

Cardiac Remodeling During the Morphogenesis of Neuroleptic Cardiomyopathy



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Abstract

Introduction: A neuroleptic cardiomyopathy NCMP belongs to secondary specific metabolic dilated cardiomyopathies. It is caused by side cardiotoxic effect of antipsychotic preparations. In its development NCMP passes three clinical stages: 1) latent, 2) developed and 3) terminal.

Aim: A morphometric study of the macroscopic heart condition in each clinical stage of NCMP.

Material and methods: The autopsy protocols of 80 dead persons with NCMP in various stages and of 100 persons who did not have any accompanying cardiac pathology were studied. For analysis of the received data the original author's method that we had developed for such studies was used.

Results: All macroscopic cardiac parameters in the case of NCMP statistically significantly differ from normal one, but no significant differences in various clinical stages of NCMP.

Conclusion: The process of cardiac remodeling on the organ level ends during the latent stage of the disease. Progression of myocardial dysfunction is connected with changes of myocardium microstructure.

Keywords: Neuroleptic cardiomyopathy; morphogenesis; remodeling of a heart; morphometric research

Introduction

Neuroleptic cardiomyopathy (NCMP) is one of serious vitally dangerous complications of psychotropic therapy, with is caused by a side cardiotoxic effect of antipsychotic drugs, as classical, and atypical [1-9]. This disease belongs to secondary specific metabolic dilated cardiomyopathies [10,11] and is characterized by a diffuse myocardial involvement, by a drastic reduction of its contractile function and, as consequence, by a progressive congestive chronic heart failure (CHF) [1,10,12,13]. In its development NCMP passes three clinical stages: 1) a latent one, clinically fully compensated one, 2) a full-scale (developed. manifesting) one, when cardiac disorders are clearly detected, but without evident signs of CHF, and 3) a terminal one, when the clinical picture of CHF comes to the foreground [10,14]. As you know all changes of function of some or other organs, especially the heart, are initially caused by it structural changes which are a physical substrate of pathophysiological shifts and reflect the morphogenesis of a pathology [15]. During the

morphogenesis of NCMP, the heart undergoes a remodeling process at the macroscopic (organ) level of the organization. As L a Bokeria and co-authors (2010) [16] point out, initially the remodeling of the heart in any pathology has a compensatory-adaptive nature, aimed at preserving the pumping function of the heart. However, with the development of the disease compensatory capabilities of the heart are exhausted, there is a failure of adaptation, and manifests myocardial dysfunction. But until now, a deep comparative morphological study of the macroscopic heart condition in each clinical stage of NCMP, including those associated with the process of remodeling, has not been conducted. Therefore, the aim of this study is to eliminate – at least in part – the existing gap.

Material and Methods

The autopsy protocols of 80 dead persons in the age from 16 to 77 years (60 men and 20 women) were studied, in which the NCMP

was revealed by section. In 36 of these patients the disease was in the latent stage (group II), in 15 patients it was in the developed one (group III), and in 29 patients it was in the terminal one (group IV). As a control, we studied the autopsy protocols of 100 persons (50 men and 50 women) in the age from 18 to 82 years who died from non cardiac causes and who did not have any accompanying cardiac pathology and this fact was verified by autopsy (group I). The cardiac parameters, which were received in this group, are taken as a relative norm (RN).

The following parameters were measured on the macroscopic level: heart mass (m), linear dimensions, perimeter of venous valve openings, and thickness of a wall of ventricles. For analysis of the received data we used an original method that we had developed for such studies [17]. For this analysis the outer volume of heart without atria (V) was determined and two relative parameters (both in percent) were calculated: 1) C_v - coefficient of volume, this coefficient shows a part of the total volume of heart (without atria), and this part falls on the volume of cavities of ventricles; and 2) C_l - coefficient of the left ventricle, this coefficient shows the volume size of the left ventricle with respect to the total volume of both ventricles. In addition, two other parameters were calculated which use a gravimetric characteristic of the heart (m): mass-volume ratio (MVR) and index of density of myocardium (IDM). A growth of MVR is evidence of a hypertrophy of myocardium, and its diminution is an indication for dilatation of cavities of heart ventricles. IDM clearly shows a strongly expressed correlation with such objective parameters of microstructure of cardiac muscle as stromal-parenchymatous ratio and rate of interstitial edema [17], which quantitatively describe a condition of its intercellular matrix. The received results were statistically processed by the nonparametric Mann-Whitney's U-criterion with significance level of distinctions 95% and more ($p \leq 0.05$).

Results

Table 1: Macroscopic characteristic of heart during NCMP morphogenesis.

Gr.	m	V	Kv	Kl	MVR	IDM
I	300	131.6	32.1	39.1	2.28	4.42
II	355 1	163.5 1	41.4 1	40.2	2.17	6.06 1
III	358 1	165.8 1	42.6 1	40.3	2.16 1	6.24 1 2
IV	361 1	167.5 1	43.2 1	40.6 1	2.15 1	6.36 1 2 3

Note: 1 – statistically significant distinctions with gr. I.

2 – statistically significant distinctions with gr. II.

3 – statistically significant distinctions with gr. III.

The results of research which has been conducted on the organ level are presented in the Table 1. As follows from its analysis, all macroscopic cardiac parameters in the case of NCMP statistically significantly differ from RN. At the same time, no significant differences of m, V and MVR were found in various clinical stages of NCMP. The dynamics of value C_v have the same character. At the same time, the values C_l differs from RN only in the terminal stage of NCMP, and to a significantly lesser degree than C_v . Changes of IDM are the most important ones. The values of this parameter grow already in the latent stage of NCMP (group II) and steadily progress later on.

Discussion

On the basis of analysis of detected cardiac changes, which take place in the process of remodeling of the heart in different clinical stages of NCMP, the morphogenesis of the disease seems to be the following. In the case of NCMP the cardiomegaly develops already during the latent stage of the disease and does not distinctly progress subsequently. This is proved by the absence of significant differences of m, V and MVR in different clinical stages of NCMP. At the same time, changes of C_v and C_l tell about a uniform dilatation of both heart ventricles with some predominance of the left one, only in the late phases of NCMP morphogenesis (terminal stage). On the contrary, an initially progressive growth of IDM tells about the developing damages of myocardium microstructure, in particular, about changes of its intercellular matrix.

Thus, the received data are evidence of the fact that the process of the cardiac remodeling, which takes place in the course of NCMP development on the organ level, ends when the disease passes to the full-scale stage. Further progression of a myocardial dysfunction leads to the development of CHF and is determined by the growing changes of microstructure of cardiac muscle. In other words, appearance of clinical manifestations of NCMP is accompanied by transition of cardiac remodeling to the deeper (tissue and cellular) organizational levels. This thesis is confirmed and convincingly proved by results of morphometric research of myocardium microstructure changes in various stages of NCMP morphogenesis, which correspond to the clinical stages of the disease course [18-20]. Though, as they say, it is a completely different story.

Conclusion

The conducted research has proved that in the course of NCMP morphogenesis cardiac remodeling on the organ level is observed. In the latent stage of the disease the macroscopic cardiac remodeling reflects the compensatory-adaptive processes which are directed towards preservation of the pumping function of a heart. The full-scale stage of NCMP is characterized by termination of remodeling on the organ level, and the further progression of myocardial dysfunction, which is to the maximum expressed in the

terminal stage of the disease, takes place because of the pathologic changes of myocardium.

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