Gonadal function of female patients with Noonan syndrome

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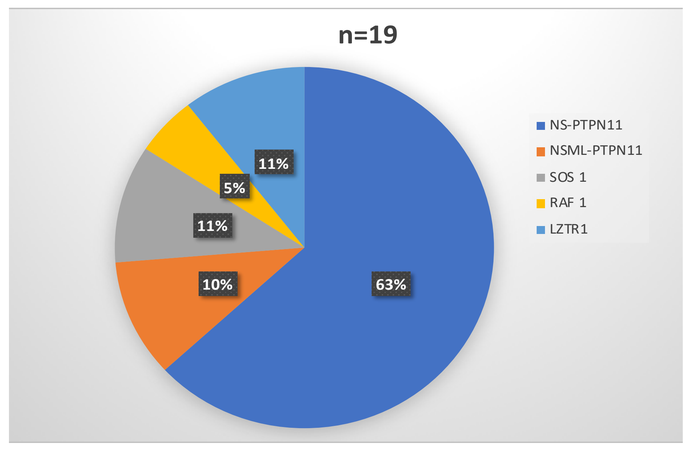
Context: Abnormalities in the hypothalamo-pituitary-gonadal axis have long been reported in Noonan syndrome (NS) but few data are available in particular in female patients.

Objective: The aim of this study was to evaluate the gonadal function of NS females from childhood to adulthood.

Design: We performed a retrospective chart review in female patients with a genetically confirmed diagnosis of NS.

Patients and Methods: Two patient groups were identified. The 'paediatric group' (n = 19) consisted of NS girls/adolescents with available clinical (including Tanner stages and age of first menstruations) and/or hormonal data (including gonadotropins, inhibin B, and anti-Müllerian hormone [AMH]) who were followed at the Children's Hospital, Toulouse, France, between 2008 and 2018. The 'adult group' (n = 99) consisted of women who were referred for molecular testing to the Department of Genetics of Robert-Debré Hospital, Paris, France.



Results:

In the 'paediatric group', 12 (63.2%) children had entered puberty and the age at pubertal onset and at menarche were 12.0 and 14.7 years respectively, corresponding to a delay of $1^{1/5}$ to 2 years compared with the general healthy population. The patterns of secretion as well as the values of serum AMH and inhibin B were normal in NS girls and adolescents, suggesting a normal ovarian function.

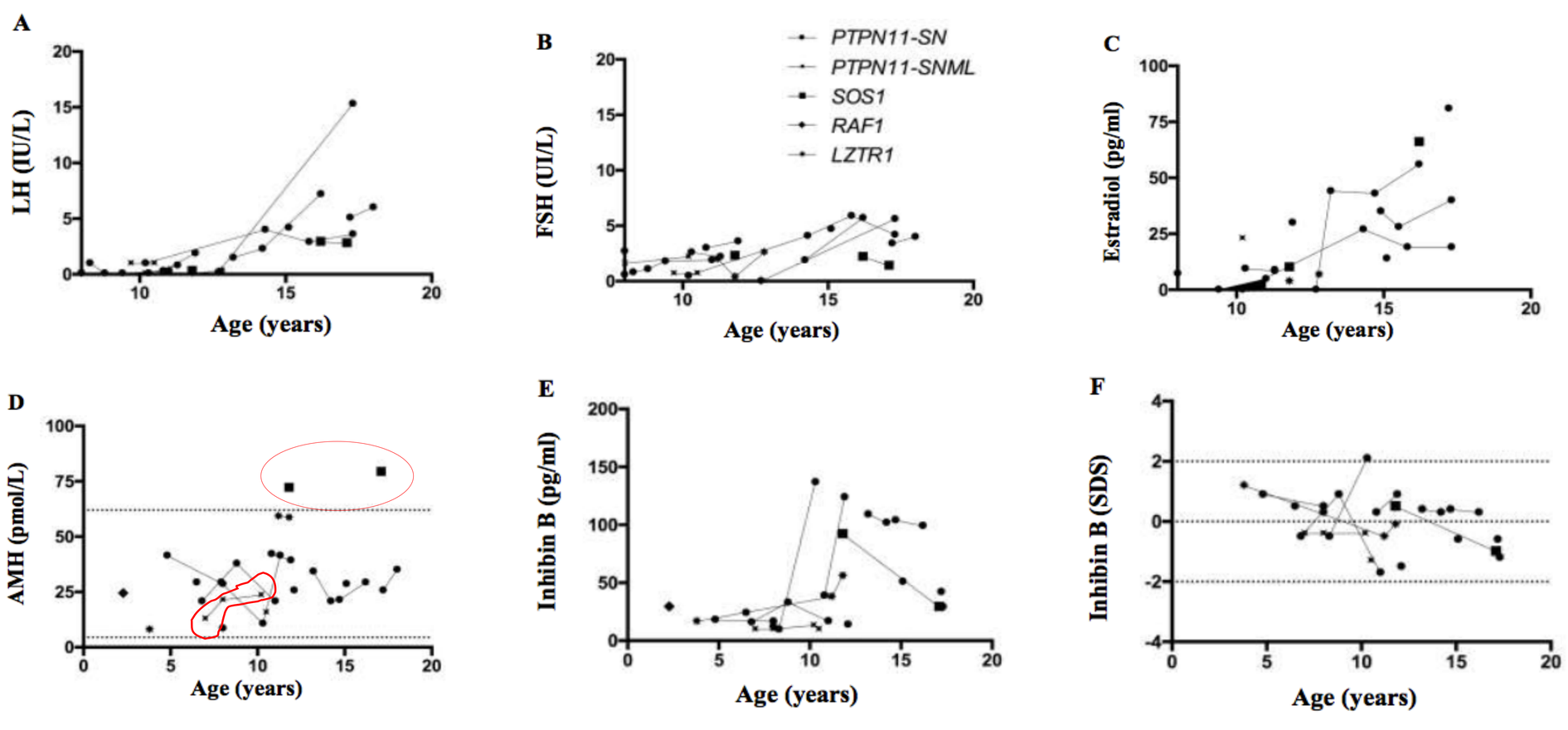


Table 1. Comparison of serum inhibin B levels SDS in NS girls with the normal reference values and according to genotype

	n patients	n measures	Mean (SD)	Median (IQR)	Estimated mean (95% CI)	P*
All patients	17	29	0.0 (0.9)	0.3 (-0.5; 0.5)	0.0 (-0.4; 0.3)	0.94†
Genotype						
NS-PTPN11	11	20	0.1 (0.9)	0.3 (-0.5; 0.7)	0.1 (-0.3; 0.5)	0.55†
NSML-PTPN11	2	4	-0.6 (0.4)	-0.4 (-0.9; -0.4)	-0.6 (-1.1; -0.2)	0.01†
SOS1	2	2	-0.2 (1.0)	-0.2 (-1.0; 0.5)	-0.2 (-1.3; 0.8)	0.66†
LZTR1	2	3	0.2 (0.9)	-0.1 (-0.5; 1.2)	0.2 (-0.8; 1.2)	0.68†
Comparisons *vs NS-PTPN11*						
NSML-PTPN11	-	-	-0.8	-	-0.8 (-1.4; -0.2)	0.01
SOS1	-	-	-0.4	-	-0.4 (-1.5; 0.8)	0.53
LZTR1	-	-	0.1	-	0.1 (-1.0; 1.1)	0.87

* Estimated means, confidence intervals (CI) and p-values were calculated using a linear mixed model for repeated measures with a robust variance estimator.

† Means SDS were compared with those of the general population using the one-sample Student test, assuming an average SDS of 0 in the general population.

In the 'adult group', the mean age of first menstruations available in 30 women was 14.7 years (range: 9.6 – 19.0 years). Sixty-one women (61.6%) had 1 to 4 children and none of the 99 women reported involuntary childlessness nor treatment for infertility.

Conclusions:

NS females display normal albeit delayed onset at puberty and a normal ovarian function.

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