



Published in final edited form as:

J Pediatr Endocrinol Metab. 2011 ; 24(0): 831–833.

Unexpected finding of an intact distal vagina in an infant with mixed gonadal dysgenesis

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Abstract

Mixed gonadal dysgenesis (MGD) is a form of sex chromosome disorder of sex development with large phenotypic variability. Patients with MGD typically have asymmetric and ambiguous genitalia with a combination of Müllerian and Wolffian duct derivatives. Prenatal androgen exposure results in variable degrees of phallic enlargement and a urogenital sinus. Here, we report an infant with ambiguous genitalia due to MGD. Despite marked evidence of prenatal androgen exposure, there was a completely intact distal vagina.

Keywords

disorder of sex development; mixed gonadal dys-genesis; urogenital sinus

Case report

A term infant was born with ambiguous genitalia consisting of a 2.0×0.8 cm phallic structure with chordee, non-palpable gonads, separate vaginal and urethral openings, and prominent rugated labioscrotal folds (Figure 1A). Testing for congenital adrenal hyperplasia was negative. Müllerian inhibiting substance (MIS) was 33.6 pmol/L (RR for males: 111–348 pmol/L; females: <51 pmol/L). Testosterone at baseline was 0.2 nmol/L and increased to 3.1 nmol/L following an hCG stimulation test (male RR: 6.2–25.5 nmol/L). FSH at 13 days indicated primary gonadal dysfunction. A peripheral karyotype was 45,X/46,XY, consistent with mixed gonadal dysgenesis (MGD). The patient's laboratory data are summarized in Table 1.

A pelvic ultrasound showed a normal appearing uterus with no visible gonads. Genitogram revealed intact Müllerian structures with a normal appearing uterus, cervix, and vagina (Figure 1B). There was no confluence between the vagina and urethra, and therefore, no urogenital sinus (UGS). After multidisciplinary care conferences, a female gender assignment was made. This decision was based on family preference, the presence of internal female structures and future potential for carrying a pregnancy, and evidence that individuals with disorders of sex development similar to our case do well when raised in either gender (1).

Given the risk for malignancy in dysgenetic gonads, the infant underwent bilateral laparoscopic gonadectomy at 6 weeks (2). A right-sided streak ovary and left-sided dysgenetic gonad were found on both visual examination and histopathology (Figure 1C and D), consistent with the diagnosis of MGD (3). Future surgeries for cosmetic repair have been deferred until the child is older.

Discussion

The category of sex chromosome disorders of sex development (DSD) refers to conditions in which sex chromosome aneuploidy is present. MGD is one form of sex chromosome DSD characterized by a 45,X/46,XY karyotype with ambiguous and asymmetric genitalia (4). Interestingly, this same karyotype is associated with a broad phenotypic spectrum ranging from normal males to girls with Turner syndrome to MGD (5). Precisely what factors are responsible for the ultimate phenotype in any given case are unknown.

In normal female sexual differentiation, the vaginal cord proliferates and migrates downward adjacent to the urethra to create a separate opening on the perineum. Prenatal androgens inhibit this migration, resulting in a persistent confluence between the vagina and urethra. The location of the UGS changes relative to prenatal androgens, moving proximally towards the bladder neck with increasing dose and duration of exposure (6). Prenatal androgen exposure also results in external virilization by acting on genital skin androgen receptors. One would anticipate some degree of urogenital confluence given the degree of external virilization in our patient, but there was a separate and intact distal vagina and normal vaginal introitus.

In MGD, there is subnormal testosterone secretion from dysgenetic Leydig cells. The variability of prenatal androgen secretion throughout gestation may account for the discrepancy between the external and internal virilization in our patient. The gonads may have secreted androgens below some necessary threshold early in gestation, allowing for downward migration of the vagina to the perineum. The finding of normal Müllerian structures in our patient also suggests insufficient MIS secretion by Sertoli cells. Therefore, there appears to have been minimal testicular function during the critical time of Müllerian differentiation and vaginal development, but sufficient testosterone biosynthesis later in gestation to cause partial external virilization. This variation could be explained by a delay of Leydig cell maturation. Differences in androgen sensitivity within urogenital tissues may have also contributed to our patient's phenotype.

To our knowledge, the constellation of external virilization and an intact distal vagina has not previously been reported in patients with 45,X/46,XY MGD. This case expands the broad phenotypic spectrum of patients with MGD.

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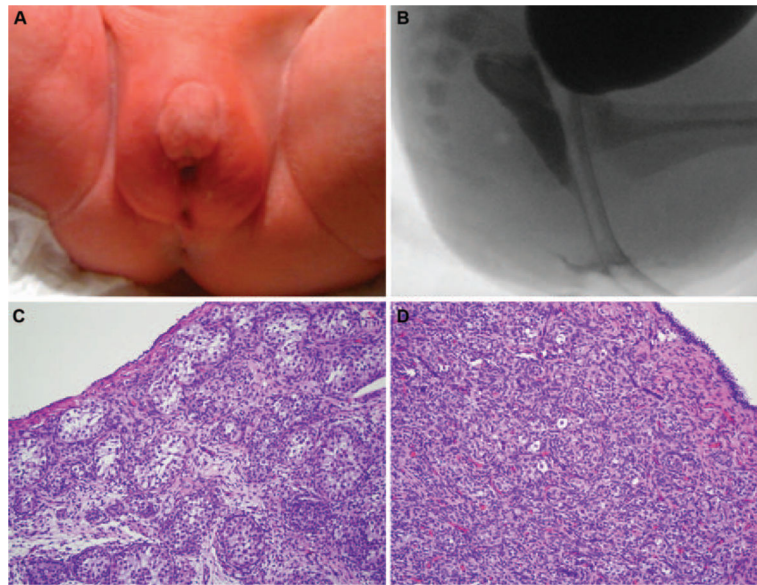


Figure 1.

(A) External virilization and ambiguous genitalia. (B) Genitogram demonstrating completely separate urethral and vaginal tracts. (C) Hematoxylin and eosin stain at 200 \times magnification of dysgenetic gonad with immature ovarian and testicular components. There are areas of solid tubules arranged in sheets and cords with immature Sertoli and germ cells admixed with dense, wavy ovarian-like stroma. Germ cells are noted adjacent to the basement membrane, and primitive seminiferous tubules are present in areas of decreased stromal density. (D) Streak ovary tissue composed of wavy ovarian-like collagenous stroma and scattered, small, and thin tubules. Classic monotonous germ cell tubules are seen closer to the capsule.

Table 1

Laboratory data.

Laboratory study	Value	Age-specific reference ranges ^{a,b}
17-hydroxyprogesterone	Day 2: 28 nmol/L Day 3: 13.8 nmol/L	<30.3 nmol/L ^a
FSH	Day 3: 4.2 IU/L Day 13: 18 IU/L	Male: 0.26–3 IU/L ^b Female: 1–4.2 IU/L ^b
LH	0.2 IU/L	0.02–0.3 IU/L ^b
Total testosterone (baseline before hCG)	0.2 nmol/L	Male: 2.5–13.9 nmol/L ^b Female: 6.9–22.2 nmol/L ^b
Total testosterone (after 1500 IU of hCG every other day for 3 doses)	3.1 nmol/L	Male: 6.2–25.5 nmol/L ^b
Müllerian inhibiting substance (MIS)	33.6 pmol/L	Male: 111–348 pmol/L ^b Female: <51 pmol/L ^b
Karyotype	45,X/46,XY	

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