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Cardiac syndrome X — the present knowledge

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Summary

The aim of this work was to define the notion of cardiac syndrome X based on latest research, determine its connection with mental disturbances and present the current therapeutic directions. Cardiac syndrome X was distinguished in 1973 to describe a group of patients with coronary syndrome symptoms despite normal coronary vessels in coronarography. Many years have passed since then, but the syndrome definition and the diagnostic criteria still arouse controversy. It is estimated that 10 to 20% of persons who undergo coronarography suffer from cardiac syndrome X, a vast majority of them being perimenopausal women. That patient population suffers from anxiety disorders, depressive symptoms and sleep disturbances much more frequently than does general population. Treatment includes a range of medicines with various mechanisms of action, but their effectiveness is limited; non-pharmacological actions are a significant part of the therapy. The patient group with cardiac syndrome X requires periodic follow-ups because prospective observation has shown that it is a risk group concerning development of atherosclerosis and acute coronary syndrome.

Key words: cardiac syndrome X, anxiety, depression.

Introduction

Cardiac syndrome X (CSX) is often considered one of the forms of ischemic heart disease. It occurs more often in women, especially perimenopausal women. In its course, patients exhibit typical or atypical stenocardial pain and features of cardiac muscle ischemia are determined in an ECG examination or a cardiac stress test, however, epicardial coronary arteries do not display any significant stenoses in coronarography, which could be responsible for the reported complaints.

It has been known for many years that most patients with this syndrome show emotional disturbances, which are rarely noticed by patients themselves and their treating physicians. Persons with diagnosed CSX are hard to treat effectively.

Cardiac syndrome X: the notion

To distinguish a patient population demonstrating stenocardial pain with normal coronarography results, Harvey Kemp [1] coined the term 'cardiac syndrome X' in 1973. The complaint pathogenesis and the definition of the syndrome itself has remained unclear from the very beginning. A synonymous term of 'microvascular angina' (MVA) was introduced in 1988 in order to define more precisely the origin of the symptoms [2]. This was reflected in the ESC (European Society of Cardiology) 2013 guidelines on the management of stable coronary artery disease, where it was described as microcirculation vascular dysfunction. However, further research [3, 4] showed that not all of the patients with diagnosed CSX suffered from coronary microcirculation disturbances. It must be underlined that the chest pain suffered by patients with cardiac syndrome X has numerous pathophysiological causes which probably fall within the range from non-cardiac origin to coronary microvascular dysfunction (CMD) [5, 6]. Marinescu et al. [7] suggest that the latter factor should be considered as especially important because it is based on ischemia as the original pain cause and entails a much worse prognosis.

One notices controversy over the CSX diagnostic criteria in subsequent works published in the last several decades, but this is still a diagnosis of exclusion. The essence of cardiac syndrome X as anginal pain with a normal coronary vessel angiogram is basically sustained. In their extensive work from 2015, Agrawal et al. [8] list more restrictive diagnostic criteria, as do other authors [9, 10]. Those include: stress-induced anginal pain, ST segment lowering during anginal pain, normal epicardial coronary arteries in angiography, absence of spontaneous or (ergonovine or acetylcholine) induced spasm of epicardial coronary arteries as well as absence of cardiac or systemic diseases related to microvascular dysfunction such as hypertrophic cardiomyopathy and diabetes. In a newer work, Ong et al. [11] list standardized diagnostic criteria for research concerning patients with MVA. Those include: symptoms pointing to cardiac muscle ischemia, objectively documented cardiac muscle ischemia, absence of obstructive coronary artery disease (CAD) as well as confirmed reduced coronary flow reserve and/or induced microvascular spasm.

Vermeltfoort et al. [12] present an interesting analysis of 57 articles from the PubMed base: they obtained nine definitions of CSX and 43 exclusion criteria for its diagnosis. The most important ones are: valvular heart disease, diabetes, left ventricular hypertrophy, arterial hypertension, and cardiomyopathy. One should also mention: renal failure, history of myocardial infarction, left ventricular dysfunction, hepatic dysfunction, arrhythmias, inflammatory disease, gastrointestinal disorder, systemic disease, dyslipidemia, nicotinism, thyroid gland dysfunction, obesity, alcoholism, mental illnesses (this term is not specified by the authors of the article, most likely it

refers to psychoses), and anemia. The same authors also point to the special unclarity of one basic criterion – normal epicardial coronary arteries. They note that most researchers do not define that criterion precisely in their works, which actually leads to including patients with coronary artery disease ranging from minimal lesions to 50% vessel lumen stenoses. Therefore, the authors postulate paying special attention to the necessity of dispelling all the related doubts.

A single-center study [13] including 139 subjects complaining of chest pain without diagnosed CAD revealed irregularities in 76.3% of the patients, such as epicardial vessel endothelial dysfunction, microcirculation disturbances, latent disseminated epicardial atherosclerosis, and myocardial bridges. However, the same study found out that, after applying the IVUS (Intravascular Ultrasound) method, all of the patients demonstrated at least slight signs of atherosclerosis [13]. Eight years before, Camici et al. [14] suggested a set of exclusion criteria to make the group of patients with CSX uniform. Those include: the presence of LBBB (left bundle branch block), even the slightest irregularities in coronary vessel angiography, diabetes, arterial hypertension, hyperlipidemia, valve diseases, epicardial artery spasm, and cardiomyopathy. On the contrary, other authors [15, 16] have suggested that diabetes and arterial hypertension are actually CSX risk factors and as such cannot constitute exclusion criteria. A recently published monograph [17] lists the following independent CSX risk factors: less than 55 years of age; no cigarette smoking, diabetes, hyperlipidemia, arterial hypertension or positive family history of premature coronary artery disease in patient history; and a high positive result of the exercise stress test (EST). The scoring system proposed by the authors is simple and objective and precisely distinguishes between CSX and obstructive CAD in women with typical chest pain and positive EST.

Frequency of occurrence of CSX is estimated at 10–20% of patients undergoing coronarography. Approximately 60–70% of patients with CSX are women, often those in the perimenopausal period, after menopause and after ovariectomy. The symptoms usually appear when the patient is 45–50 years old [18–21]. Anatomical differences are also responsible for the more frequent occurrence of the syndrome in women.

85% of patients with coronary artery disease show domination of the right coronary artery, 8% exhibit left coronary artery domination and in 7% the proportions are level. Left coronary artery domination is more frequently determined in patients who undergo coronarography and show no lesions in epicardial coronary vessels. The described vascularization variability is also more common in women, which may suggest the potential role of sex in the development of unobstructive CAD, including CSX [22].

Literature analysis shows that other hypotheses for CSX development include: increased reactivity of the adrenergic system, adenosine system irregularities, insulin resistance of peripheral tissues, estrogen deficiency in women, excessive widening of small arteries at rest, an advantage of the vasoconstriction response over the vasodilation response after vasospastic and relaxing stimuli as well as disturbances of sensation for pain stemming from improper perception and hypersensitivity [23, 24].

Based on the above information, it seems reasonable to expect that making a diagnosis of CSX in a patient must be preceded by thorough differential diagnosis. A clinician's main task is to exclude the possible non-cardiac causes of the reported complaints, which are actually fairly common. They include: anxiety and depressive disorders, esophagus diseases, cholelithiasis, spine degeneration, lung and pleura diseases, and Tietze syndrome (a rarer cause). Of course, one can imagine a situation in which these diseases coexist with each other, but then it seems to be controversial to clearly define the cardiac nature of pain and make a diagnosis of CSX. Subsequently, cardiac causes of chest pain must be taken into account; these include: coronary artery spasm, Barlow's syndrome, arterial hypertension, pulmonary hypertension, aortic valve defects, hypertrophic cardiomyopathy, dilated cardiomyopathy, and storage diseases [25].

The survival prognosis is good, but prevalence is high and recurrent chest pain episodes result in frequent hospitalization and low quality of life. Throughout the disease duration, the intensity of its symptoms decreases only in approximately 30% of patients and deteriorates in as much as 10–20% of them, which forces more intense diagnostics and leads even to disability. Anginal symptoms become more frequent and prolonged, appear at lower levels of physical exertion or even at rest and become less sensitive or resistant to drug treatment, which impairs normal daily activities and results in high rates of temporary absence and retirement from work [15]. The lifetime healthcare cost for a woman with cardiac syndrome X in the USA is approximately 1 million USD [26].

On the other hand, an interesting standpoint is presented in Bugiardini et al. [27], who, based on a ten-year-long observation, postulate that women diagnosed with cardiac syndrome X and exhibiting an inadequate microvascular response to acetylcholine receive special care because, in view of the study results presented in the paper, this is a risk group concerning development of atherosclerosis and acute coronary syndrome. In other works [28], authors prove the significance of both pro-inflammatory and anti-inflammatory factors in CSX pathogenesis.

The psychiatric aspect of cardiac syndrome X

For a long time, researchers have underlined certain relationships between cardiac syndrome X and mental disturbances, mainly anxiety disorders. Studies show that 20% of persons with a normal coronarography result exhibit panic disorders and over 60% of women and 50% of men meet the criteria for the generalized anxiety disorder [29, 30].

Many years ago Wielgosz et al. [31] proved that a high hypochondria result in the Minnesota Multiphasic Personality Inventory (MMPI) was the strongest determinant of continuous chest pain in patients without coronary vessel stenosis. On the other hand, the probability of diagnosing CAD during coronarography is lower in women with anxiety disorders in their medical history who suffer from chest pain [32]. It has recently been reported [33] that, among patients with normal coronarography results, anxiety, depressive symptoms and sleep disturbances in the course of chest pain are

more common in women than in men; the somatization tendency is also higher in women. However, the chest pain duration in those female patients is shorter.

Rosen et al. [34], state that disturbed pain perception may stem from hypersensitivity of the organism to physiological changes of catecholamine levels. This was confirmed by the PET examination results of women with cardiac syndrome X: during the pain, they demonstrated an increase in the degree and area of brain activation in comparison with patients suffering from typical coronary artery disease. In another work, the same authors [35] put forward a conclusion that in cardiac syndrome X, pain threshold lowering takes place in the thalamus.

Regardless of the abovementioned research works, another group of researchers [36] managed to prove differences in feeling fear during stenocardial pain in persons with panic disorder, coronary artery disease and cardiac syndrome X. It seems significant that fear as the dominant feeling was present in 48% of patients with cardiac syndrome X and only in 4% of patients with coronary artery disease.

In one of the latest works [37], published in 2018, the researchers assessed 110 subjects with diagnosed CSX using the Hospital Anxiety and Depression Scale (HADS). Those persons had not been psychiatrically diagnosed or treated before. The obtained results were compared with those of a control group without chronic diseases (100 persons). The total score of the HADS questionnaire and the anxiety subscale (HAD-A) score was significantly higher in the CSX group, which also scored higher on the depression subscale (HAD-D), but the latter difference was not statistically significant. A deeper analysis concerning sex showed significantly higher parameters on the depression scale in the population of women. The compared groups did not differ in the marital status, age or education level. A clinical level of anxiety was determined in 56.4% of patients with CSX and 34% of persons from the control group, while a clinical level of depression was revealed in 47.4% and 30% of them respectively [37]. Moreover, the anxiety subscale score in the described study proved to be an independent risk factor for the development of CSX.

Both the abovementioned work and certain earlier studies present consistent results in the scope of the relationship between the education level and experienced stress and anxiety levels: patients with lower education have scored higher on the anxiety subscale and reported a greater number of stressful events from the past. This has led to a hypothesis that patients with CSX are more commonly exposed to stress and mental disturbances. Similar results were obtained in a 2012 study [38] involving 4,583 subjects: it confirmed the negative correlation between education and the perceived stress level measured using the Goldberg General Health Questionnaire (GHQ-12). Moreover, the researchers deemed the HADS scale a simple and costless tool for a quick, basic assessment of the patient's emotional state. They also concluded that interventions aimed at improving the quality of life as well as psychological support were particularly beneficial to women and people with lower education levels.

In 2013, Jespersen et al. [39] analyzed a group of patients who underwent their first coronarography due to suspected stable angina. To do that, they used the Seat-

tle Angina Questionnaire and the HADS scale. The examination detected persistent anginal complaints (symptoms present at least for one month) in 64% of patients with disseminated CAD (the vessel lumen stenosis determined in coronarography did not exceed 49%) and in as much as 49% of patients without any stenosis whatsoever. Interestingly, such symptoms were determined only in 41% of patients with a stenosis equal to or exceeding 50%. Moreover, the frequency of anxiety and depressive symptoms was significantly higher in patients with long-term anginal pain. Furthermore, persistent anginal symptoms were strongly associated with anxiety, depressive symptoms, impaired functioning in the society and low quality of life regardless of the CAD advancement level [39]. The last study we would like to cite [40] was carried out by Turkish scientists and confirms the previous observations. The researchers compared a group of CSX patients with a group of CAD patients in terms of concomitant mental disturbances and the quality of life. They proved a high frequency of mental disturbances and a noticeable impairment of the quality of life in persons suffering from CSX. Anxiety disorders were present in 64% of CSX patients, 29% of which met the criteria of anxiety disorders with panic attacks, 21% – phobia-type anxiety disorders and 14% –generalized anxiety disorders. In the control group, which included persons with chest pain and angiographically confirmed coronary artery disease, the frequency of anxiety disorders reached 19%, 6% of which were diagnosed as anxiety disorders with panic attacks, while 13% were phobia-type anxiety disorders. Somatoform disorders were diagnosed in 24% of the CSX group subjects and only in 4% of persons from the control group.

Treatment

The still insufficiently described etiology of cardiac syndrome X makes it a controversial and simultaneously fascinating disease entity which often borders on cardiology and psychiatry. That special relationship results in higher expectations concerning treatment effectiveness and improvement of the quality of life for patients suffering from that syndrome.

The coexistence of emotional disturbances and the poor quality of life of persons with cardiac syndrome X seems to be strongly related to the level of social support and isolation. That relationship was confirmed by the results of a study involving women with CSX who were divided into two groups: a group receiving support and a control group, subjected to 12 months of observation. The analyzed parameters were assessed using: the Health Anxiety Questionnaire (HAQ), the HADS, the SF-36, the York Angina Beliefs Scale, and the ENRICHD Social Support Instrument (ESSI). Moreover, the researchers gathered information about hospitalization and appointments (primary care physician and cardiologist). As a result, the social support level on the ESSI was higher in the group of women receiving support. Moreover, only 29% of women in that group made at least one appointment with a primary care physician in connection with their symptoms (in comparison with 54% of women in the control group). Therefore, one must highlight that participation in support group meetings increases the sense

of social support and thus contributes to lower expectations of the healthcare system and reduces health-related misconceptions of patients with CSX. Consequently, this may significantly reduce the costs borne by the state due to irrelevant diagnostics and treatment [41].

Recognized methods of pharmacological treatment of patients with proved cardiac muscle ischemia include: 1) beta-blockers (effectiveness: 75%), including new generation ones which exert a vasodilation action in the endothelium (e.g., nebivolol) and may be more effective; 2) statins (they improve the vasodilation properties of the endothelium); 3) calcium channel blockers (less effective than beta-blockers); 4) ranlosin (a medicine with an anti-anginal action; it inhibits the late sodium current); 5) angiotensin-converting-enzyme inhibitors (ACE-I). At least several studies [42, 43] indicate that nitrates, which exert a short-term action and significantly improve the stress test results in persons with CAD, do not produce the same effect in patients with MVA. Therefore, they are not recommended because they do not reduce the anginal symptoms in patients with CSX. Literature includes studies recommending the use of ivabradine, which inhibits the If current (pacemaker current, funny current) in the sinus node and selectively reduces the heart rate. This leads to a reduction of cardiac oxygen consumption and improves the coronary blood flow by prolonging the diastole. Villano et al. [44] have proved that ivabradine significantly reduces the angina pectoris symptoms in patients with MVA. Potentially useful conclusions are also found in a study carried out in 2009 [45], which consisted in a 20-week sertraline therapy administered to patients with CAD and depressive symptoms. Afterwards, a significant improvement of endothelium functioning was noticed. That confirmed the previously described beneficial influence of a therapy with an antidepressant from the selective serotonin reuptake inhibitor (SSRI) group on endothelium functioning in patients with coronary artery disease and concomitant depression.

Aminophylline and tricyclic antidepressants in small doses (e.g. imipramine 50 mg/day) are also sometimes applied in the anti-anginal treatment in CSX, but the results are much worse. Though there is a hypothesis that improved condition of certain patients may be related to the analgesic action of imipramine [46], such treatment entails a much higher risk of adverse effects.

One of newer reports [47] is particularly interesting as it highlights the effectiveness of vitamin D in the therapy of the described syndrome. The study in question shows that a therapy with large doses of vitamin D (300,000 IU in an intramuscular injection every two weeks throughout two months) in patients with CSX and concomitant vitamin D deficiency significantly reduces the ischemia symptoms by direct action on the cardiovascular system. The author points out that the beneficial effect of vitamin D on the cardiovascular system is proven, however, recent publications [48] indicate that the effect of in vitro experiments is not reflected in population studies.

Non-pharmacological treatments include cognitive behavioral therapy (CBT), the effectiveness of which was proved after eight weeks of its application in a group of women with retrosternal pain and normal coronarography results. Consequently, the anxiety level was lowered, the depressive symptoms were reduced and the effort

tolerance increased [49]. In a study conducted by Moore et al. [50], an eight-week long CBT reduced the number of hospitalizations from 2.4 to 1.78 per year per patient and shortened the hospitalization time in days from 15.48 to 10.34 per year per patient. In general, relevant literature suggests small to moderate benefits from psychological interventions, especially CBT, and considers hypnotherapy as a possible alternative [51]. One should also pay attention to mindfulness-based therapy (MBT) and autogenic training, which reduce the anxiety and depressive symptoms as well as perception of stress. This, in turn, is associated with the arterial blood pressure lower than its baseline value as well as improved heart functioning [52–54].

A significant supplementation of pharmacotherapy and psychotherapy is lifestyle modification – appropriate physical activity, cardiac rehabilitation, giving up cigarette smoking, body weight normalization, and Mediterranean diet [55, 56].

With the drug-resistant form, one can apply more advanced methods such as late electrical stimulation or spinal cord stimulation [57].

Recapitulation

Cardiac syndrome X remains a disease with a complex and not fully explained etiology. Its frequency of occurrence is estimated at 10–20% of patients undergoing coronarography. It prevails in women (70%) aged 45–55. In view of the above data, one must stress that the survival prognosis is good, but the quality of life prognosis is unfavorable because treatment effectiveness is still low. In a sense, this syndrome may be treated as a disorder which borders on cardiology and psychiatry because patients unexpectedly often show concomitant emotional and somatoform disorders, while administered antidepressants frequently reduce chest discomfort intensity and improve the quality of life. Therefore, it seems that concurrent use of cardiological drugs and SSRI group drugs is the most favorable pharmacotherapeutic variant of this controversial clinical unit.

Until now, diagnosis of CSX was indubitably diagnosis by exclusion of other ailments resulting in discomfort in the chest. The bare definition of basic criterion of CSX already, which is “right depiction of epicardial coronary arteries in coronarography” is imprecise. To the right depiction different authors include: lack of arteriosclerotic changes, minimal or up to or equal to 50% of vascular stenosis arteriosclerotic changes. The result of cardiac stress test remains a controversial criterion too, as it could be negative or difficult to interpret. The only certain criterion is a presence of pain which could be typical or atypical for coronary conditions as well. Because of the fact that conditions of pain regard the chest and hemodynamically irrelevant but still lesions of coronary arteries most often appear in coronarography, this disease entity has always been considered a form of coronary arterial disease. However, brand new guidelines of the European Cardiology Society from 2019 regarding diagnosis and treatment of coronary disease do not include CSX. However, they include microvascular angina, which is characterized by typical stenocardiac ailments existing alongside the physical exertion and myocardial ischemia shown in non-invasive tests

and lack of lesions or presence of angiographically irrelevant lesions (40–60%) [58]. Nowadays, interventional cardiologists have additional diagnostic tools to functional evaluation of myocardial ischemia. These tools are, among other ones, coronary flow reserve (CFR) and microcirculatory resistance (IMR), which enable confirmation or exclusion of the presence of myocardial ischemia in patients with angiographically irrelevant lesions. IMR values higher than/equal to 25 units or CFR values lower than 2.0 with the lack of changes in epicardial coronary vessels obtained using these tests could imply microvasculature anomalies. Patients with such values should be under cardiological surveillance. Remaining patients, those in whom microvasculature dysfunction and other potential somatic causes of chest-pain have been ruled out, should undergo psychiatric diagnosis.

In the light of these data, one could have reasoned doubts as for the classification of CSX. Thus, according to authors, it ought to be considered whether CSX still constitutes a form of coronary heart disease or is just a variant of anxiety disorders. If so, CSX would be closest to somatoform disorders, regarding autonomic dysfunctions existing under the somatic form in vascular system and distinguishing the individual clinical unit would not make sense.

It should be also taken into account that the presented syndrome might be heterogeneous. Perhaps the syndrome includes several different forms, some of which could meet the criteria of anxiety disorders, while the others – the more diagnostically transparent ones – could meet the criteria of cardiological disorders. It concerns microvascular angina as a patophysiological mechanism of CSX which is possible to identify. It should be highlighted though that this viewpoint is solely effect of the author's reckoning.

So the question should be posed: are anxiety disorders independent, often coexisting with CSX in cardiological understanding, disease entity or CSX is the special variant of anxiety disorders, e.g., somatoform ones? In our opinion this question still remains without a substantial answer. Agreement on consistent viewpoint, undoubted diagnostic criteria and algorithms of treatment constitutes a challenge for clinicians and is of special importance in the context of high societal costs.

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