CARDIAC INVOLVEMENT IN SARCOIDOSIS

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Abstract: *Sarcoidosis is an inflammatory systemic disease defined by the presence of noncaseating epithelioid granuloma. The aetiology is multifactorial, environmental and genetic factors competing in generating the immunological reactions that are responsible for the tisular lesions in sarcoidosis. The diagnosis of cardiac sarcoidosis can be extremely difficult when other sites of involvement are lacking. There are no specific diagnostic or screening tests for this disease besides demonstrating the presence of noncaseating epithelioid granulomas on endomyocardial biopsy specimens (rarely used). Delayed-enhanced magnetic resonance imaging and positron emission tomography proved to have the best sensibility and specificity in detecting and evaluating the effects of steroid therapy in cardiac sarcoidosis. Early diagnosis and initiation of corticotherapy are essential for improving the long term prognosis of this disease.*

Keywords: *cardiac sarcoidosis, early diagnosis, delayed-enhanced magnetic resonance imaging, positron emission tomography, corticotherapy*

Rezumat: *Sarcoidoza este o afecţiune sistemică inflamatorie, caracterizată prin prezenţa granulomului epitelioid necazeificat. Etiologia este plurifactorială, factori ambientali şi genetici concurând în generarea unor reacţii imunologice responsabile de alterările tisulare prezente în sarcoidoză. În lipsa altor manifestări sistemice, diagnosticul sarcoidozei cardiace poate fi extrem de dificil. În afara evidenţierii granulomului sarcoid prin biopsie endomiocardică (practicată rar), nu există un test diagnostic sau metode de screening specifice acestei boli. Rezonanţa magnetică nucleară cu amplificare tardivă şi tomografia cu emisie pozitronică s-au dovedit a avea cea mai mare sensibilitate şi specificitate în diagnosticul precoce şi monitorizarea evoluţiei sub terapie a sarcoidozei cardiace. Diagnosticul şi instituirea precoce a corticoterapiei sunt esenţiale în vederea îmbunătăţirii prognosticului pe termen lung al acestei afecţiuni.*

Cuvinte cheie: *sarcoidoză cardiacă, diagnostic precoce, rezonanţă magnetică nucleară cu amplificare tardivă, tomografie cu emisie pozitronică, corticoterapie*

Sarcoidosis is a multisystemic disease of unknown aetiology that affects mainly the young adult and which, in most of the cases, presents with bilateral hilar adenopathy, pulmonary infiltrates and ocular and skin lesions but any other organ may be involved. The diagnosis is established when clinical and imagistical findings correlate with histological evidence of noncaseating epithelioid granuloma.(1)

The first case of cardiac sarcoidosis was described by Bernstein et al. in 1929.(2) Though relatively rare, cardiac involvement in sarcoidosis is of a major importance because of its grim prognosis and difficulties of diagnosis it implies.

Sarcoidosis is an ubiquitary disease with a highly variable incidence depending on age, sex, race and geographical area, that is established to be about 16,5‰ for men and 19‰ for women.(3) In Romania the prevalence of sarcoidosis is appreciated to be about 4‰.(4) In necropsy studies, cardiac involvement in sarcoidosis varies between 20 – 30%.(5) Cardiac sarcoidosis is more frequent in Japanese population, affecting particularly the women aged over 50 years. Only about 5% of cardiac sarcoidosis cases have a clinical expression, the rest having an asymptomatic course.(6) By now, the aetiology of sarcoidosis remains unknown, multiple factors being incriminated in the determinism of this disease. The most accepted hypothesis suggests that some (unknown) environmental or infectious antigens could trigger an exaggerated immune reaction in genetically susceptible hosts. The various incidence of sarcoidosis in different ethnic groups and familial aggregation reported cases sustain the hypothesis of the genetic factor.

In present, is considered to be as a pathogenetic mechanism in sarcoidosis an abnormal immune response to certain antigens that involves antigen-presenting cells, T helper lymphocytes (particularly T_{H1} lymphocytes), cytokines and chemokines that play a role in local cellular recruitment and in the development of sarcoid granuloma. In essence, the modulation of the immune reaction in the sites involved depends on the local balance between T helper and T suppressor lymphocytes: T helper amplify and T suppressor attenuate the cellular immune processes.(4)

Recent studies have established a correlation between a mutant gene – BTNL2 – and sarcoidosis. Butyrophilin-like 2 (BTNL2) gene, located on the

chromosome 6 in the class II major histocompatibility complex (MCH) region, encodes a protein related to B_7 costimulatory molecules family which function as secondary signals in the activation process of T lymphocyte as well as in the modulation process of T-cell tolerance.(7,8) Some of these molecules function as negative signals, decreasing T-cell response and playing an important role in T-cell tolerance regulation while others function as positive secondary signals, up-regulating T-cell activation. An efficient immune response depends on the balance existing between the positive and negative costimulatory molecules. The protein encoded by BTNL2 gene acts as a negative secondary signal in T-cell activation. BTNL2 mutation results in a nonfunctional protein, tilting the balance in favour of positive costimulatory molecules and determining thus an exagerated activation of T-cell.[9] Recently, it has been reported an isolated cardiac sarcoidosis case in which was demonstrated the presence of mutant BTNL2 gene.(10) However, it has not been established that this genetic disorder would represent a risk factor for isolated cardiac sarcoidosis.

Other studies suggest there is an association between sarcoidosis and the allelic variation at the HLA-DRB_1 locus.(11) Also, in some groups of patients was recorded a genetic predisposition in producing high levels of TNF_α that could play a role in the immune processes in sarcoidosis.(12) Anyway, it is obvious there is a polygenic determinism in sarcoidosis and the studies on this field are only at the beginning.

From the clinical point of view, cardiac involvement may occur at any point in the course of the systemic disease. Cardiac sarcoidosis may evolve isolated (without lung or other organs involvement) or may be the initial presentation. Spectrum of clinical manifestations is wide and unspecific, varying from the asymptomatic presence of noncaseating epithelioid granulomas, conduction disturbances (AV blocks, bundle brunch or fascicular blocks), atrial/ventricular arrithmias, mitral insufficiency, ventricular aneurysm, pericarditis to congestive heart failure. Not very seldom, sudden death occurs as the debut modality of the disease.(13)

The diagnosis of cardiac sarcoidosis may be extremely difficult, especially when other sites of involvement are lacking. Cardiac sarcoidosis diagnosis is confirmed when noncaseating epithelioid granulomas are evidentiated on the endomyocardial biopsy specimens. Yet, due to its highly invasive character and, especially, because of the unhomogeneous distribution of the sarcoid granulomas in cardiac structures that leads to an evidentiation of the noncaseating epithelioid granulomas in less than 25% of cases, this diagnostic method is very rarely used.(14) The present criteria for the diagnosis of cardiac sarcoidosis are those established by the Japanese Ministry of Health and Welfare in 1993. (table no. 1)

As for the imagistic diagnosis of cardiac sarcoidosis, many studies have demonstrated that Gadolinium delayed enhanced magnetic resonance imaging and positron emission tomography (^{18}F-FDG PET) have the highest sensibility and accuracy in the early diagnosis and in monitorization of evolution under treatment of cardiac sarcoidosis, proving to be highly superior to scintigraphic techniques (^{201}Ta perfusion scintigraphy, ^{67}Ga or ^{99m}Tc captation scintigraphy).[15,16,17,18] However, these investigations are limited by high costs and reduced availability. Cardiac ischemic disease is important to be excluded when establishing the diagnosis of cardiac sarcoidosis and this is possible by performing a coronary angiography.

Table no. 1. The Japanese Ministry of Health and Welfare Diagnosis Guidelines for Cardiac Sarcoidosis (1993)

Diagnosis guidelines for cardiac sarcoidosis	
Histological criteria	Emphasis of noncaseating epithelioid granulomas on the endomyocardial biopsy specimens
Clinical criteria	Emphasis of noncaseating epithelioid granulomas in an extracardiac site of involvement plus item (a) and ≥ 1 of items (b) – (e)
	(a) EKG: complete right bundle brunch block, left axis deviation, AV block, ventricular tachycardia, premature ventricular contractions (> 2 gr. Lown), abnormal Q or ST-T changes
	(b) Echocardiography: abnormal wall motion, regional wall thinning or dilatation of the left ventricle
	(c) Scintigraphy: perfusion defects by ^{201}Ta myocardial scintigraphy, abnormal accumulation by ^{67}Ga or ^{99m}Tc myocardial scintigraphy
	(d) Cardiac catheterisation: abnormal intracardiac pressure, low cardiac output, abnormal wall motion, depressed ejection fraction of the left ventricle
	(e) Myocardial biopsy: interstitial fibrosis or cellular infiltration (even if these findings are nonspecific)

Without treatment, cardiac involvement in sarcoidosis has a grim long-term prognosis. Sudden death and congestive heart failure are the most feared complications these patients confront with. There are no studies to certify the long-term efficacy of a certain therapeutic scheme but it was demonstrated that early diagnosis and early and long-term administration of corticosteroids, before systolic dysfunction occurs, substantially improve the clinical outcome. Some studies suggest that beginning the therapy with low doses of prednisone would practically have a similar effect as administrating a high initial dose of corticosteroid.(19)

In conclusion, cardiac sarcoidosis is a rare disease but, due to its unspecific manifestations and diagnostic difficulties, it can determine a high rate of

mortality in these patients.

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