Common Underlying Mechanisms of Multiple Sclerosis and Epilepsy

Subjects: Biology

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Despite the significant differences in the pathological background of neurodegenerative diseases, epileptic seizures are comorbidity in many disorders such as Huntington disease (HD), Alzheimer's disease (AD), and multiple sclerosis (MS). Regarding the last one, specifically, it has been shown that the risk of developing epilepsy is three to six times higher in patients with MS compared to the general population. In this context, understanding the pathological processes underlying this connection will allow for the targeting of the common and shared pathological pathways involved in both conditions, which may provide a new avenue in the management of neurological disorders.

Keywords: multiple sclerosis ; demyelination ; epilepsy ; seizure ; neurodegeneration

1. Introduction

Multiple sclerosis (MS), the most common cause of non-traumatic neurological disability in young adults, is characterized by inflammatory demyelination in both white and gray matters, followed by axonal injury and loss. Although focal demyelinated lesions are the main hallmark of MS, diffuse inflammation and axonal damage are present in normal appearing white matter (NAWM), as well as in gray matter [1]. Axonal loss is shown to be a feature of clinical disease onset throughout all stages [2]. During the progression of the disease, several structural changes may lead to decreased functional connectivity between neuronal networks, which leads to several complications [3][4]. As a result, patients with MS may develop a wide range of symptoms including paralysis, mental changes, cognitive impairment, depression, and even epilepsy [1].

Epilepsy is one of the most common neurological disorders, involving people of all ages and both sexes, although its prevalence is slightly higher in men [5]. It has higher incidence rates in developed countries, where it can reduce the patient's life quality [6]. The causes of epilepsy are diverse and involve a variety of pathological mechanisms [7]. People with epilepsy show frequent seizures, severe learning and memory disabilities, cognitive impairments, depression, anxiety, and abnormalities in physical functions [6]. Moreover, epileptic seizures lead to aberrant synchronous discharge in a network of neurons, which might occur after diverse brain insults, such as traumatic brain injury (TBI), stroke, and intracerebral hemorrhages [8][9]. There are three different types of seizures based on the origin within the brain: partial, generalized, and unclassified. Partial seizures initially affect a certain area of the brain. Generalized epilepsy arises when two cerebral hemispheres are affected by abnormal electrical activity and unclassified seizures have an unknown onset [10][11]. The cause of epilepsy in many patients is also unknown, but head trauma, genetic mutations, autoimmune diseases [12], and focal cortical dysplasia [13] are among the possible causes.

The abnormal synchronous neuronal discharge, a clinical feature of epilepsy, has been reported to be a comorbidity in other many neurological disorders, as well as in neurodegenerative diseases such as Huntington disease (HD), Alzheimer's disease (AD), vascular dementia, brain tumors, and autism [8][14]. Likewise, epileptic seizures have been accepted as a part of the disease spectrum of MS, and epilepsy is slightly more common in people with MS [15]. In this sense, the association between MS and epileptic seizures does not appear to be a coincidence, but a bidirectional relation. It was not long after Jean Martin Charcot introduced MS as a novel disorder of the central nervous system (CNS), that Wilhelm Leube described an MS patient with seizures in 1871, which was the first evidence of epilepsy in MS [16]. Since then, seizures have been accepted as a part of the disease spectrum in MS. Similarly, although HD, AD, and other neurodegenerative diseases differ in their pathological background and symptoms, epileptic seizures might be involved in their etiology [17][18][19][20]. Indeed, epileptic patients have a higher chance of developing other neurological alterations. Hence, understanding the basis of the link between neurological disorders and epilepsy has important consequences for treatment, diagnosis, and management.

2. Seizure Occurrence in the Context of Demyelinating Disorders

Although different demyelinating conditions are associated with seizures, their prevalence and clinical characteristics are different among patients. Epilepsy prevalence is 0.27–1.7% in the general population [21], however, it occurs more frequently in patients with MS [22][23]. In a review of 30 published clinical series representing a total of 19,804 patients with MS, Koch et al. estimated the prevalence of epileptic seizures at the range of 0.5–8.3%, with the average of 2.3% [22]. Similarly, in a large cohort of 5041 patients with MS, the prevalence was 2% [23], which is about three times higher than in the general population. A recent systematic review supported these previous data, estimating that the incidence and prevalence of seizures in patients with MS were 2.28% and 3.09%, respectively [24]. As we mentioned above, in addition to MS, several studies have reported seizures along with other demyelinating disorders, such as antibodies associated demyelinating diseases and progressive multifocal leukoencephalopathy (PML).

MOG antibody disease (MOGAD) is an inflammatory demyelinating disease of the CNS characterized by the presence of anti-MOG autoantibodies (MOG-Abs). Myelin oligodendrocyte glycoprotein (MOG) is a membrane protein expressed on the outermost surface of myelin sheaths, which is thought to be important in the myelination process. MOG-Abs have been strongly associated with several demyelinated disorders such as acute disseminated encephalomyelitis (ADEM), pediatric MS, transverse myelitis, optic neuritis (ON), and neuromyelitis optical spectrum disorders (NMOSD), but are rarely detected in patients with MS [25][26][27]. There is growing evidence reporting a link between the presence of MOG-Abs and seizures, occurring in combination with demyelination or even as an isolated phenomenon [28][29][30][31]. In several case reports, patients with MOG-Abs developed seizures as the first sign prior to demyelination or in a subsequent disease course [29][31][32]. However, the clinical spectrum of these seizures and the contribution and importance of MOG-Abs on seizure development remain unclear. In addition to MOG-Abs, antibodies against AQP4 (water channel protein aquaporin-4) have also been considered as a sensitive and highly specific serum hallmark of the NMOSD [33]. AQP4 is a protein required for a normal rate of water exchange across the blood–brain interface. Consequently, in 2015, the International Panel for antigen NMO Diagnosis (IPND) revised the diagnosis criteria based on the presence or absence of AQP4-Abs [34]. Moreover, a proportion of patients who met the criteria for NMOSD but lacked AQP4-Abs were seropositive for MOG-Abs [33][34]. Both associated demyelinating diseases develop seizures, however, they are more common in patients with MOG antibody-associated demyelination than in patients with AQP4 antibody-associated demyelination [28], which is thought to be related to cortical and subcortical lesions [35]. Even though seizure occurrence was highly associated with gray matter lesions, the prevalence of seizures was 18% in patients with progressive multifocal leukoencephalopathy (PML), in which demyelination is thought to be restricted to the white matter [36]. More details on the characteristics of patients with demyelinating disorders who developed seizures are summarized in **Table 1**.

Table 1. Characteristics of patients with seizure associated demyelinating disorders.

Demyelinating Disease	Epilepsy Prevalence	Clinical Manifestation	MRI Findings	Most Frequent Seizure Type	Electroencephalographic (EEG) Characteristics	Possible Pathophysiological Mechanism	Ref.
Multiple sclerosis	0.5–8.3% with an average of 2.3%	Earlier onset of MS symptoms Worse cognitive performance in patients with frequent seizures or status epilepticus	Cortical and juxtacortical lesions Extensive cortical inflammation lower brain volumes Temporal lobe damage: Hippocampus, lateral temporal lobe, cingulate, and insula Cortical thinning and alteration of diffusion metrics in temporal lobe including insular cortex and cingulate gyrus	Partial secondary generalized	Diffuse asynchronous theta activity Synchronous rhythmic slow waves Focalized flattened EEG patterns Focal abnormalities	Temporal lobe cortical pathology Inhibitory GABA interneuron cell loss in layers IV and VI Reduced cortical thickness in the middle temporal gyrus Type I GMLs mostly in middle temporal gyrus Decreased GABA in left hippocampus and posterior cingulate cortex of RRMS Presence of cortical lesions Progressive brain atrophy	[37] [21] [22] [23] [38] [39] [40] [41] [42] [43]

Demyelinating Disease		Epilepsy Prevalence	Clinical Manifestation	MRI Findings	Most Frequent Seizure Type	Electroencephalographic (EEG) Characteristics	Possible Pathophysiological Mechanism	Ref.
Progressive multifocal leukoencephalopathy		18%	New-onset seizures	Lesions adjacent to the hemispheric cortices	Simple and complex partial seizures Partial seizures with secondary generalization	-	-	[36]
Antibody-associated demyelination	MOG-IgG *	20.5% **	Encephalopathy Younger onset age Higher EDSS score Meningeal irritation Fever, headache, nausea and vomiting CSF leukocytosis	Inflammatory cortical brain lesions Subcortical white matter lesions Deep white matter lesion including periventricular and corpus callosum Cerebral peduncle less optic nerve and spinal cord involvement	Generalized tonic clonic seizure	Background theta to delta rhythm Intermittent low amplitude fast waves Focal sharp-wave Complex and asymmetric focal slow waves	-	[28] [35] [44] [45]
	AQP4-IgG ***	1%	-	-	-	-	Slow K^+ clearance	[28] [46]

GABA: Gamma-Aminobutyric Acid; GMLs: Gray matter lesions; EDSS: Expanded Disability Status Scale; CSF: Cerebrospinal fluid; RRMS: relapsing-remitting MS. * MOG-Abs associated demyelination is related to several demyelinated disorders such as acute disseminated encephalomyelitis (ADEM), pediatric MS, transverse myelitis, optic neuritis (ON), and AQP4-Abs negative neuromyelitis optica spectrum disorders (NMOSD). ** A recent meta-analysis of 14 studies reported that general probability of seizure occurrence in patients with MOG-Ab-associated disease is 20.5%, particularly in children. Furthermore, the occurrence of seizure in patients with ADEM-like phenotype of MOG-Ab-associated disease is 37.3% [45]. *** Antibodies against AQP4 is a criterion for NMOSD diagnosis.

2.1. Seizures as A Clinical Manifestation of Multiple Sclerosis (MS)

Several studies have reported that patients with MS are three to six times more likely to suffer from epileptic seizures than the rest of the population [47]. However, the origin, the extent, and the importance of epileptic seizures in patients with MS remain ambiguous. Some studies have suggested that seizures could affect patients at any stage of the disease's progression. It is also suggested that the severity and course of MS might be correlated to the occurrence of epilepsy [48]. In this sense, a recent retrospective cohort study with 14,545 MS cases and 43,635 controls have strongly suggested a direct association between the severity and duration of MS and the incidence of seizures. While the cumulative incidence of epilepsy in relapsing-remitting MS (RR-MS) was 2.2%, this value in patients in progressive stage was 5.5%, and continuously increased to 5.9% with increasing the duration of disease in patients with disease duration of ≥34 years. Furthermore, patients whose Expanded Disability Status Scale (EDSS) score was more than 7 had a cumulative incidence epilepsy of 5.3% [48]. Although patients with progressive forms of the disease might be more likely to suffer from epilepsy [48][49], some researchers suggested that seizure might be the first clinical manifestation at the time of MS diagnosis in 10.5% of patients [23][36]. Based on radiological findings, Hussona and co-workers reported a case series of patients whose only clinical manifestation were seizures, and their radiological findings showed abnormalities compatible with demyelination, which meets the criteria for clinically isolated syndrome (CIS) or early MS [50]. In addition, it has been shown that seizures may occur during the relapse in a subset of patients [38], which could be associated with cognitive impairment. Furthermore, seizures are more common in patients with early-onset MS (5.5% in pediatric MS) [21][51], which have poor prognosis toward disability and death. In turn, decreased brain volumes and poor cognitive function are also reported in patients with frequent or uncontrolled seizures [21]. Interestingly, patients with seizures appearing at MS onset or relapses usually do not experience recurrent seizure; by contrast, those patients with seizures associated to cognitive impairment and progression of the disability were more likely to experience recurrent seizure [38]. Additionally, a study developed in a cohort of 5041 patients with MS has suggested that there are no differences in gender, duration, and course of MS between those patients with MS suffering from seizures and those who never experienced seizure in any course of their disease [23]. This notion is also supported by other studies [21][41].

The fact that almost all type of seizures have been associated with MS [22] suggests an involvement of MS pathological mechanisms in the etiology of seizures, even though partial seizures with secondary generalization have been shown to be the most prevalent in patients with MS [38], and a review of 30 studies have shown a similar prevalence of primary or secondary-generalized seizures, which accounts for nearly two-thirds of all seizures in MS [22]. Electroencephalography (EEG) analyses in patients with MS reported abnormalities in brain electrical activity, such as asynchronous theta activity, synchronous rhythmic slow waves, and focal flattened EEG patterns [38]. Moreover, in a cohort of 5041 patients with MS, 63% of those who experienced seizures also showed abnormal EEG. Importantly, slow background, focal spikes, focal waves, and ictal discharge have also been reported in patients with MS (**Table 2**) [23]. In spite of this, the incidence of seizures in patients with MS does not follow a similar pattern. Hence, in some cases, seizures occur rarely and are associated with relapses, while in others, seizures may be the first signs of MS disease at the time of diagnosis. In addition, some patients with MS with cognitive impairment suffer from seizures recurrence [21][23][38][51].

Table 2. Summary of published studies on epileptic seizures in patients with MS.

Type of Study	Number of Patient with MS	Patients with Seizures (Percentage)	Predominant Seizure Type					Seizure Occurrence at MS Onset	Seizure Occurrence before MS Onset	Seizure Occurrence after MS Onset	Ref.
			Simple Partial	Complex Partial	Secondary Generalized (sGTCS)	Generalized Tonic Clonic	Status Epilepticus				
Cohort	5041	102 (2%) In 67 patients (1.3%), epileptic seizure could not be explained by any cause other than MS	34 (50.7%)	Less frequent	28 (41.8%)	33 (49.3%)	18 (26.9%)	7 cases	26 case	69 case	[23]
Retrospective review of the records	310	10 (3.2%)	2	1 case of simple partial	6	2	2 cases of sGTCS	4 cases	Not reported	Not reported	[21]
Retrospective registered-based study	14,545	Cumulative incidence: 502 (3.5%) (CI 3.17–3.76) The 5-year prevalence: 1.7% (CI 1.54–1.98)	Single seizure was present in 3.0% (CI 2.77–3.32) of patients with MS				0.48%	Not reported	Not reported	Not reported	[48]
Systematic review	32 studies	Incidence: 2.28% (CI: 1.11–3.44%), at the range of 0.65–5.97% Prevalence: 3.09% (CI: 2.01–4.16%) at the range of 0.89–8.06%	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	[24]
Retrospective review of the records	1267 *	22 (1.74%)	Focal onset in 17 patients (77.3%)		14 out of 17 patients with MS (82.4%)	5 (22.7%)	3 (13%)	-	2 (9.1%)	16 (72.7%)	[47]
Cohort	428	13 (3%)	10 (77%)		Half of patient with focal seizure (38.5%)	3 (23%)	0	4 (31%)	-	8 **	[40]
Retrospective cross-sectional epidemiological study	431	19 (4.4%) 14 cases with active epilepsy	4 cases	3 cases	11 cases	-	5 (36%)	2	1	11 cases	[52]

* The first appearance of seizures for four patients (18.2%) could not be explained by the assessment of their medical records. ** One remaining patient was considered as clinically isolated syndrome. CI: 95% confidence interval; sGTCS: Secondary generalized tonic clonic seizure.

Since epilepsy is a significant comorbidity in MS, clarifying whether the patients with MS are at increased risk for developing seizures is important. Moreover, it is unclear to what extent seizures can exacerbate the clinical course and long-term prognosis of MS.

2.2. Possible Pathophysiological Processes Underlying Seizure Development in Patients with MS

The pathophysiological mechanisms that explain the link between MS and epilepsy are still under investigation. Although MS was initially conceptualized as a white matter demyelinating disease, it is now well known that gray matter lesions (GMLs) and atrophy are more frequent than previously suggested [21]. In addition, there is evidence that gray matter lesions occur from the earliest stages of the disease [54]. This leads to the hypothesis that cortical lesions in MS may play an epileptogenic role, explaining the seizures' appearance in patients with MS. This notion is well supported by studies based on the magnetic resonance imaging (MRI), longitudinal studies, and postmortem tissue analyses that have shown more cortical lesions and atrophy in patients with a higher prevalence of epilepsy [21][55]. Furthermore, some MRI and double inversion recovery (DIR) repetitive studies have revealed that formation of new juxta-cortical and/or cortical lesions are associated with generalized seizures in most patients with MS with epilepsy [37][40][56], suggesting an involvement of cortical and subcortical lesions in the development of seizures. Although it appears to be an association between the extent of cortical and subcortical lesions and the presence of seizures, not all patients with MS with gray matter lesions

developed seizures [41]. Therefore, it is likely that lesions in some cortical regions are more prone to trigger seizuregenesis. In this regard, Calabrese and co-workers have reported severe damage in the temporal lobe of RR-MS, with seizures compared to those patients without seizures. Regional analysis revealed that the most affected gray matter regions in RR-MS epileptic patients were the hippocampus (14.2%), the lateral temporal lobe (13.5%), the cingulate (10.0%), and the insula (8.4%). Furthermore, cortical thinning was observed in the middle temporal gyrus, fusiform gyrus, cingulate gyrus, and in the insula of epileptic RR-MS, compared to other patients with RR-MS [41]. Collectively, the gray matter atrophy and neuronal loss in patients with MS appear to occur in structures associated with mesial temporal lobe epilepsy. In another study, Nicholas et al. confirmed middle temporal gyrus thinning and the loss of GABAergic interneuron in layers IV and VI by examining the postmortem entorhinal cortex of patients with MS with seizures. Even though the loss of inhibitory interneurons seemed to be related to GMLs, it was not explained by inflammation and mitochondrial dysfunction within the type I gray matter lesions [42].

Abnormalities in the GABAergic system may be associated to seizure incidence in patients with MS. In this sense, a recent study has revealed a selective vulnerability of inhibitory interneurons to demyelination. There is a specific loss of parvalbumin-positive GABAergic interneurons in the cortex of postmortem secondary progressive MS (SP-MS), suggesting that specific interneuron subtypes are vulnerable to neurodegeneration in the cortex of patients with MS. In an animal model of cortical demyelination, it has also been confirmed that the selective susceptibility of parvalbumin fast spiking interneurons are secondary to cortical demyelination [57]. Since the balance between excitatory and inhibitory activities is crucial for the maintenance of the neuronal network's stability, a reduction in inhibitory neurons may trigger epilepsy in patients with MS. The loss of inhibitory interneurons is exacerbated by disease progression, supporting association between the severity and duration of the MS, and the incidence of seizures [48]. In turn, by using magnetic resonance spectroscopy (MRS), Cao and co-workers also reported abnormalities in the GABAergic system. Hence, the level of GABA concentration was lower in the posterior cingulate cortex and the left hippocampus of RR-MS, which was likely to be due to GABAergic neuronal loss [43].

In addition, a reduction in ATP production in demyelinated lesions and disturbances in ion homeostasis may induce Ca^{2+}-mediated degeneration in GABAergic inhibitory interneurons in the MS motor cortex [39]. Given that hippocampus is more susceptible to energy failure mediated by mitochondrial dysfunction [58], impaired ATP production as a consequence of inflammatory demyelination may lead to inhibitory interneuron degeneration, leading to disturbances in the excitatory-inhibitory balance of the neuronal network. Another possible mechanism underlying hyper-excitability following demyelination is a switch in sodium channel expression within the neurons whose axons have been damaged. This abnormal sodium channel expression may activate silent sodium channels, leading to hyper-excitability and abnormal impulse activity. This additional mechanism may contribute to the pathophysiology of epileptic seizures in patients with MS [59].

Taken together, epileptic events in patients with MS might be a consequence of gray matter atrophy, hippocampal lesions, and GABAergic interneuron loss. However, there are few studies focusing on the molecular mechanisms, which trigger seizures in MS. Additionally, available data on the mechanisms of neurodegeneration and the mechanisms by which inhibitory interneurons are more vulnerable to degeneration are insufficient. Even though cortical lesions are found in most of patients with MS with seizures, it remains unclear whether specific neuronal networks are more vulnerable to demyelination and undergo degeneration. If cortical lesion load increases the risk of epilepsy, as suggested by several researchers, an increased prevalence of epilepsy among patients with SP-MS should be expected. However, there are still controversies regarding which clinical characteristics of MS are associated with the occurrence of epileptic seizures.

While the demyelination-induced seizure has been addressed for decades in patients with MS, there are still two open questions without a definite conclusion: (1) How might myelin deficiency lead to neuronal hyper-excitability? (2) What are the contributions of glial cells? Given that the notion that epilepsy occurs due to changes in neuronal properties has now been challenged [60], which cellular and molecular changes during demyelination may lead to alterations in neuronal activity triggering seizuregenesis? To answer this question, the use of cuprizone as an experimental model of demyelination has reported new data in this field.

2.3. Cuprizone Induced Demyelination as a Model for Epilepsy

Since its first application in research, cuprizone (CPZ) has been used to study the processes involved in de- and remyelination, despite the fact that its exact mechanisms of action remain rather elusive. Some preliminary studies have reported the occurrence of seizures in mice fed with 0.3% CPZ diet for 7 weeks; however, the mechanisms underlying the seizures were not addressed in these studies [61][62]. Indeed, research in this area did not characterized seizures induced by CPZ until 2008, when Hoffman et al. reported that chronic CPZ diet treatment at the same concentration used for

induction of MS model led to short but frequent spike neuron discharges in the EEG. In addition, cuprizone-treated mice exhibited generalized tonic clonic seizures induced by handling or other types of sensory stimulation. Furthermore, a massive demyelination and axonal degeneration were reported in the dorsal and ventral areas of hippocampus formation, areas often involved in seizures [63]. However, the role of glial cells and the susceptibility of different neuronal subpopulations remained unknown. In this sense, a recent study has revealed that chronic demyelination induced by CPZ leads to seizure activity in the dorsal hippocampus. Furthermore, some changes were found within the CA1 pyramidal hippocampal area after 9 weeks of CPZ treatment, including extensive demyelination, loss of parvalbumin (PV^+) inhibitory interneurons, widespread gliosis, and a transient decrease in aquaporin-4 (AQP4) expression [64]. Loss of interneurons following CPZ feeding is not surprising, since half of the cortical myelin located in layer 2/3 and a quarter in layer 4 ensheathes the axons of inhibitory neurons, especially parvalbumin-positive basket cells [65]. Reactive astrogliosis is a common feature of demyelination and seizure, which is found in both human postmortem and animal models [60][66]. In this cuprizone model, an increase of Kir4.1 protein was revealed.

Glial cells have a significant role in modulating brain water transport through AQP4 channels [67]. Therefore, changes in its expression, as occurs in the cuprizone experimental model, may disturb osmolality and the resting membrane potential and subsequently lead to hyper-excitability [68]. AQP4 downregulation was also reported in seizure animal models [69]. Furthermore, AQP4-lacking mice have a prolonged seizure duration, which confirms its role in the maintenance of homeostasis [68]. Since AQP4 is indirectly involved in potassium homeostasis, changes in the expression of inward rectifier potassium channel Kir4.1 might be involved in seizuregenesis by increasing the extracellular potassium concentration [70].

A complete understanding of the pathological mechanisms underlying CPZ intoxication could be of the greatest importance to study the seizure development secondary to demyelination and to claim the validity of MS and epilepsy therapies developed in this model. Further studies are needed to elucidate the effects of CPZ on different hippocampal interneuron subtypes and their role in the initiation of seizures. Likewise, a deep understanding of the pathophysiology underlying the inhibitory cell loss in chronic demyelination may pave the way for a better understanding of seizure development secondary to MS and its clinical management.

3. Conclusions

Although epileptic seizure has been thought to be a comorbidity of MS for more than 150 years, this subject has attracted more attention recently. Furthermore, evidence in recent years has clearly shown that myelin damage is a comorbidity for epilepsy. Increased attention to shared pathological mechanisms underlying demyelination and epilepsy will provide a better insight into the link between MS and epilepsy, and could result in better management. However, significant progress in determining the common pathological mechanisms in detail is still expected. This could help to develop therapeutic agents for managing both conditions. Likewise, a deeper understanding of the shared pathological mechanisms suggests that the disease-modifying drugs for one pathology may help to manage the other. We hope that the current knowledge on the pathological events reviewed in this entry helps to provide greater insight for researchers working on this bidirectional connection.

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