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 dysfunction (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.

References


Disclosure Statement

The authors have nothing to disclose.

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First visit features MGD PGD p-Value
Mean age at first visit (years) 3.8 2.58 0.434
Inital sex assignment (M:F) 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 length (cm) 46.1 48.2 <0.001
EM5 (at birth) 4.82 5.48 0.355
Presence of uterus 14/24 8/35 0.005
Dysmorphic 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).

<table>
<thead>
<tr>
<th>Histological Diagnosis</th>
<th>Mixed Gonadal Dysgenesis</th>
<th>Partial Gonadal Dysgenesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streak gonad</td>
<td>Right Gonad</td>
<td>Left Gonad</td>
</tr>
<tr>
<td>Streak gonad</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Dysgenetic tests</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>Prepubertal tests</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Adult normal tests</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Testicular torsion</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Testicular Tumor</td>
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<td>0</td>
</tr>
<tr>
<td>Not evaluated</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>No gonadal tissue</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>25</td>
<td>25</td>
</tr>
</tbody>
</table>

If absent or not evaluated gonads are not taken into account, there are significant differences between groups (MGD: 7 streaks and 36 testicular tissue gonads; PGD: 7 streaks and 39 testicular tissue gonads) (p<0.091).

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-Value
Learning disabilities 2/20 (10%) 4/34 (12%) 0.842
Cardiac malformations (echocardiography) 5/21 (23%) 3/4 (*)
Urinary tract malformations (abdominal echography) 3/32 (14%) 6/33 (18%) 0.855
Thyroid function 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.

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