Long term follow up of patients with 46,XY Partial Gonadal Dysgenesis accordingly gender assignment

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Introduction

46,XY partial gonadal dysgenesis (PGD) patients have a spectrum of atypical genitalia, testosterone production and gender assignment. Studies on the follow-up of 46,XY PGD till adulthood are scarce providing incomplete data on prognosis to inform the parents.

Objectives

To analyze the long term outcomes of 46,XY PGD patients regarding testosterone production, social sex adaption, germ cell tumor risk and genotype.

Material and Methods

Retrospective longitudinal study conducted at Hospital das Clinicas of São Paulo. We selected patients with 46,XY karyotype, with atypical genitalia and no testosterone synthesis defects after hCG stimulation test. They had also mullerian derivates or gonadal dysgenesis at histologycal studies. 28 patients were followed up till adulthood (11 in the female social sex and 17 in the male social sex and). Molecular diagnosis by Sanger method included screening of *SRY*, *SF1, WT1, CBX2, MAPK3*, *FGF9*, *FGFR2, GATA4* genes for mutation and MLPA for *DAX1* for duplication. The allelic variants were classified accordingly the ACMG guidelines.

Results

The chronological age of first visit ranged from 10 days to 43 years and of the last visit ranged from 17 to 53 years. Follow up ranged from 3 to 26 years.

-In the female social sex group, at first evaluation, 2/11 patients were previously gonadectomyzed; 5/9 patients had preserved testosterone (T) production (3 of them during/after puberty) (Table 1).

-In the male social sex group, 8/14 patients had preserved testosterone production at first evaluation, but only 5 of them developed spontaneous puberty (Fig.1). At adulthood, 2/5 patients undergone bilateral gonadectomy due to bilateral testicular tumors and 3 patients maintained testosterone levels, despite unilateral gonadectomy (Table 2).

-There was no association between social sex at adulthood and testosterone production (Fig 2.) or genotype (Tab.3). Social sex change was observed in one patient in both groups, one from male to female and the other to female to male. All patients were well adapted to social sex (64% had a steady partner and 76% had complete sexual intercourse).

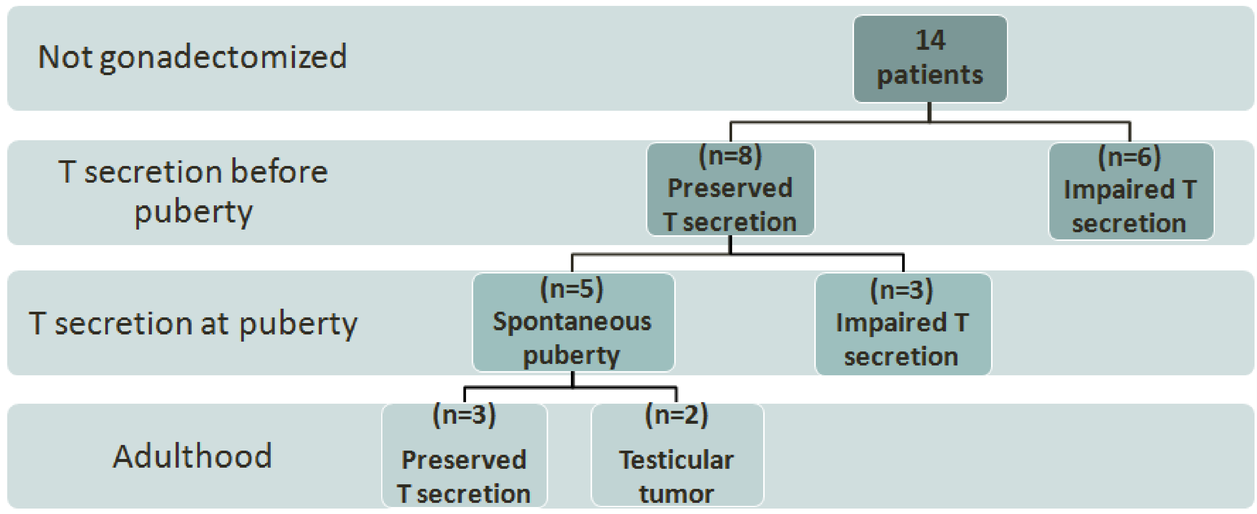
-Gonadal tumor was observed only in patients gonadectomyzed after puberty (2 of 10 patients, one due to *WT1* mutation and the other with unknown molecular etiology, both with cryptorchid gonad).

- Molecular defects were found in 11/28 patients (Table 3).

Table 1- Phenotype of 46,XY female social sex patients at first visit

Stage	Prepuberty			Puberty			Adulthood		
Patient	1	2	3	4	5	6	7	8	9
Age (years)	1.9	1.2	3.7	9.4	11	13.4	43	30	31
Clitoris/ Phallus (cm)	1.0x0.6	2.5x1.0	3.0x0.9	3.0x0.9	6.0x2.0	3.0x1.0	Previous surgery	Micro penis	4.1x1.5
Gonad location	Bilateral cryptorchidism								
Basal T (ng/dL)	<10	76	25.1	116	414	295	324	29	35
T pos hCG (ng/dL)	24	574	337	NA	NA	NA	NA	NA	38
LH (U/L)	NA	<1.0	NA	5.1	18.4	24	32	10	57
FSH (U/L)	NA	<0.6	NA	50	74	69	52	40	18

Fig.1- Follow up of T production in 46,XY PGD male social sex patients



Tab.2- Phenotype of 46,XY PGD male social sex patients with preserved T secretion at adulthood

Patient	10	11	12
Age (last visit)	17	17.6	21
Basal T (ng/dL)	561	625	482
LH (U/L)	14	11	11
FSH (U/L)	26	25	24
Phallus (cm)	8.0x3.0	7.5x2.5	9.2x2.5
Z phallus	-3.3	-3.6	-2.6
Testis final size (cm)	6.7x2.1	4.0x2.5	4.3x2.0

Fig.2- Final social sex and T production in 46.XY PGD patients

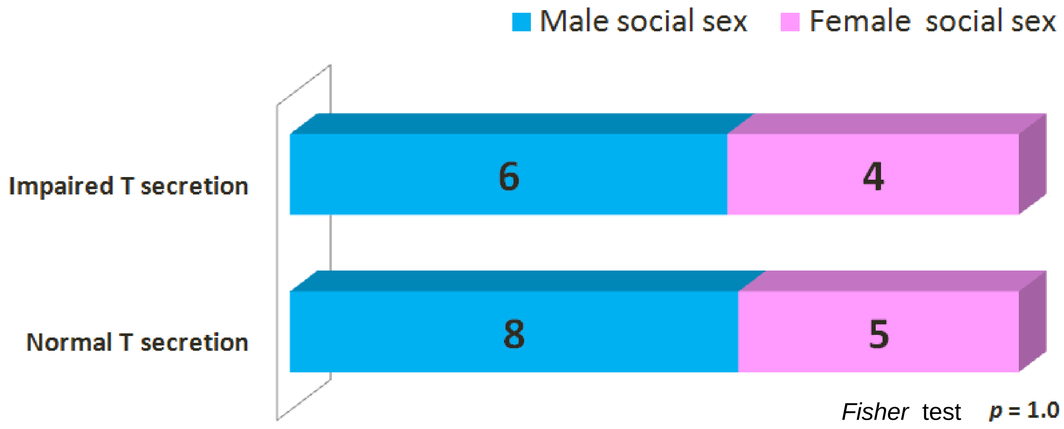


Table 3- Allelic variants found in 46,XY PDG patients

Gene	Mutation	Protein alteration	Preserved T production	Allelic variants classification (according ACMG criteria)
SF-1	c.633C>G	p.Thr211*	NA	Likely pathogenic
	c.77G>A	p.Gly26Glu	No	Likely pathogenic
	c.1073T>C	p.Leu358 Pro	Yes	Likely pathogenic
	c.1058_1065del	p.Ser378*	No	Likely pathogenic
SRY	c.89 G>T	p.Arg30Ile	Yes	Likely pathogenic
	c. 53 G>A	p.Ser18Asn	No	Likely pathogenic
WT-1	c.742 A>T	p.Lys248*	No	Pathogenic
	IVS 9+4C>T	Splice site change	Yes	Pathogenic
CBX2.2	c.T394C	p.Cys132Arg	No	Likely pathogenic
MAP3K/ FGFR2	c.1916 T>C/ c.182C>T	p.Leu639Pro/ p.Ser453Leu	Yes	Likely pathogenic

Conclusion

Most of the 46,XY PGD patients had an adequate social sex adaption and sexual activity. Testosterone production at puberty was maintain in 40% of the patients. There was no association between testosterone secretion and the male social sex. Gonadal tumor was observed in 20% of the patients, all of them orchiectomyzed after puberty. Likely pathogenic variants were found in 37% of the patients by Sanger sequencing and no relation between molecular defects and testosterone production was found.

References: *Assumpção JG. et al. J Mol Med 2002; Domenice S. et al. Hum Genet 1998; Mitchell CL. Harley VR. Mol Genet Met 2002;Biason A. et al*

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