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Genetic etiologies and gender outcomes of patients with disorders of sex development presenting with asymmetric gonads

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Introduction

- Individuals with mixed gonadal dysgenesis (MGD) present a 45,X/46,XY karyotype with a testis on one side and a streak on the other side. In contrast, ovotesticular disorder of sex development (DSD) is applied to an individual who has both well-developed ovarian and testicular tissues.
- Patients with MGD and ovotesticular DSD can present with asymmetric gonads. A differential diagnosis between the two conditions has important clinical implications for gender assignment.
- Differential diagnosis of these conditions is based on karyotype and pathological findings of gonads. However, it is difficult to differentiate without a knowledge of histological findings of the gonads and determine sex of rearing and to predict long-term outcomes.

Objectives

- This study investigated the clinical features, karyotype, sex of rearing, and pubertal outcomes of patients with MGD and ovotesticular DSD.

Methods

- This study included 25 patients with DSD who presented with asymmetric gonads. Presenting features, karyotype, sex of rearing, and pubertal outcomes were reviewed retrospectively.

Results

Clinical characteristics at presentation

- All 25 patients presented with ambiguous genitalia at median age of 1 month (range, 1 day to 1.6 years). Eleven of 14 patients with ovotesticular DSD (78.6%) and 10 of 11 patients with MGD (90.9%) presented with asymmetric gonads.
- They manifested labioscrotal deformity (60%), hypospadias (60%), clitoromegaly (36%), cryptorchidism(28%), and micropenis (20%).
- Mullerian duct remnants were found in 17 of 25 patients (68%).

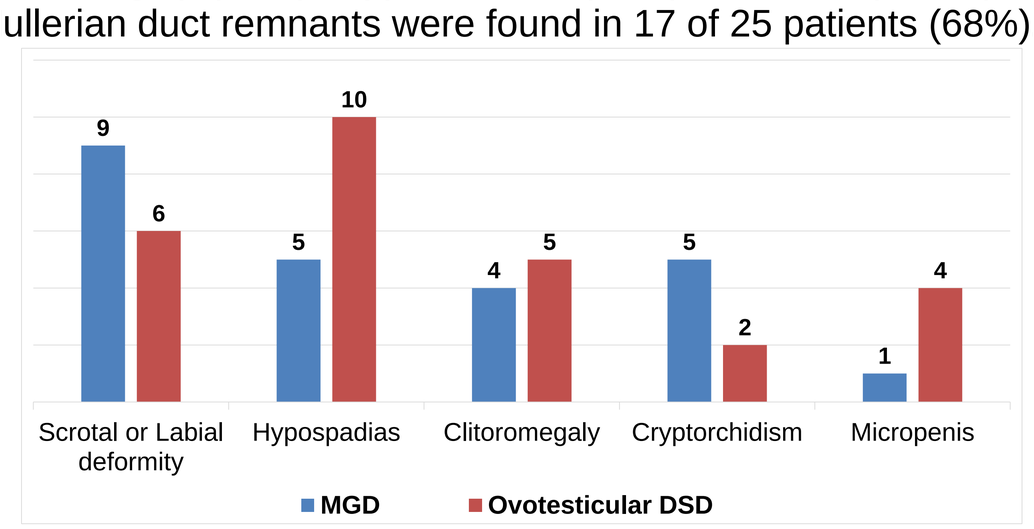

Fig. 1. Clinical presentation of patients with ovotesticular DSD and MGD

Diagnosis by pathological findings

- Gonadectomy or biopsy was performed at median age of 2.9 years (range, 1 month to 15.1 years). Subsequently, 11 patients were diagnosed with MGD, whereas 14 patients were ovotesticular DSD.
- In 14 patients with ovotesticular DSD; karyotype was 46,XX in 10 (71.4%), 45,X/46,XY in 3 (21.4%) patients, and 46,XX/46,XY in one patient (7.1%).
- In 11 patients with MGD; karyotype was 45,X/46,XY in 6 (54.5%), 46,XY in two patients (18.2%), and other mosaicisms in three patients (27.3%): 45,X/46,X,del(Y)(q11.23), 45,X/46,X,add(Y)(p.11.3), and 45,X/47,XY,+del(Y)(q12).

Sex of rearing and clinical course

- Eight of 11 patients with MGD (72.7%) were raised as males, while 8 of 14 patients with ovotesticular DSD (57.1%) were assigned as males.
- Among 8 male-assigned patients with ovotesticular DSD, unilateral gonadectomy was performed in 6 patients. In 6 female-assigned patients, three patients underwent bilateral gonadectomy, while the other three underwent unilateral gonadectomy.
- Seven male-assigned patients with MGD underwent unilateral gonadectomy. Three female-assigned patients underwent bilateral (n = 1) or unilateral (n = 2) gonadectomy.

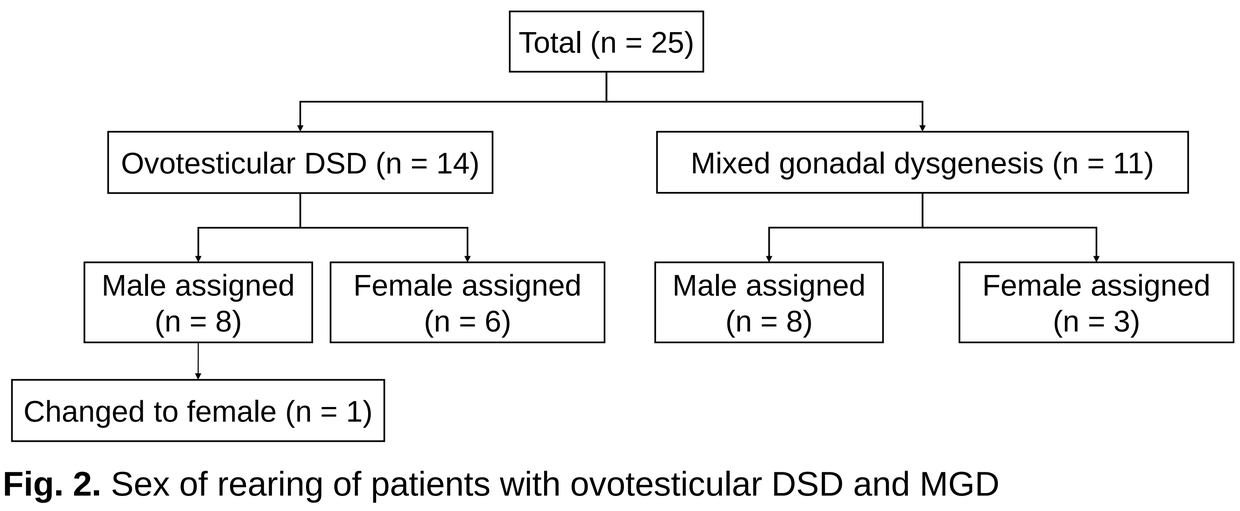

Fig. 2. Sex of rearing of patients with ovotesticular DSD and MGD

Table 1. Clinical and cytogenetic features of patients with ovotesticular DSD

Patient	Karyotype	Mullerian duct remnants	Gonadectomy	Sex of rearing	EMS
1	45,X /46,XY	-	Unilateral gonadectomy	M	8
2	46.XX		Bilateral gonadectomy	F	5
3	46,XX	-	Unilateral gonadectomy	F	7.5
4	46,XX	-	Unilateral gonadectomy	M	9
5	46,XX	+	Unilateral gonadectomy	M	10
6	46,XX	+	Unilateral gonadectomy	M	8
7	46,XX	+	Unilateral gonadectomy	M	9
8	46,XX	-	Bilateral gonadectomy	F	3
9	46,XX	+	Unilateral gonadectomy	M	7.5
10	45,X /46,XY	+	Unilateral gonadectomy	M	9
11	45,X /46,XY	+	Bilateral gonadectomy	F	3.5
12	46,XX	+	Unilateral gonadectomy	F	7.5
13	46,XX	+	Unilateral gonadectomy	F	2.5
14	46,XX /46,XY	+	Unilateral gonadectomy	M	8

Table 2. Clinical and cytogenetic features of patients with mixed gonadal dysgenesis

Patient	Karyotype	Mullerian duct remnants	Gonadectomy	Sex of rearing	EMS
15	45,X/46,XY	+	Unilateral gonadectomy	F	2.5
16	46,XY/45,X	+	Unilateral gonadectomy	M	10.5
17	45,X /46,XY	+	Unilateral gonadectomy	M	8.5
18	45,X /46,XY	+	Unilateral gonadectomy	M	8
19	45,X /46,XY	-	Unilateral gonadectomy	M	6.5
20	46,XY	+	Unilateral gonadectomy	M	8
21	45,X /46,XY	+	Bilateral gonadectomy	F	3
22	45,X /46,XY	+	Unilateral gonadectomy	M	7.5
23	47,XYY/45,X	-	Unilateral gonadectomy	M	11.5
24	45,X /46,XY	+	Unilateral gonadectomy	M	8
25	46,XY	+	Bilateral gonadectomy	F	1

- Two patients with MGD and seven with ovotesticular DSD reached pubertal age. Among them, one phenotypic male with MGD and five patients with ovotesticular DSD showed spontaneous puberty.
- One male-assigned patient with ovotesticular DSD (Subject 7) showed gender identity problems and gender dysphoria at age 20 years and changed gender as female.
- The one female with MGD showed hypergonadotropic hypogonadism and has been treated with estrogen replacement therapy since 11 years of age.

Conclusions

- Patients who presented with asymmetric gonads have a wide clinical, cytogenetic, and histopathological spectrum.
- Pathological findings of gonads are necessary for differential diagnosis of MGD and ovotesticular DSD.
- Further studies are needed to establish appropriate treatment strategies and gender outcomes.

References

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Disclosure statement

The authors have nothing to disclose.