Review article

Mechanisms of neurobehavioral abnormalities in multiple sclerosis: Contributions from neural and immune components

Rafael Lazo-Gómez a, Gloria de Lourdes Llamosa-García Velázquez b, Diego Mireles-Jacobo a, Marco Antonio Sotomayor-Sobrino c,

a Neuroscience franchise, Novartis Pharma México, Calzada de Tlalpan 1779, San Diego Churubusco, 04120 Coyoacán, CDMX, Mexico
b Dirección de Enseñanza e Investigación, Hospital Central Norte de PEMEX, Campo Matillas 52, San Antonio, 02720 Azcapotzalco, CDMX, Mexico
c Facultad de Ciencias, Universidad Nacional Autónoma de México, Mexico

A R T I C L E   I N F O

Article history:
Received 29 September 2018
Received in revised form 21 December 2018
Accepted 10 January 2019
Available online 21 February 2019

Keywords:
Neurobehavioral abnormality
Cognitive decline
Neuroinflammation
Neurodegeneration
Excitotoxicity
Multiple sclerosis

A B S T R A C T

Multiple sclerosis-related neurobehavioral abnormalities are one of the main components of disability in this disease. The same pathological processes that explain demyelination periods and neurodegeneration also allow the comprehension of neurobehavioral abnormalities. Inflammation in the central nervous system caused by cells of the immune system, especially lymphocytes, and by resident cells, such as astrocytes and microglia, directly modulate neurotransmission and synaptic physiology, resulting in behavioral changes (such as sickness behavior) and amplifying the degenerative mechanisms that occur in multiple sclerosis. In addition, neuronal death caused by glutamate-mediated excitotoxicity, alterations in GABAergic, serotonergic, and dopaminergic neurotransmission, and the mechanisms of axon damage are of foremost importance to explain the reduction in brain volume and the associated cognitive decline. Neuroinflammation and neurodegeneration are not isolated phenomena and various instances of interaction between them have been described. This presents attractive targets for the development of therapeutical strategies for this neglected component of multiple sclerosis related disability.

© 2019 International Federation of Clinical Neurophysiology. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Contents

1. Introduction ................................................................. 40
2. Contribution of the immune-pathological components of MS to NBAs ................................................................. 40
3. Contribution of neuropathological mechanisms to the NBAs in MS ................................................................. 41
4. Conclusions ................................................................. 44

Ethics approval and consent to participate ................................................................. 44
Consent for publication ................................................................. 44
Availability of data and material ................................................................. 44
Competing interests ................................................................. 44
Funding ................................................................. 44
Authors’ contributions ................................................................. 44
References ................................................................. 44

* Corresponding author.
E-mail address: drsotomayormarco@ciencias.unam.mx (M.A. Sotomayor-Sobrino).

https://doi.org/10.1016/j.cnp.2019.01.004
2467-981X/© 2019 International Federation of Clinical Neurophysiology. Published by Elsevier B.V.
This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
1. Introduction

Multiple sclerosis (MS) is a neuroinflammatory disorder of autoimmune nature, characterized by demyelination and neurodegeneration, which causes neurological impairment. It occurs more frequently in young adults, being the main cause of non-traumatic neurological disability in this population (Giovannoni et al., 2016). Since it usually presents during the most economically productive period of life, the costs incurred and the associated functional decline negatively impact the quality of life of the people affected (Trisolini et al., 2010).

MS can cause disability in any functional system (Giovannoni et al., 2016). However, cognitive impairment and neurobehavioral abnormalities (from now on, both referred as neurobehavioral abnormalities, NBAs) associated with MS has received less attention. In fact, the French neurologist Jean-Martin Charcot mentions it in the original description of the disease as “a marked weakening of the memory, the concepts are formed slowly, and the mental and emotional faculties are completely dull” (Özkabas et al., 2015). Recent studies have consistently shown that alterations in cognition and behavior provoke and contribute to disability in MS (Glanz et al., 2007; Feuillet et al., 2007; Potagas et al., 2008; Rao et al., 2011) (Table 1).

It is common to consider that demyelination of inflammatory origin predominates during the first stages of the disease, clinically manifested by episodes of reversible neurological deficit (relapses); while in the late stages neurodegenerative processes lead to irreversible disability (progression) (Correale et al., 2016). Evidence shows that these divisions are artificial and that both processes occur throughout the natural history of the disease (Glanz et al., 2007; Potagas et al., 2008; Rao et al., 1991). For instance, the disease-modifying treatments (DMTs), which target inflammatory demyelination, not only diminish the frequency of relapses but also ameliorate some of the NBAs associated with MS (Mattioli et al., 2015; Ultz et al., 2016; Özkabas et al., 2016). This suggests that both processes operate simultaneously and that their understanding could point to novel therapeutic targets to achieve an integral management of the disease. In agreement, some clinical markers of disease progression are associated with the presence of NBAs (Table 2).

Experimental allergic encephalomyelitis (EAE), an experimental model of MS, has been useful to elucidate the pathological mechanisms that underlie NBAs. It is induced by the subcutaneous or intraperitoneal administration of the myelin oligodendrocyte glycoprotein, or its fragments, in mammals (more frequently in rodents). This results in a disease with varied neurological manifestations (weakness, fatigue, paralysis, ataxia) with relapses and recoveries similar to those of MS, which also includes NBAs (Robinson et al., 2014). The resulting demyelination occurs predominantly in the optic nerves and spinal cord, with relative preservation of the brain and hippocampus (Ziehn et al., 2010). However, there is evidence that alterations in synaptic transmission in the non-affected regions cause, at least in part, the NBAs observed in this model (Mandolesi et al., 2010). This fact reinforces the idea that these alterations might explain these symptoms in patients with MS (Centonze et al., 2010).

Although inflammatory demyelination is the pathological hallmark of MS, the resulting defects in action potential speed and spreading can only partially explain the neurobehavioral symptoms of MS. Although several mechanisms have been described to explain NBAs in MS, none of them is unique for MS and are common to other neurodegenerative or neuropsychiatric disorders. In this review, we explore the contribution of mechanisms different to inflammatory demyelination that might cause the NBAs associated with MS, first from an immunopathological perspective, and then from a neuropathological point of view.

Table 1

| Symptom                  | Frequency (%) | Reference(s)                  |
|--------------------------|---------------|--------------------------------|
| Fatigue                  | 85–95         | Jongen et al., 2012; Bergandal et al., 2007 |
| Depression               | 24            | Marrie et al., 2015           |
| Anxiety                  | 22–26         | Marrie et al., 2015           |
| Cognitive decline        | 45–60         | Bergandal et al., 2007        |
| Decreased processing speed | 20–30       | Nabavi and Sangelaji, 2015    |
| Altered attention         | 25            | Nebel et al., 2007            |

Table 2

Main clinical factors of MS associated with the onset of neurobehavioral symptoms.

| Symptom                          | Reference(s)       |
|----------------------------------|--------------------|
| Progressive form of the disease  | Benedict and Zivadinov, 2011; Borghi et al., 2013 |
| Evolution >5 years after diagnosis | Benedict and Zivadinov, 2011; Nebel et al., 2007 |
| Early start (before 18 years of age) | Benedict and Zivadinov, 2011 |
| EDSS >4.0                        | Nebel et al., 2007 |
| Altered vocabulary (according to the Weschler Adult Intelligence Scale Vocabulary test) | Borghi et al., 2013 |
| Grey matter degeneration         | Borghi et al., 2013 |
| Presence of cortical lesions     | Borghi et al., 2013 |
| Increased width of the third ventricle (as an indicator of brain volume loss) | Borghi et al., 2013 |
| Low premorbid intelligence       | Borghi et al., 2013 |
demyelination process seems to be indirect. Some studies report that self-reactive immunoglobulins secreted by plasma cells into the CNS facilitate phagocytosis of myelin components and other cellular components by macrophages or microglia, activate complement proteins and produce diffuse neuroinflammation (Dendrou et al., 2015; Siffrin et al., 2010). These immunoglobulins generate the oligoclonal bands in the cerebrospinal fluid (Bankoti et al., 2015; Kuerten et al., 2016). These structures express the chemokine CXCL13, which induces the proliferation, antigenic selection, and maturation of autoreactive B lymphocytes (Siffrin et al., 2010).

The effects of inflammatory mediators on peripheral organs (especially those near the vagus nerve), circumventricular organs (vascular organ of the endplate, organ of the postrema area, endocrine hypothalamus) and on the choroidal plexuses result in a series of stereotyped behaviors known as sickness behavior (SB). SB is characterized by fever, secretion of stress hormones (by activation of the hypothalamic-pituitary-adrenal –HPA– axis), anorexia, anhedonia, adynamia and social isolation (Dantzer, 2006). These effects might explain the higher incidence of depression and fatigue in patients with chronic inflammatory disorders (Miller and Raison, 2015). In addition, it has been shown that patients with major depressive disorder have higher levels of inflammation markers in peripheral blood (such as C-reactive protein, IL-1β and TNFα) (Miller et al., 2009). Also, non-steroidal anti-inflammatory drugs have antidepressor effects, as has been shown for acetylsalicylic acid in an animal model of chronic mild stress (Bhatt et al., 2016) and for celecoxib in patients with major depression (Na et al., 2016).

In patients with MS, similar findings have been observed. Recent studies found that 80% of affected people report fatigue as a disabling symptom (Nagaraj et al., 2013), half report other cognitive disorders (Jongen et al., 2012) and another proportion report depression or anxiety (Marrie et al., 2015; Bergental et al., 2007) (see Table 1). The SB generated in the EAE model is similar to the cognitive impairment associated with MS, which suggests that there are common mechanisms that could represent therapeutic targets. For example, rituximab improves fatigue and mood (Kuerten et al., 2016). Also, vagus nerve stimulation, already used for the clinical management of treatment-resistant depression (Carreno and Frazer, 2017; O’Reardon et al., 2006), reduces the production of proinflammatory cytokines, decreases the permeability of the blood-brain barrier and improves the functional status in an animal model of traumatic brain injury (Neren et al., 2016). These observations suggest that vagus nerve stimulation might have a role in the treatment of some of the neuropsychiatric manifestations of MS.

3. Contribution of neuropathological mechanisms to the NBAs in MS

As previously stated, factors related to brain atrophy, such as grey matter degeneration and increased width of the third ventricle (Borghi et al., 2013) are also linked to NBAs in MS. Brain atrophy in MS is secondary, at least in part, to neuronal death, loss of synaptic density and axonal degeneration (Mandolesi et al., 2010), thus the mechanisms that lead to these phenomena could explain these symptoms and offer therapeutic targets.

One of the most relevant mechanisms of neuronal death is glutamate-mediated excitotoxicity (Kostic et al., 2013). Glutamate is the most abundant excitatory neurotransmitter of the CNS and is involved in multiple cognitive processes, such as learning, memory, attention and the modulation of emotional states. This neurotransmitter is a ligand of two types of receptors: metabotropic (receptors with seven transmembrane domains, coupled to G proteins) and ionotropic. Even though the activity of metabotropic receptors is involved in the cognitive processes previously enumerated, their importance is lower compared to ionotropic receptors (Swanson et al., 2005). The ionotropic glutamate receptors are permeable channels of cations (especially sodium -Na⁺- and calcium -Ca²⁺-). Three types of ionotropic receptors have been described according to pharmacological techniques: selective to N-methyl-D-aspartate (NMDA), α- amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainate. The composition of subunits, relative abundance, synaptic localization and kinetic characteristics of these receptors change according to the studied region of the nervous system, and this serves for the functional purposes of the involved circuits (Barnes and Sievin, 2003).

Although the activation of these ionotropic receptors is necessary for many physiological processes, their excessive activation causes glutamate-mediated excitotoxicity, which may not be limited to neurons, but may also affect glial cells and oligodendrocytes (Dormer et al., 2005). The massive influx of Ca²⁺ into the intracellular compartment leads to the activation of proteases, lipases, and endonucleases, which degrade cellular components and produce intracellular signaling molecules, which perpetuate these processes. Also, excess Ca²⁺ is buffered by the mitochondria, in an attempt to regulate its intracellular concentration, which can lead to a loss of transmembrane potential and then to energy failure. The increase of Ca²⁺ generates stress of the endoplasmic reticulum, activates the response to misfolded proteins, and compromises the ability to maintain postsynaptic structures. Additionally, the entry of cations into the intracellular space causes a loss of transmembrane polarity. This depolarization leads to the uncontrolled release of neurotransmitters, and an inability to maintain the physiological processes of import and export of energy substrates (such as lactate and glucose) and ions (such as potassium, calcium, and sodium). These processes finally, in isolation or together, lead to the activation of pathways of death, such as apoptosis or necrosis (Mehta et al., 2013).

During neuroinflammation episodes, the concentration of glutamate in the cerebral parenchyma increases due to overexpression in macrophages, dendritic cells and the microglia of the ζ2 system transporter, which works by importing cysteine into the cells in exchange for glutamate (Scannevin and Huganir, 2000). However, in a recent study, blocking the expression of the ζ2 system transporter protected from demyelination and attenuated the infiltration of inflammatory cells in the CNS, contrary to what was expected, suggesting that this antipporter is involved in the migration of T lymphocytes to CNS (Pampliega et al., 2011). On the other hand, Dormer et al. (2005) found that the increase in glutamate concentration due to inhibition of GLT-1 and GLAST transporters is toxic to oligodendrocytes, which could contribute to immune-mediated demyelination.

Besides, inflammatory mediators potentiate glutamate-mediated excitotoxicity. For example, TNFα decreases the expression of the GluR2 subunit of the AMPA type receptor in neurons, which causes these receptors to be permeable to Ca²⁺ (Mehta et al., 2013). The activation of the TNFα receptor in astrocytes decreases the expression of the excitatory amino acids transporter type 1 (EAAT1) in patients with progressive MS (Pitt et al., 2003). Also, the activation of microglia by TNF induces the secretion of glutamate, brain-derived neurotrophic factor (Takeuchi et al., 2006) and of TNF (Kuno et al., 2005), which could stimulate the secretion of more glutamate through positive feedback loop.
Alterations in neurotransmission and the synaptic structure, even when there is no evidence of neuronal death, are involved in cognitive deterioration in animal models of MS. For example, the induction of EAE in rodents decreases the density of excitatory postsynaptic structures in the CA1 area of the hippocampus, a region of the brain involved with memory, learning, and spatial orientation. This finding is dependent on the phagocytic activity of the microglia. These alterations were avoided with the in vivo administration of NMDA receptor agonists. It is worth noting that this protection became evident only when the blockade of these receptors was carried out in the initial stages of the EAE induction (Bellizzi et al., 2016). In another study, the administration of glatiramer acetate (GA), one of the first DMTs developed for MS, prevented changes in some electrophysiological parameters of spontaneous excitatory postsynaptic potentials (EPSPs) of striatum median spiny neurons in EAE mice, even since presymptomatic stages. These changes were partially dependent on the activation of microglia by a Th1 cytokine profile. Also, GA decreased the denervation of parvalbumine-positive GABAergic interneurons in the EAE mice (Gentile et al., 2016). Also, ganaxolone, a synthetic neurosteroid agonist of GABA AR, ameliorated the NBAs and the clinical scores in animal models of MS (Gentile et al., 2013). (Fig. 1).

Excitotoxicity results not only from excessive glutamatergic neurotransmission, but also from insufficient inhibitory inputs to counterbalance excitatory signals. The main inhibitory neurotransmitter in the mammalian CNS is γ-aminobutyric acid (GABA). GABA mediates its effects through a ligand-gated chloride-permeable channel (the GABA-A receptor) or through a metabotropic G-protein-coupled receptor (the GABA-B receptor). GABAAR opening results in chloride influx and membrane hyperpolarization, which inhibits neuronal activity (Tatti et al., 2017). Whatever causes insufficient GABAAR activation might also cause hyperexcitability and, ultimately, excitotoxicity. GABA failure as a cause of excitotoxicity has been previously implicated in other neurodegenerative disorders, such as motor neuron disease (Ramírez-Jarquín et al., 2014) and its role in MS is accumulating.

Reduced levels of extracellular GABA are found in the white matter of patients with MS, regardless of the clinical phenotype (Paul et al., 2014; Cawley et al., 2015; Cao et al., 2018). Lower levels of GABA, as assessed by MRI spectroscopy, are associated with motor disability and cognitive impairment (Cawley et al., 2015; Nantes et al., 2017). Indeed, a very recent study found that reduced GABA concentrations in the posterior cingulate cortex were correlated with altered executive function while low levels in the hippocampus were linked to deficits in verbal memory (Cao et al., 2018).

These findings might be explained by the effects of secreted interleukin (IL) 1β from infiltrating autoreactive T lymphocytes. In the hippocampus of EAE mice IL1β reduces GABAergic neurotransmission due to a loss of inhibitory synaptic inputs (Mori et al., 2014). Similar observations have been made in the cerebellum (Mandolesi et al., 2012) and striatum (Rossi et al., 2011). These results suggest that the modulation of GABAergic neurotransmission is a potential target for the development of therapeutic strategies for NBAs in MS. For example, siphonamid, a sphyngosine-1-phosphate receptor antagonist in approval for secondary progressive MS (Kappos et al., 2018), prevents the degeneration of parvalbumine-positive GABAergic interneurons in the EAE mice (Gentile et al., 2016). Also, ganaxolone, a synthetic neurosteroid agonist of GABAAR, ameliorated the NBAs and the neuroinflammation associated with the induction of EAE in mice (Paul et al., 2014). However, other classical agonists of GABAAR, such as benzodiazepines and barbiturates, have failed to improve the clinical scores in animal models of MS (Gillain et al., 2014).

There is evidence that other neurotransmitters are altered in animal models and patients with MS. Serotonin, a neurotransmitter derived from the essential amino acid tryptophan, participates in cognitive processes, such as attention (Wingen et al., 2008). During inflammatory events, stimulation by interferons and prostaglandin E2 increases the expression of indoleamine-2,3-dioxygenase, which synthesizes kynurenic acid from tryptophan, in the cells of the innate immune system. Overexpression of this enzyme may limit the availability of substrate for the synthesis of serotonin and, at the same time, the accumulation of kynurenes, which have significant effects on the functioning of the CNS.
For example, kynurenic acid inhibits the release of dopamine (which is involved in the reward system) and is an antagonist of glutamate receptors, whereas quinolinic acid is an agonist of glutamate receptors and can potentiate glutamate-mediated excitotoxicity (Vécsei et al., 2012). Importantly, in patients with MS, high concentrations of kynurenine are observed in early stages of the disease (Török et al., 2016). In addition, the kynurenine profile in CSF correlates with the progression of disability and has potential as a biomarker, since it can differentiate between progressive and recurrent forms of the disease with an accuracy close to 90% (Lim et al., 2017).

Dopamine is one of the essential neurotransmitters for attention and motivation (Felger et al., 2016). The proinflammatory conditions promote the oxidation of tetrahydrobiopterin, which can block the synthesis of dopamine (Dobryakova et al., 2015). In patients with MS, alterations in dopaminergic neurotransmission between the striatum and the prefrontal cortex are related to some cognitive symptoms, such as fatigue, depression and decreased attention (Haider et al., 2011).

Several mechanisms underlying axonal degeneration in MS have been described, including oxidative stress. In fact, in demyelinating lesions of patients with MS, there is a high concentration of nitric oxide (NO) (Smith et al., 2001), whereas it has been observed that NO causes axonal degeneration in an EAE animal model, which decreases with antioxidants (Campbell et al., 2012). Evidence shows that free radicals produce mitochondrial dysfunction since they increase the permeability of the internal membrane, damage mitochondrial DNA and generate pro-apoptotic complexes in axons of patients with MS (Campbell et al., 2011). Similarly, in the cerebral cortex of patients with MS deletions in the mitochondrial genome and alterations in the electron transport chain support mitochondrial dysfunction as causal of axonal degeneration (Trapp and Stys, 2009). Demyelination and mitochondrial dysfunction generate energy failure that compromises the viability of the affected axons and, finally, of the neurons (Nicholls, 2004).

Another key point to mention is the compensatory mechanisms to maintain the driving speed in the axons, which consist of modifications in the expression and distribution of ion channels activated by voltage, and which can be deleterious. In particular, the sodium channels, which under normal conditions locate in the Ranvier nodes, increase their expression and are located diffusely after demyelination. These changes promote the accumulation of intracellular sodium, with the consequent loss of transmembrane potential, reverse functioning of the Na\(^+\)/Ca\(^{2+}\) antiporter and excessive calcium intake to the intracellular compartment (Dutta and Trapp, 2007). Persistent axonal damage leads to the retrograde Wallerian degeneration observed in white matter with acute demyelination (Singh et al., 2017) as well as in chronic active lesions (Trapp and Stys, 2009). However, this process of degeneration has also been documented in gray matter and even in neurons without myelin, suggesting that this process develops independently of damage to myelin (Singh et al., 2017).

Microglial cells can have a protective or harmful effect on the CNS, which depends in large part on the microenvironment, that is, on the relative local abundance of cytokines and signaling molecules. The activation by IFN-\(\gamma\) produces differentiation, or polarization, towards a pro-inflammatory phenotype associated with neurodegeneration (M1). On the other hand, IL-4 allows polarization towards a state that favors neurogenesis, oligodendrogeneration and is anti-inflammatory (M2) (Cherry et al., 2014). A recent study found that most of the activated microglia have the M1 phenotype in the cerebrospinal fluid of patients with MS; however, multiple clones with M2 phenotype were also identified. The authors concluded that the CNS of patients with MS presents an environment that promotes the activation of microglia towards both phenotypes, probably as a compensatory mechanism to tissue damage (Vogel et al., 2013).

Another mechanism that might add to the development of NBAs in MS mediated by microglia is synaptic pruning. Complement proteins C5a and C1q, among others, mark dendritic spines without synaptic activity in order to be phagocytosed by microglial cells (Paolicelli et al., 2011). Although this process was first described in the developing nervous system, a direct association exists between the activation of complement proteins and the loss of brain volume in pathologies characterized by cognitive impairment, such as Alzheimer-type dementia (Hong et al., 2016). A high concentration of C1q, C3b and C4d complement proteins are present in demyelinating lesions, and to a lesser extent in gray and white matter, in necropsies performed in patients with MS compared to healthy controls. In addition, a relationship between protein levels and the time of diagnosis suggest their involvement in neurodegeneration associated with MS (Michailidou et al., 2017).

Given these findings, it has been proposed that microglia could be a therapeutic strategy for neuroinflammation and cognitive impairment associated with MS. For example, the administration of minocycline, which inhibits the activation of microglia, has neuroprotective effects in animal models of brain damage (Scholz et al., 2015; Madeira et al., 2015). Since this drug has an acceptable and clinically proven safety profile, there are ongoing clinical trials in humans, which show a delay in the progression of CIS to MS (Metz et al., 2017).

Although astrocytes are the most abundant glial cells of the CNS, their role in the pathophysiology of MS was not clear until recently. Astrocytes react early to molecules associated with cell damage (e.g., heat shock protein 90, extracellular DNA andadenosine) of the CNS through Toll-like receptors, these being the first to respond during activation of the innate immune system, as well as to cytokines in the tissue. In response, astrocytes secrete cytokines (such as IL6, IL1\(\beta\), TNF\(\alpha\), and tumor growth factor \(\beta\)) and chemokines (such as CCL2, CCL5, CXCL10, CXCL12, and IL8). These molecules modulate the permeability of the blood-brain barrier, promote the activation of leukocytes and microglia, and stimulate the migration of the latter towards the injured tissue (Correale and Farez, 2015). Moreover, activation of astrocytes could have a neurotoxic effect, because astrocytes increase secretion of glutamate and adenosine triphosphate in sites where there is damage to myelin (Brosnan and Raine, 2013).

The mechanisms of neuronal and glial death discussed so far impact the efficiency of neuronal networks to integrate information, which leads to network collapse. A wealth of data obtained from humans by several methods based on MRI supports the idea that alterations in connectivity are the substrate of NBAs in neurodegenerative disorders (Ahmed et al., 2016), and in MS (Nave KA, 2010; Schoonheim et al., 2015). However, the diversity of methods and inconsistencies in subject selection have hindered reaching conclusions on the characteristic network alterations underlying NBAs in MS. Brains of people with MS show increased activation and connectivity, which reflect compensatory changes to demyelination, axonal loss and neuron death (Schoonheim et al., 2010). NBAs are clinically apparent when these changes are not enough to cope with the pathologic process underlying MS, which is a consequence of decreased network efficiency (Schoonheim et al., 2015). No specific networks are preferentially targeted in MS, rather graph analysis approaches have highlighted that whole-brain network inefficiency is causal to NBAs in MS (Helekar et al., 2010).
4. Conclusions

Neurobehavioral abnormalities and cognitive impairment are common throughout the natural history of MS, although they are not well acknowledged in the clinical setting. Together, they negatively impact the quality of life of people who suffer from MS. However, some advances have been made, as in recent clinical guidelines, there is greater emphasis on the recognition of NBAs as a marker of suboptimal response to treatment.

NBAs originate from the complex interaction between cells of the immune system, glia, and neurons in the context of autoimmune characteristic of MS. Most current DMTs control to a greater or lesser extent the inflammatory component of the disease, but show have not shown to halt neurodegeneration. Also, their impact of NBAs have not been thoroughly studied and the few available results are unsatisfactory. There is an unmet need in developing therapeutic strategies to ameliorate disability associated with NBAs. Understanding the relationship between the immune and nervous system in MS offer new therapeutic avenues, such as the modulation of glutamate, GABA or monoamine neurotransmission. Given the intricate and complex interplay of the pathophysiology mechanisms involved treatments aimed to NBAs will have to address both components, immune and neural.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

Not applicable.

Competing interests

Rafael Lazo-Gómez and Diego Mireles-Jacobo work for Novartis Pharma Mexico.

Funding

The preparation of this review did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors’ contributions

Gloria Llamas and Marco Antonio Sotomayor-Sobrino wrote and critically reviewed the manuscript. Rafael Lazo-Gómez wrote, critically reviewed the manuscript and designed the figure. Diego Mireles-Jacobo critically reviewed and corrected the english version of the manuscript.

References

Ahmed, R.M., Denneyev, E.M., Irshid, M., Ittner, A., Naismith, S., Ittner, L.M., Rohrer, J.D., Halliday, G.M., Eisen, A., Hodges, J.R., Kiernan, M.C., 2016. Neuronal network disintegration: common pathways linking neurodegenerative diseases. J. Neurol. Neurosurg. Psychiatry 87, 1234–1241.

Bantli, J., Apeltesin, L., Hausser, S.L., Allen, S., Albertolle, M.E., Witkowska, H.E., et al., 2014. In multiple sclerosis, oligodendrocyte bands connect to peripheral B-cell responses. Ann. Neurol. 75, 266–276.

Barnes, C.N., Slevin, J.T., 2003. Ionotropic glutamate receptor biology: effect on synaptic connectivity and function in neurological disease. Curr. Med. Chem. 10, 2059–2072.

Bellizzi, M.J., Geathers, J.S., Allan, K.C., Gelbard, H.A., 2016. Platelet-activating factor receptors mediate excitatory post synaptic hippocampal injury in experimental autoimmune encephalomyelitis. J. Neurosci. 36, 1330–1346.

Benedict, R.H.B., Zivadinov, R., 2011. Risk factors for and management of cognitive dysfunction in multiple sclerosis. Nat Rev. Neurol. 7, 332–342.

Bergendal, G., Fredriksson, S., Almkvist, O., 2007. Selective decline in information processing in subgroups of multiple sclerosis: an 8-year longitudinal study. Eur. Neurol. 57, 193–202.

Borghi, M., Cavallio, M., Carletto, S., Ostacoli, L., Zuffranieri, M., Picci, R.L., et al., 2013. Presence and significant determinants of cognitive impairment in a large sample of patients with multiple sclerosis. PLoS One 8, e69820.

Brosnan, C.F., Raine, C.S., 2013. The astrocyte in multiple sclerosis revisited. Glia 61, 453–465.

Campbell, G.R., Ohno, N., Turnbull, D.M., 2012. Mahad DJ. Mitochondrial changes within axons in scleroses: an update. Curr. Opin. Neurol. 25, 149–153.

Campbell, G.R., Zabreava, I., Reeve, A.K., Krishnan, K.J., Reynolds, R., Howell, O., et al., 2011. Mitochondrial DNA deletions and neurodegeneration in multiple sclerosis. Ann. Neurol. 69, 481–492.

Cao, G., Edden, R.A.E., Gao, S., Li, H., Gong, T., Chen, W., Liu, X., Wang, G., Zhao, B., 2018. Reduced GABA levels correlate with cognitive impairment in patients with relapsing-remitting multiple sclerosis. Eur. Radiol. 28, 1140–1148.

Cawley, N., Solanky, B.S., Muhlert, N., Tur, C., Edden, R.A., Wheeler-Kingshott, C.A., Miller, D.H., Thompson, A.J., Ciccarelli, O., 2015. Reduced gamma-amino butyric acid concentration is associated with physical disability in progressive multiple sclerosis. Brain 138, 2584–2595.

Centonze, D., Muzio, L., Rossi, S., Furlan, R., Bernardi, G., Martino, G., 2010. The link between inflammation, synaptic transmission and neurodegeneration in multiple sclerosis. Cell Death Differ 17, 1083–1091.

Cherry, J.D., Olshowka, J.A., O’Banion, M.K., 2014. Neuroinflammation and M2 microglia: The good, the bad, and the inflamed. J. Neuroinflammation. 11, 98.

Correale, J., Farez, M.F., 2015. The role of astrocytes in multiple sclerosis progression. Front. Neurol. 6, 180.

Correale, J., Gaitán, M.J., Ysraelt, M.C., Fisil, M.P., 2016. Progressive multiple sclerosis from pathogenic mechanisms to treatment. Brain 140, 527–545.

Dantzer, R., 2006. Cytokine, sickness behavior, and depression. Neurol. Clin. 24, 441–460.

Dendrou, C.A., Fugger, L., Freise, M.A., 2015. Immunopathology of multiple sclerosis. Nat. Rev. Immunol. 15 (9), 545–558.

Dobryakova, E., Genova, H.M., DeLuca, J., Wylie, G.R., 2015. The dopamine imbalance hypothesis of fatigue in multiple sclerosis and other neurological disorders. Front. Neurol. 6, 52.

Domercq, M., Etxebarria, E., Pérez-Samartín, A., Matute, C., 2005. Excitotoxic oligodendrocyte death and axonal damage induced by glutamate transporter inhibition. Glia 52, 36–46.

Dutta, R., Trapp, B.D., 2007. Pathogenesis of axonal and neuronal damage in multiple sclerosis. Neurology 68 (Suppl 3), S22–S31.

Felger, J.C., Li, Z., Haroon, E., Woolwine, B.J., Jung, M.Y., Hu, X., et al., 2016. Inflammation is associated with decreased functional connectivity within cortico-striatal reward circuitry in depression. Mol. Psychiatry 21, 1358–1365.

Feuillet, L., Reuter, F.,Audouin, B., Malivola, I., Barrau, K., Ali Cherif, A., et al., 2007. Early cognitive impairment in patients with clinically isolated syndrome suggestive of multiple sclerosis. Mult Scler. 13, 124–127.

Gentile, A., Rossi, S., Studer, V., Motta, C., De Chiara, V., Musella, A., et al., 2013. Glatiramer acetate protects against inflammatory synaptopathy in experimental autoimmune encephalomyelitis. J. Neuroimmune Pharmacol. 8, 651–663.

Gentile, A., Musella, A., Bullitta, S., Freegna, D., De Viito, F., Fantozzi, R., Piras, E., Gargano, F., Borsellino, G., Battisti, L., Schubart, A., Mandolesi, C., Centonze, D., 2016. Siponimod (BAF312) prevents synaptic neurodegeneration in experimental multiple sclerosis. J. Neuroinflammation. 13, 207.

Gilani, A.A., Dash, R.P., Jivrajani, M.N., Thakur, S.K., Nivsarkar, M., 2014. Evaluation of GABAergic transmission modulation as a novel functional target for management of multiple sclerosis: exploring inhibitory effect of GABA on glutamate-mediated excitotoxicity. Adv. Pharmacol. Sci. 2014, 623276.

Giovannoni, G., Burtkueven, H., Hüb-Bahljet, S., Hobart, J., Kohbelt, P., Geiger, E., et al., 2016. Brain health: time matters in multiple sclerosis. Mult. Scler. Relat. Disord. 9, 55–548.

Glanz, B.L., Holland, C.M., Gauthier, S.A., Amoussa, E.L., Lipkota, Z., Houthens, M.C., et al., 2007. Cognitive dysfunction in patients with clinically isolated syndromes or newly diagnosed multiple sclerosis. Mult Scler. 13, 1004–1010.

Haidar, L., Frischer, M.T., Frischer, J.M., Bauer, J., Höffberger, R., Botond, C., et al., 2011. Oxidative damage in multiple sclerosis lesions. Brain. 134, 1914–1924.

Haidar, L., Zizzari, T., Höffberger, R., Bagnato, F., Grahnert, G., et al., 2016. The topography of demyelination and neurodegeneration in the multiple sclerosis brain. Brain. 139, 807–815.

Hagen, K., Maton, J.C., Maton, E., Bartley, K., Stosis, M., Saldana-King, T., Montague, P.R., Hutton, G.J., 2010. Functional brain network changes associated with maintenance of cognitive function in multiple sclerosis. Front. Hum. Neurosci. 4, 219.

Hong, S., Dissing-Olesen, L., Stevens, B., 2016. New insights on the role of microglia in synaptic pruning in health and disease. Curr. Opin. Neurobiol. 36, 128–134.

Jongen, P.J., Ter Horst, A.T., Brands, A.M., 2012. Cognitive impairment in multiple sclerosis. Minerva Med. 103, 73–96.

Kappos, L., Bar-Or, A., Coe, B.A.C., Fox, R.J., Giovannoni, G., Gold, R., Vermersch, P., Arnold, D.L., Arnold, S., Scherz, T., Wolf, C., Wallström, E., Dahlke, F., 2018.
Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study. Lancet 391, 1263–1273.

Kostic, M., Zeljkovic, N., Stanojlovic, L., 2013. Multiple sclerosis and glutamate toxicity. Neurol. Sci. 34, 1121–1132.

Kuerten, S., Schickel, A., Kerkloh, C., Recks, M., Addicks, K., Ruddle, N., et al., 2016. The development of tertiary lymphoid organs in the central nervous system facilitates detrimental spreading of the MPN-specific T cell response (F1464). J. Clin. Invest. 129, 190–172(7).

Kuno, R., Wang, J., Kawanokuchi, J., Takeuchi, H., Mizuno, T., Suzumura, A., 2005. Autocrine activation of microglia by tumor necrosis factor-α. J. Neuroimmunol. 166, 111–126.

Lim, C.K., Bilgin, A., Lovejoy, D.B., Tan, V., Bustamante, S., Taylor, B.V., et al., 2017. Kynerinene pathway metabolomics predicts and provides mechanistic insight into multiple sclerosis progression. Sci. Rep. 7, 41473.

Lucas, R.M., Hughes, A.M., Ljoo, M., Ponsoby, A. L., Dwyer, D.E., Taylor, B.V., et al., 2011. Epstein-Barr virus and multiple sclerosis. J. Neurol. Neurosurg. Psychiatry 82, 1142–1148.

Madeira, M.H., Boa, R., Santos, P.F., Ambrosio, A.F., Santiago, A.R., 2015. Contribution of microglia-mediated neuroinflammation to retinal degenerative diseases. Mediators Inflamm. 2015, 6730900.

Mandolese, G., Grasselli, G., Musumeci, G., Centonze, D., 2010. Cognitive deficits in experimental autoimmune encephalomyelitis: Neuroinflammation and synaptic degeneration. Neuro Sci. 31 (Suppl 2), S255–S259.

Mandolese, G., Grasselli, G., Musumeci, A., Centonze, D., 2012. GABAergic signaling and connectivity on Purkinje cells are impaired in experimental autoimmune encephalomyelitis. Exp. Neurol. Dis. 46, 414–424.

Marie, R.A., Reingold, S., Cohen, J., Shreve, O., Troiano, M., Sorenson, P.S., et al., 2015. The incidence and prevalence of psychiatric disorders in multiple sclerosis: a systematic review. Mult. Scler. J. 21, 305–317.

Mattoli, F., Stampa-Paloni, F., Scarpati, C., Capri, R., 2015. Natolazumab significantly improves cognitive impairment over three years in MS: Pattern of disability progression and preliminary MRI Findings. PloS ONE 10, e0131803.

Mehta, A., Prabhakar, M., Kumar, F., Deshmukh, R., Sharma, P.L., 2013. Excitotoxicity: Bridge to various triggers in neurodegenerative disorders. Eur. J. Pharmacol. 698, 6–18.

Metz, L.M., Li, D.K.B., Traboulsee, A.L., Duquette, P., Eliasziw, M., Cerchiaro, G., et al., 2014. Long-term use of fingolimod on cognitive status in patients with multiple sclerosis: Prospective, double-blind, randomised, phase 3 study. Lancet 384, 956–966.

Mandolesi, G., Grasselli, G., Musumeci, G., Centonze, D., 2010. Cognitive deficits in experimental autoimmune encephalomyelitis: Neuroinflammation and synaptic degeneration. Neuro Sci. 31 (Suppl 2), S255–S259.

Mehta, A., Prabhakar, M., Kumar, F., Deshmukh, R., Sharma, P.L., 2013. Excitotoxicity: Bridge to various triggers in neurodegenerative disorders. Eur. J. Pharmacol. 698, 6–18.

Metz, L.M., Li, D.K.B., Traboulsee, A.L., Duquette, P., Eliasziw, M., Cerchiaro, G., et al., 2014. Late-onset cognitive impairment after fingolimod treatment in multiple sclerosis patients with no pre-existing cognitive impairment: A post hoc analysis of the COMBINE study. Brain 138, 758–768.

Merritt, J.E., Koski, L., 2017. GABA and glutamate levels correlate with MTR and clinical findings in patients with multiple sclerosis: a case series. Neurol Sci. 38, 533–534.

Nagai, K., Taly, A.B., Gupta, A., Prasad, C., Christopher, R., 2013. Prevalence of psychiatric disorders in multiple sclerosis: a systematic review. Mult. Scler. Int. 2013, 965742.

Nabavi, S.M., Sangelaji, B., 2015. Cognitive dysfunction in multiple sclerosis: Mechanisms and treatment options. J. Res. Med. Sci. 20, 533–543.

Narad, R., Ablon, J., 2017. Cognitive dysfunction in multiple sclerosis: a double-blind, randomised, phase 3 study. Lancet 391, 1263–1273.

Shaw, J.L., Ho, C., Vescio, S., Chung, C., Dickenson, H.A., 2017. Contribution of microglia-mediated neuroinflammation to retinal degenerative diseases. Mediators Inflamm. 2015, 6730900.

Nagai, K., Taly, A.B., Gupta, A., Prasad, C., Christopher, R., 2013. Prevalence of psychiatric disorders in multiple sclerosis: a systematic review. Mult. Scler. Int. 2013, 965742.

Nagai, K., Taly, A.B., Gupta, A., Prasad, C., Christopher, R., 2013. Prevalence of psychiatric disorders in multiple sclerosis: a systematic review. Mult. Scler. Int. 2013, 965742.

Nagai, K., Taly, A.B., Gupta, A., Prasad, C., Christopher, R., 2013. Prevalence of psychiatric disorders in multiple sclerosis: a systematic review. Mult. Scler. Int. 2013, 965742.

Nagai, K., Taly, A.B., Gupta, A., Prasad, C., Christopher, R., 2013. Prevalence of psychiatric disorders in multiple sclerosis: a systematic review. Mult. Scler. Int. 2013, 965742.

Nagai, K., Taly, A.B., Gupta, A., Prasad, C., Christopher, R., 2013. Prevalence of psychiatric disorders in multiple sclerosis: a systematic review. Mult. Scler. Int. 2013, 965742.

Nagai, K., Taly, A.B., Gupta, A., Prasad, C., Christopher, R., 2013. Prevalence of psychiatric disorders in multiple sclerosis: a systematic review. Mult. Scler. Int. 2013, 965742.

Nagai, K., Taly, A.B., Gupta, A., Prasad, C., Christopher, R., 2013. Prevalence of psychiatric disorders in multiple sclerosis: a systematic review. Mult. Scler. Int. 2013, 965742.

Nagai, K., Taly, A.B., Gupta, A., Prasad, C., Christopher, R., 2013. Prevalence of psychiatric disorders in multiple sclerosis: a systematic review. Mult. Scler. Int. 2013, 965742.

Nagai, K., Taly, A.B., Gupta, A., Prasad, C., Christopher, R., 2013. Prevalence of psychiatric disorders in multiple sclerosis: a systematic review. Mult. Scler. Int. 2013, 965742.

Nagai, K., Taly, A.B., Gupta, A., Prasad, C., Christopher, R., 2013. Prevalence of psychiatric disorders in multiple sclerosis: a systematic review. Mult. Scler. Int. 2013, 965742.

Nagai, K., Taly, A.B., Gupta, A., Prasad, C., Christopher, R., 2013. Prevalence of psychiatric disorders in multiple sclerosis: a systematic review. Mult. Scler. Int. 2013, 965742.

Nagai, K., Taly, A.B., Gupta, A., Prasad, C., Christopher, R., 2013. Prevalence of psychiatric disorders in multiple sclerosis: a systematic review. Mult. Scler. Int. 2013, 965742.

Nagai, K., Taly, A.B., Gupta, A., Prasad, C., Christopher, R., 2013. Prevalence of psychiatric disorders in multiple sclerosis: a systematic review. Mult. Scler. Int. 2013, 965742.

Nagai, K., Taly, A.B., Gupta, A., Prasad, C., Christopher, R., 2013. Prevalence of psychiatric disorders in multiple sclerosis: a systematic review. Mult. Scler. Int. 2013, 965742.

Nagai, K., Taly, A.B., Gupta, A., Prasad, C., Christopher, R., 2013. Prevalence of psychiatric disorders in multiple sclerosis: a systematic review. Mult. Scler. Int. 2013, 965742.
Further reading

Achiron, A., Chapman, J., Magalashvili, D., Dolev, M., Lavie, M., Bercovich, E., et al., 2013. Modeling of cognitive impairment by disease duration in multiple sclerosis: a cross-sectional study. PLoS One 8, e71058.

Chang, A., Smith, M.C., Yin, X., Fox, R.J., Staugaitis, S.M., Trapp, B.D., 2008. Neurogenesis in the chronic lesions of multiple sclerosis. Brain. 131, 2366–2375.

Evonuk, K.S., Baker, B.J., Doyle, R.E., Moseley, C.E., Sestero, C.M., Johnston, B.P., et al., 2015. Inhibition of system Xc transporter attenuates autoimmune inflammatory demyelination. J. Immunol. 195, 450–463.

Freedman, M.S., Selchen, D., Arnold, D.L., Prat, A., Banwell, B., Yeung, M., et al., 2013. Treatment optimization in MS: Canadian MS Working Group updated recommendations. Can. J. Neurol. Sci. 40, 307–323.

Giannakopoulou, A., Grigoriadis, N., Bekari, C., Lourbopoulos, A., Dori, I., Tsingotjidou, A.S., et al., 2013. Acute inflammation alters adult hippocampal neurogenesis in a multiple sclerosis mouse model. J. Neurosci. Res. 91, 890–900.

Werner, P., Pitt, D., Raine, C.S., 2001. Multiple sclerosis: Altered glutamate homeostasis in lesions correlates with oligodendrocyte and axonal damage. Ann. Neurol. 50, 169–180.