Chapter

Epileptic Focus in Drug-Resistant Epilepsy: Structure, Organization, and Pathophysiology

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Abstract

The chapter focuses on how different cutting-edge techniques can be used to study electrophysiological, pathomorphological, and biochemical changes in the "epileptic focus" area of the cerebral cortex and white matter to see how epileptic seizures become drug-resistant and how it affects the other regions of the brain. The authors highlight the significance of neuroinflammation and apoptosis in the epilepsy pathogenesis providing EEG characteristics and describing structural changes in the cortex and white matter under such conditions as focal cortical dysplasia and epileptic leukoencephalopathy. Particular focus is given to structural and functional changes in the hippocampus and the role of hippocampal sclerosis in epilepsy. Key conceptions regarding the epileptic focus formation are outlined.

Keywords: drug-resistant epilepsy, epileptic focus, pathomorphology, FCD, hippocampal sclerosis, leukoencephalopathy, apoptosis, neuroinflammation

1. Introduction

The mechanisms leading to the development of epilepsy have become an area of active research. There is still no pathogenetic treatment for epilepsy, and there is no way to prevent this pathology development [1] with focal temporal lobe epilepsy being the most frequent type (approximately 80% of cases) [2]. The disease progression from the "epileptic neuron" to the "epileptic brain" and an increase in mental and cognitive disorders remain problems beyond solution for epileptology [1, 3–5]. Structural forms of epilepsy are the most difficult for drug correction, and most of them belong to drug-resistant epilepsy (DRE). Mesial temporal epilepsy, the structural basis of which is mesial temporal sclerosis, or hippocampal sclerosis is a more common form of temporal epilepsy. The etiopathogenesis of mesial

temporal sclerosis has been the subject of active discussion since its first description by Sommer [6]. While the pathogenesis of hippocampal sclerosis remains a controversial and unclear issue, the role of the hippocampus in the development of medial temporal epilepsy is obvious. In the absence of effective medical treatment, the only effective, however the most radical, way is surgical intervention, in which the affected area of the brain is isolated and removed, which can help get rid of epileptic seizures. However, only half of the patients show positive results [3]. It is the heterogeneity of structural lesions and significant differences in functional and molecular biological state of cells that can play a key role not only in the pathogenesis of epilepsy but also in triggering insensitivity to drug therapy, as well as in determining the disease prognosis [7].

2. Neurophysiological correlates structural and functional disorders in temporal lobe epilepsy

2.1 Functional zones of the epileptic focus

The pathogenetic basis of epilepsy is the pathological system of the epileptic focus formed by constellations of neurons with grossly altered excitability parameters, which underpins their tendency to hypersynchronization and generation of discharge activity [8]. An epileptic focus displays the properties of a pathological determinant in the formation of a pathological system.

An epileptic focus should be considered as a set of several zones, each of which determines its own aspect in the clinical and neurophysiological picture of epilepsy: (1) the seizure-onset zone, (2) the symptomatogenic zone, (3) the zone of irritation (irritation), (4) the zone of functional deficiency, and (5) the zone of epileptogenic damage (epileptogenic focus) (**Figure 1**). The concept of focal epilepsy implies the presence of the so-called epileptogenic zone—a set of pathologically altered neuronal formations that make up the determinant generator in the epileptic system [8, 9]. Effective surgical treatment is believed to depend on the possibility to remove the epileptogenic zone, which results in complete release from seizures.

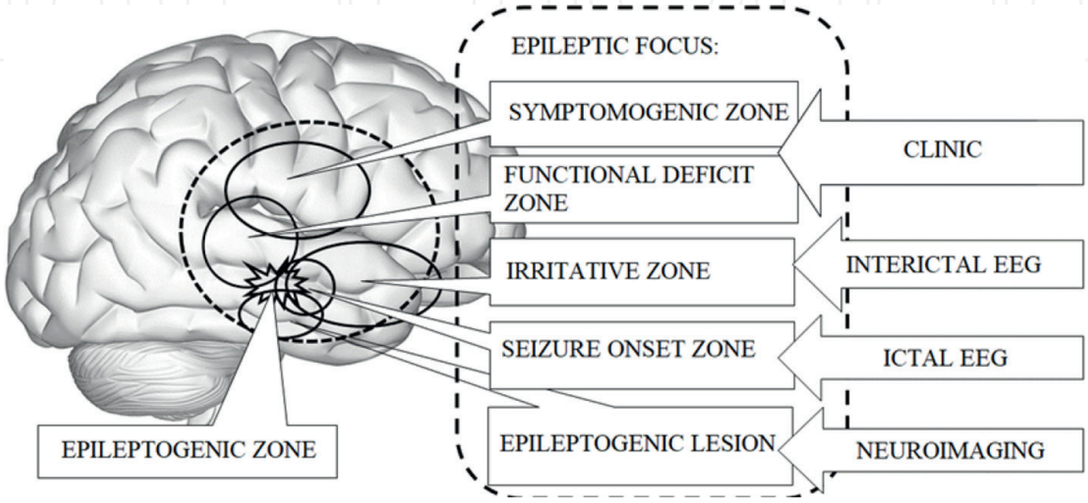

Figure 1.
Structural and functional organization of epileptic focus (scheme).

The zone of epileptogenic damage is an area of structural changes in brain tissues. Intrahemispheric and convexital tumors, cavernomas, arteriovenous malformations, and other structural changes may be associated with the development of epilepsy. These forms of epilepsy are qualified as structural epilepsy (in previous classifications—symptomatic epilepsy). Neuroimaging studies are conducted to identify epileptogenic damage.

The symptomatogenic zone is an area of the cortex, the activation of which during the circulation of epileptic discharges forms a clinical picture of a typical epileptic seizure for a patient. For greater accuracy of localization of the symptomatogenic zone, video recording of the seizure is used. Detailed clinical manifestations of the seizure are formed with a significant spread of pathological activity in the cortex. Consequently, the symptomatogenic zone is often more widespread than the seizure-onset zone. *The zone of functional deficiency* is an area of the cortex, the dysfunction of which in the post-access (less often—in the inter-access) period determines the clinical symptoms of "loss."

The seizure-onset area, that is, the cortex area generating hypersynchronous discharge activity when an epileptic attack occurs is the closest to the epileptogenic zone. To localize the seizure onset, an attack (ictal) should be registered with electroencephalography (EEG) and video recording of an ictal event. The irritative zone in the cortex is localized by the interstitial (interictal) epileptiform activity registered on the EEG [10].

2.2 Epileptic focus identification

To accurately localize the epileptic focus, for surgical resection purposes including, all patients undergo a comprehensive clinical neurological and electrophysiological examination (EEG), video EEG registering an epileptic seizure typical for a patient, in some cases invasive monitoring is carried out, neuroimaging examination (high-field magnetic resonance imaging (MRI) and positron emission tomography).

The reference method for detecting the zone of epileptic activity with structural temporal epilepsy is scalping video EEG monitoring when an ictal event is registered. In a complex diagnostic situation, when the scalping EEG does not allow to accurately localize the seizure-onset area, continuous invasive monitoring of the bioelectric activity of the brain is recommended [11]. When clinical and electroencephalographic data indicate possible involvement of the hippocampal complex in the epileptic system, invasive monitoring of the bioelectric activity of deep brain structures is performed: Spenser-type electrodes are installed stereotaxically in the basal and medial parts of the temporal cortex, in the hippocampus and amygdala, and less often in other structures. The choice of target structures is based on clinical picture analysis, scalp video EEG monitoring results, and ictal events semiology [12].

2.3 Bioelectric activity of the hippocampus

The dominance of slow-wave delta-band activity has been shown to be the distinctive feature of bioelectric activity tracks in the presence of hippocampal sclerosis as it accounts for up to 50% of the spectral power (**Figure 2**). Bioelectric activity tracks registered in the hippocampus without signs of structural lesions were not parametrically homogeneous. Two subgroups were clearly distinguished: a subgroup of hippocampus with bioelectric activity parameters similar to the group of damaged hippocampus and a subgroup of hippocampus, the spectral composition of activity of

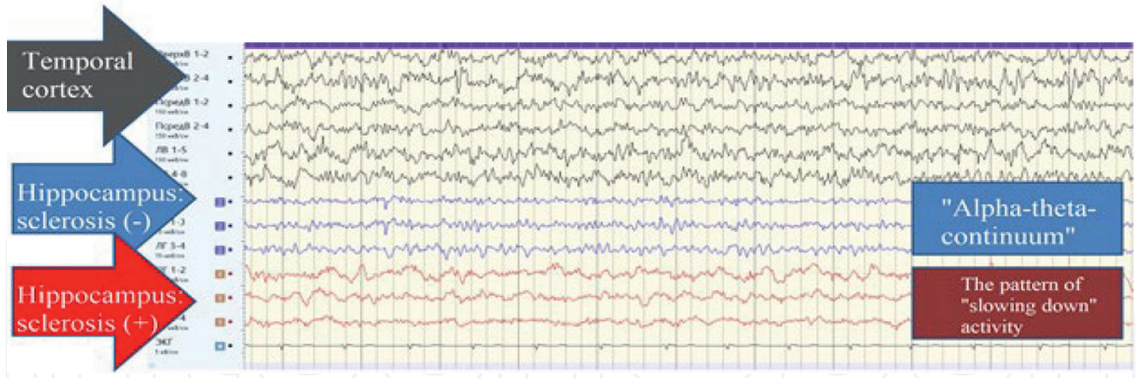

Figure 2.
Extraoperative monitoring of bioelectrical activity of the temporal cortex and hippocampus.

which was mainly in the alpha range. The similarity of the parameters of bioelectric activity in the second subgroup and in the group with obvious structural changes in the hippocampus suggests that hippocampal lesions did not reach the level necessary for damage signs neuroimaging, but the compromise of the hippocampus was sufficient to form a slow-wave pattern of "loss of activity" [13].

To clarify the mechanisms of bioelectric activity formation in the hippocampal complex, we performed a coherent analysis of amplitude-frequency parameters. Low coherence values in the analyzed lead pairs allow concluding that the bioelectric activity recorded in the hippocampus area is generated by the hippocampus itself and do not originate in the nearby areas of the temporal lobe cortex. Of course, it is not possible to completely exclude the possibility of electrical activity from brain areas in which invasive electrodes have not been implanted. However, this process is unlikely, judging by very low values of the coherence coefficients in the lead pairs under study.

Thus, bioelectric activity of the hippocampal complex in its structural lesion specifically features stable registration of the epileptiform activity of the average index with delta activity domineering and making up to 40–50% of the spectral power [13]. In the absence of neuroimaging signs of hippocampal complex structural lesions, the pattern of bioelectric activity can be predominantly formed by the activity of *theta* and *alpha* frequency ranges and may be similar to the slow-wave pattern in hippocampal sclerosis. This may be another evidence of the unified thalamic mechanisms of generating activity of alpha and theta frequency ranges known as the "alpha-theta continuum" conception [14, 15].

2.4 General anesthesia effects on the hippocampus bioelectric activity in epilepsy

When performing intraoperative examinations, it is important to take into account the general anesthesia type. Total intravenous anesthesia using drugs, such as propofol, which have a pronounced GABA-positive effect, in medium-effective doses causes the generation of high-frequency activity [16]. This makes it difficult to verify discharge epileptiform activity on electrocorticography (ECoG) and on electrosubcorticography (EsubCoG). In this regard, during neurosurgical operations, which are performed on patients with DRE, preference is given to inhaled anesthetics (**Figure 3**).

At the same time, the dose of a general anesthetic should not cause the formation of periodic flash-suppression patterns on the ECoG, and even more so on the EEG, since with such deep depression, epileptiform stigmata are either not registered [17, 18] or the source of their generation becomes difficult to localize [19, 20].

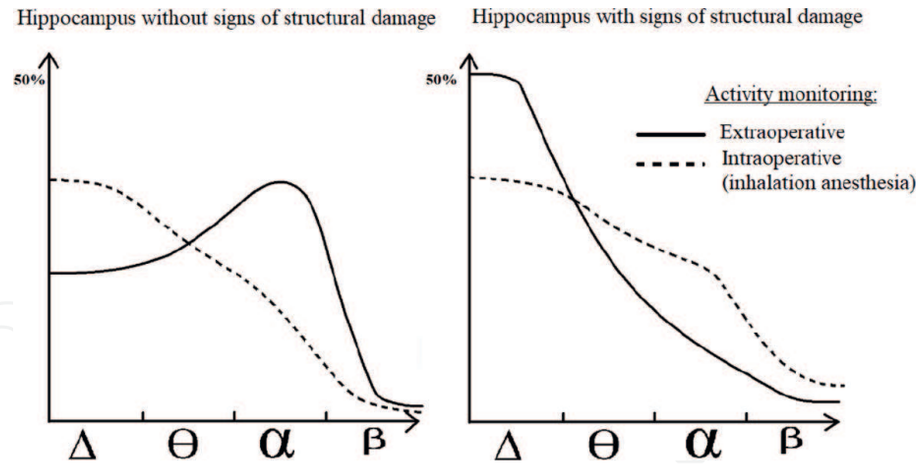

Figure 3.
Changes in the amplitude-frequency parameters of the bioelectrical activity of the hippocampal complexes under the action of inhalation anesthetic sevoflurane (scheme).

3. Pathomorphology of epileptic foci

3.1 Structural heterogeneity of the epileptic focus

Morphological studies of the brain in epilepsy have been actively conducted for 60–70 years. Structural changes in people suffering from epilepsy were found to be nonspecific and occur in different combinations in almost all patients. When studying the issues of epileptic foci localization, more attention is paid to the verification of nosologically determined forms of pathologies (tumor, malformations, etc.) and the so-called "sclerosis" of the hippocampus, which are attributed to the epileptogenic component of the epileptic system [21, 22]. Most studies of the epileptic activity zone focused on the neuronal complexes of the cortex and subcortical formations, and more specifically, on a damaged ("sick") neuron, or rather, a group of neurons capable of generating overexcitation with its spread to other brain structures or to the brain as a whole. However, epilepsy of different origins reveals significant structural changes not only in the gray but also in the white matter of the brain. However, little attention is paid to nonspecific morphofunctional characteristics of changes developing in the epileptic focus [22, 23].

During the pathomorphological examination of biopsies of the temporal lobe and hippocampus from the epileptic foci zone, a permanent complex of pathomorphological changes is verified, representing a combination of various pathological processes of both dysplastic and secondary degenerative-dystrophic and reactive-adaptive nature, accompanied by the development of substitutive gliosis and atrophy, including the hippocampal formation [7, 23]:

- cortex architectonics distortion (focal cortical dysplasia, foci of neuronal prolapse, and atrophy);
- reactive-destructive changes in cortical neurons (dystrophic changes of neurons, "shadow cells," satellitosis, and apoptosis);
- heterotopy of neurons into white matter;
- myelin damage and demyelination;

- rarefication of white matter and microcysts;
- sclerosis and dystonia of small vessels, angiomatosis;
- cellular astrocytic gliosis of white matter with oligodendroglia hyperplasia;
- hippocampal sclerosis with neuronal lesion and astrocytic gliosis.

3.2 Structural changes in the temporal lobe cortex

3.2.1 Focal cortical dysplasia (FCD)

Focal cortical dysplasia (FCD) is most often associated with structural DRE, including MR-negative or former cryptogenic. FCD is a type of cerebral cortex development disorder as a result of abnormal proliferation of neurons and glia, due to neuronal migration distortion and pathology of post-migration development [24–30]. They are characterized by a triad of histological signs [31]: disorders in the cerebral cortex layers formation (dyslamination) (type I), the presence of dysmorphic neurons and balloon cells (type II) (**Figure 4A, C,** and **D**). In addition, according to I. Blümcke et al., there are 2 more signs [32]: smoothness of the border between gray and white matter with the presence of a large number of heterotopic neurons in the white matter and myelination disorder in the adjacent white matter. Dyslamination to varying degrees always occurs with all variants of FCD but is especially pronounced with type I FCD. Dysmorphic neurons are characterized by

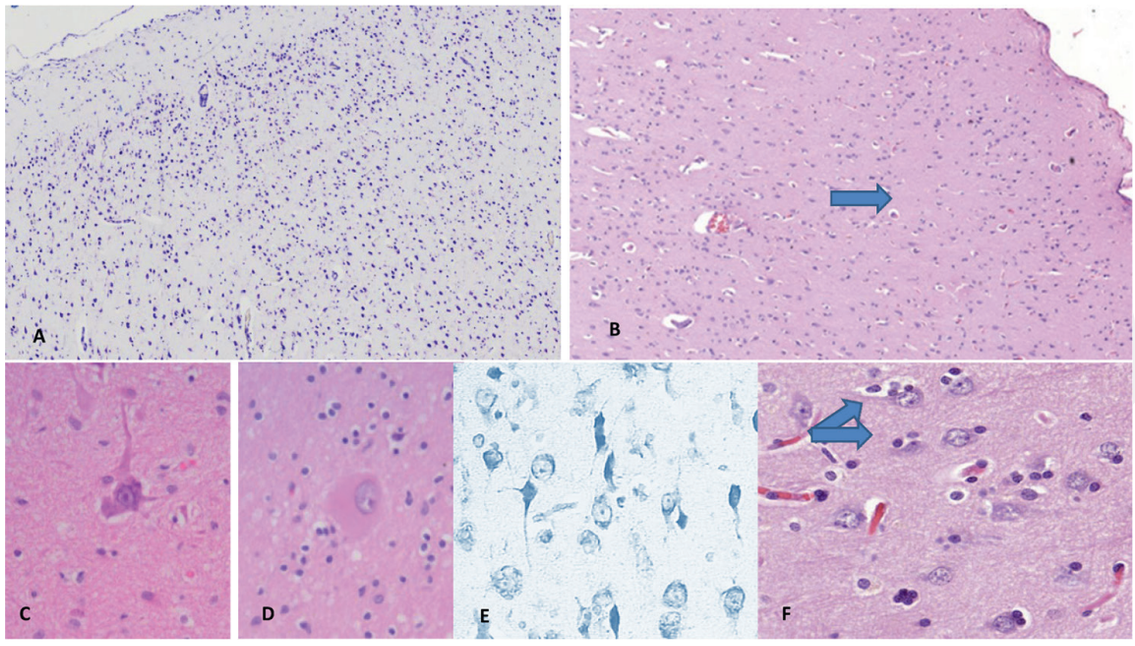

Figure 4.
Structural changes of the gray matter of the brain. A—Disorders of horizontal lamination and area of increased cellularity of the molecular layer. Nissl stain, x 100. B—Atrophic changes in the cortex: Disorders of architectonics with foci of neuronal prolapse (indicated by an arrow) and severe scalloped marginal layer of the cortex. H&E, x 100. C—Dysmorphic neuron (enlarged, with thickened processes, aggregation and displacement of the Nissl substance to the cell membrane. H&E, x 400. D—A large ballon cell with an opalescent "vitreous" cytoplasm with no Nissl substance. H&E, x 400. E—Most neurons are in a state of acute swelling with the phenomena of neuronophagy. Individual cells are in a state of wrinkling. Nissl stain, x 400. F—Ischemic changes in neurons, satellitosis, and neuronophagy (indicated by an arrow). H&E, x 400.

a significant increase in cell size, large cell nuclei; abnormal location of the Nissl substance (with a shift to the cell membrane); and accumulation of neurofilaments in the cytoplasm (type IIa) [32]. The presence of balloon cells is a distinctive feature of type IIb FCD. Balloon cells are found in all layers of the cortex (including layer I) and are represented by enlarged cells, often with the presence of several nuclei ("poly-nuclear" with "bridges" between them) and opalescent "vitreous" cytoplasm with the absence of Nissl substance [33].

Type III PCDs are a combination of cortical lamination disorders with other local pathological changes in the brain. The most common variant is a combination of cortical dysplasia with hippocampal sclerosis.

3.2.2 Reactive-destructive changes in cortical neurons

In the cortex, reactive-dystrophic and destructive changes of neurons are observed in nerve cells (**Figure 4E**). Neurons with hydropic dystrophy, chromatolysis, and vacuolization of the cytoplasm, alternate with hyperchromic shrunken cells. Among the altered neurons, "shadow cells" are identified that have retained the outlines of the cytoplasm with complete lysis of the nucleus. These changes are accompanied by moderately pronounced satellite disease and neuronophagy (**Figure 4F**). Reactive-destructive changes of neurons in the epileptic focus are accompanied by the ease of triggering membrane potentials, also contribute to the selective loss of GABA-ergic synaptic terminals, and are considered as morphological manifestations of partial neural deafferentation. In turn neural deafferentation causes hypersensitivity of cortical neurons to the perception of hypersynchronous discharges and determines increased spontaneous neural activity and sensitivity of synaptic receptors [34].

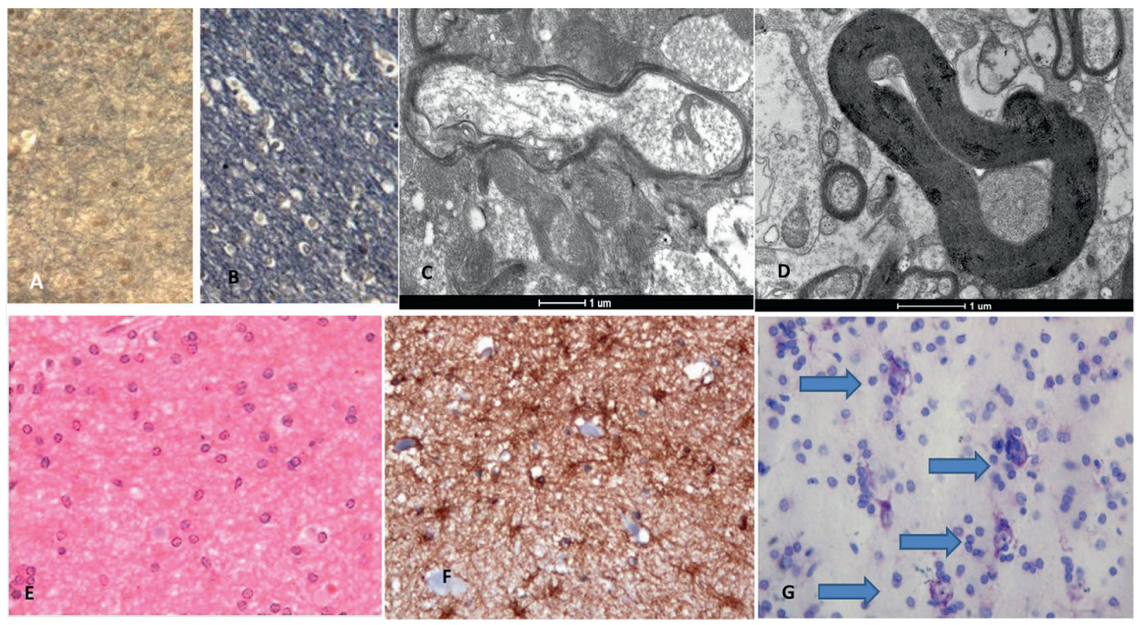

Figure 5.
Structural changes of white matter. A—White matter demyelination in a patient with DRE. Spielmeyer staining absent, × 200; B—Spielmeyer staining white matter rich in norm myelin. × 200; C—Longitudinal section of myelinated fiber with areas of granular myelin decay. Electronogram, × 16,500; D—Hypermyelination and destruction of the axial cylinder. Electronogram. × 20000; E—Increased cellularity of white matter due to glial elements (gliosis). H&E, x 400; F—Astrocytic gliosis. Immunohistochemistry with antibodies to GFAP, x 400; and G—Ectopic neurons (indicated by an arrow) among gliosis. Nissl stain, x 400.

3.2.3 Foci of prolapse and atrophy of the cortex

In patients with DRE, all cases under study have demonstrated architectonic disturbances in the temporal lobe of the brain at the site of neuron death due to areas of complete loss of nerve cells and/or small-cell areas of small atrophied neurons and single gliocytes, as well as the phenomenon of cortical atrophy with a scalloped gyrus surface and a compacted neuropile of the I layer (**Figure 4B**).

3.3 Structural changes of white matter

3.3.1 Damage to the myelin sheath

In biopsies of patients with epilepsy with Spielmeyer staining for myelin, areas of weakly colored fibers, an indistinct border with the bark due to the depletion of fibers by myelin has been revealed (**Figure 5A–D**). During electron microscopic examination, significant damage to the myelin sheaths of axons is recorded, as manifested by myelin stratification, homogenization of its layers, and complete demyelination of axons. Most axons with damaged myelin sheaths retain their viability. This indicates that demyelination is not a secondary process and is not associated with the death of neurons and its processes. In addition, along with demyelination, depletion of the white matter by neurofilaments has been observed, that is, a decrease in the number of neuronal axons. Research data shows that the occurrence of epilepsy is associated with damage to the myelin sheath [23, 35–37]. Demyelination of fibers in the focus of epileptiform activity and adjacent pathways cause transverse neurotransmission and generalization of nerve impulses with simultaneous involvement in epileptogenesis of various brain regions. Experimental studies have found that epilepsy reduces not only the amount of the main protein myelin but also the number of mature oligodendrocytes [35, 37].

3.3.2 Gliosis

Glial proliferation is considered to be a pathological substrate of epilepsy [38–40]. Gliosis is an integral part of the pathomorphological changes that are found in epileptic foci. Gliosis in the white matter is a uniform distribution of gliocytes with rounded stamped nuclei, and some cells have an optically empty cytoplasm, representing drainage forms of oligodendrogliocytes (**Figure 5E** and **F**). Immunohistochemical examination reveals clusters of intensely colored hypertrophied reactive astrocytes with pronounced processes.

Recent studies have revealed the involvement of electrical synapses (gap junction) in epileptogenesis, and it has been noted that the expression of the astrocytic protein connexin (connexin—C×43) is increased in patients with epilepsy associated with brain tumors and hippocampal sclerosis [41, 42].

The authors associated the increase in the amount of the C×43 protein with an increase in synaptic connections caused by intense electrochemical activity in "epileptic conditions." Thus, being not directly involved in the origin of paroxysmal discharges, the distribution patterns of C×43 protein can be involved in the development of (hyper) synchronization of neural discharges, providing a "short circuit" between electrically activated neurons, acting as "bridges" between different clusters of neural hyperexcitability, thus allowing the rapid spread of electrical activity [42, 43].

Clinical and morphological studies have recently proved that gliosis in DRE is not a pathological but an adaptive (protective) reaction: The more intense the proliferation of astrocytes, the milder the disease proceeds [44]. These data confirm the importance of glia in the pathogenesis of epilepsy. The research has shown that proliferation of oligodendroglial-like cells in epileptic foci can serve as a substrate for multifocal brain damage, which requires repeated resections. The specific neurophysiological mechanisms of excitability and epileptogenesis in oligodendroglial hyperplasia remain unclear since glial cells lack an action potential. Oligodendroglial hyperplasia may have direct or indirect effect on the population of subgranular cortical layer's neuronal cells with subsequent disruption of neural network activity and may represent an epiphenomenon due to repeated seizures from an unidentified focus [45].

3.3.3 Heterotopic neurons in the white matter

A typical morphological finding is heterotopic neurons in the subcortical zone. Random neurons of medium size, usually with the phenomena of hydropic dystrophy, are located in the deeper parts of the white matter (**Figure 5G**). A. Palmini et al. (2004) was introduced the term "mild developmental disorders of the cerebral cortex" due to the presence of a large number of clusters of heterotopic neurons located in the molecular layer of the cortex or in the subcortical white matter [29]. This persistent phenomenon is attributed to characteristic signs associated with FCD [32]. It is still unclear whether the density of heterotopic neurons in the white matter increases in patients with epilepsy and what the threshold for diagnostic confirmation of small cortical malformations should be [46], since the severity of these pathological signs correlates with preoperative MRI and is a clinically significant prognostic biomarker, in particular, for the result after surgery for epilepsy [47]. According to our data, in patients with epilepsy, the number of neurons in the white matter is significantly higher compared to other pathologies without epilepsy [7].

3.3.4 Microcystis

The white substance has a porous or microcystic structure (**Figure 6A–C**). There is a rarefication up to the microcystic transformation of white matter, the appearance of criblures with the expansion of spaces around the vessels. Thin collagen fibers are visible in the walls of some cysts. Electron microscopic examination revealed that the marginal zone of the cavities consists of three components. The distinctive feature of the internal component is its constant thickness (0.18–0.20 microns). It is represented by electron-dense material, in which fibrils are distinguishable. The main feature of the second (intermediate) component is a large number of collagen fibers. In some cases, they are visible even with light microscopy on preparations stained by the Van Gieson and Mallory methods. The outer component of the marginal zone is represented by edematous processes of astrocytes.

Damage to the vessels often causes the appearance of pseudocysts. However, they could develop in the outcome of inflammation and loss of myelin as well. In some cases, brain death can be assumed to occur due to ischemia and/or damage by blood plasma.

3.3.5 Angiopathy

Degenerative vascular changes are a typical phenomenon in the epileptic focus area. These are characterized by sclerosis or hyalinosis of the walls, formation of

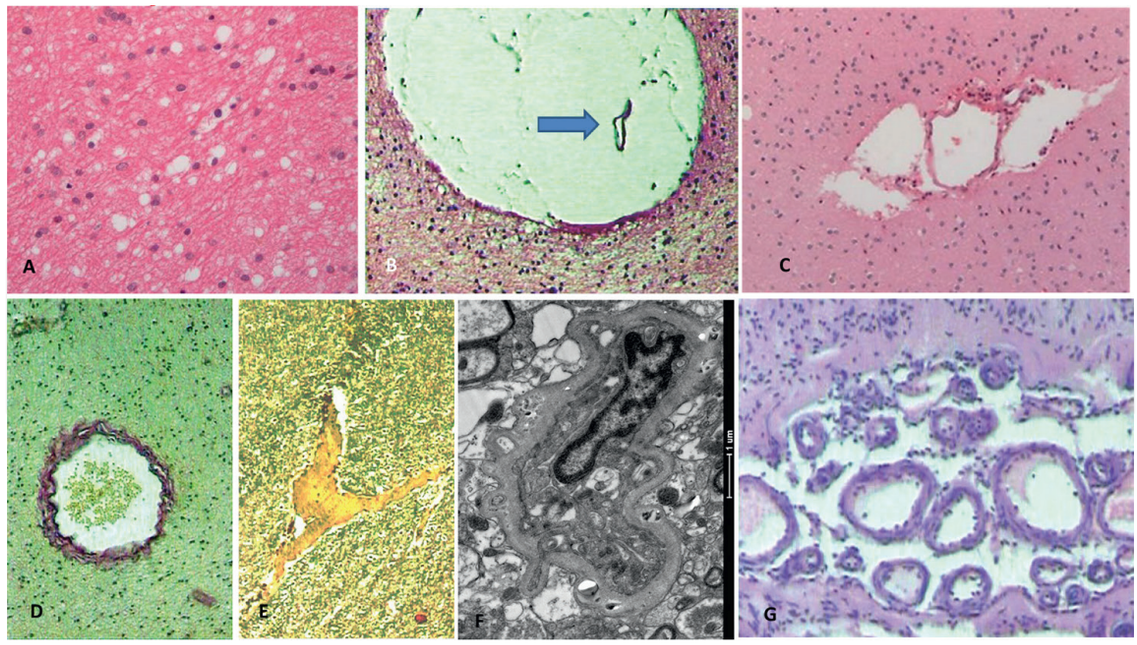

Figure 6.
Microcysts and angiopathy white matter. A—Microcystic transformation of white matter. H&E, x 400; B—Criblyura in white matter. A wide perivascular space forming a cavity. There is a small vessel in the lumen. H&E, x 200; C—Perivascular micro-cavity as a result of encephalolysis. H&E, x 200; D—A vessel with sclerosis thickened wall. Van Gieson stain, x 200; E—Dilated vein with uneven contours, with blood stasis. The sclerosed vein wall forms invaginates. Van Gieson stain, x 200; F—Unevenly thickened basement membrane of the spasmodic capillary. Electronogram. × 11500; and G—Foci of angiomatosis in the subarachnoid space. H&E, x 200.

convolutes and invaginates, and an increase in the diameter and wall stretching (**Figure 6D** and **E**).

Ultrastructural studies record damage to the capillary bed involving all elements of the blood-brain barrier (BBB) (**Figure 5F**). The nuclei of endotheliocytes are deformed and multilobed, and the cytoplasm is edematous. The basement membrane loses the clarity of contours, becomes loose, and uneven in thickness, marked by delamination and vacuolization foci. The perivascular coupling is represented by edematous processes of astrocytes, and many fragments of capillaries are completely devoid of it. In these zones, myelinated axons with significantly damaged myelin are closely attached to the vessels.

There were signs of restructuring the vascular bed with the formation of foci of angiomatosis. The changes detected are attributed to the consequences of chronic hemodynamic disorders, aggravating hypoxia in the tissues, which in turn contributes to the development of convulsive states.

3.4 Hippocampal sclerosis

Hippocampal sclerosis is a common morphological substrate in temporal lobe epilepsy and is characterized by hippocampus cellular structure disorders, that is, neuronal death and gliosis [32, 33, 48]. Although the generally accepted meaning of "sclerosis" (from the Greek word *scleros*—seal) is the sealing of an organ with the replacement of parenchymal cells by connective tissue, in the pathology of the nervous system, it also implies gliosis [49]. This phenomenon is also called mesial temporal sclerosis, incisural sclerosis, or "Ammon's horn sclerosis" [50]. Along with the death of neurons and proliferation of glia in hippocampal sclerosis, dispersion of

granular cells of the dentate gyrus is detected [51]. It is characterized by the expansion of the granular layer, the separation of cells from each other with a violation of the compact dense structure, and their spread into the molecular layer (**Figure 7**). The presence of hippocampal sclerosis and extra-hippocampal pathology is called "dual pathology," which occurs in 5–34% of cases of temporal lobe epilepsy [50, 52].

However, in addition to structural changes in the hippocampal formation, functional ones are also distinguished, which include loss of GABAergic neurons, lack of reelin, axonal springing of mossy fibers, and neurogenesis. Loss of hippocampal neurons can also be observed in other pathological conditions, including neurodegeneration, aging, and ischemia, but the nature of neuronal loss varies significantly [53] and usually affects the subiculum [54, 55].

While the pathogenesis of hippocampal sclerosis is still a controversial and unclear issue, the role of the hippocampus in the development of medial temporal epilepsy is obvious. The normal cytoarchitectonics of the hippocampus, the density of neurons in it, and their unidirectional spatial orientation create conditions for hyperexcitability along synaptic and extra-synaptic ephaptic pathways [5]. According to experimental data, the hippocampal formation has the lowest threshold of convulsive readiness, 10 times lower than that of the sensorimotor cortex [56]. It was previously assumed that the death of neurons, cellular reorganization, and glial proliferation in the hippocampus during its sclerosis lead to increased excitability of granular cells of the dentate gyrus, which spreads from the hippocampus and generates an epileptic seizure [57]. The death of inhibitory interneurons, the formation of synapses, and the proliferation (springing) of mossy fibers of excitatory neurons can also lead to the formation of a focus of hyperactivity. Some authors believe that the growth (springing) of mossy fibers is a compensatory-restorative process [58].

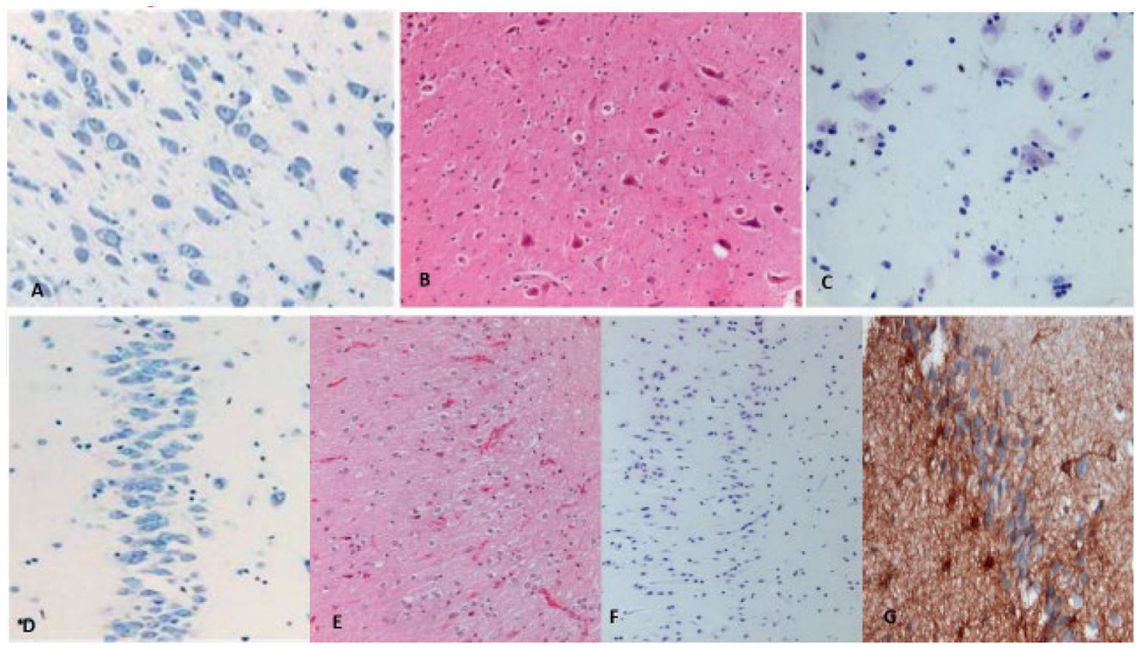

Figure 7.
Hippocampal sclerosis. A—The nucleus of the hippocampus, without significant changes. Nissl stain, x 200; B—Severe disorders of cytoarchitectonics, atrophic changes in the form of foci of prolapse of neurons in the nuclei of the hippocampus, up to the emptying of structures. H&E x 200; C—Preserved neurons with the phenomena of satellite disease. Nissl stain, x 400; D—Dentate gyrus without significant changes. Nissl stain, x 200; E—Dispersion of the granular layer of the dentate gyrus. H&E, x 200; F—Bifurcation of the granular layer of the dentate gyrus. Nissl stain, x 200; and G—Astrocytic glial proliferation in the dentate gyrus. Immunohistochemistry with antibodies to GFAP, x 400.

Comparison of the two groups (with and without epilepsy) against the totality of the neuron density values and glia cellularity allows us to state that the hippocampus in patients with DRE is a homogeneous cluster, regardless of the degree of morphological changes, which indicates the formation of a specific "epileptic" hippocampus in this category of patients [59].

While the epileptic system is being formed, the hippocampus can act as a "generator" of increased arousal, the primary focus of epilepticism, and can also be involved in the process of epilepticism of the brain as a result of triggering extra-hippocampal forms of the disease.

4. Glioneuronal apoptosis

Astrocytes are known to play an important role in epileptogenesis [60–62]. Astrocyte apoptosis is assumed to activate during and after a convulsive attack and may contribute to neuronal death and epileptogenesis [63]. Our studies have demonstrated that apoptosis can be observed mainly in oligodendrocytes, single astrocytes, and a small part of neurons only (**Figure 8**) [40, 64, 65].

A study on rat oligodendrocyte culture showed that oligodendrocyte apoptosis in the epilepsy model was higher than in the control one [66]. There is evidence that NK cells can induce apoptosis in both neurons and mature oligodendrocytes via the FAS-FAS-L pathway [67]. The main function of oligodendrocytes is the formation of axon myelin sheaths. In epilepsy, the number of mature oligodendrocytes and the

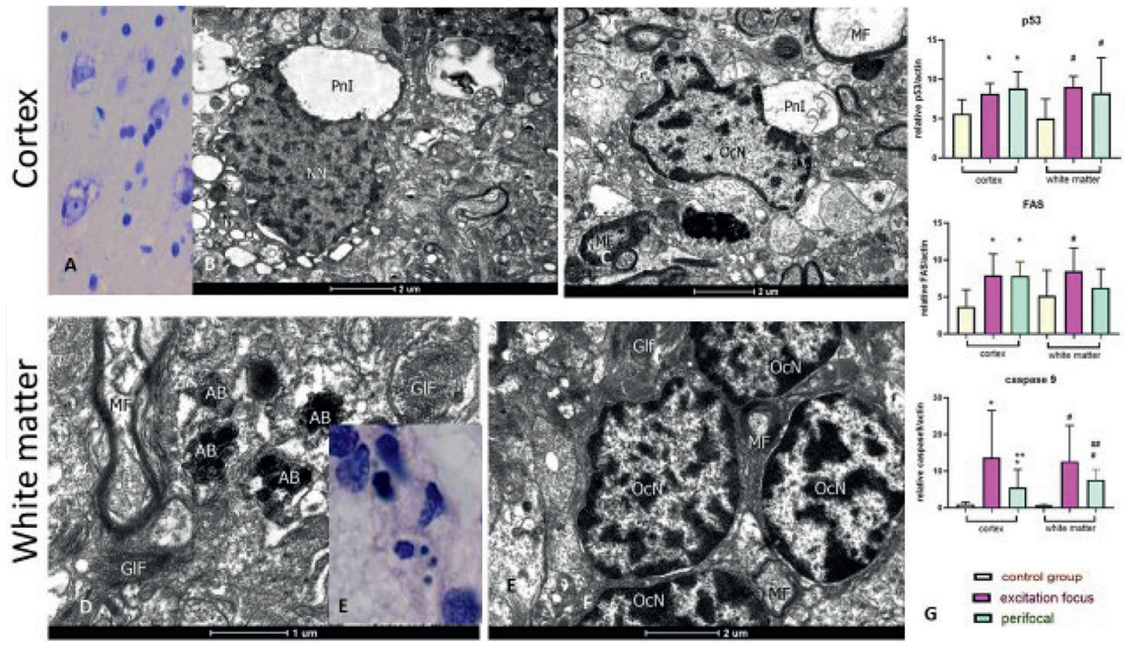

Figure 8.
*Glioneuronal apoptosis in the epileptic focus of the temporal lobe. A—Destructive changes in neurons (deformation of the nuclei, pronounced vacuolization, and local cytoplasmic tigroid). Increase in the number of glial cells. Nissl staining, ×400; B—Vacuoles and perinuclear inflation in an apoptotic neuron (N); ×8200; C—Perinuclear inflation in the oligodendrocyte; ×8200; D—Apoptotic bodies in the intercellular space;×16,500; E—Apoptotic bodies in the white matter of the brain. Nissl staining, ×1000. Immersion; F—The initial stage of apoptosis. An accumulation of oligodendrocytes in the white matter of the brain, the heterochromatin of which is distributed throughout the nucleus in large conglomerates. OcN: Oligodendrocyte nucleus, GlF: Gliofibrils, MF: Myelin fibers; ×8200; and G—Histogram of the content of proapoptotic proteins in cortical and white matter biopsies of patients with DRE compared to control group patients. *Cortex, $p<0.05$; #white matter, $p<0.05$. Electronogram—B, C, D, and F.*

amount of myelin decreases [35]. In the hippocampus of rats, the loss of myelin and oligodendrocytes begins in the acute phase and progresses in the latent and chronic phases of epileptogenesis [68].

The survival of oligodendrocytes depends on many factors, including the condition of astrocytes, which secrete growth factors important for the survival of neurons, glia, and glial proliferation [7]. The loss of oligodendrocytes leads to an imbalance of excitation and inhibition in the brain and provokes the formation of an epileptic focus or exacerbates the severity of epilepsy [35].

5. Neuroinflammation

5.1 The cytokine levels in blood plasma in drug-resistant epilepsy

According to experimental and clinical data, DRE is characterized by the presence of neuroinflammation in an epileptogenic focus [69]. Glial cells, such as astrocytes and microglia, produce and release cytokines and chemokines, which play an important role in the development of chronic neuroinflammation in epilepsy [70]. Cytokines can have both pro- and anticonvulsant activity, acting on AMPA and NMDA receptors and having a neurotoxic effect. Detecting cytokines such as TNF-α, IL-1, and IL-8 in the blood typically indicates acute inflammation. Their effects are regulated by the pro-inflammatory IFN-γ, IL-12, and inflammatory inhibitors, such as IL-10, expressed in response. We studied the cytokine levels in blood plasma samples of DRE patients (multiplex analysis). However, our results demonstrate a normal level of the studied cytokines, except for an increased level of TNF-α and insufficient IL-2. IL-2 is known to promote the regeneration of neurons after their damage, and also stimulates the proliferation and differentiation of oligodendrogliocytes. The revealed insufficient level of IL-2 may be one of the reasons for the decrease in the bioavailability of therapeutic drugs, depending on the function of the blood-brain barrier (BBB). BBB changes in many pathologies of the central nervous system, including activation of adhesion molecules in the vascular lumen, increased adhesion and transmigration of leukocytes, increased permeability of tight contacts, and extravasation of plasma proteins [71]. Earlier experimental and clinical studies have found that BBB permeability increases in foci of long-term epilepsy, and artificially induced BBB dysfunction leads to the appearance of epileptic foci in previously healthy brains [72, 73].

IL-4 is involved in balancing neuroinflammation. Our data showed an increase in IL-4 levels, which may indicate its response to the appearance of TNF-α in the blood. An increase in IL-4 levels may be compensatory for slowing down the synthesis of cytokines of the primary response [74]. The reduced level of IL-8 detected by us may contribute to increased adhesion of neutrophils activated by pro-inflammatory cytokines to endothelial cells. This is how endothelial damage and increased BBB permeability occur [74]. Astrocytes secrete chemokines (EGF, TGF-β, and VEGF), which directly affect endothelial cells. The high content of chemokines in the blood of DRE patients indicates the activation of astrocytes and the negative effect of neuroinflammation on the BBB [75].

5.2 The expression of cytokines in neural tissue in DRE

The study of the content of pro-inflammatory cytokines in the epileptogenic focus itself and its perifocal zone allowed us to assess the course and degree of

neuroinflammation depending on their epileptogenic activity. Our study showed the presence of neuroinflammation and apoptosis in brain tissues. The content of pro and antiapoptotic proteins and pro-inflammatory cytokines (p-NF-kB, TNF-α, p53, FAS, caspase-3, caspase-9, etc.) was analyzed in biopsies of gray and white matter of the temporal lobe of the brain of DRE patients obtained intraoperatively (Western blotting). In the cortex and white matter of the perifocal zone, an increased content of proapoptotic proteins (TNF-α, p53, FAS, caspase-3, caspase-9) has been found against an imbalance of protective pathway proteins (p-NF-kB—p. 65 and p. 105). In the epileptic focus, the process of neuroinflammation prevails over the process of apoptosis. In the samples we took, an increased content of TNF-α cytokine was detected both in the epileptic focus and in the perifocal zone of the focus in the cortex and white matter of the temporal lobe of the brain. Similarly, increased expression of the FAS receptor was observed in the epileptic focus of gray and white matter of the temporal lobe as compared with the values of the control group. In the perifocal zone of the epileptic focus, the expression of FAS was increased only in the cortex, while an upward trend was observed in the white matter. The high content of TNF-α has been found in biopsies of the cortex and white matter of the temporal lobe against the increased expression of the FAS-L receptor, which may indicate activation of immune cells in the brain of DRE patients and neuroinflammatory processes in these areas. In the perifocal zone, these processes may occur as well, however, less intensively [76].

Pro-inflammatory cytokines are known to grow in number during seizures, which increases the excitability of neurons and results in recurrent seizures, cell death, and inflammation development [77].

Thus, epileptic seizures, accompanied by neuroinflammation and apoptosis with blood-brain barrier distortion in the background, have a mutually provoking effect and contribute to pathological process to be sustained (**Figure 9**).

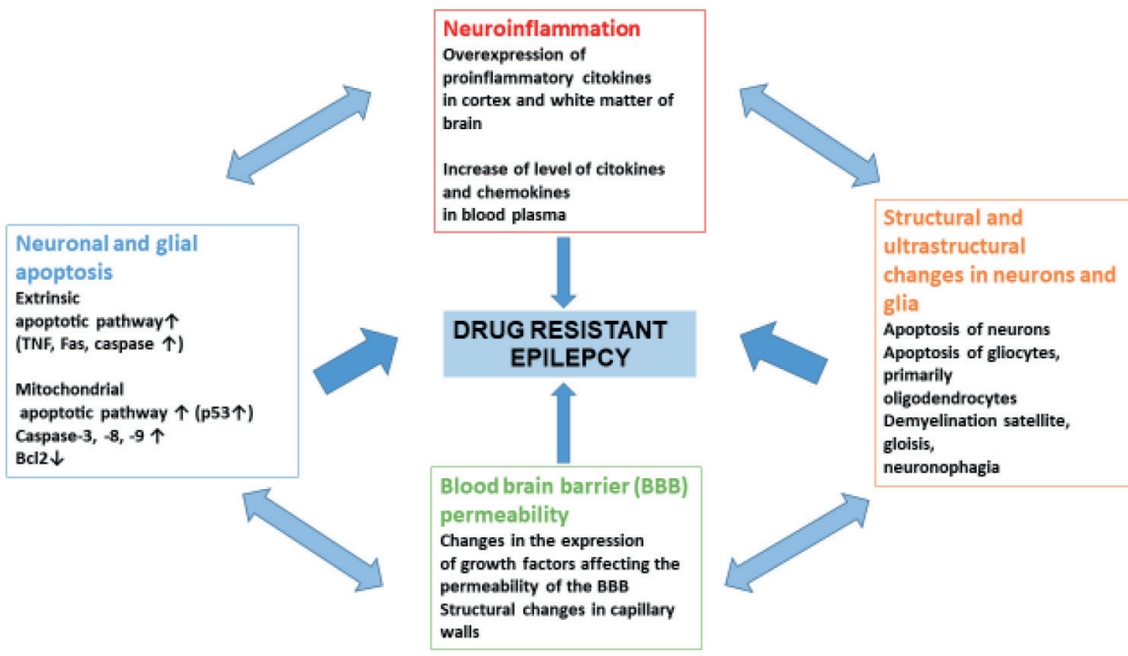

Figure 9.
Pathogenesis of drug-resistant epilepsy (scheme).

6. Epileptic leukoencephalopathy

Changes in brain tissue and its membranes are nonspecific, but the complexity of these nonspecific processes creates a morphological picture of damage and compensatory adaptive processes characteristic of epilepsy. Significant changes are observed in the white matter. Demyelination, angiopathy, and microcysts of white matter, as well as cellular gliosis, which are usually described in epileptic foci, were qualified by O.N. Gaykova (2001) as the syndrome of "epileptic leukoencephalopathy"[23]. This was the first step toward a syndrome approach in the clinical and pathomorphological characterization of epilepsy. Radical structural changes in the white matter in DRE are a zone characterized by discharge and microcystic transformation as a result of cell death, demyelination as a result of repeated seizures, increasing hypoxia with the angiopathy in background, and the blood-brain barrier distortion. The loss of substance in an epileptic focus with reactive astrocyte proliferation is qualified as a parenchymal atrophy of the brain and may already serve as an epileptogenic focus (**Figure 10**).

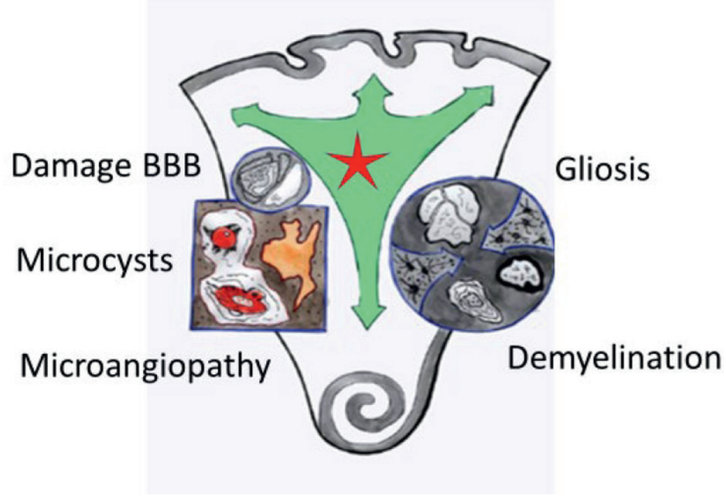

Figure 10.
The epileptogenic role of the structural lesion of white matter (leukoencephalopathy) in the epileptic focus (scheme) (author's drawing by professor O.N Gaikova [78]).

7. Conclusions

The research data demonstrate the heterogeneity and complexity of etiopathogenetic interactions representing the morphogenesis of structural changes detected in the epileptic activity zone (epileptic focus), as a stable epileptic system is forming. The area of epileptic foci in DRE is characterized by the depletion of white matter with myelin and neuronal processes, replaced by astrocytic gliosis and manifested in rarefaction of the neuropile with parenchymal or/and perivascular cystic transformation of brain tissue leading to the formation of epileptic leukoencephalopathy, which in itself can be qualified as epileptogenic focus. Neuronal and oligodendroglial apoptosis in combination with neuroinflammation form a self-sustaining pathological focus, which leads to the progression of the disease and the occurrence of relapses. Reactive-destructive processes in the hippocampus with an outcome in atrophy and

the hippocampus sclerosis reveal specific features and can also be qualified as the structural basis of the drug-resistant epileptic system and can become a factor of epilepticism. In addition, the revealed insufficiency of compensatory and adaptive mechanisms, including glio- and neurogenesis, can ensure the progression of the process and be accompanied by a decrease in sensitivity to drug therapy.

The authors propose the conception of the epileptic focus on heterogeneous structural organization in DRE, which allows qualifying the epileptic focus as a complex structural and functional system with elements of biochemical and mediator processes being distorted, featuring numerous mutually potentiating epileptogenic and supporting epileptic system interactions, and characterized by insufficient compensatory and adaptive mechanisms that ensure the progression of the process, accompanied by a decrease in sensitivity to drug therapy [7].

The conceptual approach to heterogeneous structural organization of epileptic foci in DRE opens up prospects for developing a treatment strategy aiming to break the pathological circle by identifying the targets for therapeutic effects, including possible local lifetime mutations and gene expression.

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Conflict of interest

The authors declare no conflict of interest.

Abbreviations

DRE	drug-resistant epilepsy
EEG	electroencephalography
ECoG	electrocorticography
EsubCoG	electrosubcorticography
FCD	focal cortical dysplasia
BBB	blood-brain barrier

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