

## REVIEW

## Autoimmune diseases in Turner syndrome: an overview

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**Summary.** Turner syndrome (TS) results from a sex-chromosomal anomaly characterized by presence of one normal X chromosome and the loss of the second X-chromosome in phenotypic females. Autoimmunity has been recognized as one of the more prominent characteristics of TS. The risk of autoimmune diseases in patients with TS is approximately twice as high as in the general female population. The spectrum includes, Hashimoto's thyroiditis, coeliac disease (CD), type 1 diabetes (T1DM), alopecia areata, inflammatory bowel disease, juvenile rheumatoid arthritis and some cutaneous disorders as vitiligo and Halo nevus. This review will address the autoimmune disorders associated with TS, their pathophysiologic mechanisms and clinical characteristics. ([www.actabiomedica.it](http://www.actabiomedica.it))

**Key words:** Turner syndrome, autoimmune disorders, pathophysiologic mechanisms, clinical characteristics

### Introduction

Turner syndrome (TS) results from a sex-chromosomal anomaly characterized by presence of one normal X chromosome and the loss of the second X-chromosome in phenotypic females (1). The initial description by Henry Turner in 1938 included short stature, sexual infantilism, cubitus valgus and pterygium colli (2). The phenotype includes short stature, primary ovarian failure, some physical features resulting from consequences of fetal lymphedema and skeletal abnormalities. Congenital cardiovascular defects, osteoporosis, endocrine and metabolic disorders and hearing loss are recognized contributors for increased morbidity and mortality and decreased life expectancy in this syndrome (3).

### Increased prevalence of autoimmunity in women

In general, autoimmune diseases are more common in women than men and the explanations remain

uncertain. Estrogens seem to impact the course of human autoimmune disease. Pregnancy has also been suspected of contributing to excess autoimmunity in women explained with retention of allogenic fetal cells (4). Another factor implicated in excess autoimmunity in women involves the process of X chromosome inactivation, wherein one of the two X chromosomes undergoes inactivation or transcriptional silencing during early embryonic development. This typically results in tissue mosaicism in which approximately 50% of cells express the maternally-derived (XMat) and 50% express the paternally-derived (XPat) X chromosome. It has been proposed that X chromosome inactivation may be skewed during thymic development resulting in predominant expression of only one set of X chromosome encoded self-antigens. This may lead to inadequate thymic deletion of autoreactive T-lymphocytes, which in turn leads to impaired "self" antigen recognition and tolerance. The risk of initiation of an autoimmune reaction would be enhanced if such autoreactive T cells encounter XPat or XMat specific antigens in peripheral tissues (5, 6).

## Mechanism of autoimmunity in women with Turner syndrome

Autoimmunity has been recognized as one of the more prominent characteristics of TS (7, 8). The risk of autoimmune diseases in patients with TS is approximately twice as high as in the general female population (9). The increased risk of autoimmunity in patients with TS has also been attributed to X-chromosome haplo-insufficiency, maternal origin of the X-chromosome, excessive production of pro-inflammatory cytokines (IL-6), decrease in anti-inflammatory cytokines (IL-10, TGF- $\beta$ ), or hypogonadism. The impact of three copies of genetic material on the long arm of the X-chromosome and an increased incidence of AD in girls with the iXq karyotype have also been suggested (10,11). The excess of autoimmune antibodies is likely to result from the X chromosome defects. It has been demonstrated that genes located in the X chromosome, including a major histocompatibility complex (MHC) locus in the long arm, are involved in regulation of the immune response and altered immune tolerance (12).

Moreover, discrete disturbances in both humoral and cellular immune responses have been reported and a genetic basis has been proposed, although not established uniformly (13). More recent data suggest that in Brazilian patients with TS, the PTPN22 C1858T polymorphism may be an important genetic factor predisposing to autoimmune disease risk (14). Another study from USA showed that autoimmune susceptibility in Turner Syndrome is due to an alteration in the expression of the X-linked FOXP3 gene. FOXP3 is important in the development of regulatory T cells, and complete loss of FOXP3 expression has been shown to result in severe autoimmunity (15).

## Autoimmune diseases in Turner syndrome

Morbidity secondary to autoimmunity ranks among the more prominent syndrome-associated characteristics, where an estimated 50% of the middle-aged patients suffer from Hashimoto's thyroiditis, and the prevalence increases with age. Other diseases of possible autoimmune aetiology also prevail with an in-

creased risk of coeliac disease (CD), type 1 diabetes (T1DM), alopecia areata, inflammatory bowel disease, juvenile rheumatoid arthritis, idiopathic thrombocytopenic purpura, psoriasis and vitiligo. Furthermore, an increased frequency of cobalamin deficiency was reported, although this was not shown as secondary to pernicious anaemia with autoantibody production (16).

### 1. Autoimmune thyroid diseases and thyroid autoimmunity

Thyroid autoimmune diseases are characterized by abnormal lymphocytic activation, directed against self-antigens, i.e. thyroglobulin (Tg) and thyroperoxidase (TPO). They encompasses Hashimoto's thyroiditis (HT), a predominantly T cell mediated disease and Graves' disease, characterized by a primarily humoral response and the presence of anti-thyroid stimulating hormone (TSH) receptor antibodies (17). The relationship between thyroid disease and TS was first suggested by Atria *et al.* (18) in 1948 when they reported the postmortem findings of a small thyroid gland with lymphocytic infiltration in a young TS woman. Most HT forms evolve into hypothyroidism, although at presentation patients can be without clinical hypothyroidism and present with subclinical hypothyroidism which is a biochemical condition characterized by serum TSH above the upper limit of the reference range and serum FT4 levels within the reference range (19, 20). Interestingly, regarding the putative influence of karyotype on clinical features, some studies reported an association between autoimmune thyroiditis and the X isochromosome karyotype (21).

In the general population, the diagnosis of thyroiditis is based on clinical evidence of thyroid dysfunction, whereas in patients with TS, functional evaluation is done periodically, regardless the clinical picture, which allows the detection of subclinical changes (13).

### 2. Celiac disease

Since the 1970s, several reports have indicated an association between TS and celiac disease. The incidence of CD increases 11-fold in TS (22). The prevalence of antiendomysial antibodies positivity detected by screening in TS is 4.2% (23). Reviewing the data

in the TS population, serological screening appears to be an effective method of identifying subclinical CD. Most of the patients diagnosed with TS who also have growth retardation do not respond to growth hormone therapy if they have coexisting CD. On the other hand, some of the patients with CD who have persistent growth retardation and pubertal immaturity despite a gluten-free diet are diagnosed with TS afterwards (24). The available data and publications indicate that screening for CD should be performed in patients with TS, and intestinal biopsy should be carried out in patients with positive results (25).

### 3. Type 1 diabetes mellitus

In a Danish study, Type 1 diabetes used to appear the most common AID associated with TS (26). The reason for the increased incidence of diabetes in TS women is probably due to deranged insulin secretion by mechanisms that are not entirely clear. It has been suggested that the abnormalities of the X chromosome may influence immune tolerance, leaving TS patients more susceptible to autoimmune disease (27).

### 4. Skin manifestations

TS has been associated with several cutaneous abnormalities including an increased frequency of pigmented nevi, but few reports consider nevi in detail. Halo nevus (HN) is clinically defined as a melanocytic nevus surrounded by a halo of depigmentation. Vitiligo, a dermatologic disorder characterized by the presence of depigmented patches on the skin, has been described in the list of cutaneous findings associated with TS. In contrary to the common belief, Halo nevus, rather than vitiligo, is the typical dermatologic finding of Turner's syndrome (28).

### 5. Inflammatory bowel diseases

Inflammatory bowel diseases (IBD) affects millions of people around the world and the peak of incidence occurs between 15 and 30 years old. Two chronic disorders represent this group of diseases: CD (Crohn's disease) and UC (ulcerative colitis). It is unclear why autoimmune diseases have an increased

incidence in TS patients, but hormone therapy often used to treat these patients, seems to be a susceptibility factor to IBD occurrence (29, 30).

### 6. Rheumatic diseases and other immune-related conditions

Juvenile idiopathic arthritis (JIA) is an autoimmune condition that might be associated with Turner syndrome. The prevalence seems to be at least six times greater than would be expected if the two conditions were only randomly associated (31). Other investigators believe that it is important to consider the diagnosis of Turner's syndrome in girls with JIA, recognizing that characteristic radiographic findings such as metacarpal shortening are usually present. Conversely, suspicion of an underlying inflammatory arthritis is warranted in search for radiological findings consistent with JIA in girls with TS and joint symptoms (32). There are scarcity of literature addressing this association and the reports are relatively old.

## Conclusions

In conclusion, autoimmune diseases are prevalent in patients with TS. Despite the importance of early detection and treatment of AD, literature reports are ambiguous, and studies related to girls with TS are very few. Further study of autoimmune disorders in people with Turner syndrome may contribute to the better understanding of mechanisms in the pathogenesis of autoimmune conditions more generally. Moreover, there are no current clear guidelines for management of the several autoimmune disorders in Turner's Syndrome.

**Conflict of interest:** Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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