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Morphological Changes of A Heart in Antipsychotic Therapy

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Abstract

In the process of antipsychotic therapy the pathomorphology of the heart at the macro-and microscopic level of its organization was studied. Own morphometric method of research were applied. The macroscopic changes in the organ develop gradually during the first ten years of treatment, after which do not progress. In the future changes in the myocardial microstructure come to the fore. After 20 years of the treatment these changes become irreversible.

Keywords:antipsychotics; cardiotoxicity; duration of antipsychotic therapy; pathomorphology of heart; organ, tissue andcellular levels of organization; morphometry.

1. INTRODUCTION

It is known that all antipsychotics (AP) have a side cardiotoxic effect. [1–3]. However, the morphological changes of the heart at different levels of its organization (organ, tissue, cellular), developing in APT, practically not studied.

Currently, it is believed that the morphometric method of studying the heart, both in normal and pathological conditions, is quite adequate and promising, consistent with the principles and approaches of evidence-based medicine [7, 8]. With its help, objective results can be obtained and reasonable conclusions can be made, since the studied quantitative indicators can be evaluated statistically with a high degree of reliability [5, 6].

Based on the above, the purpose of the study was defined, namely – to study macroscopic changes of the heart and pathomorphological shifts in the myocardial microstructure, using the original author's method and its own algorithm of the morphometric research [9–11]

2. MATERIAL AND METHODS

The Interventional evaluation predicting the Oddi sphincter Before carrying out any quantitative morphological study of any organ in various diseases, it is necessary to establish the reference values of the studied parameters, which fit into the concept of a relative norm (RN) [4].

For this purpose, the morphometric parameters of the heart of 100 individuals (50 men and women each, age 18–82 years) who died of non-cardiac causes and had no heart disease were initially studied. The obtained data are taken for RN.

Then autopsy protocols of 70 deceased patients with schizophrenia (men – 41 and women – 29, age 22–77 years) which from six months to 30 years received various AP were analyzed. The final diagnosis of each deceased was verified at the autopsy.

Depending on the duration of the antipsychotic therapy (APT) material is divided into four groups (II–V): II – up to ten years (20 dead); III – from 11 to 20 years (25); IV – from 21 to 30 years (19); V – over 30 years (6).

The following organometric 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) 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) [9], which quantitatively describe a condition of its intercellular matrix.

In the manufacture of histological preparations of the myocardium from different parts of the wall of the left ventricle of the heart, paraffin filling and staining with hematoxylin-eosin were used. The method of point counting and measurement of objects with an eyepiece-micrometer were used [11, 13, 16]. Parameters were determined and coefficients characterizing the state of such structural compartments of the heart muscle as the microcirculatory bed, extracellular matrix and cardiomyocytes (CMC's) were calculated. These indicators include the following: 1) zone of pericapillary diffusion (ZPD), 2) Kernogan index (KI), (RIE), 5) specific volumes of pools of such CMC's as hypertrophied (SVHC), atrophied (SVAC) and dystrophic (SVDC).

Statistical processing of quantitative results was carried out using the computer program "Statistica 6.0 – the level of significance of differences from 95% ($P \leq 0.05$).

3. Results and Discussion

Macroscopic changes of the heart in the process of APT are presented in Table. 1.

Table 1: Macroscopic cardiac changes in APT.

Indica-tors / Groups	m	V	$К_о$	$К_л$	МОС	ИПМ
I	300±3 2–5	131,6±6,1 2–5	32,1±0,5 2–5	39,1±0,6 3–5	2,28±0,04 3–5	4,42±0,08 2–5
II	317±7 1, 3–5	141,4±5,4 1, 3–5	34,5±0,6 1, 3–5	39,7±0,6 5	2,24±0,04 3–5	4,57±0,08 1, 3–5
III	355±8 1,2	163,5±5,8 1,2	41,4±0,4 1,2,4,5	40,2±0,5 1	2,17±0,04 1,2	6,06±0,07 1,2,4,5
IV	359±8 1,2	166,7±6,3 1,2	42,6±0,5 1–3,5	40,4±0,4 1	2,15±0,04 1,2	6,29±0,04 1–3,5
V	364±5 1,2	168,7±6,3 1,2	43,8±0,6 1–4	40,8±0,4 1,2	2,16±0,03 1,2	6,38±0,06 1–4

Note: 1-5 - statistically significant differences between the groups.

The study of macroscopic parameters of the heart and the indices calculated on their basis showed the change of all these values observed in the process of APT. Moreover, in a relatively early period of treatment (group II) from relative norm statistically significantly different four of the six indicators (excluding Cl 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 AP (group IV–V), 2/3 of macroscopic parameters, except for Cv 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 (an increase in an indicator such as MΔ, showing the magnitude of the difference with RN, 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 [9].

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

The index of Cl also increases, but the intensity of the dynamics of this process is almost an order of magnitude lower than that of Cv (MΔ 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 MΔ ultimately translates to 44.3%. This fact indirectly reflects the development of significant stromal myocardial changes [9] occurring at the microscopic level in conjunction with other pathological changes.

The results of the morphometric study of myocardial changes observed in the process of APT are presented in table 2.

Table 2: Morphometric parameters of myocardium in APT.

Indicators / Groups	Microvasculature		Intercellular matrix		Cardiomyocytes		
	ZPD	KI	SPR	RIE	SVHC	SVAC	SVDC
I	111,3±17,9 3–5	1,22±0,10 3–5	8,1±5,0 3–5	7,1±4,6 3–5	10,2±5,0 3–4	4,8±3,6 3–5	2,2±2,6 3–5
II	128,5±24,0 4,5	1,32±0,11 4,5	10,3±5,8 3–5	9,8±5,6 3–5	16,9±7,2 3	8,4±5,3 3–5	5,7±4,4 3–5
III	179,7±46,7 1,5	1,51±0,19 1	41,8±8,6 1,2,4,5	37,7±8,2 1,2,4,5	37,0±8,5 1,2,4,5	23,9±7,4 1,2,4,5	13,6±6,0 1,2,4,5
IV	263,2±73,1 1,2	1,64±0,15 1,2	63,4±9,3 1–3,5	72,3±8,9 1–3	19,6±7,9 1,3	39,7±9,8 1–3	28,5±9,0 1–3
V	316,4±83,7 1–3	1,72±0,21 1,2	80,0±10,1 1–4	83,4±9,4 1–3	17,0±9,5 1,3	45,1±12,6 1–3	35,2±12,1 1–3

Note: 1–5 – statistically significant differences between the groups.

As follows from the analysis of the above data, with the increase in the duration of APT, the ratio of tissue components of the heart muscle changes significantly – statistically significant differences with a relative norm can be traced after ten years of taking AP (group III–V).

The direct consequence of the cardiotoxic action of AP is clearly expressed microcirculation disorders in the myocardium, which is indicated by significantly increasing values of ZPD and KI compared to a relative norm.

Discirculatory disorders cause changes in the microvasculature and intercellular matrix of the myocardium in the form of increase of interstitial edema and the development of myofibroses that documents the increase in RIE and SPR. These pathological processes lead to the separation of the nutritive blood capillaries and CMC's, seriously upsetting the trophic of the latter and leading to their severe damage [13, 14].

Under the influence of AP, the number of hypertrophied CMC's (level of SVHC) is subject to directional fluctuations, reaching a maximum in group III, and then significantly decreasing. Such dynamics is a reflection of the compensatory-adaptive processes occurring in the myocardium in the initial and medium-term stages of APT and gradually fading in the future, indicating the depletion of the adaptive capacity of the heart muscle.

On the contrary, increasing the time of exposure up the number of atrophied and dystrophic cardiomyocytes has been steadily and significantly growing that document the changes of such indicators as SVAC and SVDC. Moreover, the values of each of them in groups IV and V are statistically identical, the most pronounced and statistically significantly superior to those in the previous groups of observations.

This fact suggests that 20 years of APT is, apparently, the time threshold, followed by severe and irreversible degenerative and atrophic changes in the myocardium.

In parallel with the phenomena of degeneration and death of CMC's, the process of development of secondary small-focal (substitutive) cardiosclerosis is increasing, which further increases the values of SPR.

4. Conclusion

The study of the effect of APT on the heart showed that changes in the organ at the macroscopic level of its organization develop gradually during the first ten years of APT, after which they quickly reach almost the maximum and practically do not progress in the future. This reflects, if not the cessation, then a significant decrease in the rate of cardiac remodeling at the organ level, and a rise to the forefront in the development of myocardial dysfunction of microstructural myocardial damage.

Pathological changes in the myocardial microstructure, traced in APT of schizophrenia, reflect the deep tissue changes in the heart muscle dystrophic-degenerative, atrophic, sclerotic, as well as compensatory-adaptive nature, unfolding in the process of implementing the cardiotoxic effect of AP.

In this case, the processes of microcirculation and collagenogenesis in the myocardial intercellular matrix are disturbed, which is accompanied by the development of

interstitial edema and myofibrosis, leading to a decrease in the volume of the contractile parenchyma of the heart muscle. Moreover, the phenomenon of CMC's hypertrophy, which is compensatory in nature, initially increased. In the future, there is a failure of adaptation and in the foreground are their atrophic and degenerative changes, which lead to further progression of myocardial dysfunction. After 20 years of APT these structural pathological changes become irreversible.

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