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Research paper

Coronary artery anomalies in Turner Syndrome

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ABSTRACT

Background: Congenital heart disease, primarily involving the left-sided structures, is often seen in patients with Turner Syndrome. Moreover, a few case reports have indicated that coronary anomalies may be more prevalent in Turner Syndrome than in the normal population. We therefore set out to systematically investigate coronary arterial anatomy by computed tomographic coronary angiography (coronary CTA) in Turner Syndrome patients.
Methods: Fifty consecutive women with Turner Syndrome (mean age 47 years [17–71]) underwent coronary CTA. Patients were compared with 25 gender-matched controls.
Results: Coronary anomaly was more frequent in patients with Turner Syndrome than in healthy controls [20% vs. 4% ($p = 0.043$)]. Nine out of ten abnormal cases had an anomalous left coronary artery anatomy (absent left main trunk, $n = 7$; circumflex artery originating from the right aortic sinus, $n = 2$). One case had a tubular origin of the right coronary artery above the aortic sinus. There was no correlation between the presence of coronary arterial anomalies and karyotype, bicuspid aortic valve, or other congenital heart defects.
Conclusion: Coronary anomalies are highly prevalent in Turner Syndrome. The left coronary artery is predominantly affected, with an absent left main coronary artery being the most common anomaly. No hemodynamically relevant coronary anomalies were found.

1. Introduction

Turner Syndrome is a condition in which females lack an entire X chromosome or parts thereof. A range of congenital cardiovascular malformations are associated, potentially necessitating medical and surgical treatment.[1] The most frequent malformations include bicuspid aortic valve, aortic coarctation, and/or partial anomalous pulmonary venous return. The aorta is often aneurysmal, may have abnormal branching vessels, and the risk of aortic dissection is high as 40 per 100,000 person years compared to 6 per 100,000 person years in the general population.[2,3]

These abnormalities and the associated morbidity explain part of the increased mortality in Turner Syndrome.[4,5] However, case reports also describe anomalous coronary arteries in Turner Syndrome, which may also contribute to increased morbidity and mortality.[6] In our own clinical experience, we have also frequently encountered abnormal courses or origins of one or both coronary arteries, so awareness of the risk of coronary artery anomalies is crucial. Individuals who require aortic root replacement at young age where coronary artery disease was not expected and dedicated coronary imaging was not recommended may experience surgical

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complications and mortality as a result.[7,8]

The genetic background for congenital cardiovascular malformations in Turner Syndrome is unknown, but recent data suggest an association to genetic abnormalities on the short arm of the X chromosome (Xp).[9] However, a number of other genes have also been linked to the development of congenital cardiac anomalies but a causal relationship has yet to be established. Recently, the European Society of Cardiology published a position statement on congenital coronary artery anomalies,[10] presenting views on both normal and abnormal coronary embryogenesis and pathophysiology. This inspired us to examine if women with Turner Syndrome had a high prevalence of coronary anomalies.

We therefore set out to systematically investigate coronary arterial anatomy by computed tomographic coronary angiography (Coronary CTA) in Turner Syndrome patients and relate the findings to the presence of other congenital cardiovascular anomalies and karyotype.

2. Methods

2.1. Study population

Fifty females with karyotypically proven Turner Syndrome were examined with a computed tomography coronary angiography (coronary CTA) over two-year period. Forty-five participants were recruited from a cohort study of cardiovascular health in Turner Syndrome. Non-coronary findings from this cohort study have previously been published.[11–13] An additional five Turner Syndrome women had a coronary CTA performed due to considerations regarding aortic root replacement. All participants were asymptomatic and without known coronary artery disease. A group of 25 females served as controls (Table 1).

2.2. Computed tomography coronary angiography

Computed tomography coronary angiography (Coronary CTA) was performed using a dual-source CT scanner (SOMATOM Definition Flash; Siemens, Forchheim, Germany) with prospective electrocardiographic triggering acquisition performed in all patients and controls. In the event of a heart rate ≤65/min or >65/min, the RR scan intervals were 65%–75% and 40%–70%, respectively. Data acquisition was performed using 100 or 120 kV tube voltage in patients weighing ≤70 or >70 kg, respectively. The imaging studies were evaluated by two coronary CTA experts, who were blinded to all clinical data.

The coronary artery anatomy was classified according to the ESC position paper into the following subgroups[9]: A) Anomalies of coronary artery connection; B) Anomalies to the aorta/systemic circulation; C) Anomalous coronary artery ostium location within or near the proper aortic sinus; D) Anomalous coronary artery ostium location at improper aortic sinus–wrong sinus; E) Single coronary artery; F) Anomalous coronary artery ostium location outside sino-tubular aorta; G) Anomalies of intrinsic coronary artery anatomy; H) Anomalous coronary artery ramification; and I) Anomalous myocardial/coronary artery interaction. The coronary arterial system was classified as right dominant when the posterior descending artery originated from the right coronary artery (RCA). Left dominance was defined when the posterior descending artery originated from the left circumflex artery (LCx). A balanced dominant coronary system was categorized when the posterior descending artery originated from the RCA in combination with a large posterolateral branch originating from the LCx entering the posterior interventricular groove.[14]

Table 1
Demographics of participants.

	Controls n = 25	Turner syndrome n = 50
Age (years)	53 (26–70)	47 (17–71)
Weight (kg)	71 (47–99)	57 (40–84)
Height (cm)	170 ± 7	148 ± 7
BMI (kg/m^2)	25.0 ± 4	26.5 ± 4

2.3. Aortic valve morphology

In most cases, the morphology was determined by echocardiography or MRI. Two cases had an aortic valve prosthesis. In these cases, the surgical notes were retrieved for assessment of valve morphology.

2.4. Ethics

Informed consent was obtained from all participants, and the study protocol conforms to the ethical guidelines of the Declaration of Helsinki and is approved by Aarhus County Ethical Scientific Committee (Denmark) (#2012-500-12).

3. Statistical methods

Mathematical computations were performed using Stata Statistical Software: Release 12.1 (College Station, TX: StataCorp LP) and R 3.1.3 (R Foundation for Statistical Computing, Vienna, Austria). Normality was assessed by Q-Q-plots of absolute or log-transformed values and box-plots were scrutinized for outliers. Comparisons of continuous variables were performed using Student's independent *t*-test (mean ± SD or for transformed values, as median with range) or Mann–Whitney *U* test (median with range) as appropriate. Comparison of nominal variables were performed using the likelihood ratio test for 2 × 2 tables[15] or Fisher's exact test if one or more cells contained zero counts. Contingency tables larger than 2 × 2 were analyzed with the exact test for multinomial data. A p-value <0.05 was considered significant.

4. Results

Demographic data are summarized in Table 1. The patient's karyotypes were 45, X in 28 cases, with 20 cases having other karyotypes compatible with Turner Syndrome (Supplementary Table 1).

Seventeen Turner Syndrome patients had a bicuspid aortic valve (34%) and nine (18%) were diagnosed with aortic coarctation. The two patients with mechanical valve prostheses had bicuspid aortic valves prior to operation. Four women had partial abnormal pulmonary venous drainage. One of these four patients also had aortic coarctation and a bicuspid aortic valve. Fig. 1 displays an overview of the different congenital heart defects related to the presence of a coronary anomaly and karyotype.

Detailed and conclusive coronary CTA images were obtained in all cases (Figs. 2–3). Compared to the control group, Turner Syndrome women had a significantly different coronary arterial distribution with a higher prevalence of left dominant coronary anatomy: Right dominance Turner Syndrome: 60% vs. Controls: 76%; left dominance, Turner Syndrome: 28% vs. Controls: 20%; and balanced dominance, Turner Syndrome: 12% vs. Controls: 4% (overall, p = 0.01).

Abnormal coronary arterial anatomy was found in 20% in Turner Syndrome (Table 2). In 9 out of 10 abnormal cases, the left coronary artery was involved with either an absent left main (LM) (Fig. 2A) or LCx originating from the right aortic sinus (Fig. 2B). In only one case,