

## Morphogenesis of Neuroleptic Cardiomyopathy in Morphometric Light

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### Abstract

**Aim:** A comparative morphometric study of heart condition on the organ level of its organization in each clinical stage of neuroleptic cardiomyopathy.

**Methods and Results:** In compliance with the modern requirements of evidential medicine the morphometric method of a research differing in objectivity and high informational content is used. For analysis of data from organometry of heart an own original method was used. It was found that on the organ level the process of cardiac remodeling ends during the latent stage of the disease. Progression of myocardial dysfunction is connected with the changes.

**Conclusion:** During the morphogenesis of an antipsychotic cardiomyopathy a certain definition of the stage of clinical manifestations of a disease corresponding to the remodeling of the heart at the organ level is observed.

**Keywords:** *Neuroleptic cardiomyopathy; Morphogenesis; Remodeling of heart; Organ level; Morphometric research*

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### Introduction

Neuroleptic cardiomyopathy (NCMP) due to the cardiotoxic side effect of antipsychotic medicines is one of the most serious and life-threatening complications of psychotropic therapy [1-4].

NCMP passes through 3 stages in its development: 1) a latent one, clinically fully compensated one, 2) a full-scale one, when cardiac disorders are clearly detected, but without evident signs of CCF, and 3) a terminal one, when the clinical picture of a progressive congestive chronic cardiac failure (CCF) comes to the foreground [5-7]. It is well-known that all changes of function of some or other organs, tissues and cells are initially caused by their structural damages which are a physical substrate of pathophysiological shifts [8]. It follows from this thesis that various cardiac disorders in patients with NCMP, which are characteristic for a certain stage of the disease, are based on morphologic changes of heart on various organizational

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levels (organ, tissue, and cellular one), and these changes reflect the morphogenesis of this pathology. But until now, a deep comparative morphological study of heart condition on each of the before-named levels and in each clinical stage of NCMP has not been performed.

The aim of the present study is to eliminate - at least, partially - the existing gap regarding the organ level of organization of the heart.

### **Material and Methods**

According to the modern doctrine of morphology as a science, a merely descriptive method of research is not enough for a correct and objective characteristic of pathologic changes being observed; it is strongly necessary to use objective criteria of functional morphology [9,10] and to be guided by the principle of unity of pathology on various research levels; this principle was postulated by Avtandilov GG [10] in the past.

Therefore, it seems actual to research a morpho functional condition of heart in patients with NCMP by use of morphometric research methods which meet modern requirements of the evidence-based medicine [11,12] and allow to objectivize the received results and the made conclusions, because final values of the parameters, which are studied, have the quantitative form and can sufficiently easily be analyzed statistically [9,10].

At the same time, it is known that a quantitative morphologic characteristic of changes of each organ in the case of its any pathology should start with a specific landmark; this concept is so-called the norm [13].

Therefore, at the research beginning the results of autopsy protocols of 100 persons (50 men and 50 women) in the age from 18 to 82 years were analyzed who not have a concomitant cardiac pathology and died of non-cardiac causes (group I). The obtained in this group cardiac parameters were taken as relative norm (RN). Then 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 full-scale stage (group III), and in 29 patients it was in the terminal stage (group IV). The final diagnosis of each deceased was verified at the autopsy.

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 what we had developed for such studies [14]. For this analysis the outer volume of heart without atria (V) was determined and two relative parameters (both in percent) were calculated: 1) Cv - 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) Cl - 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 (SPR) and rate of interstitial edema (RIE) [14], which quantitatively describe a condition of its intercellular matrix.

The obtained quantitative results were processed statistically by the nonparametric Mann-Whitney's U-criterion with the level of significance of differences of 95% and more ( $p \leq 0.05$ ).

## Results

In the (Table 1) the results of research are presented which has been conducted on the organ level. Analyzing the data of this table it is possible in the case of the NCMP to detect statistically authentic differences from the PH of all macroscopic parameters of the heart.

At the same time, no significant differences of m, V and MVR were found in various clinical stages of NCMP. The dynamics of values Cv has the same character. At the same time, the values CI differs from RN only in the terminal stage of NCMP, and to a significantly lesser degree than Cv. 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 on the organ level of organization of the heart in different clinical stages of NCMP, the morphogenesis of the disease seems to be the following.

The cardiac remodeling in the form of cardiomegaly due to ventricular hypertrophy and dilatation develops already during the latent stage of NCMP and does not progress clearly in the future.

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 Cv and CI 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 progredient growth of IDM tells about the developing damages of myocardium microstructure, in particular, about changes of its intercellular matrix [14].

So, the received results of the study show that the remodeling of the heart at the organ level that occurs during the morphogenesis of NCMP practically comes to an end when the disease goes into a full-scale stage.

Further progression of a myocardial dysfunction leads to the development of CCF and is determined by the growing changes of microstructure of cardiac muscle.

In other words, the manifestation of the clinic of NCMP marks the transition of cardiac remodeling to the deeper, that is tissue and cellular, levels of its organization.

## Conclusion

In the latent stage of the disease, the macroscopic cardiac remodeling reflects the compensatory-adaptive processes which are directed towards preservation. The full-scale stage of NCMP is characterized by termination of remodeling on the organ level, and the further progredient 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, what leads to a fatal CCF.

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