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Review

Current controversies in turner syndrome: Genetic testing, assisted reproduction, and cardiovascular risks☆

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ABSTRACT

Patients with Turner syndrome (TS) require close medical follow-up and management for cardiac abnormalities, growth and reproductive issues. This review summarizes current controversies in this condition, including: 1) the optimal genetic testing for Turner syndrome patients, particularly with respect to identification of Y chromosome material that may increase the patient's risk of gonadoblastoma and dysgerminoma, 2) which patients should be referred for bilateral gonadectomy and the recommended timing of such referral, 3) options for assisted reproduction in these patients and associated risks, 4) the increased risk of mortality associated with pregnancy in this population, and 5) how best to assess and monitor cardiovascular risks.

Introduction

Turner syndrome is a heterogenous genetic disorder caused by loss of the short arm of the X chromosome, and it affects approximately 1 out of 2500 newborn females. Classic Turner syndrome associated with 45,X karyotype occurs in approximately 45% of cases and is characterized by short stature, ovarian insufficiency, nuchal folds, low hairline, low set ears, high-arched palate, widespaced nipples (shield chest), left-sided cardiac anomalies, cubitus valgus (wide carrying angle), shortened fourth metacarpal, and nail abnormalities. Mosaic Turner syndrome accounts for the remaining 55% of cases and has a highly variable phenotype depending on the region(s) of missing X chromosome and/or the proportion and location of affected cells. Due to the variable and often more subtle phenotypic characteristics caused by mosaic X chromosome loss, diagnosis of these patients is often delayed or missed. Conversely, as genetic techniques become more sensitive, lower levels of mosaicism are being identified. It is unclear whether patients with low-level mosaicism share similar risks and require similar monitoring as patients with classic Turner syndrome.

Endocrinologists are charged with evaluation and management of growth failure, ovarian insufficiency and estrogen replacement, and infertility. In addition, endocrinologists guide families toward subspecialty management of additional issues, such as cardiac abnormalities. For general reviews of these topics, readers are referred to Refs. [1–3]. This review focuses on the controversial issues of genetic testing for Y chromosome material as it relates to risk of gonadoblastoma and need for prophylactic gonadectomy, as well as assisted reproduction in patients with significant peri-partum cardiovascular risks. Although firm guidelines have not yet been established regarding these issues, we aim to provide the reader with recommendations for their clinical practices.

Genetic testing for Y chromosome material

The presence of Y chromosome material is associated with increased risk of gonadoblastoma and germ cell tumors in patients with Turner syndrome (reviewed in Ref. [4]). Unfortunately, cryptic mosaicism for Y chromosome material may not be detected by standard cytogenetic techniques, which typically analyze 20–30 peripheral lymphocytes in metaphase [5]. Therefore, specific molecular testing for Y chromosome material must be performed in patients for whom the diagnosis is not clear (i.e. patients with a 45,X karyotype, see Figure 1). The preferred method for such testing is fluorescent in situ hybridization (FISH) for the Y-centromere

Abbreviations: FISH, fluorescent in situ hybridization; SRY, sex-determining region of Y; PCR, polymerase chain reaction; TSPY, testes-specific protein Y-linked; MRI, magnetic resonance imaging; CAIS, complete androgen insensitivity syndrome; FSH, follicle stimulating hormone; AMH, anti-Mullerian hormone; ART, assisted reproductive technology; IVF, in vitro fertilization; PAPVR, partial anomalous pulmonary venous return; BSA, body surface area; ASI, aortic size index; EKG, electrocardiogram.

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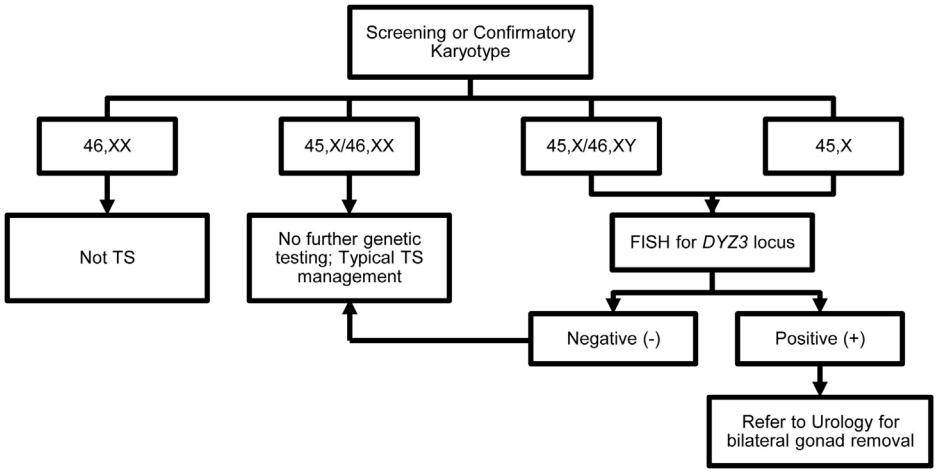

Figure 1. Recommended genetic testing for Turner syndrome.

using a probe to the *DYZ3* locus because this region is linked to gonadoblastoma risk [6–8]. Importantly, FISH for the *SRY* gene is not specific to this region, and polymerase chain reaction (PCR) is susceptible to contamination [9].

All patients with 45,X karyotype should be evaluated specifically for Y chromosome material. Patients with mosaic Turner syndrome identified cytogenetically whose second cell line contains an additional chromosome that is either an X or derived from an X do not require further molecular testing because, by definition, the origin of their mosaicism has been determined. True sex chromosome monosomy (45,X or 45,Y) is incompatible with life; the presence of at least a partial second sex chromosome in a mosaic fashion is necessary [10]. The mosaicism is hypothesized to arise from the presence of a second ("rescue") embryonic cell line that comprises only a small percentage of adult cells and consequently is not detected by conventional cytogenetic analysis. Thus, patients with 45,X karyotype may have a second cell line containing Y chromosome material that increases their risk of gonadoblastoma.

There is wide variability in the reported prevalence of Y chromosome material, gonadoblastoma, and dysgerminomas in Turner syndrome, likely due to differences in clinical practice regarding methods of genetic testing, recommendation for gonadectomy, and pathology analysis. A review of three studies in 2005 revealed that Y chromosome material is present in 8–12% of patients with Turner syndrome. Approximately 27% of this subset of patients have histologically-confirmed gonadoblastoma and 4% of these patients have evidence of malignant transformation (14% of patients with gonadoblastoma) [11]. The etiology of gonadoblastoma and mechanism of transformation to germ cell tumors are unclear [12]. Although a specific gene mutation has not been associated with this neoplasm, several groups have provided evidence that *TSPY* is the gonadoblastoma-susceptibility gene located within the centromeric region of the Y chromosome (reviewed in Ref. [8]). Interestingly, there is some evidence that gonadoblastoma is a congenital, rather than progressive, disorder due to fetal germ cell dysgenesis [13]. In fact, gonadoblastoma has been identified in infants with Turner syndrome. There is a theoretical concern that growth hormone therapy may increase the risk of gonadoblastoma and/or malignant transformation, but no evidence supporting this has been presented to date.

Because of the uncertain pathophysiology and natural history of gonadoblastoma, it is recommended that all patients with either 45,X/46,XY mosaic karyotype or 45,X with positive *DYZ3* FISH analysis be referred for bilateral gonadectomy [14]. However, it is important to keep in mind that identification of Y chromosome material in peripheral blood samples does not necessarily reflect presence of Y chromosome material in gonadal tissue [15], which is most likely directly related to gonadoblastoma formation. An age threshold for gonadectomy has not been established in this patient population, particularly because evidence is lacking that screening with ultrasound, MRI, or serum tumor markers are sufficiently sensitive to identify gonadoblastoma prior to transformation to germ cell tumor [14]. Unfortunately, gonadal biopsy is likely also insufficiently sensitive to identify all cases of gonadal Y chromosome material, gonadoblastoma, and/or germ cell tumor, as only a small tissue region is analyzed.

It is unclear if patients with previously established 45,X non-mosaic Turner syndrome who had never been assessed for Y material in the past should now undergo retrospective targeted search, and if there should be an age cutoff for this. In the absence of evidence, it is reasonable to retroactively perform FISH for *DYZ3* locus in patients with previously-identified 45,X karyotypes. Those patients with positive *DYZ3* FISH should be referred to Urology and Reproductive Endocrinology for discussion of the risks and benefits of gonadectomy. Further studies are needed to address these important questions.

Because patients with classic and 45,X/46,XY mosaic Turner syndrome have low fertility potential, gonadectomy may be considered of little consequence. However, many patients and their families may have difficulty consenting to a procedure that reduces or eliminates that potential, particularly when the risks associated with delaying or refusing gonadectomy are somewhat unclear. Patients with complete androgen insensitivity syndrome (CAIS) face similar considerations because they are also at increased risk for gonadoblastoma and germ cell tumors, although they are unable to carry a pregnancy [16]. Bilateral gonadectomy is recommended in all patients with CAIS but is often delayed until after puberty because most patients with CAIS develop secondary female sex characteristics at the appropriate pubertal age due to conversion of elevated testosterone levels to estrogen. The decision to delay gonadectomy also may be more appropriate in the CAIS population because of the lower rate of gonadal dysgenesis compared to patients with Turner syndrome, although there certainly are proponents of early gonadectomy in all cases given the malignant potential of intra-abdominal dysgenic gonadal tissue.

Reproductive potential

Between 15% and 40% of adolescents with Turner syndrome undergo spontaneous puberty, although only 2–10% have