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Review

Comorbidity of multiple sclerosis and epilepsy: More questions or answers?

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The literature data of the last three decades on the problem of comorbidity of multiple sclerosis (MS) and epilepsy have been analyzed, such as issues of pathogenesis, clinical course, prognosis, and treatment of this dual pathology. Epileptic seizures occur in 2–3% to 5.9% of patients with MS, which is 3–6 times more common than in the general population. The incidence of epilepsy raises with increasing duration and severity of MS, with its progressive course, and also depends on the effect of drugs for the treatment of MS. There is no unanimity in the literature on the age and gender characteristics of the occurrence of epileptic seizures in MS. Probable mechanisms of MS comorbidity and epilepsy are analyzed. Data on certain common pathophysiology of MS and epilepsy and the concept according to which the model of epilepsy in MS is considered as a network disease are presented. Data on clinical manifestations and diagnosis of comorbid MS with epilepsy are presented. Epileptic seizures can occur at any stage of MS: before the clinical manifestations, at the onset of the disease, in the late stages, or can indicate exacerbation of MS. Types of epileptic seizures with a dual diagnosis (MS + epilepsy) are diverse. The majority of patients (up to 87.5%) have focal seizures (aware or unaware) or focal seizures to bilateral tonic-clonic, and a small share of patients have seizures of unknown origin. Most researchers believe that patients with MS and epilepsy have a more severe MS course and a worse long-term prognosis. The main directions of MS treatment and the impact of such treatment on the development of epileptic seizures are highlighted. Data on the effect of some disease-modifying drugs for the treatment of MS on the course of epilepsy and, on the other hand, on the impact of some antiseizure medications on the course of MS are presented. It is concluded that patients with MS have individual profiles and inter-individual variability of epileptogenicity. The principles of treatment of epileptic seizures/epilepsy in patients with MS are proposed.

Keywords: Multiple sclerosis, epilepsy, comorbidity, seizure, treatment.

Introduction

The modern classification of epilepsy (2017) of the International League Against Epilepsy (ILAE) emphasizes the role of determining its etiology and taking into account comorbidities for correct diagnosis and treatment [1]. Epilepsy in individual groups of patients, previously defined together under the term "symptomatic epilepsy", is now studied with a wider etiological stratification, e.g., epilepsy after a stroke, autoimmune epilepsy, or epilepsy after encephalitis [2]. In the era of personalized care, such data are of great importance to clinicians who are trying to adapt treatment with maximum effectiveness for a patient.

A comprehensive search in multidisciplinary and specialized databases, such as MEDLINE/PubMed, EMBASE/Excerpta Medica, Cochrane Library, and Open Access Journals directory was chosen to study and analyze literature data on various aspects of the comorbidity of multiple sclerosis (MS) and epilepsy. Inclusion criteria for this review were relevant English-language articles published between January 1990 and January 2023 that discussed the prevalence, pathogenesis, diagnosis, course, prognosis, and treatment of two comorbidities – multiple sclerosis and epilepsy. We used the search terms "multiple sclerosis" (all fields) and "comorbidity" (all fields) and ["epilepsy" (all fields) OR "seizure" (all fields)]. We screened 1,402 publications, assessed titles and abstracts, and excluded a further 1,129 sources that did not match the research topic. 273 articles were analyzed in detail and additional 195 were excluded. 78 articles were selected for analysis and subjected to full-text analysis. The final list of references was compiled based on the topic of this review and the relevance of published data over the past 10 years. In the review, we also included older fundamental or outstanding studies in the field.

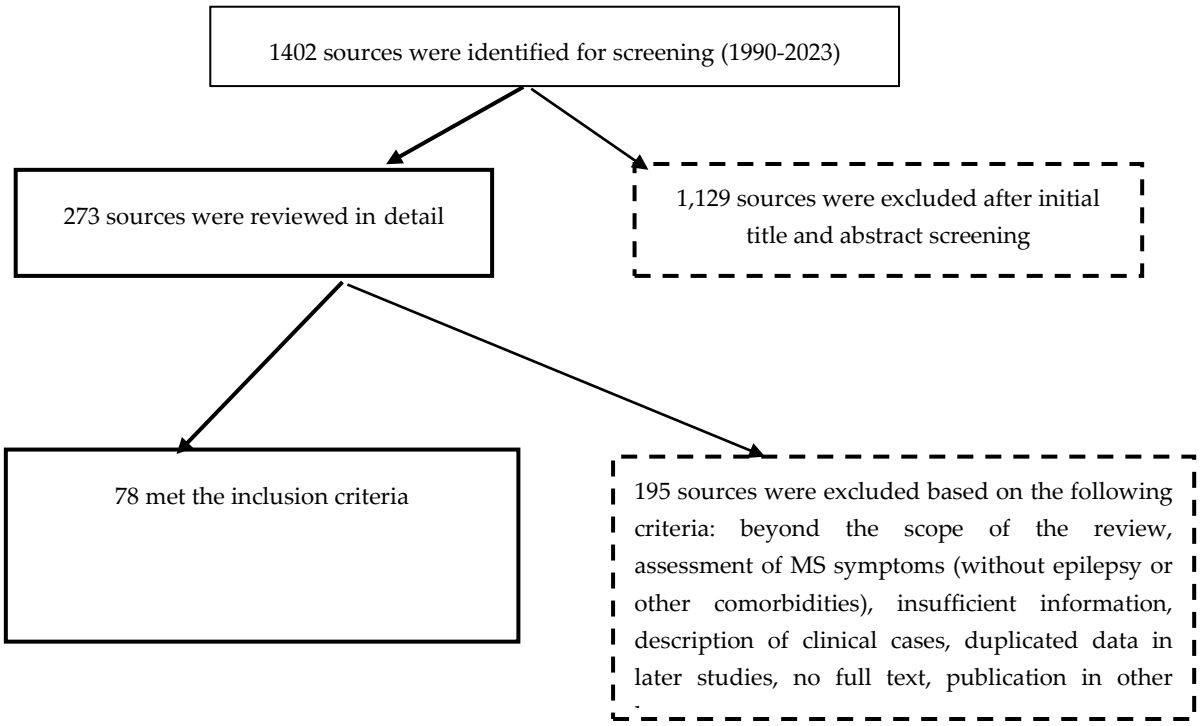

Figure 1. The flowchart of the study

Comorbidity of multiple sclerosis. Multiple sclerosis (MS), as a chronic long-term progressive disease, causes a significantly higher risk of comorbid pathologies compared to individuals of the same age without MS. Certain diseases are particularly common in MS patients.

Thus, according to comprehensive systematic reviews [3,4], the most frequent accompanying disorders in MS are depression (23.7%), anxiety (21.9%), hypertension (18.6%), hypercholesterolemia (10.9%), chronic lung diseases (10%), bipolar disorder (5.83%). Autoimmune diseases generally accompany <5% of patients with MS, the most common

being thyroid disease (2.08–10%), psoriasis (0.39–7.74%), and type I diabetes [5,6]. More frequent occurrence of comorbid neurological disorders has been reported in patients with MS: stroke and other cerebrovascular events [7], migraine [8-10], restless legs syndrome [11], sleep disorders [12,13], and neuropathic pain [14].

In the literature, data on the deterioration of cognitive functions at all stages and in all subtypes of MS are widely presented, and they are considered to be the result of a decrease in the volume of hippocampus and cortical gray matter, damage to other strategically important areas of the brain [15,16]. Several studies have been conducted regarding the possible relationship between MS and Alzheimer's disease, but such comorbidity has not been conclusively proven [17,18]. Other psychiatric disorders have also been studied in patients with MS in addition to depression, anxiety, and bipolar disorder, the rate of which remains insufficiently studied: psychosis, schizophrenia, alexithymia, and alcohol and drug abuse [4,14,19].

American researchers [20] generally identified three groups of diseases that present a clinically higher risk for patients with MS: any cardio-metabolic diseases (of the cardiovascular system, liver, kidneys, diabetes, atherosclerosis), musculoskeletal (arthrosis, rheumatoid arthritis, osteoporosis, etc.) and psychiatric disorders (anxiety, depression, insomnia, central pain, personality disorders, alcohol and drug addiction, etc.). In general, comorbidity is believed to be associated with the earlier progression of disability in MS [21,22].

Paroxysmal states (PS) are quite common in MS, which occur in 1.6–17% of cases in the form of epileptic and non-epileptic syndromes, of which 24% occur as initial manifestations of the disease and are associated with dysfunction of specific anatomical structures of the central nervous system (CNS) [23,24]. Non-epileptic PS is characterized by multiple, short, sudden, and stereotyped episodes: motor (dyskinesias, muscle spasms), sensory (paresthesia, pain), and autonomic, which can last from seconds to minutes, tend to cluster, and can persist for days to months after the onset and are more specific to the relapsing-remitting course of MS [23]. Although nonepileptic PS are common, they remain underrecognized and represent a diagnostic challenge in differentiating from true epileptic seizures, which occur quite frequently in MS.

Incidence and prevalence of epilepsy in patients with MS. The connection between MS and epilepsy has been known for more than 150 years. Shortly after J. M. Charcot presented MS as a new disease of the CNS, in 1871, Wilhelm Leube described a patient with MS and seizures, which was the first sign of epilepsy in MS [25]. Since then, the incidence and prevalence of epilepsy in patients with MS, its clinical features, and possible pathogenesis, taking into account the pathomorphological changes of the brain, have been studied.

Epileptic seizures occur in 2–3% to 5.9% of patients with MS and 3–6 times more often than in the general population [26–30]. As it was determined in a retrospective study of the Swedish population registry, which included 514, 545 patients with MS, the incidence of epilepsy grew with the increase in the duration and severity of the major disease, with its progressive course, and was dependent on the effect of drug therapy for MS [31]. In addition to MS, several studies have reported seizures in other demyelinating disorders, such as myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) and progressive multifocal leukoencephalopathy [32,33].

Age and gender characteristics. There is no unanimity in the literature regarding the age characteristics of the onset of epileptic seizures in MS. For example, in an Iranian study [34], seizures occurred more often (8.5%) with an earlier onset of MS (under 16) compared to 2% among older individuals, and the results of Swedish authors [31], on the contrary, indicate that seizures are more common in patients who have had MS for more than 34 years (5.9%).

It is widely known that women suffer from MS more often than men do (ratio 2.8:1) [20]. Most studies also indicate a predominance of females (from 77.3% to 86.2%) who had a combination of MS and epilepsy [30], other authors did not find convincing data on such gender characteristics [27,35].

Probable mechanisms of comorbidity of MS and epilepsy. The major cause of the simultaneous occurrence of MS and epilepsy has not yet been possible to determine, and the pathophysiological mechanisms explaining this connection continue to be the subject of modern studies. Elucidating why patients with demyelinating diseases are at increased risk for seizures provides some insight into epileptogenesis, which is driven by a combination of gray matter lesions and inflammation, and disease-modifying therapeutic techniques for MS are likely to affect it [36]. The expansion of our knowledge about the role of inflammation in the progression of epilepsy and MS is evident, but these mechanisms are considered very complex and not fully understood [37]. In recent years, there has been a clear

understanding that MS is a disease not only of the white matter of the brain but also of the gray matter with its hyperexcitability [38,39], especially in cortical and juxtacortical foci [40]. A recent systematic review of 90 articles [41] concluded that larger areas of white matter lesions were associated with smaller gray matter volumes or lower cortical thickness. The most consistent relationship between white matter lesions and gray matter atrophy was observed in the early (relapsing) type of disease and less often in progressive MS. There is increasing evidence that epileptic seizures, in turn, damage myelin sheaths [42]. Therefore, in the context of MS, seizures may exacerbate demyelination, reflecting the fact that the two diseases share some common pathophysiology. Understanding the pathological processes underlying this relationship will allow us to target common and shared pathological pathways associated with both diseases, which may lead to new approaches to the treatment of these neurological disorders [33]. Nevertheless, it should be remembered that patients with MS have individual profiles and interindividual variability of epileptogenicity [37], which is manifested in the different course of epilepsy in MS.

Publications from 20 to 30 years ago [43,44] analyzed the relationship between the semiology of seizures and the potential location of epileptogenic plaques using MRI and suggested that there is a correlation between the somatotopic description of seizures and the localization of cortical-subcortical plaques. This conclusion has recently been revised. Thus, in 2019, a new concept was proposed, according to which the model of epilepsy in multiple sclerosis is considered a network disease, which can have major clinical significance since clinical symptoms can be analyzed in the context of not only structural but also functional changes in the brain [37]. Therefore, the "exact" linking of the clinical manifestation of a seizure to the localization of a certain focus of demyelination, as postulated earlier, is no longer so certain. However, in our opinion, only some of the numerous cortical-subcortical lesions in MS are very likely to cause seizures/epilepsy, and cortical lesions can only be considered as a risk factor for the manifestation of seizures or epilepsy, but cannot provide an answer as to why they occur in some patients, and not in others.

Clinical manifestations and diagnosis. Epileptic seizures can occur at any stage of MS development: before the occurrence of its clinical manifestations [45,46], at the onset of the disease [30,40], at its late stages (after 8–23 years) [48], they may indicate MS exacerbation [47], especially in the relapsing-remitting type of the disease course [16]. Some authors, on the contrary, believe that most often, epilepsy joins MS with a secondary progressive course [2,48,49]. A combination of epilepsy with primary progressive MS is quite rare [44]. The absence of seizures in such patients may be associated with fewer brain lesions on MRI, especially with a non-periventricular distribution compared to patients with relapsing-remitting and secondarily progressive disease.

A separate opinion has been expressed [46] that epileptic seizures in MS are not always related to the demyelinating process, and they may occur in almost half of the patients as a result of a competing alternative pathology (traumatic brain injury, cerebrovascular disorders, infections, tumors, etc.), especially with increasing duration of the disease. In our opinion, it may explain the interindividual heterogeneity of the clinical course of epilepsy in MS.

Some patients have isolated seizure incidents during the entire course of the disease; others have them quite often. According to German authors [50], 40.4% of patients had only one seizure during a year, 59.6% had repeated seizures, 39% of latter patients were considered drug-resistant, and 9.7% had status epilepticus. Cases have been described, where temporal lobe seizures were the first manifestation of MS and the only symptom for years (from 4 to 10), and these patients had a positive CSF test for oligoclonal bands and typical MRI features of MS [45]. In this context, an important issue is the correct diagnostic interpretation of the first (and sometimes the only) or isolated seizures, since they can be acute symptomatic attacks that occur in close temporal and neurobiological relationship with acute structural brain damage during the debut or exacerbation of MS without recurrences during remissions. In this case, they are not subject to the diagnosis of epilepsy [51]. Such attacks by their nature are provoked, that is, they are the brain's response to an extreme trigger (as defined by the Commission on Epidemiology of the International Antiepileptic League [52]) and do not require the diagnosis of epilepsy and antiepileptic treatment. Acute symptomatic attacks may be triggered by yet undefined temporary changes (a potential epileptogenic role of edema during MS relapse is possible [53]), while "epilepsy" may be caused by already permanent brain restructuring in the area of chronic plaques [44].

The risk of relapse after the first seizure in MS has been reported to range from 57% to 94%, with lower estimates in larger studies [54]. In another publication [55], the survival-adjusted 10-year risk of epilepsy after the first seizure was

52%, with no difference between relapsing MS and age- and sex-matched controls, with an even higher risk in MS patients with initial status epilepticus (86%), but the subgroup was small and the study was based solely on descriptive data. Epileptic seizures as the only manifestation of MS relapse are a rather controversial issue, which has been reported in many studies [44,56]. In the literature, there are observations of the appearance of epileptic seizures in patients with MS without any other signs of MS relapse, except for asymptomatic active cortical lesions on MRI of the brain. However, patients could possibly have other minor neurological symptoms before seizures, which disappeared before the detailed examination. [2,43].

Therefore, about half of patients with a single epileptic seizure have a high risk of repeated seizures, regardless of whether the first one was acute symptomatic or a remote manifestation of the existing structural pathology of the brain. In the latter case, it is possible to establish a diagnosis of epilepsy and consider treatment, according to the practical (clinical) definition of epilepsy in 2014 [57]. As stated in the evidence-based guidelines of the American Academy of Neurology (AAN) and the American Epilepsy Society (AES), the risk of a subsequent seizure in any etiology of epilepsy (including MS) increases with previous brain damage, epileptiform EEG findings, significant pathology on MRI, and the presence of nocturnal seizures [58]. Some patients with MS may have all or most of these conditions.

Although the diagnosis of MS largely depends on the presence of characteristic lesions on brain MRI, there is diagnostic uncertainty as to whether these foci are actually related to the seizure onset zone because cortical lesions are difficult to detect during routine imaging [59]. To improve the differential diagnosis of MS with alternative diseases, including a better understanding of the typical features of cortical and juxtacortical brain foci, practical "Guidelines for lesion assessment in multiple sclerosis" were published following a workshop in 2018 in Milan, Italy, involving international experts in MS and neuroradiology [59].

In routine practice, electroencephalography (EEG) is rarely used to diagnose MS. However, during the EEG examination of patients with MS without epilepsy, 4% of them revealed epileptiform activity [60], which, according to the authors, along with the slowing down of the posterior dominant rhythm, indicates the degeneration of the gray matter. In the future, it can help predict the course of the disease and serve as an alternative or auxiliary tool to imaging techniques for the detection and monitoring of cerebral cortex lesions, especially for early diagnosis, even before the development of clinical manifestations. Therefore, some EEG results may have prognostic value, so their use in diagnosis is underestimated [47].

According to the literature, the rate of epileptiform disorders on the EEG with a double diagnosis (MS+epilepsy) is very heterogeneous. Thus, in one study [2] the first EEG showed epileptiform discharge in 38% and non-specific pathology in 40%, and in another [61] a much higher percentage of patients (84.6%) had epileptiform disorders. In the work of Australian authors, focal pathology in the form of focal slowing or interictal epileptiform discharge over the temporal or frontotemporal regions of the brain was detected in 70% of patients with MS and epileptic seizures [49]. It has been noticed that interictal epileptiform EEG disturbances are more common (>50%) in patients whose MS was diagnosed already after the onset of epileptic seizures [46]. EEG epileptiform activity can serve as a diagnostic criterion in differentiation from non-epileptic paroxysms, which are dyskinesias, transient somatosensory phenomena, transient ataxia, or aphasia. Such phenomena arise as a result of impaired transmission between demyelinated fibers and are well treated with membrane-stabilizing drugs such as carbamazepine, which in such cases, is even more effective than in focal epileptic seizures [2, 51].

Types of epileptic seizures in MS. The majority of patients (up to 87.5%) have focal seizures or focal seizures to bilateral tonic-clonic, and a small part of patients have seizures with an unknown onset for some time [30,49]. It is logical to assume that seizures in MS are focal since this disease is characterized by multiple, including cortical and juxtacortical foci in the brain [40,48]. One of the studies [62] compared the degree of damage to the temporal cortex in patients with and without relapsing-remitting MS and epilepsy. The analysis of changes showed that the hippocampus (14.2%), the lateral temporal lobe (13.5%), the cingulate gyrus (10.0%), and the insula (8 .4%) with cortical thinning phenomena and changes in diffusion parameters on MRI were affected the most in the first group, compared to the group of patients without seizures. These areas of the temporal lobe are most often affected in structural epilepsy (up to 56%) and unaware automatisms prevail in such cases [51]. However, another study [63] reported that in MS, among focal seizures, simple (aware) seizures occur approximately twice as often as complex

(unaware), while this dependence is diametrically opposite in the general population [64]. Therefore, there are discrepancies in the evaluation of the clinical manifestation of seizures in MS.

Course and prognosis. The views of scientists on the course and prognosis of dual pathology (MS+epilepsy) differ significantly. The work at the beginning of our century [43] demonstrated the absence of a statistically significant difference in demographic and clinical parameters, as well as in the EDSS (Expanded Disability Status Scale) in the group of MS patients without epileptic seizures compared to the group with seizures. In addition, before this study, patients with epilepsy were followed for 12 years after the first seizure and did not show a greater progression of MS compared to MS patients without seizures/epilepsy.

However, in recent publications, researchers postulate that patients with this dual pathology have a more severe course of MS with increasing cognitive deficits, increased EDSS scores, and more severe and rapidly increasing cortical atrophy than patients without epilepsy [47,65]. Moreover, assessing the prognostic value of epilepsy arising in the settings of MS, some authors claim that epilepsy acquired in this way is associated with a significant risk of death, although, as its cause, it still occurs rarely and does not lead to the transformation of the course of MS into the secondary progressive type [66]. And some scientists [30] believe that it is still unclear whether (and to what extent) manifestations of epilepsy in patients with MS affect the clinical course and long-term prognosis. It should be noted that epilepsy in MS is marked by an unexpectedly high ratio of patients with status epilepticus – from 9.7% [50] to 36% [29] and increased sensitivity to the side effects of antiseizure medications (ASMs) compared to patients with epilepsy of other etiology [47,63,67]. Such a rare variant of epilepsy as epilepsia partialis continua has also been described in patients during MS exacerbation [68,69].

A recent publication on the clinical and MRI evaluation of patients with a 30-year history of MS [70] demonstrated the role of cortical atrophy and the number of its focal lesions in the increasing disability of patients, and these changes distinguished secondarily progressive MS from relapsing-remitting type. Another confirmation that comorbid epileptic seizures occur more often in the severe course of MS is the study [29], where the average EDSS at the time of the first seizure was already 6.5, which indicates a high level of disability. These findings are consistent with the notion that the severity of MS is associated with a high risk of epileptic seizures, which, in turn, are markers of the severity of the MS course and indicate a cause-and-effect relationship between accumulated brain damage and epilepsy [29,66,67]. This once again confirms the fact that the combination of MS and epilepsy is a pathology with a bidirectional connection.

Issues in the treatment of dual pathology. The treatment of MS is divided into three main directions, where epileptogenic effects are not excluded [48,71,72]:

First, it is symptomatic treatment, which includes a significant number of pharmacological and non-pharmacological agents of different orientations, which can have a significant potential proconvulsive effect (e.g., baclofen, fluoroquinolones, tricyclic antidepressants, and cytostatics).

Second, it is the treatment of MS exacerbation with high doses of corticosteroids (methylprednisolone 1000 mg/d). Such treatment usually has no side effects on the central nervous system, given its short duration (3–7 days).

Third, a disease-modifying therapy (DMT) for MS, including beta interferons, glatiramer acetate, some monoclonal antibodies, and several modern drugs that act on different areas of the immune system, the use of which can become a trigger for epileptogenesis.

It is reported that beta interferons and glatiramer acetate not only provoke epileptic seizures but can also cause the appearance of a second disease – epilepsy [48]. It is also noted that the treatment of MS with natalizumab is associated with the risk of developing progressive multifocal leukoencephalopathy (PML), which, in turn, can lead to refractory temporal lobe epilepsy [71]. Given the fact that the use of natalizumab, alemtuzumab, and other monoclonal antibody agents can lead to PML development, which can manifest as seizures, the risk of their use has not been accurately assessed. At the same time, experimental data suggest that treatment with fingolimod, a modulator of sphingosine-1-phosphate receptors, exerts a disease-modifying antiepileptic effect based on anti-inflammatory properties, potent neuroprotection, anti-gliotic effect, myelin protection, reduction of mTOR signaling pathway and activation of microglia and astrocytes [72]. It is worth noting that not all risks of seizures/epilepsy due to the use of disease-modifying therapy in MS have been conclusively determined. The potential of developing new comorbid conditions

increases with the approval of new DMT drugs and thereby an increased number of consecutive treatments in the same patient [77,78].

On the other hand, there are data in the literature about the negative effect of some antiseizure medications on the course of MS, although randomized double-blind studies of the effectiveness of ASMs in seizures in MS patients have not been conducted [63]. Therefore, it is necessary to choose at least such drugs that would not worsen the existing ataxia, tremor, or cognitive disorders. Some MS patients may take ASMs to treat other common MS symptoms, such as pain, tonic spasms, migraines, or depression, while others may use medications associated with increased seizure frequency [48]. Some ASMs, interacting with vitamin D and melatonin, have been found to deepen neurological deficits in MS patients [73]. In addition, side effects from the use of anticonvulsants, as indicated above, occur quite often. There are data that they were noted in the form of symptoms of intoxication in about 37% of patients [67]. The greatest number of side effects (in 55.5% of patients) occurred when carbamazepine was prescribed compared to gabapentin (17.0%) and lamotrigine (18.1%) [74]. A high rate of discontinuation of carbamazepine at low doses was observed, and even in 33.3% of cases, the use of the medication simulated a relapse of MS. These data echo a Swedish study [2], which found that carbamazepine is the most frequently prescribed ASM, but with a low treatment retention rate (52%) due to drug side effects. The same level (about 50%) is reported for valproic acid and phenytoin. At the same time, 75% of patients continued to take the so-called "new" ASMs (lamotrigine, levetiracetam, gabapentin). This indicates better tolerability of these drugs.

Seizures may be drug-resistant in patients with MS and chronic epilepsy; however, the prognosis is quite good in patients who have provoked seizures only during MS relapse [75]. As indicated above, such seizures (within 7 days of MS exacerbation) can be considered acute symptomatic and do not require prescribing ASMs.

When should epilepsy treatment in a patient with MS start? According to evidence-based recommendations [58], immediate initiation of ASM treatment after the first unprovoked seizure of any epileptic etiology reduces the risk of relapse during the first 2 years of therapy but it does not improve the long-term (> 3 years) prognosis. Therefore, clinicians' recommendations for immediate initiation of ASM treatment after a first seizure should be based on an individualized assessment evaluating the risk of relapse against the side effects of anticonvulsants and taking into account the patient's wishes.

There are very few publications on the effectiveness of the treatment of epileptic seizures in MS, and their results are contradictory. As is commonly known, 25–30% of patients remain pharmacoresistant in the general population of epilepsy patients. This percentage is higher in MS with chronic epilepsy and ranges from 39% [50] to 56% [2] according to various data and due to this factor, the combination of MS and epilepsy leads to faster disability [76]. If seizures appear only during MS exacerbations, their prognosis is generally considered good [75]. Perhaps this is due to small groups of patients and different frequencies of seizures in them. In light of the latest data about the inflammatory process in epilepsy, the possibility of epileptogenesis prevention by actual treatment of MS is emphasized, and this is a strong argument for faster initiation of treatment for both diseases [37].

To illustrate the given data, we present a clinical case.

Patient O., female, 32 years old.

Complaints of weakness and numbness in the legs, episodes of dizziness, general fatigue, and occasional wobbly gait.

The patient's maternal aunt has been suffering from multiple sclerosis since the age of 30 and is currently confined to a wheelchair.

Medical history:

The first episode of the disease occurred three years ago (January 2020), when she lost vision in her right eye for the first time and experienced pain when moving it. Retrobulbar neuritis was diagnosed. MRI of the brain revealed 3 foci of demyelination: two – periventricular near the anterior horns of the lateral ventricles bilaterally and one focus – in the brainstem. The patient was diagnosed with clinically isolated MS syndrome in the form of retrobulbar neuritis of the right eye. After the pulse therapy with methylprednisolone 1000 mg IV for 5 days, the patient's condition improved – her vision was restored.

Four months later, the patient had her first unprovoked epileptic seizure: she felt numbness in her left arm, and tonic tension in the hand muscles, after which she lost consciousness, fell and developed tonic-clonic convulsions. After 3 days, a sensorimotor seizure reoccurred with a disturbance of awareness without transition to bilateral tonic-clonic, and a week later – two more such seizures. A follow-up MRI was performed. The appearance of new foci of demyelination was noted (Fig. 2).

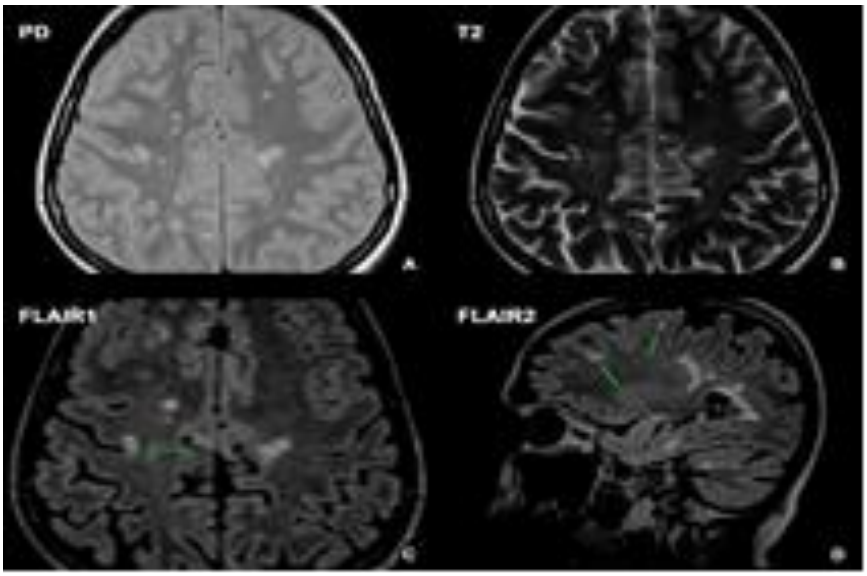

Figure 2. Foci of an irregular oval shape with clear contours, hyperintense MR signal on T2/FLAIR, and hypointense on T1 are visualized bilaterally juxtacortically, periventricularly in the white matter of the frontoparietal and temporal lobes, perpendicularly to the corpus callosum ("Dawson's fingers"), in the brainstem and cerebellar peduncles. Their maximum dimensions in the right parietal lobe are up to 10x9mm, and in the left parietal lobe – 14x8mm. Some of the periventricular foci of the right and left cerebral hemispheres have signs of diffusion restriction on the DWI/ADC map. The U-shaped, 9x6mm dimensions focus, marked by an arrow, is located juxtacortically on the right in the frontoparietal region and could be the seizure onset zone

EEG examination: in the settings of periodic slowing, epileptiform discharge (sharp waves, sharp-and-slow-wave complexes) were registered in the frontocentral areas bilaterally (Fig. 3).

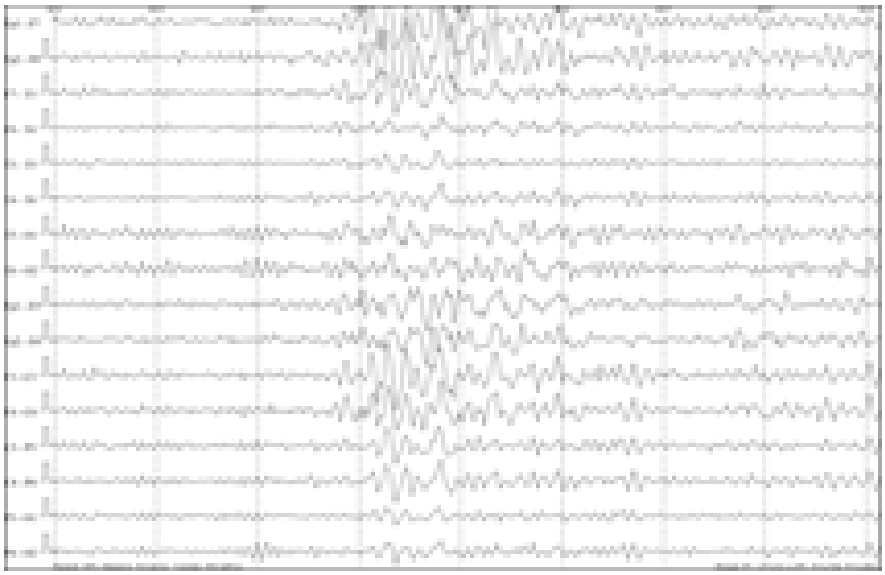

Figure 3. Patient O., female. 32 y.o. EEG performed immediately after the onset of epileptic seizures

Neurological status: high tendon reflexes with extended reflexogenic zones, bilateral Babinski sign; intention when performing coordination tests from the upper and lower limbs bilaterally, swaying in Romberg's test. The patient received pulse therapy with methylprednisolone, and the ASM lamotrigine was prescribed with a dose titration of up to 200 mg per day. The MS treatment strategy was discussed with the patient, and the spectrum of DMT was introduced.

Taking into account the activity of the pathological process, the family history, the appearance of a second exacerbation of MS within a year with MS progression, and the addition of comorbid epilepsy to the structure of the disease, the patient was prescribed DMT – a recombinant humanized monoclonal antibody against CD 20 cells – the ocrelizumab drug. Follow-up EEG examination three months after (Fig. 4) did not reveal epileptiform discharges.

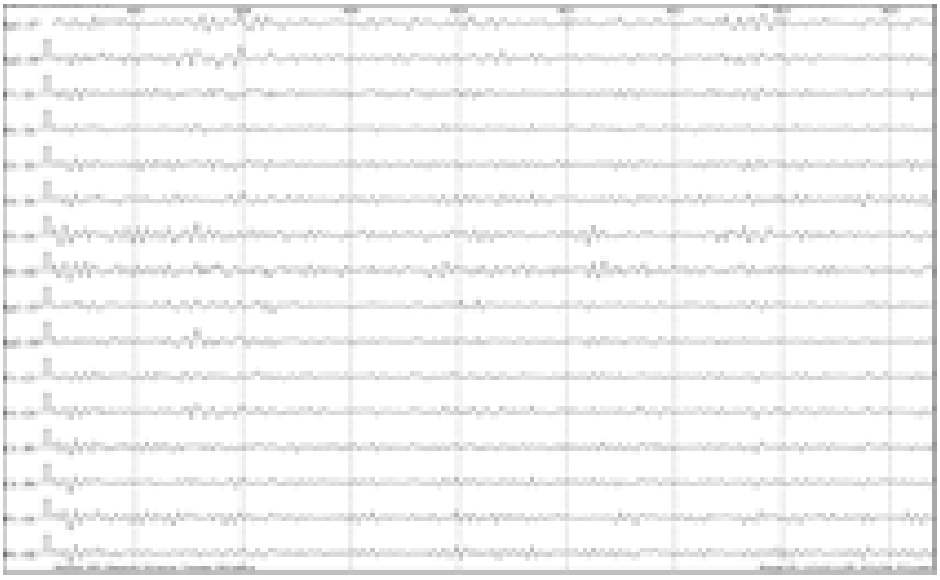

Figure 4. Patient O., female. 32 y.o. EEG performed three months after starting treatment with lamotrigine and ocrelizumab

MS exacerbations, epileptic seizures, and clinically significant side effects of drugs have not been observed by the beginning of 2023. The patient is under the constant supervision of a neurologist.

This clinical case allows us to emphasize the importance of the urgent prescription of DMT (ocrelizumab) simultaneously with ASM (lamotrigine) to achieve remission of two comorbidities. Epileptic seizures developed during MS exacerbation with the appearance of new juxtacortical demyelination foci. Lamotrigine was prescribed as the first-line drug of choice according to the type of epileptic seizures and the patient's gender. The treatment was effective, as confirmed by clinical data and EEG results. Ocrelizumab did not cause the worsening of epilepsy.

Based on the analysis of the literature data of the last years, we can conclude that issues of pathogenesis, clinical course, prognosis, and treatment of dual pathology (MS + epilepsy) are not finally resolved, and in most cases are even contradictory. We can agree with the opinion that there is a bidirectional relationship between multiple sclerosis and epilepsy. A possible associated pathophysiological pathway is considered. In multiple sclerosis, the combined gray and white matter lesions with inflammatory phenomena can affect epileptogenesis.

MS patients have individual profiles and interindividual variability in epileptogenicity. This can explain the fact that no evidence-based recommendations for the treatment of these patients have been developed until now.

We postulate that the epileptic manifestation may mean a relapse or exacerbation of the demyelinating and inflammatory process in MS. In this case, over time, this paroxysmal condition can be integrated into the extended scale of the degree of disability. Epileptogenesis is an active process, and the ultimate unsolved issue is whether DMT in MS can prevent or mitigate the course of comorbid epilepsy. Based on literature data and our own experience, the following principles of epileptic seizure/epilepsy treatment in patients with MS can be proposed:

1. When prescribing treatment with DMT for patients with MS and epilepsy, some drugs from the group of monoclonal antibodies (ocrelizumab) and fingolimod (a modulator of sphingosine-1-phosphate receptors) may be preferred.
2. Beta interferons, glatiramer acetate, and natalizumab should not be recommended for patients with MS and epileptic seizures, especially those with unspecified paroxysmal episodes in the past and a possible family history of epilepsy.
3. The use of ASMs – sodium channel blockers, and hepatic enzyme inducers (carbamazepine, phenobarbital, benzonal, phenytoin) is not recommended in patients with MS and epilepsy, as they increase the risk of interaction with drugs for the treatment of MS, increase the risk of side effects, and decrease patient compliance.
4. Seizures that occur only during an MS exacerbation probably do not require long-term treatment. Therefore, in the event of epileptic seizures, a brain MRI with a contrast agent should be performed to rule out an exacerbation in such patients with a confirmed diagnosis of MS.
5. In general, the need to prescribe ASMs is chosen individually, taking into account all comorbidities.
6. ASMs are prescribed according to ILAE recommendations, in monotherapy, according to the type of epileptic seizures, giving preference to new-generation medications with minimum drug interactions: lamotrigine, levetiracetam, and gabapentin.

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