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Review

Autoimmunity and Turner's syndrome

Ana Lleo [a,b], Luca Moroni [a], Lisa Caliari [a,b], Pietro Invernizzi [a,c,*]

[a] Center for Autoimmune Liver Diseases, Department of Internal Medicine, IRCCS Istituto Clinico Humanitas, Rozzano, Italy
[b] Department of Translational Medicine, Università degli Studi di Milano, Rozzano, Italy
[c] Division of Rheumatology, Allergy and Clinical Immunology, University of California, Davis, CA, United States

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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.

* Corresponding author at: Center for Autoimmune Liver Diseases, IRCCS Istituto Clinico Humanitas, Via A. Manzoni 113, 20089 Rozzano, Italy. Tel.: +39 02 82245128; fax: +39 02 82245191.
E-mail address: pietro.invernizzi@humanitas.it (P. Invernizzi).

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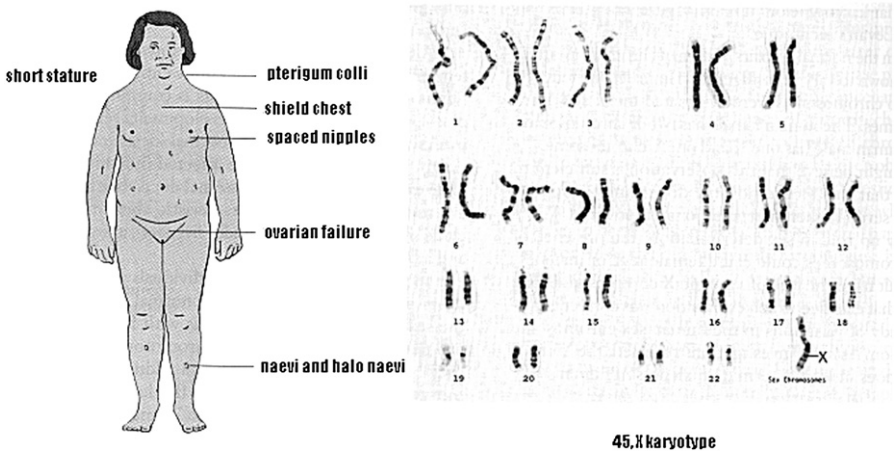

Fig. 1. Clinical features of Turner Syndrome/45,X karyotype.

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