A multicenter study on long-term outcomes in 59 males with 45,X/46,XY mosaicism

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The authors have no conflicts of interest related to the presented data

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Endocrine Disruption of Male Reproduction and Child Health

Background

45,X/46,XY mosaicism is a rare karyotype with a broad phenotypic variation. In patients with a male or predominantly male phenotype, impaired genital development and statural growth have been observed, but little is known about long-term outcomes. Larger multicenter studies are needed.

Objectives

The aim of this study is to investigate long-term outcomes, namely gonadal function, growth and co-morbidities, in a larger group of males with 45,X/46,XY mosaicism.

Method

Using the I-DSD Registry and DSDnet network, all centers with males with 45,X/46,XY mosaicism were invited to participate in this multicenter study. Only post-pubertal patients that had reached near adult height were included. In total, 22 centers were invited, 19 centers responded, and 17 centers supplied data on a total of 59 males. Patients were grouped in two groups ('genital anomalies' and 'other') according to whether they were diagnosed due to genital abnormalities or not. Appropriate statistical tests were applied when comparing the two groups.

Results

In total, 34 males were diagnosed due to genital abnormalities at birth and 25 were diagnosed due to other reasons such as prenatal screening, growth abnormalities, puberty disorders, and infertility, thus making up the 'genital anomalies' and 'other' groups, respectively. A comparison of the two groups can be seen in Table 1. Overall, the external masculinization score (EMS) at time of diagnosis, the rate of spontaneous pubertal onset and testosterone treatment (Tx) differed significantly between the two groups. Furthermore, final heights in cm and height SD scores were significantly different as well although most patients were short. No differences were found in rates of comorbidity or gonadal neoplasia between the groups. Overall, 15.2% had renal malformations and 31.7% had cardiac malformations. 12.1% had gonadal neoplasia.

Conclusion

This is the largest study of long-term outcomes in male patients with 45,X/46,XY mosaicism to date, made possible only by its multicenter design. The karyotype is reflected with varying degrees of severity in phenotype. When comparing patients according to whether they were diagnosed due to genital abnormalities at birth or not, it appears that patients diagnosed at birth have poorer gonadal function. Most patients, nonetheless, enter puberty spontaneously indicative of good Leydig cell function. Furthermore, patients in the 'genital anomalies' group appear to be shorter; however in general the patients do not appear to grow according to genetic potential. The overall prevalence of gonadal neoplasia and comorbidities appears to be relatively high. It is important to note that the study design (retrospective and multicenter) introduces biases to the data and limits the conclusions.

	Diagnosed due to:				p-value
	Genital anomalies		Other		
	Median (range) or yes/no	n	Median (range) or yes/no	n	
Age					
Age at presentation (median, range)	0.00 (0.00 to 4.92)	34	19.50 (0.00 to 49.00)	22	**<0.001***
Age at last evaluation (median, range)	18.79 (13.97 to 70.20)	33	29.33 (13.44 to 58.63)	24	0.078
Genital phenotype					
EMS (median, range)	4.00 (1.00 to 9.50)	23	12 (10 to 12)	17	**<0.001***
Spontaneous pubertal onset (yes/no)	21/10	31	22/2	24	**0.049***
Testosterone treatment (yes/no)	16/15	31	3/15	18	**0.018***
Growth					
Final height (cm) (median, range)	156.85 (143.00 to 169.20)	30	164.40 (141.10 to 187.70)	20	**0.003***
Height SD (median, range)	-3.35 (-5.80 to -1.25)	30	-2.21 (-4.10 to 1.13)	20	**0.004***
Target height SDS – final height SDS (median, range)	-2.49 (-4.18 to -1.22)	23	-2.21 (-3.44 to -0.96)	13	0.296
Growth hormone treatment (yes/no)	13/18	31	4/16	20	0.135
Comorbidity					
Renal malformations (yes/no)	5/26	31	2/20	22	0.686
Cardiac malformations (yes/no)	9/23	32	4/18	22	0.523
Neoplasia					
Gonadal neoplasia[1] (yes/no)	4/19	23	0/14	14	0.276

Table 1: Differences between the genitalia and non-genitalia group in terms of age, genital genital phenotype, growth, comorbidities and gonadal neoplasia. [1] Gonadal neoplasia is defined as germ cell neoplasia in situ and invasive gonadal tumors. *indicates significance by a 0.05-level. *n* indicates total count of individuals with available information.

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GROWTH REPRODUCTION

55ESPE 352--P1
Gonads & DSD
Marie Lindhardt
DOI: 10.3252/pso.eu.55ESPE.2016
Poster presented at: ESPE 2016 PARIS
PosterSessionOnline.com