The research progress of syphilitic coronary heart disease

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Abstract. Background Syphilitic Cardiovascular Disease is a cardiovascular condition caused by the invasion of Treponema pallidum, the bacterium responsible for syphilis, into the human body. It encompasses a spectrum of cardiac disorders, including syphilitic aortitis, syphilitic aortic valve insufficiency, syphilitic aortic aneurysm, coronary artery stenosis, and myocardial gumma [1].

Method The research involved a comprehensive literature search in databases such as PubMed using keywords like “syphilis,” “coronary heart disease,” and “syphilitic coronary heart disease.” Selected studies were reviewed to summarize the epidemiology, pathogenesis, clinical manifestations, and current diagnostic and treatment status of syphilitic coronary heart disease.

Result and Conclusion The research emphasizes the need to consider syphilis as a potential cause in coronary artery disease cases and highlights the clinical aspects and prognosis of syphilitic cardiovascular conditions.

1. Introduction

Syphilis is a disease caused by the spirochete bacterium Treponema pallidum and can be transmitted through sexual and vertical transmission routes. Clinical manifestations typically involve localized inflammatory responses, and the course of infection can be divided into primary, secondary, latent, and tertiary stages, often spanning over a period of more than 10 years. As the disease progresses, syphilis not only affects the skin and mucous membranes but also involves nearly all tissues and organs in the body. It can impact the nervous system, leading to substantial spinal cord damage, manifesting as symptoms such as dementia and cognitive impairment. Furthermore, syphilis can damage bones, causing avascular necrosis of the femoral head, and affect the eyes, resulting in blurred vision [2]. Research by Fu and colleagues suggests that syphilis can be considered an independent high-risk factor for the prognosis of coronary heart disease [3]. Syphilis exerts adverse effects on the cardiovascular system, known as cardiovascular syphilis, provoking symptoms related to cardiovascular disease. In extreme cases, it may lead to acute myocardial infarction and severe heart failure, potentially endangering the patient's life [2]. This review aims to analyze the epidemiology, pathogenesis, symptoms, and current diagnostic and treatment status of syphilitic coronary heart disease, identify existing gaps in this field, and attempt to uncover future research directions.

Coronary heart disease can be divided into two main types: atherosclerotic coronary heart disease and syphilitic coronary heart disease. Atherosclerotic coronary heart disease, also known as coronary artery atherosclerosis heart disease, is a condition that results from the narrowing, blockage, or spasms of coronary arteries due to atherosclerosis, leading to myocardial ischemia, hypoxia, and even necrosis. On the other hand, syphilitic coronary heart disease refers to cardiovascular abnormalities triggered by the invasion of Treponema pallidum into the human body, affecting the coronary arteries and causing narrowing of the coronary artery openings, which can lead to acute myocardial ischemia. These two types of coronary heart disease have slightly different etiologies and pathogenic mechanisms but can both have serious effects on the heart and vascular systems, necessitating prompt diagnosis and treatment.

There are distinct differences between these two types of coronary heart disease. Syphilitic coronary heart disease is characterized by chronic inflammatory reactions initiated by the destructive action of Treponema pallidum on the coronary arteries, leading to narrowing of the coronary artery openings. In contrast, atherosclerotic heart disease results from endothelial cell damage caused by various factors, leading to excessive infiltration of plasma lipoproteins into the arterial wall. Simultaneously, it triggers platelet adhesion, aggregation, and the release of various active substances, further exacerbating endothelial cell injury and eventually leading to foam cell formation beneath the endothelial cells and the accumulation of atheromatous necrotic material.

2. Epidemiology

In recent decades, the incidence of late-stage syphilis has decreased due to early detection and the use of effective antibiotics [4]. However, in recent years, there has been a resurgence in syphilis incidence, with an estimated annual increase of 12 million new cases according to the World Health Organization [5]. In 2017, there were 490,000
cases of syphilis among individuals aged 7-15 globally. The prevalence and incidence of syphilis vary by region and country, with the highest prevalence found in Africa, where more than 60% of new cases occur in low- and middle-income countries. The greatest burden of syphilis in pregnant women is also observed in Africa, accounting for more than 60% of the estimated global cases [6].

In clinical practice, specialists may often focus more on the cutaneous and mucosal manifestations of this disease, while insufficient attention is given to cardiovascular syphilis, and there is limited research reported both domestically and internationally. Late-stage syphilis frequently involves the cardiovascular system, with an incidence as high as 10%, occurring 10 to 30 years or more after the initial infection. Cardiovascular syphilis can manifest as isolated aortitis, aortic valve insufficiency, coronary artery stenosis or obstruction, aortic aneurysm, and mucous myocarditis [7-9].

Fu and his colleagues indicate that syphilis-positive patients have a probability of cardiovascular involvement ranging from 10% to 12%, leading to syphilitic aortitis, syphilitic aortic valve insufficiency, syphilitic aortic aneurysm, coronary artery stenosis, and gummatous myocarditis [10]. Previous studies suggested that cardiovascular symptoms and signs typically appear 10 to 20 years after syphilis infection [11], with a predominant age range of 35 to 50 years and a higher prevalence among males. However, recent research has found that syphilitic cardiovascular damage can occur as early as 1 to 2 years after syphilis infection, affecting individuals as young as 20 years old, and with a notable increase in the number of affected females [12].

Literature suggests that approximately 10% to 30% of untreated syphilis patients may ultimately develop cardiovascular syphilis. Adequate and timely treatment of early syphilis reduces the incidence of syphilitic aortitis to 0.4%, while inadequate treatment results in an incidence rate of 17.5%. Autopsy findings reveal cardiovascular syphilis in 70% to 85% of inadequately treated cases. Irreversible damage to the cardiovascular system by Treponema pallidum is one of the important causes of death in late-stage syphilis, with syphilitic heart disease accounting for 55.7% of autopsy-confirmed cases among late-stage syphilis patients. Cardiovascular syphilis represents 10% to 39.4% of late-stage syphilis cases (active or inactive), with syphilitic aortitis accounting for 85% of these cases [13].

In late-stage visceral syphilis, cardiovascular syphilis accounts for over 90% of cases. Globally, the mortality due to cardiovascular syphilis constitutes 5% to 10% of all cardiovascular disease-related deaths. In 1956, overseas reports indicated that syphilitic heart disease accounted for 15.1% of all cardiac-related deaths. The time span from Treponema pallidum infection to the appearance of clinical symptoms and signs of cardiovascular involvement varies significantly, ranging from 9 to 40 years, with a general average of 10 to 30 years. Tianjin Medical University General Hospital once conducted an analysis of 154 hospitalized patients with cardiovascular syphilis, revealing that one patient had a disease course extending to 50 years, while the shortest time to onset was 4 years. Due to multiple factors, defining a precise time frame is challenging. In recent years, individuals infected with the human immunodeficiency virus (HIV) often experience concurrent syphilis infections. Their compromised immune function disrupts the conventional boundaries between the typical clinical symptoms and signs of primary, secondary, and tertiary syphilis. In addition to atypical clinical manifestations, symptoms from various stages may appear sequentially or simultaneously, a condition referred to as "explosive syphilis" or "malignant syphilis." This completely challenges the previous concept that cardiovascular syphilis takes 9 to 10 years to develop. There have been reported cases where the time from Treponema pallidum infection to the onset of cardiovascular involvement was as short as 2 years. The gender distribution of cardiovascular syphilis patients has also changed compared to historical records. In the past, the male-to-female ratio was 4 to 5:1, with a higher incidence in males. This was attributed to the higher estrogen levels in females, which were believed to inhibit the activity and toxicity of Treponema pallidum. However, in 2002, a study in China by Zhong Weibang and others reported 36 cases of cardiovascular syphilis with a male-to-female ratio of 16:20, indicating an increasing number of female patients, even though this was a localized study. The majority of cardiovascular syphilis cases are acquired syphilis, but a very small number may be congenital syphilis. Congenital syphilis can manifest symptoms and signs of cardiovascular syphilis or neurosyphilis, although it is rare. This rare scenario must also be considered by healthcare professionals to avoid misdiagnosis or overlooking cases. Approximately 25% to 50% of patients with syphilitic heart disease have concomitant central nervous system syphilis, and about 50% of central nervous system syphilis patients have concurrent cardiovascular syphilis. Clinicians should be vigilant in their examinations to detect and diagnose these coexisting conditions [13].

3. Pathogenesis

The pathogenesis of syphilis involves the entry of Treponema pallidum into the human body through intact mucous membranes or damaged skin. During the primary stage of syphilis, despite the presence of a large number of pathogenic spirochetes locally, the bacteria have already invaded the lymph nodes and entered the bloodstream. From a pathophysiological perspective, within an hour of infecting the human body, the pathogens can enter lymph nodes, as well as various organs and tissues such as the heart, liver, lungs, joints, brain, and meninges, through lymphatic vessels. Some may also enter the arterial lymphatics and nourishing vessels of the aorta, causing chronic inflammation, narrowing, or blockage of nourishing vessels, which can lead to ischemia in the affected area [16]. Prolonged ischemia can lead to the gradual necrosis of the middle layer's elastic fibers and muscle fibers, followed by the formation of scar tissue, forming the basis for syphilitic aortitis. Syphilitic aortitis is essentially a form of chronic inflammation in the middle layer of the aorta, characterized by infiltration of plasma cells and lymphocytes, necrosis of middle layer muscle
and elastic tissue fibers, fibrous tissue proliferation, obliterative endarteritis, and potential calcification [13]. Lesions at the coronary artery openings are one of the pathological manifestations of syphilitic aortitis, which can lead to myocardial ischemia and eventually result in coronary heart disease.

Late-stage syphilis can also lead to coronary artery narrowing, which may be related to thickening of the aortic wall; approximately 26% of patients with arteritis experience involvement of the coronary arteries [14]. Coronary artery stenosis caused by syphilis should be considered as a form of aortic disease [15]. The pathological characteristics of syphilitic aortitis include obliterative endomorteritis of the blood vessels, accompanied by chronic inflammatory infiltration, ischemic necrosis, and fibrosis in the middle layer of the aorta. The longitudinal folds in the aortic wall may be caused by aortic scarring. This differs from the pathological outcomes of atherosclerosis [16].

Syphilitic aortitis, and even congenital narrowing, can potentially lead to coronary artery stenosis, with an incidence ranging from 0.13% to 2.7% among coronary heart disease patients [7]. In the case of patients with acute myocardial infarction (AMI) who have no personal history, family history, or risk factors for coronary atherosclerosis, especially those who exhibit coronary artery membrane lesions on coronary angiography or those without distal coronary artery lesions, vigilance for arteritis-related conditions is essential. Currently, the exact incidence of syphilitic aortitis is unclear, but a clinical pathological study of 100 cases showed that only 17% of patients were clinically diagnosed with syphilitic aortitis [9].

Aortitis: The hallmark of cardiovascular syphilis is aortitis, which is an inflammation of the aorta caused by the spirochete infection of the aortic media. This inflammation leads to subsequent damage and scarring.

Aortic Ring Dilatation and Valve Incompetence: The inflammation can cause dilatation of the aortic ring, leading to aortic valve incompetence. This can result in left ventricular hypertrophy as the heart works harder to pump blood through the damaged valve.

Aortic Root Dilatation and Aneurysm Formation: The inflammatory process can also lead to dilatation of the aortic root and the formation of aneurysms, which are bulges in the vessel wall that can rupture and cause life-threatening bleeding.

Coronary Artery Ostial Stenosis: Inflammation can extend to the coronary artery ostia, the openings where the coronary arteries branch off from the aorta, leading to stenosis (narrowing) of these openings. This can disrupt blood flow to the heart, potentially causing angina or myocardial infarction (heart attack).

Mucinous Myocarditis: In some cases, syphilis can cause mucinous myocarditis, which is an inflammation of the heart muscle that can affect the heart’s ability to pump blood effectively.

Vascular Endothelium Damage and Coagulation Activation: The arteritis associated with syphilis can damage the vascular endothelium and activate the coagulation mechanism, which may lead to myocardial dysfunction and infarction.


4. Clinical presentation

The fundamental alteration in syphilitic cardiovascular disease is aortitis, specifically syphilitic aortitis. This is the foundational lesion of syphilitic cardiovascular damage, and complications such as aortic regurgitation, coronary artery stenosis, and aortic aneurysm all stem from it. It accounts for 27% to 36% of cardiovascular syphilis cases and occurs in 70% to 80% of untreated syphilis patients [14]. It is most commonly found in the ascending aorta and is often discovered post-mortem, with an incidence as high as 85%. However, in the early to middle stages, patients often exhibit no obvious clinical symptoms or signs, making diagnosis challenging. Only a minority of patients may experience discomfort or dull pain in the precordial area or behind the sternum in the late stage, and very few may have significant pain. Physical examination may reveal accentuated second heart sounds or systolic murmurs in the aortic valve area. X-ray examination may show widening of the ascending aorta, occasional linear calcifications in the anterior or lateral walls of the ascending aorta. The electrocardiogram typically lacks specific changes. The symptoms, signs, and examination findings mentioned above are nonspecific, making clinical diagnosis of syphilitic aortitis quite challenging and posing a significant challenge for clinicians and radiologists. Fortunately, the advent of positron emission tomography/computed tomography (PET/CT) scans in recent years has provided new hope for early diagnosis [13].

Syphilitic aortitis can lead to coronary artery stenosis or occlusion, with an incidence of 25% to 30% in individuals with syphilitic cardiovascular disease [12]. It is relatively uncommon as a standalone condition and often co-occurs with syphilitic aortic valve insufficiency. Some studies have reported simultaneous left coronary artery stenosis and right coronary artery aneurysmal dilatation, leading to myocardial ischemia and presenting clinical symptoms similar to angina pectoris [17]. However, the onset of symptoms tends to occur at a younger age compared to typical coronary heart disease, with a predominance of nighttime episodes and longer durations. These symptoms are often less responsive to nitroglycerin. Electrocardiographic examination may reveal ST-segment depression and T-wave inversion.

5. Treatment and prognosis

Penicillin is the preferred choice for the treatment of syphilis, and the treatment plan is developed based on the stage of infection, symptoms, and whether other systems are affected. After high-quality analysis and research, it is
currently supported that intramuscular penicillin remains the best choice for syphilis treatment. Patients should be hospitalized for treatment. Before starting treatment, doctors must thoroughly assess the patient's condition, the location and severity of lesions, the presence of heart failure, severe cardiac dysfunction, and other conditions that may make immediate syphilis treatment unsuitable. If heart failure is present, it should be controlled before initiating treatment to avoid the occurrence of Jarisch-Herxheimer reactions [13].

In some syphilis patients, after receiving high-dose intramuscular penicillin for the first time, they may experience symptoms such as fever, chills, headache, dizziness, nausea, and vomiting within 24 hours (usually within 5-6 hours). At this point, it is often mistakenly thought to be a penicillin allergy. At the same time, the symptoms of syphilis worsen, especially in cardiovascular syphilis, neurosyphilis, or other visceral syphilis, which can lead to angina pectoris, heart failure, aortic rupture, or even death. This reaction is believed to be due to the release of antigens by the large number of treponemes killed by penicillin, leading to an immune response in the body. Therefore, pretreatment with prednisone and starting with a small dose of penicillin can help prevent Jarisch-Herxheimer reaction [13].

Patients with coronary artery stenosis may require surgical treatment, including coronary artery ostial dilatation and endarterectomy, coronary artery bypass grafting (CABG), and other procedures to improve myocardial blood flow.

For patients with simple coronary heart disease, emergency or elective percutaneous coronary intervention (PCI) is the primary treatment. However, for coronary artery stenosis caused by syphilitic vasculitis, CABG was more common in the past, but stent implantation has also been attempted in recent years. Currently, there is no unified standard for choosing the treatment method for coronary artery stenosis caused by syphilitic vasculitis [18]. Although in recent years, there have been reports of cases of cardiovascular syphilis patients undergoing syphilis treatment and PCI and then experiencing restenosis of stents after 13 months, as well as cases with good prognosis after syphilis treatment and CABG followed by a 1-year follow-up. However, these are all individual case reports, lacking large-scale studies to discuss which treatment method, PCI or CABG, provides a better prognosis.

Postoperative patients require oral anticoagulants and medications to stabilize plaques. The above treatments should be combined with syphilis treatment and tailored to the patient's condition to improve other accompanying symptoms. Telephone follow-up is conducted to monitor the occurrence of major adverse cardiovascular events (MACE) in all patients. It has been observed that patients with cardiovascular syphilis and concomitant coronary heart disease have a higher incidence of MACE due to aortic root widening, aortic regurgitation, and more severe coronary artery lesions, indicating a poor prognosis for this patient group [18].

6. Additional information

Application of Thromboelastography (TEG) in Conjunction with Routine Coagulation Tests to Evaluate Coagulation and Platelet Function in Coronary Heart Disease Patients with Syphilis: It has been found that the endogenous coagulation and platelet function, as well as the response to antiplatelet drugs, in coronary heart disease patients with syphilis are comparable to those in patients with coronary heart disease alone when assessed using TEG in combination with routine coagulation tests [19].

Analysis of Coronary Artery Calcification and Aortic Regurgitation in 133 Cases of Coronary Heart Disease with Positive Syphilis Serology: A retrospective analysis of 133 cases of coronary heart disease patients with positive syphilis serology revealed that the probability of aortic calcification and aortic regurgitation in patients with coronary heart disease and syphilis was significantly higher than in those with coronary heart disease alone. Moreover, the ascending aortic diameter was significantly larger in patients with coronary heart disease and syphilis compared to those with coronary heart disease alone. However, there were no significant differences in coagulation parameters, prothrombin time, international normalized ratio, activated partial thromboplastin time, and TEG-related indices between the two groups of patients [19].

7. Conclusion

In recent decades, the resurgence of syphilis has been linked to changes in people's lifestyles and increased population mobility, resulting in a rapid upward trend in the incidence of syphilis. Syphilis is characterized by its insidious progression, often only being diagnosed as a late-stage disease when complications affecting organs such as the cardiovascular and nervous systems occur. The damage to tissues and organs caused by infection with syphilis spirochetes is ongoing, and while there may be a hidden process of damage before organ damage becomes evident, these injuries have not yet exceeded the compensatory capacity of the organs, and therefore, no significant symptoms have appeared.

Currently, there is relatively more research in China on syphilis-induced cardiovascular diseases, but there is less research on whether early and latent syphilis has a related impact on the occurrence and development of cardiovascular diseases and whether it has adverse effects on patient prognosis. Therefore, more research is needed to clarify the relationship between early and latent syphilis and cardiovascular diseases. Once diagnosed with syphilitic cardiovascular disease, treatment is essential. However, for coronary artery lesions caused by syphilis, there is currently no literature reporting the benefits of choosing percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) for treatment, and further research is needed to determine the optimal treatment strategy.
In summary, research on syphilitic cardiovascular disease is still in its early stages, and with the increasing incidence of syphilis, the demand for research on the pathogenesis, clinical characteristics, diagnosis, treatment, and prognosis of this disease will become more urgent. This will help improve early diagnosis and treatment outcomes, reducing adverse consequences for patients.

Reference


