Heart and Turner syndrome

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Abbreviations:

TS= Turner syndrome. BAV= bicuspid aortic valves. CoA=aortic coarctation. BSA= Body surface area. AD=aortic dilatation. TTE=TransThoracicEchocardiography. MRI=Magnetic Resonance Imaging.

Abstract < 250

Turner syndrome (TS) is a rare disease (ORPHA #881) which affects about 50 in 100 000 newborn girls. Their karyotype shows a complete or partial loss of the second X chromosome. In TS, congenital cardiovascular malformations, such as bicuspid aortic valves and aortic coarctation are frequent, affecting 20-30% and 7-18% of the TS population, respectively. The morbidity and mortality of these patients are high and related to the presence of hypertension and/or aortic dilatation (40%), inducing aortic dissection. European guidelines published in 2017 have indicated how to monitor patients using magnetic resonance imaging (MRI) and/or echography. Different studies have shown that a cardiovascular lifelong follow-up is necessary and therefore education of patients with TS and their families represents a major issue. This review will present recent data concerning the progression of aortic diameters as well as current molecular knowledge of the cardiovascular system in patients with TS.

INTRODUCTION

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Turner syndrome (TS) is a rare disease (ORPHA #881) which affects about 50 in 100 000 newborn girls. The chromosomal disorder observed in TS, is a complete or partial loss of the second X chromosome in phenotypic females who have one intact X chromosome. The most frequent abnormalities are growth failure (>95% of cases), primary ovarian insufficiency (POI) (95%), elevated liver enzymes (50-80%), autoimmune diseases (58%) and hypertension (50%). Congenital or acquired cardiovascular diseases are present in about half of patients with TS [1,2]. Mortality of patients with TS is increased by a factor of 3 compared to the general population (SMR=3.0 [95%CI= 2.7-3.4]) [3]. It is due to cardiovascular diseases, including aortic dissection.

EPIDEMIOLOGY and KARYOTYPING

The prevalence of TS diagnosis is 50/100 000 in female newborns. It is lower when incidentally found at the adult age, as shown by the UK Biobank study including 244 848 women [4]. In a recent French study, including 1501 patients with TS, the median age at diagnosis was 9.4 years [5] In Europe, the Danish cytogenetic register identified all cases (n= 781) of TS alive in Denmark, during the period from 1970 to 2001. Their median age at diagnosis was 15.1 years.

The diagnosis of TS relies on the lymphocyte karyotype. Approximately 45% of ST patients bear the typical 45,X karyotype [6]. In most cases, the maternal X chromosome is retained and not the paternal X. Some studies have shown that a 45,X karyotype is associated with greater visceral fat accumulation, a more atherogenic and a stiffer aorta profile [7]. The other half of patients has a mosaic karyotype, including one third with structural X chromosome variants, deletion, ring and isochromosomes. The last consensus statement published in 2017 recommends a 45,X mosaicism higher than 5% in order to consider the diagnosis of TS [2]. The phenotype in mosaic patients tends

to be milder[8]. Hence, severity of the cardiovascular phenotype in TS patients is linked to the proportion of 45,X cells. Indeed, a 45,X karyotype is associated with a higher prevalence of aortic dissection, aortic coarctation and bicuspid aortic valve (BAV) [9,5]. However, recent studies have identified discrepancies between karyotypes from blood lymphocytes and buccal cell fluorescent *in situ* hybridization analysis (FISH). In our population of patients with TS, results of FISH analysis on buccal smears were different from the lymphocyte karyotype in 17/142 (12%) patients [10]. Therefore buccal cell smear has in some cases, an added value to identify potential 45,X mosaicism, compared to blood lymphocytes.

CONGENITAL MALFORMATIONS

The most prevalent congenital cardiovascular malformation is bicuspid aortic (BAV), which is present in 20% to 30% of TS patients [1,11,12]. Its prevalence is however difficult to report, since asymptomatic vascular abnormalities can remain undiagnosed until adulthood. In our reference center of rare diseases (CMERCD), the median age at diagnosis of BAV was 20 (P25-P75th: 15-30)[12]. This delayed diagnosis is probably related to the fact that cardiac echography may be difficult to perform in young children. The prevalence of BAV in TS is much higher than in the general population, where it is present in 2-3% in males and in 0.05% in females [13]. BAV is a predisposing factor for subsequent aortic dilatation and even aortic dissection [2]. Therefore, patients with TS and BAV are prone to develop AD and need cardiovascular monitoring all their life.

The second most frequent congenital aortic malformation is aortic coarctation (CoA). It is present in 7-18 % of TS patients. Conversely, the finding of CoA in a newborn girl should prompt a diagnosis of TS as it is present in 12.6 % of cases [12]. Clinically, asymetric blood pressure is in favor of the diagnosis. Neck webbing and increased antero-posterior thoracic diameter are strong predictors of arterio-veinous abnormalities in TS [14]. The frequent finding of an elongation of the transverse aorta on MRI is an equivalent of CoA. It is associated with proximal AD and is a

predisposing factor for subsequent aortic dissection [2]. The fibrotic process next to the aortic canal results in an aortic striction at the level of the aortic cross. A reverse-flow phenomenon of the left ventricular output, which results from CoA, is responsible for hypertension and AD.

Some heart and vascular abnormalities other than BAV and CoA, have been described. They include partial anomalous pulmonary venous connection, left superior vena cava, elongated transverse arch and dilatation of the brachiocephalic arteries, hypoplastic left heart syndrome, mitral valve anomalies, interrupted inferior vena cava with azygous continuation, cardiac dextroposition, ventricular septal defect, atrioventricular septal defect, pulmonary valve abnormalities and coronary artery anomalies [2]. Whether these malformations increase the risk of mortality is still unknown.

HEART RHYTHM DISTURBANCES

A resting electrocardiogram is necessary in the check-up of patients with TS. Tachycardia is more frequent than in the general population [15]. Furthermore, prolonged rate-corrected QT interval (QTc) has been described in patients with TS. Its prevalence is unknown. When resting QTc > 460 ms, exercise testing and 24h Holter monitoring should confirm the diagnosis. In such patients, drugs prolonging the QTc should be avoided. However, a recent study reports that the QTc interval in girls and women with TS is not prolonged compared to the general population. In this study, a 45,X monosomy is not associated with QTc prolongation [16].

ACQUIRED CARDIOVASCULAR DISEASE

Aortic dilatation and aortic dissection

There are two main imaging techniques for aortic evaluation: transthoracic cardiac echocardiography (TTE) and aortic magnetic resonance imaging (MRI). The aortic root should be measured at least at

the four following levels: aortic annulus, Valsalva sinuses, sino-tubular junction and tubular ascending aorta (Figure 1). Aortic diameters can also be measured at the aortic cross and the descending aorta. The cost and availability are in favor of TTE. However, clinicians trained in congenital heart disease are needed to have good quality exams. Furthermore, thoracic hypo echogenicity and artifacts due to movements during the examination, especially in infancy, are a frequent drawback of TTE. Furthermore, MRI is less operator-dependent and the whole aortic arch, including descending aorta can be evaluated. This technique is increasingly available around the world.

Due to the fact that the relationship between aortic diameter and BSA is linear only after the age of 16, aortic dimensions should be expressed with the help of Z-scores, before that age [17]. Current consensus prone that aortic diameters should be indexed to body surface area (BSA) in TS patients [2,18]. BSA calculation using Dubois and Dubois's formula incorporates weight and height. Therefore, obesity may underestimate the value of the indexed aortic diameter. It is important to take this fact into consideration, when following obese patients. Indexed aortic diameter at the level of the ascending aorta (aortic index) under the threshold of 20 mm/m² is considered normal. Surgical advice for thoracotomy with prosthetic aortic replacement procedure is discussed when the aortic index is above 25 mm/m² [18].

Few longitudinal studies have evaluated the aortic diameter progression in large cohorts of TS patients. Mortensen et al [19] found in 91 patients with TS, that the aortic progression at the level of the Valsalva sinuses and the tubular ascending levels were 0.32-±0.3 mm/y and 0.20-±0.2 mm/y, respectively, after a mean follow-up of 8.8 years. A control population of 37 women was included in the study. Aortic growth rates were similar between the two groups of women, but the variations were larger in TS than in control patients. Duijnhouwer et al. [20] studied a cohort of 171 adult patients with TS, with a mean follow-up of 6.8 years. MRI or cardiothoracic scan were performed within a cardiology department. The median aortic growth was +0.20 mm/year (IQR: 0.0-0.4) at the

level of the tubular ascending aorta, after 5.9 years. It was similar whether patients had or not a BAV or AD.

In our reference center, 197 adult patients with TS were followed-up between 2005 and 2019. The median age of our population, at the last evaluation, is 25.6. Aortic growth (mm/year) and its risk factors were recently evaluated [21]. Inclusion criteria were: ≥ 10% 45,X monosomy; ≥ 1 aortic MRI performed with 2 aortic levels available at the Valsalva sinuses and the tubular ascending aorta. The patients' files were included in the French national rare disease database (BAMARA). All aortic diameters were indexed to BSA. At baseline, AD was present in 81/197 (41.1%) and 32/197 (16.2 %) of patients, at the levels of Valsalva and ascending aorta, respectively. The aortic Valsalva diameter was larger in patients treated for thyroiditis ($P < 0.001$). Risk factors of AD were aging ($P < 0.001$) and the presence of a bicuspid aortic valve (BAV) (p = 0.002). Presence of BAV nearly doubled the risk of AD: HR=2.2 (95%CI 1.33-3.71) (Figure 2). Among the subgroup of patients with at least 2 MRIs, after a median follow-up period of 5.1 years (n = 143), AD was present in 58/143 (40.6%) and 25/143 (17.5%) of patients at the levels of Valsalva and ascending aorta, respectively. Their median aortic growth of the Valsalva sinuses remained stable. At the ascending aorta, it increased by 0.14 ± 0.61 mm/year. In our study, a past treatment of growth hormone (GH) was not a significant risk factor for AD [20].

Few studies report the incidence of aortic dissection of patients with TS [1,2]. A study from the Mayo clinic included 317 patients with TS, between 1950 and 2017 [22]. Their mean age at diagnosis of TS was nine. A karyotype was available in 202 patients and pure X monosomy was present in 75 (37%) cases. Six cases (2%) of aortic dissection were reported, occurring at a mean age of 53. Overall survival after dissection was lower in TS patients (82%) than in the general population (94%) (p 0.001). The incidence of aortic dissection diagnosed by echocardiography in a cohort of 198 Swedish women with TS, after 23 years of follow-up (1995-2018), was 110 cases/100 000 patients-years. Nine cases of aortic dissections occurred at a median age of 37 (range: 16-71). A 45,X

karyotype was present in 4 women and only 2 were alive at the end of the study. Presence of BAV increased the risk of dissection by a 4-fold factor. The associated risk factors were the presence of AD, hypertension, BAV and CoA [23]. Report of the International TS Aortic Dissection Registry showed in 20 patients [24] that 95% of them had associated cardiovascular malformations. However, in 11% of the 85 published dissection cases in 2007, TS by itself was an independent dissection risk factor [25].

Pregnancy is another known risk factor of aortic dissection. Two deaths in pregnant women with TS occurred in France, in 2010. Chevalier et al. reported the French experience of oocyte donation (OD) in 93 patients with TS. Only 37.5% had been screened with TTE or MRI before pregnancy [26]. Maternal outcomes included hypertension-related disorders in 37.8% and severe eclampsia in 4 patients. French national recommendations were established in 2009 [27] and were recently evaluated including 103 patients from 14 OD centers [28]. Neither death nor serious maternal complication occurred. A Swedish registry study reported no death after OD [27]. However, a pregnancy in women with TS should be planned as all patients should have a careful cardiovascular evaluation. If 95% of patients will receive oocyte donation (OD) in order to become pregnant, 5.6% of them will have a natural pregnancy [29]. Therefore, to make pregnancies safe for women with TS, contraindications should be respected [30], such as a previous history of aortic surgery or severe AD. In front of an indexed aortic diameter > 25 mm/m^2 alone or associated to dissection risk factors such as BAV, CoA, or uncontrolled hypertension, a pregnancy should be avoided. Between 20-25 mm/m^2 with or without those risk factors, patients should be advised that pregnancy carries a high-risk of dissection. A multidisciplinary team including materno–fetal medicine specialists and cardiologists, from reference centers for rare diseases should undertake the follow-up [2]. Aortic imaging is necessary during the first and second trimesters, then monthly during the last trimester and 2 months after the delivery. A recent retrospective study from Canada and USA, including 68 pregnancies across 10 cardiovascular centers shows that among women with TS without structural

heart disease, pregnancy did not increase the risk of cardiovascular events [31]. Those data are rather reassuring but close follow-up should be performed during and after the pregnancy.

International guidelines concerning screening for AD in patients with TS, outside of pregnancy, have been published in 2017 [2,32]. The frequency of the measures is based on the initial aortic diameter at the age of 16 years and the presence of associated cardiovascular risks factors such as CoA, hypertension and BAV. According to the guidelines, it ranges from every year to 10 years (Figure 3).

Hypertension

Hypertension is an important acquired predisposing factor for AD, aortic dissection and stroke [2]. According to different studies, the prevalence of hypertension ranges from 13 to 58% in TS patients [33,34]. Hypertension is an early finding in about 25% of pediatric patients. Abnormal nocturnal dipping is frequent and is detected by a 24h ambulatory blood pressure measurement. Home blood pressure monitoring with an appropriate device and an average of two measurements every day for 3 days can be an alternative. Early hypertension diagnosis and treatment are crucial to prevent aortic growth. Consensus blood pressure threshold is 140/90 mmHg in presence of vascular malformations (BAV, CoA, AD) and the blood pressure to reach is below 130/80 mmHg [2]. Beta-blocker or angiotensin receptors inhibitors are first line treatments in order to avoid AD [35,36]. If hypertension is present, end-organ damage is required, at the retina, kidneys and the brain. Secondary causes of hypertension include ACo and renal artery stenosis. This latter diagnosis may lead to dedicated imaging of renal arteries. In patients with a snoring history, obstructive sleep apnea needs to be searched in hypertensive patients [37]. The causes of hypertension in TS are poorly understood and probably multi-factorial. Overweight, dyslipidemia, diabetes and inflammation, impaired insulin-mediated vasodilatation, increased stimulation of sympathetic nervous system and estrogens deficiency are probably involved [33]. Increased left ventricular mass, present even before the

presence of hypertension, may also contribute to its pathophysiology [38]. Interestingly, a slight positive impact of estradiol supplementation, on the blood pressure level, has been described [39].

Coronaropathy

TS is associated with coronary artery disease (CAD). However, few data are available on CAD, in patients with TS, as few studies are published including aging adults with TS. Patients with TS have higher cardiovascular risks than the general population [40]. Their glucose homeostasis is frequently impaired with hyperinsulinemia, insulin-resistance and low first-phase insulin secretion. The risk of type 1 and 2 diabetes mellitus is increased across all ages, by 10 and 4 times, respectively. Dyslipidemia is more frequent than in the general population [2]. Body mass index (BMI) in some populations of TS is higher than in the general population. A recent study reported coronary CT angiographies performed in 168 women, without any clinical evidence of CAD (115 with TS and 53 without TS). The prevalence of CAD was similar in both populations, as well as the degree of atherosclerosis. In this study, conventional cardiovascular risk factors were involved in CAD such as weight, blood pressure, glycemia and cholesterol levels. Therefore, those parameters should be regularly assessed in patients with TS.

MECHANISMS OF CARDIOVASCULAR DISEASE

Haplo-insufficiency for gene(s) located on the short arm of the X chromosome (Xp) have been implicated in the cardiovascular phenotype [41]. As BAV are much more frequent in TS than in the general population, this suggests that the second X chromosome is a protecting factor against BAV. In a whole genome study from the GenTAC registry [42], 188 TS patients were included. BAV, aortic dimension z-scores have been used as covariates of aortopathy. This analysis revealed that one gene, named *TIMP3*, was associated with indices of aortopathy. Interestingly, *TIMP3* gene is located on Xp.

Its transcription product is a tissue inhibitor of aortic matrix metalloproteinases (TIMPs). A second gene, *TIMP1,* coding for another TIMP, is located on the X chromosome and escapes inactivation. It interacts with *TIMP3* and both are involved in the development of the aortic valve. They protect tissue integrity of the aorta media (Figure 4). Hence, two events are needed in order to increase the risk of aortopathy: the presence of a single copy of *TIMP1* due to the loss of the second X-chromosome, and the presence of the risk allele *TIMP3* [43].

In order to understand the mechanisms involved in aortic dissection, aortic histology is necessary. However, only few cases have been reported, so far [44]. Available histology showed a cystic necrosis in the aortic media, which has previously been described in other congenital aortopathies, such as Marfan syndrome [45]. Histology from TS patients showed collagen fibrosis with activation of connective tissue production. Immunochemistry showed an excessive TGFβ signaling and activation of the downstream SMAD signaling [13]. High TGFβ activity increases fibrosis and inflammation, and induces the release of metalloproteases and may eventually lead to AD and dissection. Therefore, autopsy should be promoted in TS to decipher mortality biomarkers [44].

PREVENTION AND TREATMENT

In order to slow down aortic root dilatation in patients with BAV, beta-blockers or inhibitors of angiotensin II receptor (Losartan) are advised if AD $\geq$ 20 mm/m² [46]. Those treatments are recommended in patients with Marfan syndrome. However, there is no scientific proof, so far, of a benefit of such treatments on aortic progression in patients with TS.

The best prevention of aortic dissection is to educate patients and perform their counselling. Transition between pediatric and adult hospital remains crucial. An organized transition of TS, from pediatric units to multidisciplinary adult care systems within the same reference center have beneficial impacts, at least in terms of loss to follow-up [47]. Our unit has developed a dedicated

therapeutic education program for adult patients with TS [47]. One of its goals is to increase the patient's knowledge concerning her future cardiovascular health. Furthermore, patients with TS are in general more anxious than the general population. Therefore, psychological support should be offered.

CONCLUSION

Cardiovascular outcomes remain a major issue in patients with TS. Clinicians taking care of such patients have to face a lifelong challenge in order to avoid aortic dilatation, aortic dissection and premature death. A multidisciplinary approach is needed, involving rare disease centers. Patients and their family should be aware of the risks of cardiovascular diseases, such as BAV, CoA, hypertension and pregnancy. However, data are still lacking concerning the natural history of aortic disease and the molecular mechanisms involved in the fragility of the arterial wall. Histology and genetic studies should enhance in the near future our understanding of cardiac and aortic diseases in patients with TS.

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Legend of figures

FIGURE 1:

The aortic root should be measured at least at the four following levels: aortic annulus (1), Valsalva sinuses (2), sino-tubular junction (3) and tubular ascending aorta (4)(adapted from: *Protocole de Diagnostic et de Soin Syndrome de Turner*, HAS).

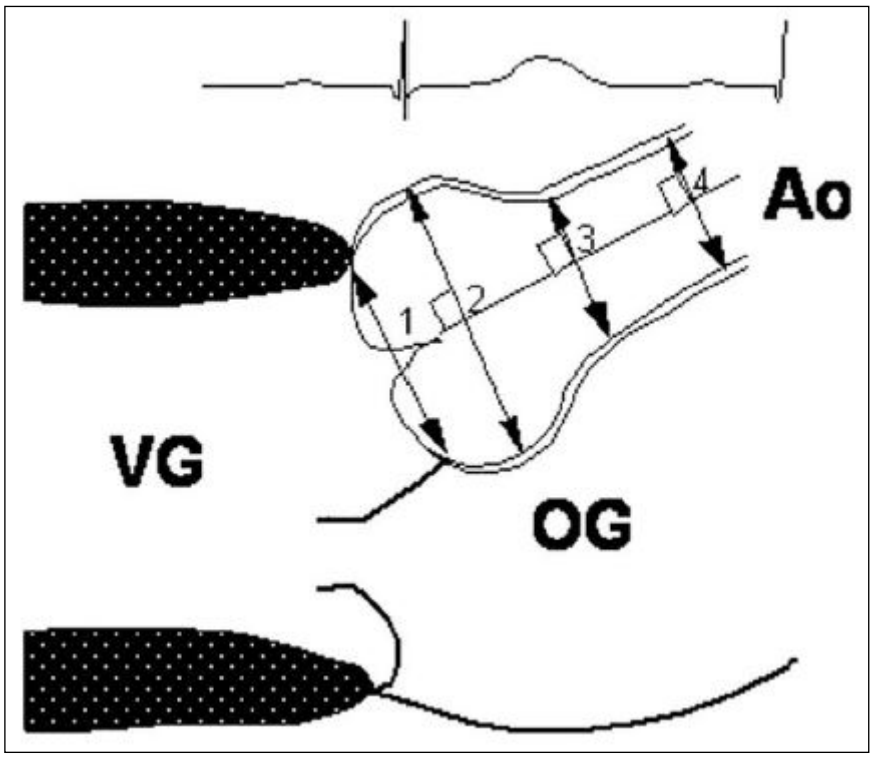

FIGURE 2:

Kaplan-Meier survival estimator without aortic dilatation (AD) of the Valsalva sinuses according to age (X axis), in the presence (black line) or the absence (dotted line) of aortic bicuspid valve (BAV) (n=197).

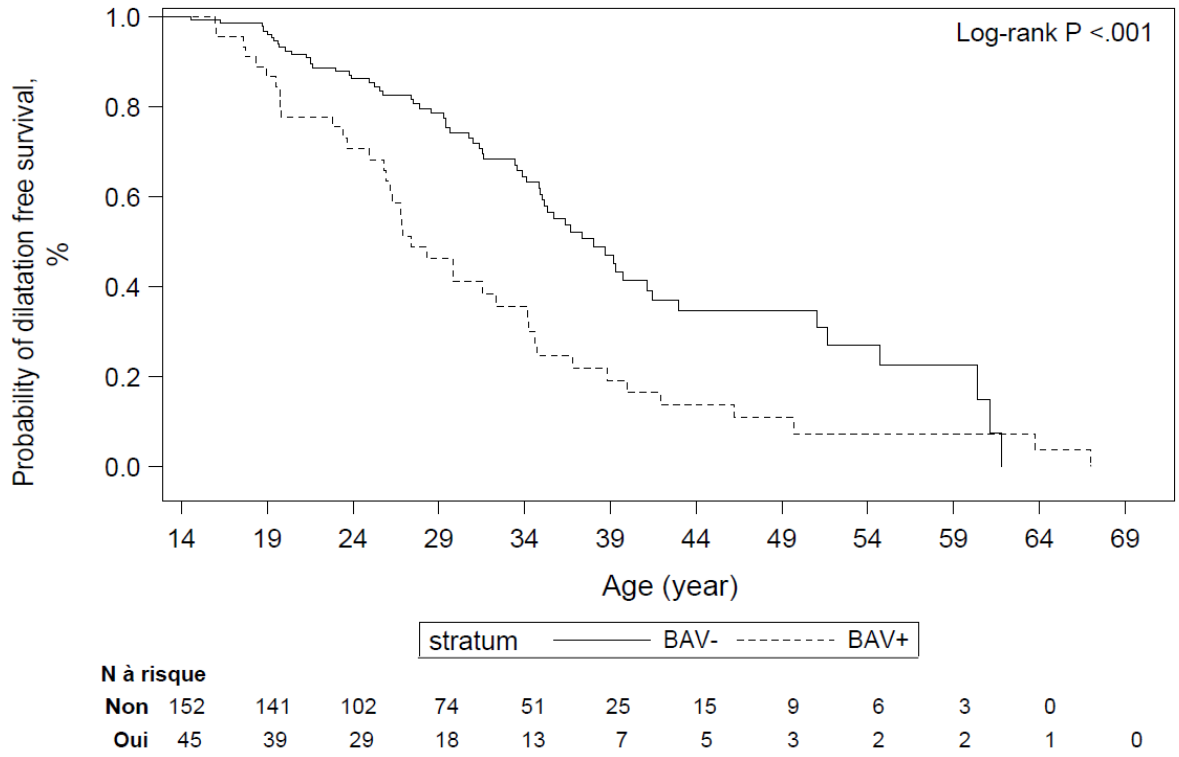

FIGURE 3:

Recommended cardiologic monitoring protocol in adult patients with TS: TTE for transthoracic echography, MRI for magnetic resonance imaging, CoA for aortic coarctation, BAV for bicuspid valve, ASI for aortic index (adapted from reference [2]).

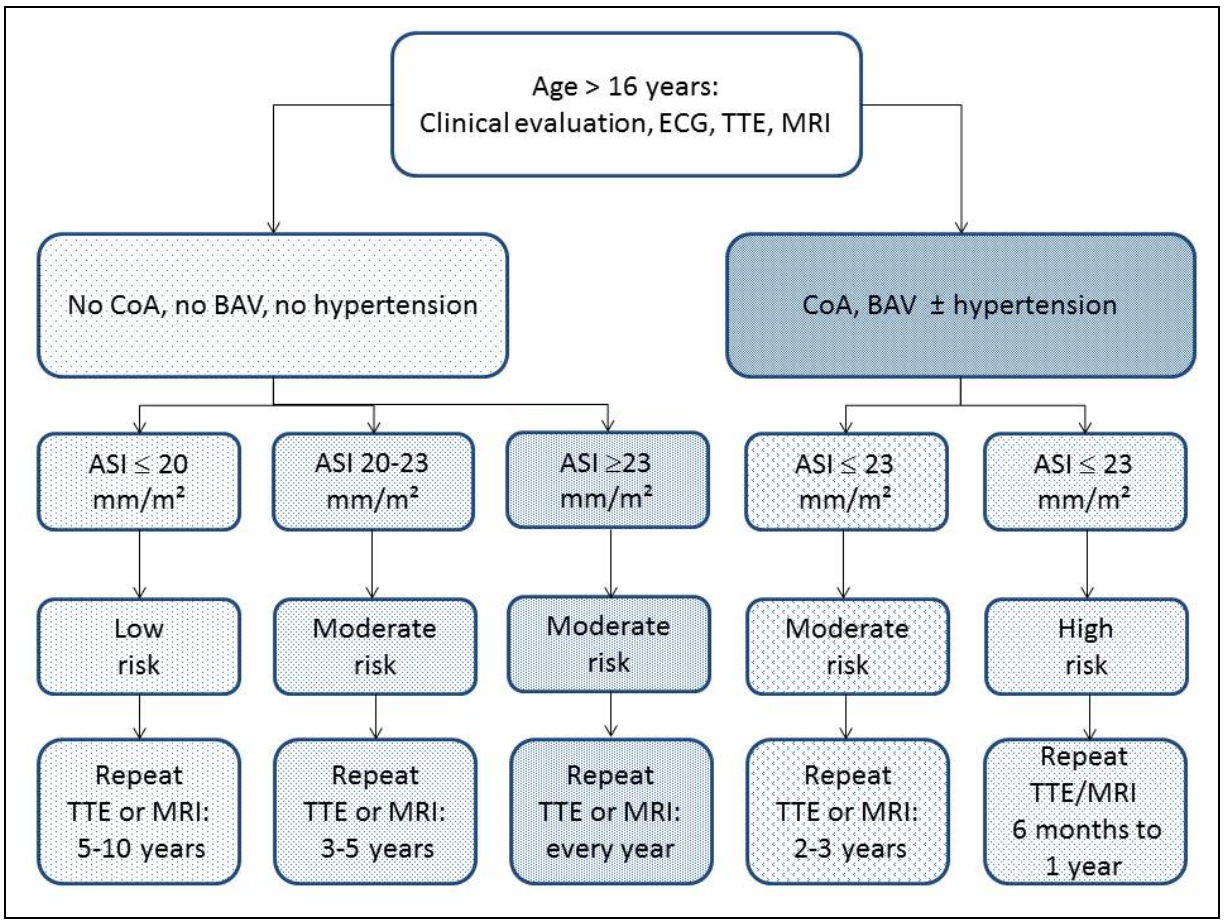

FIGURE 4:

Proposed pathophysiology of aortic media degradation in patients with Turner syndrome: TGFb for *Transforming Growth Factor Beta*; TIMPs for Tissue Inhibitors of MetalloProteases; MPs for Metalloproteases.