

0113 - COMPLETE 46,XY GONADAL DYSGENESIS: CLINICAL SPECTRUM, MOLECULAR ETIOLOGY, AND TUMOR OUTCOMES IN NINE PATIENTS

Mode: Research paper

Thematic Unit: DSD

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Background/Objectives: Complete 46,XY gonadal dysgenesis (CGD) is an infrequent condition characterized by female phenotype and streak gonads with increased risk of germ cell tumors. Variants in genes involved in gonadal determination, particularly SRY and WT1, are among the most frequent molecular etiologies. Our aim was to describe the clinical and gonadal histopathological characteristics, and the molecular findings of patients with CGD followed at a tertiary pediatric hospital.

Methods: Retrospective descriptive review of clinical records of patients with CGD followed at a tertiary pediatric center (2000-2025).

Results: Nine patients from eight families were included (P1-9). P1-4 carried SRY variants (P1-P2: c.190A>G-p.Met64Val, P3: c.202A>G-p.Ile68Val, P4: 4kb deletion Yp11.31). Siblings P1 and P2, presented with primary amenorrhea at 14.3 and 16.6 years, respectively. Both developed spontaneous telarche with biochemical hypergonadotropic hypogonadism. P1 had dysgerminoma (FIGO IA) and contralateral gonadoblastoma, while P2 had gonadoblastoma and a contralateral streak gonad. P3 was incidentally diagnosed with hypergonadotropic hypogonadism at 10.4 years. Histopathology after gonadectomy revealed streak gonads. P4 reported prior telarche that subsequently regressed, and presented at 12.6 years with constitutional symptoms and a bulky abdominal tumor with elevated BhCG (147 mUI/ml). Bilateral stage III dysgerminoma was confirmed, requiring chemotherapy, and remains disease-free after 6 years of follow-up. P5-8 carried WT1 variants (P5-6: c.1447+5G>A, P7: c.1447+1G>A and P8: c.1315C>T - p.Arg439Cys) and had previous renal involvement. P5-7 underwent prophylactic gonadectomy: P5 had bilateral gonadoblastoma at 2.9 years, P6 gonadoblastoma and contralateral dysgerminoma at 14.8 years (FIGO IC2), and P7 bilateral streak gonads at 6.8 years. Only P6 presented with spontaneous telarche despite laboratory findings consistent with hypergonadotropic hypogonadism. P8 had associated diaphragmatic hernia (Meachan syndrome) and died at 2 months of age. Gonadal histology was unavailable. P9 presented with arrested puberty at 14.1 years and declined further molecular testing beyond karyotyping. Histopathology revealed dysgerminoma (FIGO IA) and a contralateral streak gonad. Mean age at estrogen replacement initiation was 14 years, and mean final height was 162.3 cm (SDS 0.14).

Conclusion: Germ cell neoplasias are frequent in 46,XY CGD (6/8). Spontaneous breast development occurred in 55% of cases, despite hypergonadotropic hypogonadism. This manifestation of tumor-related hormone production may delay the recognition of this high



tumor-risk condition. Close monitoring of pubertal progression is essential for early suspicion. Molecular diagnosis remains fundamental for individualized surveillance and timely therapeutic decision-making.

