Partial and Mixed Gonadal Dysgenesis Cannot be Distinguished by Histological Picture: Clinical Evaluation, Histological Differences and Long Term Follow-up of 61 Brazilian Patients.

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Background

Differential diagnosis between XY partial (PGD) and mixed gonadal dysgenesis (MGD) was initially established by histological evaluation; however, when there is a 45,X lineage there are differences not only in clinical aspects but also in prognosis. Nonetheless, many present-day studies still refer to this old histological classification.

Objective

The aim of this work was to analyze clinical picture of patients with genital ambiguity due to testicular dysgenesis, with and without a 45,X lineage, and compare these conditions in terms of phenotype and prognosis.

Patients & Methods

All patients with a diagnosis of testicular dysgenesis who were seen in our service between 1989 and 2013 were selected.
Patients who fulfilled the above criteria were included:

- Genital ambiguity with a 46,XY or 45,X/46,XY karyotype (or its variants) plus:
- At least one sign of testicular disfunction (e.g. impaired testicular production) and/or histological features of gonadal dysgenesis and/or mutation in genes participating in gonadal development.

The exclusion criteria was the presence of an ovotestis or ovarian tissue.

Those with previous diagnosis of PGD who were still being followed at our service were subject to deeper cytogenetic analysis, including FISH. Patients were divided in two groups (with and without a 45,X cell line), which were compared in regard to gonadal histology, anatomy of external and internal genitalia, gonadal hormone function, presence of dysmorphic features and associated conditions; growth, puberty and fertility prognosis. Our sample included 61 patients, 25 with mosaicism (MGD) and 36 with an homogenous 46,XY karyotype (PGD).

Results and Conclusion

There were no differences between the groups in terms of age at the first visit, gestational and family history, degree of external virilization, position and histology of gonads, gonadal hormone function, spontaneous pubertal development and need for hormonal replacement, presence of associated conditions and fertility prognosis.

There were significant differences regarding sex of rearing (more often female in MGD); presence of uterus (more common in MGD); higher maternal age (in PGD); lower birth weight and length (in MGD) and short stature (more frequent in MGD).

Thus, PGD and MGD were indistinguishable in terms of gonadal histology and function and genital features, except for the higher frequency of uterus in MGD. They did differ in terms of pre and post-natal growth; in this regard, patients with MGD require specific therapeutic measures.

Therefore, the old classification based on histological findings should be abandoned in favor of that based on chromosome constitution, and screening for a 45,X lineage should be thorough in all patients with 46,XY testicular dysgenesis.

First visit features	MGD	PGD	p-Value
Mean age at first visit (years)	3,8	2,58	0,434
Inicial sex assignment (M:F:I)	11:3:10	13:7:16	0,676
Final sex assignment (M:F)	14:11	29:6	**0,023**
Parental consanguinity	1/23	1/31	1,00
Familial history of genital ambiguity	3/23	8/32*	0,326
Mean Birth weight (g)	2717	3304	**<0,001**
Mean Birth lenght (cm)	46,1	48,2	**<0,001**
EMS (at birth)	4,82	5,48	0,355
Presence of uterus	14/24	8/35	**0,005**
Dismorphic features	11/23	9/35	0,083

MGD = Mixed Gonadal Dysgenesis; PGD = Partial Gonadal Dysgenesis. M = male; F = female; g = grams; cm = centimeters; EMS = External Masculinization Score (Ahmed et al, 2000).

Histological Diagnosis	Mixed Gonadal Dysgenesis			Partial Gonadal Dysgenesis			Total
	Right Gonad	Left Gonad	Total	Right Gonad	Left Gonad	Total	
Streak gonad	3	4	7	2	5	7	14
Dysgenetic testis	12	10	22	18	16	34	56
Prepubertal testis	3	7	10	3	2	5	15
Adult normal testis	2	0	2	0	0	0	2
Testicular torsion	1	0	1	0	0	0	1
Testicular Tumor	1	0	1	0	0	0	1
Not evaluated	2	1	3	12	9	21	24
No gonadal tissue	1	3	4	1	4	5	9
Total	25	25	50	36	36	72	122

If absent or not evaluated gonads are not taken into account , the proportion of streak gonads and gonads containing testicular tissue does not differ between groups (MGD: 7 streaks and 36 testicular tissue gonads; PGD: 7 streaks and 39 testicular tissue gonads) (p=0,891).
In 19 cases of MGD and 19 of PGD both gonads received histological evaluation. Seven patients with MGD had streak gonad + contralateral testis (the traditional histological diagnosis of MGD) and 12 had bilateral testes (with or without dysgenetic features). In PGD we found a similar distribution (6 and 13, respectively) (p=0,732).

Associated conditions / complications	MGD	PGD	p-Valor
Learning disabilities	2/20 (10%)	4/34 (12%)	0,842
Cardiac malformations (echocardiography)	5/21 (23%)	3/4	(*)
Urinary tract malformations (abdominal echography)	3/22 (14%)	6/33 (18%)	0.655
Thyroid funcion impairment	7/23 (30%)	2/23 (9%)	**0.063**
Hearing loss	2/18 (11%)	5/6	(*)
Others (**)	9/22 (41%)	14/33 (42%)	

(*) not evaluated (**) psychiatric disorders, skeletal, metabolic, neoplastic and others.

Disclosure Statement

The authors have nothing to disclosure.

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