Syndrome "X"?

SENDROM "X'

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ÖZET

Tipik göğüs ağrısı, pozitif eforlu EKG testi ve normal koroner anjiyografisi X sendromunu oluşturmaktadır. Bu sendromun nedeni tam olarak bilinmemektedir. Altında yatan mekanizmada azalmış bir koroner akım rezervi ile beraber küçük koroner arterlerin tutulmasının rolü olduğu sanılmaktadır. Bazı hastalarda ise anormal bir kalp ağrı duyumu algılaması söz konusu olabilir. Özellikle kadınlarda görülen bu sendromun prognozu genellikle iyidir. Buna karşılık, sol dal bloğu bulunan bazı hastalarda sol ventrikül fonksiyonunun ileri derecede bozulduğu gözlenmiştir. Kalsiyum kanal blokörleri, beta blokörler ve anjiyotensin konverting enzim inhibitörleri faydalı olabilir.

Anahtar Kelimeler: X sendromu, Angina, Egzersiz testi, Koroner anjiyografi

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SUMMARY

Syndrome X is defined by the association of typical angina pectoris, a positive exercise stress test and normal coronary arteriogram. The casue of syndrome X is unknown. The main mechanism appears to be small coronary vessels disease with reduced coronary flow reserve. Some patients may have abnormal cardiac pain perception without altered coronary flow reserve. Long term follow-up is favourable. However, in some patients with left bundle brunch block, significant deterioration of left ventricular function is observed. Calcium antagonists, beta-blockers and angiotensin converting enzyme inhibitors may be effective.

Key Words: Syndrome X, Angina pectoris, Exercise stress test, Coronary arteriogram

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Typical chest pain (retrosternal, induced by physical activity and decreased by rest) is a good indicator of myocardial ischaemia secondary to obstructive coronary artery disease. Approximately 10 to 30% of patients undergoing coronary angiogram have no detectable coronary artery disease (1). Syndrome X is described as typical angina chest pain associated with positive exercise stress test without any detectable coronary artery disease at angiogram after other causes of anginal pain such as arterial spasm, myocardial hypertrophy or valvular disease with normal coronary arteries have been excluded. The term "Syndrome X" was first used by Kemp in an editorial review when quoting Arbogast and Bourassa (2). In their study of patients with anginal chest pain, the latter, using rapid atrial stimulation compared a group of patients with coronary artery disease with a group "X" of patients without coronary artery disease at angiogram (3). Although in the last twenty years many have studied the subject, the aetiology of syndrome X has not yet been determined.

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Syndrome X is mostly seen in females. The pain is retrosternal, generally severe and occasionally severe enough to warrant medical care (4). Classical ECG findings of myocardial ischemia (depression of ST segment) on exercise, is not always present. It is believed that this chest pain can be caused by many factors, none of which have been determined. The long term prognosis of syndrome X is generally favourable (5).

PHYSIOPATHOLOGY

In the last few years different theories have been put foreward to explain the pathophysiology of syndrome X (6-8). The cause of precordial pain in patients with normal coronary arteries has been suggested to be the diminished coronary artery flow. In 1985 Cannon and Epstein suggested the term of "microvascular angina" as they thought the pathology to be at

the level of small diameter coronary arteries which are intramural and nonvisible at angiography (7). In these patients the large diameter coronary vessels remain normal even after the test with ergonovine. An increased sensitivity of the coronary microcirculation to stimuli with vasoconstrictive agents and a decreased dilatative capacity of microvasculature was observed. These alterations are recognised as the key feature of the syndrome X. The same authors also suggest that this kind of microvascular angina could be part of a generalised smooth muscle abnormality affecting systemic arteries, the oesophagus and bronchii.

In 1991, Maseri et al suggested a new hypothesis to explain the pathophysiology of syndrome X (8). According to them the mechanism of angina In syndrome X is related to inappropriate constriction of the prearteriolar vessels causing a decrease in the reserve of coronary blood flow. Secondary to this, retrosternal pain is induced and a heterogeneous myocardial ischaemia probably occurs. Unequal distribution of small diameter vessel zones may explain the variety of vasomotor responses observed in patients with syndrome X. The constriction of arterioles also stimulates the local compensatory production of adenosine which may be the mediator responsible for precordial pain. Different causes were suggested to explain this increased constrictive activity and diminished dilatative capacity of these small diameter vessels such as structural abnormality of the microcirculation, primary absence of smooth muscles in the arteriolar wall, dysfunction in autonomic nervous system regulation with increased adrenergic tone, local deficit of endothelium-derived relaxation factor which is partially responsible for the basal vascular tonus or acquired resistance to insulin (8-12) are the most important.

METABOLIC STUDIES

Several invasive studies with rapid atrial stimulation have been performed in patients with syndrome X in order to determine myocardial production and consumption of lactates (4). Patients with coronary artery disease have increased myocardial extraction of lactate during physical activity and inhibition of fat-free acid oxidation. On the contrary, patients with syndrome X have neither an increased production of lactate nor an inhibition of fat-free acid oxidation; this is probably due to an increased activity of sympathetic nervous system (4,13).

OTHER CAUSES

As patients with syndrome X may experience severe and frequent precordial chest pain without any detectable pathology of the coronary microcirculation, some authors consider the perception of pain to be abnormal in these patients (14,15). This type of pain can also be induced during cardiac catheterisation when manipulations are performed in right heart cavities, in the aorta or even during contrast material injection into the coronary arteries. Painful injection of contrast material into coronary arteries rarely happens in patients with valvular or coronary artery diseases (15). The distortion of pain perception may explain the cause of severe pain in some patients without a significant ischaemia.

NONINVASIVE METHODS OF MYOCARDIAL ISCHAEMIA DETECTION

Although by definition, syndrome X intails typical precordial pain, positive exercise stress test and angiographically normal coronary arteries, some authors recommend that ischaemia should be documented in a objective way to complete all the criterias. Ischaemia can be documented objectively using the following tests:

1. Exercise Test

The standard exercise stress test with ECG has a good sensitivity but a relatively low specificity. Camici et al observed a normal ECG in 12 of 14 patients (86%) with pathologic coronary flow reserve (16). In the same study 16 of 29 patients (55%) with normal coronary flow had an abnormal ECG. These results indicate that factors other than myocardial ischaemia may play a role in symptoms and ECG alterations.

2. 24 Hour-Holter ECG Monitoring

24 hour-Holter ECG monitoring often shows episodes of ST segment depression but these alterations do not always correlate with a precise symptomatology. In Bugiardini's series 400 episodes of ST segment depression due to probable increased adrenergic activity were observed during the day time (17) but only 6% of these alterations were related with the chest pain.

3. Thallium-201 Scintigraphy

Thallium-201 scintigraphy with exercise (or dipyridamole administration) is frequently used to demonstrate ischaemia. The efficacy of this test is variable. Perturbation of local captation after activity and especially transient hypocaptations were noted in 15 to 45% of patients.

4. Positron Emission Tomography (PET)

Today positron emission tomography is the best non-invasive in vivo method to study coronary microcirculation. This is performed by measuring basal and maximal myocardial blood flow. In their study Geltman et al showed approximately half of the patients to have abnormal myocardial perfusion but this abnormal perfusion was mostly homogenous with low incidence of local involvement (18). Camici et al found a decrea-

sed coronary flow reserve in 30% of their patient population (16). In a more recent study comparing 29 patients with syndrome X with a control group of 12 subjects no significant myocardial blood flow disturbance was found (14).

PROGNOSIS

The long term prognosis of syndrome X is generally favourable (5). On exertion the left ventricle in systole is either normal or hypercontractile in patients with syndrome X. Some patients with left bundle branch block (LBBB) may have severe decreased left ventricular ejection fraction, both on exercise and at rest (19,20). The disturbance of left ventricular function may be a result of microvascular dysfunction and ischemia or metabolic disorder.

THERAPEUTIC ATTITUDE AND FOLLOW-UP

Follow-up and treatment of patients with syndrome X are illustrated in Figure 1. Once the diagnosis of syndrome X is made based on the classical triad, documentation of myocardial ischaemia with a thallium test or positron emission tomography is necessary. This is important in order to determine the patient subgroup with ischaemia and to follow their left ventricular function, particularly for those patients who have a risk of developing left bundle branch block. If ischaemia can not be demonstrated in a patient with syndrome X, an extracardiac cause of chest pain such as esophagus dysfunction must be excluded.

The response to treatment is variable. Sometimes the treatment may be ineffective and the patient may stay symptomatic. Two third of patients with syndrome X need medical care and almost half of the patients stop working for good (5). Some patients benefit from analgesic medication because of their actions on coronary reserve. Some benefit from treatment with beta-blockers through their action of increasing adrenergic tonus (17). Aminophylline blocks the adenosine receptors and may have a favourable effect on symptoms and ischaemic ST-segment alterations (8). Finally, angiotensin converting enzyme inhibitors (ACE) are said to have a favourable effect by decreasing ischaemia on exercise. This is probably due to their direct action on coronary microvascular tone.

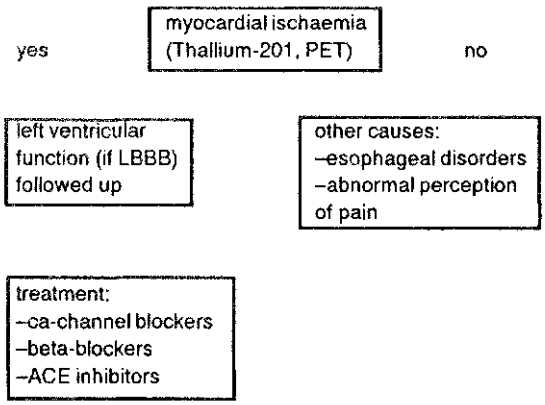

Figure 1.

In conclusion syndrome X includes multiple physlopathologic entities. Studies of coronary flow reserve show an altered response to both rapid cardiac stimulation and pharmacological vasodilatation. These findings suggest a microcirculation dysfunction but it is believed that angina pectoris is not due to altered flow of coronary reservi in all patients with syndrome X. Other factors such as esophageal disorders, increased adrenergic tonus, resistance to insulin or abnormal perception of cardiac pain, may play a role.

One and only aetiology which can be applicable to all patients has not yet been found. Hence, the letter "X" will continue to be the major figure of this syndrome.

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