Introduction to Multiple Sclerosis and other Neuroimmunological Disorders

Le Hua, MD
Eric and Sheila Samson Chair for MS Research
Director, Mellen Program for Multiple Sclerosis
Cleveland Clinic Lou Ruvo Center for Brain Health

Disclosures

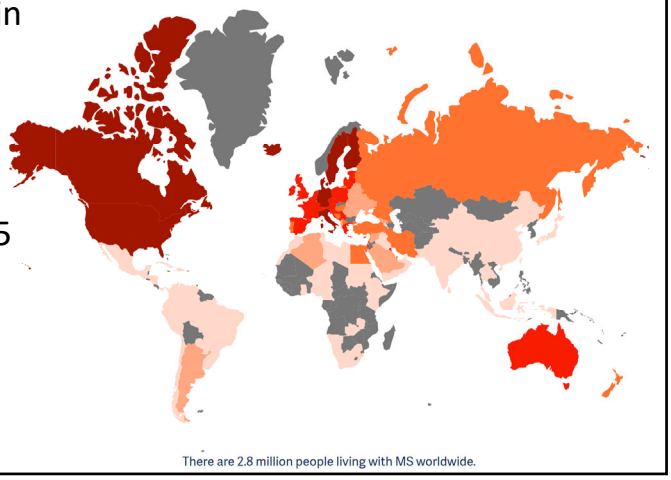
- Speaking, consulting, advisory board activities from Biogen, Genzyme, Novartis, Genentech, Bristol Myers Squibb, and EMD Serono

Objectives

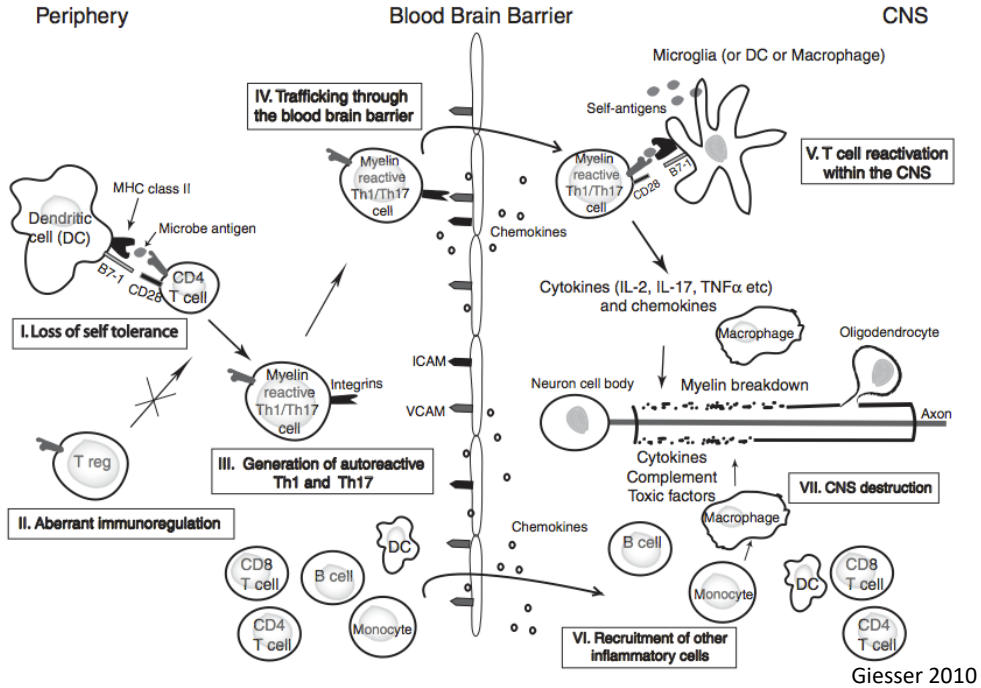
- Brief introduction to MS and how this disorder leads to dysfunction in multiple systems
- Brief introduction to other neuroimmunological disorders and their multiple system manifestations

Multiple Sclerosis

- Autoimmune demyelinating disease of the CNS
- Almost 1 million people with MS in the US
- Leading cause of non-traumatic disability in young adults
- Starts age 20-40s
- Progressive disability by age 45-55
- Minorities have worse disease
- 3:1 Female:Male



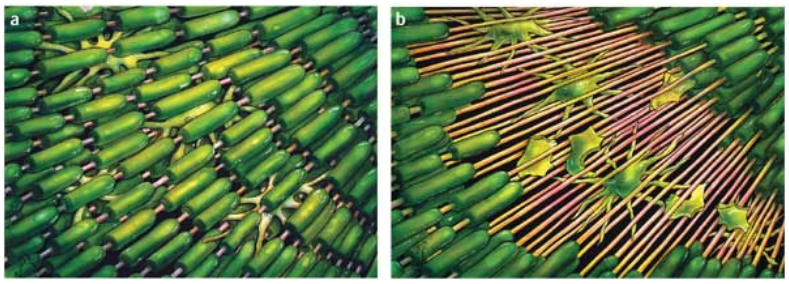
Atlas of MS 2020



Giesser 2010

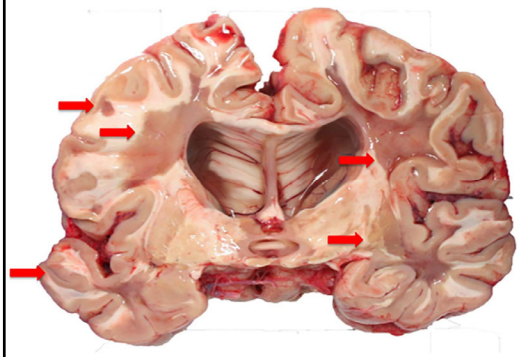
Demyelination

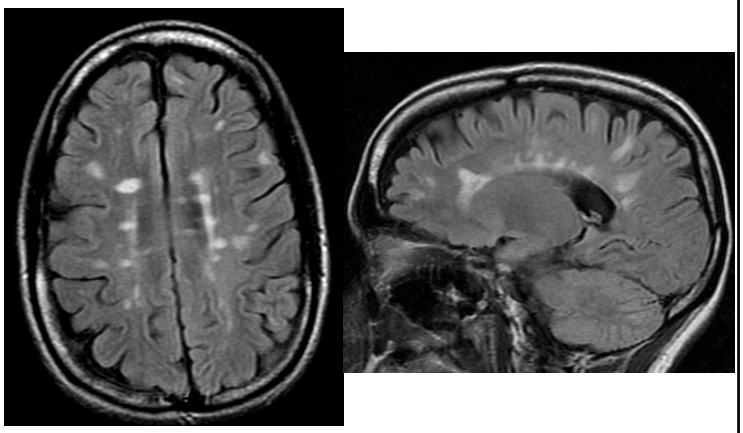
Causes slowing or blocking of conduction, alters the function of neurons.



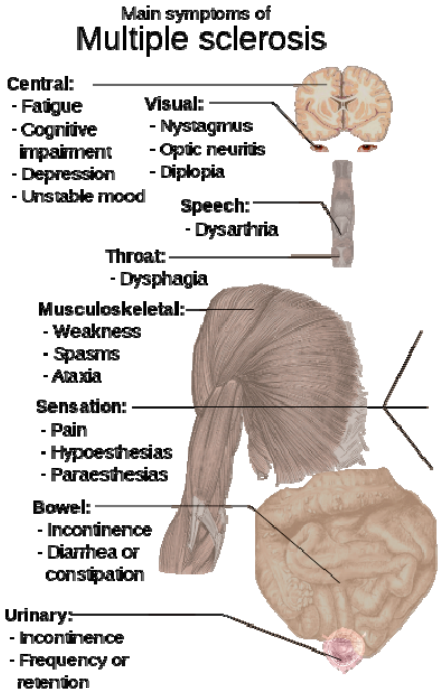
Sheridan 2004

Demyelinating Lesions: Gross Pathology and MRI



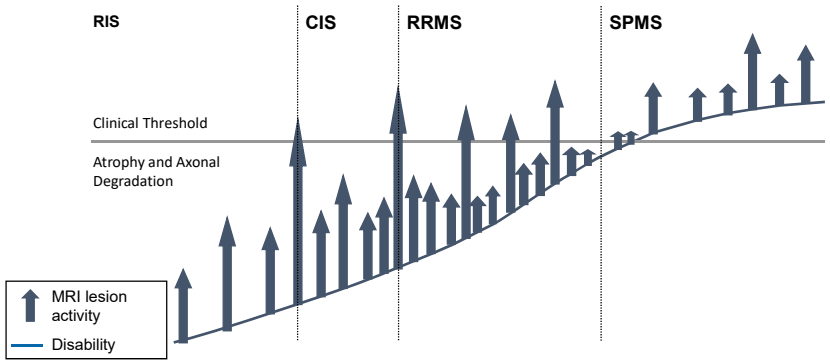


Matthews et al, 2016



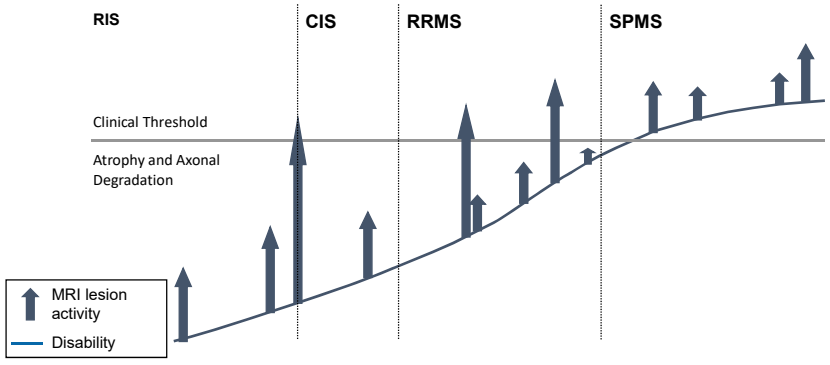
Häggström 2009

Natural History of MS

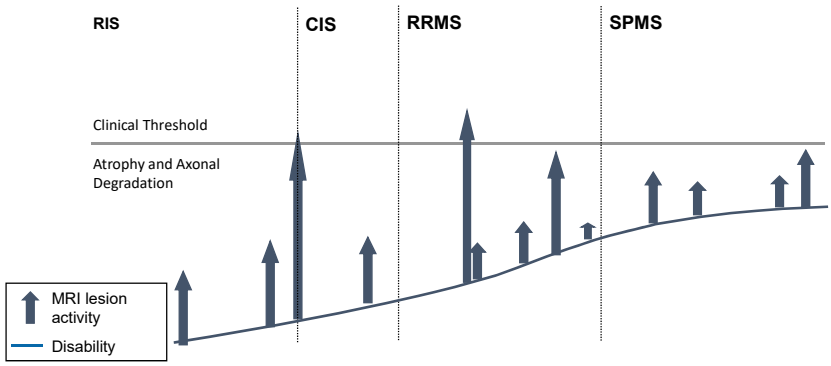


Comi 2006, Kobelt 2006

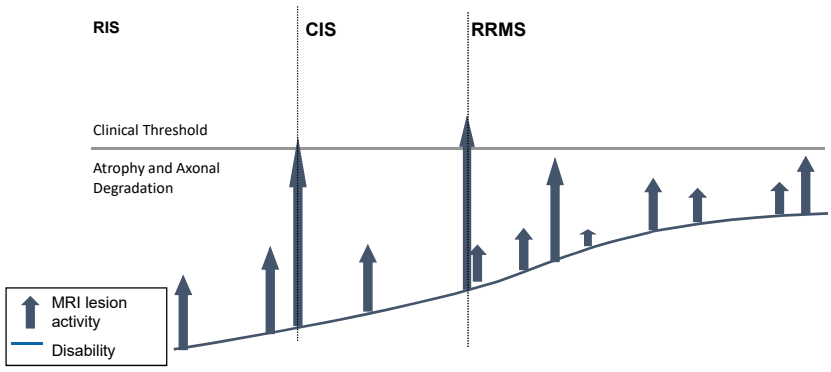
New Natural History of MS?



New Natural History of MS?



New Natural History of MS?

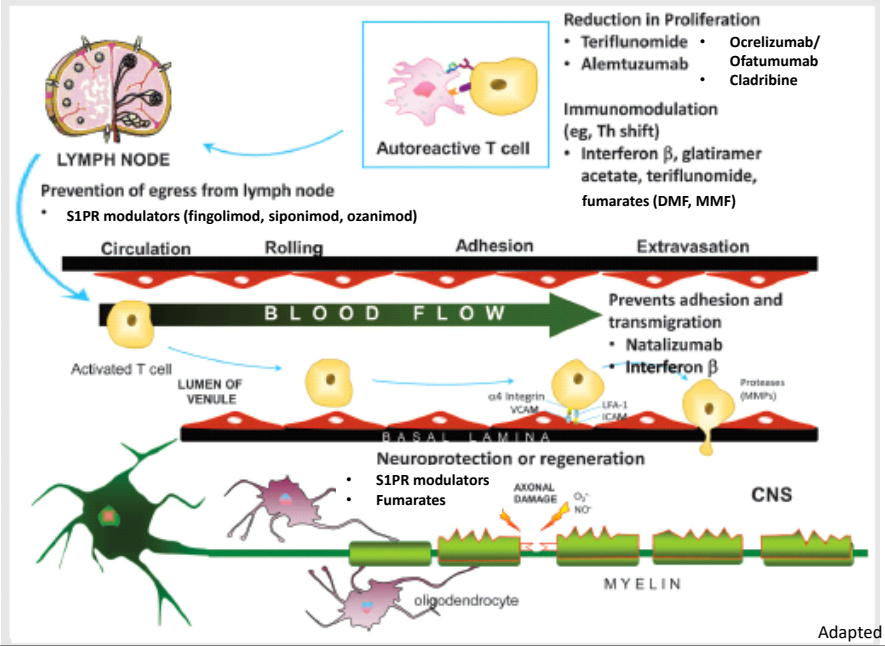


FDA Approved Disease Modifying Treatments

- interferon-β-1b (BETASERON, EXTAVIA) – 1993, 2009
- interferon-β-1a (AVONEX) – 1996
- glatiramer acetate (COPAXONE, COPAXONE 40) – 1996, 2014
  - *Generic formulations available – 2015, 2017*
- mitoxantrone (NOVANTRONE) – 2000*
- interferon-β-1a (REBIF) – 2002
- natalizumab (TYSABRI) – 2004, 2006
- fingolimod (GILENYA) – 2010
- teriflunomide (AUBAGIO) – 2012
- dimethyl fumarate (TECFIDERA) – 2013
  - *Generic formulation available - 2020*
- PEGylated Interferon β-1a (PLEGRIDY) – 2014
- alemtuzumab (LEMTRADA) – 2014
- ~~daclizumab (ZINBRYTA) – 2016 – removed from market~~
- ocrelizumab (OCREVUS) – 2017 **
- siponimod (MAYZENT) – 2019
- cladribine (MAVENCLAD) – 2019
- diroximel fumarate (VUMERITY) -2019
- ozanimod (ZEPOSIA) – 2020
- ofatumumab (KESIMPTA) – 2020
- monomethyl fumarate (BAFIERTAM) - 2020

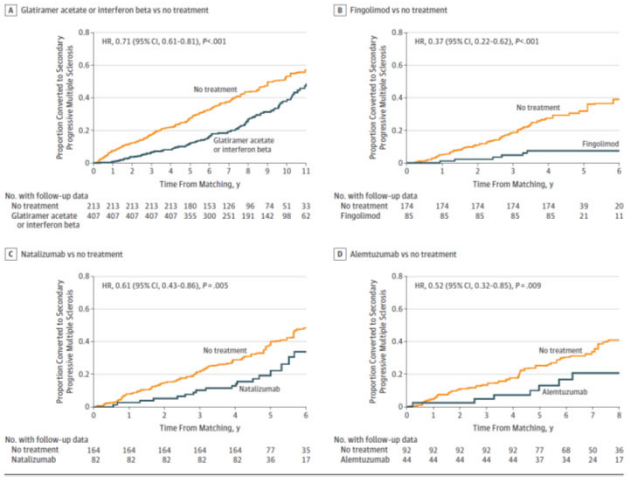
*also approved for secondary progressive MS, progressive relapsing MS
**also approved for primary progressive MS

How DMTs work

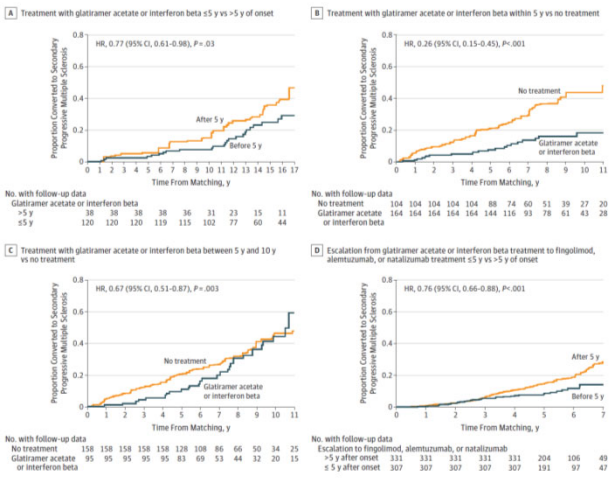


Adapted from Freedman 2013

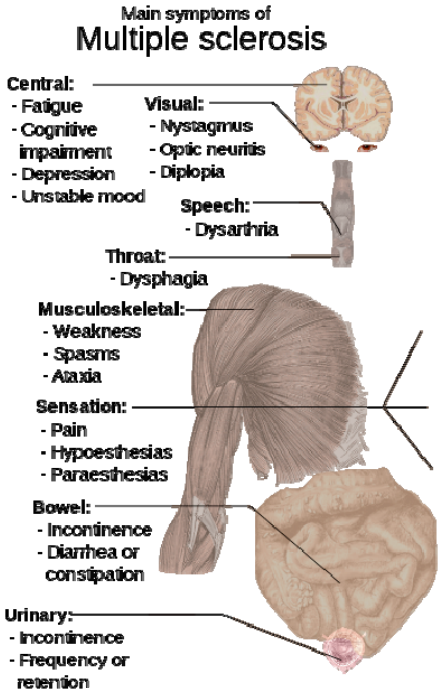
Impact of DMT on Reducing Disability



Impact of Early Treatment, <5 vs >5 years



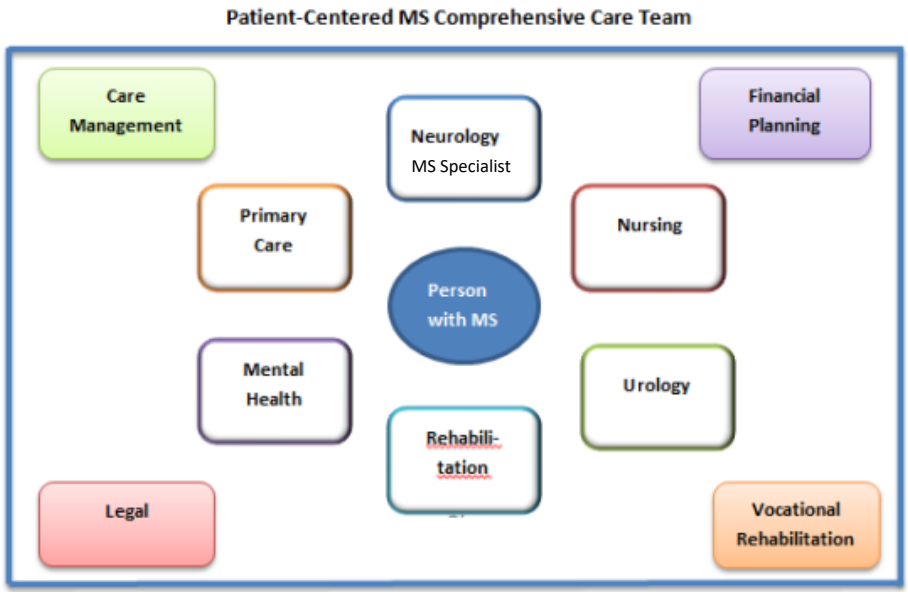
Brown et al, 2019



Häggström 2009

Symptoms

- Depression/Anxiety/Other psychiatric disorders – up to 50% depression
- Pain/Spasticity – up to 86% report pain, 70-80% report spasticity
- Urinary difficulties – 70%
- Sexual Dysfunction – 50-90% men, 40-85% women
- Bowel difficulties- 39-73%
- Gait difficulty/Limited mobility – 64% with trouble walking
- Tremor – up to 80%
- Cognitive Difficulties – 40-70%
- Sleep/Fatigue – 70-90% report fatigue
- Vision symptoms/eye movement abnormalities



Differentiating MS or not

- Everything blamed on MS but NOT everything is due to MS
- If not classic neurological symptoms, then need to find other causes
- If progression of symptoms not as expected, then need to find other causes
    - Stable patient on disease modifying therapy
    - Worsening despite treatment

Differentiating MS or not

- Pain – low back pain, headache
- Sensory disturbances – radiculopathies, compression neuropathy
- Vertigo – BPPV
- Blurry vision – refractory errors
- Insomnia
- Regardless of cause- treat symptoms

Symptomatic Treatments

- Walking – dalfampridine
  - Strength, endurance, fatigue, heat intolerance, vision
- Spasticity – baclofen, tizanidine, BZD, botulinum toxin
- Neuropathic pain – gabapentin, pregabalin, TCAs, duloxetine, lidocaine patch, capsaicin
- Fatigue – amantadine, modafinil, armodafinil
  - *off label
- Cognition – donepezil, memantine
- Bladder – oxybutynin, tolterodine tartrate, tamsulosin, botulinum toxin
- Depression/Anxiety – SSRIs, SNRIs, TCAs
- Insomnia – sleep study, hygiene, melatonin
- Nutrition, Exercise, Physical and Occupational Therapy, CBT/mindfulness

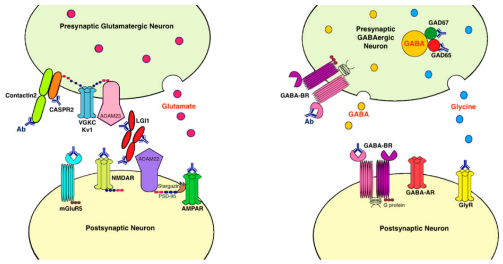
Comorbidities

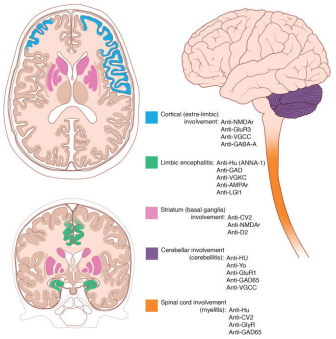
TABLE 9-1 Common Comorbidities and Their Impact on the Diagnosis and Disease Course of Multiple Sclerosis

Comorbidity	Increases the Risk of Developing Clinically Isolated Syndrome/ Multiple Sclerosis	Increases the Risk of Diagnostic Delay	Increases the Risk of Multiple Sclerosis Relapse	Increases the Risk of Disability
Depression		X		X
Anxiety		X		X
Hypertension		X		X
Migraine			X	
Hyperlipidemia			X	
Ischemic heart disease		X		X
Cerebrovascular disease		X		X
Obesity	X	X		X
Multimorbidity (≥3 comorbidities)		X	X	X

Tobin 2019

Autoimmune Encephalitis





Radiologykey.com 2019; McKeon 2020; Kao et al 2021

Table 1. Classic Antibody Biomarkers of Autoimmune Encephalitis.

Name/antigen	Main neurological presentation	Main oncological associations
Synaptic specificities		
AMPAR	Encephalitis, seizures	Thymoma, SCLC, breast carcinoma
AQP4	Neuromyelitis optica, encephalitis in children (ADEM-like phenotype)	Breast carcinoma, thymoma, and others in elderly individuals
DPPX	Encephalitis with prominent dysautonomia with gastrointestinal hypermotility and psychiatric manifestations, myoclonus, rigidity, exaggerated "startle"	B cell neoplasia
$GABA_AR$	Encephalitis with prominent seizures	Thymoma, lymphoma
$GABA_BR$	Encephalitis with prominent seizures	SCLC, thymoma
Glycine receptor	Progressive encephalomyelitis with rigidity and myoclonus, stiff-person syndrome	Thymoma, lymphoma, Breast cancer
IgLON5	Sleep disorder (NREM and REM), and brain stem dysfunction	No cancer association
LGI1, Caspr2	Limbic encephalitis, faciobrachial dystonic and other seizures, peripheral nerve hyperexcitability, neuropathy	Thymoma
mGluR1	Cerebellar ataxia, brainstem encephalitis, dysgeusia	Hodgkin lymphoma
mGluR5	Limbic encephalitis	Hodgkin lymphoma
MOG	Optic neuritis, myelitis, acute disseminated encephalomyelitis	No cancer association
Neurexin 3a	Encephalitis, seizures	No cancer association
NMDAR	Psychosis, catatonia, seizures, encephalitis, dyskinesias, dysautonomia and hypoventilation	Ovarian teratoma
PCA-Tr (DNER)	Cerebellar ataxia, brainstem encephalitis	Hodgkin lymphoma
Cytoplasmic and nuclear specificities		
AK5	Limbic encephalitis, anxiety	No associated cancer
Amphiphysin	Encephalomyelopathy, stiff-man syndrome, neuropathy	Breast carcinoma, SCLC
ANNA-1 (Hu)	Encephalomyelitis, polyneuropathy and sensory neuronopathy, dysautonomia (with gastrointestinal dysmotility), ataxia	SCLC
ANNA-2 (Ri, Nova 1/ Nova2)	Opsoclonus myoclonus, jaw dystonia, laryngospasm, brainstem encephalitis	SCLC, breast carcinoma
ANNA-3	Encephalitis, polyneuropathy	SCLC
CRMP5	Encephalomyelitis, retinitis, chorea, radiculoplexopathy, cranial and other polyneuropathies	SCLC, thymoma
GAD65	Stiff-person syndrome, cerebellar ataxia, encephalitis (limbic and/or other) with predominant seizures, myelopathy	Rare
GRAF	Cerebellar ataxia and brainstem	Ovarian carcinoma
GFAP	Meningoencephalomyelitis, papilledema	Ovarian teratoma, diverse adenocarcinomas
ITPR1	Cerebellar ataxia, brainstem, neuropathy	Lung adenocarcinoma
KLHL11 (Kelch-like protein 11)	Brainstem encephalitis, cerebellar ataxia, accompanied by hearing loss	Seminoma, testicular germ cell tumors
Ma2	Limbic and brainstem encephalitis	Seminoma, testicular germ cell tumor
Neurochondrin	Brainstem encephalitis	No associated cancer
NIF, light chain	Cerebellar ataxia, encephalopathy, myelopathy	Neuroendocrine (SCLC, Merkel cell carcinoma)
PCA-1 (Yo)	Cerebellar ataxia, neuropathy (rare)	Mullerian tumors
PCA-2 (MAP1B)	Encephalitis, cerebellar ataxia, peripheral neuropathy	SCLC
PDE10A	Encephalopathy, movement disorders	Renal cell and lung adenocarcinoma
Septin 5	Cerebellar ataxia with brainstem encephalitis and predominant oculomotor deficits	No associated cancer

AK5: adenylate kinase 5; AMPAR: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; ANNA: anti-neuronal nuclear antibody; AQP4: aquaporin-4; Caspr2: contactin-associated protein-2; CRMP: collapsin response-mediator protein; DPPX: dipeptidyl-peptidase–like protein-6; GABA: γ-aminobutyric acid; GAD: glutamic acid decarboxylase; GFAP: glial fibrillary acidic protein; GRAF1: GTPase regulator associated with focal adhesion kinase 1; ITPR1: inositol 1,4,5-trisphosphate receptor type 1; LGI1: leucine-rich, glioma inactivated 1 protein; mGluR: metabotropic glutamate receptor; MAP1B: microtubule-associated protein 1B; MOG: myelin oligodendrocyte glycoprotein; NIF: neuronal intermediate filaments; NREM: non-rapid eye movement; NMDAR: N-methyl-d-aspartate receptor; PCA: Purkinje cell cytoplasmic antibody; REM: rapid eye movement; SCLC: small-cell lung carcinoma.

Conclusions

- Multiple Sclerosis – autoimmune neurodegenerative disease of CNS targeting myelin
- Other neuroimmunological disorders – autoimmune targets to CNS or PNS
- Multiple system manifestations
  - Symptoms will depend on neuroanatomical involvement