Educational Case

Educational Case: Multiple sclerosis

Ariana Pape, MD, Laurie L. Wellman, PhD, Richard M. Conran, MD, PhD, JD [*]

Eastern Virginia Medical School, Norfolk, VA 23507, USA

The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see https://www.journals.elsevier.com/academic-pathology/news/pathology-competencies-for-medical-education-pcme.[1]

Primary objective

Objective NSC3.3: Multiple sclerosis. Describe the pathogenesis, clinical presentation, and gross and microscopic pathologic features of multiple sclerosis.

Competency 2: Organ System Pathology; Topic NSC: Nervous System – Central Nervous System; Learning Goal 3: Spinal Cord Disorders.

Secondary objective

Objective NSC6.1: Autoimmune mechanisms in multiple sclerosis. Describe the autoimmune mechanism mediated by CD4$^+$ T cells that react against self-myelin antigens in multiple sclerosis and outline the clinicopathologic features of the disease.

Competency 2: Organ System Pathology; Topic NSC: Nervous System – Central Nervous System; Learning Goal 6: Demyelinating Disorders.

Patient presentation

A 32-year-old woman with no past medical history presents to the emergency room with a 6-month history of waxing and waning uni-lateral visual impairment and facial numbness. She was well until 6 months ago when she noticed the onset of right-sided facial numbness and blurred vision lasting several weeks. She states that three episodes have occurred during the past 6-month time period. There was no associated muscle weakness of the facial muscles. Earlier today, upon waking up, the patient noted a sudden onset of blurry vision in her right eye and numbness on the right side of her face. She states she has not observed any muscle weakness, gait disturbance, fever, or urinary incontinence.

Diagnostic findings, Part 1

Physical examination reveals a well appearing, anxious woman. Vital signs are temperature: 98.6 °F, heart rate: 82 beats per minute, blood pressure: 116/84 mmHg, respiratory rate: 16 breaths per minute. Neurologic exam reveals 20/20 vision in the left eye and 20/100 vision in the right eye. Muscle strength is 5/5 in all extremities. There is uni-lateral loss of sensation on the entire right half of the face; otherwise, all other cranial nerves are intact. Romberg sign is negative, and no gait disturbances are noted. Cardiac, pulmonary, and abdominal examinations are unremarkable.

Questions/discussion points, Part 1

What is the differential diagnosis based on the clinical findings?

Relapsing-remitting visual deficits are suggestive of optic neuritis which, along with new-onset facial neuropathy manifesting as numbness, are most suggestive of a central nervous system (CNS) demyelinating disease. Demyelinating disorders that affect the CNS can be grouped by their etiologies, which includes inflammatory, infectious, and toxic-metabolic-nutritional (Table 1). Among inflammatory disease processes, the relapsing-remitting nature of vision deficits in a woman in her 30s raises multiple sclerosis (MS) highest in the differential diagnosis, discussed below. In addition to MS, other demyelinating disorders in the differential include neuromyelitis optica spectrum disorder (NMOSD) and acute disseminated encephalomyelitis (ADEM). NMOSD present with relapsing-remitting neurological symptoms and lesions on magnetic resonance imaging (MRI) studies are similar to those in MS. However, lesions in NMOSD are characteristically limited to the spinal

Table 1
Disorders that may present with myelin loss in the central nervous system, peripheral nervous system, or both.

	CNS myelin affected	PNS myelin affected
Inflammatory disorders		
Multiple sclerosis (MS)	+	−
Acute disseminated encephalomyelitis (ADEM)	+	−
Neuromyelitis optica spectrum disorder (NMSOD)	+	−
Guillain-Barré syndrome	−	+
Chronic inflammatory demyelinating polyradiculoneuropathy	−	+
Infectious disorders		
Progressive multifocal leukoencephalopathy (PML)	+	−
Toxic-metabolic-nutritional disorders (leukodystrophy)		
Lysosomal storage diseases		
Krabbe disease (β-galactosidase deficiency)	+	+
Metachromatic leukodystrophy (arylsulfatase deficiency)	+	+
Peroxisomal disorders		
Adrenoleukodystrophy	+	+

Abbreviations: CNS, central nervous system; PNS, peripheral nervous system.

cord and optic nerves, whereas MS characteristically has cranial involvement in addition to the spinal cord and optic nerves. ADEM is rarely confused with MS as it is usually a monophasic, self-limiting, post-viral, or rarely post-vaccination disease of childhood. It typically presents with acutely evolving, multifocal CNS disease, whereas in MS, the neurological deficits during initial presentation or a relapse are usually limited to a single site or a few sites. ADEM can rarely manifest with relapses, although, in this setting, MRI lesions are typically more extensive and symmetric than MS.

Infectious etiologies of CNS demyelination include progressive multifocal leukoencephalopathy, Lyme disease, and neurosyphilis. Progressive multifocal leukoencephalopathy is an infection of oligodendroglial cells by the JC virus leading to demyelination in the setting of immunodeficiency (e.g., acquired immunodeficiency disease or iatrogenic immunosuppression). The optic nerve is myelinated by oligodendroglial cells; therefore, the optic nerve is affected in progressive multifocal leukoencephalopathy and not in peripheral nervous system (PNS) demyelinating diseases like Guillain-Barré syndrome or chronic inflammatory demyelinating polyradiculoneuropathy. Early disseminated stage 2 lyme disease can present with recurrent cranial neuropathies in the context of meningitis.

Inherited toxic-metabolic-nutritional disorders that lead to loss of myelin (leukodystrophy) include the lysosomal storage diseases Krabbe disease and metachromic leukodystrophy, as well as the peroxisomal disease adrenoleukodystrophy. These disorders typically present in childhood with a slow, progressive course, eventually leading to symptoms in both the CNS and PNS due to loss of myelin. Adrenoleukodystrophy also leads to adrenal cortex dysfunction due to steroid hormone production deficits, manifesting clinically as Addison disease. The leukodystrophies are inherited, with an autosomal recessive inheritance in Krabbe disease and metachromic leukodystrophy and an X-linked pattern of inheritance in adrenoleukodystrophy.

Inflammatory disorders that can mimic MS include cerebral vasculitis, systemic lupus erythematosus, Sjogren syndrome, and neurosarcoidosis. These disorders only rarely present initially with neurological symptoms, and systemic signs and symptom characteristics of these disorders are usually present. MRI studies and laboratory testing performed on blood and cerebrospinal fluid (CSF) can help differentiate between an inflammatory demyelinating disorder and infectious and inflammatory disease processes. Arteriovenous malformations can result in relapsing-remitting, single-site neurological symptoms similar to MS,

but MRI and computed tomography angiography can distinguish vascular malformation from other disorders. Similarly, tumors in certain locations can mimic MS symptoms. Pituitary adenomas, craniopharyngiomas, and meningiomas can occur in the sella turcica region and compress on the optic chiasm and optic nerves resulting in visual deficits, although characteristically with a progressive loss of vision rather than with relapsing and remitting symptoms.[2,3]

Define the different clinical subtypes (phenotypes) of multiple sclerosis

In 1996, the US National MS Society defined three phenotypes of MS, which were later refined by Lublin et al., in 2013: relapsing-remitting (RRMS), secondary-progressive (SPMS), and primary-progressive (PPMS).[4] RRMS is defined as having relapses that last at least 24h and have complete or partial remission of symptoms between attacks. RRMS can transform into SPMS, which is where symptoms are no longer stable between relapses and instead there is progressive accumulation of disability. PPMS is when a patient initially presents with a progressive accumulation of disability, without a period of RRMS beforehand.

In addition to refining the definitions of the MS phenotypes, Lublin et al. introduced a new category: the clinically isolated syndrome (CIS). A CIS is defined as the first clinical presentation of a disease that could be MS but has yet to fulfill the dissemination in time (DIT) criteria required to diagnose MS. DIT will be described in more detail below, but as it requires at least two attacks to have occurred, MS cannot be diagnosed at the initial presentation. The inclusion of CIS as a subgroup of MS allows patients with probable MS to begin treatment earlier than before its inclusion. Another concept the Lublin group added was active vs. not active MS. Active MS is defined as a patient with clinical evidence of a relapse or a new gadolinium-enhancing lesion on a current MRI. Conversely, not active MS is a patient without clinical evidence of a relapse or a new lesion on MRI. "Active" and "not active" are used as modifiers to the MS phenotype; thus, a patient can have RRMS – active, or SPMS – not active. Lublin et al. used 1 year as the minimum time frame to assess for activity; thus, if the annual MRI for MS activity showed no new lesions, and there were no clinical relapses in the past year, the patient would have "not active" MS. However, no recommendation for what time frame to use was given in this article, and in 2020, Lublin et al. published an article to clarify the necessity of defining a time frame in which to define activity or else this modifier would have little meaning.[5]

What are the diagnostic criteria for multiple sclerosis?

The diagnosis of MS incorporates a combination of clinical, imaging, and laboratory criteria, which are compiled by an expert panel and then revised periodically, most recently in 2010 and 2017.[6,7] These criteria are termed the McDonald criteria, after the lead author on the paper detailing the criteria that were originally composed in 2001.[8] Due to the reliance on the combination of information, as there is no single laboratory test that can diagnose MS, consideration and exclusion of alternative disease processes is critical to the diagnostic workup. To diagnose MS, you must demonstrate dissemination of lesions in the CNS in space and time (DIS/DIT). DIS and DIT are defined as either clinical or radiologic evidence of greater than one lesion at different anatomical locations, separated in time by a period of complete or partial remission. The McDonald criteria define different ways DIS and DIT can be demonstrated to make the diagnosis. In a patient with a relapsing-remitting presentation of MS, DIS can be demonstrated through either:

- Objective, clinical evidence of ≥2 lesions or
- ≥ 1 symptomatic or asymptomatic MS-typical T2 lesions in 2 or more areas of the CNS: periventricular, juxtacortical/cortical, infratentorial, or the spinal cord.

DIT can be demonstrated through either:

- ≥ 2 typical MS attacks separated by a period of remission,
- The simultaneous presence of both enhancing and non-enhancing symptomatic or asymptomatic MS-typical MRI lesions,
- A new T2-enhancing MRI lesion compared to a baseline scan, or
- The presence of CSF-specific oligoclonal bands.

If, however, a patient initially presents with a continual progression of disability, MS can still be diagnosed if they have had at least 1 year of disability progression and two of the following:

- ≥ 1 symptomatic or asymptomatic MS typical T2 lesions (periventricular, juxtacortical/cortical, or infratentorial),
- ≥ 2 T2 spinal cord lesions, or
- The presence of CSF-specific oligoclonal bands.[6]

What imaging is indicated and what results would support a diagnosis of MS?

An MRI of the brain and spinal cord is extremely important in the diagnosis of MS as it is very sensitive in detecting white matter abnormalities. To diagnose MS there should be at least one typical MS lesion in at least two areas that are characteristic of MS. A typical MS lesion is a focal hyperintensity on a T2 weighted sequence, round/ovoid in shape, ranges from a few millimeters to 1–2 cm in size, and is at least 3 mm in its long axis. Characteristic locations include periventricular (in direct contact with the lateral ventricles, without intervening normal white matter), juxtacortical/cortical (in direct contact with the cortex, without intervening normal white matter), infratentorial (in the brainstem, cerebellar peduncles, or cerebellum), or anywhere in the spinal cord (the cervical cord is the most frequently involved). Another feature characteristic of MS lesions is gadolinium enhancement. Gadolinium enhancement is seen in acute MS lesions and is transient, usually lasting 4 weeks or less. This feature can help support the DIT criteria of diagnosis, as the presence of gadolinium-enhancing and nonenhancing lesions confirms the presence of new and chronic lesions.[9]

What laboratory testing is indicated and what results would support a diagnosis of MS?

CSF analysis and serum antibody testing can be useful, especially when the clinical picture is not "classic" for MS to support or cast doubt on the diagnosis of MS. In the workup of MS, CSF analysis should include white blood cell count, red blood cell count, protein concentration, glucose level, immunoglobulin G (IgG) index, and oligoclonal band testing. The white blood cell count, protein concentration, and glucose levels are helpful in ruling out MS; white blood cell counts can be mildly elevated in MS, but very high counts ($>50/mm^3$), low glucose level, and high total protein are more indicative of infection than MS. A high red blood cell count likely indicates a traumatic tap, which may make the other tests uninterpretable, so a CSF analysis with high red blood cells should be interpreted with caution. An IgG index (IgG_{CSF}/IgG_{Serum})/($Albumin_{CSF}/Albumin_{Serum}$) is indicative of how much IgG is being produced in the CSF and is used instead of just measuring the level of IgG in the CSF because peripherally produced IgG can cross the blood–brain barrier and be measured in the CSF. Another method to detect CSF-specific IgG is oligoclonal bands. Through isoelectric focusing and immunoblotting, antibodies can be visualized as dark bands. Oligoclonal bands are antibodies seen only in the CSF and not in the patient's serum. Two or more oligoclonal bands in the CSF suggest intrathecal production of IgG (as seen in MS) rather than a systemic production of IgG that is being leaked into the CSF. In the latter case, the bands of IgG antibodies being detected in the serum would be observed in the CSF as well.[10]

Another laboratory test that is sometimes used in the workup of MS is testing the serum for the presence of antibodies. There is no specific antibody associated with MS, but detection of specific antibodies can help rule out MS. Antibodies against an aquaporin-4 water channel in astrocytes is seen in NMOSD and can help rule out MS if present. Anti-myelin oligodendrocyte glycoprotein (anti-MOG) targets one of the proteins found in myelin, and though once thought to be indicative of MS, it has been discovered to be a separate entity, termed anti-MOG syndrome. The clinical course of anti-MOG syndrome is like ADEM in pediatric patients, whereas adults typically show optic neuritis and brainstem encephalitis. Importantly though, pediatric and adult patients with seropositive anti-MOG titers don't ever fulfill diagnostic criteria for MS, further solidifying anti-MOG syndrome as a separate entity from MS.[11]

What electrophysiologic testing could be performed and what results would support a diagnosis of MS?

Evoked potentials (EPs) are used to measure electrical activity in areas of the brain and spinal cord. There are different types of EPs, and the ones most used in MS are visual (testing the optic nerve) and motor EPs. There are certain situations EPs can be helpful: when the MRI is equivocal or to predict the aggressiveness of the disease. MRI is more sensitive than an EP and is better at diagnosing MS, but if the MRI is equivocal, an EP can be used to help support or rule out the diagnosis. Second, EPs are better at predicting the clinical course of MS as it can detect early or even subclinical demyelination prior to its visualization on MRI. EPs can be used to monitor a patient, and if an EP is positive, more aggressive treatment can be initiated.[12]

Diagnostic findings, Part 2

Lumbar puncture and blood draw are performed, and CSF and serum obtained for additional studies. The results are listed in Tables 2 and 3. T2 FLAIR MRI images of the brain, optic nerves, and spinal cord are also obtained (Fig. 1). Focal hyperintensities are seen in the brain, right optic nerve, and spinal cord. The clinical presentation, imaging, and lab data are consistent with MS as the diagnosis.

Questions/discussion points, Part 2

Describe the epidemiologic features of MS

MS is a disorder that leads to disability in young adults. Patients are usually between 15 and 45 years of age when symptoms present. The mean age of onset is from 28 to 31 years. The age of onset varies among the clinical subtypes (phenotypes). RRMS has an earlier onset, averaging between 25 and 29 years, with SPMS presenting at a mean age between 40 and 49 years of age. The estimated male to female ratio is 1.4–2.3 to 1. Geographic variation exists with MS more common in northern latitudes. In the US, the estimated prevalence is 1–1.5 per 1000 individuals.[2,13]

Table 2
Cerebrospinal fluid (CSF) values.

Test	Reference range	Patient's results
Color	Colorless	Colorless
Turbidity	Clear	Clear
Clot	Negative	Negative
RBC (cells/mm^3)	<1	0
WBC (cells/mm^3)	0–5	3
Neutrophils (%)	0–6	0
Lymphocytes (%)	40–60	95
Monocytes (%)	15–45	5
Glucose (mg/dL)	40–70	61
Protein (mg/dL)	15–45	40

Table 3
Additional results.

Test	Reference range	Patient's results
IgG, CSF (mg/dL)	0–4.5	7.2
Albumin, CSF (mg/dL)	5–34	31
IgG, serum (mg/dL)	620–1520	1129
Albumin, serum (g/dL)	3.5–4.9	3.8
IgG index	0.32–0.60	0.78
Oligoclonal bands, CSF	No Bands	10 bands identified in CSF; absent in serum
Myelin basic protein, CSF (mcg/L)	2.0–4.0	2.1
Anti-aquaporin 4 antibodies (U/mL)	<1.6	<1.6
Anti-myelin oligodendrocyte antigen antibodies (titer)	<1:10	<1:10

Abbreviation: CSF, cerebrospinal fluid.

How does autoimmunity play a role in the mechanism of MS?

Normally, when a dendritic cell detects a foreign antigen, it presents the antigen to CD4$^+$ T cells and releases cytokines that induce inflammation and helps shape the adaptive immune system. In MS, dendritic cells are overactivated and migrate through the blood–brain barrier to induce Th1 and Th17 differentiation in the CNS. The proportion of Th17 to Th1 cells is also increased in the peripheral blood of MS patients during acute relapses. Th17 releases matrix metalloproteinase and granulocyte macrophage colony-stimulating factor, which increases blood–brain barrier permeability and recruits bone marrow-derived monocytes, respectively. Th1 and Th17 are both involved in ectopic lymphoid follicle formation and play a role in activating B-cells. In MS patients, B-cells produce autoantibodies that mediate demyelination and axonal disruption. Also, memory B-cells differentiate into CSF plasma cells, which produce antibodies that manifest as oligoclonal bands on protein electrophoresis. B-cells are important regulators of the immune system, and this regulatory function is defective in MS patients, leading to autoreactive B-cells and an overactive immune system. In addition to B-cells and T-cells, astrocytes, 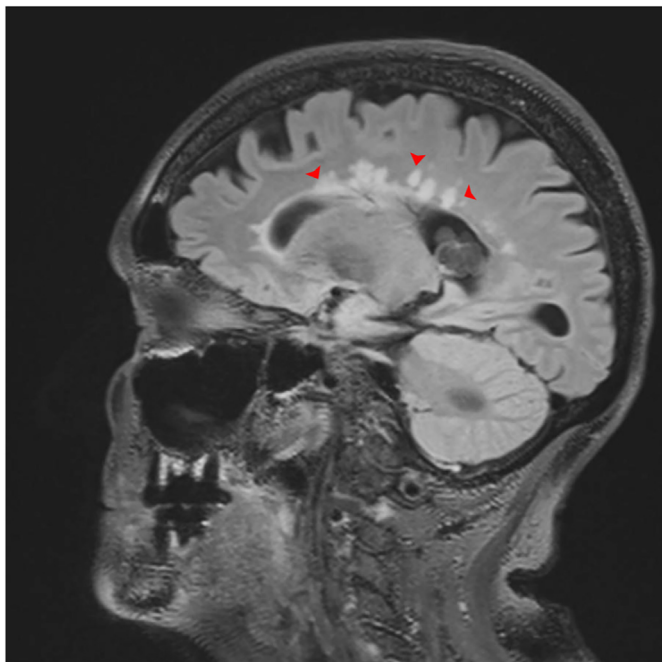the gut microbiome, and dieting patterns are also thought to play a role in the immune response in MS patients. Astrocytes play an important role in maintaining the blood–brain barrier and regulate the activity of microglia and oligodendrocytes. Dysfunction in these processes is thought to contribute to demyelination, axonal damage, and infiltration of pro-inflammatory leukocytes into the CNS.[2,14]

Describe the gross and histological findings observed in the brain from a patient with multiple sclerosis

Fig. 2 is a picture from an autopsy patient with MS who died of an unrelated cause. There are several well-circumscribed, gray-tan, irregularly shaped paraventricular and juxtacortical plaques (arrows), representing chronic MS plaques that are demyelinated. On histology, active plaques can be recognized by the presence of foamy macrophages, which are stripping myelin from axons and digesting it in lysosomes (Figs. 3 and 4). In chronic plaques, there is little to no myelin left, which is highlighted with the Luxol fast blue stain which stains myelin blue (Figs. 5–7).[2]

Do a patient's acute exacerbation symptoms correlate with pathologic findings?

Clinical symptoms of acute exacerbations are correlated histopathologically with focal inflammatory demyelinating white matter lesions. Inflammatory cells recruited from the circulation, mostly T-cells and macrophages, accumulate in the lesions and eventually lead to partial/complete demyelination. Overall, white matter demyelination and peripheral immune cell accumulation are pathological hallmarks of an acute plaque and correlate with clinical symptoms. Additionally, edema associated with the inflammatory lesion likely contributes to the observed functional deficits, especially in regions with low swelling capacity, such as the spinal cord. Both demyelination and compression of nerve fibers lead to reduced conduction velocity and sometimes complete conduction block.[15]

Describe the pathological hallmarks of progressive disease

Although there is likely some crossover, disease progression is characterized more by neurodegeneration than focal, autoimmune-driven inflammation like that of acute relapses. In the later chronic stages of MS, all aspects of the neuron undergo degenerative changes including axons, cell bodies, dendrites, spines, and neurotransmitter metabolism. The direct mechanism leading to neurodegeneration is unknown, but possible mechanisms include microglia activation, reactive oxygen species, and
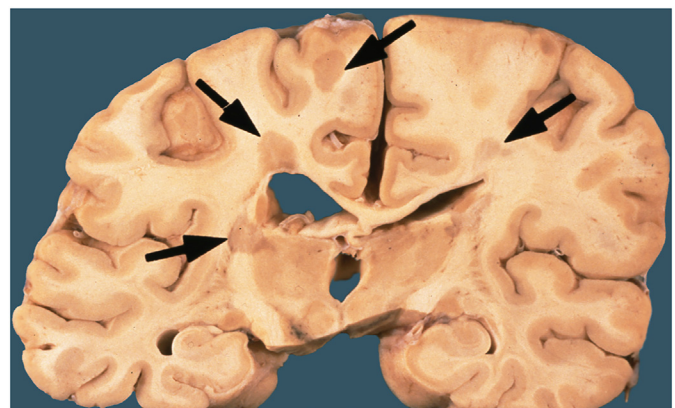

Fig. 1. Parasagittal MRI image demonstrates several periventricular demyelinating plaques (red arrowheads) referred to as Dawson fingers in multiple sclerosis. Reproduced with permission from Harrison Klause, MD, EVMS, Norfolk, VA. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Fig. 2. Multiple sclerosis. In a coronal section of brain, multiple sharply defined, tan-gray plaques are identified in the white matter, adjacent to the right ventricle (paraventricular), involving the cortex at the gray matter-white interface (juxtacortical), and in other locations (arrows).
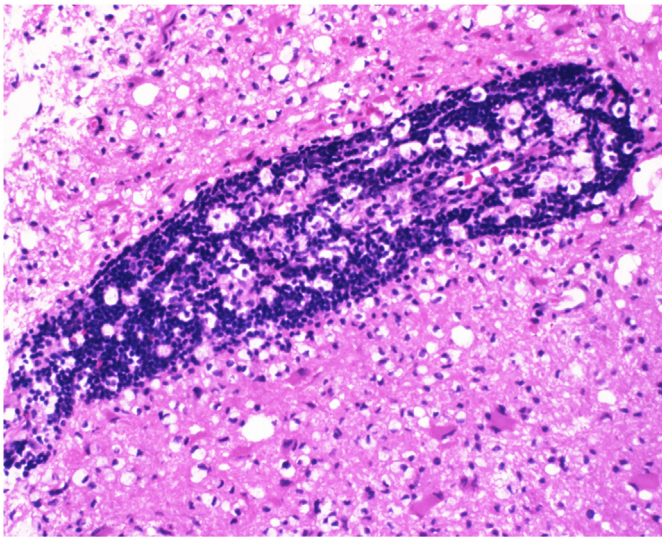
Fig. 3. Active MS plaque shows abundant foamy macrophages, which are ingesting the myelin breakdown products, accompanied by an intense lymphocytic perivascular infiltrate (perivascular cuffing) (H&E stain, intermediate magnification).

Fig. 5. A coronal section of midbrain at the interface between the pons and midbrain shows several areas of demyelination, most notably centrally within the cerebral peduncle, within the corticospinal fiber tract (arrowhead) (Luxol fast blue stain, no magnification). Reproduced with permission from the College of American Pathologists. AUB, 1996 Education Programs. Northfield, IL: College of American Pathologists; 1996. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

mitochondrial dysfunction. The triggers of neurodegeneration seen in chronic, progressive MS are the "normal appearing" white matter (NAWM) lesions and tissue damage in the gray matter. NAWM appears normal in routine stains and imaging; however, detailed histological studies reveal diffuse gliosis, microglial activation, vascular fibrosis, perivascular cuffing by inflammatory cells, perivascular lipofuscin, abnormal endothelial tight junctions, blood–brain barrier breakdown, and/or vessels containing proliferating endothelial cells. Axonal loss has also been observed in NAWM. Notably, NAWM lesions correlate better with clinical disability than focal inflammatory white matter lesions. In addition to white matter, gray matter is damaged in progressive MS. Damage can extend throughout the cortex and subcortical regions. An
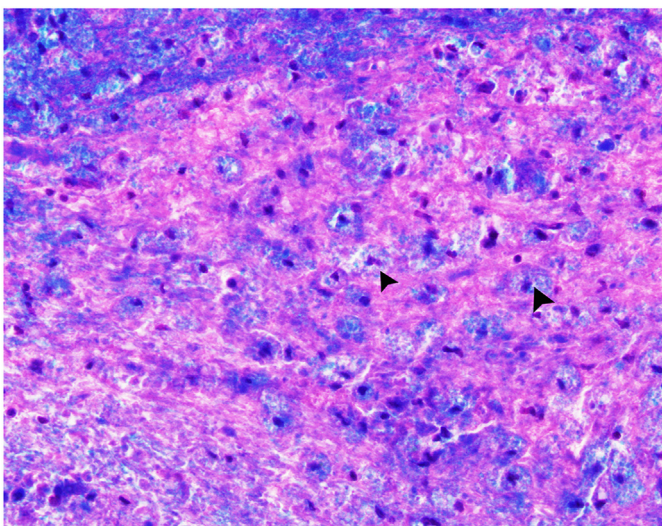
important element of gray matter damage is meningeal inflammation. Lymphoid structures resembling B-cell follicles form in the meninges. They are found extensively in patients with primary progressive MS who exhibit a more severe clinical course.[16,17]

Fig. 4. Foamy macrophages (arrowheads) are distended with myelin breakdown product (Luxol fast blue stain, high magnification). Reproduced with permission from Suzanne Zein-Powell, MD, Methodist Hospital, Houston, TX. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)
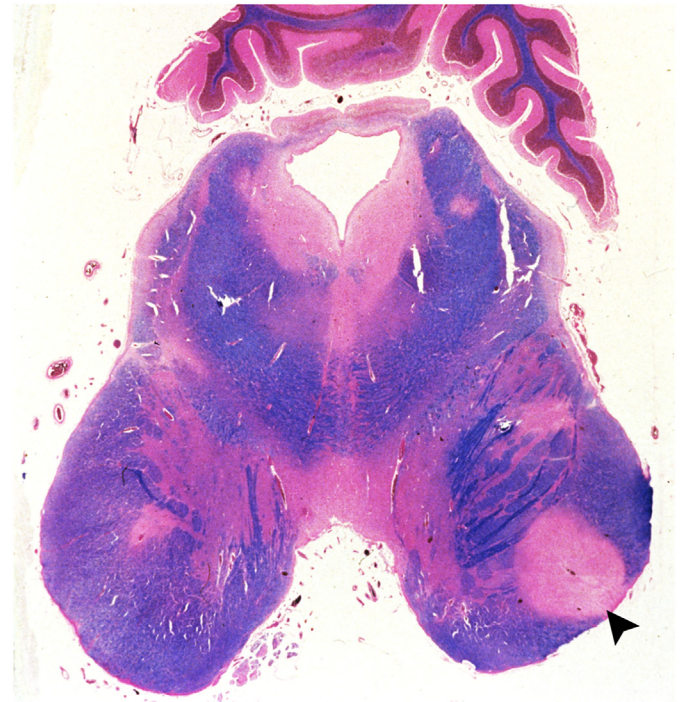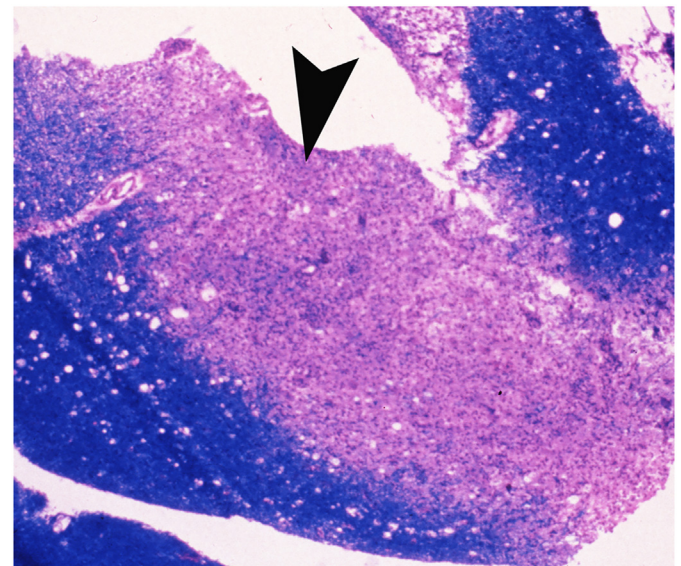

Fig. 6. On histological examination, the brain shows an area of demyelination with axonal preservation (arrowhead) seen as the tan-gray plaque on gross examination. (Luxol fast blue stain, intermediate magnification). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)
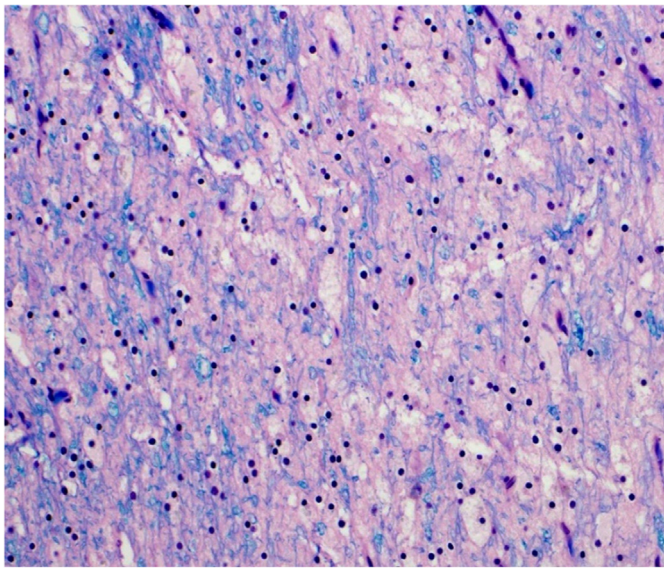
Fig. 7. Chronic plaque at interface with normal white matter. The axons are retained within the plaque; however, many have not been remyelinated. In addition, macrophages and lymphocytes are decreased in number in a chronic plaque, so the cellularity within a chronic plaque is less than in an active/acute plaque (Figs. 3 and 4). (Luxol fast blue stain, intermediate magnification). Courtesy of Philip Boyer, MD, PhD, Brody School of Medicine, Greenville, NC. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Describe remyelination in MS

Remyelination in the CNS is accomplished by oligodendrocytes, and in MS patients, they contribute to the complete or partial resolution of clinical symptoms in RRMS. Remyelination is dependent on adult oligodendrocyte progenitor cells (OPC) as preexisting, mature oligodendrocytes cannot add to the pool of myelinogenic oligodendrocytes. It is thought that the main reason remyelination fails in MS is because OPC become quiescent and unable to differentiate, but there are likely other factors that contribute to the failure to remyelinate. For example, reactive astrocytes secrete inhibitors of remyelination at the site of demyelination. Similarly, clearance of myelin debris is an important step in remyelination since it contains remyelination inhibitors. The macrophages and activated microglia that are responsible for phagocytosis of debris also secrete various neutrophilic factors. There is also an age dependent decline in remyelination, and this is more clearly due to decreased differentiation of OPC. Mechanistically, it is thought that aged OPC become less responsive to factors that induce differentiation through dysfunction of the mTOR pathway. Finally, remyelination also depends on the location in the CNS. For example, periventricular lesions are less amenable to remyelination than subcortical lesions. Overall, as patients age and the disease progresses, there is less remyelination of lesions, correlating with progressive clinical dysfunction.[18]

How is MS treated?

Treatment is multifactorial including counseling, physical therapy, exercise and pharmacotherapy. Pharmacotherapy consists of medications directed at immunosuppression or immunomodulation.[2] Although not curative, pharmacotherapy may ameliorate symptoms. Disease modifying therapeutic agents depends on which clinical subtype (phenotype) (CIS, RRMS, SPMS, and PPMS) the patient presents with. Monoclonal antibodies (natalizumab, ocrelizumab, rituximab, ofatumumab, and alemtuzumab) may be indicated for active disease. Fumarates (e.g. dimethyl fumarate) and sphingosine 1-phosphate receptor modulators (e.g. fingolimod) are other considerations along with injectable agents, such as recombinant human interferon beta-1b, recombinant human interferon beta-1a, and glatiramer acetate. Healthcare workers need to consider the risk benefit of selected agents, given the potential adverse effects including infection.[2,19–21]

Teaching Points

- Multiple sclerosis (MS) is a chronic demyelinating disorder of autoimmune etiology in which the clinical findings are separated in both time and space.
- MS presents with symptoms usually between 15 and 45 years of age. It is twice as common in women and has a prevalence between 1/1000 persons in the US.
- The diagnosis of MS incorporates a combination of clinical, imaging, and laboratory data to show dissemination of lesions in space and time, along with the consideration and exclusion of alternative diagnoses.
- Laboratory testing contributes to the diagnostic workup of a patient with MS in the differential diagnosis; however, no single laboratory test, in isolation, is diagnostic of MS.
- The most characteristic finding seen on MRI are T2-hyperintense and/or gadolinium contrast-enhancing T1 cerebral hemisphere periventricular, juxtacortical, infratentorial, and spinal cord white matter lesions.
- The presence of CSF-specific oligoclonal bands can substitute for MRI data demonstrating dissemination in time.
- Autoimmunity is thought to play an important role in the pathogenesis of MS, involving T and B cell dysfunction.
- Acute exacerbations are characterized by demyelination, inflammation, and edema.
- Chronic, progressive disease is characterized by neurodegeneration, axonal damage, normal appearing white matter lesions, and gray matter abnormalities.
- Remyelination is thought to play a role in the partial or complete recovery of neurological function in relapsing-remitting MS.
- As MS progresses and patients age, remyelination lessens and neurological dysfunction becomes permanent.
- Treatment of MS is multifactorial including counseling, physical therapy, exercise, and pharmacotherapy.

Conflict of interest

Funding

Acknowledgments

References

1. Knollmann-Ritschel BEC, Regula DP, Borowitz MJ, Conran R, Prystowsky MB. Pathology competencies for medical education and educational cases. *Acad Pathol*. 2017;4:1–36. doi:10.1177/2374289517715040
2. Margeta M, Perry A. The Central Nervous System. In: Kumar V, Abbas AK, Aster JC, eds. *Robbins and Cotran Pathologic Basis of Disease*. 10th ed. Philadelphia, PA: Elsevier; 2021:1241–1304.
3. Scolding N. The differential diagnosis of multiple sclerosis. *J Neurol Neurosurg Psychiatry*. 2001;71:9–15.
4. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology*. 2014;83(3):278–286.
5. Lublin FD, Coetzee T, Cohen JA, Marrie RA, Thompson AJ. The 2013 clinical course descriptors for multiple sclerosis: a clarification. *Neurology*. 2020;94(20):1088–1092.

6. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol.* 2011;69(2):292–302.
7. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol.* 2018;17(2):162–173.
8. McDonald WI, Compston A, Edan G, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the international panel on the diagnosis of multiple sclerosis. *Ann Neurol.* 2001;50:121–127.
9. Filippi M, Preziosa P, Banwell BL, et al. Assessment of lesions on magnetic resonance imaging in multiple sclerosis: practical guidelines. *Brain.* 2019;142(7): 1858–1875.
10. Freedman MS, Thompson EJ, Deisenhammer F, et al. Recommended standard of cerebral fluid analysis in the diagnosis of multiple sclerosis: a consensus statement. *Arch Neurol.* 2005;62(6):865–870.
11. Reindl M, Waters P. Myelin oligodendrocyte glycoprotein antibodies in neurological disease. *Nat Rev Neurol.* 2019;15(2):89–102.
12. Fuhr P, Kappos L. Evoked potentials for evaluation of multiple sclerosis. *Clin Neurophysiol.* 2001;112:2185–2189.
13. Olek MJ, Mowry E. Pathogenesis and epidemiology of multiple sclerosis. In: Up to Date, Gonzalez-Scarano F, Dashe JF. eds, Waltham, MA. Updated August 2021. Accessed September 20, 2021. https://www.uptodate.com/contents/pathogenesis-and-epidemiology-of-multiple-sclerosis?topicRef=1689&source=see_link.
14. Grigoriadis N, van Pesch V. ParadigMS Group. A basic overview of multiple sclerosis immunopathology. *Eur J Neurol.* 2015;2(22 Suppl):3–13. doi:10.1111/ene.12798. PMID: 26374508.
15. Kipp M, Nyamoya S, Hochstrasser T, et al. Multiple sclerosis animal models: a clinical and histopathological perspective. *Brain Pathol.* 2017;27:123–137.
16. Allen I, McQuaid S, Mirakhur M, et al. Pathological abnormalities in the normal appearing white matter in multiple sclerosis. *Neurol Sci.* 2001;22:141–144.
17. Calabrese M, Favaretto A, Martini V, et al. Grey matter lesions in MS: from histology to clinical implications. *Prion.* 2013;7(1):20–27.
18. Cunniffe N, Coles A. Promoting remyelination in multiple sclerosis. *J Neurol.* 2019; 268:30–44.
19. Olek MJ, Mowry E. Initial disease-modifying therapy for relapsing-remitting multiple sclerosis in adults. In: Up to Date, Gonzalez-Scarano F, Dashe JF. eds, Waltham, MA. Updated August 2021. Accessed September 20, 2021. https://www.uptodate.com/contents/initial-disease-modifying-therapy-for-relapsing-remitting-multiple-sclerosis-in-adults?topicRef=1688&source=see%E2%80%A6.
20. Olek MJ, Mowry E. Disease-modifying therapies for multiple sclerosis: pharmacology, administration, and adverse effects. In: Up to Date, Gonzalez-Scarano F, Dashe JF. eds, Waltham, MA. Updated August 2021. Accessed September 20, 2021. https://www.uptodate.com/contents/disease-modifying-therapies-for-multiple-sclerosis-pharmacology-administration-and-adverse-effects?topicRef=1687&source=see_link.
21. Olek MJ, Mowry E. Treatment of secondary progressive multiple sclerosis in adults. In: Up to Date, Gonzalez-Scarano F, Dashe JF. eds, Waltham, MA. Updated August 2021. Accessed September 20, 2021. https://www.uptodate.com/contents/treatment-of-secondary-progressive-multiple-sclerosis-in-adults?topicRef=1687&source=see_link.