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Original Article

Cardiac syndrome X: Clinical characteristics revisited

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ARTICLE INFO

Article history:
Received 7 February 2014
Accepted 25 April 2015
Available online 4 June 2015

Keywords:
Cardiac syndrome X
Syndrome X
Normal epicardial coronaries
Non-obstructive coronaries
Coronary angiography

ABSTRACT

Background: Cardiac syndrome X includes a heterogenous group of patients with angina but normal epicardial coronaries in angiography.
Objective: Our objective was to study the clinical characteristics of patients with cardiac syndrome X.
Methods: Data of patients who underwent coronary angiography over a period of one year was retrospectively analyzed. Those with normal or non-obstructive coronaries in angiography with chest pain were included in this study.
Results: 1203 patients underwent coronary angiography during the study period. 105 (8.7%) patients fulfilled the inclusion criteria. There were 52 (49.5%) males and 53 (50.5%) females including 31 (29.5%) postmenopausal women. Many patients had atherosclerotic risk factors. Typical angina and atypical chest pain were reported by 63 (60%) and 42 (40%) patients, respectively. ECG was normal in 46 (43.8%) and abnormal in 59 (56.2%) patients. The most common abnormal finding in ECG was ST-T changes seen in 49 (46.7%) patients. Regional wall motion abnormality with mild left ventricular systolic dysfunction was seen in 4 (3.8%) patients while 101 (96.2%) patients had normal ventricular function in echocardiography. TMT was positive for inducible ischemia in 35 (33.3%) patients and inconclusive in 10 (9.5%) patients. Angiography showed normal epicardial coronaries in 85 (80.9%) patients.
Conclusions: Cardiac syndrome X constitutes a significant subset of patients undergoing coronary angiography. It is essential to identify and treat them specifically for microvascular angina. Many of them have atherosclerotic risk factors but their presentation is different from those with obstructive coronaries.

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http://dx.doi.org/10.1016/j.ihj.2015.04.022

1. Introduction

It is not infrequent to encounter patients with angina or angina-like chest pain having normal or near-normal epicardial coronaries in angiography.[1,2] The term "Syndrome X" was first introduced to define this diagnostic combination by Kemp et al in 1973.[3] Now this entity is known as "Cardiac Syndrome X" (CSX) and it must be differentiated from "Metabolic Syndrome X" and Coronary Artery Disease (CAD). The former is characterized by abdominal obesity, hypertension, reduced high density lipoprotein cholesterol, hypertriglyceridemia and insulin resistance,[4] while the latter is characterized by atherosclerotic obstructive coronaries.

The etiology of CSX is heterogenous.[5,6] The proposed etiologies are (i) endothelial dysfunction, (ii) microvascular dysfunction or spasm and (iii) abnormal pain perception.[7,8] Patients with CSX have abnormal endothelium-dependent vasoreactivity and impaired vasodilator reserve of coronaries. Microvascular dysfunction or spasm is caused by proinflammatory cytokines released from the dysfunctional endothelium. Autonomic imbalance decreases pain threshold and leads to hypersensitivity to changes in heart rate or contractility.[7] True myocardial ischemia occurs rarely in CSX.[9]

Despite the absence of angiographic abnormalities, many patients with CSX have marked intimal thickening and atheromatous plaque in coronaries on intra-vascular ultrasound imaging.[10] Moreover, multislice computed tomography scanning has shown that the incidence of coronary calcification in CSX (53%) is significantly higher than normal controls (20%) but lower than those with obstructive CAD (96%).[11]

According to prior studies, the prognosis of patients with CSX is generally more favorable than those with obstructive CAD.[6,12,13] On the contrary, recent studies have reported adverse cardiovascular outcomes in patients with non-obstructive coronaries.[14–16] We intended to understand whether such adverse cardiovascular outcomes could be secondary to any change in the clinical characteristics of patients with CSX in the current era. Hence we undertook this study.

2. Aim

Our objective was to study the clinical characteristics of patients with cardiac syndrome X.

3. Materials and methods

This retrospective, observational study was carried out over a period of one year in a tertiary care hospital. Coronary angiograms of patients who underwent coronary angiography, for suspected ischemic heart disease, during the study periods were reviewed. Patients with normal or non-obstructive coronaries (less than 50% stenosis) in angiography with chest pain were included in this study. The following were the exclusion criteria for our study: coronary angiogram done after acute myocardial infarction, post-revascularisation status, structural heart disease, congenital heart disease and preoperative indications. Clinical profile and details of investigation such as electrocardiography, echocardiography and treadmill test were analyzed in all the patients included in this study.

Statistical analysis was performed using SPSS software (SPSS Inc. Released 2007. SPSS for Windows, Version 16.0. Chicago: SPSS Inc) and two-tailed p value <0.05 was considered significant for all analyses. Categorical variables are expressed as numbers and percentages displayed within parentheses while continuous variables with normal distribution are expressed as 'Mean ± Standard deviation'.

4. Results

A total of 1203 patients underwent coronary angiography during the study period. Of these, 105 (8.7%) patients fulfilled the inclusion criteria. The clinical profile of these subjects included in the study is depicted in Table 1. There were 52 (49.5%) males and 53 (50.5%) females ($p = 0.89$, Chi Square test) including 31 (29.5%) postmenopausal women with overall mean age of 52.9 ± 8.9 years. There were 56 (53.3%) patients with hypertension, 31 (29.5%) patients with type 2 diabetes, 17 (16.2%) patients with body mass index greater than 30 kg/m^2, 32 (30.5%) patients with dyslipidemia and 19 (18.1%) patients with smoking habit. Analysis of symptoms revealed typical angina more often than atypical chest pain present in 63 (60%) and 42 (40%) patients, respectively ($p = 0.007$, Fisher's exact test).

Resting electrocardiogram was normal in 46 (43.8%) patients and abnormal in the remaining 59 (56.2%) patients. Abnormal findings in ECG included ST-T changes in 49 (46.7%) patients, Q wave in 5 (4.8%) patients and left bundle branch block in 5 (4.8%) patients (Fig. 1). There was no statistically significant difference between normal & abnormal findings in ECG ($p = 0.09$). Echocardiography revealed regional wall motion abnormality with mild left ventricular systolic dysfunction only in 4 (3.8%) patients while the majority of 101 (96.2%) patients had normal study. Symptom-limited TMT performed based on Bruce protocol was positive for inducible ischemia in 35 (33.3%) patients and inconclusive in 10 (9.5%) patients.

Table 1 – Clinical profile.

Parameter	n (%)
Age (mean ± SD) in years	52.9 ± 8.9
Gender	
Males	52 (49.5%)
Females	53 (50.5%)
Postmenopausal women	31 (29.5%)
Atherosclerotic risk factors	
Hypertension	56 (53.3%)
Type 2 Diabetes mellitus	31 (29.5%)
BMI > 30 kg/m^2	17 (16.2%)
Dyslipidemia	32 (30.5%)
Smoking	19 (18.1%)
Symptoms	
Typical angina	63 (60%)
Atypical chest pain	42 (40%)

Note: n – number of patients; BMI – body mass index; SD – standard deviation.

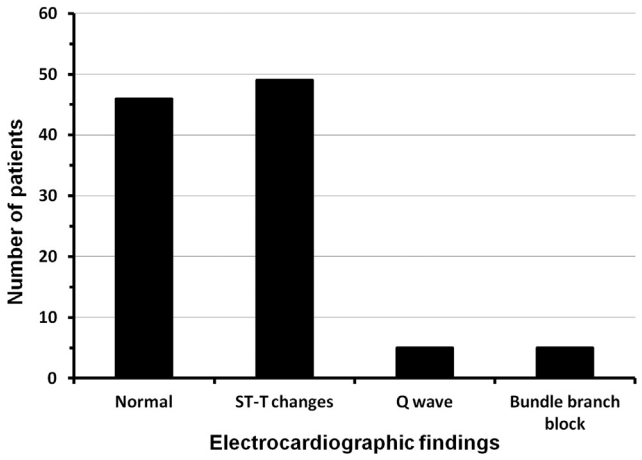

Fig. 1 – Electrocardiographic findings in patients with cardiac syndrome X.

Review of coronary angiograms (Table 2) of all the patients included in the study showed normal epicardial coronaries in 85 (80.9%) patients, minor luminal irregularities in 11 (10.5%) patients, ectasia of coronaries in 4 (3.8%) patients and slow flow phenomenon in 6 (5.7%) patients (Table 2). One (0.9%) of these patients had both coronary ectasia and slow flow phenomenon.

5. Discussion

In our study, the prevalence of CSX among those undergoing coronary angiography was 8.7%. The prevalence of CSX reported in earlier studies was 10–20%,[11] 20–30%,[17] etc depending on the inclusion criteria. There is no uniform definition of 'normal coronary arteries' for diagnosing CSX[18] in the literature. Though many studies included absolutely normal coronaries, some studies included non-obstructive lesions up to 50% stenoses.[18–21] In our study, we included patients with normal coronaries as well as non-obstructive lesions. Around four-fifths of the patients had normal coronaries in our study.

There was no gender difference in our study and around two-third of the women were postmenopausal. In contrast, prior studies have shown that CSX is more frequently seen in women[1,11,17] and many of them are premenopausal.[11,18] The postmenopausal status of women and lack of gender difference with CSX seen in our study, could be one of the contributing factors for the change in the occurrence of other clinical characteristics in patients with CSX. This in turn may adversely affect the cardiovascular outcomes in CSX as it has been recently reported.[14–16] Another reason for the worsening cardiovascular outcomes in patients with CSX would be the inclusion of non-obstructive coronaries in the definition of CSX. Lipid rich vulnerable plaques may be present in non-obstructive coronaries[22] and these are not detected during routine coronary angiography. The presence of these high risk vulnerable plaques may be predisposing factor for the worsening cardiovascular outcomes in CSX.

Clinical presentation of chest pain in CSX has always been elusive. In our study, typical angina was seen in 60% of the patients with CSX while atypical chest pain was present in 40% of the patients only. As per the literature, chest pain in CSX is more often atypical and it might resemble non-cardiac chest pain.[11] However, chest pain in CSX may be severe enough to affect the quality of life of patients. Panic disorder and exaggerated preoccupation about health may contribute to chest pain in some patients with CSX.[11]

In our study, resting ECG showed predominantly ST-T changes while ventricular systolic function in echocardiography was normal in majority of the patients with CSX. This is similar to the description of CSX in the literature.[11] Since, stress echocardiography was not done in our study, we are not able to comment on the ventricular performance during stress.[23] In our study, no other stress imaging modality than TMT was used, and it was positive for inducible ischemia in 33.3% of patients. In contrast, prior studies showed TMT positivity in 20% of patients with CSX.[11]

Atherosclerotic risk factors were quite prevalent among the patients with CSX in our study. Most of the studies on CSX including our study are based on angiogram which is a luminogram. In the initial stages of atherosclerosis, outward enlargement of wall of coronary artery occurs due to positive remodeling and luminal narrowing occurs only in the later stages.[24] Hence the effect of atherosclerosis in patients with CSX is generally underestimated. Previous studies have demonstrated the link between insulin resistance and endothelial dysfunction in CSX.[25] We did not study insulin levels in our study.

5.1. *Limitations of this study*

In our study, intra-vascular ultrasound imaging and stress echocardiography were not performed. Long-term prospective study is needed to understand the response to anti-ischemic therapy, progression of symptoms and prognosis of these patients with CSX. We are intending to address these issues in our subsequent prospective study.

Table 2 – Angiographic profile.

Parameter	*n* (%)
Normal epicardial coronaries	85 (80.9%)
Minor luminal irregularities	11 (10.5%)
Ectasia of coronaries	4 (3.8%)
Slow flow phenomenon	6 (5.7%)
Coronary ectasia and slow flow phenomenon	1 (0.9%)

Note: *n* – number of patients; LCX – left circumflex coronary artery; RCA – right coronary artery.

6. Conclusions

In conclusion, cardiac syndrome X constitutes a significant subset of patients undergoing coronary angiography. It is essential to identify and treat them specifically for microvascular angina. Many of these patients have atherosclerotic risk factors but their clinical presentation is different from those with obstructive coronaries. The postmenopausal status of

women, lack of gender difference and the inclusion of non-obstructive coronaries could be the contributing factors for the change in the clinical characteristics in the patients with cardiac syndrome X and this in turn may adversely affect their cardiovascular outcomes.

Conflicts of interest

The authors have none to declare.

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