The Genotypic and Phenotypic Variability of XO/XY Mosaicism

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Introduction: Patients with XO/XY mosaicism may have variable genotypes and phenotypes. This includes structurally normal or abnormal Y chromosomes presenting as phenotypic males, phenotypic females, or with ambiguous genitalia. They may have Turner features and require Growth Hormone therapy. They are also at increased risk for gonadal tumors.

We present 3 cases of XO/XY mosaicism that demonstrate the wide clinical variability and challenges that can arise.

	Case 1: Amniocentesis revealing XO/XY mosaicism	Case 2: A newborn with ambiguous genitalia	Case 3: A 16 year old phenotypic female with primary amenorrhea
Genotype	45,X[27%] 46,X,idic (Y) (p11.3)[73%]	45,X[80%] 46,XY[20%]	46,X,idic(Y)(p11.3) [90%] 47,X,idic(Y)(p11.3)x2 [4%] 45,X [4%] 46,XY.ish idic(Y)(p11.3) [2%]
Phenotype	Normal male external genitalia: - Appropriate stretched penile length and bulk - Urethral opening at the tip of the glans - Descended testicles	Abnormal external genitalia: - 2.5 cm phallus, appropriate erectile bulk - Grade 4 hypospadius - Perineoscrotal urethral opening - Bifid scrotum - Right testicle descended - No palpable gonad on the left side - Left inguinal hernia	Normal female external genitalia: - No clitoromegaly - No labioscrotal fusion - Tanner stage 1 for breast development - Tanner stage 5 for pubic hair Subtle Turner's features - Widely spaced nipples - Low lying hairline - High arched palate - Elongated hyperconvex nails - Multiple melanocytic nevi Height was between the 25-50% percentile
Investigations	Normal cardiac MRI and ECHO Normal renal and testicular ultrasound At 1 week of life: LH 2.5 (<10.0 U/L) FSH 2.0 (<7.0 U/L) Testosterone 6.2 nmol/L	Pelvic US – uterine structure present, no ovaries visualized. Right testicle present in inguinal canal, no left gonad visualized At 2 days of life: LH 0.5 (<10.0 U/L) FSH 2.5 (<7.0 U/L) Testosterone 3.7 nmol/L	Pelvic US – premenarchal uterus and right ovary were seen. The left ovary was not visualized. LH 39 (18.0-65.0 U/L post menopausal) FSH 79 (16.0-80.0 U/L post menopausal) Estradiol <30 (<115 pmol/L post-menopausal) TSH 2.56 (0.2-4.0 mU/L) Free T4 13.4 (9.0-23.0 pmol/L)
Clinical Course	At 8 years of age the patient fell off the CDC growth curve. He was subsequently started on Growth Hormone therapy. He entered puberty spontaneously and progressed appropriately. He has mild intellectual impairment, attention deficit, and aggression.	The patient has normal growth velocity and is tracking below the third percentile. The patient has been referred to cardiology for assessment.	The patient was started on Estrogen. She has cerebral palsy and mild intellectual impairment. Echo is pending.
Management	Testicular biopsies were done at 3 years of age. Pathology revealed normal testicular tissue.	At 3 months of age, the patient underwent left inguinal hernia repair. A small streak gonad and fallopian tube were removed from the inguinal canal. He underwent a two stage hypospadias repair at 1 and 2 years of age. Pathology was consistent with fallopian elements and a rete teste.	The patient underwent gonadectomy. Laparoscopy demonstrated a rudimentary uterus, dysplastic gonad and fallopian tube on the left, and a streak gonad on the right side. Pathology revealed both fallopian tubes and wolffian remnants, as well as bilateral streak gonads.

Clinical Pearls

1) Why and when to perform gonadectomy?
   - Patients with XO/XY mosaicism are at risk for gonadal malignancies (9.5-30%)[1] such as gonadoblastoma and dysgerminoma
   - The undifferentiated streak gonad can undergo clonal expansion under the influence of high levels of gonadotropins during puberty[2]
   - In patients with streak gonads, gonadectomy should be considered at ~16-18 years of age

2) Remember the Turner features
   - XO/XY mosaicism can have Turner-like features including short stature and cardiac defects
   - Growth Hormone therapy should be considered for growth failure, as in Turner syndrome

[1] Liu et al Human Reproduction (2014) 29(7) 1413-19
[2] Stowikowska-Hilczer J Pediatr Endocrinol Diabetes Metab (2008) 13(1) 37-42