REVIEW ARTICLE

CARDIOVASCULAR DISORDERS OF TURNER'S SYNDROME: A REVIEW

Yuan S-M, Jing H*

***Corresponding Author:** Hua Jing, Department of Cardiothoracic Surgery, Jinling Hospital, Clinical School of Medicine, Nanjing University, Nanjing 210002, Jiangsu Province, People's Republic of China; Tel.: +86-25-8480-1332; Fax: +86-25-8482-4051; E-mail: shiminyuan@126.com

ABSTRACT

A series of cardiovascular abnormalities may be associated with Turner's Syndrome (TS). Over 50% of the reported cardiovascular malformations have been bicuspid aortic valve or coarctation of the aorta alone, or in a combination, which may lead to a higher risk for infective endocarditis. Isolated dilation of the ascending aorta was often seen in TS, while aortic dissection has been increasingly observed in recent years. The aortic root dilation was found more likely to be due to a mesenchymal defect rather than atherosclerotic changes. Women with TS are often hypertensive as a result of aortic abnormality or renal vascular disorder. They have an increased risk of developing neoplasms, such as gonadoblastoma and dysgerminoma, and therefore they may require regular monitoring while receiving hormone therapy. In patients with gonadal dysgenesis, exogenous estrogen treatment poses a problem of connective tissue disorders of the great vessels. To resolve the contradiction between exogenous estrogen therapies and the hold-up of the progression of the connective tissue abnormality is a topic to be coped with. Careful clinical assessment

is mandatory in the evaluation of patients with TS with cardiovascular abnormalities.

Keywords: Aortic dilation; Cardiovascular abnormalities; Turner's syndrome (TS)

INTRODUCTION

A 45,X karyotype is a common chromosomal abnormality and is characterized by short stature, under development of secondary sexual characteristics, webbed neck and cubitus valgus. It is a genetic disorder caused by the complete or partial absence of an X chromosome in some or all cells of a female patient, which prevents the sexual and reproductive organs from developing normally and is usually associated with infertility. First described in 1938 by Dr. Henry Turner, it has been termed as Turner's syndrome (TS) (also known as 45,X syndrome) [1]. Absent, fragmented, partly deleted or structurally impaired X chromosome in some cells represents the mosaicism of TS, showing less pronounced signs than classical TS, which is characterized by absence of the X chromosome in all cells [2].

Turner's syndrome occurs in 1 of every 2,000 to 5,000 live female births [3], accounting for about 15% of all spontaneously aborted fetuses [4]. It is responsible for 7-10% of all spontaneous abortions [5]. About 75% of all fetuses prenatally diagnosed

Department of Cardiothoracic Surgery, Jinling Hospital, Clinical School of Medicine, Nanjing University, Nanjing, Jiangsu Province, People's Republic of China

with this syndrome were legally terminated in Denmark [6]. In TS, female sexual characteristics are present but under developed [7]. Shortness of stature and of neck, low posterior hair line, broad chest with widely spaced rudimentary nipples, congenital lymphoedema, redundant lax neck skin and hypoplastic nails are the most common clinical features. Turner's syndrome may be associated with cardiovascular, skeletal, renal, thyroid, cognitive and reproductive disorders and diabetes type II [8]. The renal and cardiovascular anomalies have been found in 87.5 and 45% of the patients, respectively [9]. It has been demonstrated that low circulating levels of sex hormone-binding globulin may be strong predictors for diabetes type II [10]. As the female patients with TS may have low sex hormone-binding globulin, they become very susceptible to diabetes type II [12]. Turner's syndrome is not usually associated with thrombotic events. In TS patients without thrombosis, levels of factor VIII and von Willebrand factor were much higher than those of the control female subjects [11]. Consequently, the TS patients were placed in a high risk category for cardiovascular events. Furthermore, a 3-fold increase in overall mortality and a minus 13 years life expectancy were expected [13].

Congenital cardiac abnormalities have been described in one-third to half of the patients with TS, the most common of which are bicuspid aortic valve and coarctation of the aorta [14]. Dilatations of the ascending aorta and aortic dissection may develop. Most patients with aortic dilation have an associated risk factor such as bicuspid aortic valve, coarctation of the aorta or systemic hypertension [15]. An echocardiographic evaluation of 594 TS patients revealed a significant difference in the prevalence of cardiovascular malformations between different types of karyotypes, where partial anomalous pulmonary venous drainage and aortic coarctation were more common in the patients with 45,X karyotypes, whereas bicuspid aortic valve and aortic valve disease were phenotypes of X-structural abnormalities [16]. With the popularly used atraumatic diagnostic means, cardiovascular abnormalities were increasingly screened and investigated [17]. The aim of the present article is to make a comprehensive review on the clinical features of the cardiovascular spectrum in TS patients.

CARDIOVASCULAR DISORDERS

Congenital Heart Defects. The most commonly observed cardiovascular abnormalities are congenital obstructive lesions such as bicuspid aortic valve and coarctation of the aorta. Thus, Sybert [18] found that more than half of the cardiovascular malformations of TS were bicuspid aortic valve or coarctation of the aorta alone or in combination. Some 6.9-15.0% of adults with TS have bicuspid aortic valves [16,19] and 5.5-20% coarctation of the aorta [19]. The latter abnormality in a female might be evidence suggestive of TS and it is suggested that it should be surgically corrected as soon as possible after being detected. Moreover, malformations such as partial anomalous venous drainage and aortic stenosis or regurgitation are more common in TS than in the general population [21]. It has been reported that aortic anomalous venous drainage occurred in 2.9% of TS patients [22]. Hypoplastic left heart syndrome is a congenital disorder of the left heart system that may present in TS, representing a high mortality in spite of successful surgical correction [23,24]. It has been reported that this anomaly is more likely to be associated with karyotype 45,X [25]. Hypoplastic left heart syndrome suggests that this anomaly can be another expression of the 45,X karyotype. Moreover, Ho *et al.* [26] described the prevalence of vascular abnormalities in TS including elongation of the transverse arch (49%), aortic coarctation (12%), aberrant right subclavian artery (8%), persistent left superior vena cava (13%) and partial anomalous pulmonary venous return (13%). They suggested that *in utero*, centrally localized lymphatic obstruction may contribute to these cardiovascular deformities in TS. Kutay and Yakut [27] reported absence of the right superior vena cava accidentally observed during an operation associated with congenital aortic annular hypoplasia and bicuspid aortic valve stenosis in a patient with TS. In addition, transposition of the great arteries is an alternative rare association of TS, but only one case has been reported [28]. The significant association between neck webbing and the presence of bicuspid aortic valve and coarctation in TS suggests a pathogenetic connection between fetal lymphatic obstruction and defective aortic development [29].

Aortic Dilation and Dissection. Aortic wall disorders including aortic dilation and dissection are infrequent in TS. Aortic dilation was observed in 26.7-42.0% of the patients with TS [5,20]. The location of the aortic dilation typically involves the aortic root, but occasionally extending to the aortic arch, the descending aorta, or at the repair site for a previous coarctation of the aorta [15]. Compared to the controls, the TS patients had larger diameters of the aorta at the level of the sinuses of Valsalva, the sinutubular junction, and the ascending aorta [30], but descending aortic diameter and ascending/descending aortic ratio were not [17].

The incidence of aortic dissection was estimated to be as high as 40 per 100,000 in TS patients [31], and this prevalence is increasing with age, and is especially high during adulthood, pregnancy, or delivery [5]. The predisposing risk factors for aortic dissection in TS were estimated to be coarctation, bicuspid aortic valve, and hypertension [32]. Dilation is mostly commonly present at the ascending aorta without potentially rapid progression, a similar phenomenon to that being observed in the patients with a bicuspid aortic valve without TS, showing an even prevalence of 20-30% in both children and adults [33]. Aortic dissection flap may occlude the ostium of the right coronary artery, which requires a right coronary artery bypass so as to restore the blood supply to the ventricle. In this way, both the mother and the child can be secured [34]. The risk for aortic dissection or rupture in pregnant women may be over 2%, and hence cause the patients death with a 100-fold higher risk [35]. The occurrence of fetal lymphedema, one of the common features of both Marfan's syndrome and TS, evidenced by the neck webbing and a shield chest in TS [5], was taken as the underlying etiology responsible for this lethal complication [33]. The mesenchymal defect in TS, somewhat a similar pathological change, namely, cystic medial necrosis found in Marfan's syndrome [13], was hypothesized to be resulted from an abnormality of the X chromosome, which may ultimately affect collagen synthesis [5,36].

Hypertension. Systemic hypertension affects 30% of TS patients regardless of age, and no specific cause can be identified in a majority of women [37]. The hypertension can often be nocturnal with decreased sympathovagal balance or tone and elevated N-terminal pro-BNP in comparison with

controls, indicative of discrete systolic or diastolic dysfunction [38].

Valvular Disorders. In addition to bicuspid aortic valve, the valvular disorders that may be present in TS include mitral valvular insufficiency, aortic insufficiency, aortic stenosis, and tricuspid insufficiency [39]. Furthermore, mitral valve prolapse was more likely to be seen in TS patients than in the general population, with a higher prevalence in the non 45,XO than in the 45,X karyotype [40].

Cardiac Conduction and Repolarization Abnormalities. In a case-control study including 100 TS patients, the occurrence of left posterior fascicular block, accelerated atrioventricular conduction, and T wave abnormalities were significantly higher, the PR interval was significantly shorter, and the QTc interval was significantly longer in TS patients than in age-matched controls, indicative of the potential impact of X chromosome deficiency on cardiac conduction system [41].

Aneurysm of the Left Subclavian Artery. Turner's syndrome may be associated with an aneurysm of the left subclavian artery, which were large in size located proximal to the thoracic outlet as indicated in the limited case presentations [42,43]. The histology of the surgical specimens showed disruption of the elastic fibers and deposition of acid mucopolysaccharide in the media with normal or degenerative intima. These results may be helpful in the understanding of the etiologies of such a lesion in TS patients.

Coronary Artery Disease. It has been suspected that TS patients are at greater risk of coronary artery disease due to their significantly higher blood pressure and levels of total cholesterol and low-density lipoprotein fraction as well as of lower high-density lipoprotein fraction compared to controls [44]. The cholesterol levels were significantly increased independent of age, body mass index z score, or karyotype if it was untreated TS [45], but decreased significantly during growth hormone treatment [46].

TREATMENT

Growth hormone therapy is recommended for TS patients to promote their secondary sexual development and to improve quality of life [47]. As a result, estrogen deficiency as well as estrogen

deficiency-induced memory and motor coordination problems, can be ameliorated after treatment with growth hormones [48]. Systematic clinical assessments including gynecological examinations should be regularly performed on TS patients who receive growth factor treatment due to the potential risk of developing neoplasms in these subjects [49]. The severity of aortic dilation seemed to be related to the dose of growth hormone treatment, with a beneficial effect of a larger growth hormone treatment dose [50]. Aortic root dilatation is a significant risk in women with TS and is closely dependent on blood pressure. Aortic root dilatation does not appear to be related to atherosclerosis and is more likely to be due to a mesenchymal defect [5]. Women with TS are often hypertensive as a result of aortic abnormality or renal vascular disorder. In all individuals with hypertension, with or without aortic dilation or aortic dissections, medications should be given to control the blood pressure in order to prevent coronary heart disease, heart attack or other potentially fatal complications. Beta blockers or rennin-angiotensin system antagonists may benefit TS patients in retarding the progression of aortic dilation [51]. Coarctation of the aorta and bicuspid aortic valve are commonly associated with TS, leading to an increased risk to infective endocarditis. Therefore, prophylactic antibiotics are strongly recommended for TS patients with a susceptibility of bacteremia [5,8]. In addition, diabetes type II can be well-controlled through medication with careful monitoring of blood glucose levels, healthy meal planning and exercise, *etc.* Thyroid hormone supplements can help boost underactive thyroid function in patients with hypothyroidism.

Prophylactic aortic replacement may minimize the risk of potentially fatal aortic dissection of the TS patients [51]. A patch plasty using felt reinforcement [52], tube graft insertion [53], or composite aortic valve replacement [54] with satisfactory postoperative courses have been documented in the literature. However, the situation would be more complicated and may lead to a critical condition if the TS patient had a history of previous coarctation repair [53]. In recent years, stent graft deployment was well-developed as an alternative choice to open surgery in proper cases [55].

PROGNOSIS

The prognosis for some TS patients is relative good with regular monitoring and proper management of the associated anomalies [56]. Turner's syndrome female patients are at a high risk of miscarriage and stillbirth, but the prognosis for a TS baby is good enough with normal intelligence in spite of the associated problems [57]. In a prospective study of 156 female TS patients followed for 17 years, the reduction in life expectation was 12.5 years at the age 1, 11 years at age 20, and 10 years at age 40 [13].

In general, TS is a genetic disorder where all or part of an X chromosome is missing. This condition is often accompanied by a series of cardiovascular disorders, with aortic wall abnormalities and congenital heart defects, which often require surgical intervention in addition to growth hormone therapy. Regular monitoring of the aortic root diameter and hypertension is essential and should be treated promptly in all women with TS.

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