Seizures and multiple sclerosis-more than an epidemiological association (Review)

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Abstract. In order to increase the quality of life of patients with epilepsy, it is essential to develop tools that facilitate early disease diagnosis and encourage the use of individualized therapies. The association between seizures and other neurological pathologies is well known but incompletely explained, with multiple sclerosis (MS)-seizures correlation being a relevant example. In this context, the present review aimed to highlight the most important facts related to the association between the heterogeneous group of epileptic pathology and MS, in order to provide initial directions for establishing a diagnostic and therapeutic protocol. The first part reviewed the most relevant epidemiological and clinical data on seizures; MS association. Subsequently, it highlighted the most common and actually accepted pathophysiological mechanisms that try to explain the association between the two pathologies. Finally, the importance of paraclinical investigations and the optimal choice of antiseizure-based therapies with respect to seizures associated with MS are presented, also revealing several directions that should be explored in the near future.

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Abbreviations: ASM, antiseizure medication; BBB, blood-brain barrier; CNS, central nervous system; DMT, disease-modifying therapy; EEG, electroencephalogram; GABA, γ-aminobutyric acid; MS, multiple sclerosis; NMOSD, Neuromyelitis optica spectrum disorders; PDR, posterior dominant rhythm; PLEDs, periodic lateralized epileptiform discharges; PPMS, primary progressive multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis

Key words: epilepsy, seizure, multiple sclerosis, neuroinflammation, antiseizure medication, electroencephalogram

Contents

1. Introduction

Seizures and epilepsy are correlated with increased morbidity and mortality (1) and require a personalized approach because of their association with other neurological disorders such as multiple sclerosis (MS) (2).

MS, the most common inflammatory pathology of the central nervous system (CNS), has registered a significant increase in incidence and prevalence worldwide in recent years, being an increasing burden for individuals and the healthcare systems (3). MS is also one of the main causes of disability in young individuals, having a major socioeconomic impact (4). In addition, MS is associated with significant comorbidities. Autoimmune diseases such as systemic lupus erythematosus (5) and rheumatoid arthritis (6) and Crohn's disease (7), along with other neurological disorders such as epilepsy, have a higher prevalence in patients with MS.

There are several clinical-evolutive forms of MS, with an accurate diagnosis being mandatory for the therapeutic approach. Thus, the relapsing-remitting form of MS (RRMS)

is the most commonly encountered in the young population and is characterized by clearly defined recurrent attacks followed by periods of partial or complete recovery (8). According to different studies, RRMS is the initial form of the disease in >70% of the patients (9,10). RRMS is one of the most promising neurological disorders in terms of therapeutic options, with a myriad of disease-modifying therapies (DMTs) now available (11). Besides the different types of beta interferons (the first approved DMTs for MS treatment), newer and more potent monoclonal antibodies such as Natalizumab and Ocrelizumab are now available (12). During the natural history of RRMS, the patient's clinical status may evolve towards the slow accumulation of disability in the absence of relapses, this form being known as secondary progressive MS (SPMS). Lastly, a minority of cases are diagnosed with primary progressive MS (PPMS), where the disability accumulation is slowly evolving from the beginning, with no clearly defined exacerbations, but reduced therapeutic possibilities (13). PPMS and SPMS remain a challenge for the neurologist, as currently available anti-CD20 medication and sphingosine-1-phosphate receptor modulators insufficiently slow the neurodegenerative process (14).

The correlation between MS and seizures was first noticed over 30 years ago (15), however remains to be elucidated. Seizures occurring in patients with MS have multiple similarities in terms of pathophysiology and treatment with seizures associated with other neurological pathologies (such as trauma, infection, stroke and neoplasia) (16), but particular etiopathogenic aspects should also be considered, especially for epileptic syndrome associated with MS. The exact prevalence of MS-related epilepsy is largely unknown. One study indicates that, after excluding alternative diagnoses, the exact numbers are lower than previously assumed, suggesting a possible bias in previous research (17). The widespread development and use of new DMTs and modern antiseizure medications (ASMs) open up new research directions related to possible indirect potentiation mechanisms between these two classes. In addition, there is still an unanswered question about the DMTs that are currently administered to patients with MS according to the current No Evidence of Disease Activity (NEDA) principles and their impact on secondary seizures (18).

The currently existing literature (18-20) only summarizes specific aspects of the MS-epilepsy association and offers narrow therapeutic directions which are insufficient to establish strong, internationally validated guidelines. Moreover, to the best of the authors' knowledge, the most recent similar publication to the present comprehensive approach dates back to 2008 (21), with subsequent research unable to answer the remaining therapeutic dilemmas, as there are still a number of unknowns related to the optimal diagnosis and treatment of patients with MS diagnosed additionally with epilepsy. These aspects urgently need to be elucidated to bring significant benefits to the patient's care.

Thus, the present review aimed to address in a systematic manner the debated issues related to MS-seizures association, first by presenting the most relevant epidemiological and clinical data in the literature. After revealing the intricate bidirectional correlation between the two entities, the present review subsequently attempted to explain this association by reviewing the most relevant involved pathophysiological mechanisms. Given the importance of paraclinical investigations in both MS and seizures, the present review also highlighted the contribution of electroencephalography (EEG) and brain imaging [focusing on magnetic resonance imaging (MRI)] in the diagnosis and monitoring of the two pathologies. Finally, considerations on specific therapeutical issues in patients with concomitant seizures and MS are presented, including relevant information about DMTs and ASM and their specific administration protocols in these patients. As the terms 'seizure' and 'epilepsy' were used in an interchangeable way (despite the evident difference) in some of the articles that were included in this review, it was decided to mention explicitly when data related to the MS-epilepsy association occurs.

2. Methodology and method

Search strategy and study selection. Literature research was conducted covering three of the most important online databases (PubMed, Embase and Google Scholar), using relevant keywords for the present study depending on the discussed topic. For the epidemiological facts, the following terms were used: 'Multiple sclerosis', 'seizure', 'epilepsy', 'epileptic seizures', 'convulsion' and 'epidemiology'. Only research conducted on humans (double-blind, single-blind, and unblinded trials), published in the last 20 years were included. Abstract-only articles, letters to editors, non-English language manuscripts, and studies on animal or cell models were excluded. When referring to imagistic techniques, neurophysiological investigations, and therapeutic options, Medical Subject Headings (MeSH) terms such as 'MRI', 'EEG', 'video-EEG', 'antiseizure medication', 'antiseizure drugs' were used associated with the abovementioned keywords. The same study inclusion criteria were applied. The final article selection was done by two independent reviewers (T.G.S. and D.C.A.), and, in case of debates that did not lead to a resolution, a third reviewer (B.E.I.) made the final decision on the disagreements. Fig. 1 illustrates the whole protocol.

Diagnostic criteria. The results demonstrated great variability in epidemiological, diagnostic and therapeutic data related to MS-associated seizures or epilepsy. In fact, the first step in conducting studies in this regard is the correct definition of terms, which in clinical practice can often be misleading or difficult.

According to the latest International League Against Epilepsy (ILAE) definition, epilepsy is diagnosed when at least two unprovoked seizures separated by a minimum of 24 h occur, an epileptic syndrome is confirmed, or the presence of only one single seizure was validated, but there is an additional risk of at least 60% for developing another seizure within the next 10 years (22). In the case of an epileptic seizure in an MS patient, the neurologist faces at least two problems. First, it must be clarified whether the seizure was provoked or not and, second, in the case of a single seizure, whether the risk of recurrence is at least 60%, thus allowing the diagnosis of epilepsy and initiation of appropriate treatment.

The first important fact related to MS diagnosis is represented by determining the correct subtype, as seizures may vary in type and frequency according to the MS subtype.

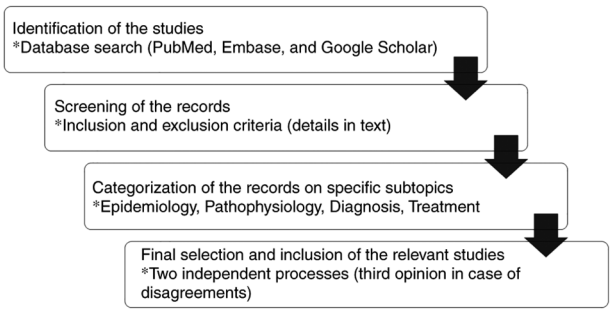

Figure 1. Detailed protocol of the search strategy and study selection.

There are several possible ways MS can evolve in a patient; the presence or absence of relapses together with the progressive course of the disease determine the existence of the following subtypes: relapsing-remitting multiple sclerosis (RRMS), primary progressive multiple sclerosis (PPMS), and secondary progressive multiple sclerosis (SPMS) (8). Another relevant aspect is related to the employed diagnostic criteria. The studies analyzed in the present review included patients with a diagnosis of definite MS according to the McDonald (23) diagnostic criteria available at the time of the research publication.

3. Epidemiological data revealing a significant association between MS and seizures

Epilepsy, the fourth most common neurological disease after migraine, stroke and Alzheimer's disease, has a significant effect at the individual level (24). According to a recent meta-analysis, there is a prevalence of 6.38 per 1,000 individuals for active epilepsy and 7.60 per 1,000 individuals with epileptic lifelong risk (25). Numerous factors influence the incidence and prevalence of epilepsy, with notable variations depending on the region. For example, a recent systematic analysis showed a higher prevalence of epilepsy in eastern, western, and southern sub-Saharan Africa regions, central and south-east Asia and central Latin America compared with other regions (26). Genetic, environmental, and cultural differences and, finally, accessibility to health services, can at least partially explain these epidemiological differences.

MS incidence and prevalence are also region-dependent. The latest data suggest an increased prevalence of MS worldwide compared with the figures from the last decade (27). Regarding the regional variability, a higher incidence is reported in Europe (based on the high rates from the north European countries), followed by the Americas, while African countries have a very low prevalence rate (27).

Available data regarding patients with MS, although highly heterogeneous, show an increased prevalence and incidence of seizures compared with the general population. An older systematic review estimated the prevalence of seizures at 3.09% and the incidence at 2.28% for patients with MS (28), being in line with more recent figures which show a pooled prevalence of 2% for seizures and 3% for epilepsy among patients with MS (29). Similar data were extracted from other studies, but with greater inter-study variability. For example, in a study conducted on a Swedish cohort, the cumulative incidence of epilepsy was 3.5% for patients with MS, compared with 1.4% for the control group (30). In a Norwegian study, Benjaminsen *et al* (2) found that the prevalence of focal epilepsy in patients with MS was 3.2%, 4.5 times higher compared with the general population. According to their results, epilepsy was associated with an increased conversion risk from relapsing-remitting multiple sclerosis (RRMS) to secondary progressive multiple sclerosis (SPMS). Engelsen and Grønning (31) report the prevalence of epilepsy at 4% in patients with MS, almost four times higher than the reported prevalence in the general population. In a study conducted by Eriksson *et al* (32) in Sweden, the prevalence of epilepsy in individuals diagnosed with MS was 3.5%, compared with 0.53-0.64% in the general population. Another Swedish study reported the 10-year cumulative risk of epilepsy to be 51.4% in patients with MS and 41.3% in the control population (33). An increased risk was observed for SPMS (60%) compared with patients with RRMS (40%), a relevant aspect also regarding the pathophysiological mechanisms. Krökki *et al* (34) noted that epilepsy is the most common comorbidity in MS, being found in 4.7% of 491 patients with defined MS. Langenbruch *et al* (17) evaluated 4,078 patients with MS and reported seizures at 1.5% and epilepsy at 0.9%. In a Japanese study by Nakano *et al* (35), the prevalence of epilepsy in patients with MS was twice as high as in patients diagnosed with neuromyelitis optica spectrum disorders (NMOSD). According to another study conducted by Koch *et al* (36) on 19,804 patients, the estimated prevalence of epileptic seizures ranged from 0.5 to 8.3%, with an average of 2.3%. Table I summarized the most relevant data from the abovementioned studies and other significant research related to this topic that was conducted during the last two decades (37-50).

Considering available data, there is a greater risk of unprovoked seizures in patients with MS, the prevalence of epileptic seizures being 2-3 times higher compared with the general population (51). However, the temporal characteristic of this association is still unclear. In most cases, epilepsy is diagnosed after MS is diagnosed, with a mean time of ~10 years between the two entities (52). One explanation for this long latency period could be related to the MS evolution phase, transition to SPMS seemingly increasing the seizure risk. Studies have indeed shown an increased association between progressive MS (PMS) and epilepsy (53). Another potential interpretation of the existing figures may suggest that epilepsy increases the risk of transition from RRMS to SPMS. However, the relatively decreased prevalence of epilepsy compared with other MS comorbidities can be partially explained by the early administration of immunomodulatory/immunosuppressive treatment.

There is, additionally, the possibility for seizure activity to be the inaugural manifestation of MS (54), including in childhood-onset MS (55). Moreover, cumulative seizure incidence is directly related to MS duration, reaching almost 6% in patients with MS with a disease duration of >30 years (56). Finally, epileptic seizures can also occur before MS is diagnosed, with different percentages depending on the study group (50). However, it is still debatable if an epileptic event without a clear cause should be considered a retrospective relapse or an associated disorder.

Table I. Most relevant epidemiologic studies on epilepsy in patients with MS in the last 20 years.

First author	Sample size	Number of patients with epilepsy	Prevalence of epilepsy (%)	(Refs.)
Nyquist P, 2001	5,715	85	1.5	(37)
Sokic D, 2001	268	20	7.4	(38)
Eriksson M, 2002	255	20	7.8	(32)
Gambardella A, 2003	350	16	4.6	(39)
Striano P, 2003	270	13	4.8	(40)
Nicoletti A, 2003	195	5	2.6	(41)
Martínez-Juárez I, 2009	122	8	6.55	(42)
Viveiros C, 2010	160	5	3.1	(43)
Nakano H, 2013	63	4	6.3	(35)
Krökki O, 2014	491	23	4.7	(34)
Lund C, 2014	332	24	6.6	(44)
Simpson R, 2014	3,826	72	1.9	(45)
Averianova L, 2017	1,850	48	2.59	(46)
Burman J, 2017	14,545	502	1.7	(30)
Laroni A, 2017	1,877	7	0.4	(47)
Passarell M, 2017	5,548	109	1.96	(48)
Mahamud Z, 2018	15,810	289	1.8	(33)
Benjaminsen E, 2019	658	20	3.1	(2)
Langenbruch L, 2019	4,078	38	1.5	(17)
Schorner A, 2019	1,267	18	1.74	(49)
Neuß F, 2021	2,285	59	2.5	(50)

MS, multiple sclerosis.

4. Relevant aspects of seizures in patients with MS

Seizure occurrence and their clinical manifestation in patients with MS is a relevant aspect that seems to be dependent on the MS form. In this context, several suggest that SPMS is associated with an increased risk of seizures compared with RRMS (2,42,50).

The risk of seizure recurrence is another topic of interest, as establishing an optimal ASM therapy remains an essential part of epilepsy management. In this regard, Langenbruch *et al* (17) observe that there are statistically significant differences depending on the form of MS disease in terms of recurrence of seizures. As the abovementioned epidemiological data suggest, PMS is associated with higher seizure risk. Moreover, the primary progressive form of MS (PPMS) shows a stronger correlation with the development of recurrent seizures, compared with SPMS (16). The same study also suggests a link between MS relapses and the occurrence of seizures. During MS exacerbations, the recurrence risk of seizures is significantly higher.

Another clinically relevant aspect for the correct diagnosis and treatment of epilepsy is the type of seizure. Although little data exists on this topic, according to Ooi *et al* 2021 (57), focal seizures are the commonest, accounting for ≤80% of the total. This is in line with other results, that suggest that the majority of these patients (>75%) suffer a transformation from focal to bilateral tonic-clonic seizures (49). Moreover, bilateral tonic-clonic seizures, frequently of unknown onset, are also considered common in patients with MS (58). By contrast, epileptic status is rare in patients with MS (50). It can be easily observed that the type of epileptic seizures in patients with MS mirrors only partially the statistical general trends in patients with epilepsy, in which bilateral tonic-clonic seizures are the most commonly encountered (56).

Atypical forms of seizures, encountered in dysphasic status and musicogenic epilepsy, have also been reported in patients with MS (59). Other (very) rare epilepsy types are also described in the literature, with Epilepsia partialis continua a relevant example. Being first described in patients with MS in 1990 by Hess and Sethi (60); only a few cases are known up to the present. Autonomic seizures, including ictal vomiting, ictal spitting, and ictal hypersalivation are rare manifestations by default and can be frequently omitted because of their non-dominant semiological features. The present study did not find any reports linking these types of seizure semiology to MS. During the course of the disease, other non-epileptic symptoms such as tonic spasms, dizziness, and diplopia may occur, probably as an expression of the axonal lesion. However, due to their origin in the spinal cord or in the brainstem, these manifestations cannot be considered of epileptic nature (61).

Last, epilepsy might be related to higher morbidity and mortality in patients with MS. Morbidity is disability-dependent, being quantified in the case of patients with MS by the Expanded Disability Status Scale (EDSS) scale (62). The most recent results from the literature suggest a correlation between increased disability status and any type of epilepsy in

patients with MS (62). Another study conducted on a cohort of Swedish patients showed a correlation between an increased EDSS score (≥7) and an increased prevalence of epilepsy compared with patients with MS without disabilities (56). Finally, Grothe *et al* (63) demonstrate in German patients with MS that the concomitant diagnosis of epilepsy correlates with a higher EDSS score at MS onset, a faster progression rate, and an increased overall disability status compared with patients with MS without epilepsy. It remains an open question if these results are sustaining a causality relationship between epilepsy and disability.

Regarding mortality, the study conducted by Mahamud *et al* (64) shows higher mortality in patients with MS with associated epilepsy, although epilepsy was in very rare cases the primary cause of death. A similar association between an increased mortality risk in patients with MS with epilepsy has recently been demonstrated in a UK cohort of patients (65). However, the results remain heterogeneous, as other studies do not assess any difference in mortality in patients with MS with and without epilepsy (66).

5. Pathophysiological mechanisms (incompletely) explaining the MS-epilepsy association

Starting with the first case reports of MS-associated epilepsy, neurologists have been searching for explanatory pathophysiological mechanisms. Despite the fact that this association has been studied from multiple perspectives, including imaging and pathology studies, current data cannot yet entirely explain it and future research is needed.

Pathological and radiological evidence. Although MS lesions typically occur in white matter, gray matter abnormalities have been long recognized in MS (67). Initially, active lesions (detected by imagistic methods) were thought to be the origin of the clinical and EEG-associated epileptic activity, but increased seizure risk in SPMS suggests that there are also other potential epileptic foci in the brain of patients with MS. Pathological anatomy first assumed the role of altered gray matter in the pathophysiology of epileptic seizures. In this regard, the older post-mortem studies that have shown a significant number of lesions in the gray matter or at the border between the cortical and subcortical parenchyma, more commonly in the temporal, parietal and frontal lobes should be mentioned (68).

Additional evidence to support common pathophysiological mechanisms has been provided by imagistic investigations. Thus, gray matter lesions and cerebral atrophy are related to the formation of epileptic foci, as longitudinal MRI studies demonstrate a correlation between a higher lesion load and greater cortical atrophy on one side and a higher prevalence of epilepsy on the other (69). It is understood that not all patients with MS with gray matter lesions and cortical atrophy develop seizures, lesion type and localization presumably being critical to epileptogenesis. The presence of lesions at the cortical or cortical-subcortical level has been associated with an increased risk of seizures (70). However, another study suggests that the location of lesions in the temporal lobe is a risk factor for seizure development in patients with MS, with lesions in the hippocampus, lateral temporal lobe, and cingulate lobe being most frequently detected (71). The relation between brain lesions and epilepsy has also been studied in the other direction. In this sense, epileptic seizures, although primarily causing changes in the gray matter, have been found to favor the presence of (demyelinating) lesions in the white matter as well (72). The association between demyelinating lesions and epileptic seizures, more precisely between relapses and the onset of new seizures, is additional proof of the MS-epilepsy association.

GABA system and ions. Several recent hypotheses attempt to clarify the molecular mechanisms connecting MS and epilepsy. Thus, on one hand, the abnormalities of the γ-aminobutyric acid (GABAergic) system play a major role in epilepsy (73) and on the other, SPMS has been associated with a loss of parvalbumin-positive GABAergic interneurons in the cortex (74). Similarly, Cao *et al* (75) demonstrate a low concentration of GABA in the posterior cingulate cortex and left hippocampus in patients with RRMS, partially explaining the loss of GABAergic neurons.

Ion and energy imbalance could be another contributing cause of epileptic seizures in patients with MS. Within demyelinating lesions, the potential decrease in ATP production and disturbances of ionic balance (primarily Ca^{2+}), may lead to neuronal degeneration. Demyelination may also have an impact on the activation of sodium ionic channels, subsequently leading to neuronal hyperexcitability (76). Among cortical regions, the hippocampus is more susceptible to decreased energy reserves, a lesser amount of available ATP potentially leading to complex ionic imbalances and a pathological activation of ion channels, that would finally result in cellular hyperexcitability and abnormal synchronized neuronal activity (77).

Neuroinflammation. Neuroinflammation is another common aspect of epilepsy and MS (78,79). More specifically, glial cells (astrocyte and activated microglia) and immune cells (T and B cells) produce pro-inflammatory cytokines that play essential roles in sustaining both pathological processes. For example, TNF-α maintains chronic inflammation and apoptosis (leading to brain atrophy) in MS by acting on the Tumor necrosis factor receptor 1 (80); while in epilepsy, by associative mechanisms (GABA receptor endocytosis, glutamate uptake stimulation and upregulation of AMPA receptors), TNF-α supports and facilitates epileptic activity (81). In MS, T lymphocytes produce IL-1B, which acts on specific receptors. Subsequently, IL-1B activates the NF-κB pathway and leads to the destruction of the blood-brain barrier (BBB), both processes supporting the chronic inflammatory status. In the case of epilepsy, IL-1B, via its direct action at the astrocyte level, inhibits GABA activity in parallel with a reduction of glutamate uptake, thus favoring an excess of excitatory neurotransmitters (82).

Human herpesvirus 6A/6B. There are also other important, still incompletely understood, molecular pathways, related to the abovementioned mechanisms (Fig. 2). An example of an interesting future direction for research is the dual role of β subfamily herpesviruses such as human herpesvirus 6A and 6B (HHV-6A, HHV-6B) in both MS and epilepsy (83). HHV-6 is considered to serve an important role in triggering

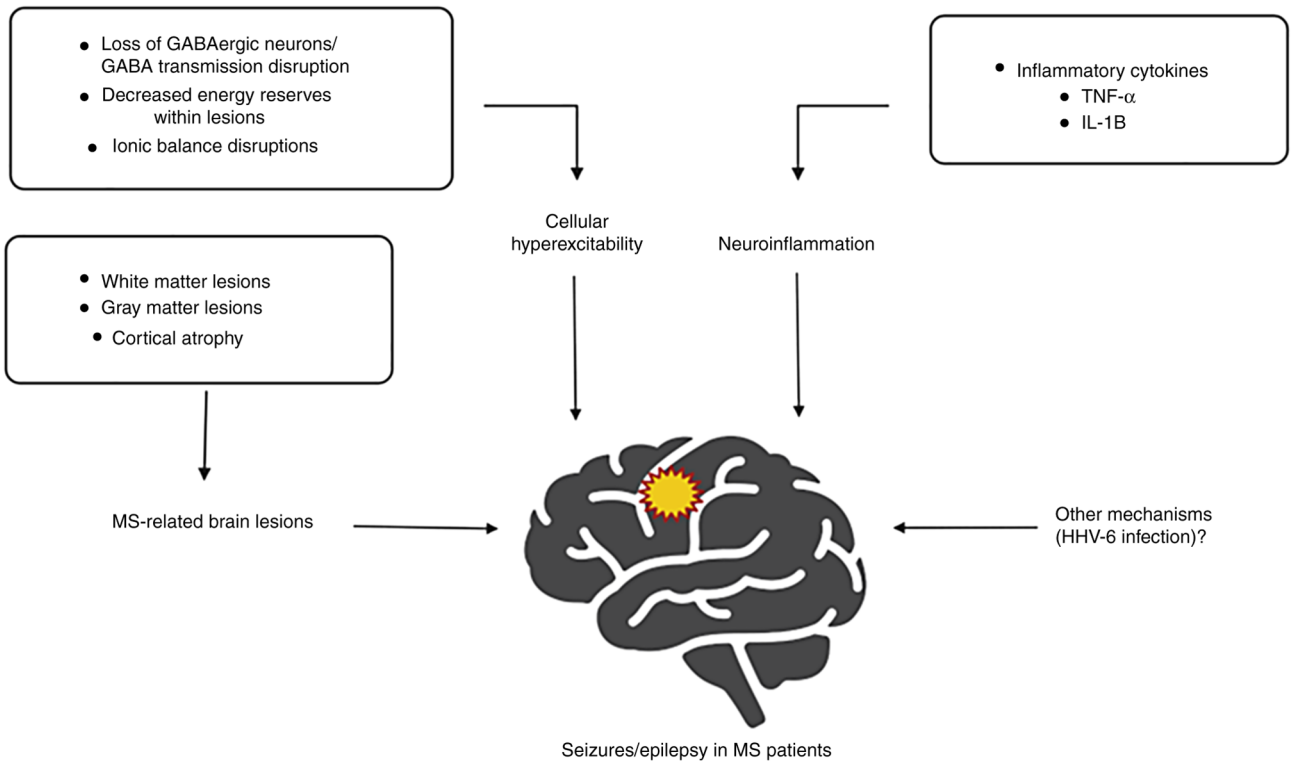

Figure 2. Known and suspected pathophysiological mechanisms related to the MS-epilepsy association. MS, multiple sclerosis; HHV-6, human herpesvirus 6; GABA, γ-aminobutyric acid.

demyelination, being associated with circulating IgM levels in patients with MS (84). Moreover, a study conducted on a large cohort determined an association between seropositivity against the HHV-6A antigen and an increased risk of developing MS (85). Regarding epilepsy, HHV viral DNA was detected in the hippocampal tissue of patients diagnosed with mesial temporal lobe epilepsy, and HHV viral proteins were detected in the astrocytes located in epileptic tissue (86). By maintaining a latent state in astrocytes, HHV-6 is able to alter the astrocyte's functions, inducing neurotransmitter imbalances that might cause epileptic seizures. HHV-6 is also suspected to affect the MAPK kinase signaling pathway, an important molecular pathway shown to be affected in status epilepticus (87). It remains to be determined whether HHV-6 alone or in combination with other precipitating factors is involved in inducing and sustaining epileptic activity in patients with MS.

6. The role of imagistic techniques in studying the MS-epilepsy association

According to the ILAE classification, structural etiology is defined by visible neuroimaging anomalies superimposable on the anatomic-electroclinical hypothesis as a predisposing factor for epileptic seizures (88). In this context, the diagnosis of structural epilepsy is established for a significant proportion of patients with epilepsy despite a possible absence of clinical findings. Although according to McDonald's criteria 2017 (23), the diagnosis of MS relies heavily on MRI-detected suggestive CNS lesions, the usual imaging techniques occasionally lack precision in terms of anatomical-clinical correlation. In early studies of epilepsy in patients with MS, a relationship between electro-clinical manifestations and pathological MRI findings was not clearly demonstrated (31,38). A possible explanation could be the fact that the MRI examination was performed during the interictal period, where the probability to find epileptic clinical and electrical markers is much lower (37). Detection of cortical lesions can be difficult in routine imaging examinations, with determination of the lesion-seizure onset areas correlation being only partially possible (89). According to one study, brain MRI identified >5 lesions in 88% of patients with MS with epilepsy, but no specific lesion distribution was reported (52). This raises the question of properly assigning the etiology according to ILAE classification, considering the fact that imagistic or electrophysiologic techniques are rarely performed in the short-lived ictal period and that new MRI lesions in MS relapses also have variable persistence with a median timeframe of 6 weeks.

The distribution of MS lesions may be related to cognitive impairment, recurrent seizures, or status epilepticus (90). Cortical or juxtacortical lesions have been found to be a precipitating factor for epileptic seizures in patients with MS in multiple studies (91,92). In these patients, continuous administration of ASMs due to the increased risk of recurrence was required. In this regard, a new entity called cortical MS is now recognized (93). Calabrese *et al* (94) report that intracortical lesions are five times more common in patients with RRMS with concomitant epileptic seizures. Another study shows that cortical and juxtacortical lesions are independent predictors of seizures, epilepsy being also related to brain lesion load and cerebral parenchyma atrophy (29). The use of newer imaging techniques for diagnosis and follow-up

[such as double inversion recovery (DIR), and high-resolution (3-7 Tesla) MRI sequences] has improved the early detection of cortical lesions (94). The currently accepted sequences for early detection of new and/or epilepsy-related demyelinating lesions are DIR, diffusion-weighted imaging (95), magnetization transfer ratio (96), and gradient echo sequences (GRE) (97). Neuroaxonal damage, astrogliosis, and demyelination lead to dysfunctions in cortical connectivity and can be quantified by myelin water fraction as well as by magnetoencephalography (98).

Apparent normally-structured gray matter analysis by unconventional quantitative MRI can stratify patients with MS at risk for epilepsy. Thus, patients with MS and with an increased rate of cortical atrophy progression are at a higher risk of developing epilepsy (an additional explanation for the correlation between SPMS and seizures) (70). Moreover, an MRI-EEG correlation may be useful for an improved understanding of the underlying pathophysiological mechanisms behind this association. At present, the causal relationship is not completely elucidated. The 'edema effect' of growing demyelinating lesions may play an important role during the relapse, and it could explain the reduction of seizures with focal onset in patients treated with corticosteroids, as well as the reduced risk of subsequent episodes in these subjects.

7. Neurophysiology in patients with MS with epilepsy-in search of specific patterns

EEG anomalies show variability in time and space and a low degree of specificity. In addition to detecting the electroclinical particularities of epileptic seizures, video-EEG and activation techniques (hyperventilation, photic stimulation, and sleep deprivation) are important tools in differentiating veritable seizures from non-epileptic psychogenic and other paroxistical events (99). To highlight the importance of clinical-electrophysiological correlation for the accuracy of the diagnosis and classification processes, current data suggest that ≤70% of patients with epilepsy had a false positive diagnosis in the general population (100). Early studies revealed EEG abnormalities in 20-60% of patients with MS, dependent on the location of the lesions, the duration, and the stage of the disease and its progression (38,40,101). Frequent abnormalities consist of diffuse asynchronous theta activity, slow rhythmic synchronous activity, and occasionally, mainly during chronic-progressive disease evolution, hypo-voltage, a potential result of the variable degree of cortical atrophy (43). Occasionally, slow focal waves or localized EEG suppression may be found (52). The interictal epileptiform activity appears to be quite rare, while an EEG amelioration or impairment usually does not positively correlate with the clinical condition (102). In addition, in patients with MS, hyperventilation may worsen underlying EEG activity and may also precipitate non-epileptic paroxysmal symptoms, such as focal paresthesia or tonic spasms in the limbs (103).

According to research, EEG examination showed an abnormal interictal pattern in approximately one-third of patients with MS who suffered seizures before being diagnosed with MS, and in more than 50% of patients with MS with onset of epileptic seizures following MS diagnosis (55). In another series of cases, EEG was considered pathological in >80% of patients (4,15). In an attempt to delineate a correlation with an interictal pattern, Dagiasi *et al* (52) demonstrated non-specific electrophysiological changes such as focal slowing in 40% of cases and epileptiform changes in 38% of the examined patients, with the mention that 46% had a seizure-free one-year time interval. Moreau *et al* (104) objectified other relevant pathological EEG patterns, such as focal spikes, focal slowing, and periodic lateralized epileptiform discharges (PLEDs), with >50% of the above cases being diagnosed with persistent seizures. In a number of cases, the observed electrophysiological changes consisted of focal slowing with isolated or grouped diffuse theta waves, with predominant bilateral frontal-temporal localization (43). PLEDs are the result of cortico-subcortical structures disconnections, being clinically associated with a focal with impaired consciousness non-convulsive status, especially in patients with longstanding MS (104). According to a reference study, bi-PLEDs can be found in other pathological conditions apart from MS, mainly related to anoxic encephalopathy and CNS infections, such patients having increased mortality rates (105). Patients with MS with epilepsy had significantly lower posterior dominant rhythm (PDR) frequency and amplitude compared with controls, with 34% having a PDR frequency of <8.5 Hz (106). The PDR frequency was negatively associated with the functional level of disability among patients. Slowing of the background rhythm and epileptiform discharges suggest degeneration of the neuronal body and may contribute to the prediction and follow-up of cortical lesions and functional disabilities among patients with MS. Therefore, electroencephalographic monitoring of the PDR spectrum can serve as an alternative or complementary tool to other detection and follow-up imaging techniques. Table II summarized the most relevant EEG patterns found in patients with MS with epilepsy.

Complementary, a retrospective study has shown that brainstem auditory evoked potentials and somatosensory potentials of the upper limb are preferentially involved in patients with MS and concomitant epilepsy (107). According to currently available literature, the main cause for this phenomenon seems to be the unilateral demyelinating lesion of the substantia nigra. However, the exact cause-effect interconnection with epilepsy is not fully determined, and future prospective longitudinal studies are required.

8. Individualized ASMs treatment and prognosis in patients with MS with epilepsy

The choice of the ASM is individualized, according to the general recommendations that consider the type of seizure, drug tolerability and related comorbidities (36). Although extensive research on the etiology of epilepsy has been conducted, there are still a number of knowledge gaps. It is also the case for patients with MS and epilepsy. In their work, Dagiasi *et al* (52) made some assumptions regarding the ASM treatment in MS patients, the most relevant being related to the clinical features, the increased incidence of epileptic status, and the sensitivity to the ASMs' adverse effects. There might be also a bidirectional relationship between epilepsy treatment and MS, thus explaining why only some ASMs were proven to be effective. In this context, some of the currently employed

Table II. Important EEG pathological patterns in patients with MS with epilepsy.

First author	Study design	Relevant findings related to EEG pathological patterns	(Refs.)
Salim A, 2021	50 patients with MS with epilepsyvs. 50 controls	Lower posterior dominant rhythm (PDR) frequency and amplitude; PDR frequency of less than 8.5 Hz in 34% of cases	(106)
Dagiasi I, 2018	Multicenter retrospective study 62 patients with MS	Focal slowing in 40% of cases; epileptiform changes in 38% of cases	(52)
Viveiros C, 2010	Case series 160 patients with MS (5 with concomitant epilepsy)	Focal slowing; isolated or grouped diffuse theta waves; EEG anomalies located predominantly bilateral frontal-temporal	(43)
Moreau T, 1998	402 patients with MS (17 with concomitant epilepsy)	Focal spikes; focal slowing; periodic lateralized epileptiform discharges (PLEDs);	(104)

MS, multiple sclerosis; EEG, electroencephalogram; PDR, posterior dominant rhythm; PLED, periodic lateralized epileptiform discharge.

ASMs with demonstrated effectiveness and potential interaction with the immune system are sodium valproate (inhibits NK cells), carbamazepine, levetiracetam (decreases inflammatory mediators in glial cell cultures), and vigabatrin (modulates humoral and cellular response) (108,109). It has been observed that MS relapse-associated seizures have a predominantly benign course, similarly to symptomatic seizures that do not require chronic ASM treatment, in contrast to seizures that occur apart from the MS activity state and require more aggressive treatment (62). However, epileptogenesis is a dynamic process that evolves over a significant period of time, and the incomplete understanding of the phenomenon prompts for early initiation of ASM treatment. With no standardized therapeutic protocol currently available, extensive research on larger cohorts is mandatory in order to establish valid guidelines.

According to a cohort study, monotherapy led to a favorable outcome in 29 patients with MS with seizures (102). In another study, Nyquist *et al* (37) found that from a group of 51 patients with MS and concomitant epilepsy, 35 (78%) had complete seizure remission under ASM therapy, five (11%) had recurrent seizures with fluctuating seizure-free intervals despite ASM administration, while another 11% developed persistent seizures. The results are not surprising, considering the heterogeneity of data available on patients with epilepsy under ASM treatment. For example, one recent 30-year longitudinal cohort study reported a 1-year seizure-free interval for >80% of the included patients under new ASM monotherapy, a percentage similar to that in the general epilepsy population (110).

Several other works reported mixed results, with a number of reporting a favorable outcome of seizures in patients with MS, such as the study conducted by Kinnunen and Wikström (15) which report that epilepsy had a spontaneous remission in almost half (10 out of 21) of the patients with MS. Other research (conducted on 51 patients with MS with epilepsy) reported that 3 out of 4 patients had persistent focal seizures (37).

Dagiasi *et al* (52) revealed that 65% of the total patients with MS included were on monotherapy with carbamazepine or phenytoin as the first therapeutic option, although they are also drugs that have significant interactions. Additionally, the authors observed a low seizure remission rate (~44%) for the MS group compared with 65% in the general population. Several explanations for these results are proposed: i) The inclusion of tertiary centers treating patients with high EDSS scores, suggesting a biased selection; ii) increased sensitivity of patients to adverse effects with limited adequate titration; iii) decreased level of determination (lower therapeutical target) in seizure management in (disabled) patients with MS compared with the general population.

Regarding ASMs tolerance, Solaro *et al* (111) demonstrate the adverse effect profile of most commonly used ASMs in patients with MS. Thus, 56% of patients treated with carbamazepine developed adverse effects, predominantly ataxic/pyramidal syndromes. Relevant side effects were also experienced by 19% of those treated with gabapentin and by 22% of patients under lamotrigine therapy. The therapeutic compliance of patients with MS to specific ASMs could be partially related to their adverse effects, which might have additive or synergistic values although there are no specific studies addressing this issue. One study showed increased therapeutic compliance to Na^+ channel blockers, but without a statistically significant difference regarding efficiency (112). Finally, another relevant aspect that might be taken into consideration is related to the adverse effects of the employed ASMs that may mimic a relapse in patients with MS, one example being ataxia (111).

According to a previous study, no positive correlations were found between immunomodulatory treatments, mainly β interferon, and epileptic seizures (36). There are, however, data suggesting that DMTs might be a factor in seizure behavior in patients with MS. Prophylactic administration of glatiramer acetate shows a protective effect on the hippocampus and

Table III. Relevant characteristics of antiseizure medication for patients with MS.

Antiseizure medication	Potential adverse effects	Modulation of the immune system	Drug interactions
Carbamazepine	Ataxic syndrome Pyramidal syndrome Gastrointestinal symptoms	Decrease of inflammatory mediators in glial cell cultures	Lowers the plasma levels of cyclophosphamide, cyclosporine, dexamethasone, methotrexate, methylprednisolone, and prednisolone
Gabapentin	Blurred/double vision Ataxic syndrome Tremor	Anti-inflammatory effects by modulating the substance P-mediated neurokinin-1 receptor	No significant interactions with DMTs or relapse acute treatment
Lamotrigine	Ataxic syndrome Skin rash Headache Blurred/double vision	Anti-inflammatory effects by inhibiting the production of IL-6, TNF-α, and IL-1β	No significant interactions with DMTs
Levetiracetam	Headache Mood changes Dizziness	Anti-inflammatory effects by inhibiting the production of IL-1β	No significant interactions with DMTs
Phenobarbital	Gastrointestinal symptoms Headache	Hypersensitivity of the immune system	Lowers the plasma levels of cyclosporine, dexamethasone, methotrexate, methylprednisolone, and prednisolone
Phenytoin	Headache Ataxic syndrome	Decrease of suppressor T cells Increase in the production of IL-6 and IL-8	Lowers the plasma levels of cyclosporine, dexamethasone, methotrexate, methylprednisolone, and prednisolone
Sodium valproate	Gastrointestinal symptoms Headache Tremor	Inhibition of NK cells	Decreased plasma level by methotrexate
Vigabatrin	Blurred/double vision Ataxic syndrome Tremor CNS depressant	Modulation of the humoral and cellular immune response	Interferon beta-increased risk of depression

MS, multiple sclerosis; CNS, central nervous system; DMT, disease-modifying therapy; NK, natural killer.

cortical myelination (113). In separate studies, Natalizumab treatment had a favorable effect on refractory epilepsy by α 4 integrin-mediated migration of T-cells towards an inflamed brain (114), while Fingolimod administration could have additional anticonvulsant and neuroprotective potential in temporal lobe drug-resistant epilepsy through the S1P-signalling pathway in inflammation and blood-brain disruption (115). These aspects suggest the hypothesis of a persistent positive inflammatory feedback loop in the MS-epilepsy interaction.

The aspects related to DMTs are also relevant for patients with MS without epilepsy, as the current treatment directions suggest a personalized approach. For example, the choice for a certain DMT depends also on the MS type. The initial therapy for mild forms of RRMS can be successfully conducted with glatiramer acetate and interferons; however, the concomitant presence of skin pathologies or hypercoagulable states impose the use of oral medication. Severe RRMS forms can be treated from the beginning with more potent therapies, Natalizumab being a valuable option as both first and second-line DMT (116). When evolving to SPMS, the patients initially with RRMS become candidates for Siponimod, the latest DMT approved for this type of MS (117). PPMS remains a challenge from the therapeutic point of view, with Ocrelizumab the first approved medication, real-world results showing a stabilization of disability progression in PPMS treated patients (118).

Symptomatic concomitant treatment of MS comorbidities such as spasticity, depression and cognitive impairment should be carefully considered, especially in patients with MS and epilepsy, with the correct selection of ASM in this context. The most commonly incriminated drugs are baclofen and aminopyridines (such as fampridine for fatigue). On the other hand, concomitant administration of melatonin and sodium valproate produced a more potent anticonvulsant effect, also decreasing the severity of audiogenic seizures in rat models (119).

Interactions between ASMs, in particular enzyme inducers, and MS-related drugs have been reported (120). Carbamazepine, phenobarbital, and phenytoin may lower plasma levels of cyclophosphamide (except for phenobarbital), cyclosporine, dexamethasone, methotrexate, methylprednisolone, and prednisolone (Table III). Dexamethasone may modulate plasma phenytoin, oxcarbazepine may alter cyclosporine levels and methotrexate may decrease plasma levels of valproic acid. Fortunately, cyclosporine and methotrexate are rarely used in MS. No interactions are reported between the new generation of ASMs and the immunomodulators

administered to patients with MS. Furthermore, no significant interactions have been reported so far between new ASMs and the currently available DMTs for RRMS, including interferons, glatiramer acetate, teriflunomide, fingolimod, dimethyl fumarate, alemtuzumab, mitoxantrone, and natalizumab while the interactions were common with the old ASMs. Indeed, a new concept is gaining ground, according to which epileptic manifestations are relapses or worsening of the MS-related inflammatory process. Epilepsy and seizures might be worth integrating as a separate item into the EDSS scale, perhaps in the cerebral functions category.

9. Conclusions

The complex association between epilepsy and MS, although observed for a long time, possesses still a number of unknowns. In recent years, research has brought new evidence that strengthens this association between the two pathologies. First, the results from epidemiological studies, although with significant heterogeneity, show a clear increase in the prevalence of seizures encountered in patients with MS. The present study considered that the figures should however be cautiously interpreted because of the cohort size variability and the influence of other well-known external factors (latitude, climate) that predispose to biases in MS diagnosis. Regarding the semiology of seizures, based on the existing literature, it can be concluded that focal and bilateral tonic-clonic seizures are the most frequently encountered in patients with MS, with atypical seizures being rare.

Second, imagistic investigations bring additional data that support a close association between MS and epileptic seizures/epilepsy. White and gray matter demyelinating lesions are both associated with an increased risk of seizures. It is hypothesized that brain imaging could become an indirect tool to assess epilepsy risk in patients with MS, with large cohort studies currently missing.

Although there are several well-founded pathophysiological hypotheses (excitatory-inhibitory neurotransmitter imbalance, ionic imbalance that causes neuronal hyperexcitability, and the role of chronic neuroinflammation), further studies are needed to fully reveal the cellular and molecular mechanisms linking the two diseases. The present study also discussed the role of HHV-6 as a potential link between epilepsy and MS, however, it must be admitted that the bidirectional relationship between MS and epilepsy remains under scrutiny, as etiological considerations for classification purposes are still not well established.

EEG examination could become a reliable tool for the optimal understanding of epileptic seizures in patients with MS. At present, according to the findings, there is no specific EEG pattern for seizures in patients with MS, with currently existing scarce literature on this topic. With the discovery of new pathological patterns specific to this category of patients, it is hypothesized that EEG and video-EEG might provide clues for a more personalized diagnosis and treatment.

Finally, choosing the optimal ASM in patients with MS with concomitant epilepsy is still a challenge for the neurologist. As illustrated above, some of the most important questions are monotherapy vs. ASM associations, the potential adverse effects, and the modulation of the immune system. With no clear treatment directions, the establishment of therapeutic protocols and proper guideline integration is mandatory, in order to improve the clinical outcome and the quality of life of patients with MS with epilepsy.

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Authors' contributions

DCA and TGS contributed to the study design and data collection (search and selection of studies). DCA and IDC contributed equally to data analysis and interpretation (final selection and inclusion of the studies). DCA, TGS and TEC prepared the first draft of the manuscript, while BEI, VSAA and IDC reviewed the manuscript and wrote its final version. All authors read and approved the final manuscript. Data authentication is not applicable.

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Competing interests

The authors declare that they have no competing interests.

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