Evaluating tumor risk and subsequent management in patients with mixed gonadal dysgenesis

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PURPOSE

The timing of gonadectomy for mixed gonadal dysgenesis (MGD) depends on the MGD phenotype-specific risk of germ cell malignancy. We summarize the initial evaluation and considerations of a patient with Turner syndrome with partial XYY MGD, and discuss the current recommendations pertaining to tumor risk and timing of gonadectomy.

CASE

Patient features concerning for Syndrome or Disorder of Sex Differentiation

Features	Our Patient
Biometrics: Short stature (> 2.5 SD below mean) Delayed Bone Age (BA)	Height at 0.15%ile, Z= -2.69 (*see Figure 1*) Chronological age of 11 years with BA of 7 years and 10 months
Phenotypic Characteristics: Low-set ears or hearing loss Broad shield-like chest High-arched palate Short 4th metacarpal Cubitus Valgus	 Hearing loss Low-set ears Short 4th metacarpal
Biochemical/Imaging Findings: Streak ovaries High FSH and LH Low estradiol Low Anti-Mullerian Hormone Confirmatory Genetic Testing	Pelvic US - small uterus with unidentifiable, likely streak ovaries Lab work - LH: 19.3 mIU/mL ; FSH 73.3 mIU/mL; AMH 0.02 ng/mL Chromosomal Microarray Analysis: mosaicism for a 45, X cell line in 13/20 (65%) cells and a 47, XYY cell line in 7/20 (35%) cells

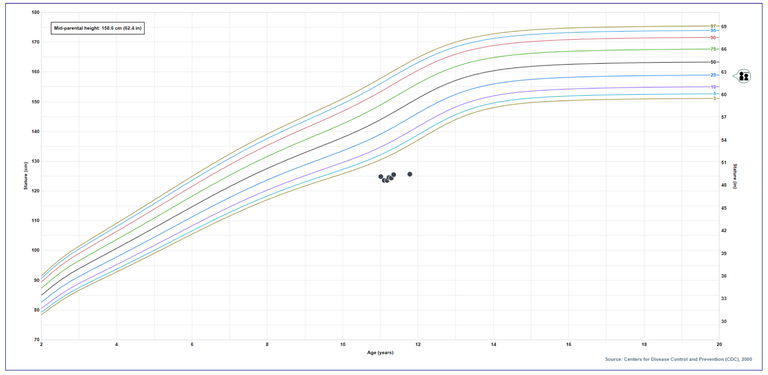

Fig 1: Height Growth Chart

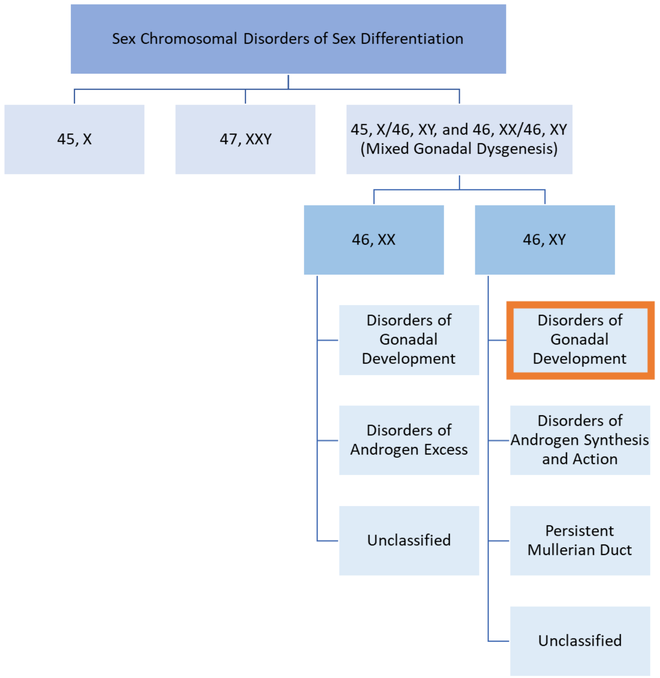

Fig 2: Disorders of Sex Differentiation Karyotypes – Orange represents our Patient
Adapted from Cools, M. Nature Reviews Endocrinology, May 2018, 14, 415-429.

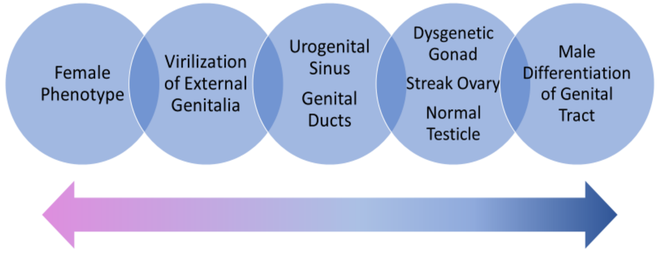

Fig 3: Phenotypes of Partial XY Gonadal Dysgenesis

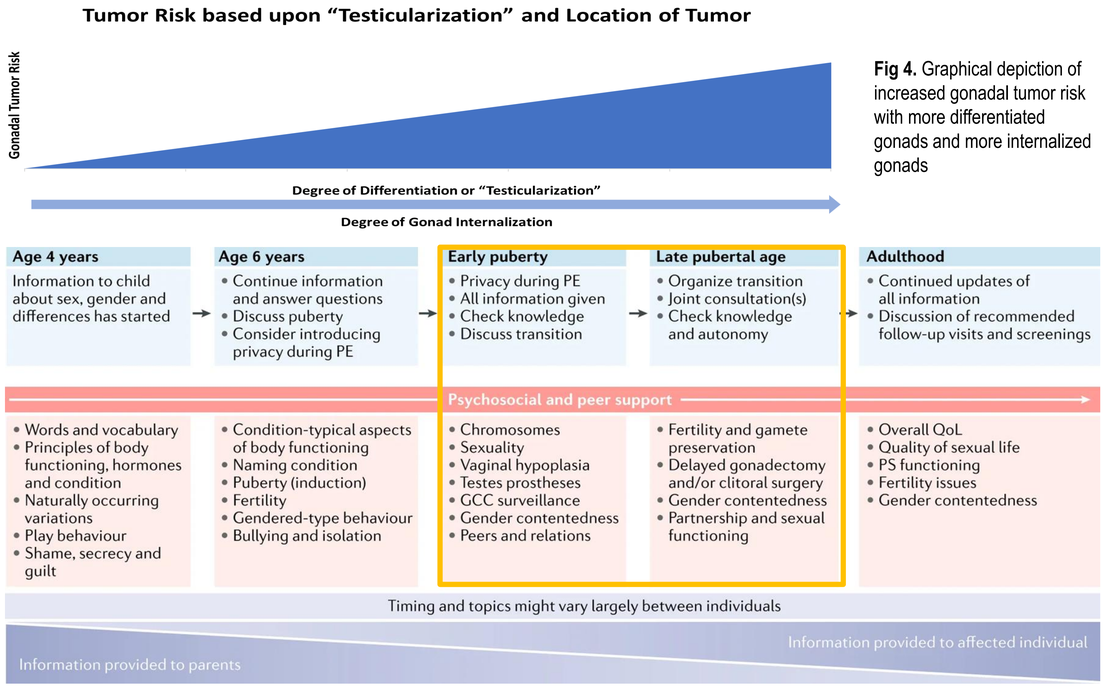

Fig 4. Graphical depiction of increased gonadal tumor risk with more differentiated gonads and more internalized gonads

Fig 5: Multidisciplinary Approach – Orange Represents our Patient *Cools, M. Nature Reviews Endocrinology, May 2018, 14, 415-429*

DISCUSSION

- Disorders of sex differentiation comprise karyotypes such as 45, X; 47, XXY; and variants of both (MGD) *(See Figure 2)*.
- MGD phenotypes are dependent on the degree of testicular development, which varies from normal-appearing males with azoospermia to our patient's Turner female phenotype *(See Figure 3)*.
- As the degree of germ cell cancer risk is also dependent on gonadal differentiation or "testicularization" and location, current gonadectomy guidelines recommend earlier gonadectomy in more virilized patients and for abdominal gonads *(See Figure 4)*.
- Given the gravity of this decision, a multidisciplinary care approach is seen to be most effective, with early involvement of the affected child in open and transparent discussion *(See Figure 5)*.

CONCLUSION

- 7-10% risk of gonadoblastoma development in patients with Turner/Partial XYY mixed gonadal dysgenesis and abdominal streak gonads.
- Low quality data regarding recommendations against routine gonadectomy in gonadal dysgenesis.
- Multidisciplinary approach including endocrinology, gynecology, and psychology that is open and transparent is imperative when making a shared decision regarding gonadectomy.