Multiple Sclerosis Pathogenesis

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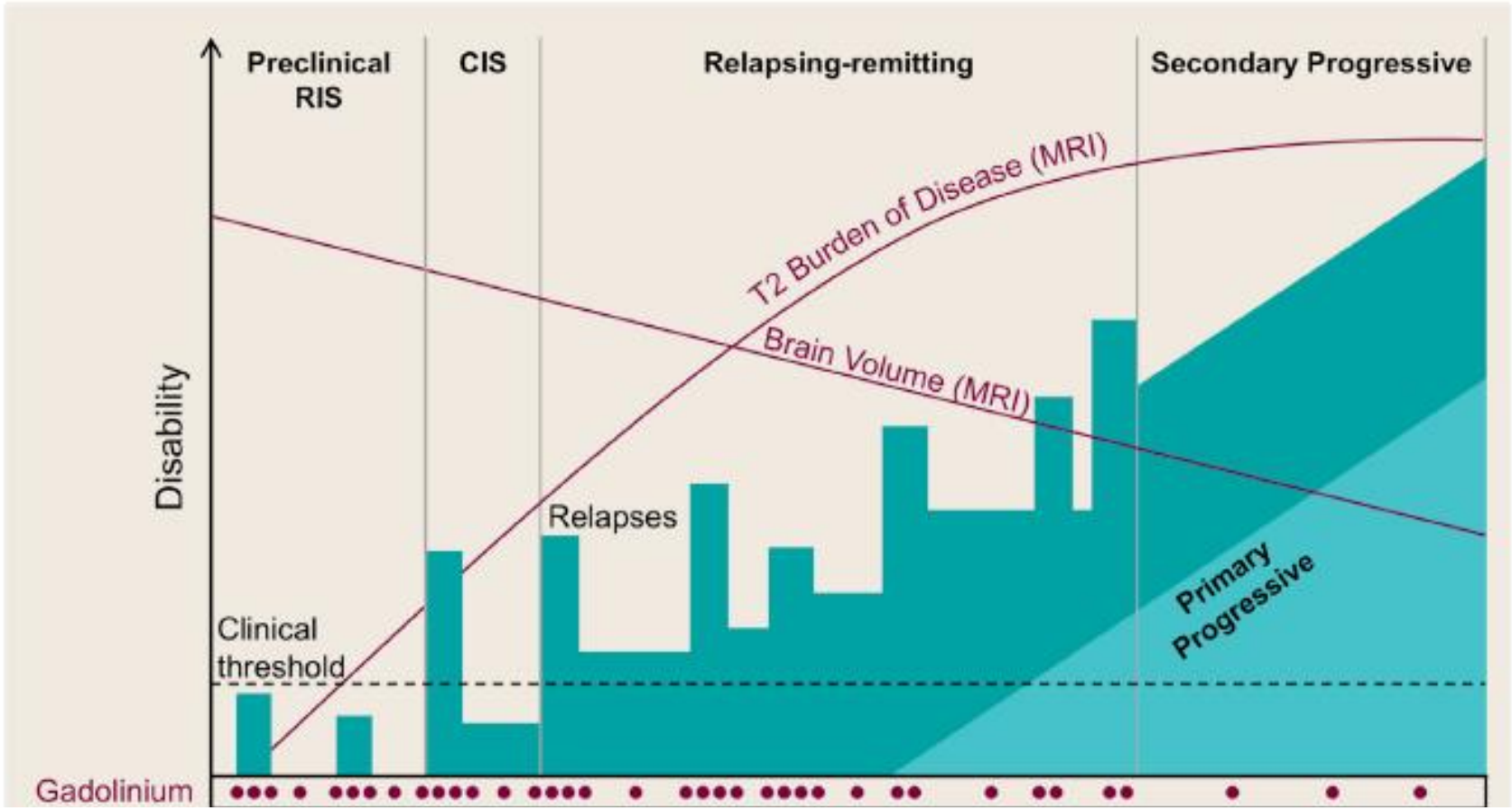
Stages of Multiple Sclerosis



Baecher-Allan, Kaskow, Weiner. Multiple Sclerosis: Mechanisms and Immunotherapy. Neuron. 2018. PMID: 29470968.

Multiple sclerosis is thought to begin before clinical symptoms are evident, and it can be discovered incidentally on MRI as a radiologically isolated syndrome (RIS). It then usually manifests as a clinically isolated syndrome (CIS), which is followed by a relapsing-remitting stage, characterized by discrete episodes of neurologic dysfunction with remission. The progressive stage involves steadily worsening disability and usually evolves from the relapsing-remitting stage, although some patients may have progressive disease from onset (primary progressive MS). MRI correlates of disease include gadolinium-enhancing lesions, which represent the breakdown of the blood-brain barrier and the movement of cells into the CNS, accumulation of T2 burden of disease, and a decrease in brain volume as measured by atrophy. Many treatments impact on relapsing forms of MS. Few treatment options are available for progressive MS.

Is MS an autoimmune disease?

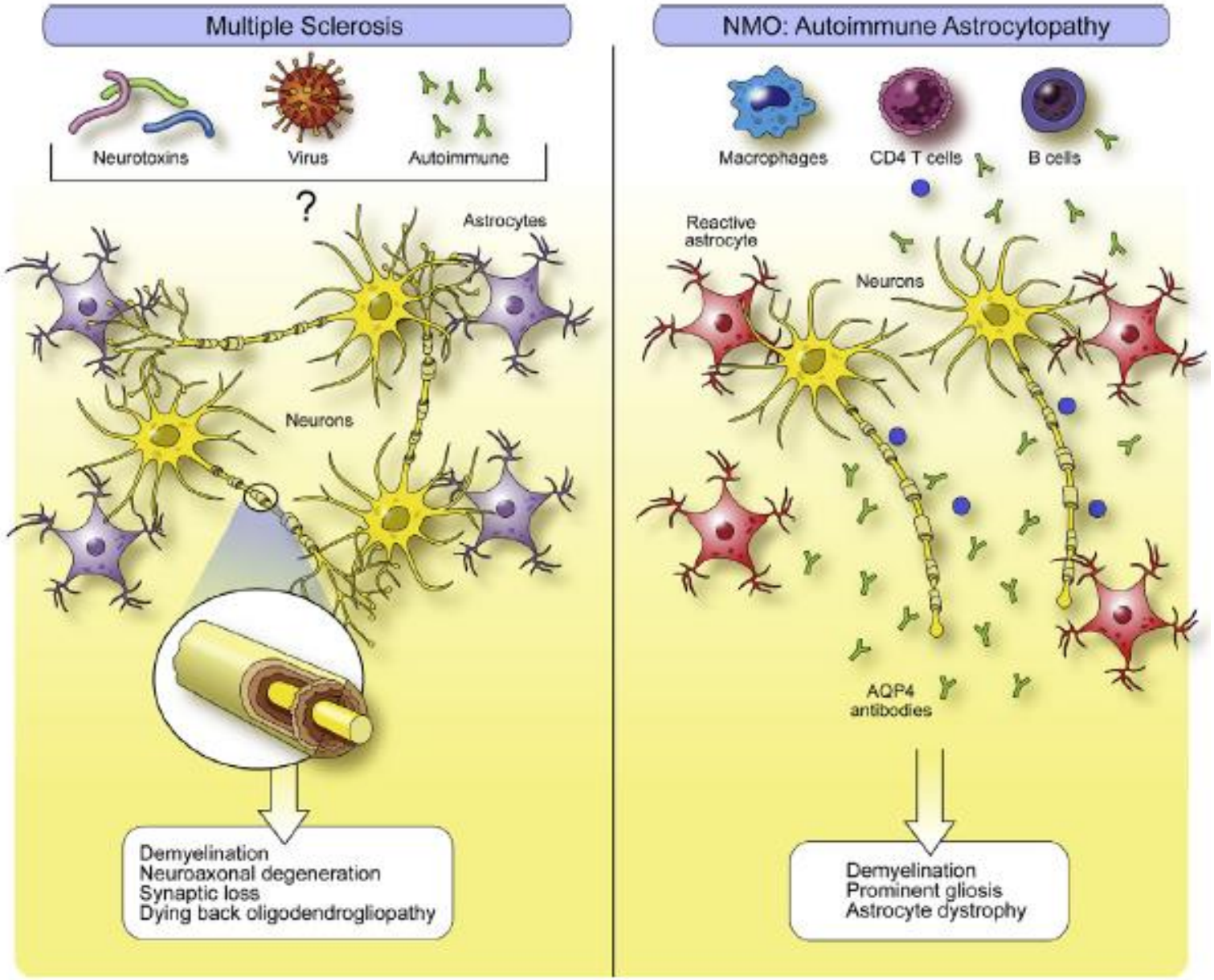


Table 1
Revised criteria for a disease to be considered autoimmune: neuromyelitis optica and multiple sclerosis

Criteria for Autoimmune Disease[7]	NMO	MS
Immune response to a precise autoantigen in all patients	aquaporin 4[22,23]	Multiple antigens have been described, not present in all patients[12,13,17–20]
Lesion reproducibility after administration of autoantibody or T cells	Exacerbation of EAE model after adoptive transfer of neuromyelitis optica Abs[27]	
Animal: induction of lesion by antigen immunization		EAE model: induced by myelin oligodendrocyte glycoprotein, proteolipid protein, myelin basic protein[28] and reactivated CD4+ T cells[29]
Autoantibody or T cell isolation form lesion or serum	aquaporin 4 antibodies[27,30]	
Autoantibody titers or T-cell levels associated with disease activity	Higher antibody titers during relapse than during remission[31]	
Autoimmune disorders or autoantigens associated with the disease	Sjogren syndrome, SLE[32]	No association in population-based cohort studies[33]
Immune absorption with purified autoantigen abrogates pathogenic autoantibody or T cell		
Reduction of autoantibody or T cell associated with clinical improvement	Plasma exchange[34]	Plasma exchange[35,36]

Lemus HN, Warrington AE, Rodriguez M. Multiple Sclerosis: Mechanisms of Disease and Strategies for Myelin and Axonal Repair.
Neurol Clin. 2018. PMID: 29157392.

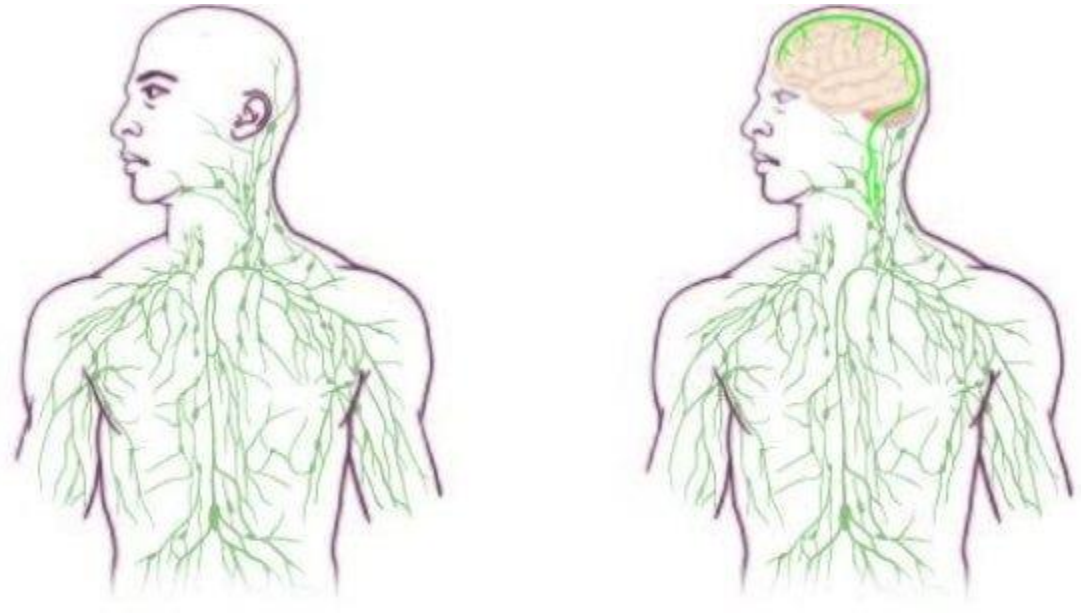
Missing link found between brain, immune system; major disease implications

Date: June 1, 2015

Summary: In a stunning discovery that overturns decades of textbook teaching, researchers have determined that the brain is directly connected to the immune system by vessels previously thought not to exist. The discovery could have profound implications for diseases from autism to Alzheimer's to multiple sclerosis.

Louveau et al. ***Nature, 2015****; PMID: 26030524.*

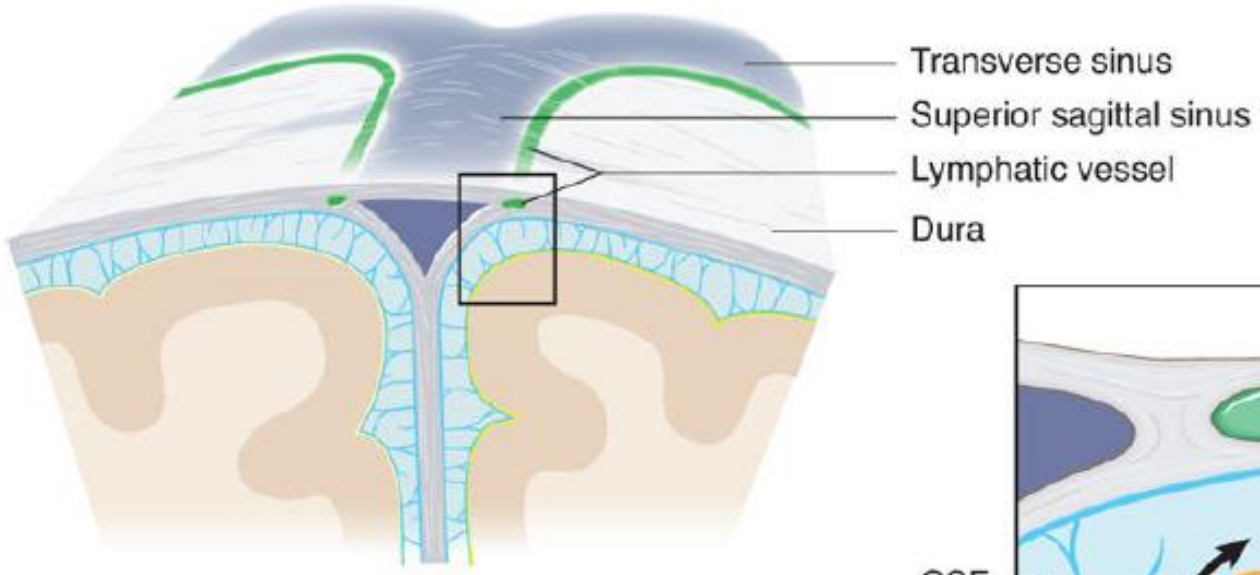
Meninges were tested for Lyve-1, a marker associated with the lymphatic endothelial cells marker (LEC). Two to three Lyve-1-expressing vessels were identified running parallel to the dural sinuses

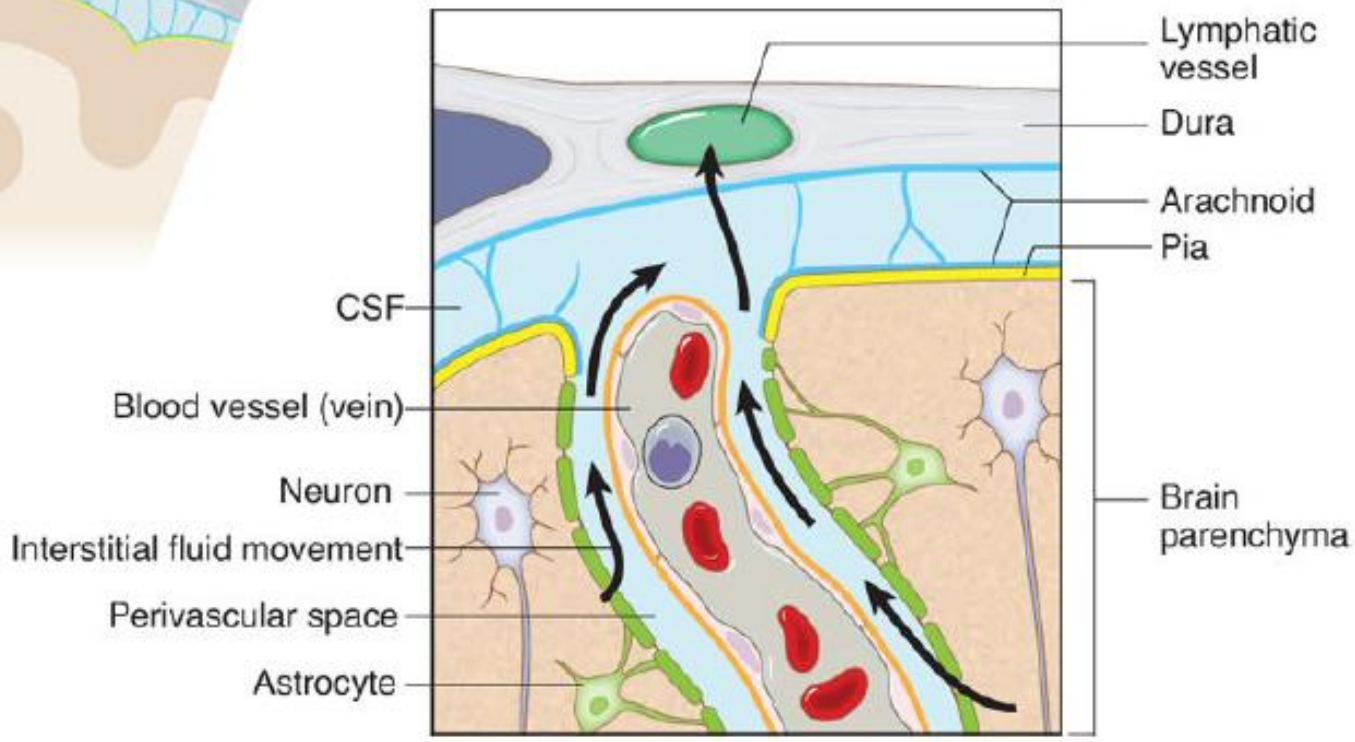


www.sciencedaily.com/releases/2015/06/150601122445.htm

Maps of the lymphatic system: old (left) and updated to reflect UVA's discovery
Credit: University of Virginia Health System (2015).

Neuroanatomy of Brain Lymphatics





"The presence of a functional and classical lymphatic system in the CNS suggests that current dogmas regarding brain tolerance and the immune privilege of the brain should be revisited. Malfunction of the meningeal lymphatic vessels could be a root cause of a variety of neurological disorders in which altered immunity is a fundamental player such as multiple sclerosis, Alzheimer's disease…"

Louveau et al. ***Nature, 2015****; PMID: 26030524.*

Neuromyelitis optica
(NMO; formerly known as Devic's disease [1894])

- ~ 10% cases of multiple sclerosis (MS) in Asia (Misu et al. Brain. 2002. PMID: 12390972.).
- Up until 2002 it was controversial whether NMO was a subtype of MS or a distinct disease.

Clinical criteria:

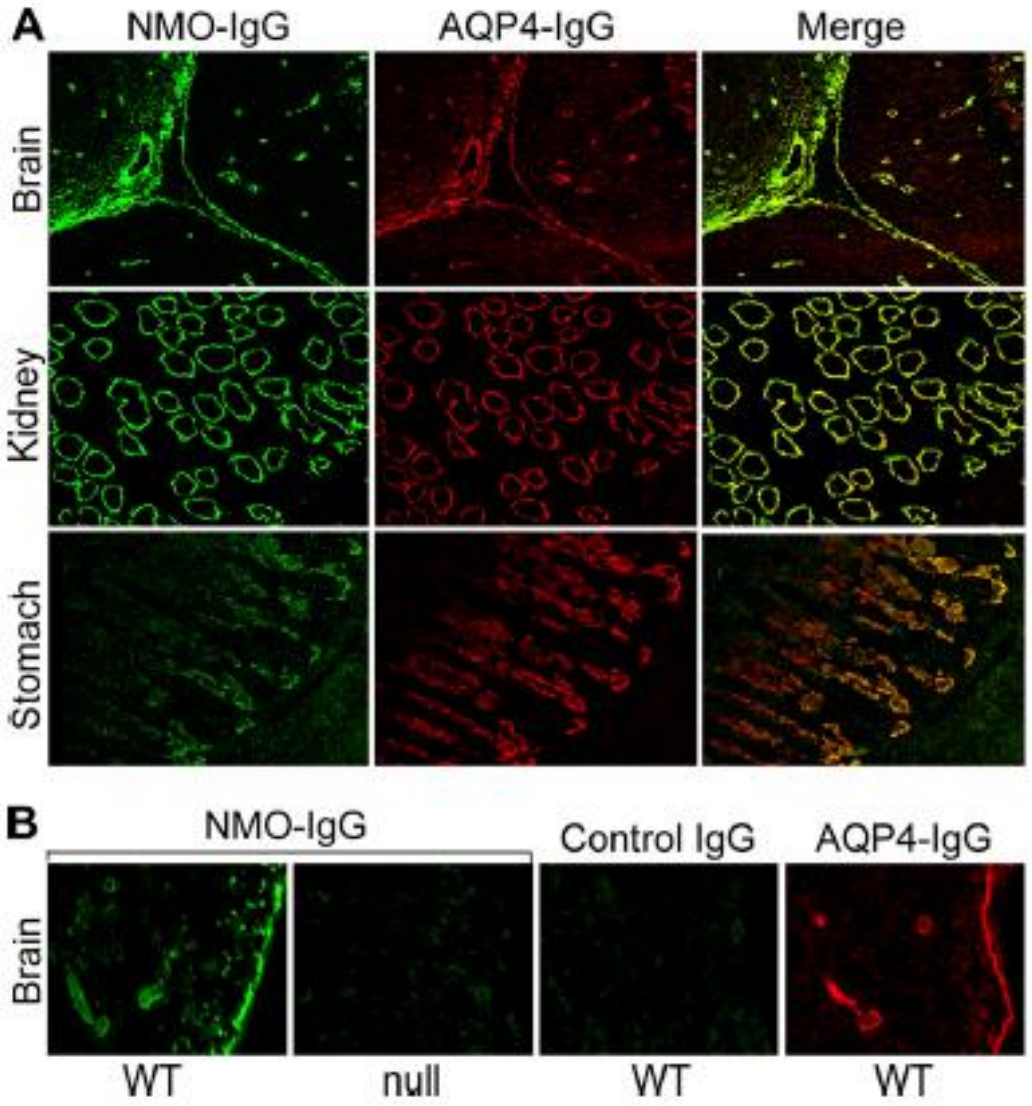
1. Normal MRI Brain
2. Longitudinally extensive (≥3 vertebral segments) signal abnormality
3. Occasional prominent CSF pleocytosis
4. Generally poor outcome of attacks, some leading to respiratory failure [20%; 2' cervical myelitis] (an uncommon complication in MS).

Phenotypic variability:

In some patients area postrema and hypothalamus may be involved as well.
Others have recurrent optic neuritis or myelitis only.
(Lemus et al. Neurol Clin. 2018. PMID: 29157392).

Immunopathology of NMO is restricted to spinal cord and optic nerves, and affects gray and white matter. IgG, IgM, and products of complement activation are deposited in a *vasculocentric pattern*
(Lucchinetti et al. Brain. 2002 . PMID: 12076996).

Immunofluorescence co-localization of NMO-IgG and AQP4-IgG



AQP4 is an integral protein of astrocytic plasma membranes and is highly concentrated in foot process domains facing microvessels where it interacts with dystrophin-associated proteins.

The AQP4 channel is the predominant water channel in the CNS. It has a pathophysiologic role in brain edema formation following water intoxication and focal cerebral ischemia. Brain edema occurring in high-grade astrocytomas is due to up-regulation of AQP4.

Lennon et al. *J. Exp. Med.* **202**, 473–477 (2005). PMID: 16087714

Immunofluorescence testing for Autoimmune Neurologic Disorders

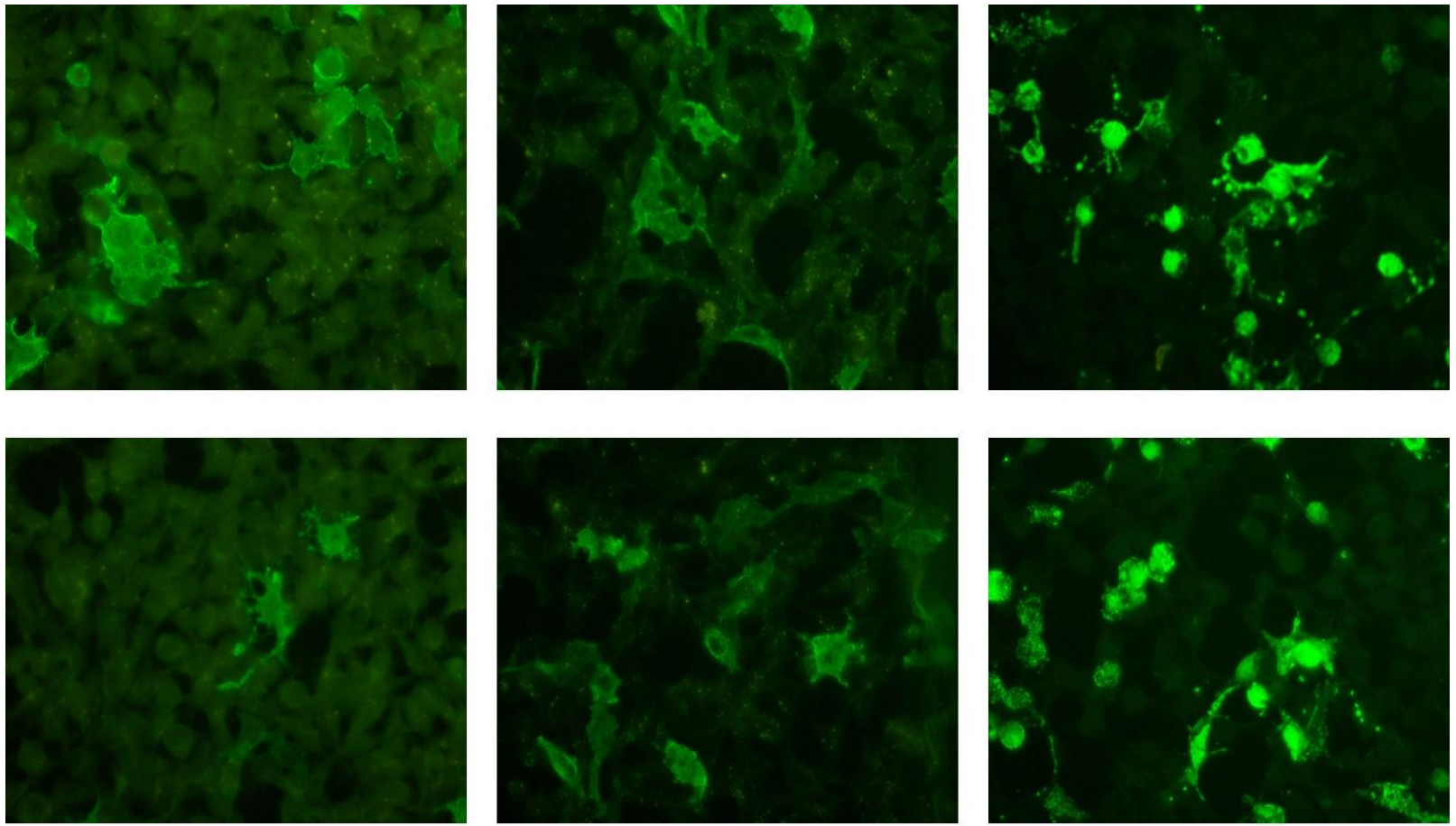
Anti-AQP4

Initially reported at a frequency of 73% in NMO

Lennon et al. Lancet. 2004. PMID: 15589308.

Currently 80% sensitivity and nearly 100% specificity using IIFT

Saeed et al. PJNS 2018.



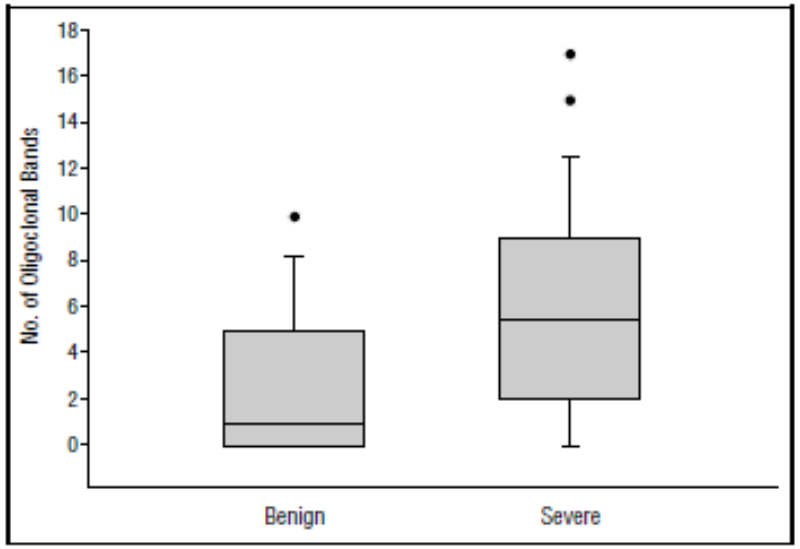
Anti-Aquaporin (AQP4) Anti-GABA Anti-NMDA

Mohammad Saeed; Tariq Gazdar; Nadir Ali Syed; and Arsalan Ahmad
Neuroimmunology Diagnostics. PJNS 2018: Vol. 13 : Iss. 2 , Article 1.

CSF Oligoclonal bands

Comparison of number of oligoclonal bands in benign vs severe multiple sclerosis. Median lines are shown within bars that represent the 25th to 75th percentile. Error bars indicate 90th percentiles; solid dots, outliers.

Avasarala et al. Arch Neurol. 2001. PMID: 11735778.



Present in 95% of MS patients

n = 314							
	n	**McDonald MS at 3 years *n* (%)**	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**Accuracy (95% CI)**	**PPV (95% CI)**	**NPV (95% CI)**
All DIS	137	111/137 (81.0)	61.7 (54.1–68.8)	80.6 (72.9–86.9)	69.7 (64.3–74.8)	81.0 (74.8–86.0)	61.0 (56.1–65.7)
DIS with + OB	101	85/101 (84.2)	47.2 (39.8–54.8)	88.1 (81.3–93.0)	64.6 (59.1–69.9)	84.2 (76.6–89.6)	55.4 (51.6–59.1)

Outcome: 2010 McDonald multiple sclerosis at 3 years.
MS = multiple sclerosis; PPV = positive predictive value; NPV = negative predictive value; OB = oligoclonal bands.

Arrambide et al. Brain. 2018. PMID: 29462277.

Presence of IgG oligoclonal bands indicates an increased risk for developing multiple sclerosis in patients presenting with clinically isolated syndromes (CIS) (McDonald et al., 2001) In the 2001 McDonald criteria for the diagnosis of MS and their 2005 revision incorporated the 'dissemination in space' (DIS) criterion comprised by the presence of two or more T2 lesions on MRI in addition to the positive oligoclonal bands (McDonald et al., 2001; Polman et al., 2005). In the 2010 revision oligoclonal bands were removed from the criteria for MS.

Antibodies to MOG and MBP in MS

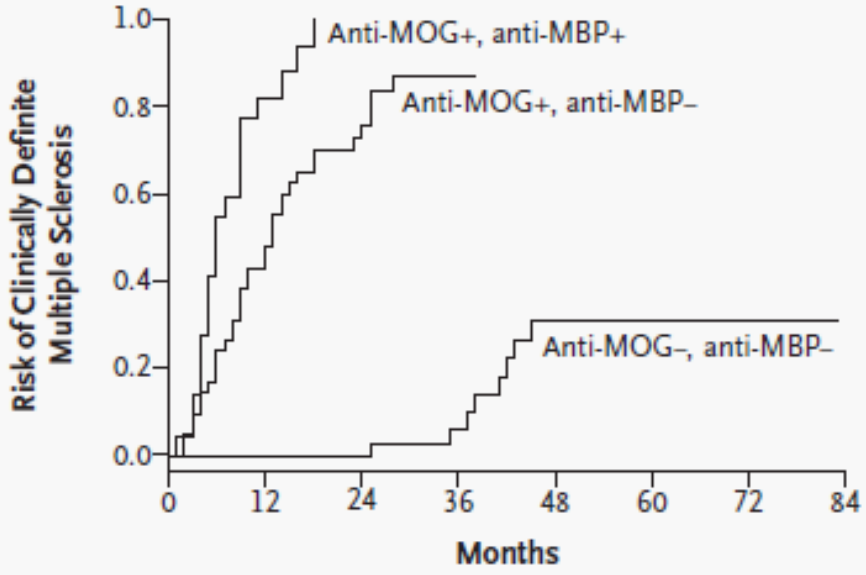


Figure 1. Kaplan–Meier Estimates of the Risk of Clinically Definite Multiple Sclerosis, According to Antibody Status.

P<0.001 for the comparison between the patients who were seronegative for antibodies against both myelin oligodendrocyte glycoprotein (MOG) and myelin basic protein (MBP) and the patients who were seropositive only for anti-MOG antibodies or for both anti-MOG and anti-MBP antibodies. Plus signs denote seropositive, and minus signs seronegative.

N=103, followed for a mean of 50 months
MOG/MBP + = 21%; MOG+ = 41%

Berger et al. NEJM. 2003. PMID: 12853586.

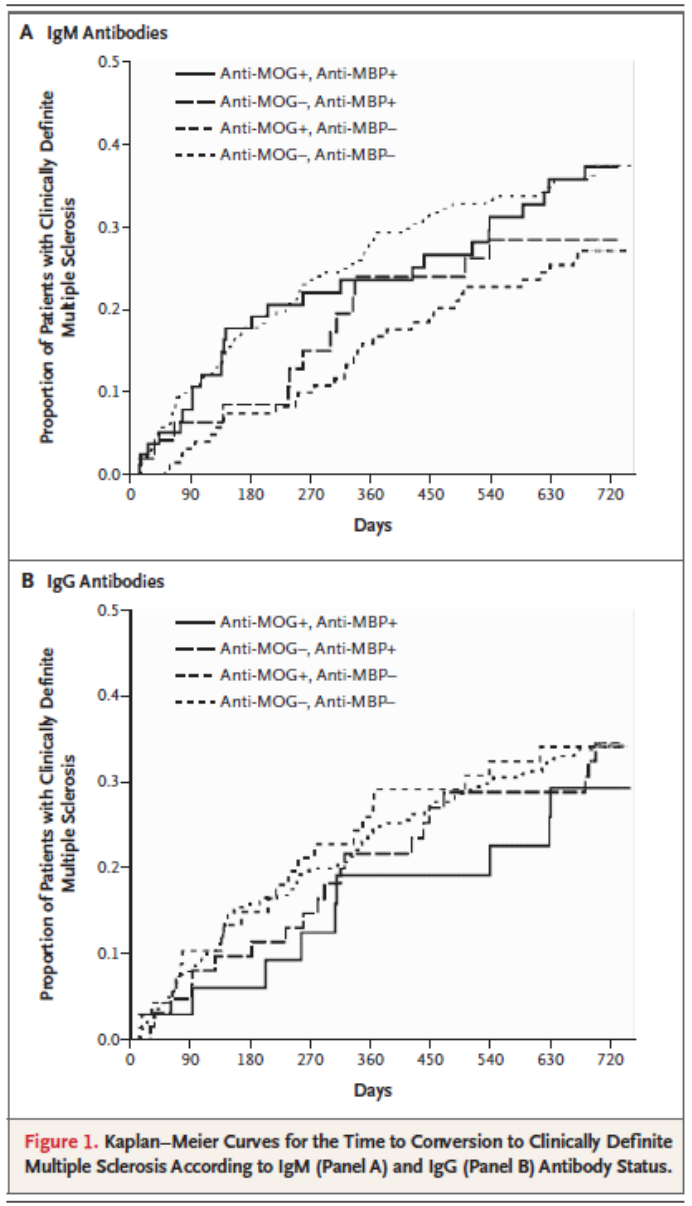


Figure 1. Kaplan–Meier Curves for the Time to Conversion to Clinically Definite Multiple Sclerosis According to IgM (Panel A) and IgG (Panel B) Antibody Status.

N=462, followed for 24 months
MOG/MBP + = (7_G+16_M) 23%; MOG+ = (15_G+26_M) 41%

Kuhle et al. NEJM 2007. PMID: 17251533.

Myelin Oligodendrocyte Glycoprotein (MOG)

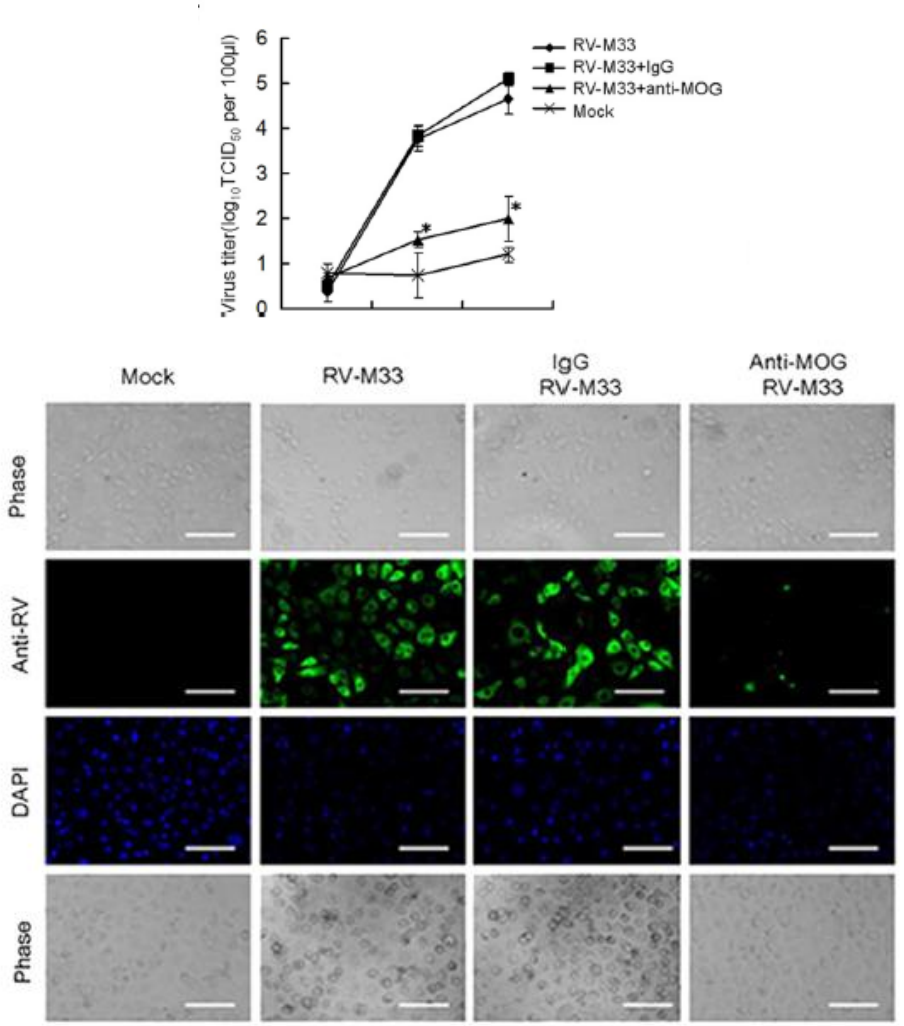
MOG is a minor component of myelin (0.01 to 0.05% of central myelin protein) that is found exclusively in the central nervous system. The N-terminal domain of MOG is expressed on the myelin surface and is easily accessible to antibodies.

The human MOG gene is located at chromosome 6 within the human leukocyte antigen (*HLA*) gene locus and functions as a *receptor* for the entry of *Rubella virus* (Cong et al. J Virol. 2011. PMID: 21880773).

Fifteen different alternatively spliced isoforms have been detected in humans. There is cross-reactivity between anti-MOG and antibodies to *Epstein-Barr nuclear antigen* (Wang et al. Neurology. 2008. PMID: 18753473)

Meta-analysis of Anti-MOG Ab sensitivity for:

- Multiple sclerosis = 5%
- Acute disseminated encephalomyelitis (ADEM) = 36%
- Seronegative NMOSD = 27%
- NMO AQP4+ = 2% (Same as controls)

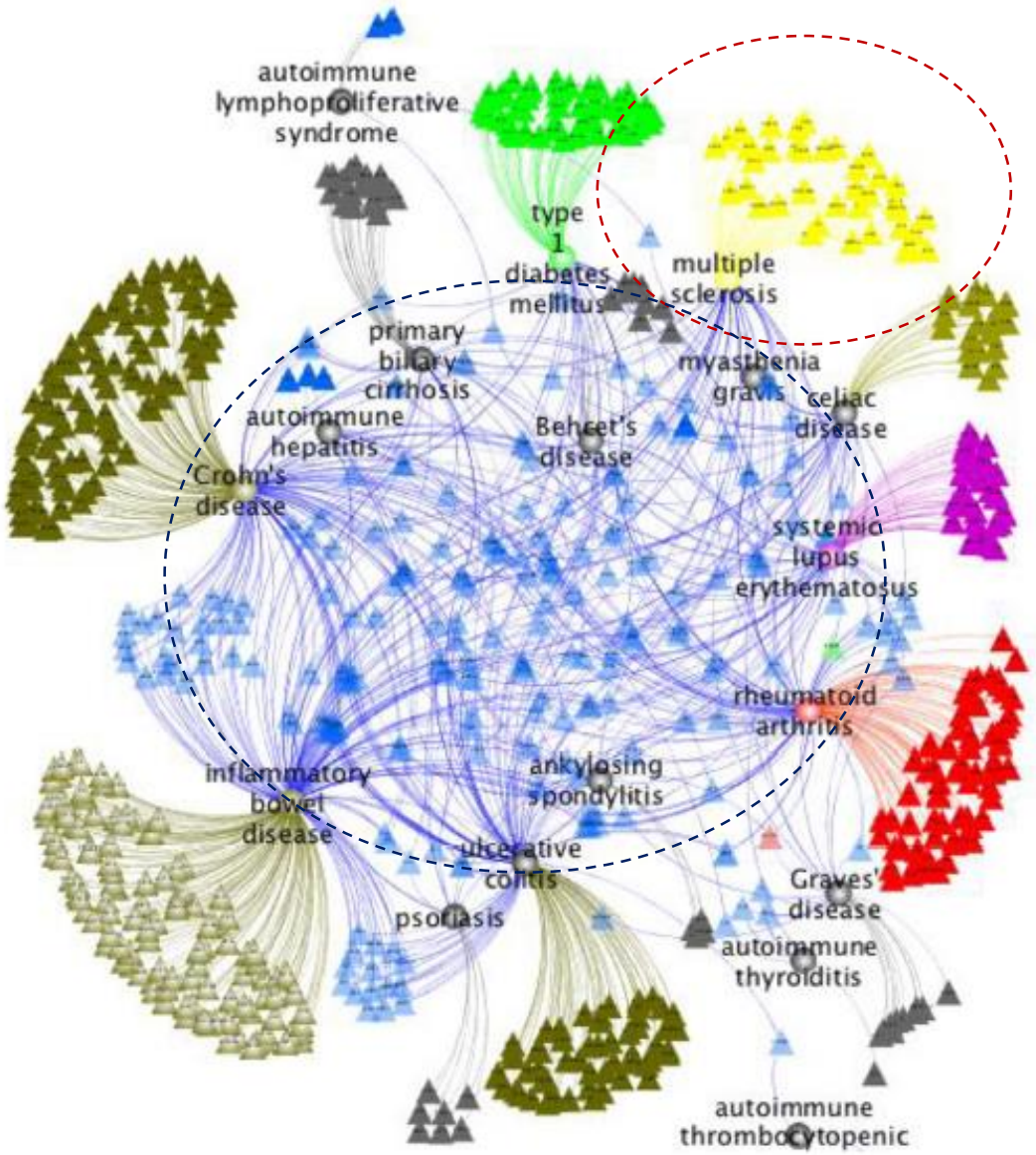


Cong et al. J Virol. 2011. PMID: 21880773

Peschl et al. Front Immunol. 2017. PMID: 28533781

Genetics of MS

Multiple sclerosis shares a large number of susceptibility genes with other autoimmune disorders. This is further evidence that MS is an autoimmune disease.



Baranzini et al. Trends Genet. 2017. PMID: 28987266.

Cigarette Smoking causes Autoimmune Diseases

Cigarette Smoke, Chemicals, UV Light, Viral Infections

↓

Oxidative stress

↓

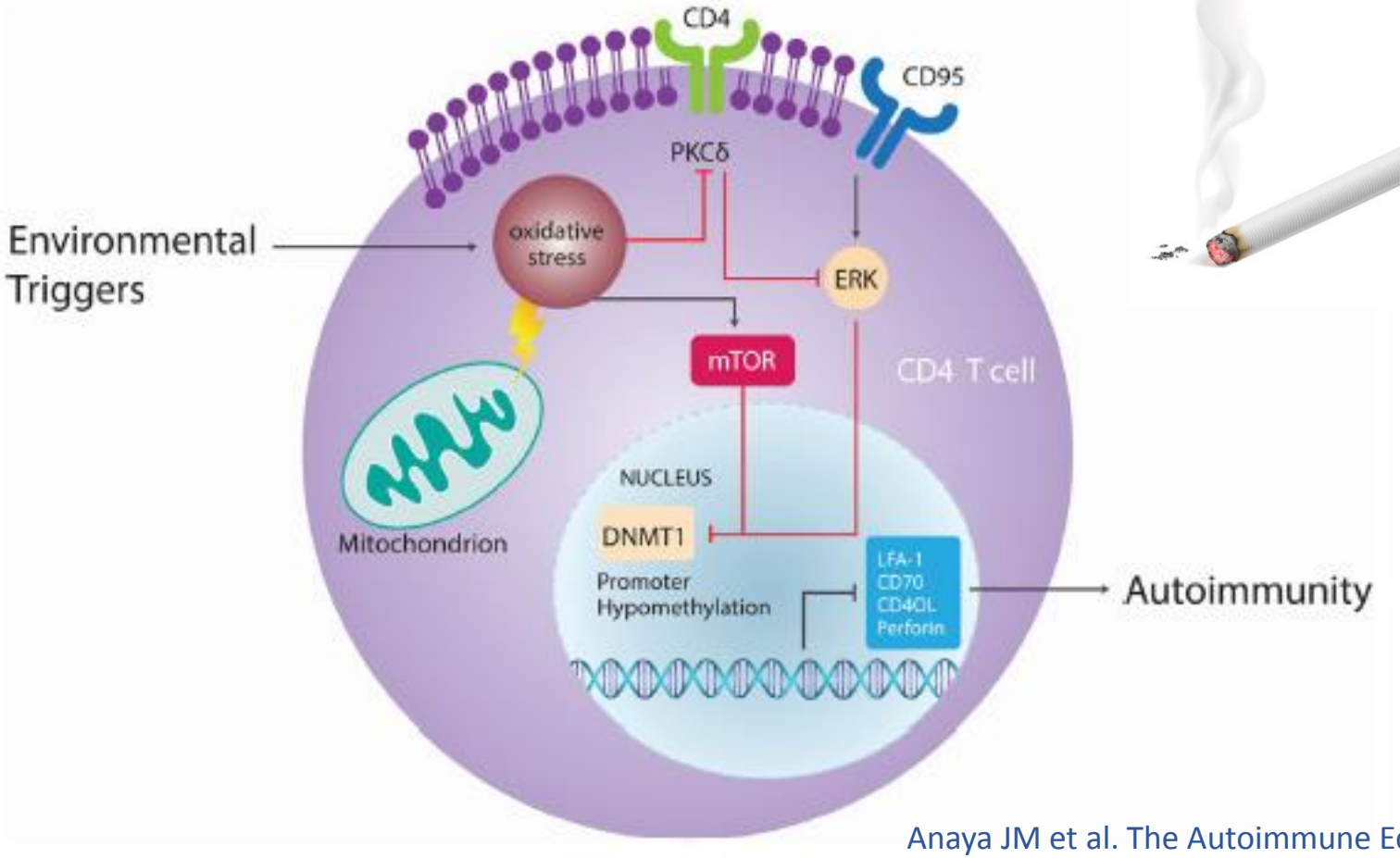
Inhibition of DNA Methyltransferase 1 (DNMT1)

↓

DNA Hypomethylation

↓

CD4+ T cells become autoreactive.



Anaya JM et al. The Autoimmune Ecology. Front Immunol. 2016. PMID: 27199979.

Epigenetic Autoimmune Ecology Pathways. Different environmental factors, such as cigarette smoke, chemicals, UV light, and viral infections cause oxidative stress, which lead to activation of the mammalian target of rapamycin (mTOR) pathway that can directly inhibit DNA methyltransferase 1 (DNMT1). Oxidative stress contributes in CD4+ T cells to site-specific decrease in phosphorylation of protein kinase C (PKC)δ T505, leading to functional loss of PKC and parallel reduction of extracellular signal-regulated kinase (ERK) phosphorylation. As a result of ERK activity, expression of DNMT1 is reduced, DNA hypomethylation occurs and CD4+ T cells become autoreactive.

Gut Microbiome

In NMO AQP4 cross reacts with a homologous sequence found in the ATP binding cassette transporter of Clostridium perfringens.

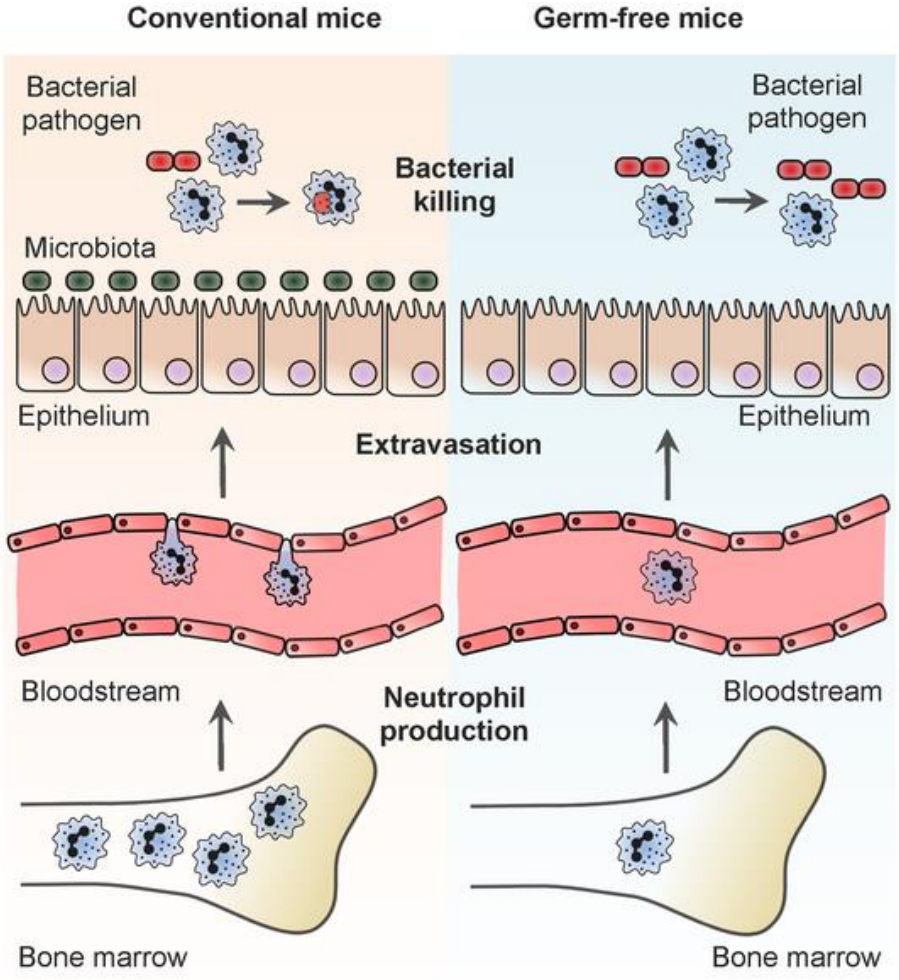
Cree et al. Ann Neurol. 2016. PMID: 27398819.

In MS Methanobrevibacter spp and Akkermansia are increased and Butyricimonas is decreased.

Vitamin D supplementation alters gut microbiota.

Baecher-Allan et al. Neuron. 2018. PMID: 29470968.

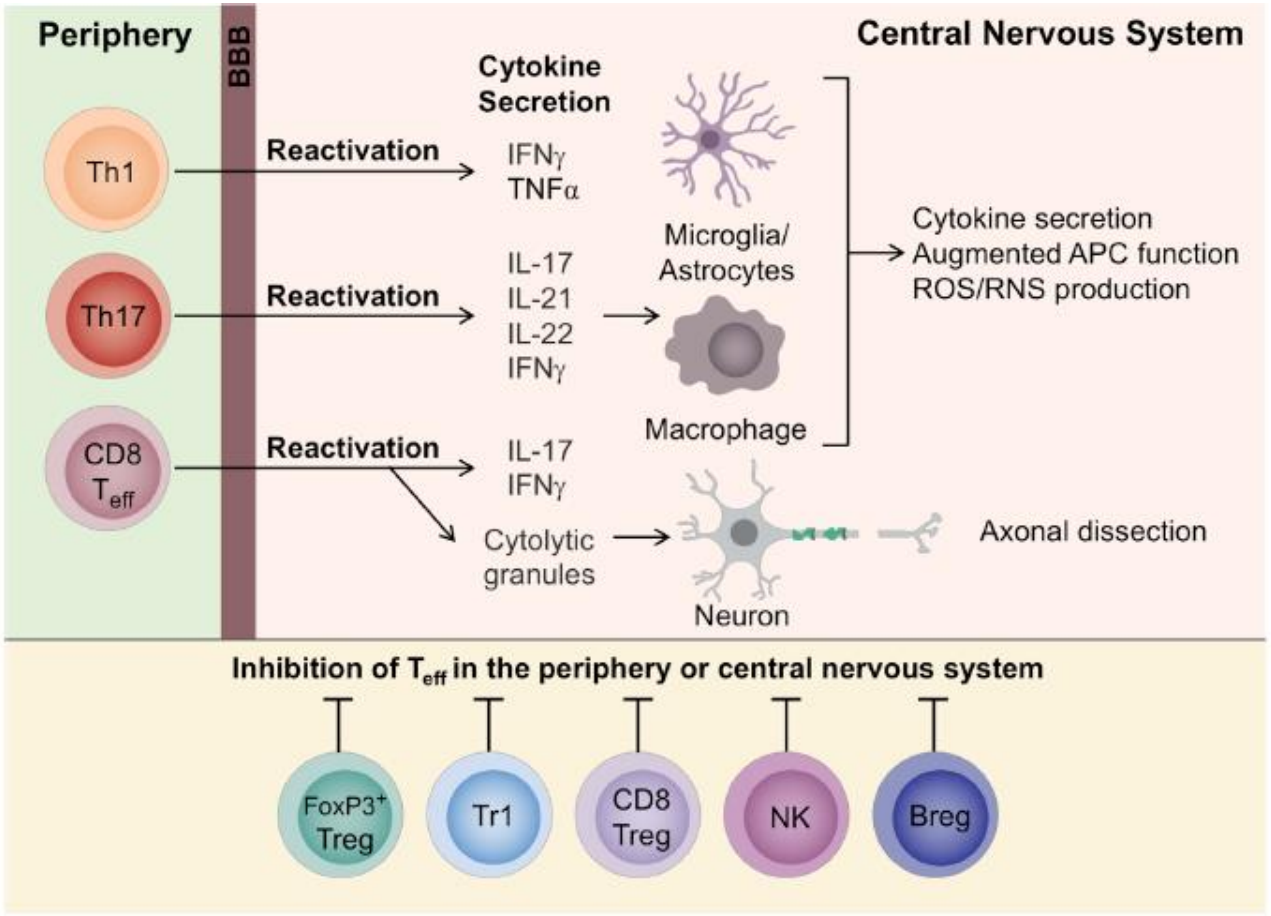
Figure 1. Systemic regulation of neutrophil production and function by the microbiota.

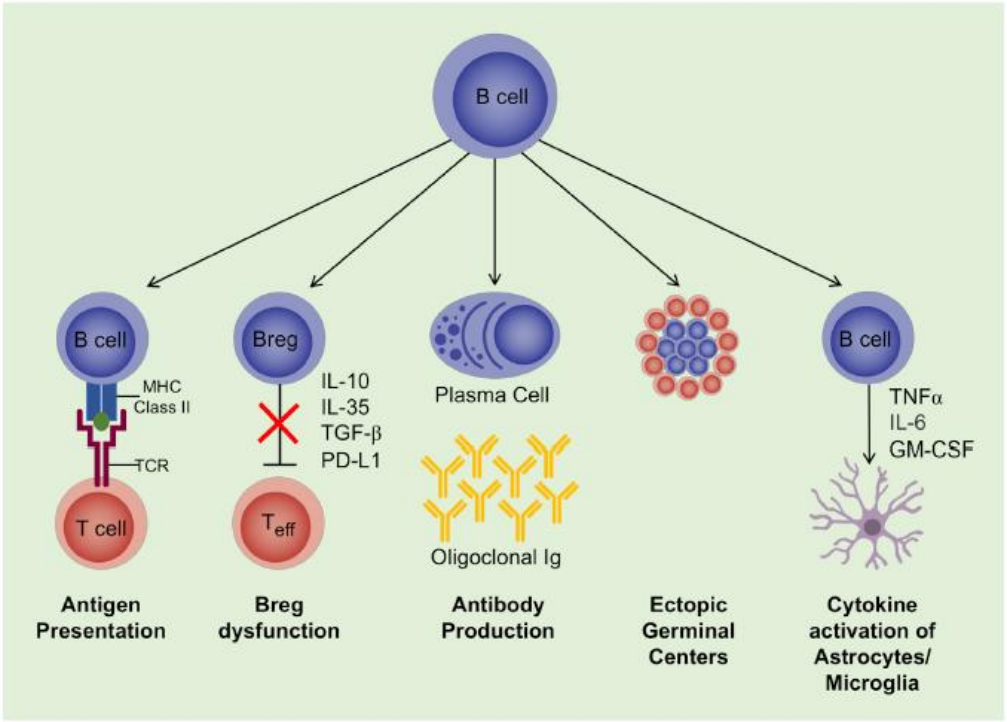


Gut Microbiome plays a major role in preventing Autoimmunity

Clarke TB (2014) Microbial Programming of Systemic Innate Immunity and Resistance to Infection. PLOS Pathogens 10(12): e1004506. https://doi.org/10.1371/journal.ppat.1004506
https://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1004506

MS: Primed Immune system activates Autoimmunity in the Brain





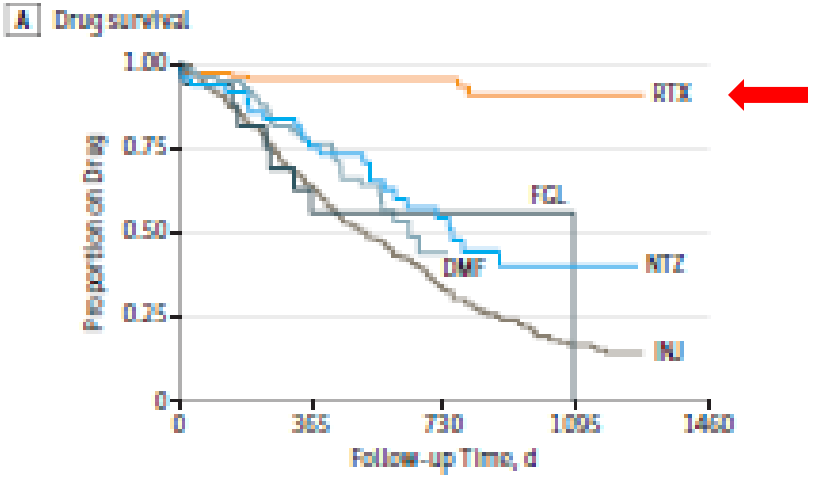
Activated T cells cross BBB into the CNS and induce inflammation along with resident CNS immune cells.

MS lesions contain CD8+ T cells, which are mostly found at the edges of lesions, and CD4+ T cells, which are found deep in the lesions.

Baecher-Allan et al. Neuron. 2018. PMID: 29470968.

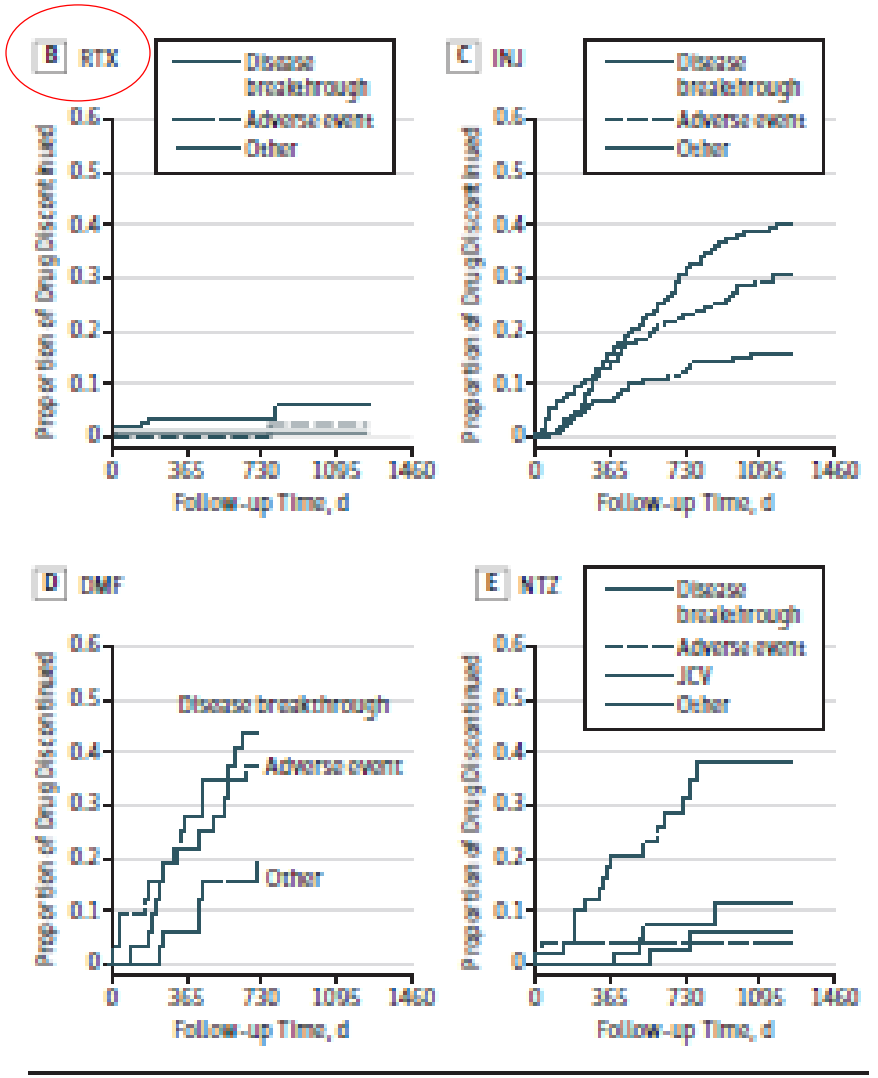
Evidence from Therapeutics that Multiple Sclerosis in an Autoimmune Disease and responds to Immunomodulation

Figure 2. Drug Survival and Reasons for Therapy Discontinuation for Treatment Groups



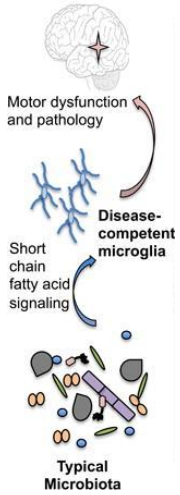
No. at risk (discontinued)

RTX	120 (2)	91 (5)	44 (5)	16 (7)
INJ	215 (0)	131 (78)	62 (138)	23 (167)
DMF	86 (0)	54 (19)	1 (32)	0 (32)
FGL	17 (0)	8 (7)	4 (7)	0 (8)
NTZ	50 (1)	35 (12)	17 (20)	8 (24)

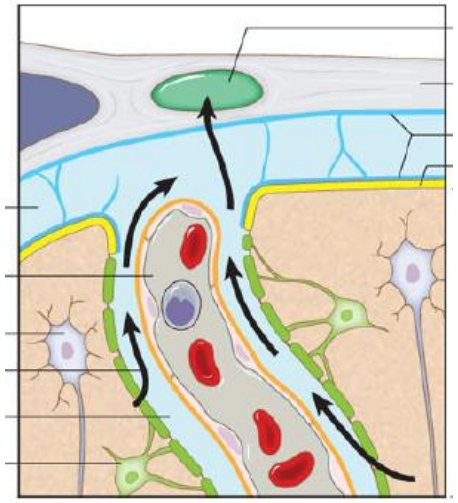


Granqvist et al. JAMA Neurol. 2018. PMID: 29309484

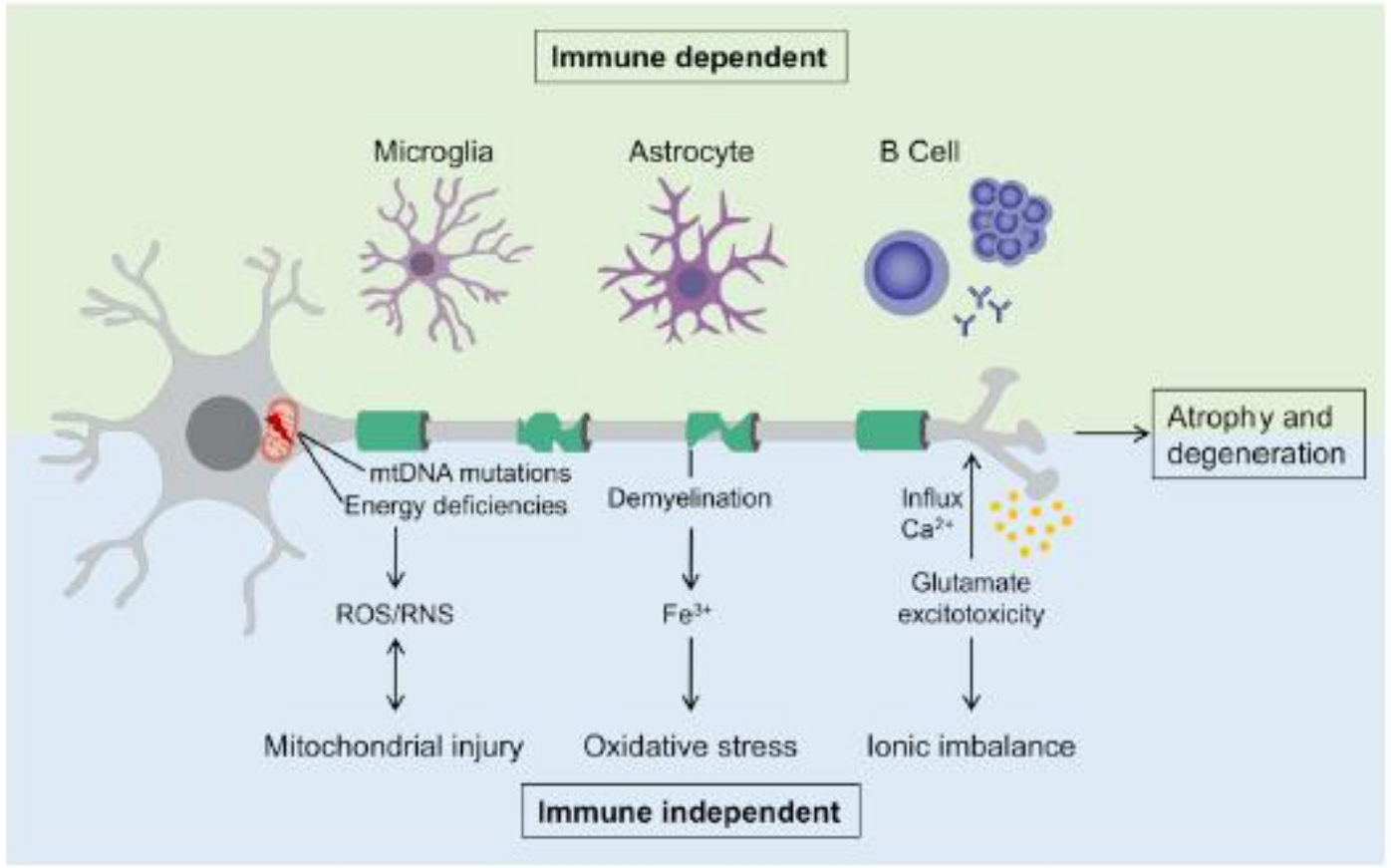
Summary: Multiple Sclerosis Pathogenesis



Environmental Trigger
Gut Microbiome
Viral Infection



Primed B and T cells enter the CNS through Dural Lymphatics



Immune mediated demyelination, oligodendrocyte destruction and axonal damage

Multiple Sclerosis Pathogenesis

This presentation is dedicated to the loving memory of Ms. Shoukat Khan President of the first MS Patient's Society of Pakistan who fought Multiple sclerosis with her unfading smile for 30 years.

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