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Clinical Update

On the Role of Prophylactic Gonadectomy in Turner Syndrome

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Keywords
Germ cell tumor
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Y-chromosome

Abbreviations
GB - Gonadoblastoma
GCNIS - Germ cell neoplasia in situ
GCT - Germ cell tumors
PCR - Polymerase chain reaction
TS - Turner syndrome
TSPY - Testis specific protein-Y

Abstract

Turner Syndrome (TS) is a chromosomal disorder with a karyotype of 45X. However, by conventional karyotyping, Y-chromosomal material is known to occur in up to 5-12% of TS patients; but it escalates to 60% when molecular diagnostic tools are used. The most commonly investigated genes were SRY, DYZ3, ZFY, and TSPY. Identifying the Y-chromatin in TS is important as it is associated with the risk of developing germ cell tumors, especially gonadoblastoma (GB). The prevalence of GB in TS is variously reported as ranging from 0 to 33%. As imaging studies cannot conclusively exclude malignancy of abdominal gonads, prophylactic gonadectomy is recommended in TS patients with Y-chromatin fragment. However, the optimal time of prophylactic gonadectomy is not known. The International Turner Syndrome Consensus Group recommends gonadectomy at the time of diagnosis, regardless of age while recent evidences suggest a more flexible approach, especially at puberty.

INTRODUCTION

Turner Syndrome (TS) is a genetic disease characterized by short stature, sexual infantilism, gonadal dysgenesis, and typical dysmorphic features. Its prevalence is approximately 1 in 2000–2500 live female births.[1] About 40%–60% of TS patients have a 45X karyotype, and the others have structural abnormalities of the X-chromosome or various kinds of mosaicism. In addition, a cell line containing a Y-chromosomal segment is present in up to 60% of TS patients.[2] Identifying Y-chromatin in TS individuals is essential as it is associated with the risk of developing germ cell tumors (GCT). Gonadectomy is generally recommended in TS females with Y-chromosome-derived material to prevent the development of GCT, especially gonadoblastoma (GB).

PREVALENCE OF Y-CHROMOSOME MATERIAL AMONG TURNER SYNDROME PATIENTS

Karyotyping identifies a normal or structurally aberrant Y-chromosome in 5–12% of the TS patients.[3] However, molecular studies such as polymerase chain reaction (PCR) and fluorescence in situ hybridization (FISH) can detect concealed Y chromosome material in TS patients, consequently escalating the Y-chromosome sequence detection frequency to approximately 60%.[3-4] The most commonly investigated genes were SRY, DYZ3,

ZFY, and TSPY.[1,3-4] To detect individuals at high risk of GCT, the TS Consensus Study Group recommended testing for Y-chromosome material only in TS patients who present with a marker chromosome or virilization.[5] However, many recent studies have reported molecular identification of Y-chromosome material in TS patients even in the absence of virilization or a marker chromosome. This finding suggested the necessity of screening for cryptic Y-chromosome in all TS patients.

PATHOGENESIS OF GERM CELL TUMORS

The biology of the development of GCT is not completely known. The peri-centromeric gonadoblastoma region of the Y-chromosome (GBY locus) is deemed to contain the presumed GB gene, for example, the testis-specific protein-Y (TSPY) gene.[6] TSPY behaves as a proto-oncogene in patients with dysgenetic gonads. An interaction of the OCT3/4 gene with TSPY is implicated in the pathogenesis of GB. OCT3/4 is essential to maintaining the pluripotent nature of embryonic stem cells and primordial germ cells.[6] GB, classified as a borderline GCT arising from sex cord and germ cells, is intrinsically linked with gonadal dysgenesis. Y-chromosome-associated GB can transform into invasive dysgerminoma or other malignant GCT, including embryonic carcinoma, teratoma, yolk sac tumor, and choriocarcinoma.

RISK OF DEVELOPMENT OF GERM CELL TUMORS

The risk of developing GB in TS patients with Y-containing material is variously quoted in several studies. As TS patients with multiple Y-variants are grouped under a single cohort in most studies, the risk stratification based on the levels of mosaicism, inclusion or exclusion of TSPY, translocated portions of the Y and other Y chromosome variants is lacking in the literature. In a systematic review by de Marqui *et al.*[4] nine studies reported the prevalence of GB ranging from 0 to 33%. In another review by Pyle *et al.*[7] 26 cases had germ cell neoplasia in situ (GCNIS)/GB (26.2%), and three patients had dysgerminoma (3%) among 99 TS patients with Y-chromosome material included from 7 studies published after 2006. In contrast, a UK cohort study published within the same time frame including 212 patients described five (2.4%) with GCNIS/GB and two (1.0%) with dysgerminoma.[8] A meta-analysis of 11 studies analyzing the association between Y-chromosome material and GB reported five cases of GB in 43 patients (11.6%) with TS-bearing Y-chromosome cell lines.[9]

The diagnosis of GCT primarily depends on pathological assessment following gonadal biopsy or gonadectomy.[3] However, multiple histological sections of the streak gonad are required to demonstrate microscopic GB. Neither ultrasonography nor magnetic resonance imaging can definitively exclude neoplasms of intra-abdominal gonads in TS patients. It may be bilateral in up to 10% of cases.[10] Since not all TS individuals with Y cell lines develop tumors, other unrecognized factors must also be present predisposing to tumor formation. Cools et.al.[11] reported a correlation between external genital phenotype as assessed by external masculinization score and presence of GCNIS/GB. However, this finding could not be replicated in other studies.[11] The clinical features of virilization may not be present in all TS subjects with GCT. Similarly, a Y-positive TS will have a higher GCT risk with abdominal gonads as compared to scrotal gonads, and the risk increases with advancing age.[7] Furthermore, the risk of GB development among patients with cryptic Y-chromosome material is similar to that of individuals possessing overt abnormalities of the Y-chromosome.[12] However, the only established risk factors for malignant transformation are older age and intra-abdominal location.[13]

ROLE OF GONADECTOMY

Coyle *et al.*[6] observed GB in four of 14 patients, of whom only one was older than six years and the youngest was just five months. Matsumoto *et al.*[14] reported a series that included seven females with

TS having Y-chromosome material, aged between 2 and 11 years. Pathologic examination revealed gonadal tumors in four subjects, the youngest of which was 2 years old. The fact that GB is thought to occur most commonly in the second decade of life may be a result of late diagnosis of TS in other series, leading to later prophylactic gonadectomy. If gonadal biopsy is done before determining the appropriateness of gonadectomy, histological examination of the biopsy specimen for TSPY and OCT3/4 expression has been recommended to improve the detection rate of GB and germ cell malignancy.[6]

Although the risk of GB in individuals with a Y-chromosome is not precisely quantified, gonadectomy for individuals with a fragment of Y-chromosome should continue to be mandatory as recommended by the recent guideline.[15] The International Turner Syndrome Consensus Group recommends that female individuals with TS and Y-chromosome material should undergo gonadectomy at the time of diagnosis, regardless of age.[15] However, others suggest gonadectomy should be considered at puberty.[7] This view is supported by the data that 42% of girls with TS with Y-chromosome material attained puberty spontaneously and 11% achieved spontaneous menarche indicative of gonadal function.[13] Recent developments have also occurred in the medical and surgical management of TS patients with GCT. Therefore, gonadectomy is no longer considered the default treatment approach for TS subjects with Y-chromosome material at the first visit. The timing of such surgery and risk of malignancy can be discussed with parents during counseling.

CONCLUSION

The prevalence of Y-chromosome material among TS subjects should be meticulously evaluated by PCR as it is inexpensive, sensitive, rapid, and allows the tracking of various sequences of Y-chromosome simultaneously. In those patients with Y-positive sequences, prophylactic gonadectomy is recommended for prevention of GB. However, the age at which the gonadectomy to be offered is inconclusive. Given the benign nature of GB there seems to be considerable advantage in doing gonadectomy at puberty.

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