal development in NS and identifying predictors of pubertal delay.

METHODS

We analyzed 116 individuals with molecular diagnosis of NS and puberty evaluation. We characterized delayed puberty as pubertal onset after 12 years in girls and 13.5 years in boys, according to parameters of the Brazilian population [2,3]. To investigate pubertal delay predictors, we divided the sample into two groups according to the presence of normal or delayed puberty and correlated them with clinical characteristics.

RESULTS

The mean age at puberty for girls was 11.9 ± 1.9 years and for boys, 12.5 ± 1.7 years, significantly later than the Brazilian population ($p = 0.025$; $p < 0.001$) (Figures 1 and 2). We identified pubertal delay in 27 (49.1%) girls and 17 (27.9%) boys ($p = 0.031$). Height gain from onset of puberty to adult height was lower in children with pubertal delay. The other differences for both sexes between the pubertal delay and normal puberty groups are described in table 1.

CONCLUSION

Pubertal delay is characteristically found in children with NS, more frequently in females. The low BMI of girls with NS could modulate the age of puberty, just as the increase in overweight/obesity in the general population has shown an effect on reducing the age of onset of puberty for girls [4].

REFERENCE S: [1] Roberts AE, et al. Noonan syndrome. The Lancet 2013;381:333–42. [2] Feibelman TCM, et al. Puberty in a sample of Brazilian schoolgirls: Timing and anthropometric characteristics. Archives of Endocrinology and Metabolism 2015;59:105–11. [3] Feibelman TCM, et al. Puberty in a Sample of Brazilian School boys: Onset and Anthropometric Characteristics. Revista Paulista de Pediatria : Orgao Oficial Da Sociedade de Pediatria de Sao Paulo 2021;39:e2019109. [4] Biro FM, Kiess W. Contemporary trends in onset and completion of puberty, gain in height and adiposity. Endocrine Development 2016;29:122–33.

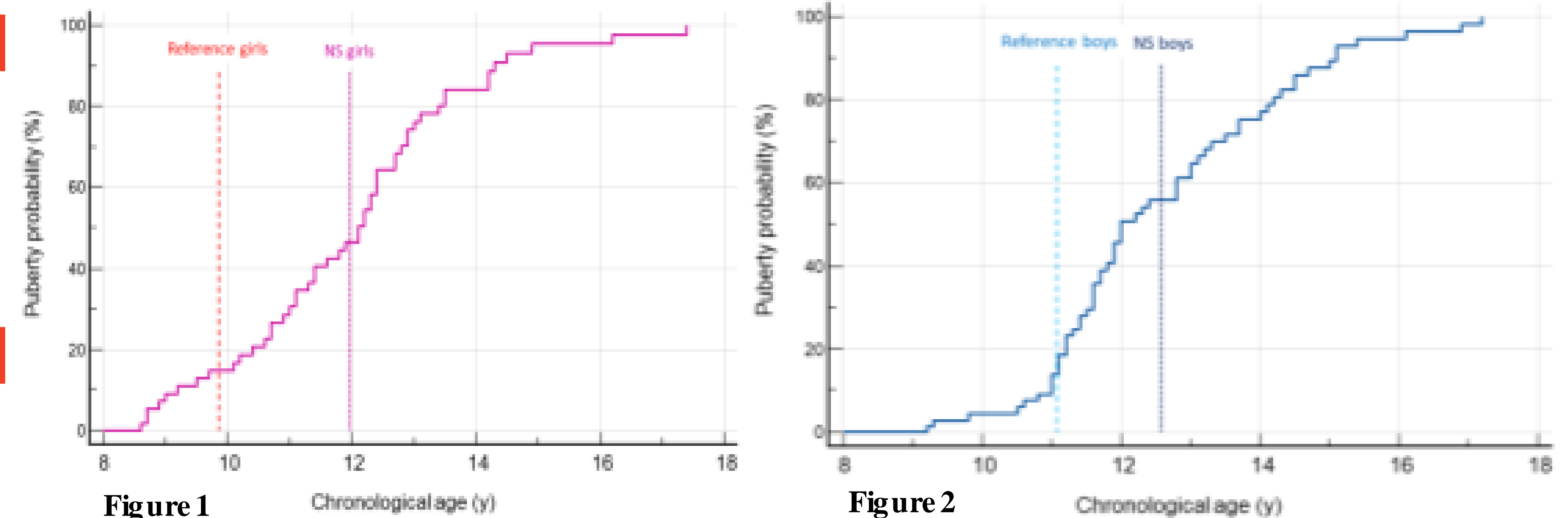


Figure 1

Figure 2

	Girls			Boys		
	Normal Puberty (n = 28)	Delayed Puberty (n = 27)	p	Normal Puberty (n = 44)	Delayed Puberty (n = 17)	p
PTPN11	19 (67,9)	15 (55,6)	0,509	34 (77,3)	14 (82,4)	1,000
Cryptorchidism	-	-	-	27 (61,4)	10 (58,8)	0,912
Heart disease	18 (66,7)	22 (84,6)	0,231	34 (77,3)	13 (76,5)	1,000
Heart failure	1 (4,5)	3 (12,5)	0,609	3 (8,1)	1 (6,7)	1,000
rhGH use	11 (39,3)	9 (33,3)	0,858	18 (40,9)	11 (64,7)	0,167
Target height SDS	$-0,8 \pm 1,2$	$-0,7 \pm 1,1$	0,681	$-0,7 \pm 0,9$	$-1,1 \pm 0,8$	0,096
Age at puberty onset (y)	$10,4 \pm 1,0$	$13,3 \pm 1,3$	<0,001	$11,6 \pm 0,9$	$14,8 \pm 1,1$	<0,001
Bone age (y)	$9,7 \pm 1,5$	$11,1 \pm 1,3$	0,012	$10,1 \pm 1,7$	$11,9 \pm 1,2$	0,002
Height SDS	$-2,0 \pm 0,7$	$-2,9 \pm 1,2$	0,001	$-2,0 \pm 0,9$	$-3,6 \pm 1,3$	<0,001
BMI SDS	$-0,5 \pm 1,2$	$-1,3 \pm 1,4$	0,029	$-0,5 \pm 1,0$	$-1,9 \pm 1,8$	<0,001
IGF1 SDS	$-0,2 \pm 1,0$	$-1,7 \pm 1,0$	<0,001	$-0,5 \pm 1,2$	$-2,4 \pm 0,9$	<0,001
Age at adult height (y)	$17,1 \pm 1,4$	$19,8 \pm 3,7$	0,046	$20,0 \pm 3,2$	$21,5 \pm 3,5$	0,234
Adult height SDS	$-2,6 \pm 0,5$	$-1,8 \pm 0,9$	0,029	$-1,9 \pm 1,0$	$-2,5 \pm 1,0$	0,081
G5-G2 age (y)	$4,5 \pm 2,4$	$3,2 \pm 1,9$	0,247	$3,6 \pm 1,3$	$4,0 \pm 2,3$	0,572
G5-G2 height (cm)	$20,3 \pm 5,9$	$13,8 \pm 6,6$	0,021	$29,4 \pm 7,1$	$20,6 \pm 5,2$	<0,001

Table 1 - Comparison of clinical characteristics between delayed and normal puberty groups in both sexes