Autoimmunity Reviews 11 (2012) A538–A543

Contents lists available at SciVerse ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

Autoimmunity and Turner's syndrome

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ARTICLE INFO

Available online 2 December 2011

Keywords:
Turner Syndrome
Autoimmunity
Genetic factors
X chromosome
HLA

ABSTRACT

Turner Syndrome (TS) is a common genetic disorder, affecting female individuals, resulting from the partial or complete absence of one sex chromosome, and occurring in approximately 50 per 100,000 liveborn girls. TS is associated with reduced adult height and with gonadal dysgenesis, leading to insufficient circulating levels of female sex steroids and to infertility. Morbidity and mortality are increased in TS but average intellectual performance is within the normal range. TS is closely associated to the presence of autoantibodies and autoimmune diseases (AID), especially autoimmune thyroiditis and inflammatory bowel disease. Despite the fact that the strong association between TS and AID is well known and has been widely studied, the underlying immunopathogenic mechanism remains partially unexplained. Recent studies have displayed how TS patients do not show an excess of immunogenic risk markers. This is evocative for a higher responsibility of X-chromosome abnormalities in the development of AID, and particularly of X-genes involved in immune response. For instance, the long arm of the X chromosome hosts a MHC-locus, so the loss of that region may lead to a deficiency in immune regulation.
Currently no firm guidelines for diagnosis exist. In conclusion, TS is a condition associated with a number of autoimmune manifestations. Individuals with TS need life-long medical attention. As a consequence of these findings, early diagnosis and regular screening for potential associated autoimmune conditions are essential in the medical follow-up of TS patients.

Contents

1. Introduction

Turner Syndrome (TS) is a rare genetic disorder, affecting approximately one out of 2500 female live births [1], due to total or partial absence of the X chromosome in germinal and somatic line. Cardinal stigmata are reduced but proportionate final height with webbing neck, cubitus valgus and ankle swelling associated with some classical clinical features (Fig. 1): premature ovarian failure and less constantly

Abbreviations: TS, Turner Syndrome; AID, Autoimmune Disease; HLA, Human Leukocyte Antigen; ICD, International Classification of Diseases; GAD, Glutamate Decarboxylase.

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doi:10.1016/j.autrev.2011.11.015

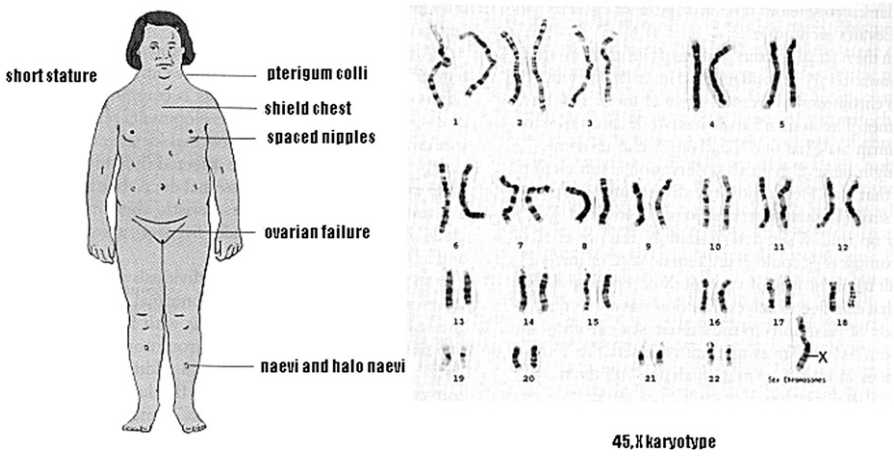

Fig. 1. Clinical features of Turner Syndrome/45,X karyotype.

phenotypic particularities such as congenital malformations, acquired cardiovascular, otological (hearing impairment), autoimmune and metabolic diseases [2–4]. More severe comorbidities and complications are present in some cases and are included in Table 1.

Around 1–2% of embryos show a 45,X genotype, but the majority gets spontaneously aborted (99%), most commonly during the first trimester of pregnancy. The clinical presentation is highly variable and slight or even normal phenotypes are possible. Several studies have suggested that growth hormone treatment improves adult height. Although the quality of life seems similar to the normal population, the presence of cardiovascular and otological diseases, and delayed feminisation are associated with an impairment of that endpoint. Early diagnosis and regular screening for potential associated complications are essential in follow-up of patients with TS [2].

After the linkage between X monosomy and phenotypic abnormalities was discovered, helped by cytogenetic techniques [5], many abnormalities, other than 45,X-karyotype, were shown to be responsible for TS (rings, deletions, isochromosomes and mosaicisms) [6]. Normally, inactivation of one X chromsome in somatic lines occurs in females after fertilization. By the way, the savage of a small region of the short arm from inactivation is vital for the normal development [7,8]. Haploinsufficiency of the loci implicated in development produces the characteristic phenotype [9].

Table 1
Features and comorbidities in Turner's Syndrome.

Characteristics	Prevalence (%)
Growth (small newborns for gestational age and retardation)	90
Ovary (ovarian failure with disgenesis)	90
Dermatologic abnormalities (oedema of the extremities, nail dysplasia, naevi and halo naevi, vitiligo, alopecia, hirsutism)	70
Oral pathology (micrognatia, tooth disgenesis or alteration of dental development, high palate)	70
Neck (Pterygium Colli – webbed neck, low back hairline, short neck)	70
Chest (spaced and inverted nipples, shield chest]	70
Otologic abnormalities (otitis media, deafness or hearing loss – conductive or sensorineural, low-set ears, deformity of the auricle]	50
Renal disease (renal agenesis, vascular abnormalities, horseshoe kidney, duplicated collecting ducts]	50
Heart and vessels (hypertension, aortic coartation, stenosis or aneurisms of the aorta, bicuspid aortic valves]	50
Osteoarticular system (cubitus valgus, osteporosis, vertebral deformities, short 4th metacarpus]	50
Thyroid disfunction (hypothyroidism, thyroid autoantibodies]	50
Liver disease (abnormal LFT, fatty liver disease]	30
Ophtalmic abnormalities (epicanthus, ptosis, strabismus, nistagmus, myopia	30

Autoimmune morbidity ranks among the more prominent syndrome-associated characteristics, and it is suggested by the fact that prevalence of AID increases with age [10]. Several disturbances in both humoral and cellular immune responses have, however, been reported and a genetic basis has been proposed, although not uniformly definite. However, despite this formal condition of immunodeficiency, abnormally frequent or atypical infections have nott been demonstrated to occur in TS patients, except for otitis media [11] while the "odd-couple" autoimmunity-immunodeficiency [12] finds an umpteenth proof in TS.

2. Related autoimmune diseases

Women with TS are at increased risk of developing a wide repertoire of AID [13–20]. The commonest diseases among these subjects are ulcerative colitis [21], Hashimoto thyroiditis [22] and, perhaps, type 1 diabetes mellitus [23]. Coeliac disease [24,25], juvenile rheumatoid arthritis [26], Addison's disease [27] , psoriasis, vitiligo and alopecia areata [13,20,28] have also been reported. Furthermore, an increased frequency of cobalamin deficiency was recently seen, although this was not shown as secondary to pernicious anaemia with autoantibody production [10]. All main karyotype groups giving rise to TS were associated with an overall from 2- to 3-fold increased risk of developing an autoimmune disease [23]. The salient observations that come from a recent Danish study by Jorgensen and colleagues include an overall 2-fold increased risk of AID, especially of the male-predominant types, for which the risk was 4-fold increased, whereas the risk of AID with a female predominance was increased 1.7-fold compared with that in women in general.

Part of the excess of male-predominant AID might be explained by the close similarity of the chromosomal setting of women with TS and men, and may reflect the hemizygosity of X-linked genes [23]. While in women with a normal karyotype a compensation occurs by the normally functioning copy on the other X chromosome, a harmful allele will be unmasked in women with TS and in men, due to X monosomy. Thus, it is possible that susceptibility to the specific male-predominant AID, for example type 1 diabetes mellitus, ankylosing spondylitis and reactive arthritis is particularly dependent on genes on the X chromosome [23]. In addition to sharing the male vulnerability to deleterious mutations or polymorphisms in X-linked genes, women with TS exhibit haploinsufficiency of genes in the pseudoautosomal region of the X chromosome which, in males, has a Y chromosomal counterpart [29,30]. This might explain the reason why the risk of male-predominant AID in women with Turner's syndrome is not only higher than that observed in women in general, but also higher than the risk in men [23]. It has been proposed that the TS phenotype may be influenced by the parental origin of the lacking X chromosome [31]. It's demonstrated that females with TS who hold some genetic material from Y chromosome have an X

chromosome of maternal origin. This subgroup of patients exhibits a 5-fold higher risk of developing AID [32]. Though, women with TS, in addition to having a higher risk of AID, are more likely to develop conditions normally characterized by male predominance [23]. No study has investigated the prevalence of combined forms of autoimmunity in TS and it is not known whether the diseases co-segregate [10]

2.1. Inflammatory bowel diseases

Ulcerative colitis and Crohn's disease often occur in association with TS. Prevalence of inflammatory bowel disease is approximately 200 per 100,000 among general population [33]. The estimated risk of inflammatory bowel diseases in TS patients is variable and ranges from 2- to 10-fold increase [34]. There are a few details that distinguish inflammatory bowel diseases in TS to that of non-TS population: Crohn's disease usually involves the colon and it's only twice as common as ulcerative colitis, they develop at younger age, are often severe, complicated with fistulae and require colectomy [35]. Inflammatory bowel diseases seem to be related to the presence of an abnormal X-chromosome than to its absence. Among women with isochromosome Xq karyotype, an almost 12-fold increased risk of ulcerative colitis was noted [16,23] inflammatory bowel diseases must be suspected in patients with TS in case of abdominal pain, anemia, diarrhea, gastrointestinal bleeding or unexplained weight loss, and are in differential diagnosis with celiac disease (also associated with TS).

2.2. Autoimmune thyroid diseases

There is a wide variability in incidence of the association between thyroid abnormalities and TS – it ranges between 4% and 50% compared with 1.5% of adult women in the general population – and the prevalence increases with age [15,22,36–38]. For what concerns Hashimoto thyroiditis, the prevalence from the first to the third decade of life is doubled [37]. A peak of incidence at the age of 15 has been described [22]. Follow-up studies revealed an annual incidence of autoimmune thyroiditis of 3.2% in TS [15]. The prevalence of thyroid-specific autoantibodies in TS population is far higher than the overt disease [39] and it is around 50% [35]. The majority of patients are diagnosed with subclinical hypothyroidism, and severe clinical manifestations are quite rare. The atrophic form is the most frequent [36]. The influence of growth hormone therapy on the production of anti-thyroid autoantibodies vs. the development of the overt disease is controversial [19,40]. Graves–Basedow disease shows a low incidence among these patients [41]. The reason for this discrepancy with autoimmune thyroiditis, despite their pathogenic and genetic relationship, may be the higher incidence of asymptomatic cases of Hashimoto thyroiditis in the general population.

X chromosome appears to be involved in the pathogenesis of Hashimoto thyroiditis [42]. Studies examining the association between certain karyotypes and autoimmune thyroid disease have lead to conflicting results. Some studies [38,43], have displayed an increased risk of autoimmune thyroid disease among women with the isochromosome Xq karyotype. Other researches failed to support this hypothesis [14,15,23].

Considering the high prevalence of thyroid autoimmune disease in TS, follow-up of thyroid function and thyroid autoantibodies is strongly recommended in management of Turner patients, also in consideration that hypothyroidism may worsen growing delay during childhood and adolescence and facilitate overweight and cardiovascular diseases, already stigmata of TS [35].

2.3. Type 1 diabetes mellitus

Type 1 diabetes mellitus used to appear the most common AID associated with TS, as showed in a Danish study based on administrative data [23]. A previous study anticipated an 11-fold increased risk of diabetes mellitus in TS population [39]. Type 1 diabetes mellitus epidemiology, however, may be affected by coding misclassification since, before ICD-9, type 1 and type 2 diabetes mellitus were classified first as a unique category. In the past, only a few cases were described in literature and no prevalence data had been communicated [44,45].

AntiGAD-65 antibody is present in a slightly higher fraction above the general population prevalence as reported across adult age-groups (4% vs. 1.1%) [10,46–48]. Although relatively small cohorts, these findings point towards a increased risk of diabetes in TS, as previously shown [34]. It may be speculated that the non-diabetic antiGAD-65 positive patients might develop diabetes subsequently [49]. Moreover, the presence of antiGAD-65 must be interpreted as indicative of more patients suffering from type 1 diabetes mellitus than expected and misclassified as type 2 diabetes mellitus. It is therefore proposed that all patients with TS and newly diagnosed with diabetes are tested for antiGAD-65 antibodies [10].

2.4. Celiac disease

The risk of developing celiac disease is 11-fold higher in TS compared to the general population [24,50]. Its prevalence varies from 2.2% to 8.1% in TS, depending of the number of patients considered as well as the prevalence of celiac disease in the study population. The symptomatic vs. asymptomatic proportion in TS patients with celiac disease reflects the pattern observed in general population [50]. Celiac disease may worsen short stature, hypogonadism and osteoporosis, already present in TS, so we reckon that celiac disease screening should be mandatory in the management of TS [35].

2.5. Skin disorders

The connection between TS and dermatological diseases has been poorly investigated. The main conditions reported to be slightly more frequent in TS are psoriasis, alopecia areata and vitiligo. Psoriasis is twice more common in TS females than in general population [51]. Alopecia areata is 3 times more frequent and seems to be related to HLA-DR and DQ loci in TS [52,53]. Karyotype is not likely to have effect on described skin abnormalities. Vitiligo affects 2.7% of TS patients vs. 1% to 2% of the worldwide population. This slight difference appears not to be significant [54] and must be due to the higher awareness of pediatricians towards this condition. Other dermatological abnormalities as halo nevi and Dupuytren contracture, whose pathogenesis is thought to be autoimmune, have been reported to be significantly more common in TS than in non-TS population [23,54].

2.6. Rheumatic diseases and other immune-related conditions

Juvenile arthritis is described in TS and its prevalence is 6-times greater than expected, particularly the oligoarticular form [55]. Association of TS with reactive arthritis and ankilosing spondilitis is not established [23]. Other studies report a possible, weak association with Addison disease [27], primay biliary cirrhosis [56] and immune thrombocytopenic purpura [23], but results are not conclusive.

3. The immunological scenario of Turner Syndrome

Although it is well known that TS patients are at higher risk of AID diagnosis – and TS subjects show a higher prevalence of isolated autoantibodies compared to general population [57–59] –, the underlying pathophysiological mechanism is still partially unknown [10]. First of all, women with TS may be at risk of a number of medical problems, other than AID, and are therefore more likely than other women to be in contact with healthcare professionals [60]. This may be a substantial cause of a higher number of diagnoses than expected and works as a confounder. Then, the complexity of the diagnostic criteria for the majority of AID often leads to the inclusion of some healthy

people, and may contribute to this overestimation. The lack of diagnoses validation studies for AID – except for inflammatory bowel diseases and rheumatoid arthritis – can play a role as well [61,62]. Moreover, what sounds to be the cause of an association may be the consequence. Families with high frequency of AID are likely to be prone to disjunctional disorders. This theory refers to the observation that in other chromosomal disorders like Down [63] and Klinefelter [64] Syndromes incidence of AID is increased as well, meaning that autoimmune aggression might alter the gametogenesis [45,64]. Finally, in general population, the majority of AID are more frequent in women [65], and this would be related to alterations of the X-chromosome genes. Recent studies suggest that a reduced exposure of self-antigens in the thymus avoids the selection of autoreactive T-cells, producing an increased risk of autoimmune disorder [66–69], and this phenomenon is likely to be induced by a non-physiological lionization [70]. Anyhow, as explained later, these subjects are more likely to develop male-predominant AID, in spite of being 100% females.

In general, we reckon that a Turner patient together with their parents represent a unique genetic and immunological population, different from ethnically matched healthy people and from patients affected by immune-related diseases but with normal karyotype.

In particular, the most important reported abnormalities are:

- Low levels of G and M immunoglobulin subclasses [71]
- Weak chemotaxis of polymorphonucleates [72]
- Low CD4/CD8 ratio [72]
- High CD16+ natural killer cell count [73]
- Impaired T-cell response to mitogens [73].

In addition, TS has been shown to be a multifaceted condition of raising immunologic interest, also given its behavioural difference with the other HLA-mediated disorder. Indeed, the ongoing studies aim to better understand special difference in adoptive response, like class I-HLA, Gm and Km immunoglobulin light and heavy chain markers [57].

Since the 1970s, scientists have known that several Major Histocompatibility Complex (MHC) alleles play a role in the pathogenesis of many AID [74] MHC has been demonstrated to be redundant and many MHC-paralogues were found outside the HLA region on 6p21.3 autosome. So this plenty of genes involved in immune response may be relevant for life [75]. It is known the existence of a MHC-locus in the long arm of X chromosome that, if lacking, causes the loss of immune adaptation to the lifetime changes in pathogens exposure pattern [35]. This finding agrees with the observation that Turner patients are prone to develop a larger repertoire of immunological diseases if compared to general population.

Nevertheless, HLA alleles underlying AID in TS are consistent:

- HLA-B14 links with 21-alpha hydroxilase mutation [76];
- HLA-Cw6 positive subjects often present halo naevi and vitiligo [54];
- HLA-DRB1*0301 is associated with autoimmune thyroid disease when exposed to *Helicobacter pylori* [77,78];
- HLA-DR7,DQ2 and HLA-DR7,DQ9 are likely to develop organ-specific autoantibodies by parental imprinting [59].

It is hard to evaluate the influence of genetic profile in respect of the immune response in TS, but the contribution must be substantial. Families with TS present a higher incidence of Gm similarity between patients and with one of the parents, HLA mother–child compatibility, HLA parental sharing and HLA segregation distortion [79,80]. It is easy to understand that this aspect links TS to the other obstetrical diseases [81,82] such as gestosis, pre-eclampsia, preterm delivery and repetitive abortion [82–85].

The only difference in histocompatibility antigens that was found in TS, when compared to general population, is a higher prevalence of a rare class I-HLA haplotypes like A31 and B38 [57,79,86,87]. It's interesting that HLA-B38, particularly in special haplotypic settings like DRB1*13, are typical of high weighted newborns [88]. That being so, TS patients are very likely to survive in spite of their chromosomic lack, also because they present this foetus-protecting HLA [89].

4. Conclusions

X-chromosome alterations seem to be essential for the development of AD in TS, but are necessarily synergic with abnormalities of parental immunogenic profile and of genes involved in adoptive immune response. Therefore, in a setting of autoimmune susceptibility, Turner patients may develop either a condition or another one depending on the HLA haplotype they hold. Further studies are needed to well establish the relationship between TS and the immune system, in order to give these patients the correct diagnostic assistance, adequate follow-up with early detection of complications and best therapeutic intervention [90].

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