

On the Question of the Timing of Development of Neuroleptic Cardiomyopathy

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Abstract

By a morphometric method of research the macroscopic changes of the heart in the process of antipsychotic therapy and in neuroleptic cardiomyopathy was determined. The aim of this work was to study an issue about the timing of this disease. The analysis of the obtained results shows that the risk of development of severe iatrogenic complications – NCMP, which is due to the side cardiotoxic effects of antipsychotic drugs, increases abruptly after ten years of psychotropic treatment.

Keywords: antipsychotics, cardiotoxicity, duration of antipsychotic therapy, neuroleptic cardiomyopathy, pathomorphology of heart, organ level of organization, morphometry.

INTRODUCTION

It is known that neuroleptic cardiomyopathy (NCMP) due to cardiotoxic side effects of antipsychotic (neuroleptic) drugs is perhaps the most serious and life-threatening complication of long-term psychotropic (antipsychotic) therapy (APT) [1–4]. However, the timing of the disease is still not specified.

Therefore, the aim of this work was to study this issue using the morphometric method of heart research at the macroscopic level of its organization.

MATERIAL AND METHODS

The use of morphometric methods to study the morphofunctional state of the heart is relevant, since it is believed that morphometric methods of research meet the modern requirements of evidence-based medicine [5, 6] and allow to objectify the results and conclusions, since the final values of the parameters under study are quantitative and easy enough to be statistically analyzed [7, 8].

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 [9]. 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).

To characterize cardiac changes in NCMP at the macroscopic level, cardiac organometry was performed in 80 deceased patients with schizophrenia (60 men and 20 women; age from 16 to 77 years), who suffered during the life of NCMP, verified at autopsy.

In addition, to study the effect of the duration of APT on the morphology of the heart the autopsy protocols of 70 patients with schizophrenia (41 men and 29 women) who died at the age from 22 to 77 years were analyzed. The final diagnosis of each deceased was verified at the autopsy.

The criteria of an exception were the expressed signs of a metabolic syndrome (the increased body weight, arterial hypertension, a diabetes mellitus), a chronic pulmonary pathology with hypertension in a small circle of blood circulation, a cachexia.

During their lives the patients received various antipsychotics in quantities corresponding to the therapeutic standard; these medicines are not rarely

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received in combination with each other. The duration of APT ranged from six months to 30 years or more. Depending on the duration of the APT material is divided into four groups (III–VI): III – up to ten years (20 dead); IV – from 11 to 20 years (25); V – from 21 to 30 years (19); VI – over 30 years (6).

The original author's method developed by me for such studies [10] was used for the analysis of the obtained data.

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 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 [10], which quantitatively describe a condition of its intercellular matrix.

The obtained quantitative results were processed statistically (computer program "Statistica 6.0") with the level of significance of differences of 95% and more ($p \leq 0.05$).

RESULTS

Macroscopic changes of the heart at NCMP and in the process of APT are presented in table. 1.

Table 1. Macroscopic cardiac changes at NCMP and in APT

Indicators Groups	m	V	C_v	C_l	MVR	IDM
I	300±3 2-6	131,6±6,1 2-6	32,1±0,5 2-6	39,1±0,6 2,4-6	2,28±0,04 2,4-6	4,42±0,08 2-6
II	359±10 1,3	165,4±6,8 1,3	42,1±1,1 1,3,6	40,3±0,6 1	2,17±0,04 1,3	6,20±0,14 1,3
III	317±7 1,2,4-6	141,4±5,4 1,2,4-6	34,5±0,6 1,2,4-6	39,7±0,6 5	2,24±0,04 2,4-6	4,57±0,08 1,2,4-6
IV	355±8 1,3	163,5±5,8 1,3	41,4±0,4 1,3,5,6	40,2±0,5 1	2,17±0,04 1,3	6,06±0,07 1,3,5,6
V	359±8 1,3	166,7±6,3 1,3	42,6±0,5 1,3,4,6	40,4±0,4 1	2,15±0,04 1,3	6,29±0,04 1,3,4,6
VI	364±5 1,3	168,7±6,3 1,3	43,8±0,6 1-4	40,8±0,4 1,3	2,16±0,03 1,3	6,38±0,06 1,3,4,5

Note: 1-6 – statistically significant differences between the groups

DISCUSSION

The analysis of the obtained results shows that in case of NCMP at the organ level of the heart study, statistically significant differences with RN in all studied morphometric parameters are found. The noted pathomorphological changes in the organometric parameters of the heart, reflecting the process of its remodeling in the development of NCMP, are briefly summarized as follows.

In NCMP, compared with RN, there is a noticeable increase in **m** and a pronounced dilation of the heart

cavities, primarily the ventricles. This is documented by increasing the values of **m**, **V**, and C_v . The C_l index also exceeds the RN, but the severity of this process is an order of magnitude lower, which indicates a fairly uniform expansion of both ventricles with some slight predominance of left dilation.

On the contrary, in contrast to the considered indicators, the values of **MVR** in NCMP are slightly reduced, indicating a certain predominance of the rate of expansion of the heart over its hypertrophy.

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The dynamics of changes in the **IDM** values, which in NCMP significantly exceed the level of RN, indirectly reflects the development of pathological processes in the myocardial stroma [10], which is confirmed by its microscopic examination.

The study of macroscopic parameters of the heart and the indices calculated on their basis observed in the process of APT showed the change of all these values. Moreover, in a relatively early period of treatment (group III) from RN statistically significantly different four of the six indicators (excluding C_1 and **MVR**). In the future, that is, ten years after the start of APT, these differences relate to all the studied organometric parameters, which allows us to consider the ten-year period of APT as a certain threshold, upon reaching which the increasing quantitative macroscopic changes in the heart pass into a new quality.

Such a circumstance should also be noted. With a sufficiently long (over 20 years) use of AD (group V–VI), 2/3 of macroscopic parameters, except for C_v and **IDM**, remain practically constant. It turns out that in the first ten years of APT changes of the heart at the organ level develop gradually, and then quickly reach almost maximum. Subsequently, they continue in the same direction, but only at the level of the trend.

This applies primarily to parameters such as **m** and **V**, which increase in the described rhythm is very significant (growth is respectively 21.3% and 28.2%), which indicates the development of cardiomegaly during APT. Moreover, the process of dilation in comparison with the phenomena of cardiac hypertrophy prevails to a certain extent, as evidenced, firstly, by a higher lability **V** compared to **m** and, secondly, even if not very pronounced, but progressive decrease in the values of **MVR** [10].

The ventricles of the heart are mainly subject to expansion, which is documented by a steady and significant increase in C_v (growth reaches 36.4%).

The index of C_1 also increases, but the intensity of the dynamics of this process is almost an order of magnitude lower than that of C_v (growth only 4.3%). This documents a more or less uniform expansion of both ventricles with only some predominance of left dilation only in the later stages of APT.

Most notably a steady increase in the values of **IDM** in relation to which the growth ultimately translates to

44.3%. This fact indirectly reflects the development of significant stromal myocardial changes [10] occurring at the microscopic level in conjunction with other pathological changes.

Having received data on organometric changes of the heart in NCMP and in the process of APT, we came up to the main goal of the study – to determine the approximate timing of taking antipsychotics, in which there is a threat of the development of such a severe iatrogenic pathology as NCMP. To do this, we consistently compare these changes in the NCMP (group II) with those in different periods of APT (group III–VI).

The analysis carried out in this direction shows that the differences between groups II and III are statistically significant in the vast majority of indicators. At the same time, there are no differences in the parameters in group II compared to those in subsequent groups of observations. In other words, the organometric changes of the heart observed during its remodeling in the morphogenesis of NCMP and after ten years of APT are almost identical. This once again shows that the ten-year period of taking antipsychotic drugs can be considered as a kind of borderline at which the growth of quantitative macroscopic changes in the heart pass into a new quality – the development of NCMP.

CONCLUSION

Organometric approach to the study of the heart at different periods of APT showed that the risk of development of severe iatrogenic complications – NCMP, which is due to the side cardiotoxic effects of antipsychotic drugs, increases abruptly after ten years of psychotropic treatment.

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