Cardiac Syndrome X

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Abstract

Cardiovascular disease remains the leading global cause of death, most attributably due to a poor diet and lifestyle. However, there is still a large cohort of people who experience cardiovascular issues due to genetic reasons. This includes patients predominantly females, suffering from Cardiac Syndrome X. This condition is mostly genetic yet may be aggravated by an unhealthy diet and poor physical lifestyle. It is believed that a combination of vasospastic muscular arteries and endothelial dysfunction in the vessels supplying the heart may be the leading causes, yet its aetiology is still under-researched. Considering this, patients commonly present with severe retrosternal chest pain, discomfort, and shortness of breath, however following methodical testing, coronary angiography and electrocardiography, no cardiovascular lesions or abnormalities are revealed. This condition may still lead to fatal cardiogenic shock since myocardial infarction may supervene due to prolonged vasospastic closure of the arteries – which is why adequate knowledge and skilful management is required.

Introduction

Cardiac Syndrome X (CSX), also called 'Microvascular Angina' is a cardiovascular event characterised by typical or occasionally even atypical anginal chest pain. Distinctively, no coronary vascular abnormalities or lesions are evident during cardiac angiography (Mahtani et al. 2023). Nonetheless, it is still a type of ischemic heart disease which predominantly occurs predominantly in perimenopausal females and still carries a high morbidity rate if not diagnosed and managed early (Agrawal et al. 2014).

This condition has generally been linked to an increased risk of deadly cardiovascular events and poor quality of life. Treating and managing the condition remains empirical since each year 4000 new people are diagnosed with this illness in the United Kingdom (Bradley and Berry 2022).

It is believed to involve arterial-endothelial vasospastic dysfunction of the epicardial arteries supplying the myocardium, which results in myocardial ischemia (MI) followed by the sensation of anginal chest pain due to the release of adenosine and Tumour Necrosis Factor (TNF)-a from the endothelium that binds to nerve endings situated within the cardiac plexus responsible for the sensation of pain (Kaski 2006).

CSX may be pharmacologically managed and treated by a conventional triple combination therapy of anti-ischemic agents including nitrates, Beta (b)-blockers and calcium-channel blockers (Jarczewski et al. 2021). Supplementary agents may be used such as Angiotensin-converting enzyme (ACE) inhibitors, hydroxymethylglutaryl-Coenzyme A (HMG-CoA) reductase inhibitors along with other specific antianginal medications like ranolazine (Chou and Saw 2014).

Methodology

In identifying material relevant to this literature review, multiple databases that carried relevant

information were used. First, a wide and comprehensive search of peer reviewed journals and articles was conducted based on a wide range of keywords including Cardiac Syndrome X, microvascular angina, genetic predisposition and sequencing, coronary angiogram, and vasospasm. In total, five major sites were used including PubMed, Elsevier, ScienceDirect, the Cochrane Library and Google Scholar. Moreover, the reference section for each article found was searched to garner additional information with regards to the topic.

Pathophysiology

The pathophysiology of CSX remains poorly understood, which explains the absence of drugs explicitly used to treat this syndrome. The following points are believed to be the key aspects of the underlying cause of microvascular angina (Kanar and Sünbül 2018):

1. An inadequate oxygen supply to the myocardium due to vasospasm of the coronary arteries following microvascular dysfunction.
2. Endothelial dysfunction due to a reduced production of Nitric Oxide (NO) from the tunica intima following exercise, which promotes vasodilation of blood vessels. This can lead to vasoconstriction and consequently myocardial ischemia and infarction.
3. It is also suggested that patients suffering from CSX may have hyperalgesia or altered pain processing in the central nervous system (CNS). This may precipitate angina-like symptoms even in the absence of significantly reduced myocardial perfusion.
4. Chronic inflammation and oxidative stress may also contribute to impaired microvascular, smooth muscle and endothelial function. It has been shown that patients with CSX also have chronically higher levels of highly specific C-Reactive Protein (hs-CRP) in serum.
5. Hormonal factors, such as oestrogen deficiency in postmenopausal women have been proposed as one of the main contributors to the development of microvascular angina since oestrogen is known to be protective against cardiovascular events in females.

Clinical History and Presentation

Patients experiencing CSX typically present with an acute history of recurring and persistent substernal chest pain or discomfort that may radiate to the jaw, neck, left arm, back or epigastrium resembling symptoms of angina (Gulati et al. 2020). The nature of the retrosternal pain is usually sharp and compressing. Often, it is triggered by emotional or physical stress (Gulati et al. 2020). However, this pain is not caused by coronary lesions. Rarely, this anginal chest may also occur at rest. Other common symptoms patients may present with include tachycardia, tachypnoea, and malaise (Vancheri et al. 2020).

A thorough history and examination should be taken in patients presenting with such signs and symptoms, prior to any invasive testing or imaging modalities, along with careful evaluation of other potential pathogenic causes that may be of cause (Crea and Lanza 2004).

Seldom will patients ever be cyanotic, hypotensive, or unconscious as this would indicate severe progression of the disease and require urgent intensive therapy for stabilisation.

Clinical History and Presentation

Non-Invasive:

1. Electrocardiography (ECG):

on a standard 12-lead ECG, many patients with CSX present with only sinus tachycardia and otherwise completely normal ECG findings. However, during an ECG-based Exercise Stress Test (EST), these patients will demonstrate transient ST-segment depression during physical exertion and may also exhibit such findings on a 24-

hour Holter Monitoring (Ong et al. 2018). Anginal chest pain during stress testing in combination with ST-segment depression, and the lack of structural abnormalities on echocardiography demonstrate an increased likelihood of CSX (Acharya et al. 2020).

2. Technetium Sestamibi (99mTc) Scan:

this imaging modality will usually show in patients with CSX a heterogenous distribution of microscopic vascular defects distributed along all the coronary epicardial arteries rather than just one single major vessel (Del Buono et al. 2021).

Invasive

1. Coronary Angiography:

patients with CSX exhibit no significant focal coronary artery narrowing on angiography, but intracoronary administration of nitro-glycerine may increase coronary perfusion indicating global coronary vasoconstriction (Fig. 1.1).

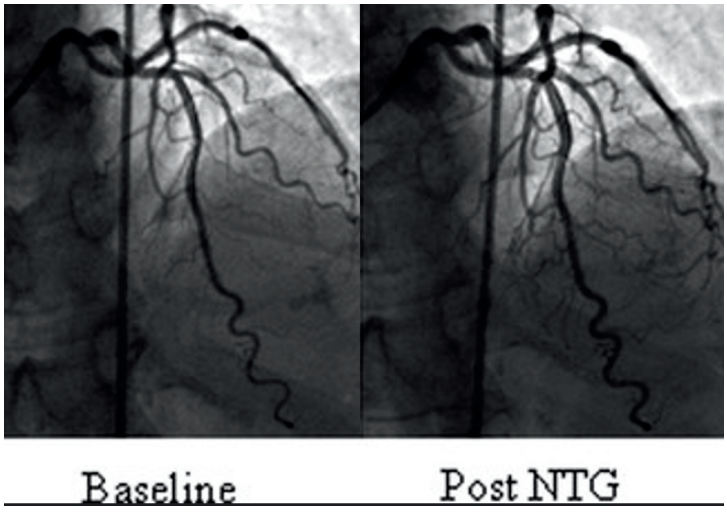

Fig. 1.1: depicting initial coronary angiography in patients with CSX followed by administration of nitro-glycerine indicating increased coronary perfusion.
Source: (Bairey Merz and Pepine 2011).

Treatment and Management

Since the aetiology of CSX is not fully understood, management of such patients may be challenging in nature. Its management ranges from controlling the modifiable risk factors to administering a triple combination therapy of ant-ischemic and antihypertensive agents.

1. Adopting a healthy heart lifestyle is of substantial benefit to these patients. This includes avoiding active and passive smoking, practising regular aerobic exercise, following a diet that is low in saturated fats and cholesterol, and even managing stress.

2. Beta-blockers (carvedilol, propranolol, and labetalol) have been demonstrated to be effective in improving exercise tolerance and symptoms in patients with CSX. More recently, third-generation beta-blockers such as nebivolol, have been shown to be potentially more effective since they enhance the vasodilatory activity of the endothelium (Soleymani et al. 2022).

Nifedipine, verapamil and diltiazem, which are calcium channel blockers, may be used as alternative therapy however are known to be less beneficial, even though they improve exercise tolerance and anginal attacks. It has also been noted that ranolazine, a new antianginal used in chronic anginal chest pain is also useful as an effective therapeutic option (Jarczewski et al. 2021).

Statins have an important role in the management of patients with CSX as they promote the vasodilatory function of the endothelium and prevent the further development and aggravation of atherosclerotic plaque in the coronary end arteries, hence, stabilising the plaque to prevent the possible rupture and consequential ischaemia of myocardium.

ACE inhibitors have shown to be advantageous, as they prevent the breakdown of bradykinin within the endothelium, which sustains vasodilatory function, further regulating microvascular tone within coronary arteries (Ford et al. 2018).

3. Analgesic medications may also be useful, based on the idea that patients with CSX have a heightened or impaired pain perception. Certain patients may benefit from the use of agents such as xanthine derivatives like aminophylline – that work by blocking the adenosine receptors within the cardiac plexus – and transcutaneous electrical nerve stimulation (TENS) (Johnson et al. 2022).

Complications

The risk for future adverse cardiovascular events, especially in females with uncontrolled anginal chest pain significantly increases, even though there are no signs of stenosis on imaging. MI, stroke, sudden cardiac death, and heart failure are subsequent examples of such events.

The quality of life in a patient with CSX significantly declines, and daily activities become more challenging. Since CSX is diagnosed in exclusion, a thorough workup is necessary which may be expensive and time-consuming. Due to the frequent failures of traditional medications for therapeutic management, the challenge of achieving therapeutic efficacy from pharmacotherapy presents additional obstacles. This frequently worsens the quality of life of CSX patients, increases and prolongs hospital stays, and furthermore limits daily activities.

Even though the prognosis of CSX remains guarded, recurrent episodes of anginal attacks necessitate periodic hospitalisation due to their high frequency of occurrence. Roughly 30% of patients experience a decline in clinical manifestations, whereas 10% endure a progressive worsening of symptoms. Individuals facing a declining course of their illness frequently encounter difficulties with diagnosis, investigations and treatment which may lead to disability (Asbury and Collins 2005).

Genetic Inheritance

An underlying genetic basis was uncovered for microvascular angina, which offers further mechanistic insight into its pathophysiology. In addition to genotyping 643 patients with this condition, researchers looked at 1536 single nucleotide polymorphisms (SNPs) in 76 genes that were linked to its pathology. SNPs in the VEGFA and CDKN2B-AS1 genes were extensively linked to microvascular dysfunction across the whole board of the researched population (Yoshino et al. 2014). Additionally, they discovered an SNP-sex interaction that could account for some of the pathophysiological variations between men and women who suffer from microvascular angina. Even though no potential SNPs were linked to the condition in females, SNPs in the MYH15, VEGFA and NT5E genes were also linked to microvascular dysfunction in males (Leopold 2014).

Conclusion

In conclusion, obstructive CAD and endothelial dysfunction show conspicuous connections to CSX, which is a difficult medical condition to diagnose, and primarily affects but is not exclusive to females. Improved knowledge of coronary vascular dysfunction will be of significant benefit to patients with CSX. Microvascular angina should remain a high research priority area due to its high prevalence, significant healthcare expenses, and dearth of information regarding effective treatment options.

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