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Pathomorphological Changes of a Myocardium in Antipsychotic Therapy

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Abstract

By a morphometric method of research the microscopic changes of the heart in the process of antipsychotic therapy was determined. The study of the effect of this therapy on the heart showed that pathological changes in the myocardial microstructure 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 neuroleptic drugs. After 20 years of the treatment these structural pathological changes become irreversible.

Keywords: *Antipsychotics; Cardiotoxicity; Duration of Antipsychotic Therapy; Pathomorphology of Heart; Tissue and Cellular Levels of Organization; Morphometry*

Abbreviations

AD: Antipsychotic (Neuroleptic) Drugs; APT: Antipsychotic Therapy; CMC's: Cardiomyocytes; KI: Kernogan Index; RIE: Rate of Interstitial Edema; SVAC: Specific Volumes of Atrophied CMC's; SVDC: Specific Volume of Dystrophic CMC's; SVHC: Specific Volumes of Hypertrophied CMC's; ZPD: Zone of Pericapillary Diffusion

Introduction

It is established that all AD, both typical and atypical, have to some extent the property of cardiotoxicity [1-3]. However, the morphological changes of the heart at different levels of its organization (organ, tissue, cellular), developing in APT, practically not studied. Therefore, the aim of this work was to study such changes at the tissue and cellular levels of the heart organization.

Materials and Methods

It is known that a quantitative morphologic characteristic of changes of each organ in the case of its any pathology must start from a definite "reference point" which is defined by the concept of a "norm" [4]. 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 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.

Then 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 AD in quantities corresponding to the therapeutic standard; these medicines are not rarely 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 (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).

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 [5,6] and to be guided by the principle of unity of pathology on various research levels; this principle was postulated by G.G. Avtandilov [6] in the past.

Therefore it seems actual to research a macroscopic condition of heart in APT by use of morphometric research methods which meet modern requirements of the evidence-based medicine [7,8] 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 [5,6].

For this reason, microscopy and micromorphometry of the myocardium (tissue and cellular levels) are carried out according to the proposed for this purpose own algorithm [9,10].

Myocardium slices from various departments of the left ventricle were filled in paraffin, cuts were painted by hematoxylin and eoziny. Respective objects were studied in 10 different fields of microscope, with necessary magnifications with the help of an ocular micrometer, the point count method was also used [5,6,11]. Such parameters as zone of pericapillary diffusion (ZPD), Kernogan index (KI), stromal-parenchymatous ratio (SPR), rate of interstitial edema (RIE) were calculated. Karyometry and cytometry of cardiomyocytes (CMCs) were performed, the specific volumes of hypertrophied CMCs (SVHC), of atrophied ones (SVAC), and - by the method of polarization microscopy - the specific volume of dystrophic ones (SVDC) were determined.

The method of polarization microscopy was used to detect dystrophic-degenerative changes in CMC. It is believed that the combination of this type of study with conventional histological and histochemical techniques allows to obtain and evaluate much more complete information about the state of CMC and their myofibrillar apparatus, which is a very sensitive indicator of myocardial damage [12]. This makes the polarization microscopy method most suitable for detecting early stages of CMC damage [12].

The above-named parameters describe a condition of three structural components of myocardium: of microvasculature (ZPD and KI), intercellular matrix (SPR and RIE), and parenchyma (SVHC, SVAC and SVDC).

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 and Discussion

The results of the morphometric study of myocardial changes observed in the process of APT are presented in table 1.

Indicators	Microvasculature		Intercellular matrix		Cardiomyocytes		
Groups	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

Table 1: *Morphometric parameters of myocardium in APT.*

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 AD (group III-V).

The direct consequence of the cardiotoxic action of AD 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 [12,13].

Under the influence of AD, 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.

Conclusion

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 AD.

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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