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Interactions between Microglia and Oligodendrocytes in the Caudate Nucleus in Attack-Like Progressive Schizophrenia[1]

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Abstract

Background: previously, the authors found ultrastructural pathology of oligodendrocytes in contact with microglia in the white matter of the prefrontal cortex in attack-like progressive schizophrenia. **Aim of the study:** to determine ultrastructural changes in microglia and oligodendrocytes in contact with each other and to analyze correlations between ultrastructural components of microglia and oligodendrocytes in the caudate nucleus of attack-like-progressive schizophrenia compared to controls. **Material and Methods:** an electron microscopic morphometric study of microglia and oligodendrocytes in contact with each other was performed in autopsy head of the caudate nucleus from the left hemisphere in 10 cases of attack-like progressive schizophrenia and 20 controls without mental pathology. Group comparisons were made using ANCOVA and Pearson correlation analysis. **Results:** we found decreased volume fraction (Vv) and the number of mitochondria in microglia and oligodendrocytes, decreased area of microglia and increased Vv of heterochromatin and area of vacuoles of endoplasmic reticulum in oligodendrocytes in schizophrenia compared to controls. The area of microglia correlates positively with the areas of oligodendrocyte cytoplasm and mitochondria in oligodendrocytes in the schizophrenia group but not in the control group. The areas of oligodendrocytes, microglia and of their nuclei correlate positively with age at onset of disease. Vv and number of mitochondria in microglia correlate positively with the same parameters in oligodendrocytes in the control group, but not in the schizophrenia group. Vv and number of mitochondria in microglia correlate negatively with the perimeter of heterochromatin in oligodendrocytes in the schizophrenia group. **Conclusion:** The obtained results showed reduced microglial reactivity in the caudate nucleus in attack-like progressive schizophrenia. Dystrophy of oligodendrocytes in schizophrenia is associated with a decrease in the size of microglia, a deficiency of mitochondria in microglia and oligodendrocytes, and disrupted bioenergetics coupling between microglia and oligodendrocytes. Dystrophic changes in microglia and oligodendrocytes in the caudate nucleus in attack-like progressive schizophrenia may be associated with dysontogenesis.

Keywords: microglia, oligodendrocytes, caudate nucleus, attack-like progressive schizophrenia, age at onset of disease
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INTRODUCTION

According to modern concepts, the structural basis for the dysfunction of neuronal networks involved in cognitive and emotional dysfunctions in schizophrenia is the disruption of the ultrastructure of synaptic contacts, myelin fibers, myelin-forming oligodendrocytes and deficiency of oligodendrocytes and their precursors in the gray and white matter of various brain regions [1–4]. Oligodendrocytes are involved in axon myelination, conduction of action potentials along axons, and organization of neuronal networks [5]. Neuronal activity can stimulate myelin formation and regeneration of myelinated fibers, improve the speed and ability to process nerve signals and maintain axonal integrity [6]. Cognitive impairment in schizophrenia is associated with impaired axonal myelination [7]. The caudate nucleus (CN) is part of the dorsal striatum, and it is involved in the planning and execution functions. Connections of the CN with the prefrontal cortex are involved in the control of goal-directed behavior [8]. The functioning of the CN is associated with the influence of afferent inputs mainly from the ipsilateral frontal lobe and with efferent connections of the CN with the hippocampus, putamen and thalamus [9, 10]. A study by functional MRI and single-photon emission computed tomography [11] showed that cognitive symptoms in schizophrenia are associated with reduced activity of afferents from the frontal cortex in the CN and a decrease in the dopamine transporter in the CN.

Our previous studies showed a reduced numerical density of oligodendrocytes and clusters (precursors) of

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Table 1 Demographic and clinical data (M ± SD)

Groups		Gender[a]	Age[b], years	PMI[c], hours	Illness duration, years	Age at onset of disease, years	CPZ, mg
Control	Age (n = 20)	12M/8F	58,25 ± 12,6	6,05 ± 1,0			
	Age < 50 (n = 6)	5M/1F	43,67 ± 5,6	5,75 ± 0,4			
	Age > 50 (n = 14)	7M/7F	64,50 ± 8,9	6,18 ± 1,1			
Attack-like progressive schizophrenia	Age < 75 (n = 10)	4M/6F	50,00 ± 16,8	5,65 ± 0,6	22,50 ± 15,5	27,60 ± 9,9	439,63 ± 307,7
	Age < 50 (n = 6)	2M/4F	39,5 ± 11,9	6,00 ± 0,3	13,67 ± 11,5	25,83 ± 12,1	407,5 ± 252,8
	Age > 50 (n = 4)	2M/2F	65,75 ± 7,4	5,13 ± 0,6	35,75 ± 10,6	30,25 ± 5,9	471,75 ± 392,8

Note: PMI — postmortem interval, CPE — chlorpromazine equivalent. Control/Schizophrenia: a) χ^2-test, (p = 0,30), b) ANOVA (p = 0,14), c)-ANOVA (p = 0,24).

oligodendrocytes in the head of the CN in schizophrenia [12, 13]. We also found ultrastructural pathology of myelinated fibers in the CN in schizophrenia, correlating with pathology of myelinated fibers in the hippocampus and prefrontal cortex [14]. The percentage of myelinated fibers with signs of axonal atrophy and swelling of the periaxonal oligodendrocyte process was higher in attack-like progressive schizophrenia compared to continuous schizophrenia in the CN and hippocampus [15]. Dystrophic changes of oligodendrocytes, including oligodendrocytes in contact with microglia, have also been found in the CN in schizophrenia [16].

Microglia contribute to normal myelinogenesis and maintenance of oligodendrocyte precursors in adulthood [17]. Microglia contribute to the regulation of myelin fiber growth and associated cognitive functions, as well as for maintaining myelin integrity by preventing myelin degeneration [18, 19]. Anti-inflammatory M2 microglia influence the differentiation of oligodendrocytes into myelinating oligodendrocytes during regeneration in the brain [20]. An immunohistochemical study [21] using the markers Iba1 and transmembrane protein 119 (TMEM119) did not reveal changes in the numerical density of microglia in the CN in schizophrenia. We have previously showed impaired microglia-neuron interactions at the ultrastructural level in the CN in schizophrenia [22] and in groups with different types of schizophrenia course [23]. The aim of the present study is to determine ultrastructural changes in microglia and oligodendrocytes in contact with each other and to analyze correlations between ultrastructural components of microglia and oligodendrocytes in the CN in attack-like-progressive schizophrenia compared to normal controls.

MATERIAL AND METHODS

The study was performed using the collection of autopsy brain structures available in the Laboratory of Clinical Neuromorphology (Head of the Laboratory Dr. Sci. (Med.) N.A. Uranova) of the Mental Health Research Centre (Director Dr. Sci. (Med.) Yu.A. Chayka).

Lifetime diagnosis of schizophrenia was made according to ICD-10. The attack-like progressive schizophrenia group consisted of 10 cases (F20.01 — 6 cases, F20.02 — 4 cases). The control group included 20 cases without psychiatric and neurological pathology (subject NO. FNFE 2019-0031). Relatives' permission for autopsy and research was obtained before taking the material.

Characterization of the schizophrenia and control groups is given in Table 1.

The studied groups did not differ by sex, age, and postmortem interval (Table 1). The causes of death were similar in both groups: myocardial infarction, pulmonary embolism, pneumonia, ischemic heart disease, and acute cardiovascular failure. Chlorpromazine equivalent during the last 1 month before death was used to account for the possible effect of neuroleptic therapy on the evaluated parameters.

Tissue of the central part of the head of the CN from the left hemisphere was studied. A detailed description of tissue fixation and processing for electron microscopic study is given in a previously published article [16]. In each case, ultrastructural sections were obtained from three randomly selected tissue blocks of the CN.

The ultrathin (60–80 nm) sections were made on the ultramicrotome UltracutE (Reichert, Germany). They were stained with aqueous uranyl acetate solution and lead citrate solution. Microphotographs from ultrathin sections were obtained on scanning electron microscopes Helios, NanoLab 660, Versa 3D microscopes (FEI, Holland) using STEM-detector for viewing and recording images in transmission mode at a magnification of 10,000x in the laboratory "Systems for microscopy and analysis" of the Center for Collective Use in Skolkovo. The ImageJ program for the analysis and processing of electron-microscopic images was used. The number of measured microglia in contacts with oligodendrocyte was 20 on average per case in the schizophrenia group and 22 in the control group. The number of oligodendrocytes measured was 21 on average per case in the schizophrenia group and 22 in the control group. The following parameters of microglia and oligodendrocytes contacting each other were evaluated: areas of cell and cell nucleus, perimeter, cytoplasmic area, nuclear-cytoplasmic ratio, area, volume fraction (Vv) and perimeter of heterochromatin, mean and total mitochondrial areas, mitochondrial perimeter,

number and Vv of mitochondria and the same parameters of endoplasmic reticulum vacuoles and lipofuscin granules.

Statistical analysis was performed using Statistica program (version 7). The normality of the distribution of the estimated parameter in the groups was tested by the Kolmogorov-Smirnov criterion. One-factor analysis of variance (ANOVA), analysis of covariance with age and postmortem interval (ANCOVA) and Pearson correlation analysis were used for statistical data processing. Pearson correlation analysis was applied to evaluate possible correlations between microglia and oligodendrocyte parameters using the criterion of group differences of correlation coefficients based on Fisher transformations and to identify the possible influence of age, postmortem interval, illness duration and age at onset of disease. Values of $p < 0.05$ were taken as statistically significant.

RESULTS

Qualitative examination showed heterogeneity of microglia and oligodendrocytes in contact with each other in both the control and schizophrenia groups. The ultrastructure of these glial cells was more preserved in the control group (Fig. 1a) than in the schizophrenia group. The latter was characterized by pronounced dystrophic changes, such as reduced cytoplasmic area of microglia, oligodendrocyte nuclei and increased heterochromatin content (Fig. 1b–d). In control cases and in schizophrenia, it was possible to observe the presence of direct physical contact of microglia cytoplasm with oligodendrocyte nucleus (Fig. 1a,b). In schizophrenia, a pronounced swelling of oligodendrocyte cytoplasm was observed in individual oligodendrocytes, and some contacts of microglia with oligodendrocytes were limited to a small fragment of the cytoplasm of these cells (Fig. 1c). Such changes were often observed near capillaries (Fig. 1c). In addition, microglial cells with a narrow rim of cytoplasm and a hyperchromic nucleus located inside the cytoplasm of astrocytes were occasionally seen in the schizophrenia cases (Fig. 1d). Swelling of mitochondria and few mitochondria were often observed in both microglia and oligodendrocytes in the schizophrenia cases.

Morphometric study showed that the numerical density of microglia in contact with oligodendrocytes was unchanged: 49,7/mm^2 in the control group and 39,5 mm^2 in the schizophrenia group ($p = 0.7$). Covariate analysis revealed a significant decrease in microglia area (–12%): [F (1,26 = 4,85, p = 0,03], microglia cytoplasm

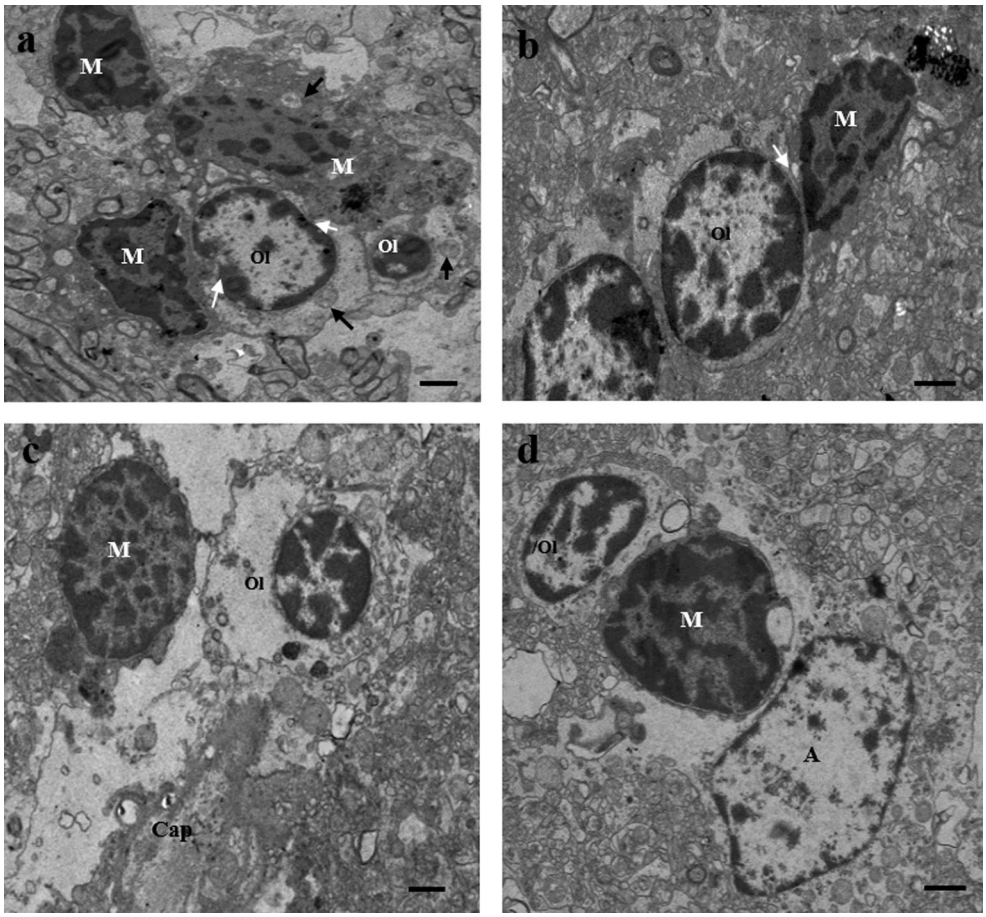

Fig. 1 The ultrastructure of microglia and oligodendrocytes in contact with each other from the control (a) and schizophrenia (b–d) brains: M — microglia, Ol — oligodendrocyte, Cap — capillary, A — astrocyte. Black arrow — mitochondria. White arrows — the contacts between microglial cytoplasm and oligodendrocyte nucleus. Scale bar — 1 μm.

(–26%): [F (1,26 = 5,62, p = 0,02], mitochondrial number (–30%) [F (1,26 = 6,14, p = 0,02] and mitochondrial Vv (–42%): [F (1,26 = 6,30, p = 0,02] in microglia (Fig. 2). In a subgroup of young patients compared to young control cases, decreased perimeter (–13%): [F (1,9 = 5,99, p = 0,04], cytoplasmic area (–27%): [F (1,9) = 5,49, p = 0,04], number of mitochondria (–60%): [F (1,9 = 6,26, p = 0,03] and an increased mean area of endoplasmic reticulum vacuoles (6%): [F (1,9 = 6,13, p = 0,03] were found in microglia compared to controls. The numerical density of microglia in this subgroup was unchanged (p > 0,2).

Covariate analysis revealed a significant increased Vv of heterochromatin (+ 12%): [F (1,26 = 5,51, p = 0,03], increased total endoplasmic reticulum vacuole area (+17%): [F (1,23 = 4,77, p = 0,04] and decreased mitochondrial number (–72%): [F (1,26 = 10,91, p = 0,003] and mitochondrial Vv (–88%): [F (1,26 = 11,9, p = 0,002] in oligodendrocytes in contact with microglia (Fig. 3). In the subgroup of young patients compared to young control cases, a decrease in mitochondrial Vv (–47%): [F (1,9 = 6,85, p = 0,03] and an increase in total vacuole area (+ 130%): [F (1,9 = 7.42, p = 0,03] were found in oligodendrocytes.

Correlation analysis showed that in the control group, Vv and number of mitochondria in microglia correlate positively significantly with similar parameters in oligodendrocytes: r = 0,46, p = 0,04; r = 0,63, p = 0,003 respectively. There are no correlations between these parameters in the schizophrenia group (Table 2). Vv and number of mitochondria in microglia correlate negatively with heterochromatin perimeter in oligodendrocytes only in the schizophrenia group: r = –0,65, p = 0,04; r = –0,7, p = 0,02, but not in the control group (Table 2). The areas of microglia and microglia cytoplasm correlate positively with the total area of mitochondria in oligodendrocytes only in the schizophrenia group: r = 0,76, p = 0,01; r = 0,75, p = 0,01. Meanwhile, microglia area correlate positively with oligodendrocyte area and oligodendrocyte cytoplasm area only in the schizophrenia group: r = 0,75, p = 0,01; r = 0,80, p = 0,005 (Table 2).

The numerical density of oligodendrocytes in contact with microglia correlate positively with chlorpromazine

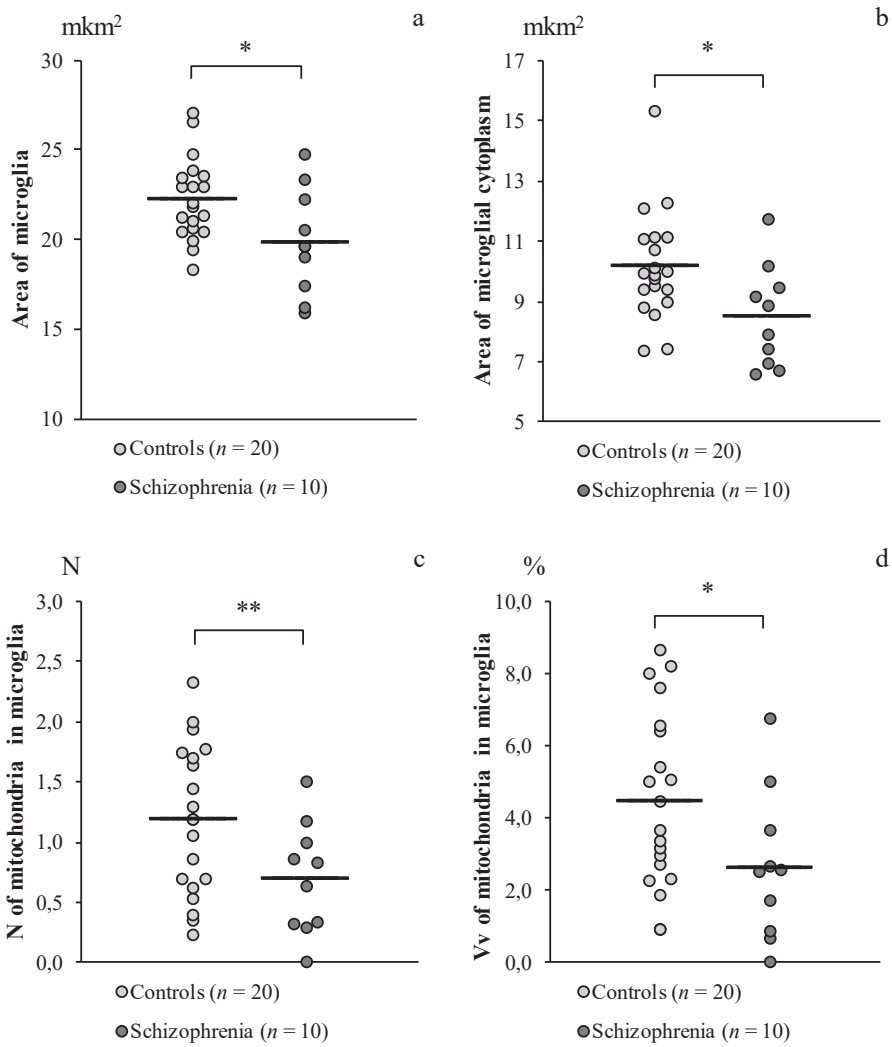

Fig. 2 Comparison of the mean values for area of microglia (a), area of microglial cytoplasm (b), the number (n) of mitochondria in microglia (c) and volume fraction of mitochondria (d) in the control group and in attack-like progressive schizophrenia group. *p < 0.05, **p < 0,01

equivalents ($r = 0.71$, $p = 0.49$). There are no correlations with age and illness duration. No effect of gender was found, but significant correlations were found with age at onset of disease (Table 3).

High significant correlation coefficients with age at onset of the disease were found for many parameters of microglia and oligodendrocytes (Table 3). Thus, the areas of microglia, cytoplasm, microglia perimeter, and the number of lipofuscin granules in microglia correlate positively with age at onset of disease: $r = 0,87$, $p = 0,02$; $r = 0,82$, $p = 0,04$; $r = 0,91$, $p = 0,01$; $r = 0,93$, $p = 0,001$. Moreover, the number of mitochondria in microglia correlate negatively with age at onset of the disease: $r = -0,83$, $p = 0,04$. In oligodendrocytes, cell area, cell perimeter, area, nucleus perimeter and cytoplasmic area correlate positively with age to onset of disease: $r = 0,85$, $p = 0,03$; $= 0,84$, $p = 0,03$; $r = 0,86$, $p = 0,02$; $r = 0,84$, $p = 0,03$; $r = 0,83$, $p = 0,04$. Heterochromatin area and perimeter and mean vacuole area in oligodendrocytes correlate positively with age at onset of disease: $r = 0,96$, $p = 0,001$; $r = 0,86$, $p = 0,03$; $r = 0,98$, $p = 0,01$.

DISCUSSION

Our study showed ultrastructural dystrophic changes in microglia and oligodendrocytes in contact with each other in the head of CN in attack-like progressive schizophrenia compared to controls without mental pathology. The changes consisted of decreased Vv and number of mitochondria in microglia and oligodendrocytes, decreased area of microglia and their cytoplasm, and increased Vv of heterochromatin and area of vacuoles of the endoplasmic reticulum in oligodendrocytes in schizophrenia compared to controls. These abnormalities were accompanied by the absence of changes in the numerical density of microglia in schizophrenia, which is consistent with the results of an immunocytochemical study using the microglial marker Iba1 (ionized calcium-binding molecule-adaptor

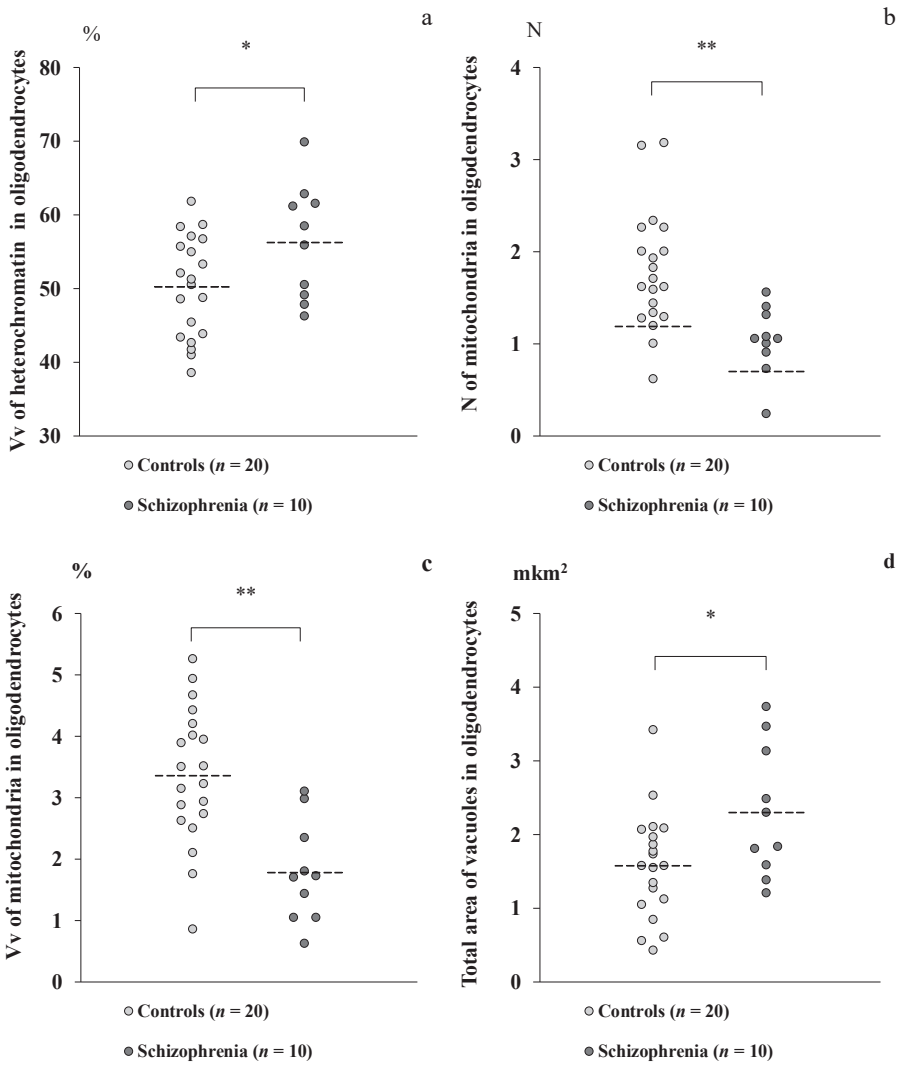

Fig. 3 Comparison of the mean values for volume fraction of heterochromatin (a), the number (N) of mitochondria (b), volume fraction of mitochondria (c) and total area of vacuoles (d) in oligodendrocytes in the control group and in attack-like progressive schizophrenia group. *$p < 0.05$, **$p < 0,01$

Table 2 Pearson correlations between the ultrastructural parameters of microglia and oligodendrocytes in contact with microglia in the control and schizophrenia groups and intergroup differences.

Parameters	Control group	Schizophrenia group	Group differences, t, p
Vv of mitochondria in oligodendrocytes	Vv of mitochondria in microglia $r = 0.46$, $p = 0.04$	$r = -0.06$, $p = 0.87$	t = 1.23, $p = 0.23$
Number of mitochondria in oligodendrocytes	Number of mitochondria in microglia $r = 0.63$, $p = 0.003$	$r = 0.21$, $p = 0.56$	t = 1.16, $p = 0.25$
Perimeter of heterochromatin in oligodendrocytes	Vv of mitochondria in microglia $r = -0.08$, $p = 0.75$	**$r = -0.65$, $p = 0.04$**	t = 1.55, $p = 0.13$
Perimeter of heterochromatin in oligodendrocytes	Number of mitochondria in microglia $r = -0.20$, $p = 0.40$	**$r = -0.70$, $p = 0.02$**	t = 1.46, $p = 0.15$
Area of mitochondria in oligodendrocytes	Area of microglia $r = 0.21$, $p = 0.36$	**$r = 0.76$, $p = 0.01$**	t = 1.72, $p = 0.10$
Area of mitochondria in oligodendrocytes	Area of microglial cytoplasm $r = 0.09$, $p = 0.72$	**$r = 0.75$, $p = 0.01$**	t = 1.96, $p = 0.06$
Area of cytoplasm in oligodendrocytes	Area of microglia $r = 0.35$, $p = 0.13$	**$r = 0.80$, $p = 0.005$**	t = 1.63, $p = 0.11$

1) and transmembrane protein 119 (TMEM119) about the absence of microgliosis in the CN in schizophrenia [21]. These results indicate a reduced reactivity of microglia in the CN in attack-like schizophrenia. It is important to note that the numerical density of microglia correlates positively with chlorpromazine equivalents (r = 0,71, p = 0,49), including in the subgroup of young patients (r = 0,99, p = 0,001), which may be due to an attempt to compensate for the reduced size of microglia and the number of mitochondria they contain. No correlations of chlorpromazine equivalents with mitochondrial parameters were found, suggesting that mitochondrial abnormalities are associated with schizophrenia. L. Kung et al. [24] showed a decrease in the number of mitochondria in presynaptic axon terminals in striatum in the schizophrenia patients not taking antipsychotic drugs compared to patients on neuroleptic therapy and to the control group. These data suggest that abnormalities in the ultrastructure and number of mitochondria in microglia are not related to the effect of antipsychotic drugs.

Correlation analysis showed that in the control group the volume fraction and the number of mitochondria in microglia correlated positively with similar parameters in oligodendrocytes. There were no correlations between these parameters in the schizophrenia group. These results showed that the correlation between the energy metabolism of microglia and oligodendrocytes, established in the normal brain, is disturbed in schizophrenia, which is consistent with the existing concept of dysregulation of microglia metabolism in schizophrenia [25]. Reduced volume fraction and the number of mitochondria in microglia in contact with neurons were also found in the head of CN in attack-like schizophrenia and in continuous schizophrenia [23]. Microglial cells with a narrow rim of cytoplasm and hyperchromic nucleus found also in the cytoplasm of astrocytes, i.e. with ultrastructural signs of apoptosis, were found in some cases of schizophrenia, which is consistent with decreased numerical density of microglia (although no significant) and with the presence of signs of microglia apoptosis in the frontal cortex in schizophrenia [26]. Mitochondrial DNA plays an important role in the regulation of apoptosis in human microglia [27].

In our study, a decrease in the volume fraction and number of mitochondria was also found in oligodendrocytes in contact with microglia in schizophrenia compared to controls. Moreover, positive correlations between microglia area, microglia cytoplasm area (reduced in schizophrenia) and total mitochondria area in oligodendrocytes (r = 0,76, p = 0,01; r = 0,75, p = 0,01) were found in the schizophrenia group in contrast to the control group. It is known that microglia activation is accompanied by an increase in their size. In our study, microglia area correlates positively with oligodendrocyte cytoplasm area only in the schizophrenia group (r = 0,80, p = 0,005). These data indicate the relationship between disturbed energy metabolism in oligodendrocytes and reduced reactivity of microglia in contact with oligodendrocytes in attack-like-progressive schizophrenia.

Taken together, these results suggest that disturbances in energy metabolism in microglia and oligodendrocytes may play a key role in the pathogenesis of schizophrenia. Our study also revealed increased volume fraction of heterochromatin in oligodendrocytes in schizophrenia compared to controls. Of note, in the present study, heterochromatin perimeter in oligodendrocytes correlate negatively with Vv and number of mitochondria in microglia. In our previous study of the head of CN [16], we also found a decrease in Vv and number of mitochondria and an increase in Vv of heterochromatin in oligodendrocytes in schizophrenia compared to controls. At the same time, in this study [16] the numerical density of concentric membrane structures (as an indicator of damage to myelinated fibers) in the CN in schizophrenia increased 4.5-fold compared to controls and positively correlated with the Vv of heterochromatin in oligodendrocytes. This study also revealed signs of apoptosis and necrosis

Table 3 Pearson correlations between the parameters of microglia and oligodendrocytes with age at onset of disease in the schizophrenia group.

Parameters	Schizophrenia group (n = 10)
Area of microglia	r = 0,73, p = 0,02
Perimeter of microglia	r = 0,91, p = 0,01
Area of microglial cytoplasm	r = 0,82, p = 0,04
Number of mitochondria in microglia	r = –0,83, p = 0,04
Number of lipofuscin granules in microglia	r = 0,93, p = 0,001
Area of oligodendrocytes	r = 0,85, p = 0,03
Perimeter of oligodendrocytes	r = 0,84, p = 0,03
Area of oligodendrocyte nucleus	r = 0,86, p = 0,02
Perimeter of oligodendrocyte nucleus	r = 0,84, p = 0,03
Area of oligodendrocyte cytoplasm	r = 0,83, p = 0,04
Area of heterochromatin in oligodendrocyte nucleus	r = 0,96, p = 0,001
Perimeter of heterochromatin in oligodendrocyte nucleus	r = 0,86, p = 0,03
Area of vacuole in oligodendrocytes	r = 0,98, p = 0,01

of oligodendrocytes in the head of CN in schizophrenia. Thus, the present study confirms the results of the previous ultrastructural study of oligodendrocytes in the CN in another sample. Previously, we also found decreased numerical density of oligodendrocytes and clusters (progenitors) of oligodendrocytes [12, 13] in the head of the CN in schizophrenia compared to the control. It is known that differentiation of oligodendroglia induces activation of mitochondrial genes, and inhibition of mitochondrial function suppresses oligodendroglia differentiation [28]. These results suggest that mitochondrial damage and deficiency in oligodendrocytes may be responsible for the decreased numerical density of oligodendrocyte clusters involved in their differentiation. Thus, the deficiency of oligodendrocytes and oligodendrocyte clusters (precursors) may be associated with impaired energy metabolism in microglia and oligodendroglia.

One of the causes of dystrophic changes in oligodendrocytes in attack-like progressive schizophrenia may be impaired expression of genes of mitochondria [29], oligodendrocytes and myelin [30, 31]. Epigenetic modifications (DNA methylation and histone modification) are key mechanisms of gene expression regulation. In schizophrenia, the activity of acetylation and methylation enzymes of nuclear histone proteins is impaired [32, 33]. Histone modifications play an important role in the regulation of transcription of genes critical for oligodendrocyte differentiation and myelination, which can lead to increased heterochromatin content in oligodendrocytes and long-term changes in gene expression in schizophrenia [32]. The study showed for the first time a negative correlation between the volume fraction, the number of mitochondria in microglia and the perimeter of heterochromatin in oligodendrocytes in the schizophrenia group, but not in the control group (Table 2). Also, in the present study and in an earlier study [34], we showed for the first time the presence of direct contact between the cytoplasm of microglia and the nucleus of oligodendrocyte groups (progenitors) in the white matter of the prefrontal cortex in schizophrenia as well as in the control group. These data suggest a possible involvement of mitochondrial deficiency in microglia in increased heterochromatin content in the nucleus of oligodendrocytes in schizophrenia. Neuroleptics have been shown to regulate acetylation and histone methylation in schizophrenia-related genes [35].

Oligodendrocytes, their mitochondria and especially oligodendrocyte progenitors (precursors) are highly sensitive to various stress factors and especially to oxidative stress [36]. Our study has shown that the most pronounced pathology of microglia and oligodendrocytes in contact with each other is associated with ultrastructural damage and mitochondrial deficiency in these cells in attack-like progressive schizophrenia. Alterations of mitochondrial metabolism in schizophrenia are associated with oxidative stress, increased lipid peroxidation with the formation of toxic aldehydes [37]. Disturbances in mitochondrial gene expression have been found in the first episode of schizophrenia [38]. Neuroleptics affect both the activity of mitochondrial genes and various enzymes [39]. Mitochondria are the most vulnerable components of neurons and glia due to the influence of various genetic factors [40] and stressors, including psychological factors. Stress is associated with bioenergetics [41]. Psychological stress is associated with the severity of positive symptoms in schizophrenia patients at the first episode of illness [6] and with the content of mitochondrial complex I protein [42]. Deficits in subjective recovery from stress are predictors of hypersensitivity to stressors and symptoms of schizophrenic spectrum disorders, including paranoid symptoms [43]. These data suggest that mitochondrial metabolic abnormalities associated with the action of both genetic and stress factors may be the initial and one of the main targets of glia damage in attack-like progressive schizophrenia. Ultrastructural damage and deficiency of mitochondria in oligodendrocytes and increased area of endoplasmic reticulum vacuoles in oligodendrocytes in schizophrenia indicate oligodendrocyte dysfunction, which can lead to the dysfunction of myelinated fibers, axons and synaptic contacts in the schizophrenia brain.

Disruptions of energy metabolism in the brain have been shown in schizophrenia (44, 45) including in the caudate nucleus (46–49) and in patients not taking neuroleptics (50, 51). Mitochondria play a major role in energy generation, reactive oxygen species and Ca + signaling (52). The functioning of mitochondria is related to the balance of their fusion and fission processes, and disruption of this balance can lead to mitochondrial dysfunction and deficiency (53). Mitochondrial fission and fusion customize cellular

processes such as calcium homeostasis and the generation of ATP and reactive oxygen species (53). Mitochondrial deficiency can lead to energy deficiency, oxidative stress and redox imbalance, and altered calcium homeostasis (52). Thus, mitochondrial deficiency in microglia and oligodendrocytes in schizophrenia is associated with mitochondrial dysfunction and impaired mitochondrial energy metabolism.

Schizophrenia is associated with impaired brain development. New insights into the genetic risk of schizophrenia are consistent with dysontogenesis, especially the stages of early brain development, in which there may be a deviation from the typical normal process of brain development that may lead to the clinical symptomatology of schizophrenia [54, 55]. Psychosis before the age of 18 years is associated with cognitive impairment, hospitalization and poor prognosis [56]. Prenatal or neonatal exposure to infectious agents such as cytomegalovirus and other viruses or parasites such as Toxoplasma gondii are risk factors for schizophrenia in individuals with a genetic predisposition to the disease [57]. Microglia contribute to normal myelinogenesis and maintenance of oligodendrocyte precursors in adulthood [17]. A neuroimaging study [58] in young schizophrenia patients found abnormal geometry of the ratio of axons and myelin sheaths in myelinated tracts associated with impaired working memory. In our study, correlation analysis showed that in the schizophrenia group, in contrast to the control group, the area of microglia (reduced in schizophrenia) correlated positively with the area of oligodendrocyte cytoplasm and the area of mitochondria in oligodendrocytes. At the same time, the areas of oligodendrocytes, microglia, and microglia nuclei correlated positively with the age of onset of disease. (Table 3). Thus, not only the relationship between the reduced area of microglia and the reduced areas of cytoplasm of oligodendrocytes and mitochondria in them was established in attack-like progressive schizophrenia, but also positive correlations are found between the areas of microglia, microglia nuclei and the area of oligodendrocytes with the age of onset of the disease. Meanwhile, no correlations of the studied parameters of microglia and oligodendrocytes with the duration of the disease and the effect of antipsychotic therapy were found. The decreased size of microglia and oligodendrocytes in attack-like progressive schizophrenia can occur as a result of impaired development of the CN under the influence of infectious agents, hypoxia during pregnancy, mitochondrial DNA mutation, mitochondrial dysfunction [59–61], which can lead to apoptosis of microglia and oligodendrocytes [26, 27, 61] or to microglial atrophy. In support of this suggestion microglial cells with a narrow rim of cytoplasm and a hyperchromic nucleus located inside the cytoplasm of astrocytes were occasionally seen in the schizophrenia cases (Fig. 1d). The numerical density of oligodendrocyte clusters (progenitors) involved in the differentiation of oligodendrocytes during development is reduced in the head of the CN in schizophrenia and does not correlate with the duration of the disease [12, 13]. Reduced volume of the CN found in untreated schizophrenia patients also does not correlate with the duration of the disease [62] which, according to the authors, confirms the dysontogenesis of CN in schizophrenia. Thus, the present study showed that dystrophic abnormalities of microglia and oligodendrocytes in CN in attack-like schizophrenia are associated with age of onset of disease, and they may be a manifestation of dysontogenesis. The present study is limited by a small sample size in the schizophrenia group and the evaluation of the effect of neuroleptic therapy on the studied parameters in the last month of patients' life.

CONCLUSION

The results showed reduced reactivity of microglia in the caudate nucleus in attack-like-progressive schizophrenia. Dystrophy of oligodendrocytes in schizophrenia is associated with a decrease in the size of microglia, deficiency of mitochondria in microglia and oligodendrocytes and disrupted bioenergetics coupling between microglia and oligodendrocytes. Dystrophy of microglia and oligodendrocytes in the caudate nucleus in attack-like progressive schizophrenia is associated with age at onset of disease, and may be a manifestation of dysontogenesis. The results expand our understanding of the role of microglia in oligodendrocyte damage in schizophrenia.

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