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Turner Syndrome with Y Chromosome: Spontaneous Thelarche, Menarche, and Risk of Malignancy

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Abstract

Study Objective: Girls with Turner syndrome with Y-chromosome material (TS + Y) are assumed to have nonfunctional gonads with increased tumor risk, therefore prophylactic gonadectomy is recommended at diagnosis. In this study we aimed to determine rates of spontaneous thelarche (ST) and spontaneous menarche (SM), and prevalence of gonadal tumor and malignancy in girls with TS + Y, to further inform discussions about gonadectomy.

Design: Retrospective review of clinical and pathology data.

Setting: Multicenter study involving 4 United States children's hospitals.

Participants: Patients included those with a genetically proven diagnosis of TS + Y and phenotypically female genitourinary exam.

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These findings were presented, in part, at the Midwest American Association of Clinical Endocrinologists meeting Chicago, Illinois, 2016; at Lurie Children's Hospital Research Scholar's Day Chicago, Illinois May 2015; and at Pediatric Endocrine Society 2016, Orlando, Florida.

Interventions: Demographic characteristics, pubertal development, and gonadal pathology data were abstracted from clinical records. Data for ST were analyzed for patients aged 13 years and older and SM for patients older than 15 years.

Main Outcome Measures: ST, SM, prevalence of gonadal tumor, and malignancy.

Results: Forty-four patients met inclusion criteria. Nineteen patients were 13 years or older; 8/19 (42%) had ST and reached Tanner stages 2–4 and 2 (11%) had normal ovarian pathology. Nineteen patients were 15 years or older; 2/19 (11%) had SM. Thirty-seven patients underwent gonadectomy; 35 had available pathology results. Gonadoblastoma was identified in 35/7 patients (19%), 1 in situ germ cell neoplasia, and 1 dysgerminoma (3%). One patient with bilateral gonadoblastoma had ST and SM.

Conclusion: In this multicenter cohort, 42% of girls with TS + Y entered puberty spontaneously and 11% had SM, supportive of gonadal function. Risk of tumor was similar to previous reports. To achieve informed decision-making, discussions about gonadectomy should incorporate potential for gonadal function and tumor risk.

Keywords

Turner syndrome with Y chromosome; Turner syndrome; Sex chromosome DSD; Infertility; Ovarian insufficiency; Gonadal dysgenesis; Gonadoblastoma

Introduction

Turner syndrome (TS) is a condition characterized by female phenotype and 45,X genotype with or without identifiable mosaicism. TS is variable in presentation and severity. The most common features of TS are short stature and premature ovarian insufficiency. Approximately 12% of girls with TS also have Y-chromosome material (TS + Y).[1] Like other girls with TS, their genitalia is phenotypically female. Individuals with a 45,X/46,XY karyotype who have any degree of virilization (ie, atypical or male-typical genitalia) are not considered to have TS.

Girls with TS + Y constitute a unique category of TS because of their risk of gonadoblastoma, a premalignant germ cell tumor with risk of malignant transformation. Reported rates of gonadoblastoma range widely from 2% to 50% and reported rates of malignant transformation are low, from 1% to 12%.[2–13] Although gonadoblastoma has been identified in infancy, malignant transformation does not typically occur until the second decade of life, although there is one report in a girl with TS + Y as young as 6 years old.[13]

In 2016, the International Turner Syndrome Consensus Group published clinical practice guidelines for TS, recommending that girls with TS + Y undergo gonadectomy at the time of diagnosis, but acknowledged this is on the basis of a low level of evidence and further research is needed.[14] The recommendation for gonadectomy at the time of diagnosis aims to prevent malignancy and is on the basis of an assumption that the gonads have little potential for hormone production or fertility.[2,3] For an individual or family, accurate information about potential future hormone function and fertility is one important factor that might inform if and when to perform gonadectomy. Supporting the need for accurate information

about ovarian function in TS + Y, infertility has been reported as the most significant stressor to patients with TS.[15] Infertility and abnormal pubertal development are also the most commonly cited reasons for couples electing termination of a pregnancy confirmed to have TS.[16]

Little evidence is available about hormone function and fertility potential in women with TS + Y. To our knowledge, only 3 case reports of women with TS + Y are available in the literature documenting spontaneous pregnancy and subsequent live birth, which shows that some women with TS + Y have gonadal function.[15–18] Incomplete understanding of potential future ovarian function and fertility for girls with TS + Y impairs counseling and informed decision-making, particularly surrounding gonadectomy. To address this knowledge gap in care and improve the informed decision-making process, a retrospective multicenter study was conducted to assess the prevalence of spontaneous thelarche (ST), spontaneous menarche (SM), and occurrence of gonadoblastoma and malignant transformation among girls with TS + Y.

Materials and Methods

Four children's hospitals participated in this retrospective chart review in which clinical characteristics and gonadal pathology from patients with TS + Y were assessed. Each hospital's institutional review board approved the study. Participants were identified at each site with the use of the ninth revision of the International Classification of Diseases codes associated with TS + Y. Search terms included: TS, TS with mosaicism, TS with X/XY mosaicism, mosaic, mosaic TS, history of TS, Ullrich-TS, XY-TS, Male TS, X Turner's syndrome, X/XY Turner mosaicism, and other variants of TS. Inclusion criteria for this study were a diagnosis of TS with presence of Y chromosome material (genetic testing for karyotype and/or fluorescence in situ hybridization [FISH] analysis) along with documentation of a phenotypically female external genitourinary exam.

The study cohort consisted of 44 individuals. Phenotypic data were gathered retrospectively from the electronic medical record using manual extraction by reviewers at each study site. The following data elements were collected: demographic characteristics, karyotype and FISH results for all tested tissues, Tanner staging by an endocrinologist, history and age of ST and SM, pelvic ultrasound (US) results before and after gonadectomy, age and indication for gonadectomy, gross pathology and histology of gonadal tissue, follow-up after gonadectomy, and any attempts at fertility preservation or pregnancy. ST was defined as breast development before exposure to exogenous estrogen and SM as menses before exposure to exogenous estrogen. Pubertal failure was defined as lack of ST by 13 years and lack of SM by 15 years, on the basis of commonly accepted normal ranges for ST and SM in women.[19,20] All deidentified data were sent to the lead site for statistical analysis.

Data were stored and analyzed in Research Electronic Data Capture software hosted at Northwestern University. Statistical analysis within Research Electronic Data Capture included descriptive statistics to summarize demographic characteristics and clinical features including karyotype information, US findings, rates of ST and SM, and pathology data. Means with SD are presented as appropriate.

Results

Data from 44 girls with TS + Y were included in this analysis and their characteristics are shown in Table 1. Peripheral blood karyotype identified Y material in all patients. Additionally, 16 had Y chromosome material identified in peripheral blood according to FISH analysis, 5 had Y chromosome material identified on gonadal karyotype, and 1 had Y chromosome material identified on fibroblast karyotype.

Gonadectomy and Malignant Transformation

Abdominal US before gonadectomy was performed in 27 patients. A prepubertal uterus was seen in 25 (93%) patients and 2 had no uterus visualized. Ovaries were visualized bilaterally in 10 patients (27%) and unilaterally in 3 (11%). Two patients (7%) with ST had no ovaries visualized on US. No masses were noted on US in any patients.

Thirty-six of the 44 patients (81%) underwent gonadectomy at an average age of 10.8 years (age range, 0.8–18 years) and pathology results were available for all 36 patients. Pathology reports confirmed 9 (25%) patients had germ cell tumors (Table 2). Of these patients, 7 (19%; 95% confidence interval, 8%−35%; age range, 6–216 months at diagnosis) had gonadoblastoma (4 unilateral, 3 bilateral), 1 had dysgerminoma (3%; 95% confidence interval, 0.1%−14%; 144 months of age at diagnosis), and 1 had nonspecific in situ neoplasia. Of those with abnormal gonadal pathology who had preoperative US (n = 7), the US examinations either showed normal gonads or gonads were unable to be visualized (no tumor was identified). One patient (age 21 years) had gonads evaluated for possible fertility preservation, and no germ cells were identified.

Spontaneous Thelarche

In this cohort, 19 of the 44 patients were older than 13 years at the time of gonadectomy or had not undergone gonadectomy. Eight of the 19 (42%) had ST; details are shown in Table 3. Age of thelarche was only available in 4 patients, so average age could not be accurately determined. Tanner staging was available in 7 of these patients (35%): 2 patients achieved Tanner 2 breast tissue, 4 patients achieved Tanner 3, and 1 patient achieved Tanner 4; the remainder were not recorded.

SM

In this cohort, 19 of the 44 patients were 15 years or older at the time of gonadectomy or had not undergone gonadectomy. Two reported spontaneous menses before gonadectomy (11%).

Discussion

Current guidelines recommend that individuals with TS + Y undergo gonadectomy at the time of diagnosis because of risk of developing gonadal tumor and potential malignant transformation. There is limited information characterizing timing of malignant transformation, ovarian function, and fertility potential among patients with TS + Y. In this study we aimed to enrich the body of evidence informing gonadectomy in TS + Y to aid counseling and informed decision-making. It is the first study, to our knowledge, to

specifically assess rates of ST and SM in patients with TS + Y so data on ovarian function and fertility potential might be better factored into consideration of gonadectomy.

In this cohort of girls with TS + Y at pubertal ages, 42% had ST and 11% had SM. Although estrogen can arise from peripheral aromatization in adipose tissue and lead to some breast development, more advanced stages of breast development and menarche suggests estrogen exposure from ovarian function. Whether this ovarian function translates to fertility potential is unknown. Borgstrom et al reported that a history of ST and SM in adult women with TS is associated with fertility potential, and that these individuals would be candidates for fertility preservation.[21] In addition, several case reports of pregnancy in women with TS + Y have been published. Thus, thelarche, menarche, and fertility are all possible in girls with TS + Y. This raises the question of whether recommendations about gonadectomy at time of diagnosis for girls with TS + Y should be reconsidered.

In evaluating recommendations for gonadectomy, understanding the risk of developing a malignancy is crucial. In the present study, the rate of gonadoblastoma was 19%, similar to previous reports. Gonadoblastoma is a premalignant lesion with the potential for malignant transformation, but if and when it will undergo malignant transformation is not known. The only established risk factors for malignant transformation are older age and intra-abdominal location.[22] There is a paucity of data about mortality from gonadal malignancy in TS + Y, but in our review of the literature, no deaths were reported.[23] In our study, the rate of malignancy was 3%, with confidence interval up to 8%, also similar to previous reports. Complete understanding of timing and progression of malignant transformation is limited because most patients have gonadectomy at early ages and thus accurate risk assessment remains difficult to determine. Monitoring for tumor using imaging is not reliable, further complicating decisions about gonadectomy. Previous studies in differences/disorders of sex development (DSD) have shown that imaging using US or magnetic resonance does not rule out a neoplasms in patients with gonadal dysgenesis.[24] Similarly, in our study, no evidence of dysgerminoma was seen on US before diagnosis.

Weighing the potential for ovarian function and fertility vs the risk of gonadal malignancy is complicated. It is useful to consider the debate about gonadectomy in DSD. Gonadectomy in DSD in the pediatric population has become increasingly controversial because of the potential benefits of endogenous hormone production, preservation of possible future fertility, and ethical concerns. One ethical consideration is assent and autonomy for decisions about reproductive organs. Some also argue that gonadectomy itself results in a physical and emotional loss for patients.[25] Other ethical issues include creating false hope for fertility potential and transmission of a genetic condition to offspring.[13,17,25] For the latter concern, some ethicists argue that individuals have the responsibility to produce the “best” offspring they can whereas others assert that this is a eugenic view and individuals with medical problems can lead happy, valuable lives.[25] Increasingly, risk of malignancy in DSD can be stratified and recommendations about timing of gonadectomy have shifted to account for lesser or greater risk.[26–28] In complete androgen insensitivity syndrome, for example, the prepubertal risk of malignancy is thought to be low, at approximately 2%. Thus, to preserve hormone function and autonomous decision-making, it is recommended to allow these individuals to undergo spontaneous puberty via aromatization of androgens and

then to perform gonadectomy postpubertally or to biopsy and follow.[28] In TS + Y the risk of malignancy might be higher, but if girls have a 42% chance of ST, and 11% chance of SM and potential fertility, we should consider an open and thoughtful discussion about all of these factors in making a decision about gonadectomy. On the basis of the existing literature, which suggests that infertility is one of the most significant concerns among families,[15] some patients and families might place greater importance on potential ovarian function, whereas others might prioritize avoidance of malignancy risk. Although further research on fertility preservation for individuals with TS + Y is needed to fully incorporate it into the decision-making process about gonadectomy, if proceeding with gonadectomy, fertility preservation options should be addressed.

Although this was a relatively large sample compared with previous studies, there are important limitations to consider. The patient cohort remains small because TS + Y is a relatively rare condition. Most patients underwent gonadectomy before pubertal age, limiting assessment of gonadal function as well as timing of malignant transformation. Additionally, this was a retrospective study, limiting the ability to obtain further information when medical records were incomplete. There was also no biochemical assessment of the pituitary-gonadal axis to confirm that ST and SM were caused by pubertal rises in gonadotropin and estradiol levels. In discussion of fertility potential, in this study we extrapolated ovarian function to the potential for fertility, but it is not known whether this will prove to be an accurate indicator. Additionally, data on anti-Müllerian hormone levels were not collected in this study, a measurement that might provide some additional data about ovarian reserve. Data including biochemical assessment and postpubertal evaluation of fertility should be assessed in the future to broaden understanding of gonadal function in TS + Y.

On the basis of our data, we suggest that multidisciplinary teams present current guidelines about gonadal management at the time of diagnosis. In addition, however, we suggest that they also discuss the complexities and unknown factors regarding this recommendation. On the basis of existing data, families can be reassured that this is rarely a decision that requires urgent action. In addressing tumor risk, it is important to discuss estimated risk and challenges in reliable monitoring, but also that malignancy is extremely rare before the second decade of life and that mortality from such cancer in TS + Y has not been reported. Patients and families should be counseled that: (1) spontaneous pubertal development and continuing ovarian function might be difficult to predict, particularly at young ages; and (2) spontaneous fertility has been reported, although very rarely, and that there are no clear data about likelihood of fertility potential. Potential contributing data, including biochemical assessment and imaging, might be useful to provide additional guidance. An individual's current ovarian function might be assessed via gonadotropin levels. Reliable biochemical assessment of ovarian reserve in the pediatric population is not proven, but it is possible that anti-Müllerian hormone levels are predictive.[21] After presenting these considerations, patients and families should weigh the factors that are most important to them and make an informed decision with the support of a multidisciplinary team.

To our knowledge, this study is the first to characterize rates of ST and SM among a large and diverse cohort of girls with TS + Y, and showed that nearly half the girls with TS + Y

have signs of estrogen exposure, which might indicate ovarian function. It also provides supporting evidence for the published frequency of gonadoblastoma occurrence and malignancy. Although future studies are needed to refine our understanding of ovarian function in this population, the data can be used to counsel about potential ovarian function and malignancy risk to allow for informed, individualized decision-making for gonadectomy in girls with TS + Y.

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Table 1

Patient Characteristics (N = 44)

Variable	Value
Age at diagnosis (n = 41)	9.5 [0–17.5] years
Race/ethnicity	
White	16 (36)
Hispanic/Latino	7 (16)
Black/African American	1 (2)
Asian	2 (5)
Unknown	18 (40)
Peripheral blood karyotype	
45,X/46,XY	26 (59)
Other karyotype *	18 (41)
Age at gonadectomy † (n = 31)	10.8 [0.3–18.0] years
Gonadal pathology † (n = 36)	
Bilateral streak gonad	22 (61)
Unilateral gonadoblastoma, unilateral streak gonad	4 (11)
Bilateral gonadoblastoma	3 (8)
Unilateral streak gonad, unilateral normal ovary	2 (6)
Unilateral dysgerminoma, unilateral streak gonad	1 (3)
Other ‡	4 (11)

Data are presented as n (%) or median [range].

* Other karyotypes include: 45,X mosaicism with 1 or more of the following: isodicentric Y chromosome; derivative X or Y chromosome resulting from sex chromosome translocation; ring sex chromosome; 47,XYY; 46,XY/47,XYY; and 47,XY+21.

† Thirty-seven patients had gonadectomy, age data were available for 31 patients, and pathology results were available for 36 patients.

‡ Other pathology results include: bilateral streak gonad with unilateral testicular tissue; dysgenetic gonad with in situ germ cell neoplasia; gonads with Leydig cell elements; and per report, “normal.”

Table 2

Patients with ST and SM

Peripheral Blood Karyotype	Age at ST, years	Age at SM, years	Gonadal Pathology	Other Pathology
46,X,der(X)t(X; Y) (q8; p11.23)	11	–	Bilateral streak gonad	Adrenal rest
45,X/46,XY	15	–	Unilateral streak gonad, unilateral normal ovary	Wolffian structures
45,X/46,XY	14	–	Bilateral streak gonads	Adrenal rest
45,X/46,XY	Unknown	17	Bilateral gonadoblastoma	–
45,X/46,XY	Unknown	–	Normal ovary	–
45,X [15]/46,X,idic(Y) (q11.1)[5]	Unknown	–	Bilateral streak gonad	–
45,X/46,XY	12	12	Bilateral streak gonad	Wolffian and Müllerian structures
45,X[4]/46,X,idic(Y) (q11.2)[46]	N/A	–	Bilateral gonads with Leydig cell elements	–

N/A, not applicable; SM, spontaneous menarche; ST, spontaneous thelarche.

Table 3

Patients with Gonadal Neoplasia

Peripheral Blood Karyotype	Gonadal Karyotype	Age at Gonadectomy, years	Gonadal Pathology	Ultrasound Result	Copies of *SRY*
Patients with dysgerminoma					
45,X/46,XY	–	16	Streak gonad, dysgerminoma	Gonads not visualized	1
Patients with gonadoblastoma					
45,X/46X,idic(Y) (p11.3)	–	1	Bilateral gonadoblastoma	Normal gonads	2
45,X/46,XY	–	2	Bilateral gonadoblastoma	Gonads not visualized	1
45,X/46,XY	–	10	Streak gonad, unilateral gonadoblastoma	Normal gonads	1
45,X/46,XY	45,X/46,XY	11	Streak gonad, unilateral gonadoblastoma	Gonads not visualized	1
45,X/46,XY	–	12	Bilateral gonadoblastoma	N/A	1
45,X/46,X, idic(Y) (q11.23)	45,X/47,XYY	N/A	Streak gonad, unilateral gonadoblastoma	N/A	2
46,X,idic(Y) (q11.23)/46,X,r(Y) (p11.3q11.23)/45,X	–	N/A	Streak gonad, unilateral gonadoblastoma	N/A	2
Patients with in situ germ cell neoplasia					
45,X/46,XY	Right gonad: 45,X[17]/47,XYY[2]/46,XY[1] Left gonad: 45, X [18]/46,XY[2]	1	Dysgenetic gonads with in situ germ cell neoplasia	Gonads not visualized	2, 2/1 *

N/A, not applicable.

* Copies of *SRY* in this individual differed in peripheral blood and gonadal tissue. Gonadal tissue was mosaic for 3 cell lines with 0, 1, and 2 copies of *SRY*.

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