VIA MEDICA
ORIGINAL ARTICLE
2012, Vol. 19, No. 3, pp. 301–308
10.5603/CJ.2012.0053

ISSN 1897–5593

Evaluation of coronary artery abnormalities in Williams syndrome patients using myocardial perfusion scintigraphy and CT angiography

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Abstract

Background: *Sudden death risk in Williams syndrome (WS) patients has been shown to be 25–100 times higher than in the general population. This study aims to detect coronary artery anomalies and myocardial perfusion defects in WS patients using noninvasive diagnostic methods.*

Methods: *This study features 38 patients diagnosed with WS. In addition to physical examination, electrocardiography, and echocardiography, computed tomography (CT) angiography and rest/dipyridamole stress technetium-99m sestamibi (^{99m}Tc-sestamibi) single photon emission computed tomography (SPECT) myocardial perfusion scintigraphy (MPS) were performed.*

Results: *Twenty-one (55%) patients were male; 17 (45%) were female. The average patient age was 12 ± 5 years (2.5–26 years); the average follow-up period was 7.2 ± 4.2 years (6 months–18 years). Cardiovascular abnormalities were found in 89% of patients, the most common one being supravalvar aortic stenosis (SVAS). CT angiography revealed coronary anomalies in 10 (26%) patients, the most common ones being ectasia of the left main coronary artery and proximal right coronary artery as well as myocardial bridging. SVAS was present in 80% of patients with coronary artery anomalies. ^{99m}Tc-sestamibi SPECT MPS revealed findings possibly consistent with myocardial ischemia in 29% of patients, and ischemia in 7 out of 10 patients (70%) with coronary anomalies shown on CT angiography ($p = 0.03$).*

Conclusions: *Coronary artery abnormalities are relatively common in WS patients and are often accompanied by SVAS. CT angiography and dipyridamole ^{99m}Tc-sestamibi SPECT MPS seem to be less invasive methods of detecting coronary artery anomalies and myocardial perfusion defects in WS patients.* (Cardiol J 2012; 19, 3: 301–308)

Key words: Williams syndrome, coronary artery abnormalities, scintigraphy, computed tomography angiography

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Received: 25.01.2012 Accepted: 29.02.2012

Introduction

Williams syndrome (WS), also known as Williams-Beuren syndrome, now recognized to be caused by a microdeletion of chromosome 7q11.23, is a multisystem disorder first identified as a distinct clinical entity in 1961 [1, 2]. The incidence is 1 in 10,000 live births [3]. Cardiovascular problems caused by deletion of the elastin gene are the main cause of morbidity and mortality and occur in 80––85% of all WS patients [2, 4, 5]. While the most common cardiovascular abnormalities are supravalvar aortic stenosis (SVAS) and peripheral pulmonary artery stenosis (PAS), any artery can potentially be involved due to a haploinsufficiency of elastin protein [2].

The leading cause of death in WS patients is sudden cardiac death. A study of approximately 300 cases showed that the risk of sudden death is 25–100 times higher in WS patients than in the general population [6]. It has also been shown to be particularly high in patients who have biventricular outflow tract stenosis with ventricular hypertrophy and those with coronary artery anomalies [7––9]. Many deaths have occured during anesthesia/ /sedation (often with cardiac catheterization), suggesting that decreased cardiac output from anesthetic agents in concert with coronary artery abnormalities altering myocardial perfusion [5, 10].

There are several studies conducted on the incidence and the course of congenital cardiac anomalies like SVAS and PAS in WS patients, whereas studies focusing on coronary artery anomalies in WS patients are rare [5]. While some studies have indicated that coronary artery lesions and sudden death are linked to the presence and severity of SVAS, the fact that there are only case reports with isolated left main coronary artery lesions suggests that this condition may be directly connected to elastin arteriopathy [11–13].

Regardless of the presence of SVAS, there is always a possibility of coronary artery involvement in WS patients, which must always be taken into account in the preoperative period, prior to administering anaesthesia [9, 10, 14]. In view of these reports, in addition to the standard electrocardiographic (ECG) and echocardiographic (ECHO) examinations, ECG-triggered myocardial perfusion scintigraphy (MPS) can be performed in order to assess the severity of coronary lesions [5, 9, 14, 15]. While there are some who even recommend coronary angiography in the preoperative period [10], the sudden death risk associated with cardiac catheterization is a serious issue [9]. In such cases less invasive methods like multidetector computed tomography (CT) angiography can be used to observe coronary anatomy (16).

Single photon emission computed tomography (SPECT) MPS is a useful noninvasive technique for diagnosing ischemia. As exercise testing cannot be performed in children with WS, dipyridamole can be used to induce pharmacologic stress. The sensitivity and specificity of exercise and pharmacologic stress for SPECT MPS can be considered as similar in children [17].

In order to evaluate coronary artery abnormalities and myocardial perfusion defects in WS patients, CT angiography and a dipyridamole stress test followed by technetium-99m (^{99m}Tc) sestamibi SPECT MPS were performed and this study design is the first extensure study investigating the occurrence of coronary artery anomalies by the use of CT angiography and MPS in a cohort of WS patients.

Methods

Study population. This study features 38 WS patients who were followed at our clinics. For each case, the diagnosis was confirmed by the clinical phenotype assessed by an experienced medical geneticist and the typical elastin gene hemizygosity shown by fluorescence in situ hybridization technique. This cross-sectional study was carried out between September 2010 and June 2011. During this period, all patients underwent detailed cardiological evaluation and all examination findings and arterial blood pressure values were recorded. In addition to the standard ECG and ECHO, ^{99m}Tc-sestamibi SPECT MPS and CT angiography were performed in all patients. The risks of ^{99m}Tc-sestamibi SPECT MPS and CT angiography were explained to the families and informed consent was obtained from all the parents. Approval for this study was obtained from the ethics committee of the university hospital.

Electrocardiogram (ECG). A standard 12--lead ECG was obtained at a paper speed of 25 mm/ /sec and an amplitude of 10 mm/mV (Nihon-Kohden ECG 6511, Tokyo, Japan). On each electrocardiogram, we calculated the heart rate, P wave duration and length, PR interval, QRS duration, and R and S wave lengths in the V_1, V_2, V_5 and V_6 leads to screen for left and right ventricular hypertrophy (LVH, RVH) according to age. Electrocardiograms were also examined for ischemic ST segment changes and pathological q waves. Bazett's formula was used to calculate the QTc interval, which was considered prolonged when ≥ 450 ms [18, 19].

Echocardiography (ECHO). M-mode, 2D and color Doppler echocardiography was performed in all patients (Vivid 3 and Vivid 7 GE, USA). When measuring the peak systolic instantaneous gradient between the prestenotic and poststenotic supravalvar segments, a difference of > 10 mm Hg was considered an indication of SVAS. The severity of stenosis was assessed according to Doppler maximum peak systolic instantaneous gradient measurements: < 25 mm Hg was considered minimal, 25––49 mm Hg as mild, 50–75 mm Hg asmoderate and > 75 mm Hg as severe. Echocardiographically, PAS diagnosis was considered as localized or diffuse stenosis in the main pulmonary artery and its branches in patients with a pressure difference of > 10 mm Hg in the branches. The severity of stenosis was assessed as in right ventricular outflow tract stenosis [20–22].

CT angiography. A 64-slice multidetector CT scanner with 400 msec gantry rotation was used for ECG-triggered angiography (Aquillon 64, Toshiba, Sweden). Patients with a heart rate of over 100 bpm were given 1–2 mg/kg metoprolol in order to decrease the heart rate. Young children were sedated with midazolam for the procedure. In order to intravenously deliver the contrast material, an 18G Intracath catheter was inserted into the antecubital vein. When the non-ionic CT contrast material delivered at 2 mL/kg and 3–4 mL/s reached maximum enhancement in the aortic root using bolus tracking, CT imaging was started.

Images were taken in the axial view, from the clavicles to the apex of the heart. Coperative pediatric patients were asked to take a deep breath and hold it. CT images of the heart in the late systolic and late diastolic phases were reconstructed from the recorded data of synchronized ECG and CT. Reconstructed images were generated on a high-performance workstation (Vitrea 2, Toshiba) from thin axial slices in the 2D maximum intensity projection (MIP) and multiplanar reformat (MPR) formats and the 3D volume rendering format. The MPR and MIP images were used to evaluate vessel walls and lumens and cardiac chambers, while the 3D images were used to evaluate coronary artery anatomy.

^{99m}Tc-sestamibi SPECT MPS. After a dipyridamole stress test, ^{99m}Tc-sestamibi SPECT MPS was performed. Young children were sedated with midazolam. Patients received a 4-minute intravenous infusion of dipyridamole at 0.56 mg/kg and 0.142 mg/kg/min, then an intravenous injection of ^{99m}Tc-sestamibi on the 7th–8th minute when maximum vasodilation was achieved, and the test was finished on the 10th minute. ECG monitoring was performed during the entire procedure. Thirty minutes after the ^{99m}Tc-sestamibi injection, the stress image was taken with the patient in supine position, starting with a 45° right anterior oblique view and ending with a 45° left posterior oblique view in a 180° arc, using a Mediso Nucline SPIRIT DH-V dual-head gamma camera. The rest image was taken 3 hours after the stress image. After the stress and the rest data was processed, the horizontal long axis, vertical long axis and short axis images were obtained. Defects were classified as 'fixed defect (FD)' (a defect that was present in both the rest and the stress SPECT images), 'transient defect (TD)' (a defect that was present only in the stress SPECT image) and 'reverse defect (RD)' (a defect that was present only in the rest SPECT image).

Additionally, using an ADAC Vertex Plus dual--head gamma camera, gated SPECT with 3-lead ECG monitoring was performed after the stress imaging in coperative patients in order to evaluate left ventricular function. Left ventricular wall motion, end-systolic and end-diastolic volumes and ejection fractions were evaluated. The stress and the rest images and the gated SPECT findings were analyzed together.

The study was approved by the local bioethical committee and all patients gave their informed consent.

Statistical analysis

Statistical Package for the Social Science 15.0 for Windows (SPSS, Chicago, IL) was used for data analysis (reliability, construct validity and internal consistency). The average values and intervals were specified as ± SD. As the number of cases was sufficient for comparing the data on concomitant congenital cardiac diseases and coronary anomalies, the chi-square test was used. Sub-group analyses were performed in order to examine the correlation between echocardiography, CT angiography and ^{99m}Tc-sestamibi SPECT MPS findings. A p value of < 0.05 was considered significant.

Results

Out of 38 Williams syndrome patients, 21 (55%) were male and 17 (45%) were female. The average patient age was 12 ± 5 years (2.5–26 years); the average follow-up period was 7.2 ± 4.2 years (6 months–18 years). All patients showed the characteristic dysmorphic feature and typical deletion on 7q11.23.

Cardiovascular abnormalities. As summarized in Table 1, 34 of 38 (89%) patients had car-

Table 1. Cardiovascular findings of 38 Williams syndrome patients.

Cardiac abnormality	34 (89%)
Stenotic lesions	
Supravalvar aortic stenosis	26 (68%)
Minimal	7 (27%)
Mild	9 (35%)
Moderate	4 (15%)
Severe	6 (23%)
Pulmonary artery stenosis	15 (39%)
Intracardiac lesions	
Mitral valve prolapse	10 (26%)
Ventricular septal defect	1 (2.6%)
Valvular pulmonary stenosis	2 (5%)
Aortic insufficiency	7 (18%)
Bicuspid aorta	1 (2.6%)
Subaortic discrete membrane	1 (2.6%)
Hypertension	10 (26%)

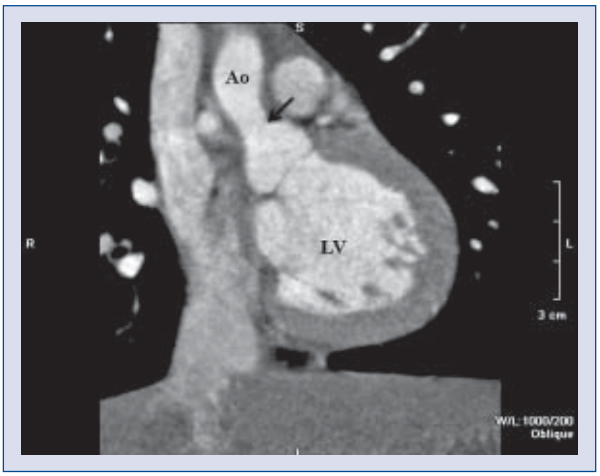

Figure 1. The image, where the left ventricle (LV) and the ascending aorta (Ao) are observed in the same slice, shows hourglass-type supravalvar aortic stenosis and poststenotic dilation (marked by an arrow).

diovascular abnormalities at of the most recent evaluation. The most common ones were: SVAS in 26 (68%) patients, PAS in 15 (39%), and MVP in 10 (26%). Less common anomalies observed were mild aortic insufficiency in 7 (18%), valvular pulmonary stenosis in 2 (5%), ventricular septal defect in one (2.6%), bicuspid aorta in one (2.6%) and subaortic discrete membrane in one (2.6%). SVAS was minimal in 7 (27%) patients, mild in 9 (35%), moderate in 4 (15%) and severe in 6 (23%); those with severe stenosis underwent surgery. None of the patients had left ventricular dysfunction or impaired ejection fraction.

When evaluated cross-sectionally, anomalies were found on the most recent ECGs of 8 (21%) patients. Two patients had right atrial dilation, one patient had RVH, one LVH, one patient right bundle branch block, two showed negative T wave, one ST segment depression and one pathologic q wave. The QTc interval was ≥ 450 ms in 3 (7.8%) patients, one of whom was operated due to severe SVAS, one had severe PAS and one had severe MVP and mild mitral valve insufficiency.

CT angiography findings. Echocardiographically detected SVAS was confirmed in all patients (Fig. 1). However, the images were insufficient to investigate patients with PAS, and no meaningful data could be obtained.

As shown in Table 2, coronary anomalies were found in 10 (26.3%) patients. Five of them (13%) had ectasia of the left main coronary artery (LMCA), two of the right coronary artery (RCA) and one of the circumflex (Cx) artery. In two patients, LMCA was absent and the left anterior descending artery (LAD) and Cx artery originated separately from the left coronary orifice, while one patient had a hypoplastic RCA. In one patient, all coronary arteries originated from the left coronary orifice, while in another patient both coronary orifices were located above the sinotubular junction and mild LMCA stenosis was seen. Finally, three patients (7.9%) had myocardial bridging that was superficial in the distal segment of LAD in two patients and deep, 3 cm long bridging was shown in the middle segment of LAD in one patient (Fig. 2).

SVAS was present in 8 out of 10 patients (80%) with coronary anomalies; SVAS was severe in half of them and had been corrected surgically. Balloon valvuloplasty was performed in one patient with severe valvular pulmonary stenosis. The physical examination and ECHO for the rest of the patients were in normal range. Statistically, there was a significant correlation between coronary anomalies and presence of SVAS ($p = 0.039$), while there was no statistical significance for the frequency of coronary anomalies and the severity of SVAS ($p > 0.05$).

^{99m}Tc-sestamibi SPECT MPS findings. As shown in Table 2, 11 out of 38 patients (29%) had findings consistent with myocardial ischemia. SVAS of varying severity was present in 9 of the patients with ischemia and was accompanied by PAS in two of them. SVAS was surgically corrected in 3 patients, 2 of which had minimal residual stenosis. MPS showed a demarcated area of nonperfusion

Table 2. Coronary CT angiography and dipyridamole ^{99}mTc-sestamibi-SPECT MPS results of 14 patients who exhibit pathological findings.

Patient #	Age [years]	Sex (M/F)	ECG finding	ECHO finding	CT angiography finding	MPS finding
1	16	M	–	Balloon valvuloplasty performed for PS, mild residual PS	LMCA absent, LAD and Cx originate separately, deep bridging in LAD	Ischemia of LV anteroseptal, anterolateral walls (RD)
2	12	F	–	Severe SVAS corrected, minimal residual SVAS	Proximal segment of LMCA ectatic (5.6 mm)	–
3	12	F	–	Minimal SVAS, moderate PS	LMCA absent, LAD and Cx originate separately, superficial bridging in LAD	Ischemia of LV anterior wall (RD)
4	7	M	–	Mild SVAS	Both coronary arteries originate from left main coronary orifice	–
5	10	M	RAD, deep Q, QTc ≥ 450	Severe PAS, RV dilatation and hypertrophy (RVP 200 mm Hg), mild SVAS	–	In the apical region, demarcated nonperfusion and ischemia of anterolateral LV possibly consistent with infarct (FD)
6	16	M	QTc ≥ 450	Severe SVAS corrected, minimal residual SVAS	Proximal segments of LMCA (6 mm) and RCA (5.7 mm) ectatic	Ischemia of LV apical anterolateral and lateral walls (TD)
7	26	F	–	Moderate SVAS, mild PAS	–	Mild ischemia of LV lateral wall (RD)
8	15	F	LVH	Severe SVAS corrected, no residual stenosis	Proximal segments of LMCA (6.4 mm), RCA (5.7 mm) and Cx (5.4 mm) ectatic	Ischemia of LV anterior wall (RD)
9	14	M	–	Minimal SVAS, VSD, MVP	Proximal segment of LMCA (5.6 mm), superficial bridging in LAD	Ischemia of LV inferolateral wall (RD)
10	12	F	–	Mild SVAS, MVP	Hypoplastic RCA	–
11	13	M	–	–	LMCA and RCA located superiorly, mild LAD stenosis	Ischemia of anterolateral LV and septum (TD)
12	16	M	–	Mild SVAS	–	Ischemia of inferolaterobasal LV (RD)
13	7	F	–	Mild SVAS, mild PAS	–	Mild ischemia of LV anteroseptal wall (RD)
14	21	F	–	Severe SVAS corrected, minimal residual SVAS	LMCA short and ectatic at proximal end (5.3 mm)	Ischemia of LV anterior wall (RD)

ECG — electrocardiography; F — female, M — male; CT — computed tomography; MPS — myocardial perfusion scintigraphy; PS — pulmonary stenosis; SVAS — supravalvar aortic stenosis; PAS — pulmonary artery stenosis; VSD — ventricular septal defect; LMCA — left main coronary artery; LAD — left anterior descending artery; Cx — circumflex artery; RCA — right coronary artery; LV — left ventricle; RAD — right atrial dilation; RV — right ventricle; RVP — right ventricular pressure; MVP — mitral valve prolapse; FD — fixed defect; TD — transient defect; RD — reverse defect

possibly consistent with infarct in the stress and the rest images of the apical area of the heart in one of the ischemic patients who had severe PAS and mild SVAS (Fig. 3). Ischemia was present in 7 out of the 10 patients (70%) with coronary anomalies seen on CT angiography, and this correlation was statisti-

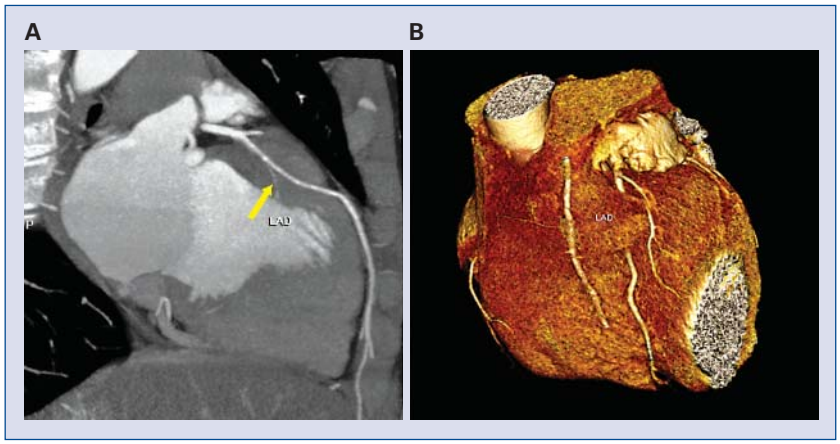

Figure 2. Two-dimensional (**A**) and three-dimensional (**B**) coronary computed tomography angiography images revealed deep myocardial bridging in the middle segment of the left anterior descending branch (LAD).

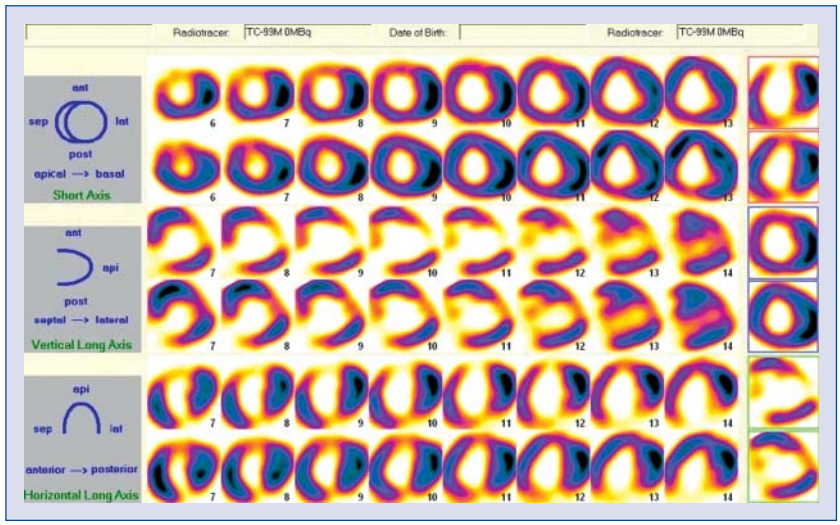

Figure 3. In a 10-year old male patient with severe peripheral pulmonary artery stenosis and mild supravalvar aortic stenosis, myocardial perfusion scintigraphy findings consistent with ischemia and an infarct in the apical region of the heart.

cally significant ($p = 0.03$). Ischemia findings were also detected in 3 patients with myocardial bridging seen on CT angiography. Notably, while one of the patients had no pathologies according to physical examination, ECG and ECHO, coronary CT angiography showed that both coronary artery orifices were located superiorly as well as LMCA stenosis, while MPS revealed findings consistent with ischemia.

We were able to perform gated SPECT in 16 out of 38 patients who underwent dipyridamole MPS. In 10 of them, left ventricular ejection fraction was within normal limits and LV wall motion was found to be normal, while in the remaining 6 patients it was considered abnormal.

Discussion

The life expectancy in WS patients has not been evaluated in comprehensive follow-up studies, cardiovascular complications are known to be the most important cause of mortality [4]. The annual risk of sudden death in WS patients has been found to be 1/1000 [6]. Several reports state that sudden death generally occurs during or immediately after the cardiac catheterization procedure [6––10]. The largest series on this field is the study on the sudden death prevalance in 19 patients between 1 month and 6 years [7]. Elevan patients in the study, has died due for sudden death occuring after sedatives or anaesthetics were administered

during cardiac catheterization or surgery. Postmortem examinations had showed coronary anomalies in 14 patients, biventricular outflow tract stenosis in 9 patients and both in 7 patients. Although sudden death seems to ocur exclusively during cardiac catheterization, there are two important points to be considered. Initially, catheter manipulations destabilize hemodynamics, trigger arrythmia and increase outlfow tract stenosis. Ischemia and arrythmia can also be triggered by the decrease of coronary blood flow during aortic root injection or coronary imaging. Second factor is that the anaesthetic agents can also disrupt hemodynamics and lead to death [5, 9, 10].

In order to predict the risk of sudden death in WS patients, it is always important evaluate fort he possible coronary lesions [5]. At this end, myocardial perfusion scintigraphy and angiography can be used in addition to standard ECG and ECHO [9, 10, 14, 23]. While some authors recommend performing cardiac catheterization and coronary angiography prior to surgery, these procedures can themselves cause sudden death [9, 10]. Furthermore, the dysmorphic facial features of WS patients may complicate intubation and tracheal ventilation, while concomitant endocrine and nephrological disorders may trigger anaesthesia-related complications [15, 24, 25]. Thus, there is a need for less invasive imaging methods that would allow to detect coronary lesions. The quality of the images obtained by magnetic resonance angiography produced is still insufficient for evaluation of coronary anatomy. Multidetector CT angiography, on the other hand, can be used to obtain more clear 3D images of coronary arteries as well as the aorta and its main branches, in children as well [16]. As of yet, there have not been any studies that use CT angiography to examine coronary lesions in WS patients. In a study which conventional angiography was used, the rate of ectasia and stenosis of coronary arteries in 26 WS patients was 27%; sinotubular junctions were found to be more narrow and the difference in pressures between the left ventricle and the artery above the sinotubular junction was larger in patients with coronary artery anomalies [11]. In our study, by coronary CT angiography coronary artery anomalies has been revealed in one fourth of all patients. None of our patients developed any complications related to the procedure. In most patients LMCA was ectatic. Notably, 80% of patients with coronary anomalies had SVAS, and half of them required surgery. This fact supports the theory that coronary artery anomalies in WS patients are often accompanied by SVAS and when coronary ostiums are faced with prestenotic pressure, it can trigger accelerated atherosclerosis, dilatation or aneurysms [5, 9, 10, 14, 26].

One important finding in our study is the previously unmentioned myocardial bridging, which was observed in 8% of our WS patients. While it is a relatively common condition in the general population, myocardial bridging may not constitute a clinical sign when very superficial, but can lead to ischemia when deep and even necessitate myotomy if there is a distal infarction [27, 28].

MPS can be used to investigate ischemia in WS patients if there are clinical, electrocardiographic or imaging findings that suggest coronary artery anomalies or ischemia. In children and patients with neuromotor retardation whose cooperation in exercise stress testing is suboptimal, pharmacological stress agents like dipyridamole can be administered [17, 29, 30]. In patients with suspected coronary anomalies, SPECT or PET MPS can help fort he final decision whether coronary angiography is needed, show myocardial viability and evaluate myocardial blood flow under conditions like physical activity [17, 31]. As atherosclerosis is very rare in children, the uses of MPS are limited. It is generally used in patients with diseases causing coronary artery stenosis and aneurysms, particularly in Kawasaki disease. Less frequently, MPS can be used in coronary fistulas, cardiomyopathies, and coronary artery anomalies concomitant with isolated or congenital cardiac diseases [17, 29–33]. The exception of being case reports, studies of MPS in WS patients have not been performed [13]. In our study, findings consistent with myocardial ischemia were detected in over one fourth of the patients who underwent dipyridamole SPECT MPS. SVAS of varying severity was present in three fourths of 11 patients with positive MPS results. When the data of ischemic patients compared with the results of coronary CT angiography, 70% of patients with anomalies on CT angiography had ischemia on MPS and that the association was statistically highly significant. Notably, although one patient had no pathology at the physical examination, ECG and ECHO, coronary angiography revealed that ostial stenosis was present and LMCA was located superiorly, while MPS showed findings consistent with ischemia. This case further supports the hypothesis that even in WS patients SVAS may not be present, but coronary artery involvement can be directly related to elastin arteriopathy.

Conclusions

Coronary artery anomalies are common in WS patients and are often accompanied by SVAS. Tak-

ing into consideration the risks involved in classic cardiac catheterization, multidetector CT angiography seems the ideal imaging method for detecting coronary lesions. Dipyridamole ^{99m}Tc-sestamibi SPECT MPS can also be used to screen myocardial perfusion defects that can be the cause of coronary artery complications.

Since most sudden deaths are related to biventricular outflow tract stenosis and coronary anomalies, early identification of the risk factors using ECHO, CT angiography and MPS may prevent this fatal prognosis. Cardiovascular follow-up protocols including CT angiography and MPS can be implemented in well-designed, multicentric, large cohort studies, and relevant measures can be considered to decrease the sudden death risk. After severral studies reported on the positive outcome of the preventure procedures, guidlines for the follow-up of cardiovascular anomalies in WS patients can be modified and inclusion of CT angiography and MPS can be considered as the routine evaluation method.

Conflict of interest: none declared

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