CASE REPORT

Gonadal Dysgenesis and Malignancy: When Should Gonadectomy Be Performed?

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Abstract

Gonadal dysgenesis is a disorder of sexual development characterized by the defective or incomplete formation of the gonads (ovary or testis) due to the structural or numerical modifications of the sex chromosomes or due to mutations in the genes responsible for gonadal development.

Two cases of unrelated phenotypically female patients are presented as a complete gonadal dysgenesis and a partial gonadal dysgenesis. Both cases were diagnosed with premalignant lesions at a prepubertal age. Even at very young ages, there is a high tumor risk, which reiterates the importance of the early diagnosis of suspected cases in order to better characterize and guide these patients. To prevent the development of malignancy, a gonadectomy is recommended as close as possible to the diagnosis.

Keywords: Child; Gonadal Dysgenesis/diagnosis; Gonadal Dysgenesis/genetics; Gonadal Dysgenesis/surgery; Gonadoblastoma; Risk Factors; Sex Chromosome Aberrations

Introduction

Gonadal dysgenesis is a subset of disorders of sexual development characterized by defective or incomplete formation of the gonads (ovary or testis) due to either structural or numerical modification of the sex chromosomes or due to mutations in the genes responsible for gonadal development.[1,2] Modifications in virilization may be caused by defects in androgen-dependent target tissues, errors in testosterone biosynthesis and testicular unresponsiveness to stimulation from the pituitary, leading to the underdevelopment of sexual male differentiation.[2-4]

Gonadal dysgenesis is characterized by gonads with a variable degree of immaturity or dysfunction that can manifest in a wide range of genital ambiguity. Gonadal dysgenesis can be classified as either complete/pure or partial/mixed, depending on the gonadal morphology. In complete gonadal dysgenesis, no gonadal development occurs and, as a consequence, patients have a female phenotype due to the lack of any gonadal steroid production. Instead, they have undifferentiated gonads - streak gonads.[1,2,4,5] In partial gonadal dysgenesis, the Y chromosome is present, so there is incomplete testis determination and the external phenotype depends on the degree of testicular function.[1] The most common karyotype of partial gonadal dysgenesis is 45,XO/46,XY.[5] Patients with Gonadal Dysgenesis are at increased risk of developing germ cell tumors, such as gonadoblastoma, carcinoma *in situ*, dysgerminoma, and seminoma.[6] Patients with complete Gonadal Dysgenesis and 46,XY karyotype have a tumor incidence of 15%-45%, which is higher compared to patients with partial gonadal dysgenesis with 45,X0/46,XY karyotype (15%-40%).[1] The presence of part of the Y chromosome is required for the malignant transformation of embryonic germ, with the sex-determining gene on the Y chromosome (*SRY*) and testis-specific protein on Y chromosome (*TSPY*) being considered the most likely candidate genes.[7,8] *SRY* encodes *a* testis-determining factor, which initiates male sex determination and *TSPY* is involved in spermatogenesis.[7,8] Mutations in the nuclear receptor subfamily 5 group A member 1 gene (*NR5A1*) account for 10%-20% of the 46,XY disorders of sexual development cases. This gene encodes a steroidogenic factor-1 that modulates *SRY* expression and initiates anti-Müllerian hormone (AMH) expression.[8] Desert hedgehog gene (*DHH*) mutations have also been identified in patients with 46,XY disorders of sexual development.[10] Growing evidence shows an association of immunohistochemical markers with premalignancy in patients older than one year, such as *TSPY* and octamer binding transcription factor 3/4 (*OCT3/4*), both expressed in

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carcinoma *in situ* and gonadoblastoma.[11,12] Other useful immunohistochemical markers appear to be the steam cell factor receptor CD117, alpha-fetoprotein, placental-like alkaline phosphatase (PLAP), and β-catein.[11]

Recent studies have demonstrated a possible role for Wilms tumor 1 (*WT1*) genotyping in 46,XY disorders of sexual development. These patients would benefit from long-term screening for Wilms tumor, nephropathy, and germ cell tumors.[4]

Gonadoblastoma is a premalignant lesion with potential for malignant transformation (most commonly for dysgerminoma) and metastization.[4] It occurs in 4.7%-25% of patients with gonadal dysgenesis and, although it is more common after puberty, cases occurring in early infancy have been reported.[4]

No standard approaches or guidelines have been established for the diagnostic workup and management of these patients.[1]

Case Report 1

Phenotypically female patient with unremarkable family history. Combined first trimester prenatal screening (nuchal translucency scan and maternal serum screening) was positive for chromosomal abnormalities namely trisomy 21 risk of 1/6. Amniocentesis revealed a 46,XY karyotype. Born at 37 weeks of gestational age with an appropriate birth somatometry. Physical examination was unremarkable, and a female phenotype was identified. Postnatal karyotype confirmed a 46,XY karyotype. Abdominal and pelvic ultrasound and magnetic resonance imaging revealed a uterus with normal dimensions for age and non-visualized gonads.

Physical examination at 3 years-old revealed a clitoral hypertrophy of 1 cm and no other abnormalities (classified as Prader I). Endocrine evaluation showed a hypergonadotropic hypogonadism with elevated basal follicle-stimulating hormone (FSH) 69.62 µUI/mL (reference range 1.0-4.2 µUI/mL) and basal luteinizing hormone (LH) 1.27 µUI/mL (reference range 0.02-0.3 µUI/mL), with normal for female sex and normal for age values of oestradiol (51.64 pmol/L), total testosterone (< 10 ng/dL), 17-hydroxyprogesterone (17OHP) (0.42 ng/mL), dehydroepiandrosterone sulphate (DHEA-S) (< 15 ug/dL), 4-androstenedione (< 0.3 ng/mL), and AMH (0.57 pmol/L). Magnetic resonance imaging revealed a uterus with normal dimensions for age, a 9 x 5 mm left gonad, and the absence of a right gonad.

An exploratory laparoscopy and a gonadectomy were performed. Histologic examination revealed a bilateral gonadoblastoma (with germ cells, sex cord cells, and calcifications) with 0.7 cm in the right gonad and 0.8 cm in the left gonad.

Molecular analysis showed a non-sense mutation of *SRY*, *c.340>T(p.Q114X)*. Immunohistochemical analysis was positive for PLAP, CD117, and WT1. No additional treatment was done. Endocrine evaluation was done six months after surgery and showed persistent hypergonadotropic hypogonadism with elevated basal FSH (21.26 µUI/mL), normal basal LH (< 0.07 µUI/mL) and no other alterations.

At 8 years-old, she has adequate psychomotor development, weight, and height at 75-90 percentile and no other physical abnormalities.

Case Report 2

Phenotypically female patient with an unknown family history. Uneventful gestation until 31 weeks of gestation age, when a cesarean section was performed due to a non-reassuring fetal state. Birth somatometry revealed a symmetric fetal growth restriction and a female phenotype was identified. There was a bilateral germinal matrix hemorrhage as a complication of prematurity. During the first 20 months, she presented with axial hypotonia, delayed psychomotor development, weight progression under the fifth percentile, height at percentile 10, cephalic perimeter at percentile 75-90, and ambiguous genitalia, classified as Prader II-III, with a 1 cm clitoral hypertrophy. Karyotype was 45,X0 (30%) / 46,XY (70%). Endocrine evaluation revealed an elevated basal FSH 1858 µUI/mL (reference range 1.0-4.2 µUI/mL), with normal for female sex and normal for age values of basal LH (0.23 mUI/mL), estradiol (95.53 pmol/L), total testosterone (< 10 ng/dL), inhibin A (10 pg/mL), and AMH (< 0.57 pmol/L). Abdominal and pelvic ultrasound and magnetic resonance imaging revealed a uterus with normal dimensions for the respective age and the absence of gonads.

At 7 years-old, an exploratory laparoscopy and a gonadectomy were performed, with the identification of streak gonads. Histologic examination revealed a bilateral gonadoblastoma with germ cells, sex cord cells, and calcifications. Molecular analysis was negative for mutations on the *SRY* gene, *NR5A1* gene, or *DHH* gene. Immunohistochemical analysis was negative. No additional treatment was done.

At 9 years-old, her weight is still under the fifth percentile, but her height is adequate and there are no other physical abnormalities. She maintains a delayed psychomotor development.

Discussion

Both cases were diagnosed with premalignant lesions at prepubertal age. Even at very young ages, there is a high tumor risk, which reiterates the importance of the early diagnosis of suspected cases in order to obtain a better characterization and guide these patients.[1,2,4]

Two unrelated phenotypically female patients are presented with case 1 as a complete gonadal dysgenesis and case 2 as a partial gonadal dysgenesis. In the first case, the diagnosis was based on combined first trimester screening and early postnatal investigation. In the second case, the presence of anomalous genitalia led to a multidisciplinary team assessment for sex assignment and long-term management.[4,13] In both cases, the early diagnosis of disorders of sexual development was important to obtain a better overall prognosis, as it anticipated the need for further investigation and the surveillance of comorbidities.

The prevalence of malignancy increases after adolescence and reaches 33% at 50 years.[5] However, there are reports of childhood malignant lesions even before one year old, described in a 9 month-old infant with complete gonadal dysgenesis and gonadoblastoma.[14,15] In fact, complete gonadal dysgenesis has a higher risk of gonadal malignancy compared to partial gonadal dysgenesis and the majority of tumors are discovered at the time of the diagnosis.[1]

Some authors hypothesized that undifferentiated gonads with male-type germ cells are under high gonadotropin stimulation which, would favor neoplastic growth.

Gonadectomy is effective in malignancy prevention. On the other hand, hit as a negative impact on body image and on the development of secondary sexual characters, thereby leading to infertility and requires hormone replacement therapy.[13]

Female phenotypic patients with complete gonadal dysgenesis have a high risk of gonadoblastoma and gonadal dysgerminomas, and the risk increases with age, so bilateral gonadectomy is consistently recommended during early childhood after diagnosis.[1]

In female phenotypic patients with partial gonadal dysgenesis, recommendations for screening and gonadectomy are highly variable, since there is a lack of algorithms to classify the risk of malignancy.[1] Some approaches suggest that molecular diagnosis may be a good predictor of tumor risk, so the time to perform gonadectomy would depend on the result of the molecular analysis.[2,15] However, if the identification of risk factors, such as mutations in the *SRY* gene, strongly predispose one to the development of gonadoblastoma, their absence does not eliminate the risk of malignant transformation. Based on the risk of malignancy and insufficient gonadal function, a gonadectomy should also be performed in phenotypically female patients with partial gonadal dysgenesis.[2,15]

Our clinical cases reinforce the benefit of early intervention as prepubertal patients may have premalignant lesions. In both patients, histology revealed immature germ cells confirming the diagnosis of gonadoblastoma. In both cases, a molecular analysis of the gonadal dysgenesis was performed. Immature germ cells can be identified by positivity for factors typically expressed in early fetal germ cells, such as PLAP.[6] Immunohistochemical markers seem promising in detecting the risk of malignancy or premalignant lesions, but not all are screened in current practice. Management guidelines are required for these patients. Hormone replacement therapy should be performed after gonadectomy.[2,13] In the second case, there was a genotype and phenotype like Turner syndrome associated with short stature. In such cases, there may be eligibility for growth hormone therapy, but only after gonadectomy. Psychological follow-up is recommended and should be included in the long-term treatment of gonadal dysgenesis.[5,13,16]

WHAT THIS CASE REPORT ADDS

- Even at very young ages, there is a high tumor risk, which reiterates the importance of the early diagnosis of suspected cases in order to better characterize and guide these patients.
- Gonadectomy should be performed on all patients with complete gonadal dysgenesis, during early childhood after diagnosis.
- Gonadectomy should be performed on all patients with partial gonadal dysgenesis and female phenotype.
- The time to perform gonadectomy on partial gonadal dysgenesis and female phenotype is not consensual, but it seems prudent to anticipate surgery as close as possible to the diagnosis.
- Psychological follow-up is recommended and should be included in the long-term treatment of gonadal dysgenesis.

Conflicts of Interest

The authors declare that there were no conflicts of interest in conducting this work.

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The authors declare that they have followed the protocols of their work centre on the publication of patient data.

References

1. McCann-Crosby B, Mansouri R, Dietrich JE, McCullough LB, Sutton VR, Austin EG, et al. State of the art review in gonadal dysgenesis: Challenges in diagnostic and management. Int J Pediatr Endocrinol 2014;2014:4. doi: 10.1186/1687-9856-2014-4.
2. Ladjouze A, Donaldson M. Primary gonadal failure. Best Pract Res Clin Endocrinol Metab 2019;33:101295. doi: 10.1016/j.beem.2019.101295.
3. Hersmus R, Stoop H, White SJ, Drop SL, Oosterhuis JW, Incrocci L, et al. Delayed recognition of disorders of sex development (DSD): A missed opportunity for early diagnosis of malignant germ cell tumors. Int J Endocrinol 2012;2012:671209. doi: 10.1155/2012/671209.
4. Kathrins M, Kolon TF. Malignancy in disorders of sex development. Transl Androl Urol 2016;5:794-8. doi: 10.21037/tau.2016.08.09.
5. Liu A, Shi H, Cai Z, Liu A, Zhang D, Huang H, et al. Increased risk of gonadal malignancy and prophylactic gonadectomy: A study of 102 phenotypic female patients with Y chromosome or Y-derived sequences. Hum Reprod 2014;29:1413-9. doi: 10.1093/humrep/deu109.
6. Pleskacova J, Hersmus R, Oosterhuis W, Setyawati B, Faradz S, Cools M, et al. Tumor risk in disorders of sex development. Sexual Dev 2010;4:259-69. doi: 10.1159/000314536.
7. Tajouri A, Ben Gaied D, Hizem S, Boujelben S, Maazoul F, M'rad R, et al. Functional analysis of mutations at codon 127 of the SRY gene associated with 46,XY complete gonadal dysgenesis. Sex Dev 2017;11:203-209. doi: 10.1159/000478718.
8. Lau YF, Li Y, Kido T. Gonadoblastoma locus and the TSPY fene on the human Y chromosome. Birth Defects Res C Embryo Today 2009;87:114-22. doi: 10.1002/bdrc.20144.
9. Werner R, Mönig I, Lünstedt R, Wünsch L, Thorns C, Reiz B, et al. New NR5A1 mutations and phenotypic variations of gonadal dysgenesis. PLoS One 2017;12:e0176720. doi: 10.1371/journal.pone.0176720.
10. Baldinotti F, Cavallaro T, Dati E, Baroncelli GI, Bertini V, Valetto A, et al. Novel familial variant of the desert hedgehog gene: Clinical findings in two sisters with 46,XY gonadal dysgenesis or 46,XX karyotype and literature review. Horm Res Paediatr 2018;89:141-9. doi: 10.1159/000485507.
11. McCann-Crosby B, Gunn S, Smith EO, Karaviti L, Hicks MJ. Association of immunohistochemical markers with premalignancy in gonadal dysgenesis. Int J Pediatr Endocrinol 2015;2015:14. doi: 10.1186/s13633-015-0010-6.
12. Kohva E, Miettinen Pj, Taskinen S, Hero M, Tarkkanen A, Raivio T. Disorders of sex development: Timing of diagnosis and management in a single large tertiary center. Endocr Connect 2018;7:595-603. doi: 10.1530/EC-18-0070.
13. Raza J, Zaidi SZ, Warne GL. Management of disorders of sex development: With a focus on development of the child and adolescent through the pubertal years. Best Pract Res Clin Endocrinol Metab 2019;33:101297. doi: 10.1016/j.beem.2019.101297.
14. Patel PR, Pappas J, Arva NC, Franklin B, Brar PC. Early presentation of bilateral gonadoblastomas in a Denys-Drash syndrome patient: A cautionary tale for prophylactic gonadectomy. J Pediatr Endocrinol Metab 2013;26:971-4. doi: 10.1515/jpem-2012-0409.
15. Abacı A, Çatlı G, Berberoğlu M. Gonadal malignancy risk and prophylactic gonadectomy in disorders of sexual development. J Pediatr Endocrinol Metab 2015;28:1019-27. doi: 10.1515/jpem-2014-0522.
16. Lee PA, Nordenström A, Houk PC, Ahmed SF, Auchus R, Baratz A, et al. Global disorders of sex development update since 2006: Perceptions, approach and care. Horm Res Paediatr 2016;85:158-80. doi: 10.1159/000442975.

Disgenesia Gonadal e Malignidade: Quando Deve Ser Realizada uma Gonadectomia?

Resumo:
A disgenesia gonadal é um distúrbio do desenvolvimento sexual caracterizado por formação defeituosa ou incompleta das gónadas (ovário ou testículo) devido a modificações numéricas ou estruturais dos cromossomas sexuais ou devido a mutações nos genes responsáveis pelo desenvolvimento das gónadas. São apresentados dois casos de doentes fenotipicamente do sexo feminino, um com disgenesia gonadal completa e uma disgenesia gonadal parcial. Ambos os casos foram diagnosticados com lesões pré-malignas na idade pré-púbere. Mesmo em idades muito jovens, existe um alto risco neoplásico, o que reitera a importância do diagnóstico precoce de casos suspeitos, a fim de melhor caracterizar e orientar esses pacientes. Para prevenir o desenvolvimento de malignidade, recomenda-se uma gonadectomia, o mais próximo possível do diagnóstico.

Palavras-Chave: Aberrações dos Cromossomas Sexuais; Criança; Disgenesia Gonadal/cirurgia; Disgenesia Gonadal/diagnóstico; Disgenesia Gonadal/Genética; Fatores de Risco; Gonadoblastoma