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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				

Table 2
Clinical findings, karyotype and patient therapy with neoplasia.

Patient	Karyotype	Tumor	Age at diagnosis of tumor (yrs)	Tumor treatment	Alive	Therapy	Autoimmune diseases
1	45,X	Meningioma Melanoma Meningioma	42 48.2 49	Surgery Surgery Surgery	yes	HRT	thyroiditis
2	45,X/46,X,isoY	Gonadoblastoma *in situ* Melanoma *in situ*	14.9 37.9	Surgery Surgery	yes	HRT Beta-blockers	_
3	45,X	Basocellular carcinoma Basocellular carcinoma	42.1 45.7	Surgery Surgery	yes	HRT Hydrocortisone	_
4	45,X	Melanoma *in situ*	38.7	Surgery	yes	GH-HRT	_
5	45,X	Basocellular carcinoma	43.8	Surgery	yes	HRT mesalazine	Crohn's disease
6	45,X,t(5; 6)(p13,p23)/46,X,isoYp(q11.2),t(5; 6)(p13; p23)	Non secreting pituitary adenoma	18.9	_	yes	GH- HRT Beta-blockers	Celiac disease Raynaud phenomenon
7	45,X	Glioma	30.9	_	yes	GH- HRT	
8	46,X, inv dup(X)(pter > q26::q26 > q13)	Hepatocarcinoma	16	Surgery Chemotherapy	no	GH-HRT	–
9	45,X	Mucinous cystic carcinoma of the pancreas	42.3	Surgery	yes	HRT Levothyroxine	Autoimmune thyroiditis
10	45,X	Follicular thyroid carcinoma	23.8	Surgery Radioiodine	yes	GH-HRT	–
11	45,X/46,X,delX(q)	Breast invasive ductal cancer	33.8	Surgery Chemotherapy Radiotherapy	yes	GH-HRT	Atrophic gastritis
12	45,X/46,XX	Breast giant fibroadenoma	12	surgery	yes	–	–
13	45,X/46,Xi(y)(q11.1)	Dysgerminoma	8.1	surgery	yes	–	–
14	45,X[a]	Gonadoblastoma *in situ*	17.8	surgery	yes	GH- HRT	_

HRT = hormone replacement therapy; GH = growth hormone.
[a] Presence of occult Y fragment at fluorescent *in situ* hybridization analysis.

Table 3
Clinical findings, karyotype and patient therapy with adenomioma of the gallbladder (GA).

Patient	Karyotype	Number of GA	Age at GA diagnosis	Therapy	Associated autoimmune disease	Associated tumor
1	45,X	1	27.4	GH- HRT Levothyroxine	Autoimmune thyroiditis	Follicolar thyroid carcinoma
2	45,X/46,XX	1	15	-	_	Breast giant fibroadenoma
3	46,X, psu dic (X) (qter p11::p11qter)	1	28.9	GH-HRT	_	_
4	45,X/46,X i(Xq)	1	43.8	GH-HRT	_	_
5	45,X	1	37.4	GH- HRT	_	_
6	45,X	1	46.2	HRT betablockers	Autoimmune thyroidits	_
7	45,X,t(5; 6)(p13,p23)/46,X,isoYp(q11.2),t(5; 6)(p13; p23)	1	17.7	GH-HRT betablockers	Autoimmune thyroidits Celiac disease	Non secreting pituitary adenoma
8	45,X	1	22.1	GH-HRT Mesalazine	_	_
9	45,X/46,X,r(X)(p1q1)	2	37.8	HRT Lamotrigine	_	_
10	45,X	>2	34	GH-HRT	–	Glioma
11	45,X	1	50	HRT	–	
12	45,X	1	31.7	G H-HRT Levo-thyroxine	Autoimmune thyroidits	

karyotype 45,X (58.33%) and 5 (41.67%) non 45,X chromosome ($p = 0.454$). No differences between 45,X and non-45,X karyotypes were detected for age at diagnosis of AG (35.57 ± 9.92 vs 28.67 ± 12.47, $p = 0.15$), hormonal treatment (GH $p = 0.45$; HRT $p = 0.17$) or presence of associated autoimmune diseases ($p = 0.6$). In four subjects, the AG was associated with the neoplasia ($p = 0.10$); in these girls the age at AG diagnosis was significantly lower in comparison with TS without tumors (23.55 ± 8.8 vs 37.27 ± 9.39, $p = 0.017$).

5. Discussion

Turner syndrome is a genetic disorder of females with well-described karyotypic abnormalities and phenotypic features (Gravholt, 2005; Hassold et al., 1998; Jacobs et al., 1995). Mortality in women with Turner syndrome is 3-fold higher than in the general population for almost all major causes of death, and at all ages with the greatest excess mortality in later adulthood (Gravholt, 2005; Gravholt et al., 1998; Naeraa et al., 1995).

The risk of cancer in patients with TS has been suggested but studies are lacking. In the literature only two studies have been published involving a large number of patients with Turner syndrome. The other reports describe sporadic cases. Schoemaker (Schoemaker et al., 2008), in a British multicentric study on Turner patients, reported that the overall risk of cancer was similar to that expected in the general population, but that the risk of CNS tumors

in women with complete 45,X (with meningioma being the most frequent type) was 8.2 times greater that in the normal population. Hasle et al. (Hasle et al., 1996) reported in a multicentric study in Danish TS patients a seven-fold increased incidence of colon cancer, but no significant associations with others cancers. The role of TS-associated genes and hormonal therapy in the development of tumors was also discussed.

In the two aforementioned studies, a 3.5% and 2.1% prevalence of neoplasia in the TS population was reported in Denmark and in the Great Britain population, respectively (Hasle et al., 1996; Schoemaker et al., 2008). In our TS cohort the tumor prevalence was higher (19.5%) in comparison with these reported data. In our group of patients, we confirmed the high prevalence of CNS and gonadal tumors in patients with the Y signal, as well as the presence of skin tumors. In these multicentric studies the correlation between neoplasia and hormonal treatment was not evaluated. In our patients, the presence of tumors was not influenced by treatment with GH or estrogen-replacement therapy; also the study of hormonal receptors in the patient with breast invasive ductal carcinoma resulted negative. The differences in the frequency and type of neoplasia might be explained by genetic differences among the populations or by the methods of follow-up.

The overall age at the neoplasia diagnosis was lower in our Turner patients in comparison with the age reported in the Italian Cancer Registry Associazione Italiana Registri Tumori, (http://www.registri-tumori.it/cms/) and in a high percent of cases (35.7%) the neoplastic lesion occurred under the age of 18 years.

We confirmed an increased risk for CNS tumors and, as reported by Pier et al. (Pier et al., 2014), an association between TS, multiple meningiomas and skin tumors was also noted. The presence of multiple meningiomas and skin neoplasia in TS may be coincidental, but a possible association cannot be excluded.

Growth hormone has been suggested to play a role in the malignant transformation and progression of a variety of cancers. Given the ability of GH and IGF-1 to promote cell proliferation, cell movement and angiogenesis, and to suppress apoptosis, it is not surprising that the GH/IGF-1 axis is thought to influence cancer biology, cancer risk and carcinogenesis (Chhabra et al., 2011). In fact the GH/IGF1 axis has been implicated in the growth rate of CNS neoplasms (Jostel et al., 2005; Andersen et al., 2013; Claus et al., 2013; Pines, 2011; Shih-Hsiang et al., 2006; Swerdlow et al., 2002). However, to our knowledge, there are no conclusive studies demonstrating an increased risk of these neoplasms following GH therapy. In TS, no association between CNS and GH therapy has been reported, nor previous cases of non secreting pituitary adenoma described in TS. GH replacement does not increase the risk of recurrence in patients with non secreting pituitary adenoma (Pines, 2011). Thus, the association between neoplasm and hormonal therapy in our patient might be considered casual.

GH is known to up-regulate molecular signaling pathways implicated in the pathogenesis of melanoma (Chhabra et al., 2011; Bourguignon et al., 1993; Oakes et al., 1992). Although an increased number of benign nevi have been reported in TS, the decreased melanoma rate in this population suggests that some protective factor is active (Lowenstein et al., 2004). No influence of GH on melanoma development was suggested in our TS cohort, since two out of three patients with melanoma had not been treated with GH.

A number of studies have also focused on the possible relationships between the characteristics of female endocrine status and melanoma risk; however, the link between melanoma and HRT use, and reproductive factors remains controversial (Gandini et al., 2011). Despite hormone HRT during the entire lifespan of females with TS, HRT does not seem to be linked to an increased risk of melanoma.

Turner patients evolve towards autoimmunity much more frequently than people with a normal karyotype without any relevant excess of the putative immunogenetic risk markers (Elsheikh et al., 2002; Gravholt et al., 1998; Larizza et al., 2009). This underscores the great influence of X-chromosome abnormalities on the development of autoimmune disorders and suggests an epistatic interaction of X genes with immune response genes. Interestingly, one of the human MHC-paralogues is located on the long arm of the X chromosome, so that anyone with a defect in this region might have less efficient control of the pathogenic repertoire during her lifespan (Larizza et al., 2009).

A possible link between cancer and autoimmune diseases has been suggested (Eisenlohr and Rothstein, 2006; Kiss et al., 2010). Some autoimmune diseases, such as Sjogren's syndrome, rheumatoid arthritis and systemic lupus erythematosus have been associated with the development of lymphoproliferative malignancies (Kiss et al., 2010), and a plethora of autoantibodies have been found in patients with solid tumours (Bei et al., 2009). The factors influencing this association are not yet completely known; although both immunosuppressive medication and uncontrolled disease activity play potential roles (Eisenlohr and Rothstein, 2006). Our study suggests that autoimmune diseases in the TS population are not linked to cancer, since diagnosis of neoplasia was not more frequent in patients affected by autoimmune disease, however further investigations are needed to better define the possible association with cancer and autoimmunity. Given the fact that some organ-specific autoimmune diseases are considered at higher risk of tumors, for TS subjects affected by athrophic gastritis, Crohn's and celiac diseases, thyroiditis, a rigorous follow-up is mandatory.

Although TS patients show increased morbidity due to thyroid disorders, the risk of thyroid cancer does not seem to be increased (Elsheikh et al., 2002; Gravholt et al., 1998). However, Cabanas et al. (Cabanas et al., 2005) reported two unrelated pediatric patients with TS in which papillary thyroid carcinoma was detected during or several years after GH treatment. Our young TS girl, without associated autoimmune thyroid disease, presented a follicular thyroid carcinoma after treatment with GH. Considering that thyroid carcinoma is a rare neoplasm in the young, it is possible that the co-occurrence of this carcinoma with TS was not a chance association.

The mucinous cystic micro-invasive carcinoma is the only pancreatic cancer reported in a TS patient, already described by the surgeon who performed the removal of the lesion (Pizzi et al., 2013).

TS patients are known to have elevated liver enzyme levels and an increased prevalence of liver abnormalities, for example, focal nodular hyperplasia, related to vascular anomalies; however, rarely have TS cases with hepatic neoplasm been reported (Espat et al., 2000; Morotti et al., 2007). According to Morotti et al. (Morotti et al., 2007), in our 16-year old TS girl a hepatocarcinoma was diagnosed after GH treatment; the young age at occurrence may suggest a possible causal association between the lesion and therapy.

In this retrospective evaluation, the risk for breast cancer in TS was not greater than in the general population and an association between GH therapy and breast tumors was not noted. A risk of developing gonadal neoplasia in patients with TS and Y chromosome material has been confirmed (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). No large bowel cancer was detected (Hasle et al., 1996; Schoemaker et al., 2008).

No cases of adenomioma gallbladdder have been previously reported in TS. In the general population, AG diagnosis is usually performed histologically after cholecystectomy and the reported prevalence is 2–5%. We observed a higher prevalence in TS (15.3%),

without an association between AG and karyotype, hormonal therapy or autoimmune disease. The relation between adenomyomatous hyperplasia (AMH) and gall bladder carcinoma is unclear. Although classically considered to be a hyperplastic lesion, several reports have shown not only a causative relation between adenomyomatous hyperplasia (AMH) and gall bladder carcinoma, but also an actual neoplastic degeneration arising in AMH (Lauwers et al., 1995). In some cases the an adenoma could be one of the intermediate steps in the carcinogenic sequence (Lauwers et al., 1995). The possibility of malignant degeneration might be clinically important. As AG can be easily recognised with ultrasonography, any unusual modifications of the sonographic structure or development of a mass necessitate rigorous follow-up. Early recognition of degenerative changes is vital as early gall bladder cancer has a distinctly better prognosis than advanced disease (Lauwers et al., 1995).

6. Conclusion

In our TS population an increased prevalence of neoplasms was reported, particularly under 18 years. No correlation between genetic make up, treatment, associated autoimmune disease or neoplasia was found. An high prevalence of AG was also noted and it could be indicative of a predisposition to tumors. Therefore, through clinical and screening practices during the follow-up of TS patients are necessary for early neoplasia detection. Further studies are mandatory to define the overall risk of cancer, and to determine the pathogenetic role of the loss of the X chromosome and the effects of hormonal therapy.

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Conflicts of interest

None declared.

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