

Is MS affecting the CNS only?

Lessons from clinic to myelin pathophysiology

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Abstract

MS is regarded as a disease of the CNS where a combination of demyelination, inflammation, and axonal degeneration results in neurologic disability. However, various studies have also shown that the peripheral nervous system (PNS) can be involved in MS, expanding the consequences of this disorder outside the brain and spinal cord, and providing food for thought to the still unanswered questions about MS origin and treatment. Here, we review the emerging concept of PNS involvement in MS by looking at it from a clinical, molecular, and biochemical point of view. Clinical, pathologic, electrophysiologic, and imaging studies give evidence that the PNS is functionally affected during MS and suggest that the disease might be part of a spectrum of demyelinating disorders instead of being a distinct entity. At the molecular level, similarities between the anatomic structure of the myelin and its interaction with axons in CNS and PNS are evident. In addition, a number of biochemical alterations that affect the myelin during MS can be assumed to be shared between CNS and PNS. Involvement of the PNS as a relevant disease target in MS pathology may have consequences for reaching the diagnosis and for therapeutic approaches of patients with MS. Hence, future MS studies should pay attention to the involvement of the PNS, i.e., its myelin, in MS pathogenesis, which could advance MS research.

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Glossary

AMS = axo-myelinic synapse; **CCPD** = combined central and peripheral demyelination; **CNP** = cyclic nucleotide phosphodiesterase; **dMAG** = degraded form of MAG; **Ig-CAM** = immunoglobulin-like cell adhesion molecule; **MAG** = myelin-associated glycoprotein; **MBP** = myelin basic protein; **NFasc** = neurofascin; **NMDAR** = NMDA receptor; **NRG1 type III** = neuregulin-1; **OPC** = oligodendrocyte progenitor cell; **PAD** = peptidyl arginine deiminase; **PLP** = proteolipid protein; **PNS** = peripheral nervous system; **P0** = myelin protein 0; **RRMS** = relapsing-remitting MS.

MS is the most common cause of acquired neurologic disability in young adults.¹ It is pathologically characterized by a combination of inflammation, demyelination, and axonal degeneration in the CNS, which, ultimately, results in neurologic disability.² Clinically, MS is very heterogeneous, resulting in an array of symptoms.³ Although it is generally regarded as a disease restricted to the CNS, several studies have reported that some patients with MS also have demyelination in the peripheral nervous system (PNS),⁴⁻⁸ where axonal fiber demyelination is correlated with a reduced mean myelin sheath thickness and internode length.⁴ For instance, conduction abnormalities in peripheral nerves suggestive of demyelination were observed in patients with MS,⁷ and magnetic resonance neurography has shown a higher occurrence of PNS abnormalities in patients with MS compared with controls.⁸ These observations suggest that a common pathologic process may underlie CNS and PNS demyelination in a subset of patients with MS.⁹ Furthermore, central and peripheral myelin share many molecules, such as myelin basic protein (MBP) and myelin-associated glycoprotein (MAG),¹⁰⁻¹³ which could lead to autoimmune reactivity to myelin antigens in both the CNS and the PNS.

Based on these findings, it is tempting to hypothesize that MS, despite being considered a canonical CNS disorder, can also affect the PNS. Therefore, in this review, we focus on the myelin composition and axo-myelin interaction in the CNS vs PNS, the biochemical myelin alterations that contribute to MS pathology, and a number of MS clinical observations supporting impaired functioning of the PNS in addition to the CNS, which could have an impact on disease monitoring and treatment.

Clinical observations in MS: the overlooked involvement of the PNS

The onset of MS is usually during early adulthood, and the prognosis of the disease is highly variable.¹⁴ Currently, 3 main types of clinical MS are acknowledged with common patterns of symptoms associated with various levels of inflammation: relapsing-remitting MS (RRMS), primary progressive MS, and secondary progressive MS.¹⁵ In patients with MS, CNS dysfunction can cause a wide range of symptoms and results in the considerable clinical heterogeneity of MS. For example, patients can have sensory disturbances, optic neuritis, limb weakness, fatigue, cognitive impairment, depression, pain, bladder, bowel and sexual dysfunction, and/or spasticity.¹⁶⁻¹⁸

At the moment, there is still no curative treatment available for MS. Several drug therapies have been approved during the last 20 years, which mainly aim to reduce inflammation in the CNS. However, there is increasing evidence that these therapies are most effective during the early phases of the disease, while there is active inflammation of the brain and spinal cord.¹⁹ The diagnosis of MS is based on established clinical, imaging, and spinal fluid observations, also known as the 2017 McDonald criteria.²⁰ Of interest is that the criteria used for the diagnosis of MS are all focused on CNS pathology and related clinical dysfunction, which are at the forefront of the disease.

Although the majority of clinical and pathologic studies on MS have specifically concentrated on the CNS, the involvement of the PNS in MS is not an entirely new concept, being already reported early in the 20th century.^{4-6,9,21} In these studies, the pathology observed in the PNS could be due to confounding factors such as malnutrition and vitamin deficiency.^{5,6,22} In addition, the presence of PNS pathology was considered exceptionally rare in chronic MS²³ and more associated with a specific acute, aggressive form of MS.^{4,24} In those early days, the *in vivo* diagnosis of MS was uniquely based on clinical observations and not confirmed by MRI. Therefore, it is possible that the diagnosis of MS in those patients was not correct. Conversely, more recent investigations examining PNS involvement in patients diagnosed with MS according to the McDonald criteria exclude those patients with risk factors for neuropathy and for vitamin deficiency or malnutrition.^{8,25,26}

Clinical and neurophysiologic observations have repeatedly described peripheral nerve dysfunction in MS, and pathologic studies have confirmed peripheral nerve demyelination in biopsies or autopsies of patients with MS. For example, single pathologic studies described a reduction of myelin thickness²¹ and demyelinating activity, including the invasion of myelin sheaths by macrophages and by inflammation involving mononuclear cells⁴ in the peripheral nerves of patients with MS. In addition, neurophysiologic investigations have mentioned that almost 30% of the examined patients with RRMS presented at least 1 abnormality on standard nerve conduction velocity of the tibial, sural, or peroneal nerve.²⁵ In another study, electrophysiologic abnormalities of the peripheral nerves were observed in 28% of the participating patients with MS with concomitant clinical signs in 12% of the patients with MS.²⁶ In addition, magnetic resonance neurography investigations have highlighted that patients with MS have significantly more lesions in the

sciatic nerve, tibial, and peroneal nerves compared with healthy controls.⁸ Also by MRI in 79.2% of the patients with MS, contrast enhancement of the trigeminal nerve extended to the distal part of the nerve was found, which indicated pathology of peripheral myelin.²⁷ Recently, a patient with established MS in our MS Center Amsterdam presented with radicular pain that coincided with MRI abnormalities in the nerve root L4. Other possible diagnoses (such as compression, infection, or inflammatory disorders other than MS) were excluded (figure 1). Overall, these findings indicate that the PNS is affected in, at least a subset of, patients with MS based on clinical symptoms, neurophysiologic examinations, and on imaging and pathologic observations. It could also be argued that the common concept about inflammatory demyelinating diseases of the CNS and PNS being distinct entities should be revised. Instead, they could represent a broad spectrum of possible manifestations of CNS and PNS demyelination. These diseases would vary in regional distribution, clinical course, and pathology. Prototypical MS would be at one end of the spectrum (demyelination in CNS), chronic inflammatory demyelinating polyneuropathy at the other end of the spectrum (demyelination in PNS), and combined central and peripheral demyelination (CCPD) in between (demyelination in both the CNS and the PNS).^{28–32} Hence, the spectrum view is a potential explanation for the heterogeneity observed within the diseases and the overlapping features reported between the diseases.^{28,30,33} PNS involvement in MS can then be placed between prototypical MS and CCPD on the spectrum. Of interest, also CNS involvement can affect a PNS disease, namely acute motor axon neuropathy, which might be caused by molecular mimicry.³⁴ Notably, the spectrum view of MS would have important consequences for the pathophysiologic concepts, disease monitoring, and future treatments of the diseases. By focusing on patients with MS who have both CNS and PNS demyelination, we may gain insight into the mechanisms underlying demyelination. To this end, it is relevant to compare CNS and PNS myelin to indicate possible target sites.

Composition of CNS and PNS myelin

The loss of myelin during MS is of critical clinical and pathologic importance. Myelin produced by either oligodendrocytes (CNS) or Schwann cells (PNS) extends from the glial plasma membrane and spirally enwraps axonal segments.³⁵ The myelinated axonal segments are also known as internodes, whereas the unmyelinated axonal segments are called the nodes of Ranvier (figure 2A).² The node of Ranvier lies between the outermost paranodal loops of adjacent myelin sheaths. The innermost paranodal loop is adjacent to the juxtaparanode, which borders the internode proper.³⁶ Myelin in the CNS and PNS is thought to have the same vital function, namely saltatory impulse propagation along the axon.² As demyelination has been established in the PNS as is in the CNS, it is of interest to compare the anatomic structure and molecular constituents of CNS myelin to PNS myelin, which may give insight into possible overlapping or divergent factors attacked during the demyelination process.

Anatomic structure

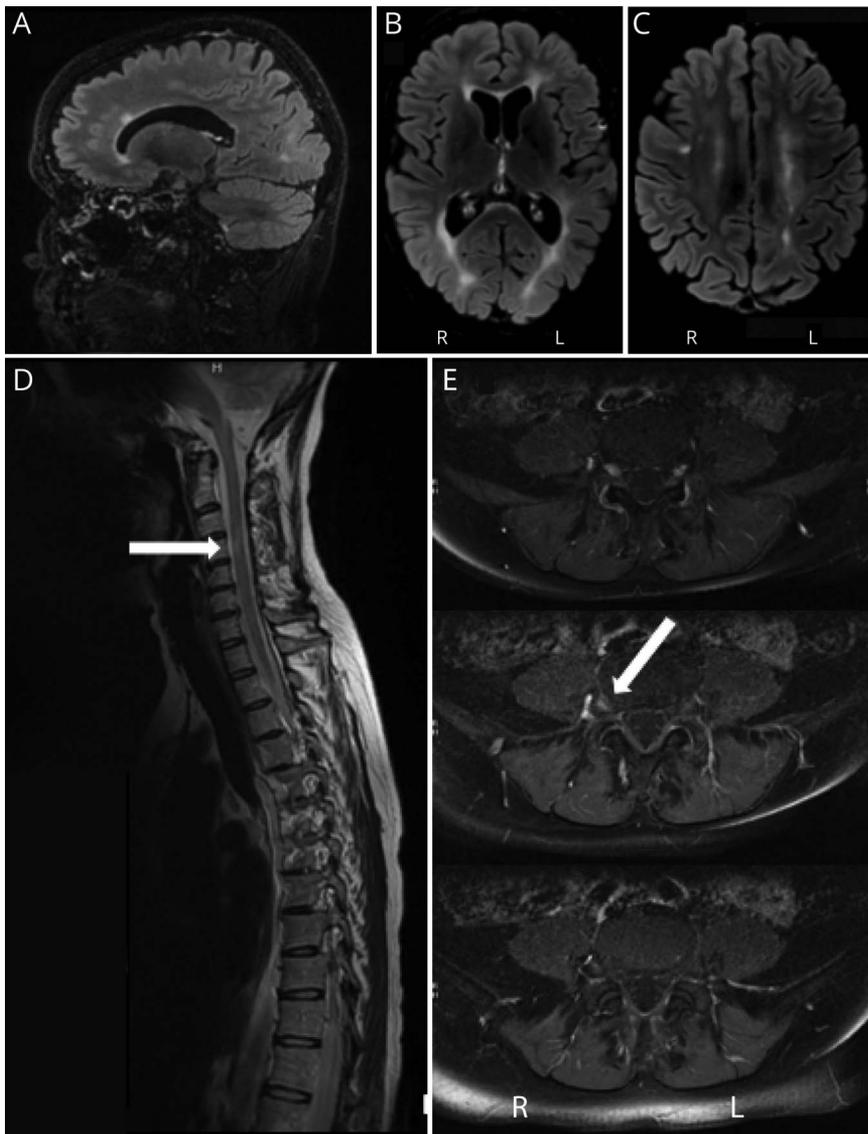
Myelin sheaths in the CNS and PNS exist of a compact and a noncompact domain. Compact myelin consists of double-layered glial plasma membranes that are closely apposed at both intracellular and extracellular surfaces. These surfaces can be visualized by major dense lines and intraperiod lines, respectively. In noncompact myelin, the double-layered membranes do not compact. The majority of PNS myelin consists of compact myelin; noncompact myelin is found in paranodes and Schmidt-Lanterman incisures. The most external layer of myelin apposes to the Schwann cell basal lamina.³⁷ The lateral borders of the Schwann cell cytoplasm are tipped with microvilli, which are in contact with the nodal axolemma.^{38,39} In the CNS, myelin is compact except for the myelinic channel system, consisting of a single channel of cytoplasm around the perimeter of the oligodendrocytic process, which includes both the abaxonal (portion of myelin far from the axonal process) and adaxonal (portion of the myelin close to axonal process) surface, as well as paranodes and transient openings of previously compacted myelin in some CNS fibers. It connects the most distal part of the myelin sheath with the soma of the oligodendrocyte.³⁶ A distinctive structural feature of CNS myelin are the radial components. These structures consist of a series of radially arranged intralaminar strands spanning the myelin sheath and resemble tight junctions.³⁷ Hence, radial components primarily hinder the diffusion of material through the CNS myelin sheath and make it less permeable.⁴⁰ Unlike the PNS, myelin sheaths in the CNS do not have a basal lamina or microvilli. Some nodes are in contact with perinodal astrocytes or oligodendrocyte progenitor cell (OPC) processes, but the function remains unknown.⁴¹ Thus, CNS myelin and PNS myelin both exist of compact and noncompact domains, but they also have distinctive components.

Molecular constituents

Myelin consists of multiple components and has a high lipid-to-protein ratio comprising about 70%–85% of the dry weight in both CNS and PNS myelin.^{42–44} Only small quantitative differences between the lipid composition of the 2 types of myelin have been reported. In both CNS and PNS myelin, the most abundant lipids present are cholesterol, glycolipids (cerebroside and cerebroside sulfate), and ethanolamine glycerophosphatides. Of interest is that CNS myelin contains more glycolipids and less sphingomyelin compared with myelin in the PNS (table).^{42,43}

Proteomic studies have identified the presence of over 1,200 different proteins in CNS myelin and 545 different proteins in PNS myelin using mass spectrometry.^{13,45} CNS and PNS myelin each express a distinct set of proteins (table).^{37,46} However, 44% of the identified myelin proteins are shared by PNS and CNS myelin.¹³ The most dominant proteins of CNS and PNS myelin are proteolipid protein (PLP) and myelin protein 0 (P0), respectively, and might be involved in the myelin compaction.^{2,12,13} PLP is a tetraspan transmembrane protein,¹² which is important for various myelin-related cellular events, and several mutated myelin tetraspans are known to cause neuropathies. Transmembrane protein P0 is an immunoglobulin-like cell adhesion molecule (Ig-CAM) and

Figure 1 MRI observations in the CNS and PNS of a patient with MS



MRI scans of a patient who was diagnosed with MS based on clinical presentation in combination with the presence of CNS lesions suggestive of demyelination with dissemination in space and time. The diagnosis was confirmed by the presence of unique oligoclonal bands in the spinal fluid, in the absence of any other inflammatory signs that are atypical for MS such as a severe pleiocytosis. In addition, we excluded a diagnosis of neurosarcoidosis, systemic inflammatory condition, or central nervous infection. At 18 months after the diagnosis of MS, the patient developed severe radicular pain in the trajectory of L4 on the right side, with an absent patellar tendon reflex. Subsequent MRI and laboratory investigations systematically ruled out neurosarcoidosis, infection of the CNS, or a systemic inflammatory condition. (A–C) FLAIR images of multiple confluent lesions periventricular, juxtacortical, and in the corpus callosum with a Dawson finger aspect. (D) Focal hyperintensity (arrow) on the T2-PD-weighted image of the spinal cord at the level of C4. There was also a smaller lesion (not depicted) at the level of Th8–Th9. A follow-up scan 1 year after these images showed a new, small, focal lesion at the level of C2–C3. (E) At 6 months after the images shown in (A–D), 3 axial T1-weighted images after contrast enhancement on the level of the exit of root L4 of the spinal cord were made. We observed isolated intradural contrast enhancement of the nerve root L4 with some postganglionic nerve root enhancement (arrow). There was neither spinal disc protrusion nor nerve root compression. No leptomeningeal enhancement was seen. The patient with MS gave permission to present the imaging data as shown in this figure.

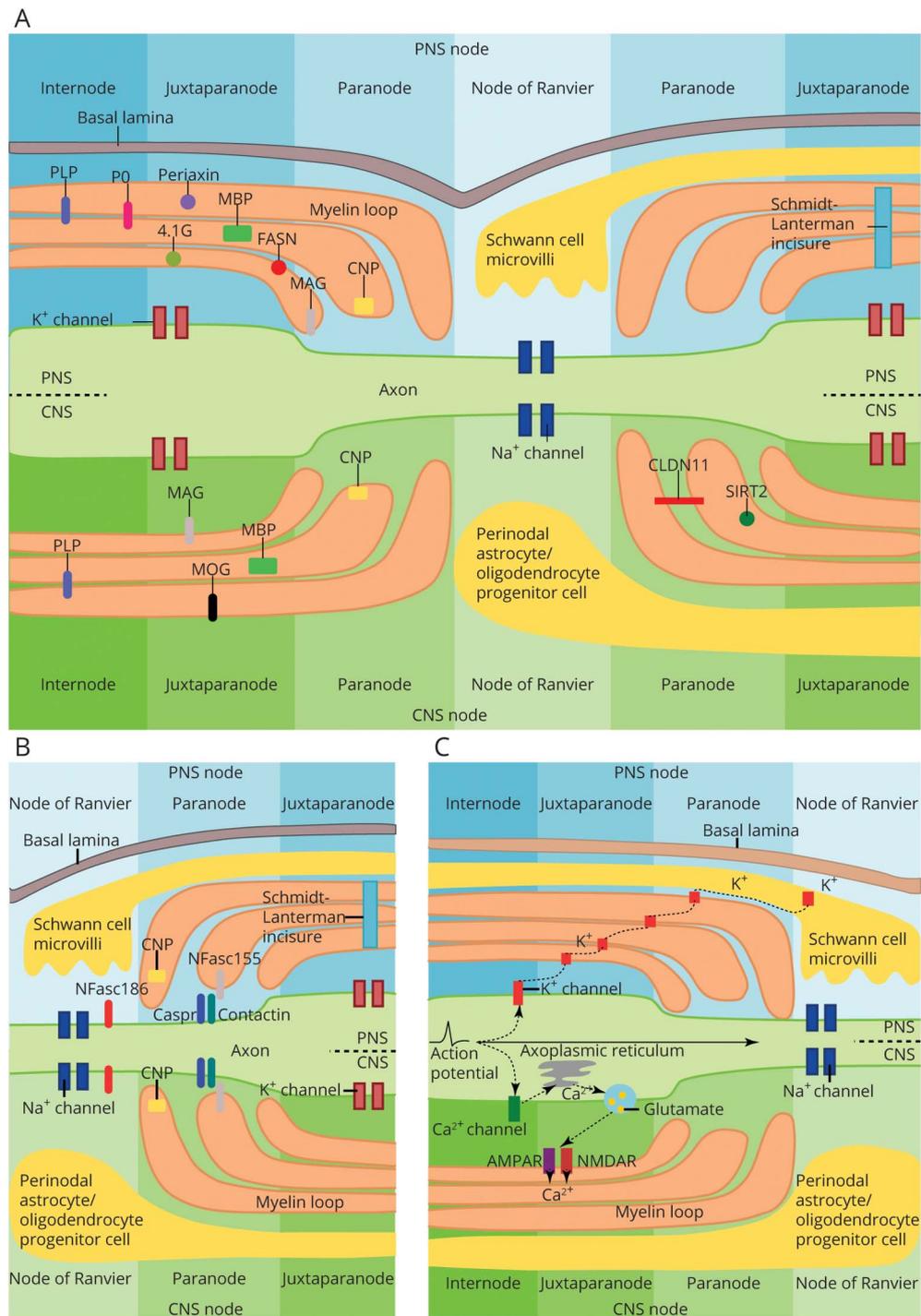
mediates the adhesion of the extracellular myelin surfaces.^{13,47,48} Periaxin is the second most abundant protein in PNS myelin and is a scaffolding protein.^{2,13,49} Periaxin is expressed before P0, MBP, or MAG and is suggested to play an important role during ensheathment and myelination in the PNS.⁴⁹ In the CNS and PNS, MBP accounts for 8% of the myelin proteins and mediates the intracellular adhesion of cytoplasmic surfaces between individual layers of compact myelin.^{12,13,50} MBP is a highly heterogeneous protein as a result of alternative splicing and posttranslational modifications such as N-terminal acylation, GTP- and ADP-ribose binding sites, deamidation, methylated arginine, methionine sulfoxide, phosphorylation, and deimination of arginyl residues.^{51,52} In the CNS of shiverer mutant mice, which do not express MBP, major dense lines are missing. This can be rescued by expressing the MBP gene in transgenic shiverer mice.⁵³ Of interest, loss of major dense lines is not observed in the PNS of

shiverer mice because the cytoplasmic domain of P0 can compensate for MBP loss.^{54,55} The remaining identified myelin proteins have a relative low abundance compared with the CNS and PNS myelin proteins described above.^{12,13}

An example of a protein, which despite its low abundance (0.2%) is thought to play an important role in PNS myelin, is the myelin protein P2.¹³ In particular, P2 seems to be strongly involved in lipid homeostasis of myelinated Schwann cells.⁵⁶ The protein is sufficient to induce clinical, electrophysiologic, and neuropathologic characteristics of experimental allergic neuritis.⁵⁷

Thus, CNS and PNS myelin each have a unique but also partly overlapping lipid and protein profile. In particular, the overlapping or functional compensating lipids and proteins may be considered as common target in the demyelination process of CNS and PNS during MS.

Figure 2 The periaxonal region of a myelinated axon in the CNS is similar to the PNS



(A) Overview of the myelinated axonal domains in the CNS and PNS. The upper half shows an axon that is myelinated by a Schwann cell, including the basal lamina, microvilli, Schmidt-Lanterman incisures, sodium (Na^+) channels and potassium (K^+) channels, and myelin proteins that are highly abundant in the PNS. The lower half represents an axon that is myelinated by an oligodendrocyte, including the process from a perinodal astrocyte/oligodendrocyte progenitor cells (OPCs), Na^+ channels and K^+ channels, and myelin proteins that are highly abundant in the CNS. (B) NFasc155 and NFasc186 are required to ensure the integrity of the clustered Na^+ and K^+ channels in the CNS and PNS. Paranodal NFasc155 binds to axolemmal Caspr and Contactin to form the paranodal complex and ensure paranodal integrity. Axolemmal NFasc186 ensures nodal integrity by clustering Na^+ channels at the node of Ranvier. (C) The periaxonal region is suggested to function as a synapse in the CNS and PNS. The upper half represents a myelinated axon in the PNS. On arrival of the action potential, the voltage-gated K^+ channel opens, resulting in a potassium efflux into the periaxonal region. Potassium is taken up by the myelin sheaths and eventually exits the myelin via nodal abaxonal voltage-gated K^+ channels. The lower half represents a myelinated axon in the CNS. On arrival of the action potential, the voltage-gated periaxonal calcium (Ca^{2+}) channel initiates subsequent calcium release from the axoplasmic reticulum. This results in the release of glutamate into the periaxonal region, which in turn binds to myelinic AMPA receptors (AMPA) and NMDA receptors (NMDARs) to stimulate Ca^{2+} release in the myelin.^{58,e18} CLDN11 = claudin 11; CNP = cyclic nucleotide phosphodiesterase; FASN = fatty acid synthase; MAG = myelin-associated glycoprotein; MOG = myelin oligodendrocyte glycoprotein; P0 = myelin protein 0; PLP = proteolipid protein; SIRT2 = sirtuin 2; 4.1 G = band 4.1-like protein G.

Table Overview of the lipid and protein composition in CNS and PNS myelin

Myelin content	CNS	PNS
Lipids		
Total lipid	78.0%	71.3%
Cholesterol	19.7%	27.1%
Total glycerophosphatides	24.8%	21.5%
Ethanolamine glycerophosphatides	11.2%	11.2%
Serine glycerophosphatides	5.3%	5.6%
Choline glycerophosphatides	8.3%	4.7%
Sphingomyelin	5.1%	10.8%
Glycolipids	19.4%	11.9%
Unidentified	9%	N/A
Proteins		
PLP	17%	0.2%
PO	ND	21%
Periaxin	ND	16%
MBP	8%	8%
CNP	4%	0.5%
MOG	1%	ND
MAG	1%	0.3%
Sirtuin 2	1%	ND
Claudin 11	1%	ND
Fatty acid synthase	ND	1%
Band 4.1-like protein G	ND	1%
Others	67%	52%

Abbreviations: CNP = cyclic nucleotide phosphodiesterase; MAG = myelin-associated glycoprotein; MBP = myelin basic protein; MOG = myelin oligodendrocyte glycoprotein; N/A = not applicable; ND = not detected; PLP = proteolipid protein; PNS = peripheral nervous system. The lipid and protein compositions are shown in percentages of total myelin.^{12,13,42,43}

Axo-myelin interaction in the CNS vs PNS

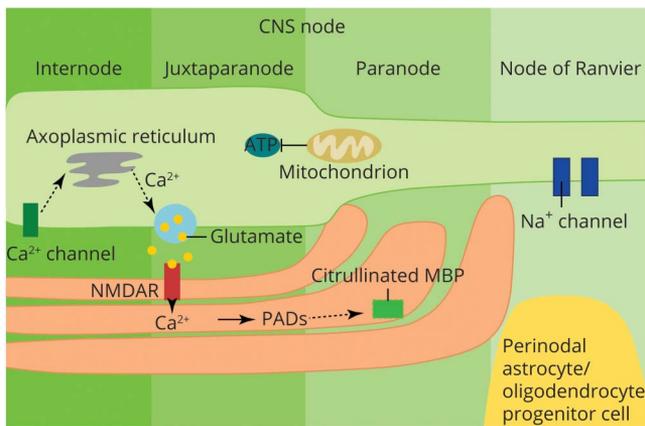
The interaction between axons and myelinating glial cells is required for the initiation of myelination and subsequent maintenance to protect the axon and seems to be affected in MS.^{35,58} Myelinating glia determine the axonal diameter,^{59,60} help define the nodal and internodal domains of the axolemma,^{e1,e2} and provide survival signals to neurons.³⁵ In turn, axons provide signals to regulate myelin formation.^{2,35} In the PNS, the initiation of myelination is completely controlled by axonal signals.³⁵ Axon caliber is a key signal for myelination by Schwann cells, and axons above a threshold size of $\sim 1 \mu\text{m}$ diameter are typically myelinated.^{e3} The

axon diameter can be measured based on the abundance of neuroregulins, for example, neuregulin-1 (NRG1 type III) present on the axon surface, which is sensed by Schwann cell receptor tyrosine kinases erbB2 and erbB3.^{e4,e5} Similar to the PNS, only a selection of axons in the CNS becomes myelinated.² The threshold axonal diameter for myelination in the CNS is $0.4 \mu\text{m}$.^{e6} Although NRG1-ErbB signaling is not essential for CNS myelination, overexpression of NRG1 also stimulates myelination by oligodendrocytes.^{e7,e8} Beside axonal signals, CNS myelination is also controlled by additional mechanisms such as spatial density of OPCs, electrical activity, and cues from other glial cells.² This difference in myelination initiation of the CNS and PNS suggests that oligodendrocytes have acquired additional mechanisms to control myelination.

After myelination has been initiated, myelinating glia maintain neuronal health, axonal diameter, and axolemmal organization. In turn, axons are responsible for the myelin integrity.³⁵ For instance, a tight association between axons and myelinating glia is essential for the integrity of the molecular domains of the axolemma.^{e1,e2} In both the CNS and the PNS, paranodal neurofascin (NFasc)155 binds to axolemmal Caspr and contactin to form the paranodal complex (figure 2b). This complex is essential for the formation of the septate-like axo-myelinic junctions that prevent the invasion of sodium and potassium channels into the paranode. Furthermore, axolemmal NFasc186 is required to ensure nodal integrity by clustering sodium channels at the node of Ranvier.^{e1,e2} PO has been identified as an additional binding partner of NFasc155 and NFasc186 in peripheral myelin. Loss of its transcriptional regulators histone deacetylase 1 and 2 resulted in impaired axon-Schwann cell interaction.^{e1} It is unknown whether NFasc155 and NFasc186 also have an additional binding partner in CNS myelin. In addition, myelin protein cyclic nucleotide phosphodiesterase (CNP) is required to maintain the integrity of the specialized domains. In the CNS, loss of CNP disrupts the axoglial interactions and results in the disorganization of nodal sodium channels and paranodal Caspr.^{e9} It has not been reported whether CNP deficiency in the PNS also disorganizes nodal and paranodal components. However, it has been shown that loss of CNP causes peripheral hypermyelination and axonal loss and reduces noncompact myelin.^{e10} This suggests that CNP is required for axo-myelin maintenance in both the CNS and the PNS.

In contrast to degenerated axons in the PNS, degenerated axons poorly regenerate in the CNS.^{e11} For instance, inhibitors of regeneration, called myelin-associated inhibitors, have been found specifically in CNS myelin. These include ephrin-B3, MAG, Nogo-A, and myelin oligodendrocyte glycoprotein. MAG is the only myelin-associated inhibitor that is also expressed in the PNS myelin.^{e12} However, the high concentration of laminin in the PNS overrides the inhibitory effect of MAG.^{e10} There are also myelin components that seem to prevent axon degeneration, such as oligodendrocytic peroxisomes or myelin proteins PLP and CNP. Loss of these components results in the formation of axonal spheroids and subsequent axonal degeneration.^{e14–e16}

Figure 3 The axo-myelinic synapse in the CNS might be involved in the pathogenesis of MS



It is thought that oligodendrocytes produce lactate that is transported to the axonal mitochondria for the production of ATP. If the oligodendrocyte is unable to transport lactate, this would result in a reduction of axonal ATP. This in turn results in the pathologic depolarization of the axon. As a consequence, voltage-gated calcium (Ca^{2+}) channels become activated and cause an increased release of Ca^{2+} from the axoplasmic reticulum and a subsequent increase of glutamate release into the periaxonal region. Glutamate activates the myelinic NMDA receptor (NMDAR), resulting in the activation of Ca^{2+} -dependent peptidyl arginine deiminases (PADs). PADs will citrullinate myelin basic protein (MBP), which hinders the function of MBPs and might lead to the breakdown of myelin.⁵⁸

According to new discoveries in the CNS, axons are able to form an axo-myelinic synapse (AMS) with myelin (figure 2c). Action potentials depolarize the internodal axolemma, which is detected by voltage-gated calcium channels located on the axonal surface. These calcium channels initiate subsequent calcium release from the axoplasmic reticulum, resulting in the release of glutamate in the periaxonal space located between the myelin sheath and axolemma. Glutamate then activates the myelinic AMPA and NMDA receptors (NMDARs) leading to a calcium influx into the myelin.^{e17} It is postulated that the AMS is responsible for the myelin structural dynamics and couples electrical activity to the metabolic output of the oligodendrocyte.⁵⁸ In the PNS, the periaxonal space also seems to function as a synapse. Action potentials result in the opening of axonal potassium channels, leading to an increase of potassium in the periaxonal space, which is subsequently taken up by myelin via tight junctions.^{e18}

In conclusion, reciprocal signaling between neurons and oligodendrocytes or Schwann cells is required for myelination and the maintenance of the myelinated axons. An important distinction between myelination in the CNS and PNS is that axonal expression of NRG1 type III alone is sufficient to initiate myelination by Schwann cells but not by oligodendrocytes. Although the CNS and PNS use similar mechanisms to maintain the interaction between the axon and myelin, such as paranodal complexes and AMSs, differences have been observed. Furthermore, the axons in the CNS are more prone to degeneration, which can be partly explained by CNS-specific axo-glia signaling.

Biochemical alterations in CNS vs PNS myelin during MS

Damage to myelin can result in demyelination of the axon, which makes the neuron prone to degeneration. Hence, remyelination is required to restore normal neural signaling. Most people have the innate ability to reestablish any damaged myelin in the CNS. However, patients with MS eventually lose this ability for reasons that are not entirely understood yet.^{e19} Several biochemical changes affecting CNS myelin have been identified in patients with MS. Unlike the CNS, far less studies have been performed that investigated the biochemical alterations in the PNS myelin of patients with MS. This might be the result of the persisting dogma according to which MS exquisitely affects the CNS.⁸

White matter MS lesions are heterogeneous and can be divided into 4 fundamentally different types of demyelinating lesions. One group of lesions, accounting for 25% of all active lesions, was characterized by preferential loss of the periaxonal Ig-CAM MAG. Other highly abundant CNS myelin proteins (PLP, MBP, and CNP) were still present within the partly damaged myelin.^{e20} In studies using MAG-deficient mice, it was found that in face of a normal CNS/PNS myelination process, the periaxonal myelin sheath contained intracytoplasmic depositions and inclusion bodies.^{e21} Of interest, a uniform widening of the periaxonal myelin sheath was also observed during the pathologic examination of MS brains. In contrast, the outer myelin sheaths are often still intact in early lesions.^{e22,e23} These findings all suggest that demyelination can be initiated by a process starting in the innermost myelin layers, also called a dying-back oligodendropathy.

Consistent with this hypothesis are the findings from a study that investigated the breakdown of myelin sheaths in several CNS demyelination models. In this study, the myelin protein required for compact myelin formation, MBP, was targeted by elevating the intracellular calcium levels. This led to the displacement of MBP and subsequent myelin fragmentation by the breakdown of the innermost myelin lamellae into vesicular structures.^{e24} As mentioned, MBP is a very heterogeneous protein due to alternative splicing and posttranslational modifications.⁵¹ A mass spectrometry study found that phosphorylation of MBP is strongly reduced or even absent in myelin of patients with MS compared with healthy myelin. Furthermore, arginine methylation of most MBP components is decreased in MS.^{e25} Moreover, citrullinated MBP levels are increased in patients with MS compared with healthy individuals.^{e25,e26} Because these posttranslational modifications affect the charge, conformation, and hydrogen bonding of MBP, it is suggested that these alterations compromise the ability of MBP to form stable myelin multilayers and compact myelin. Hence, the altered levels of MBP observed in patients with MS would result in a loss of compact myelin and unstable myelin multilayers. Citrullination/deimination of MBP is an enzymatic reaction involving the conversion of arginine to

citrulline by a family of 5 citrullinating enzymes known as peptidyl arginine deiminases (PADs).^{e25} Mice exhibiting upregulation of PAD2 have increased levels of citrullinated MBP and show subsequent demyelination. Clusters of PAD2 were found in the periaxonal regions of these mice, which supports the theory of a dying-back pathology.⁵² It has been shown that citrullinated MBP has lost its ability to compact myelin and that it is more vulnerable to proteolytic attack. Hence, MBP citrullination might increase myelin breakdown during MS.^{e27} Increased citrullinated MBP is found in areas of ongoing demyelination and strongly correlates with the severity of MS.^{e28,e29} This suggests a central role for deimination of MBP in the pathogenesis of MS.^{e29} Recently, a new mouse model was introduced showing that a primary myelinopathy can trigger secondary pathologic inflammation. In this model, called cuprizone autoimmune encephalitis, a brief cuprizone treatment increased MBP citrullination. This led to biochemically destabilized myelin followed by a pathologic demyelinating immune response comparable to active MS plaques.^{e30} Of interest, drugs targeting PAD are able to attenuate inflammatory demyelination in animal models and may hold promise for MS.^{52,e30} It is possible that certain patients with MS have increased amounts of citrullinated MBP in PNS myelin. As mentioned, deimination of MBP hinders its ability to compact CNS myelin.⁵² It has been shown that PAD2 and PAD3, the enzymes responsible for deimination, are coexpressed with MBP in cultured rat and human Schwann cells. Furthermore, citrullinated proteins were observed in cultured Schwann cells of patients having peripheral lesions.^{e31}

Besides the role of MBP in MS pathology, the role of the MAG is also attracting a lot of interest. As mentioned above, pathologic studies in newly forming MS lesions often show a preferential loss of MAG,^{e20} and other investigations have underlined a higher degree of formation of a degraded form of MAG (dMAG) in the brain of patients with MS compared with non-neurologic controls.^{e32,e33} MAG is proteolyzed into dMAG by a putative cysteine protease (cathepsin-L) acting on the amino acid sequence 512–513 of the MAG depriving the molecule of the majority of its intracellular myelin compartment, making it soluble and allegedly less functional.^{e34} MAG being a sialic acid binding lectin and playing a role as an adhesion molecule to hold axon and myelin together,^{e35} it is then possible that a reduced MAG functionality might affect the stability of the AMS, contributing to the pathologic cascade of mechanisms that might lead to demyelination. Because this protein has a similar periaxonal distribution in healthy CNS and PNS myelin (MAG is additionally located in the paranodal and incisive membranes of PNS myelin),^{e36} its expression may also be decreased in peripheral myelin. For example, *Mag*-null mice show dysmyelination and axonal degeneration in both the CNS and the PNS.^{e37} Furthermore, a disrupted organization of central and peripheral periaxonal regions is observed in *Mag*-null mice.^{e38} Hence, these studies suggest that MAG might not only be reduced in central myelin but also in peripheral myelin.

Because the myelin pathology seems to start at the most distal myelin compartment, it has recently been hypothesized that the AMS is involved in the pathogenesis of MS.⁵⁸ MS genome-wide association studies have identified mutations that are important for glutamate homeostasis.^{e39} An altered glutamatergic transmission might establish an environment of chronic excitotoxicity, via myelinic NMDARs or additional mechanisms, resulting in biochemically altered myelin.⁵⁸ Myelinating oligodendrocytes provide metabolic support for mitochondria by transporting lactate to the axons.^{e40} Lactate is reconverted into pyruvate and subsequently used by axonal mitochondria for ATP production.^{e41} Thus, the inability of oligodendrocytes to transport lactate would reduce the axonal ATP production. This results in a pathologic depolarization of axons due to ion transporter failure. This would in turn activate the voltage-gated calcium channels and excessive release of calcium from stores, leading to glutamate excitotoxicity in the periaxonal space (figure 3).⁵⁸ The resulting excessive calcium entry through myelinic receptors can lead to the deimination of MBP by the calcium-dependent enzyme PAD and subsequent breakdown of the adaxonal myelin into vesicular structures.^{52,58,e24,e30} Schwann cells also express NMDARs, suggesting that the overactivation of myelinic NMDARs might also result in hypercitrullination of MBP in the PNS myelin.^{e31,e42} However, whether patients with MS also experience glutamate toxicity in the PNS remains unknown.

It has also been shown that paranodal and juxtaparanodal tethering proteins are diffusely distributed in demyelinated lesions of patients with MS.^{e43,e44,e45} Disruption of paranodal and nodal structures was also observed in a model of PNS demyelination. This resulted in the loss of septate-like junctions, allegedly affecting the stability of the axon-myelinic unit. Thus, demyelination in the PNS might be related to an altered expression of nodal, paranodal, and juxtaparanodal molecular structures. These findings suggest that the myelin integrity is harmed, which negatively affects the induction and fast propagation of electric signals along axons in the CNS and PNS.^{e1}

To conclude, multiple biochemical alterations have been discovered in CNS myelin of patients with MS. Several of the alterations are related to the periaxonal region, suggesting that the CNS demyelination observed in MS might be initiated by a dying-back oligodendropathy. Multiple studies have shown that patients with MS may experience PNS demyelination in addition to loss of myelin in the CNS,^{4–6,8,9,21,25,26} but how this pathology relates to each other needs to be elucidated.

Summary and outlook for PNS myelin impairment in MS

To date, the prevalent dogma is that MS is a demyelinating disorder of the CNS,⁸ leaving the PNS relatively unaffected. However, multiple studies reported clinical symptoms,

pathologic findings, electrophysiologic examinations, and imaging data that are indicative of PNS dysfunction, i.e., peripheral demyelination in patients with MS.^{4–9,25} Whether there are common pathologic processes underlying demyelination in the CNS and PNS (in a subset of) patients with MS is currently unknown. Of interest is that the myelin lipid composition is very similar between the CNS and PNS^{42,e46} and that 44% of the proteins are similarly present in CNS and PNS myelin.^{12,13} The initial process of PNS myelination is completely regulated by axonal signals, whereas CNS myelination has acquired additional mechanisms.^{2,35} In both the CNS and the PNS, axonal and myelin components are required to ensure the integrity of nodal and internodal domains.^{e1,e2} Furthermore, the periaxonal space seems to function as a synapse in CNS and PNS myelin.^{e17,e18}

Myelinated axons depend on myelinating glia for support and maintenance. Any disturbance in the myelin has the potential to hinder axo-myelin interaction. During MS, several biochemical alterations have been observed in CNS myelin that affect this interaction. For example, a subtype of MS lesions shows preferential loss of MAG.^{e20} Furthermore, increased levels of citrullinated MBP are found in MS, which might be caused by glutamate excitotoxicity in the AMS.^{58,e28,e29} Moreover, several autoantigenic myelin proteins have been identified.^{10,11} Besides that, it has recently been observed that myelin lipids are globally altered in MS brains.^{e47} In addition, the nodal, paranodal, and juxtaparanodal domains are disrupted during MS.^{e44} Because numerous biochemical alterations in myelin of the CNS suggest a dying-back oligodendropathy,^{52,e20,e22–e24} it might be interesting to focus on the periaxonal region as an important disease target during future studies.

Based on the overlap in myelin content between the CNS and PNS, and on studies in animal models of MS, we propose that several alterations in CNS myelin can also take place in PNS myelin and subsequently affect the axo-myelin interaction. For example, the PNS myelin can be affected by loss of MAG,^{e38–e40} hypercitrullination of MBP,^{e41,e42} and disturbed myelin domains.^{e1,e2} Because multiple clinical observations suggest that the PNS is affected during MS, it is important to further examine potential biochemical alterations in PNS myelin during MS.

What is the consequence of PNS involvement in MS?

PNS involvement in MS might be more frequent than is generally assumed. We propose that clinical observations of PNS dysfunction should be more explicitly questioned and tested for. In addition, PNS involvement also has consequences for research studies on MS. Studies on the PNS should be taken into account to accomplish better understanding of the pathophysiologic mechanism underlying MS and possibly also other demyelinating diseases. It will enable new concepts including the search for a possible common pathologic mechanism for PNS and CNS

demyelination. When using human material in this search, future studies could study the myelinated or demyelinated peripheral nerves from patients with MS and controls, which will be accessible through biopsy which the CNS is not.^{e48} Furthermore, longitudinal studies examining both CNS and PNS dysfunction may be beneficial to unravel the primary or secondary PNS involvement to CNS pathology. When including PNS analysis in the diagnostic protocol, it may direct to a subtype of patients with MS that has not been recognized thus far and offers opportunities for lower strain disease monitoring and a therapeutic approach that fits with the spectrum of demyelinating pathology.

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Antonio Luchicchi, PhD	Amsterdam UMC, the Netherlands	Critically revised the work
Eva M.M. Strijbis, MD, PhD	Amsterdam UMC, the Netherlands	Critically revised the work and delivered the data for figure 1
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Anne-Marie van Dam, PhD	Amsterdam UMC, the Netherlands	Conceived the idea for the article and critically revised the work

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