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Neoplasia in Turner syndrome. The importance of clinical and screening practices during follow-up

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ABSTRACT

Aim of the study: Turner syndrome (TS) patients show increased morbidity due to metabolic, autoimmune and cardiovascular disorders. A risk of neoplasia is also reported. Here, we review the prevalence of neoplasia in a cohort of Turner patients.
Methods: We retrospectively evaluated 87 TS women. Follow-up included periodic ultrasound of the neck, abdominal and pelvic organs, dermatologic evaluation and fecal occult blood test. Karyotype was 45,X in 46 patients. During follow-up, 63 girls were treated with growth hormone, 65 with estro-progestin replacement therapy and 20 with L-thyroxine. Autoimmune diseases were present in 29 TS.
Results: A total of 17 neoplasms in 14 out of 87 patients were found. Six skin neoplasia, 3 central nervous system tumors, 3 gonadal neoplasia, 2 breast tumors, 1 hepatocarcinoma, 1 carcinoma of the pancreas and 1 follicular thyroid cancer were detected. Age at tumor diagnosis was higher in 45,X pts than in those with other karyotypes ($p = 0.003$). Adenomioma gallbladdder (AG) was detected in 15.3% of the patients, with a lower age in girls at diagnosis with an associated neoplasia in comparison with TS without tumors ($p = 0.017$). No correlation between genetic make up, treatment, associated autoimmune diseases and neoplastia was found.
Conclusion: In our TS population an increased neoplasia prevalence was reported. A high prevalence of AG was also noted and it might be indicative of a predisposition to neoplasia. Further studies are needed to define the overall risk for neoplasia, and to determine the role of the loss of the X-chromosome and hormonal therapies.

1. Introduction

Turner syndrome (TS) is a genetic condition caused by complete or partial absence of an X chromosome (Gravholt, 2005; Hassold et al., 1998; Jacobs et al., 1995). It is the most commonly diagnosed sex chromosome abnormality in women, affecting 1/2000–2500 female live births and is usually associated with retarded growth, reduced adult height and gonadal dysgenesis. The phenotype is thought to be the result of an haploinsufficiency of genes on the X chromosome that escape X-inactivation in early embryogenesis (Gravholt, 2005; Hassold et al., 1998; Jacobs et al., 1995). Women with Turner syndrome have increased gonadotropin concentrations from infancy and low levels of estrogens. Growth-hormone (GH) treatment is often given during infancy to increase attained height (Saenger et al., 2001; Saenger, 1999; Rosenfeld et al., 1998) and hormonal replacement therapy (HRT) prescribed to initiate and sustain sexual maturation (Gravholt, 2005; Saenger et al., 2001).

Several studies have documented that TS patients show increased morbidity due to disorders including: metabolic and thyroid disturbances, ischemic cardiopathy and arterial hypertension (Elsheikh et al., 2002; Gravholt et al., 1998; Naeraa et al., 1995). However, the risk of developing cancer, except cancer of the large

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bowel and gonadoblastoma in patients with Y chromosome sequences, does not seem to be increased (Gravholt et al., 2000; Ogata and Matsuo, 1995; Hasle et al., 1996; Tsuchiya et al., 1995; Saenger, 1993; Rocco de Oliveira et al., 2009; Bianco et al., 2006; Mazzanti et al., 2005). Recently, Pier et al. (Pier et al., 2014) suggested a possible increased risk of neoplasia in TS. The authors were not able to prove causation between neoplasia and TS, but they suggested a possible association with X-chromosome gene haploinsufficiency, and/or treatment of associated medical problems such as short stature, estrogen deficiency and reduced fertility. Knowledge of the tumor risk is important in terms of parental counselling, prognostic implications, and for clinical and screening practices during the follow-up of these patients (Pier et al., 2014).

Here, we review the prevalence of neoplasia in a cohort of young and adult patients with TS. The correlation between tumor and genetic and hormonal aspects were also evaluated.

2. Patients and methods

We retrospectively evaluated 87 women (mean age at evaluation 30.1 ± 11.5 yrs) diagnosed with TS between 1980 and 2014 (mean age at TS diagnosis 7.5 ± 5.4 yrs) who attended the Endocrinological Unit of our Department. Follow-up (average 23.3 ± 9.7 yrs) included periodic ultrasound of the neck, pelvic organs, dermatologic evaluation and fecal occult blood test. In 78 patients abdominal ultrasound was also performed.

Karyotype was determined with the cytogenetic method and resulted 45,X in 46, X-mosaicism in 21 girls and structurally abnormal X chromosome in 21. In two 45,X patients fluorescent *in situ* hybridization analysis (FISH) evidenced the presence of an occult Y fragment.

Twenty-nine (33.3%) TS subjects presented with associated autoimmune diseases (Table 1). During follow-up, 63 girls (72.4%) were treated with growth hormone (GH), 65 (74.7%) with hormonal replacement therapy (HRT) and 20 (22.9%) with L-thyroxine. The clinical and genetic features and treatment of patients are reported in Table 1.

The study was approved by the ethics committee of our Institution. Before enrolment patients or their guardian provided written consent.

3. Statistical analysis

Categorical variables were described as count and percentage and compared between groups by means of the chi squared test. Quantitative variables are described as the mean and standard deviation and compared with the *t*-test, as normally distributed. The Shapiro-Wilks test was used to assess normality. Stata 14.0 (StataCorpLP, College Station, TX, USA) was used for all calculations; all tests were two-tailed and a p-value<0.05 was considered as statistically significant.

4. Results

A total of 17 neoplasms in 14 of 87 (16.1%) patients were found; in three patients multiple neoplasia were noted. The topographic distribution of lesions was as follows:

- 6 skin neoplasia (35.2%): 3 basocellular carcinoma; 1 melanoma (in a patient with multiple meningiomas); 2 melanoma *in situ*;
- 3 central nervous system (CNS) tumors (17.6%): 1 multiple meningioma; 1 non secreting pituitary adenoma; 1 glyoma in the occipital region;
- 3 gonadal neoplasias (17.6%): 1 ovarian dysgerminoma and 2 gonadoblastoma *in situ*;
- 2 breast tumors (11.7%): 1 juvenile fibroadenoma (with local recurrence) and 1 invasive ductal cancer (BRAC1 and BRAC2 negative; negative for hormonal receptors);
- 1 hepatocarcinoma (5.8%);
- 1 mucinous cystic micro-invasive carcinoma of the pancreas (5.8%);
- 1 follicular thyroid cancer (5.8%).

Clinical findings, karyotype and therapies for all the patients with neoplasia are reported in Table 2.

Of the TS subjects with neoplasia, 8 had karyotype 45,X (57.14%) and 6 (42.86%) X-mosaicism or structurally abnormal X chromosome (p = 0.479). Five out of the 6 skin neoplasia were diagnosed in 45,X patients, breast tumors only in non-45,X patients and gonadal neoplasia in patients positive for the Y signal.

The presence of the tumors was not influenced by treatment with GH (p = 0.32) or HRT (p = 0.078).

Mean age at the tumor diagnosis was 26.8 ± 12.5years. In 5 out of 14 patients (35.7%), the lesion occurred under the age of 18 yr. In 45,X patients the age was significantly higher than in those with other karyotypes (33.9 ± 3.5 vs 17.3 ± 3.6; p = 0.003). No association between neoplasia and autoimmune diseases was found (p = 0.53). In 12 of the 78 patients (15.3%) who underwent abdominal ultrasound, adenomioma of the gallbladdder (AG) (single in 10 pt and multiple in 2) was detected.

The clinical findings, karyotype and therapies of the patients with AG are reported in Table 3. Among TS subjects with AG, 7 had

Table 1
Clinical characteristics and patient treatments, according to karyotype.

Characteristics	Karyotype			p 45,X vs Non 45,X
	Total (n = 87)	45,X (n = 46)	Non 45,X (n = 41)	
Mean age at TS diagnosis (years)	7.5 ± 5.4	7.1 ± 5.7	7.9 ± 5.1	p = 0.7
Mean age at evaluation (years)	30.9 ± 11.5	33.0 ± 11.6	28.6 ± 11.2	p = 0.04
Average follow-up (years)	23.3 ± 9.7	25.8 ± 10.0	20.7 ± 8.8	p = 0.01
Autoimmune diseases (n. of pt, %)	29 (33.3%)	18 (39%)	11 (26.8%)	p = 0.16
Thyroiditis	23 (26.4%)	16 (34.7%)	7 (17%)	p = 0.05
Celiac disease	5 (5.75%)	2 (4.3%)	3 (7.3%)	p = 0.44
Crohn's disease	1 (0.03%)	–	1 (2.4%)	–
Raynaud phenomenon	1 (0.03%)	–	1 (2.4%)	–
Atrophic gastritis	2 (0.06%)	1 (2.1%)	1 (2.4%)	p = 0.60
Treatment (n. of pt. %)				
Growth hormone	63 (72.4%)	32 (69.5%)	31 (75.6%)	p = 0.34
Estro-progestin	65 (74.7%)	38 (82.6%)	27 (65.8%)	p = 0.06
Thyroxine				