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Postinfectious epilepsy: clinical and diagnostical features

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SUMMARY

Background. Neuroinfections increase the risk of developing epilepsy. For many years, it was believed that acute infectious diseases, such as tick-borne encephalitis virus and meningococcus played a leading role in the emerging epileptic process of postinfectious etiology. Regarding a role for chronically persistent infections, it has not been fully explored.

Objective: to identify clinical, diagnostic, and morphological features of locally induced postinfectious epilepsy, both at disease onset upon emergence of the first epileptic seizures during acute infectious process and at their recurrence in a chronically persistent infection.

Material and methods. The study included observations of 1500 patients with locally induced epilepsy admitted and treated from 2007 to 2017 in various medical inpatient and outpatient institutions. Post-infection locally induced epilepsy with clear causality link between previous neuroinfection and onset of epileptic seizure was found in 127 patients (Group 1). During initial visits, infectious agents in a cohort of patients with recurrent epileptic seizures manifested as chronic persistent infection were suspected in more than 1/3 of the 1373 subjects who sought medical care comprising 550 people (Group 2). In addition to the clinical evaluation of patients, instrumental studies were performed, including routine electroencephalography (EEG), sleep video-EEG monitoring, magnetic resonance imaging (MRI), and some patients underwent pathomorphological examination using electron microscopy and histological techniques.

Results. Gross and marked diffuse disturbances in brain bioelectrical activity were most often detected (58% and 31%, respectively) during video-EEG monitoring in Group 1, whereas moderate alterations were recorded less frequently (11% of observations). In Group 2, the majority of diffuse disturbances in brain bioelectrical activity were of moderate level (79%) followed by mild and irritative changes recorded less frequently (in 21% of cases). MRI data showed that disorders of the amygdala-hippocampal system were observed in 41 (32%) and 211 (38%) patients in Groups 1 and 2, respectively. Histological and electron microscopic data revealed a number of morphological disorders in patients with locally induced postinfectious epilepsy common with earlier described mitochondrial encephalomyopathies (mitochondrial megaconia and pleioconia) as well as a set of specific manifestations typical to such pathology.

Conclusion. The conducted clinical, neurophysiological, neuroimaging, and pathomorphological studies of postinfectious epilepsy revealed specific features underlying its development at different stages, from its onset in acute infectious process to chronization in persistent infection. It was found that a comprehensive analysis of the presence and impact of infectious agents in patients with epileptic seizures is important for course and prognosis of postinfectious epilepsy, which is relevant for timely diagnosis and development of specific pharmacotherapy.

KEYWORDS

Neuroinfection, infectious diseases, epilepsy, locally induced epilepsy.

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Постинфекционная эпилепсия: особенности клиники и диагностики

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РЕЗЮМЕ

Актуальность. Нейроинфекции повышают риск развития эпилепсии. Многие годы считалось, что ведущую роль в генезе эпилептического процесса постинфекционной этиологии играют острые инфекционные заболевания – вирус клещевого энцефалита и менингококк. Что же касается хронически протекающих персистирующих инфекций, то их роль не до конца изучена.

Цель: выявить клинические, диагностические и морфологические особенности локально обусловленной эпилепсии (ЛОЭ) постинфекционной этиологии как в дебюте заболевания при появлении первых эпилептических приступов на фоне острого инфекционного процесса, так и при их повторении на фоне хронически протекающей персистирующей инфекции.

Материал и методы. Материалом для данного исследования послужило наблюдение 1500 пациентов с ЛОЭ, находившихся на стационарном и амбулаторном лечении в различных лечебных учреждениях в период с 2007 по 2017 гг. Постинфекционная ЛОЭ с четкой причинно-следственной связью между перенесенным нейроинфекционным заболеванием и дебютом эпилептических приступов имела место у 127 больных (1-я группа). В когорте пациентов с повторяющимися эпилептическими приступами при первичных обращениях наличие инфекционных факторов в генезе ЛОЭ в виде хронически протекающей персистирующей инфекции было заподозрено более чем у 1/3 лиц из 1373 человек, обратившихся за медицинской помощью, что составило 550 человек (2-я группа). Таким образом, итоговая выборка включила 677 человек. Помимо клинической оценки состояния пациентов были выполнены инструментальные исследования, в т.ч. рутинная электроэнцефалография (ЭЭГ), видео-ЭЭГ-мониторинг сна, магнитно-резонансная томография (МРТ), а ряду пациентов также было проведено патоморфологическое исследование с применением электронно-микроскопических и гистологических методик.

Результаты. При видео-ЭЭГ-мониторинге у пациентов 1-й группы наиболее часто выявлялись грубые и выраженные диффузные нарушения биоэлектрической активности головного мозга (58% и 31% соответственно), а умеренно выраженные фиксировались реже (11% наблюдений). Во 2-й группе большинство диффузных нарушений биоэлектрической активности головного мозга были умеренно выраженными (79%), а легкие и ирритативные регистрировались реже (в 21% случаев). По данным МРТ, нарушения со стороны амигдало-гиппокампальной системы наблюдались у 41 больного (32%) в 1-й группе и у 211 (38%) во 2-й группе. В результате гистологических и электронно-микроскопических исследований у больных с ЛОЭ постинфекционной этиологии выявлен ряд общих морфологических нарушений с описанными в литературе митохондриальными энцефаломиопатиями (мегакония и плейокония митохондрий), а также совокупность специфических проявлений, характерных для данной патологии.

Заключение. Выполненные клинические, нейрофизиологические, нейровизуализационные и патоморфологические исследования при постинфекционной эпилепсии позволили выявить специфические особенности развития данного заболевания на разных его этапах – от зарождения на фоне острого инфекционного процесса до хронизации при персистирующей инфекции. Установлено, что комплексный анализ наличия и воздействия инфекционных агентов у пациентов с эпилептическими приступами имеет большое значение в течении и прогнозе постинфекционной эпилепсии, что представляется актуальным для своевременной диагностики и разработки специфической медикаментозной фармакотерапии.

КЛЮЧЕВЫЕ СЛОВА

Нейроинфекция, инфекционные болезни, эпилепсия, локально обусловленная эпилепсия.

ИНФОРМАЦИЯ О СТАТЬЕ

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Конфликт интересов

Авторы заявляют об отсутствии необходимости раскрытия конфликта интересов в отношении данной публикации.

Вклад авторов

Авторы сделали эквивалентный вклад в подготовку публикации.

Для цитирования

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INTRODUCTION / ВВЕДЕНИЕ

According to some authors, the basis of several neurological disorders, including epilepsy, lies in the neuroinfection agents [1–5]. For many years, it was believed that acute infectious diseases such as tick-borne encephalitis and meningococcus played a leading role in the genesis of the epileptic process of postinfectious etiology [5–11]. As for chronically persistent infections that are somewhat tropic to the central nervous system and cause chronic inflammation, such as human herpes simplex viruses (mainly types 1, 2, 6, 7, and their various combinations), cytomegalovirus, Epstein–Barr virus (mononucleosis), human immunodeficiency virus, as well as toxoplasma and mycoplasmas, their role in the development of the epileptic process has been studied in experimental and clinical conditions [12–18].

However, the phenomenon of infection persistence is a variant of macro- and microorganism interaction at the cellular level, allowing the pathogen to remain in the human body for an extended period. These processes may be facilitated by weakened genetic control of the immune response [12, 19, 20]. Prolonged antigen stimulation in the presence of persistent infection leads to chronic inflammation and the formation of an immune deficiency-like reaction, which, combined with inherited immune system deficiencies, particularly factors predisposing to epilepsy, and the initiation of demyelination mechanisms, can lead to the chronicization of the pathological process and the development of epilepsy [21–24][1]. Some authors have suggested a relationship between chronic inflammation and the development of hippocampal sclerosis, which not only leads to the occurrence of epileptic seizures but also to a severe, often status epilepticus course of the disease and even drug resistance [25–27].

In addition, a significant amount of scientific research shows that oxidative stress, which causes damage to the major components of the cell (lipids, proteins, nucleic acids, glycogen, etc.), also plays an important role in the pathogenesis of epilepsy [28, 29]. Thus, chronic

[1] Gaykova O.N. Changes in the white matter of the brain in temporal lobe epilepsy. Thesises of Dr. Med. Sc. Diss. Saint Petersburg; 2001.

inflammation and oxidative stress caused by persistent neuroinfection may not only contribute to the formation of the epileptic process but also influence the development of drug resistance in patients with postinfectious forms of epilepsy. However, evidence of neuroplasticity in the central nervous system has been obtained, which, in some patients, can result in a relatively favorable course of the disease, albeit temporary, even in the presence of comorbid epilepsy and chronic persistent neuroinfection [30].

Despite many studies on the epileptogenesis of post-infectious etiology, the correlation between clinical, diagnostic, and morphological features remains insufficiently explored, which is the focus of this study.

Objective: to identify clinical, diagnostic, and morphological features of locally induced postinfectious epilepsy, both at disease onset upon emergence of the first epileptic seizures during acute infectious process and during their recurrence in a chronically persistent infection.

MATERIAL AND METHODS / МАТЕРИАЛ И МЕТОДЫ

This retrospective, non-randomized study observed 1500 patients with epilepsy from 2007 to 2017 who were receiving inpatient and outpatient treatment at various clinics of Saint Petersburg and the Leningrad Region.

Inclusion and exclusion criteria / Критерии включения и исключения

The inclusion criteria were the onset of epilepsy during acute infection and recurrent seizures during persistent infection. Patients who refused hospitalization with lumbar puncture or complete diagnostic testing for verification of the pathogen were excluded.

Patient groups / Группы пациентов

Group 1 consisted of 127 patients with post-infection epilepsy, where there was a clear cause-and-effect relationship between a previous neuroinfectious disease (such as acute meningitis or meningoencephalitis) and the onset of epileptic seizures. Group 2 included 550 patients who presented with recurring epileptic seizures at their initial visit and had suspected infectious factors in the genesis of their epilepsy, such as chronic persistent infection. This group consisted of over one-third of the 1373 patients seeking medical care.

Therefore, the final sample size included 677 individuals divided into two study groups.

Examination methods / Методы обследования

All patients included in the study underwent clinical-neurological examinations, neurophysiological evaluations (including electroencephalography (EEG) with mandatory sleep recording), neuroimaging (brain magnetic resonance imaging (MRI) using a specialized epilepsy program), laboratory tests (blood, cerebrospinal fluid, and saliva analysis for infectious markers), and in some cases, histological and electron microscopy examinations prepared according to standard protocols [31, 32].

Magnetic resonance imaging

The MRI scans were performed at Bekhterev National Medical Research Center of Psychiatry and Neurology using Atlas Exelart Vantage XGV scanner (Canon, Japan) with a magnetic field strength of 1.5 Tesla. A standard 8-channel head coil was used for brain imaging. The MRI protocol included fast spin echo (FSE) sequences to obtain T1-weighted images (T1WI) and T2-weighted images (T2WI), as well as fluid attenuated inversion recovery (FLAIR) sequences to suppress the signal from free water while preserving the baseline T2WI.

The parameters for obtaining T2WI were as follows: TR (repetition time) 4300, TE (echo time) 105, FOV (field of view) 25.0, MTX (matrix) 320, ST (slice thickness) 6.0, Gap 1.2, FA (flip angle) 90/160. The parameters for obtaining T1WI were as follows: TR 540, TE 15, FOV 5, MTX 256, ST 6.0, Gap 1.2, FA 90/180. The FLAIR sequence had the following parameters: TR 1000, TE 105, FOV 25, MTX 224×320, ST 6.0, Gap 1.2, FA 90/180.

For targeted examination of the medial basal regions of the temporal lobes, an additional protocol was used, including FLAIR-oblique Cor and Ax: Real IR-oblique Cor sequences with a slice thickness of 2.2 mm. These images were acquired in oblique axial (parallel to the long axis of the hippocampus) and oblique coronal (perpendicular to the long axis of the hippocampus) planes, which demonstrated the structures of the medial basal regions of the temporal lobes, including the entorhinal cortex, head, body, and tail of the hippocampus, and the temporal horns of the lateral ventricles and basal cisterns. The parameters for the FLAIR sequence were as follows: TR 8000, TE 105, FOV 22.0, MTX 30, ST 2.2, Gap 0.6, FA 90/180. The parameters for the Real IR sequence: TR 3450, TE 18, FOV 22, MTX 320, ST 2.2, Gap 0.6, FA 90/160.

Histological and electron microscopic studies

Biopsy specimens of the quadriceps muscle were taken from patients of both groups under local anesthesia for light microscopy and electron microscopy. For light microscopy, the biopsy fragments were fixed in 10% neutral formalin, washed in water, dehydrated in ascending concentrations of alcohol (from 70 to 96 degrees), and then embedded in paraffin. The resulting paraffin sections, with a thickness of 7–10 microns, were stained with hematoxylin and eosin, analyzed under a light microscope, and photographed at magnifications of 200–600 times.

For electron microscopy, the material was fixed in a 2.5% solution of glutaraldehyde prepared in a phosphate buffer for 4–18 hours, and then post-fixed for an hour in a 1% solution of osmium tetroxide in the same phosphate buffer (the buffer pH was 7.4 in both cases). After rinsing in the same buffer and dehydration in ascending concentrations of alcohol 70–96 degrees and acetone, the specimens were immersed in a mixture of epoxy resins and subjected to polymerization in a thermostat at temperatures ranging from 37 to 60

degrees for 2–3 days. The resulting semi-thin sections, with a thickness of no more than one micron, were stained with a 1% solution of toluidine blue using the Nissl method, analyzed and photographed under a light microscope at magnifications ranging from 200 to 1000 times. Ultra-thin sections, with a thickness of 200–400 nanometers, were then prepared from the same blocks for analysis in a transmission electron microscope JEOL 100 CX (Japan) at magnifications ranging from 8 to 33 thousand times, and these were photographed to obtain electronograms. The electronograms were digitized to obtain illustrations.

Ethical aspects / Этические аспекты

The study was consistent with the principles of the Helsinki Declaration of the World Medical Association (Fortaleza, Brazil, 2013). All included patients have signed a form of written informed consent to participation in the study and the results publication.

Statistical analysis / Статистический анализ

Statistical data analysis was performed using the Statistica for Windows software package (StatSoft Inc., USA) in accordance with recommendations for processing the results of medical-biological research [33]. All research results underwent multifactor analysis, based on matrices of pairwise correlations between elements of the original data matrices. Numerical results of morphological and cytochemical studies were processed using variation statistics methods. The differences were considered statistically significant at $p<0.05$.

RESULTS AND DISCUSSION / РЕЗУЛЬТАТЫ И ОБСУЖДЕНИЕ

Laboratory and instrumental studies / Лабораторные и инструментальные исследования

In 127 patients from Group 1, in 30% of the observations, serous meningoencephalitis was observed in the debut of epileptic seizures, in 3.5% – purulent meningoencephalitis, in 11.5% – infectious mononucleosis, in 9% – cytomegalovirus infection, in 15% – childhood infectious diseases contracted in adulthood (most often chickenpox), in 3% – chlamydia, in 7% – tick-borne encephalitis, in 1% – borreliosis, in 3% – human herpes simplex virus with clinical manifestations, in 1% – active chronic mycoplasmal infection, in 16% – unspecified and mixed infections.

In Group 2 (patients with recurrent epileptic seizures), the presence of chronically persistent infection was suspected based on the prolonged (persistent) subfebrile condition, which was often observed in the prodrome of epileptic seizures, as well as the encephalitic and asthenic symptomatology with signs of inflammation according to general clinical and instrumental studies.

Laboratory examination of biological media in patients from Group 2 with recurrent epileptic seizures and a diagnosed epilepsy revealed herpetic mixed infection, confirmed by positive polymerase chain reaction analysis with antigens of herpes simplex virus types 1 and 2, Epstein–Barr virus, cytomegalovirus, human herpes virus types 6 and 7 in various combinations (**Table 1**). The absolute majority consisted of patients with recurrent epileptic seizures and the presence of human herpes simplex viruse types 6 and 7, Epstein–Barr virus, and cytomegalovirus, as well as their various combinations.

It should be noted that in clinical observation of patients with detected mixed infection, epileptic seizures occurred as complex partial, secondarily generalized tonic-clonic seizures with high frequency (11.79±5.65 per month), with a tendency towards serial and status course, and 70% of patients had pharmacoresistance. At the same time, in patients with one type of identified chronic infection and/or infection in an inactive phase (after a course of treatment), epileptic seizures more often occurred as simple and complex partial seizures, and secondarily generalized seizures were observed less frequently (4.60±1.75 per month) (**Table 2**).

In addition, most patients in from Group 1, according to clinical-neurological examination, had focal neurological, pyramidal, encephalopathic, and even meningeal symptoms, which were etiological reflections of a previous acute infectious process – 127 patients (100%).

In Group 2 (patients with chronically persistent infection), neurological symptoms were less significant and in most cases (478 (87%)) were represented by asthenic,

Table 1. Results of laboratory diagnostics for neuroinfection-related markers in biological fluids (polymerase chain reaction analysis)

Таблица 1. Результаты лабораторной диагностики маркеров нейроинфекций в биологических средах (анализ полимеразной цепной реакции)

Antigens / Антигены	Number of patients, % / Число пациентов, %
HPV	6,29
Mycoplasma antigens / Антигены микоплазмы	9,45
Chlamydia antigens / Антигены хламидий	7,27
HSV 1/2	10,24
CMV	19,69
EBV	51,97
HHV 6	69,29
HHV 7	39,37

Note. *HPV – human papillomavirus; HSV – herpes simplex virus; CMV – cytomegalovirus; EBV – Epstein–Barr virus; HHV – human herpes virus.*

Примечание. *HPV (англ. human papillomavirus) – вирус папилломы человека; HSV (англ. herpes simplex virus) – вирус простого герпеса; CMV (англ. cytomegalovirus) – цитомегаловирус; EBV (англ. Epstein–Barr virus) – вирус Эпштейна–Барр; HHV (англ. human herpes virus) – вирус герпеса человека.*

Table 2. Infectious agent-related clinical characteristics of epileptic seizures

Таблица 2. Клиническая характеристика эпилептических приступов в зависимости от этиологии инфекционного возбудителя

Infectious agent / Инфекционный агент	Number of patients, n / Число пациентов, n	Frequency of epileptic seizures per month, n / Частота эпилептических приступов в месяц, n		p
		Simple focal (without seizures) / Простые фокальные (без судорожного компонента)	Complex focal, including secondary generalized / Сложные фокальные, в т.ч. с вторичной генерализацией	
Type 1 infection / 1-й тип инфекции	225	4,45±3,95	4,60±1,75	<0,01
Mixt-infection / Микст-инфекция	452	1,5±2,35	11,79±5,65	

vegetative-dystonic, moderate hypertensive-hydrocephalic, and/or cephalalgic syndromes, which limited their usual activities (p<0.05).

Video-EEG monitoring / Видео-ЭЭГ-мониторинг

During video-EEG monitoring in patients from Group 1 with the onset of epileptic seizures against the background of an acute infectious process, gross and pronounced diffuse disturbances in the bioelectrical activity of the brain were most frequently detected (58% and 31%, respectively), while moderately pronounced disturbances were less commonly observed (11% of observations). As for local and paroxysmal disturbances, most patients in this group showed changes with the most frequent localization in the temporal and/or fronto-temporal regions, and the epileptic (epileptiform) activity in the form of individual sharp waves, sharp-slow and spike-slow wave complexes were not characterized by stability and relative constancy, indicating an immature focus of epileptiform activity (p<0.001).

In Group 2 (patients with post-infectious epilepsy and the presence of chronically persistent infection), according to video-EEG monitoring, most diffuse disturbances in the bioelectrical activity of the brain were moderately pronounced (79%), while mild and irritative disturbances were less frequently observed (in 21% of cases). Repeat EEG studies showed that in the absolute majority (72%) of patients in the second group, localized epileptiform activity in the form of a persistent focus was detected, and in 28% of observations, more than one focus of epileptiform activity was identified (**Fig. 1**).

Brain MRI / МРТ головного мозга

Brain MRI in patients with locally induced postinfectious epilepsy revealed internal and/or external compensatory hydrocephalus (43%), asymmetry of lateral ventricles and/or enlargement of the temporal horn of one of them (72%), expansion of subarachnoid space fissures (33%), local or diffuse cortical atrophy (32%), craniovertebral anomalies (32%), hippocampal sclerosis and its various structural variations such as inversion or rounded shape (36%), cystic-gliotic changes (27%), intracerebral arachnoid cysts (5%) (**Table 3**).

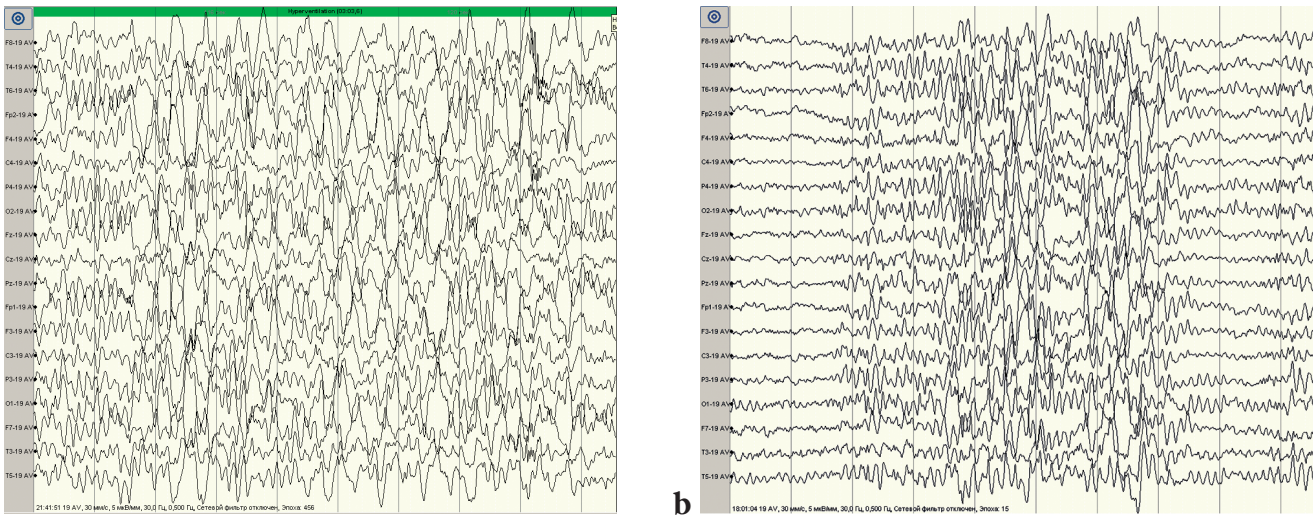


Figure 1. Results of electroencephalographic monitoring in two patients from Group 1 (**a**) and Group 2 (**b**)

Рисунок 1. Результаты электроэнцефалографического мониторинга у двух пациентов из 1-й (**a**) и 2-й (**b**) групп

Table 3. Infectious agent-related clinical characteristics of epileptic seizures based on magnetic resonance imaging (MRI) data

Таблица 3. Клиническая характеристика эпилептических приступов в зависимости от этиологии инфекционного возбудителя по результатам магнитно-резонансной томографии (МРТ)

MRI pathology / МРТ-изменения	Number of patients, n / Число пациентов, n		p
	Group 1 / 1-я группа	Group 2 / 2-я группа	
Internal and/or external substitutional hydrocephalus // Внутренняя и/или наружная заместительная гидроцефалия	127	164	<0,01
Asymmetry of lateral ventricles / Асимметрия боковых желудочков	124	363	<0,05
Expanded arachnoid space fissures / Расширение щелей субарахноидального пространства	103	120	<0,01
Local or diffuse cortical atrophy / Локальная или диффузная атрофия коры	22	194	<0,05
Craniovertebral anomalies / Краниовертебральные аномалии	41	176	<0,01
Impaired hippocampi / Нарушения гиппокампов	32	211	<0,01
Cystic-gliotic changes / Кистозно-глиозные изменения	21	161	<0,05
Intracerebral arachnoid cysts / Внутримозговые арахноидальные кисты	5	29	<0,05
Foci of demyelination / Очаги демиелинизации	3	184	<0,05
Others / Others	6	28	>0,05

Disorders of the amygdalo-hippocampal system were observed in 41 patients (32%) from Group 1 and 211 patients (38%) from Group 2, indicating a predisposition to epileptic seizures in both observation groups.

Patients with locally induced postinfectious epilepsy and multiple sclerosis showed a predominance of cortical and subcortical demyelination foci, focal cortical atrophy of various locations, and pseudotumorous demyelination foci (**Fig. 2**) [34].

Histological and electron microscopic studies / Гистологическое и электронно-микроскопическое исследования

Histological examination of muscles in patients from Group 2 with locally induced postinfectious epilepsy revealed lymphomacrophagal infiltrates, indicating moderate muscle inflammation that correlated with the duration of the infectious process. Cross-striation was weakly expressed. Many muscle fibers were split, sometimes appearing snake-like and showed signs of hypotrophy (Fig. 3). Multinucleation, which is a genetic reflection of chronic pathological (infectious) process, was occasionally observed. In some muscle fibers, nuclei were located in the center of the fiber, which may indicate genetic rearrangements triggered by persistent chronic infection.

In electron microscopic examination of biopsies in patients from Group 2 with post-infectious locally induced postinfectious epilepsy etiology, the transverse striation of muscle bundles was often absent, and in some areas, the myofibrils were arranged chaotically. In the examined biopsies, I-discs were less defined than Z-discs, however, the thickness of the latter was variable, and their fragments were found in the space between the bundles of myofibrils. This fact indicates a decrease in the contractile ability of the muscles, which can be caused by prolonged (chronic) exposure to infectious agents. This is also evidenced by the varying thickness of the myofibrils, their thinning and ruptures, as well as the serpentine-like structure of the fibers. In addition, in certain areas, images of lysis of entire bundles of myofibrils, often at the level of I-discs, were observed. In these areas, large transparent vacuoles of the sarcoplasmic reticulum were present, and glycogen was practically absent (**Fig. 4**).

In addition, electron microscopic examination of biopsies in patients from Group 2 with post-infection epilepsy revealed numerous altered mitochondria (pleioconia) with transparent contents due to the disappearance of matrix and cristae, and some of them had visible small granules. Giant-sized mitochondria (megakonia) with disrupted cristae and granules of unclear origin were frequently observed in the examined biopsies, as well as mitochondria with a denser structure but without clear differentiation of matrix and cristae. Similar mitochondria were found among bundles of myofibrils with complete absence of striations. Vacuoles containing dense bodies, which were likely mitochondria with poorly distinguishable matrix and cristae, were also present in these areas of myocytes. Transparent vacuoles with disrupted membranes, representing tubules of the sarcoplasmic reticulum, were found in immediate proximity to the altered mitochondria (**Fig. 5**).

One particularly interesting fact is that, in addition to the aforementioned changes in muscle fibers, there were also large formations that had thickened walls and contained various organelles of muscle cells, including individual tubules of the sarcoplasmic reticulum, altered mitochondria, glycogen, ribosomes, and polysomes (**Fig. 6**). This fact, in our opinion, may be characteristic of post-infectious epilepsy, as it is not characteristic of other nosological forms based on our observations and literature data. The presence of such mitochondria may also indicate mutations

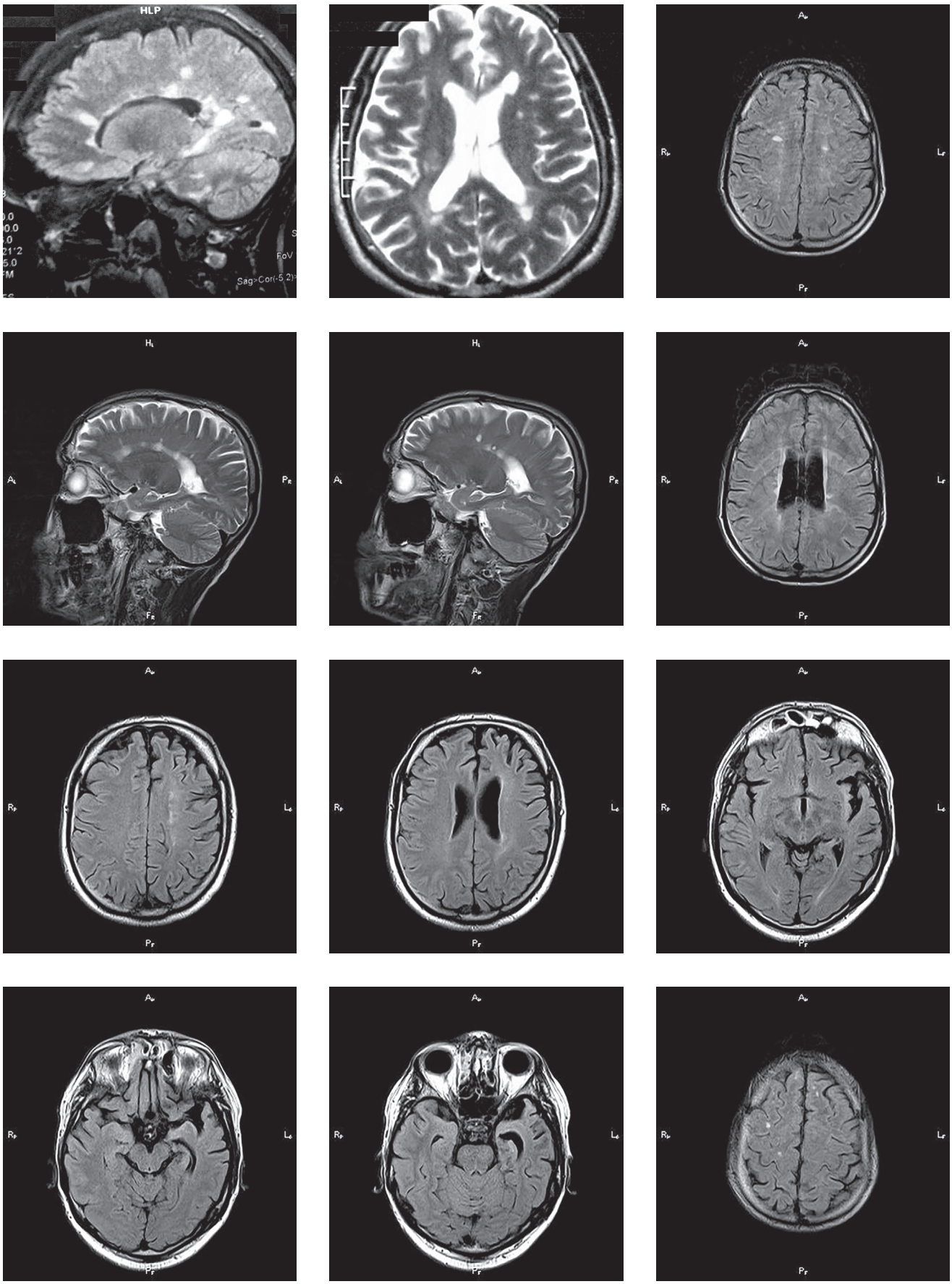


Figure 2. Magnetic resonance images of patients with locally induced epilepsy and multiple sclerosis

Рисунок 2. Магнитно-резонансные томограммы головного мозга у пациентов с локально обусловленной эпилепсией и рассеянным склерозом

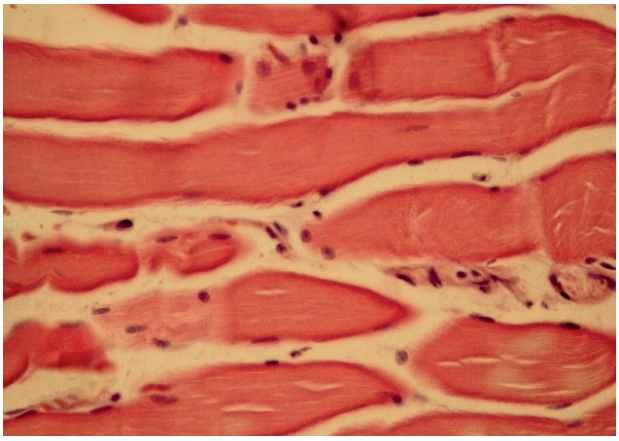


Figure 3. Biopsy specimen of a patient from Group 2 showing fiber splitting, weak transverse striation, and moderate lymphocyte-macrophage infiltration (hematoxylin and eosin staining, magnification ×600)

Рисунок 3. Участок биоптата пациента из 2-й группы с расщеплением волокон, слабой поперечной исчерченностью и умеренной лимфомакрофагальной инфильтрацией (окраска гематоксилином и эозином, ув. ×600)

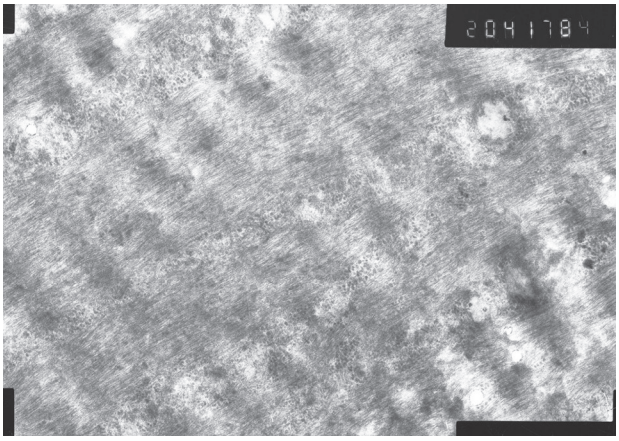
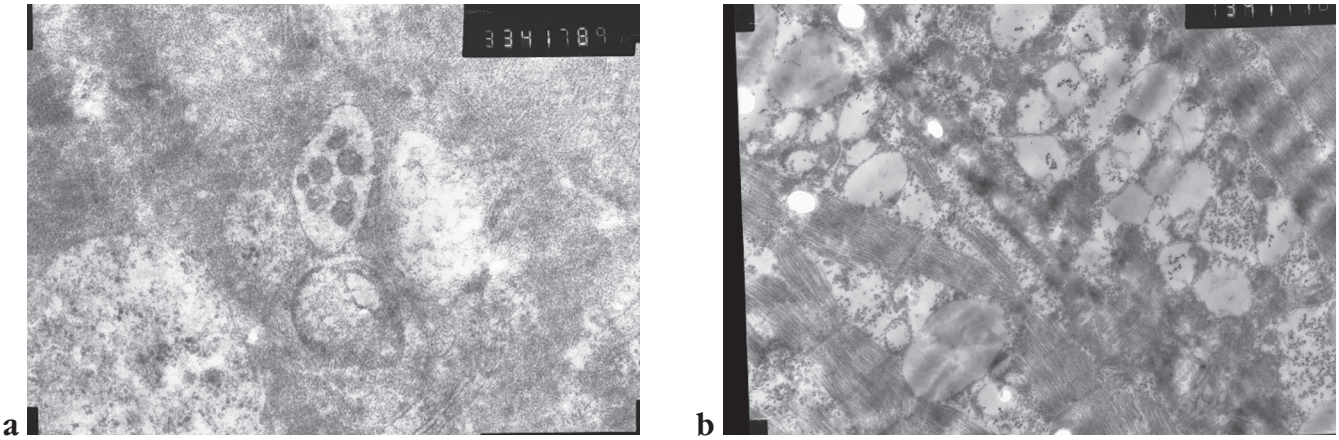


Figure 4. Electronogram of biopsy specimen of a patient from Group 2 with post-infection locally induced epilepsy showing chaotic arrangement of myofibrils (magnification ×20,000)

Рисунок 4. Электронограмма биоптата пациента из 2-й группы с локально обусловленной эпилепсией постинфекционной этиологии с хаотическим расположением миофибрилл (ув. ×20 000)



a **b**

Figure 5. Electronograms:
a – large weakly osmiophilic vacuoles of varying contents (magnification ×33,000); **b** – lipids and numerous mitochondria with disrupted matrix and cristae (magnification ×13,000)

Рисунок 5. Электронограммы:
a – крупные слабо осмиофильные вакуоли с различным содержимым (ув. ×33 000); **b** – липиды и многочисленные митохондрии с разрушенными матриксом и кристами (ув. ×13 000)

in mitochondrial DNA that occur under the influence of chronic inflammatory and/or infectious processes.

Besides, in severely damaged areas of myocardial cells, there were observed accumulations of glycogen on one hand and accumulations of small transparent bubbles of unclear origin on the other. We would venture to suggest that they may be associated with the ongoing infectious process in the examined patients (**Fig. 7**).

Patients from Group 1 presented extensive areas of myolysis, which were often found near the sarcolemma in the biopsy of the quadriceps muscle under light microscopy, and nuclei in the form of chains were located at a certain distance inside the muscle (**Fig. 8a**). In addition to these structural abnormalities, the muscle fibers themselves often had a snake-like loose arrangement, and large lympho-macrophage infiltrates, stained purple with hematoxylin, were found inside bundles of myofibrils (**Fig. 8b**).

No fully preserved muscle cells without any changes to their organelles were found in the bioptate under electron microscopy. On the contrary, both mild and severe myolysis

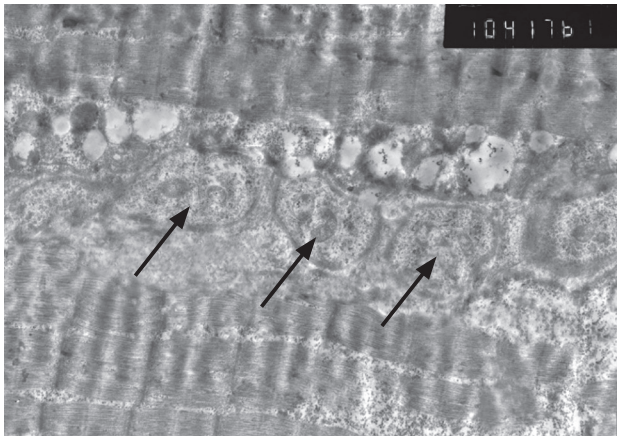


Figure 6. Atypical inclusions (arrows) among myofibrils in biopsy specimens:
a – magnification ×10,000; **b** – magnification ×20,000

Рисунок 6. Нетипичные включения (стрелки) среди миофибрилл в участках биоптата:
a – ув. ×10 000; **b** – ув. ×20 000

were detected in the myocytes of the bioptate. The presence of a large number of capillaries in the endomysium and their close contact with muscle cells is noteworthy. These contact areas often have a layer of loose collagen, which may be an indirect sign of inflammatory changes in the muscle. Areas of myolysis are often observed beneath the sarcolemma, and they typically contain accumulations of mitochondria (pleiokonia) with altered matrix and cristae, lipids, and lysosomes (**Fig. 9a**). Extensive areas of myolysis within the muscle are also found, and longitudinal splitting of bundles of myofibrils with loss of Z-discs, and less frequently I-discs, can be observed in these areas (**Fig. 9b**).

Myolysis often occurs near disrupted Z-discs, and there, pairs of altered mitochondria with elongation, resembling dumbbells, are frequently found, as if replacing these discs (**Fig. 10**).

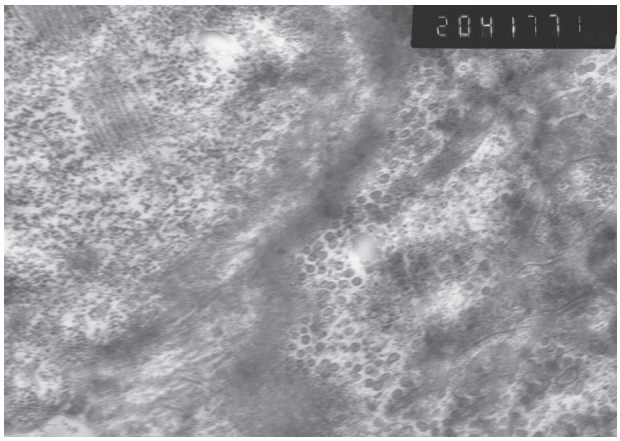


Figure 7. Biopsy specimen with profoundly altered pattern of myofibrils and overall structure of myocytes (magnification ×20,000)

Рисунок 7. Участок биоптата с сильно измененным рисунком миофибрилл и всей структуры миоцита (ув. ×20 000)

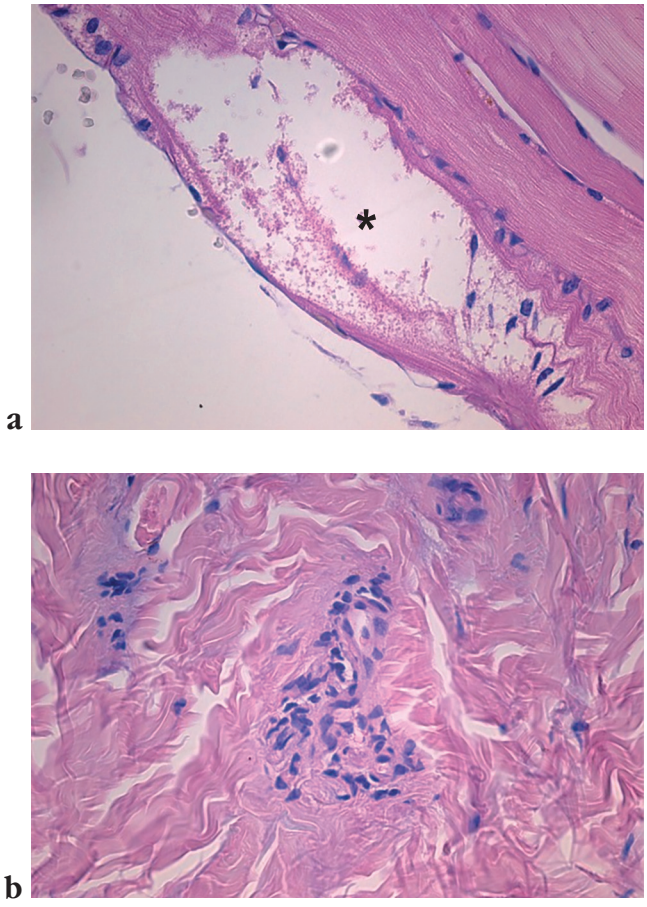


Figure 8. Results of light microscopy:
a – extensive area of myolysis (*) (magnification ×400;
b – lymphocyte-macrophage infiltrate within a bundle of snake-like myofibrils at the center of the image (center, magnification ×1,000)

Рисунок 8. Результаты световой микроскопии:
a – обширный участок миолиза отмечен звездочкой (ув. ×400); **b** – в центре снимка – лимфо-макрофагальный инфильтрат внутри пучка змеевидных миофибрилл (ув. ×1000)

Often in areas of myolysis against the background of disrupted myofibrils, Z-discs are randomly arranged or absent. Mitochondria exhibit pronounced disruptions in the matrix and cristae, resulting in vacuolization. Quite often, these mitochondria have a ring-like structure, inside and outside of which lipids are located (**Fig. 11**), in close contact with the mitochondria. Myofibrils are absent in these areas.

Thus, during morphological analysis of biopsies from patients with post-infection epilepsy, clear damage to the typical muscle structure can be observed, with pronounced changes in organelles in certain areas. This, in turn, can lead to significant impairments in muscle function in patients with epilepsy and chronically persistent infection.

Overall, our histological and electron microscopic studies in patients with post-infection etiology of epilepsy revealed a number of common morphological abnormalities seen in literature-described mitochondrial encephalomyopathies (megakaryocytes and pleiokaryocytes of mitochondria), as well as a combination of specific manifestations characteristic of this pathology.

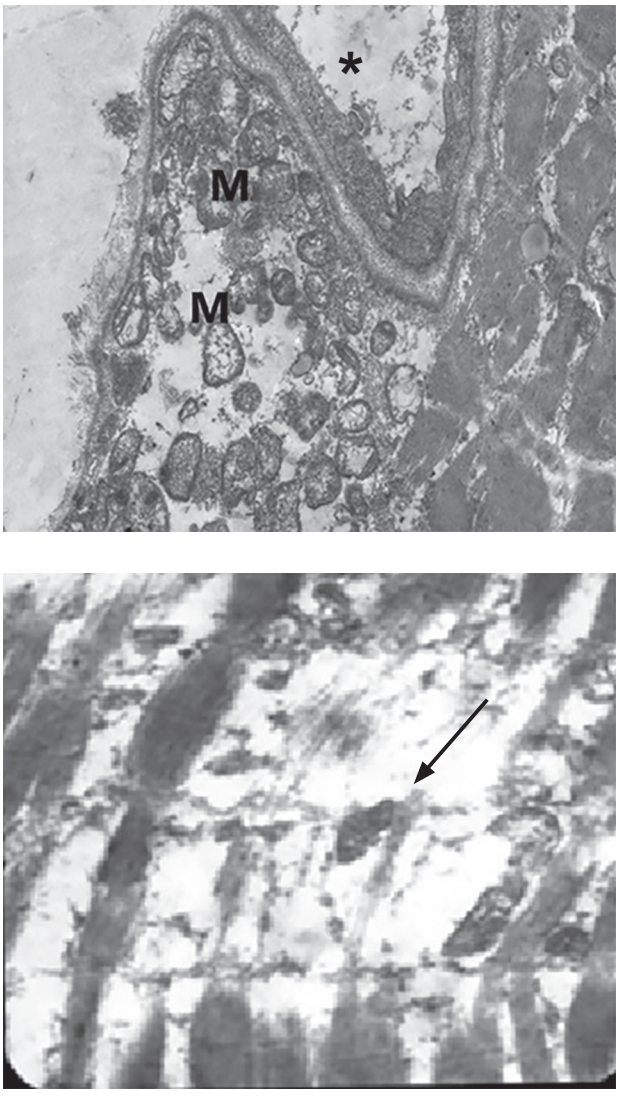


Figure 9. Results of electron microscopic examination: **a** – area of myolysis beneath sarcolemma filled with numerous semi-disrupted mitochondria (M) and a capillary fragment (asterisk) in close contact with the muscle (magnification ×8,000); **b** – large area of myolysis (arrow) within the muscle with disc disruption and fully disappeared myofibril bundles (magnification ×8,000)

Рисунок 9. Результаты электронно-микроскопического исследования:
a – участок миолиза под сарколеммой, заполненный многочисленными полуразрушенными митохондриями (М) и фрагмент капилляра (отмечен звездочкой) в тесном контакте с мышцей (ув. ×8000); **b** – крупный участок миолиза (стрелка) внутри мышцы с разрушением дисков и полным исчезновением пучков миофибрилл (ув. ×8000)

CONCLUSION / ЗАКЛЮЧЕНИЕ

Thus, the clinical, neurophysiological, neuroimaging, and pathomorphological studies conducted in post-infection epilepsy allowed us to identify specific features in the development of this disease at different stages – from its inception during an acute infectious process to its chronicization with persistent infection. It has been established that a comprehensive analysis of the presence and impact of infectious agents in patients with epileptic seizures is of great importance in the course and prognosis of post-infection epilepsy, which is relevant for timely diagnosis and the development of specific pharmacotherapy.

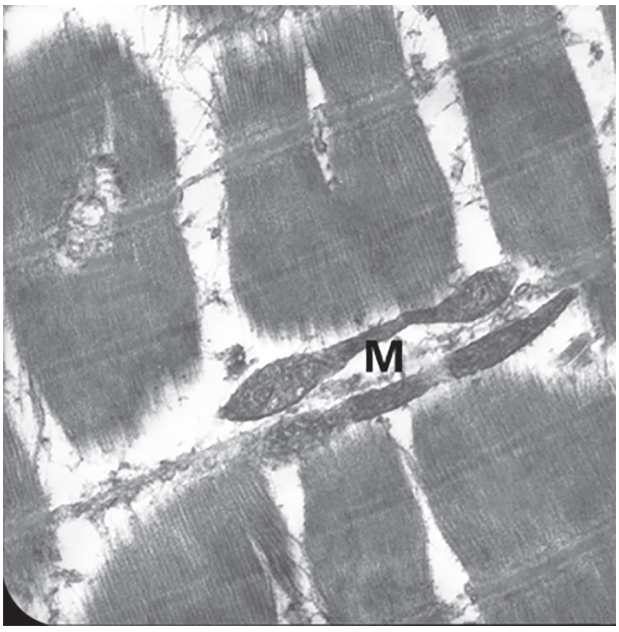


Figure 10. Altered mitochondria (M) in the place of muscle Z-discs (magnification ×10,000)

Рисунок 10. Измененные митохондрии (М) на месте Z-дисков мышцы (ув. ×10 000)

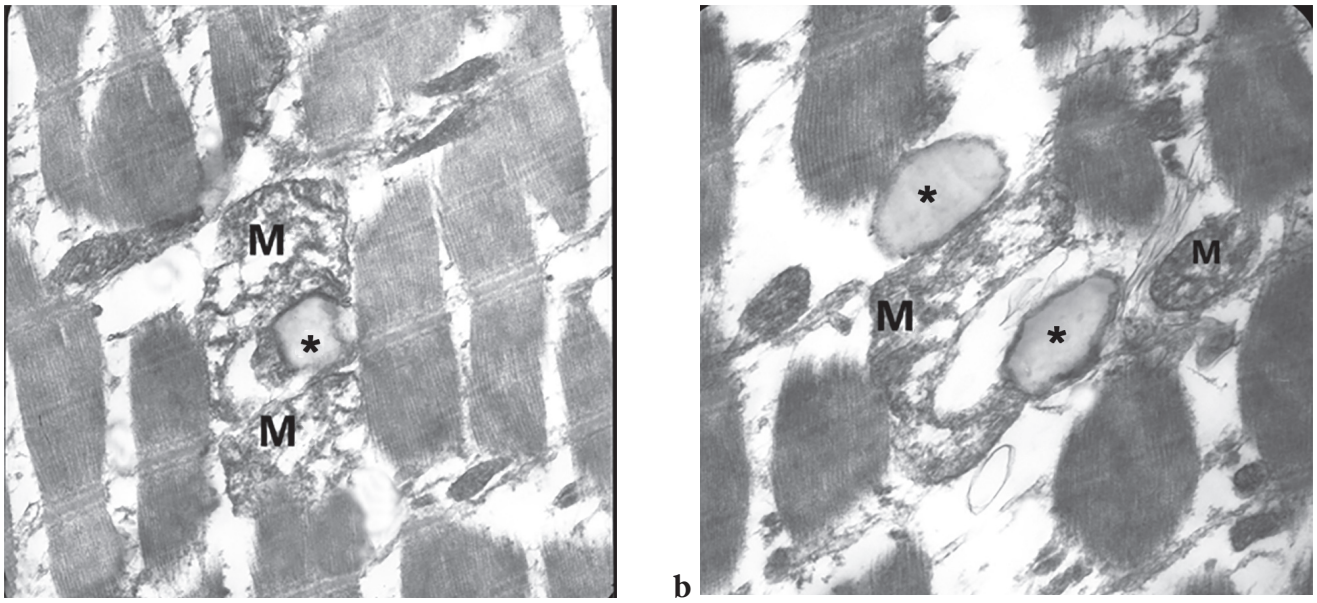


Figure 11. Irregularly shaped mitochondria (M) with altered structure in areas of myolysis (lipids are marked with asterisks):
a – magnification ×8,000; **b** – magnification ×10,000

Рисунок 11. Митохондрии (М) неправильной формы с измененной структурой в участках миолиза (звездочками отмечены липиды):
a – ув. ×8000; **b** – ув. ×10 000

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