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Age Factor in the Antipsychotic Cardiomyopathy: Morphometric Study

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Abstract

By a morphometric method of research and calculation of Cohen's coefficient the force of impact of an age factor on pathomorphological changes of heart at the different levels of his organization at development of a neuroleptic cardiomyopathy was determined. It is established that at patients of different age crucial importance plays not an age factor, but side cardiotoxic effect of antipsychotics leading finally to develop.pment of the neuroleptic cardiomyopathy.

Keywords

Antipsychotics; Cardiotoxicity; Neuroleptic cardiomyopathy; Pathomorphology of heart; levels of organization, Morphometry; Influence of age.

Introduction

As a result of active therapy of both the main mental and concomitant somatic pathology, the life expectancy of mental patients, in particular those suffering from schizophrenia, has increased significantly *(Volkov VP [1,2])*.This process is accompanied by a significant increase in the duration of antipsychotic therapy (APT), thereby significantly lengthening the time of damaging cardiotoxic effects of antipsychotics (AP) on the heart, which is fraught with the development of severe life-threatening iatrogenic pathology- neuroleptic cardiomyopathy (NCMP) *(Volkov VP, et al. [3–6])*. In parallel, natural ontogenetic involutional processes develop in the heart *(Volkov VP [7])*. How these two factors interact among themselves and how their joint influence is reflected in a morphologic condition of a heart – this question remains open. In the special literature any information on this problem is not found. Meanwhile, the clarity is of a great practical importance, since AP is usually prescribed by the psychiatrists, who are usually poorly informed about the nuances of cardiology *(Thomas SH [8])*. 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 *(Avtandilov GG [9,10])* and to be guided by the principle of unity of pathology on various research levels; this principle was postulated by GG Avtandilov *(Avtandilov GG [9])* in the past.

Therefore, it seems actual to research a morphofunctional condition of heart in patients with NCMP by use of morphometric research methods which meet modern requirements of the evidence-based medicine *(Grinkhalkh T , Klyushin DA [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 *(Avtandilov GG [9,10])*. The aim of the present study is to eliminate – at least, partially – the existing gap by studying the effect of age on macroscopic changes in the heart (organ level of its organization) in patients with NCMP.

Material and Methods

Then autopsy protocols of 140 patients with schizophrenia (83 men and 57 women) who died at the age under 35 years and over 55 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. .The observations were divided into four groups: I and II were respectively 42 young and 39 elderly patients receiving AP, but had no heart disease and died of non-cardiac causes; groups III and IV included 27 young and 32 elderly patients suffering from NCMP. The following parameters were measured on the macroscopic (organ) 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 author's method what we had developed for such studies *(Volkov VP [13])*. 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. 2) Cl - coefficient of the left

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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) *(Volkov VP [13])*, which quantitatively describe a condition of its intercellular matrix. The myocardium of 18 young (men-10, women-8) and 43 elderly patients (men-32, women-11) distributed in four selected groups as follows: I-12, II-6, III-20, IV-23 studied micromorphometrically. 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 *(Avtandilov GG, Gutsol AA, et al. [9, 10, 14])*. Such parameters as zone of pericapillary diffusion (ZPD), Kernogan index (KI), SPR, 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 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). Mathematical analysis of the obtained quantitative data included the calculation of such an index as the effect's size by J. Cohen *(Cohen J, et al. [15,16])*, which in quantitative terms determines the effect of the studied factor on a particular object of study *(Cohen J, Shmukler AB, et al. [15,17])*. It is believed that the inclusion of the Cohen coefficient (d'C) in the mathematical data processing tool strengthens the rigor of the study and gives more weight to the analysis, conclusions and recommendations *(Hall S [18])*. The following gradation of d'C is accepted: insignificant-less than 0,20; small-0,20-0,49; average-0,50-0,79; big-0,80 and above *(Cohen J, Shmukler AB, et al. [15,17,19]*. Negative d'C values indicate the opposite direction of the effect [19]. The obtained quantitative results were processed statistically (computer program "Statistica 6.0") with the level of significance of differences of 95% and more ($p \leq 0.05$). The d'C calculation is performed automatically using a computer calculator [19].

Results and Discussion

The comparison of the studied ECG indices in groups I and II *(table 1)* identifies the pronounced and statistically significant ontogenetic changes in four of the six parameters. So, with age m accrues while V though also increases, but only at the level of a trend. Owing to this fact the level of MVR too, although slightly, but still statistically significant, raises.

Table 1. Macroscopic parameters of the heart in the study groups

Indicators / Groups	m	V	K_v	K_l	MVR	IDM
I	**283** ±7 2–4	**127,1** ±5,8 3,4	**32,0** ±0,5 3,4	**40,0** ±0,5 2,4	**2,22** ±0,07 2	**4,16** ±0,14 2-4
II	**312** ±6 1,3,4	**134,7** ±6,7 3,4	**32,2** ±0,5 3,4	**38,5** ±0,6 1,3,4	**2,32** ±0,06 1,3,4	**4,60** ±0,12 1,3,4
III	**350** ±13 1,2	**160,2** ±6,3 1,2	**41,9** ±0,7 1,2	**39,7** ±0,7 2,4	**2,18** ±0,05 2	**6,09** ±0,17 1,2
IV	**367** ±12 1,2	**170,1** ±8,1 1,2	**42,3** ±0,9 1,2	**40,8** ±0,09 1–3	**2,15** ±0,07 2	**6,30** ±0,16 1,2

Note: 1-4 – statistically significant differences between the groups

The value of Kv practically does not change, which indicates the absence of the age-related expansion of the cardiac ventricles. On the contrary, the ratio of the ventricular volumes changes with age in favor of the right, as in group II Kl goes down considerably and statistically significantly.

In old age IDM also increases significantly. This is not surprising, since it is established that this indicator reflects changes in the intracellular matrix of a myocardium, in particular, the degree of myofibrosis *(Volkov VP [13])*, which is often observed during the age-related involutive processes occurring in a heart muscle *(Volkov VP [7])*.

The calculation of d'C in the compared groups I and II *(table 2)* shows that the influence of an age factor on such organometric parameters of the heart as m and IDM corresponds to an average degree, on K- an insignificant one, and on the others-a small one. The data presented in both tables are fully consistent.

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Table 2. Cohen's coefficient (d'C) in the study groups

Indicators / Groups	m	V	K_v	K_l	MVR	IDM
I	**283**	**127,1**	**32,0**	**40,0**	**2,22**	**4,16**
	±7	±5,8	±0,5	±0,5	±0,07	±0,14
	2–4	3,4	3,4	2,4	2	2–4
II	**312**	**134,7**	**32,2**	**38,5**	**2,32**	**4,60**
	±6	±6,7	±0,5	±0,6	±0,06	±0,12
	1,3,4	3,4	3,4	1,3,4	1,3,4	1,3,4
III	**350**	**160,2**	**41,9**	**39,7**	**2,18**	**6,09**
	±13	±6,3	±0,7	±0,7	±0,05	±0,17
	1,2	1,2	1,2	2,4	2	1,2
IV	**367**	**170,1**	**42,3**	**40,8**	**2,15**	**6,30**
	±12	±8,1	±0,9	±0,09	±0,07	±0,16
	1,2	1,2	1,2	1–3	2	1,2

In the course of a cardiac remodeling in the development of NCMP (group III and IV) there is a leveling effect of the latter on the severity of ontogenetic shifts of the organometric parameters *(table 1)*. Very weakly expressed the age-related morphological changes of the heart on the pathological background created by the presence of NCMP are statistically significant only in such an indicator as Kl. This reflects some prevalence of an enlargement of the left ventricle compared to the right one *(Volkov VP [13])*. The sizes d'C for all compared indicators in groups III and IV *(table 2)* are in limits of borders small and insignificant. In other words, the force of the influence of an age on the macroscopic condition of the heart in patients suffering from NCMP is extremely small, and all the identified changes are caused by the development of the this iatrogenic pathology.

The results of a comparative analysis of the dynamics of indicators in paired groups I-III and II–IV, that is in persons of the same age respectively without NCMP and in the presence of one, once again convincingly confirm the proposed situation. In both pairs of the compared groups, the development of NCMP leads to a marked remodeling of the heart, which is documented by the statistically significant changes in the vast majority of the studied organometric parameters *(table 1)* The power of an influence ("size effect") of the development of NCMP at any age for the vast majority of the studied quantitative indicators is very high *(table. 2)*. This fact proves the crucial importance of NCMP in cardiac remodeling at the organ level of the organization definitively. Thus, the carried-out analysis of the dynamics of macromorphometric parameters of the heart in the aspect of ontogenesis and the development of NCMP shows the absence of any significant influence of an age factor on the state of the studied organ in the presence of NCMP. Quantitative results of the conducted morphometric studying of a myocardium on groups of a research and results of the calculation of d'C are presented in tables 3 and 4. Their analysis allows allocating the following key points.

Table 3. Micromorphometric parameters of the myocardium in the study groups

Indicators / Groups	Microvasculature		Intercellular matrix		Cardiomyocytes		
	ZPD	KI	SPR	RIE	SVHC	SVAC	SVDC
I	**105,5** ±8,4 2-4	**1,17** ±0,05 2-4	**6,5** ±1,7 2-4	**4,0** ±0,9 2-4	**5,7** ±1,1 2-4	**1,9** ±0,3 2-4	**1,3** ±0,5 2-4
II	**122,8** ±10,4 1,3,4	**1,33** ±0,07 1,3,4	**11,4** ±2,1 1,3,4	**13,3** ±1,6 1,3,4	**19,3** ±1,7 1,3,4	**10,6** ±0,9 1,3,4	**4,0** ±0,7 1,3,4
III	**238,3** ±14,2 1,2	**1,51** ±0,12 1,2	**56,1** ±3,7 1,2	**58,8** ±2,9 1,2	**24,6** ±1,9 1,2	**32,7** ±3,2 1,2	**24,3** ±1,3 1,2
IV	**253,6** ±11,8 1,2	**1,69** ±0,15 1,2	**61,1** ±4,1 1,2	**62,3** ±3,3 1,2	**26,8** ±2,7 1,2	**37,3** ±3,4 1,2	**26,1** ±1,9 1,2

Note: 1-4 - statistically significant differences between the groups

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Table4: Cohen's coefficient (d'C) micromorphometric parameters of the myocardium in the study groups

Indicators	Microvasculature		Intercellular matrix		Cardiomyocytes		
Groups	ZPD	KI	SPR	RIE	SVHC	SVAC	SVDC
I-II	0,653	0,981	0,914	2,923	3,679	6,237	1,657
I-III	2,551	0,794	3,735	5,362	2,719	2,771	4,978
II-IV	2,567	0,563	3,36	3,486	0,649	1,851	2,738
III-IV	0,262	0,287	0,28	0,246	0,203	0,306	0,237

Comparison of all studied indicators in groups I and II *(table 3)* reveals the pronounced and statistically significant ontogenetic changes expressed to varying degrees, but having the identical focus on ascending. This indicates that as the body ages the all structural components of the heart muscle-microvasculature, stroma (extracellular matrix), and parenchyma (CMCs) – are deeply damaged. During ontogenesis the processes of microcirculation in the myocardium and collagenogenesis in its extracellular matrix are gradually disturbed, which is accompanied by the development of interstitial edema and myofibrosis, which, in turn, lead to parenchymatous damages. At the same time, along with the phenomena of compensatory-adaptive nature, a dystrophic-degenerative and an atrophic changes that significantly reduce the contractile reserves of the myocardium and cause an age-related increase in manifestations of myocardial dysfunction are deployed at an advanced rate. The calculation of d'C in the compared groups I and II *(table 4)* confirms the strong influence of an age factor on the structure of the heart muscle in persons without cardiac pathology. On the contrary, with the development of NCMP (group III and IV) its leveling effect on the degree of severity of ontogenetic shifts in the myocardium is observed *(table 3)*. That is NCMP causes so deep morphological injuries of a myocardium that the age changes on such pathological background are practically not caught. This is also evidenced by the monotonic values of d'C for each compared indicator *(table 4)* which are near the lower limit of the gradation interval designated as "small". This suggests that the strength of the influence of age on the state of a cardiac muscle in patients suffering from NCMP is extremely small, and all the identified changes are due to the development of specified iatrogenic pathology. The results of a comparative analysis of the dynamics of indicators in paired groups I–III and II–IV, that is in persons of the same age respectively without NCMP and with the development of such, confirms this thesis once again convincingly. In both pairs of the compared groups, NMMC is accompanied by deep and statistically significant pathomorphological shifts in the myocardium, affecting all its structural components *(table 3)*. It is important to note that "size effect" of the development of NCMP at any age for the vast majority of the studied quantitative indicators is very high *(table 4)*. Thus, the carried-out analysis of the dynamics of the morphometric parameters of a myocardium in the aspect of ontogenesis and the development of NCMP shows the absence of any significant influence of an age factor on the condition of the heart muscle in mentally ill patients in the presence of NCMP.

Conclusion

Generalizing everything told, it is possible to note that at the development of NCMP in patients of different age the crucial importance in the genesis of various pathological changes of the heart at the different levels of its organization (organ, tissue and cellular) has not an age factor, but the side cardiotoxic effect of AP leading eventually to the development of NCMP.

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