

# Is there a relationship between non-obstructive coronary artery disease or cardiac syndrome X and migraine? An integrated multi-disciplinary approach

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Hell J Nucl Med 2016; 19(3): 193-195

Published online: 10 December 2016

## Abstract

Non-obstructive coronary artery disease (CAD) which is mostly called cardiac syndrome X (CSX) is noted in about 30% of men and 40%-60% of women and seems to be incremental. In addition, frequent myocardial perfusion defects with various levels of severity are often seen in this disease. Recently, we noticed that the frequency of migraine in patients with CSX was noticeably higher than in healthy people and in CAD patients. This may support the evolving story that CSX is related to migraine and to chest pain and that CSX and migraine may have a similar pathophysiology. Hence, myocardial perfusion imaging could be used as a complement any diagnostic test to support the relation between CSX and migraine.

## Introduction

Among individuals with chest pain who underwent coronary angiography to rule out probable ischemic heart disease (IHD), cases of "normal" or "non-obstructive" coronary artery disease (CAD) were noted in about 30% of men and 40%-60% of women and this percentage seems to be increasing [1]. Many authors refer to this condition as cardiac syndrome X (CSX), although there is no consensus on this terminology [2].

Cardiac syndrome X is described as a typical chest pain either with a normal or near normal coronary angiogram and with or without electrocardiographic (ECG) findings, or as an atypical chest pain with a normal or near normal coronary angiogram a positive non-invasive exercise tolerance test or myocardial perfusion scan and with or without ECG findings [3].

Patients with different clinical findings such as coronary artery spasm (Prinzmetal's or variant angina), left ventricular hypertrophy, hypertension, valvular heart disease, diabetes mellitus and bundle branch block are not included in this syndrome [3]. What's more, this subgroup of patients, based on reoccurring evidence has worse outcome [4].

The precise pathophysiological mechanism of CSX is not well understood. Chest pain has been due to microvascular dysfunction, metabolic abnormalities, endothelial dysfunction and infection [3, 5-7]. In addition, transcellular, intracellular disorders of the cardiomyocytes cause angina in these patients. New technologies which include integration of genomic, epigenomic, transcriptional, and metabolomic data allow to launch patient-centered management in the milieu of precision medicine [4,8].

In a prior study of ours CSX patients, frequent perfusion defects with various levels of severity were often observed. More than 30% of these individuals had at least one perfusion defect [9]. It has also been reported that myocardial perfusion abnormalities were patchily distributed throughout myocardium [10].

## Cardiac syndrome X and migraine

Recently, we demonstrated that the frequency of migraine in patients with CSX was appreciably higher than in healthy people and CAD patient groups. This suggests that CSX may be a manifestation of migraine or of migraine equivalents [11].

Parallel to that, Roldau (2014) assessed the manifestations and outcomes and also evaluated the association between angina and headache as a manifestation of migraine exacerbation. They studied 33 patients with migraine headaches at an earlier onset than angina. All had taken medications prior to visiting the emergency department (ED) [12].

The authors, concluded that angina can be a complication of migraine, the treatment should be centered on migraine control and migraine should be included in the differential diagnosis list for chest pain [12].

In addition, Rose et al. (2004) proposed a new chapter in this evolving story. In a population-based investigation in four societies of aging African Americans and whites (the Atherosclerosis Risk in Communities study), they determined that migraine headaches are related to angina, which was stronger in cases of migraine with aura. However, there was no relationship between a lifetime history of migraine or other headaches and coronary heart disease events [13]. These and other authors concluded that migraine is related to chest discomfort but not to cardiac events [13-17]. Thus, it is recommended that neurologists should investigate and also manage vascular risk factors in migraines, rule out silent myocardial ischemia when appropriate, and utilize Triptan therapy for individuals with moderate or severe migraines (US Headache Consortium Guidelines) [15].

As noted above, the exact pathogenesis of CSX remains uncertain, but the two main hypotheses are: a) Coronary microvascular dysfunction, and b) Abnormal cardiac pain sensitivity [18]. Nevertheless, the link of CSX and migraine has not been well addressed in the literature. The term "cardiac migraine" defines the angina-like chest pain with ischemic change and normal coronary angiography in individuals complaining of migraine headaches [19].

### Messages for nuclear medicine practitioners

We have studied by nuclear medicine, cardiology and neurology studies the history of migraine headaches in a nuclear cardiology laboratory and found several new patients diagnosed with CSX who had prior history of migraine. Interestingly, some patients developed migraine headaches after Nicorandil administration, as reported earlier [20].

This may complement the evolving story of CSX and migraine and suggest that chest pain and migraine could have a similar pathophysiology. Myocardial perfusion imaging can be applied as a complement to other diagnostic and clinical examinations by studying coronary ischemia in flow limiting CAD.

As a rule, these coronary ischemia defects are considered as false-positive based on coronary angiography and would account for the low specificity of MPI in ruling out the identification of CAD [21-31]. Such a term may not be reasonable even in the absence of known prior conditions such as small vascular disease. It is recommended that these issues, especially cardiac physiologists should be further studied.

Furthermore, borderline perfusion defects on MPI, in patients with a history of migraine without known small vascular diseases should be more studied [32-35].

Graf et al prospectively assessed the incidence of a dysfunctional microcirculation and persuaded predictive parameters of a diminished CFR in 79 patients with typical angina and a normal angiogram and 10 control subjects; CFR was calculated by <sup>13</sup>N-ammonia rest/dipyridamole PET and associated with clinical parameters. In about two thirds of patients, anginal pain can be clarified by a decreased CFR. Risk

factors have a cumulative negative impact on CFR. A clinical cardiac risk factor analysis permits estimation of individual probability of microvascular dysfunction in a significant proportion of these patients. Nevertheless, CFR measurements are advised for those with an intermediate number of risk factors (NRF) [36].

Since a "near-normal" or "normal" angiogram because of its "less than very good" diagnostic results is not diagnostic of CSX additional diagnostic modalities should be kept in mind in short-term and long-term management of CSX [4]. Clinical cardiology approach is always important [8, 37-39].

*In conclusion*, while there are many diagnostic and pathophysiological data as for the relationship between CSX and migraine it seems that migraine is related to angina but not to coronary artery disease.

*The authors declare that they have no conflicts of interest*

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