Maturitas 79 (2014) 471–475

Contents lists available at ScienceDirect

Maturitas

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

Review

Management of Turner syndrome in adult life and beyond

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ARTICLE INFO

Article history:
Received 16 August 2014
Accepted 19 August 2014

Keywords:
Turner syndrome
Gonadal dysgenesis
Primary amenorrhea
Osteoporosis
Congenital malformations
Metabolic abnormalities

ABSTRACT

Objective: To describe in practical terms the clinical management in adult life of patients with Turner syndrome.
Material & methods: Systematic review of the literature and practical issues. An evaluation of clinical trials, meta-analysis, case reports and reviews assessing the management of different conditions related to Turner syndrome was done using the following data sources: Medline, PubMed (from 1966 to July 2014) and the Cochrane Controlled Clinical Trials Register, Embase (up to July 2014).
Results: Extracted information is summarized here on karyotype, screening of malformations, malformations debuting in adult life, final height, treatments with growth hormone, cardiovascular risk, endocrino-metabolic and liver abnormalities, sensorineural disorders and osteoporosis and its treatment.
Conclusions: This review provides recommendations for the management of adult patients with Turner syndrome and insight into the associated medical complaints. A link between karyotypes and clinical features suggests a novel hypothesis to explain the different phenotypes and clinical abnormalities of these patients.

Contents

1. Introduction

Turner syndrome (TS) is one of the more common genetic disorders, associated with abnormalities of the X chromosome, and occurring in about 50 per 100,000 live-born girls. Monosomy 45X0 is the most frequent form (up to 60% of cases), but other karyotypes are possible, including mosaic patterns [1].

Many abnormalities have been linked to TS, most of them originating with the haplo-insufficiency of genes that are normally expressed by both X-chromosomes. The typical features of TS are short stature and ovarian failure. Medical care has consequently been focused on early and prenatal diagnosis and on following pediatric guidelines for treatment with growth hormone and pubertal management [2]. Currently, it has become more evident that patients with TS are susceptible to some disorders that begin

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http://dx.doi.org/10.1016/j.maturitas.2014.08.011
0378-5122/

or progress during adult life, such as osteoporosis, hypothyroidism, diabetes, dyslipidemia and non-congenital cardiac and nephro-urological changes [1]. Morbidity and mortality are increased, and life expectancy is reduced by up to 13 years, mainly by cardiovascular disease [3,4].

Special care during adulthood is necessary and although it has been proposed that adults should also be followed by their primary care practitioners [3] these women have substantial health concerns and deserve coordinated care from a variety of specialties. Guidelines are still required on: the control of the sensorineural and endocrine disorders associated with TS; the associated malformations; and counseling on reproductive and sexual health [5]. Gynecologists should act as primary care providers by taking responsibility for the management of these patients, maintaining and taking control of hormone replacement and referring them to other specialties if required. In the present review, we describe the management of patients with TS in adult life.

2. Bone development anomalies and subsequent bone complaints

Short stature and ovarian failure due to gonadal dysgenesis are the main clinical stigmata, accompanied or not by other dysmorphology secondary to lymphedema [6,7]. An association between karyotype and phenotype has been recognized, but it is not predictable [8]. For instance, external dysmorphology and nephrologic or cardiac malformations are common in pure monosomy [9], whereas 40% of patients with mosaic patterns present spontaneous menarche with fewer external features [8]. In addition, isochromosome is associated with sensorineural and immunological disorders, without congenital malformations [10,11].

Short stature is almost an invariable finding in women with TS, whose average mean final adult height is close to 150 cm. A primary bone defect related to SHOX and PHOG genes on the distal part of the short arm of the X and Y chromosomes (Xp11-22, Yp11) as well as a partial insensitivity to growth hormone (GH) have been suggested as main causes of short stature in TS patients. In one study, TS girls receiving treatment with GH were on average 7 cm taller than those who were not [12]. It is recommended to begin GH treatment 4 years before estrogen replacement [9]. The addition of oxandrolone associated with GH seems to increase height gain and slow breast development without affecting body mass index [12].

Mutations in SHOX and PHOG genes could also explain some skeletal abnormalities in TS, such as cubitus valgus or short fourth metacarpal. Haplo-insufficiency of SHOX expression could explain other features, such as chronic otitis media, prominent ears, and problems in learning how to suck, blow, eat or articulate [13]. Lymphedema is caused by an absence or hypoplasia of lymphatic vessels and is generally identified at birth, but improves overtime. Other external physical disorders linked to TS are epicanthus, deformity in the pinna, micrognathia, cleft palate, short neck, pterygium colli, short limbs and genu valgum [14].

It has been hypothesized that osteoporosis and short stature could be due to a primary defect in bone formation since SHOX and PHOG [13] and some other genes located on the X-chromosome are associated with connective tissue changes [15]. A reduction in peak bone mass by 25% has been described in TS patients and the incidence of fracture in girls and women with TS is 3 times higher than in normal controls [16]. GH treatment for at least one year, together with estrogen replacement started before 12 years of age, improve bone mineral density and reduce fracture risk [16].

3. Ovarian dysgenesis and reproductive concerns

After the third month of gestation, TS fetuses suffer an accelerated depletion of oocytes with an increase in ovarian stromal fibrosis. Consequently, ovarian failure occurs in most cases within the first few months or years of life. Despite the fact that primary amenorrhea is common in TS, the incidence of spontaneous puberty is 8% in patients with the 45X0 karyotype, while it is found to be as high as 40% in women with mosaicism [17,18].

After the induction of puberty with estrogens, most females with TS require long-term estrogen replacement therapy, with the aim of preventing osteoporosis, reducing risk factors for atherosclerosis and improving aspects of cognitive function [13,17,19]. Hormone therapy is suggested with natural estrogens, oral or transdermal, since ethinyl-estradiol used in contraceptive pills has been associated with adverse effects on liver enzymes, lipid metabolism and blood pressure in women with Turner karyotype. In women with TS, replacement therapy improves some cognitive deficits (reaction time, non-verbal processing speed, short-term memory) [20]. Therefore, the use of estrogen replacement up to physiological doses should be maintained until the expected age of menopause [13].

A Y-chromosome may be detected in up to 6% of TS patients, the karyotype that may lead to the development of gonadoblastoma. Therefore, early prophylactic removal of the gonads is recommended in those cases, given that the risk increases with age [17].

Spontaneous pregnancies occur in less than 5% of TS patients, with an increased risk of congenital malformations or chromosomopathies. Oocyte donation and *in vitro* fertilization should be recommended. Nevertheless, the risk of first trimester miscarriage is higher, probably due to uterine hypoplasia and some uterine ischemia during pregnancy [21].

4. Congenital cardiovascular defects and disease in adult life

Cardiovascular complications are the main cause of mortality in TS [22]. The major ones are dilation of the root of the aorta, hypertension, and bicuspid aortic valve [23]. In addition, mortality due to ischemic heart disease is up to 7 times higher in women with TS. Cardiovascular complications in TS are mainly related to hypogonadism [4] but differences in X-chromosome gene expression may also contribute, since genes involved in the control of cardiovascular function have been found on the X-chromosome.

Isolated bicuspid aortic valve is the most common congenital malformation; however, it may occur together with other congenital defects, such as aortic coarctation. This combination leads to a progressive valvular dysfunction by valve calcification and may cause aortic stenosis or regurgitation in adulthood. Coarctation of the aorta affects 10% of women with TS; it causes hypertension and severe lymphedema, perhaps due to abnormal lymphatic flow by compression of the ascending aorta [13].

Other abnormalities, such as partial anomalous venous drainage and mitral valve prolapse, are more common among TS women, and left-side cardiac anomalies are associated with endocarditis, which means that prophylactic antibiotics are essential before surgical procedures. However, the major risk for TS patients is aortic dissection, which may occur at any age, causing sudden death. Hypertension, a bicuspid aortic valve and dilated aortic root are risk factors for dissection, making antihypertensive treatment in women with two of these three disorders advisable. Accordingly, echocardiography should be included in the assessment of TS patients and should be undertaken periodically. Electrocardiography should be carried out along with the imaging studies because