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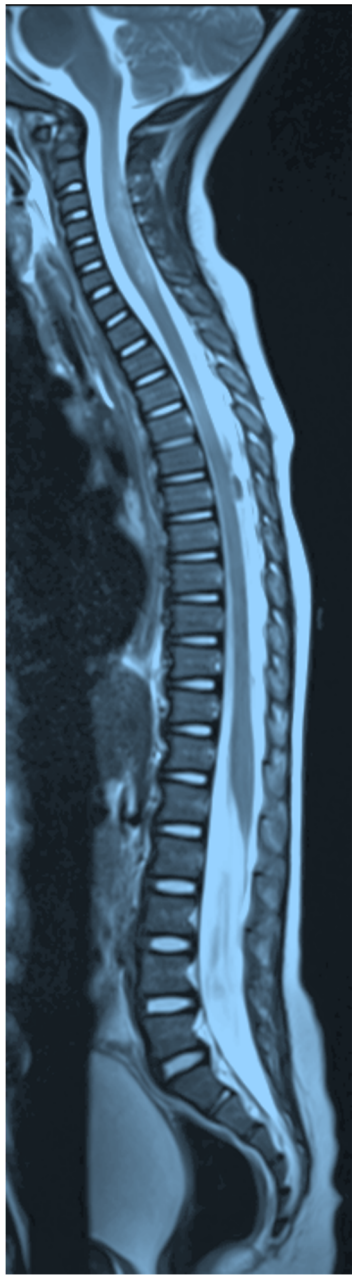
~~Transverse~~ Myelitis: What it is …and what is not…

Carlos A. Pardo, MD
Johns Hopkins Myelitis and Myelopathy Center



Johns Hopkins Myelitis & Myelopathy Center

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Our Team at JH Myelitis and Myelopathy Center

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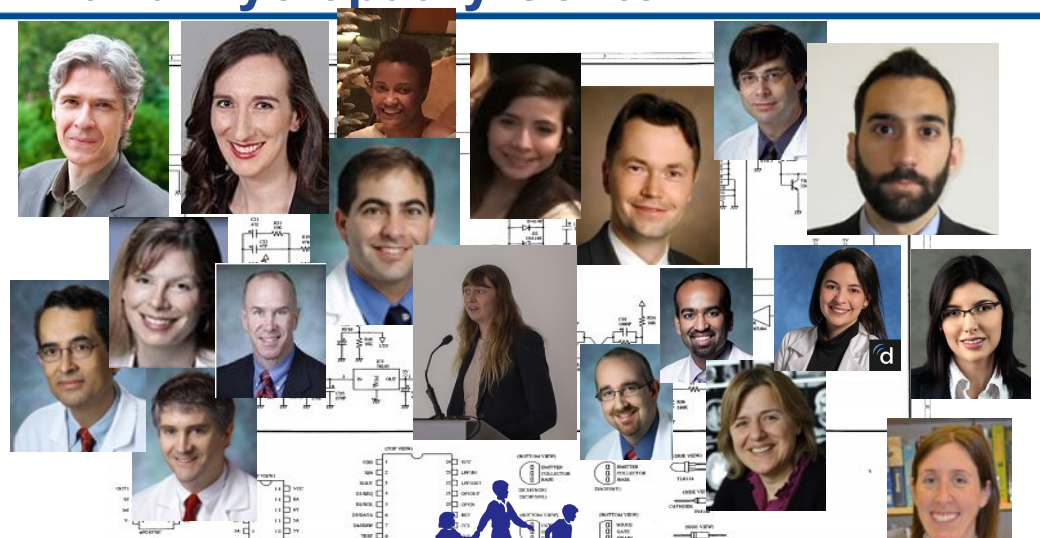

Our collaborators at

Kennedy Krieger Institute

JOHNS HOPKINS
TRANSVERSE MYELITIS
CENTER

The Johns Hopkins
PROJECT RESTORE
Restoring hope, function, and lives to MS & TM patients

THE TRANSVERSE MYELITIS ASSOCIATION

SRNA
connect. care. cure.
Siegel
Rare Neuroimmune
Association

Bart McLean Fund for Neuroimmunology Research

Objectives

- To understand the concepts of myelopathy vs. myelitis
- To discuss the diagnostic approach for the diagnosis of acute myelopathies and myelitis.
- To review the evolving concepts of myelopathies and their differential diagnosis
- **…and to convince you to abandon the diagnosis of transverse myelitis and adopt a etiological diagnosis**

Transverse Myelitis: A historical perpective

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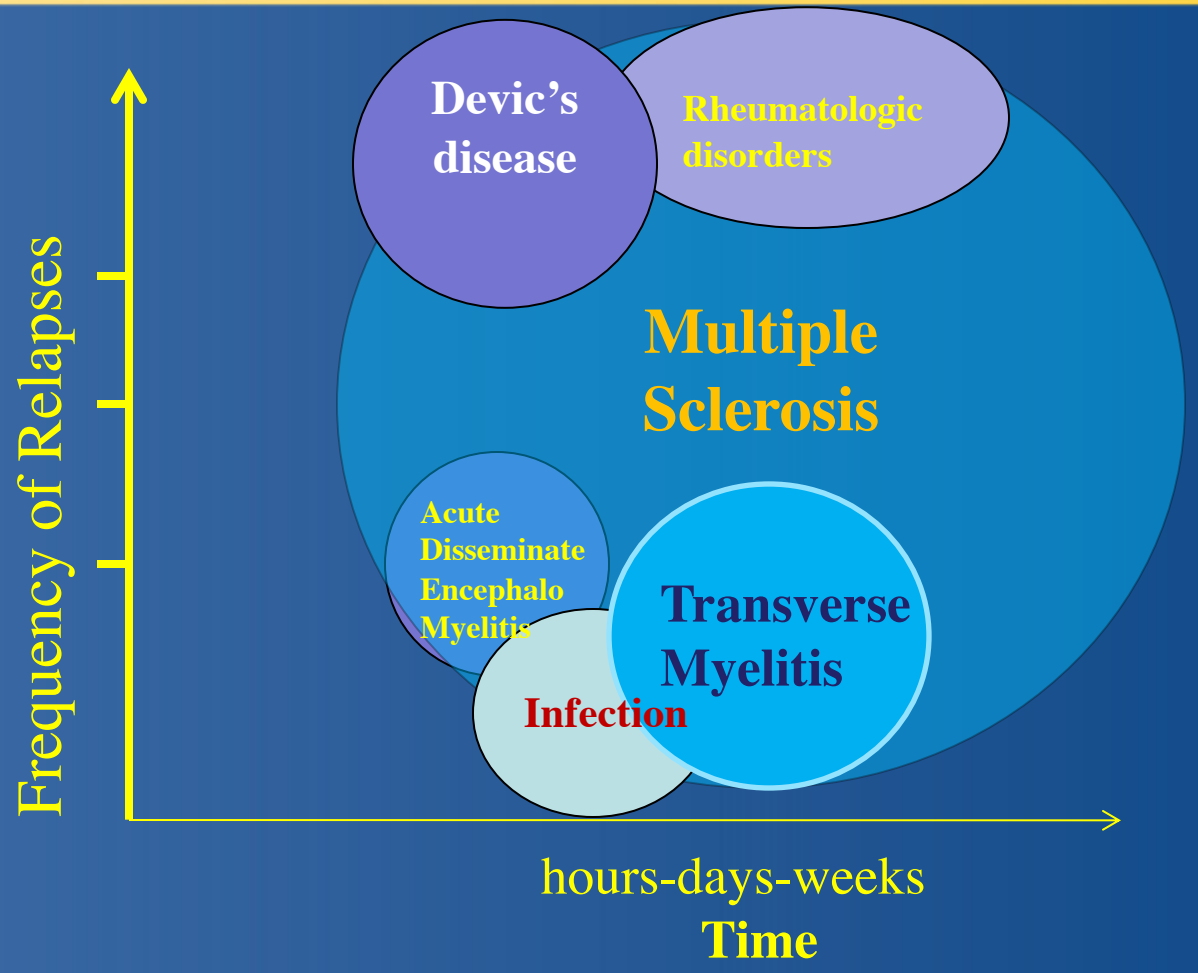
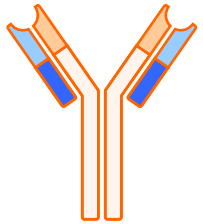
Back in the 90's

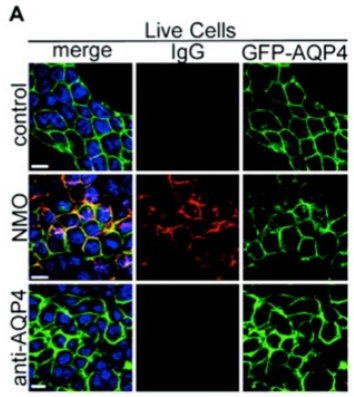


A Major Break on Understanding Myelitis: Finding NMO

A pathogenic antibody model of NMO



NMO-IgG

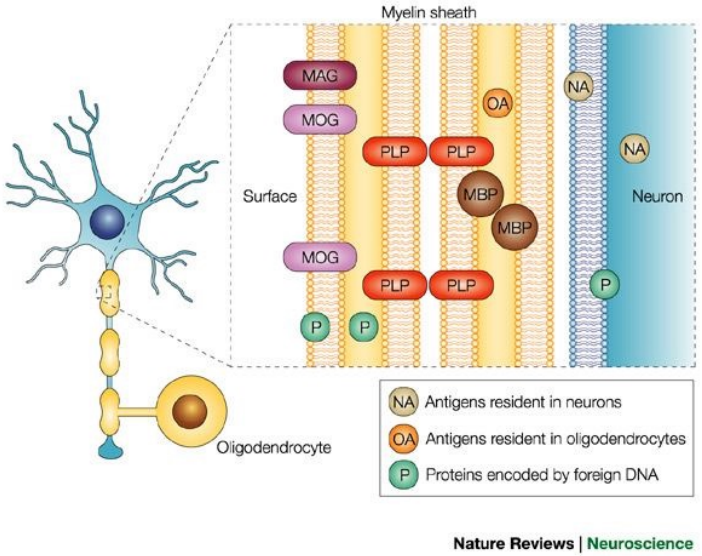


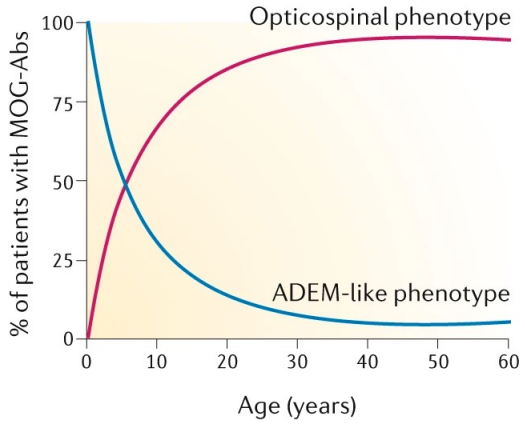
Aquaporin-4

1. ~~Transverse~~ **Myelitis**
   a) Longitudinally extensive (> 3 vertebral segments)
   b) CSF pleocytosis > 50 WBC/mm3
   c) Recurrence
2. **Optic neuritis**
   a) Bilateral
   b) Recurrent
3. **Not multiple sclerosis**
   a) MRI brain – no “symptomatic” lesions
   b) NMO-IgG seropositivity
   c) No CSF oligoclonal bands

Hinson, S. R. et al. Neurology 2007;69:2221-2231

Rediscovery of Myelin Oligodendrocyte Glycoprotein (MOG) as Pathogenic Target in Neuroinflammatory Disease





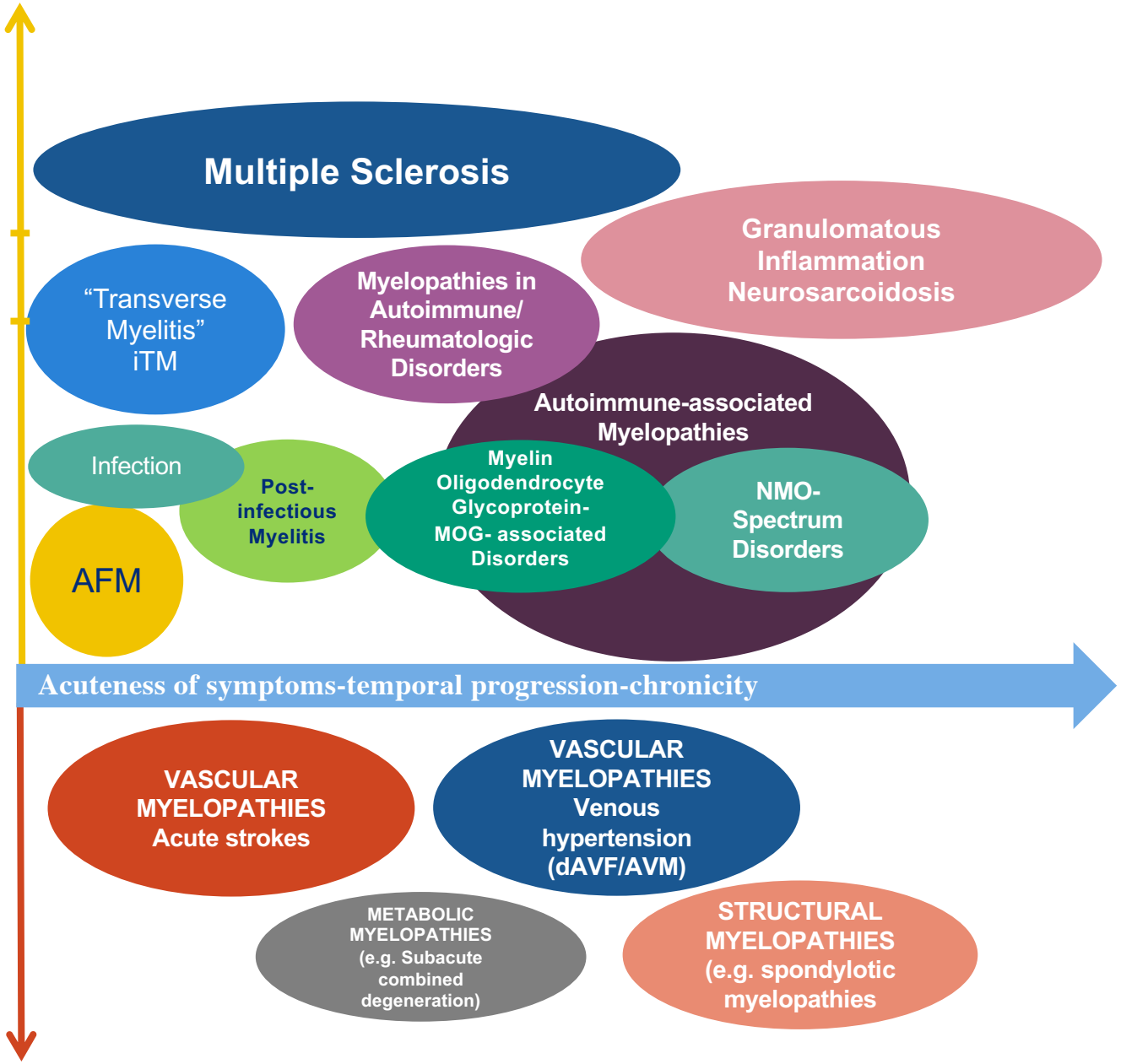
MOG-antibody associated disease

- More often in childhood than adulthood
- Frequently monophasic (recurrent when present with optic neuritis)
- Brain lesions look “fluffy” and spinal cord lesions are longitudinal extensive
- Bilateral optic neuritis and chiasm involvement
- CSF: Pleocytosis, rare OCBs

The spectrum of Myelopathies in 2021

Inflammatory Myelopathies Aka “myelitis”

Non-Inflammatory Myelopathies



Why we are still using the term Transverse Myelitis?

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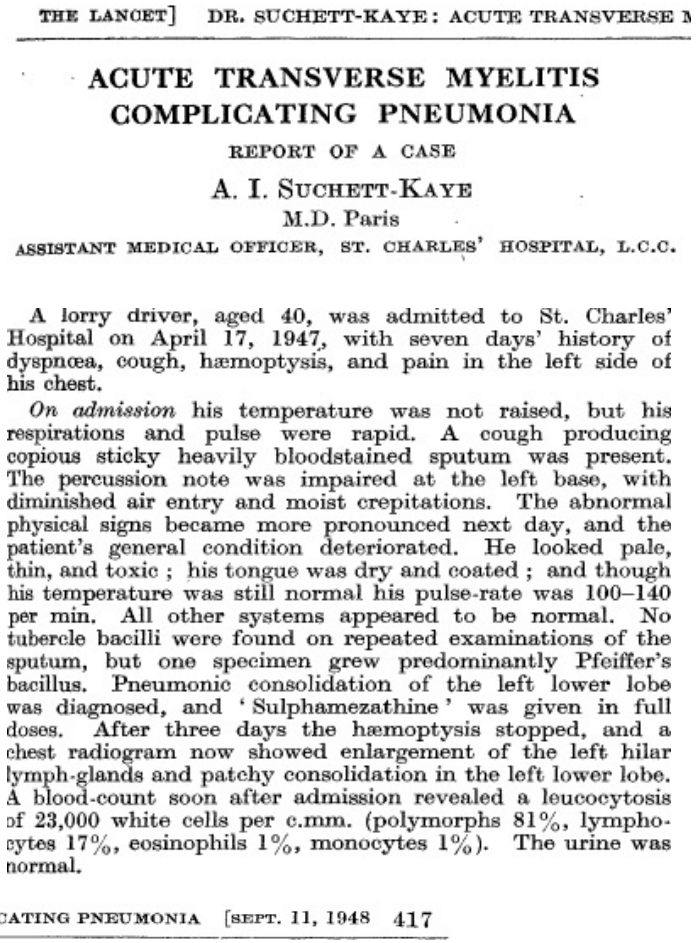
Term Origin

"Acute Myelitis"

- H.C. Bastian: Special diseases of the spinal cord. 1, 1479-1483 (1882)

"Infectious Myelitis"

- T.M. Rivers: Viruses. *JAMA* 92, 1147-1152 (1929)
  - F.R. Ford: The nervous complications of measles: with a summary of literature and publications of 12 additional case reports. *Bulletin of Johns Hopkins Hospital* 43, 140-184 (1928)



THE LANCET] DR. SUCHETT-KAYE: ACUTE TRANSVERSE M

ACUTE TRANSVERSE MYELITIS COMPLICATING PNEUMONIA

REPORT OF A CASE

A. I. SUCHETT-KAYE
M.D. Paris
ASSISTANT MEDICAL OFFICER, ST. CHARLES' HOSPITAL, L.C.C.

A lorry driver, aged 40, was admitted to St. Charles' Hospital on April 17, 1947, with seven days' history of dyspnœa, cough, hæmoptysis, and pain in the left side of his chest.

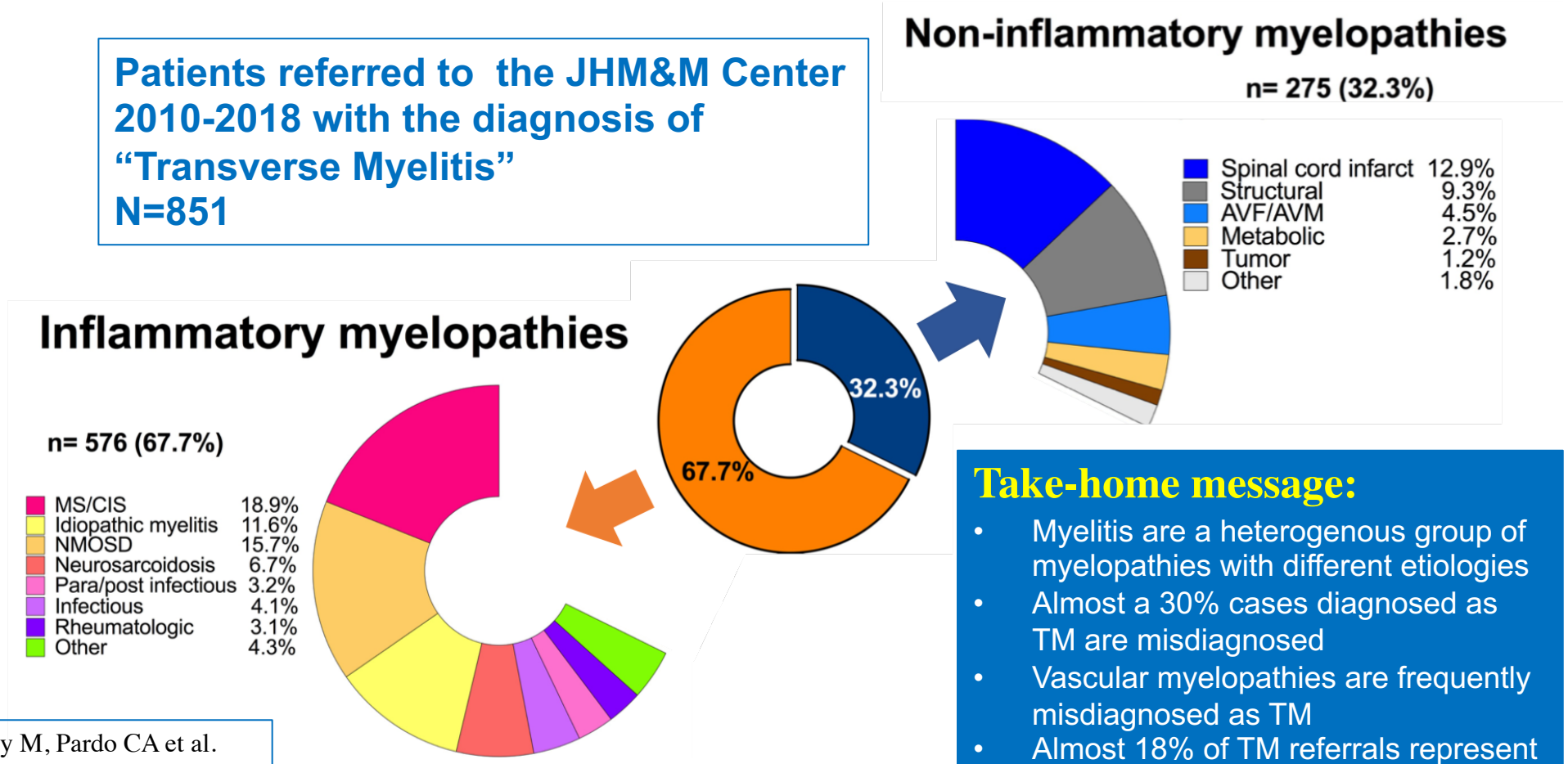
On admission his temperature was not raised, but his respirations and pulse were rapid. A cough producing copious sticky heavily bloodstained sputum was present. The percussion note was impaired at the left base, with diminished air entry and moist crepitations. The abnormal physical signs became more pronounced next day, and the patient's general condition deteriorated. He looked pale, thin, and toxic; his tongue was dry and coated; and though his temperature was still normal his pulse-rate was 100–140 per min. All other systems appeared to be normal. No tubercle bacilli were found on repeated examinations of the sputum, but one specimen grew predominantly Pfeiffer's bacillus. Pneumonic consolidation of the left lower lobe was diagnosed, and 'Sulphamezathine' was given in full doses. After three days the hæmoptysis stopped, and a chest radiogram now showed enlargement of the left hilar lymph-glands and patchy consolidation in the left lower lobe. A blood-count soon after admission revealed a leucocytosis of 23,000 white cells per c.mm. (polymorphs 81%, lymphocytes 17%, eosinophils 1%, monocytes 1%). The urine was normal.

Should we continue using the diagnosis of transverse myelitis?

Why is it important to determine etiological diagnosis??

No everything the glitters in the spinal cord is transverse myelitis!!

Patients referred to the JHM&M Center 2010-2018 with the diagnosis of "Transverse Myelitis"
N=851

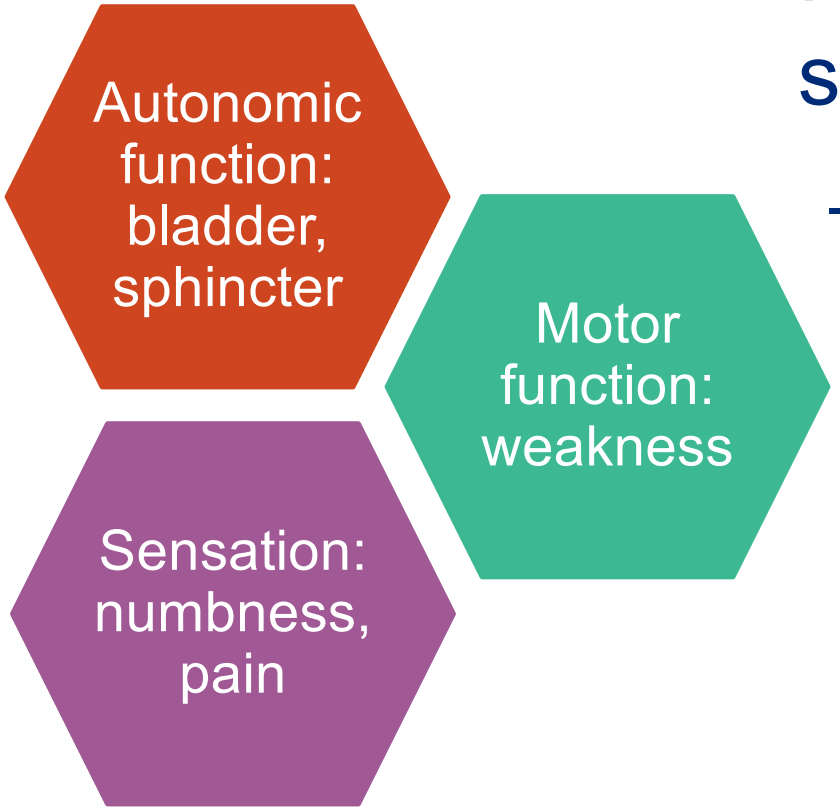


Take-home message:

- Myelitis are a heterogenous group of myelopathies with different etiologies
- Almost a 30% cases diagnosed as TM are misdiagnosed
- Vascular myelopathies are frequently misdiagnosed as TM
- Almost 18% of TM referrals represent vascular etiologies

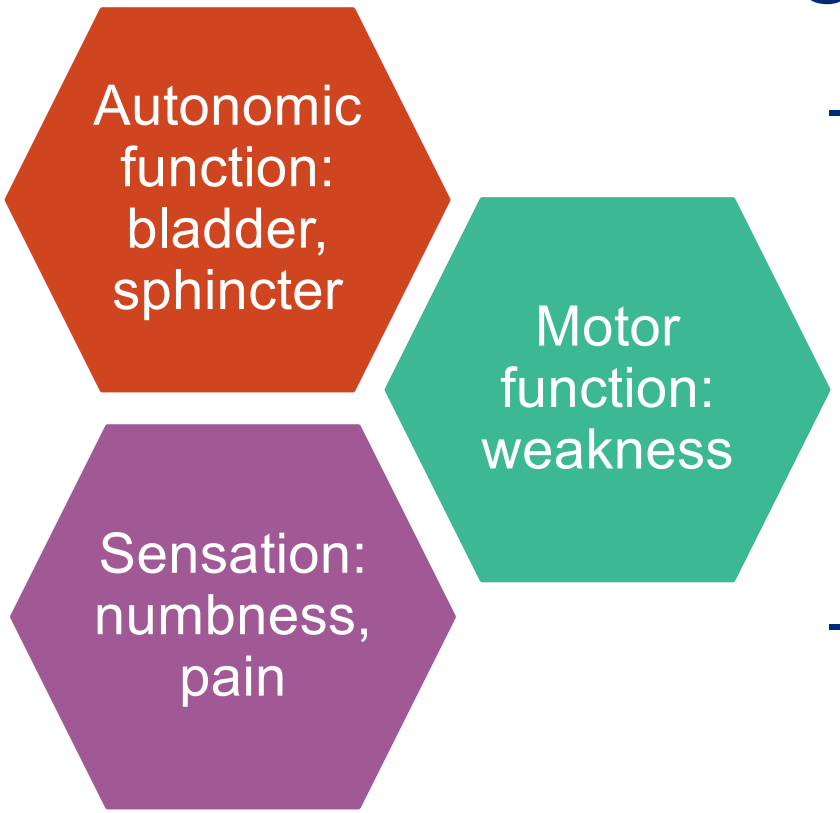
Murphy O, Mealy M, Pardo CA et al. JHM&M Center 2019, unpublished

Multiple Faces of Myelopathies & Myelitis: A Clinical Problem



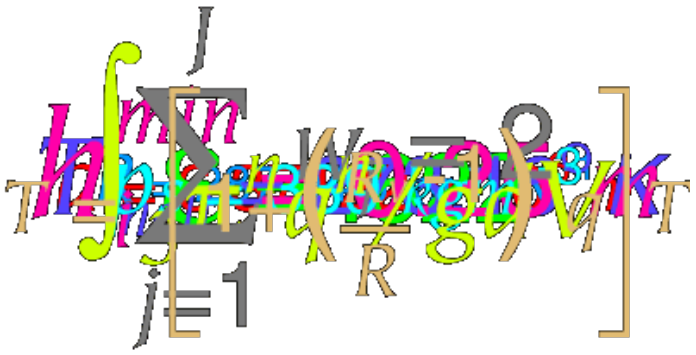
- First steps in the evaluation os suspected myelopathies:
  - Recognize the symptoms of myelopathy:
    - Weakness
    - Sensory problems, numbness, tingling, “banding sensation”
    - Bladder incontinency, increase urinary frequency
    - Gait disturbances, unsteadiness

Multiple Faces of Myelopathies & Myelitis: A Clinical Problem

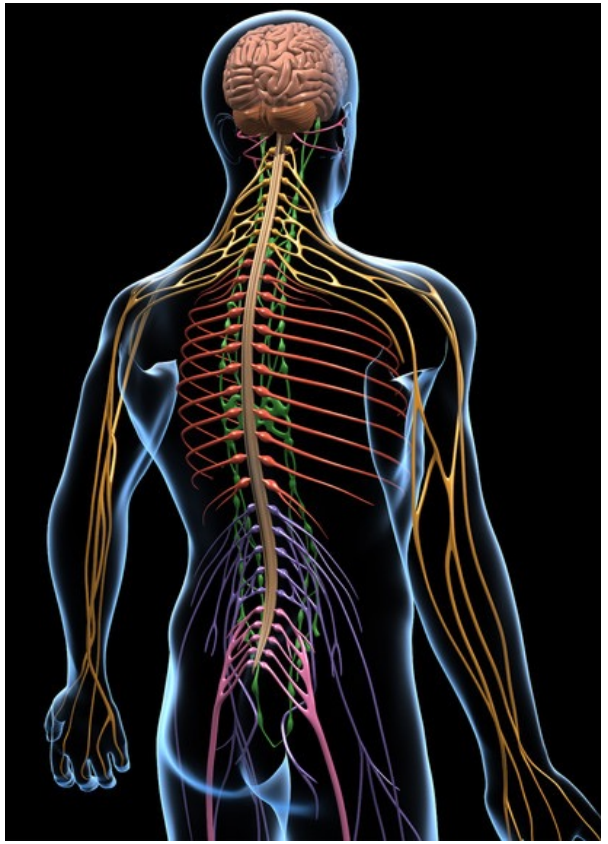


- Second steps in the evaluation:
  - Identify the time-profile, onset and evolution of the symptoms:
    - Hyperacute onset, minutes, few hours
    - Acute: day to few days
    - Subacute: several days
    - Chronic: several weeks and months
  - **Did the symptoms plateau or keep evolving?**

Equations of Spinal Cord Disorders



$$\sum_{i=1}^{N} X_i = X_1 + X_2 + \ldots + X_N$$



Host

Lesion Location

Temporal Profile

Etiology

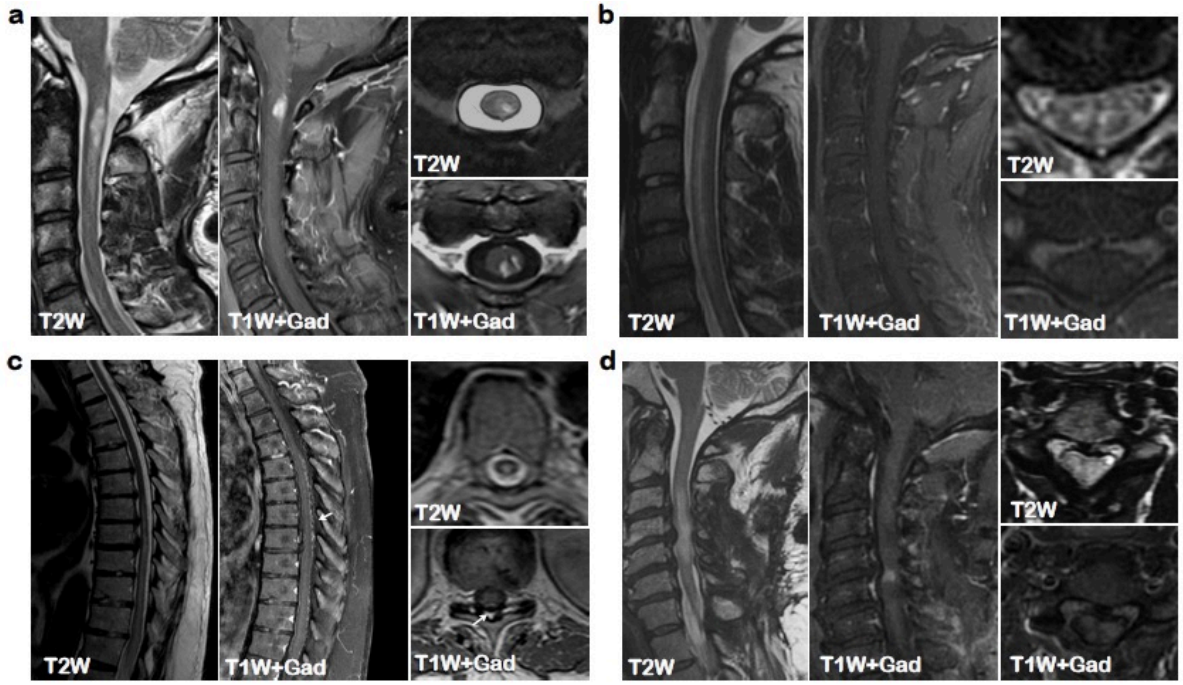
$$\text{Myelopathy} = \sum_{Time\ profile}^{age} * \ lesion\ location \begin{pmatrix} white\ matter \\ gray\ matter \end{pmatrix} extension\ x^k a^{n-k}$$

Myelitis? Vascular Myelopathy? How to differentiate them?

- Temporal Profile (Clinical History)
- Localization (History & Examination)
- Localization and extension of the lesion(s) (Examination & MRI)
- **Characteristics of the lesion: inflammation vs. vascular (MRI, CSF, spinal angiogram)**

Spinal Cord MRI

- Assessment of lesion(s), patterns of distribution and enhancement
- Patterns of MRI spinal cord lesions help to establish a diagnosis of myelopathies



Clues a spinal cord MRI may provide for diagnosis:

- Pattern of involvement
  - Gray vs. white matter
  - Focal vs. multifocal
  - Longitudinal extensive vs. tumefactive
- Enhancement
  - Focal, peripheral, central, extensive
  - Meningeal
  - Root enhancement

BRAIN MRI

- Lesion(s) present
- Enhanced lesions

CSF Analysis in Myelopathies

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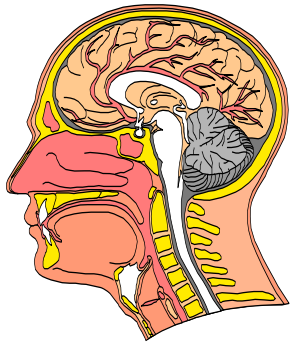
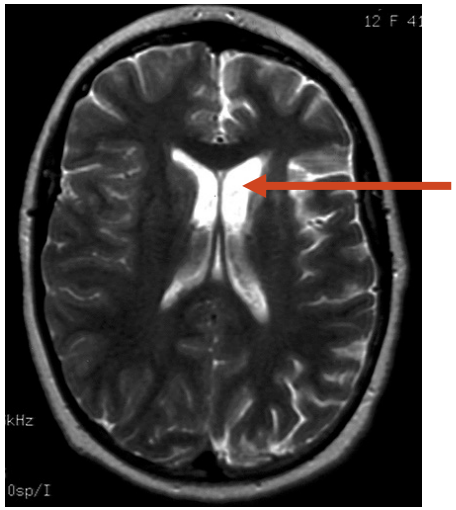
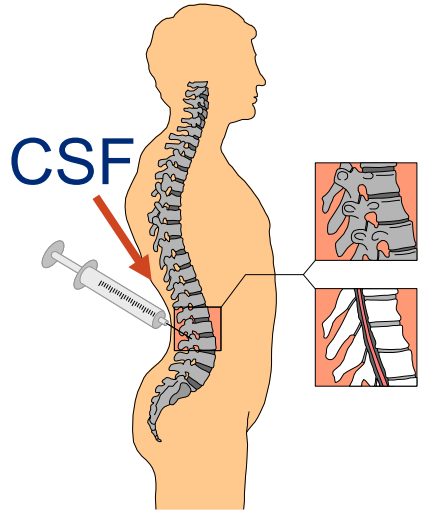
How are we able to assess inflammatory Markers in-vivo?





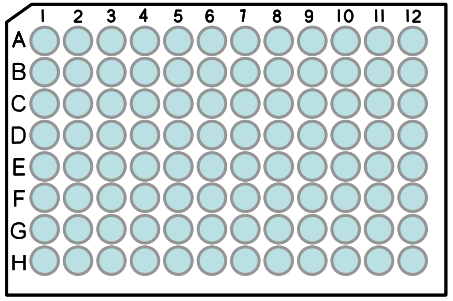


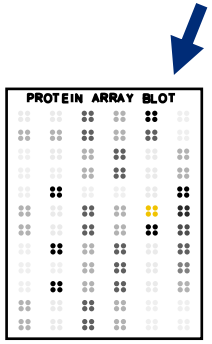
Cerebrospinal fluid (CSF)

- Cells
- Proteins
- Immunoglobulins (IgG index)
- **Oligoclonal bands (OCB)**
- Virus PCR
- Immuno assays (e.g., IgM WNV)

Assessment of Cytokines and chemokines in CSF: Expression profile and quantification

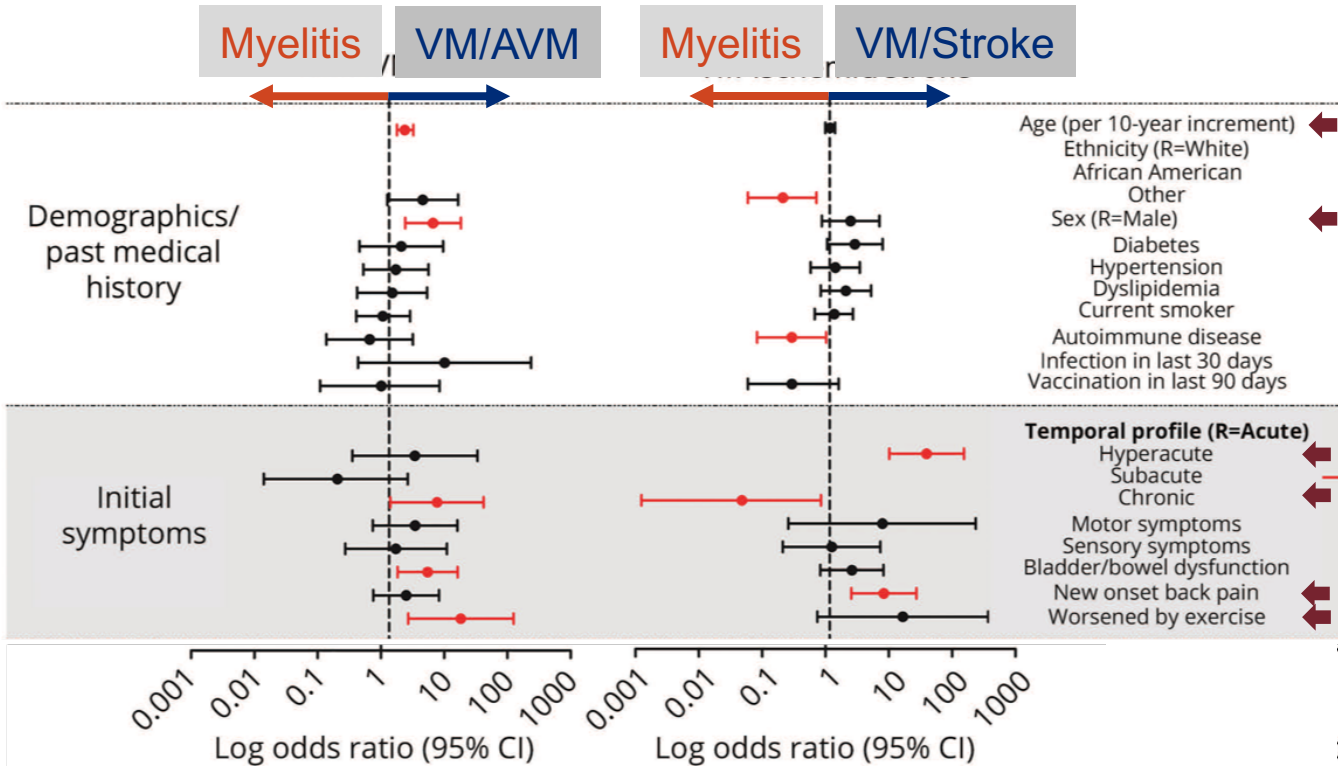
Multiplexed flow cytometric techniques





- **Antibodies (eg. MOG, AQP-4)**
- **Acute phase reactants**
- **NF-L**
- **Cytokines & Chemokines**
- **Other markers**

Clinical Biomarkers and Predictors of Vascular Myelopathy



Take home messages

- Older age and being male are factors in VM/dAVF
- History of autoimmune disorders influence presence of myelitis
- Hyperacute onset and onset of back pain are frequently associated with strokes of the spinal cord

Barreras P, Fitzgerald KC, Mealy MA, et al. Clinical biomarkers differentiate myelitis from vascular and other causes of myelopathy. Neurology. 2018;90(1):e12-e21. doi:10.1212/WNL.0000000000004765

Age of Onset in Myelopathies

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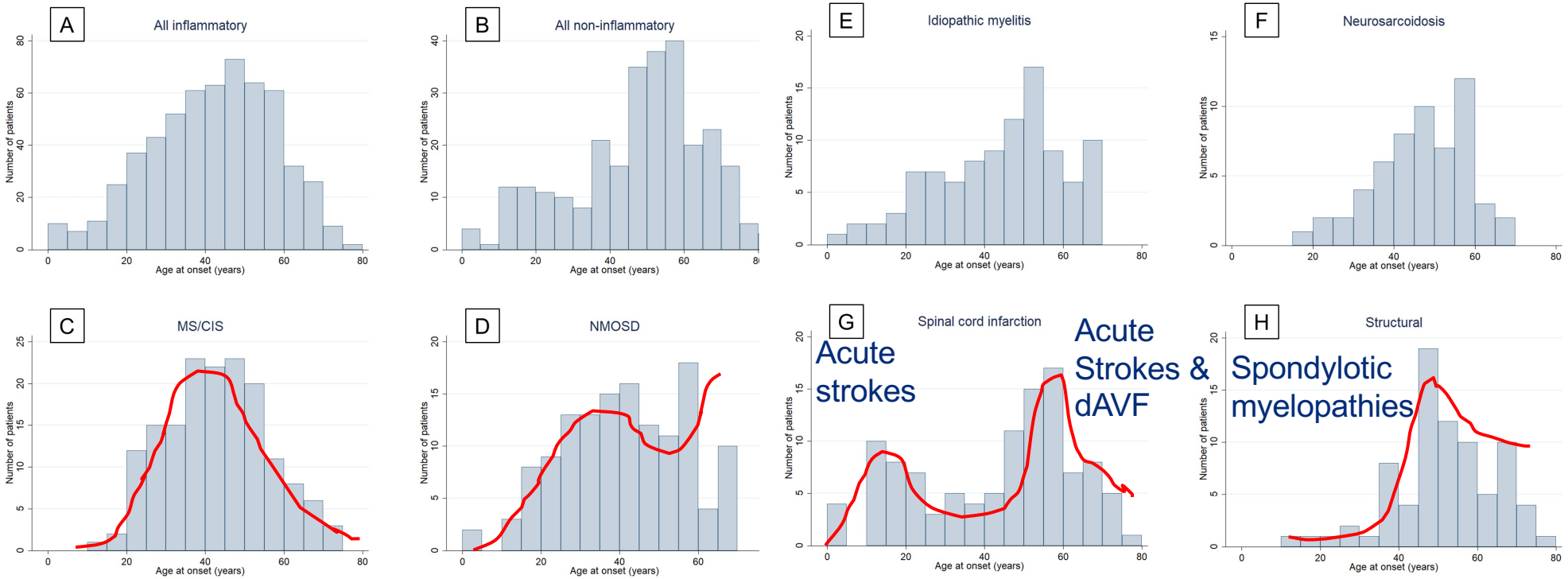
Another key element for diagnosis of myelopathies

$$\text{Myelopathy} = \sum_{\textbf{Time profile}}^{age} * \textit{lesion location} \begin{pmatrix} \textit{white matter} \\ \textit{gray matter} \end{pmatrix} \textit{extension}\, x^k a^{n-k}$$



Inflammatory myelopathies such as MS occur mostly in young adults
Vascular myelopathies (strokes) have a bimodal distribution but most of the chronic vascular myelopathies (dAVF) occur in older patients

Onset of Symptoms

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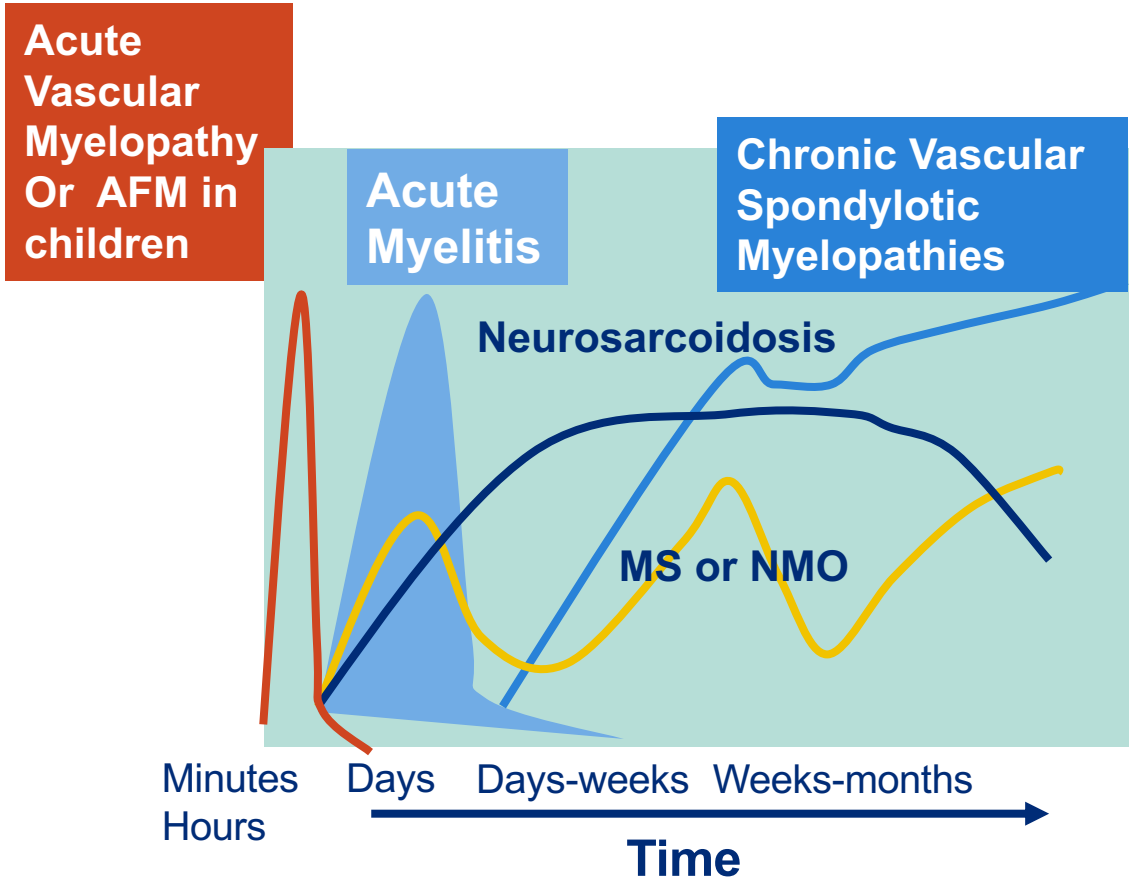

Hyperacute symptoms
(minutes-few hours)

Acute symptoms
(Several hours-few days)

Subacute symptoms
(several days-weeks)
Chronic
(Several weeks-months)

Relapsing & Remitting symptoms

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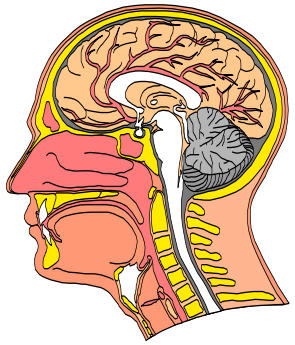

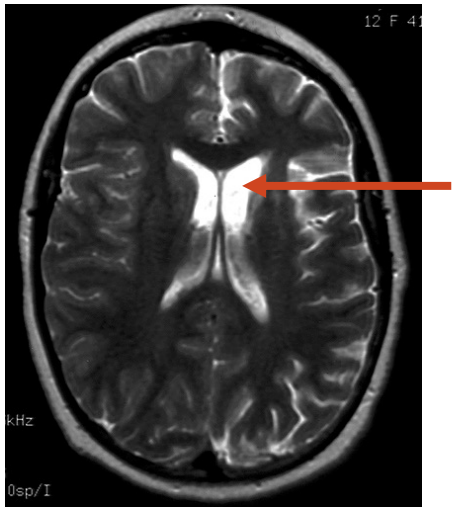

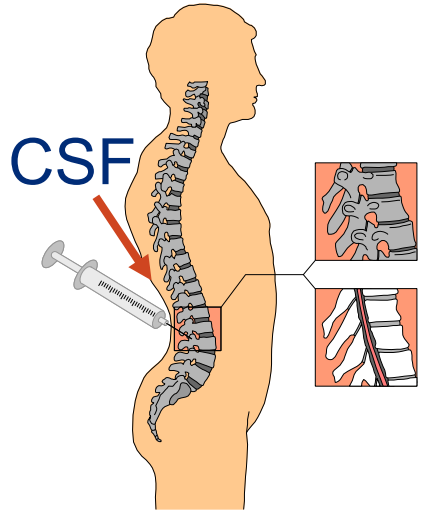

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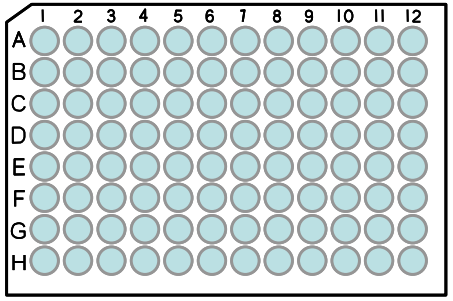

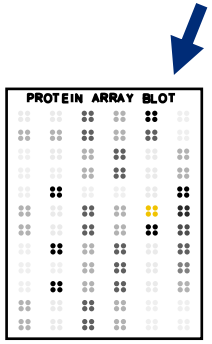

- **Antibodies (eg. MOG, AQP-4)**
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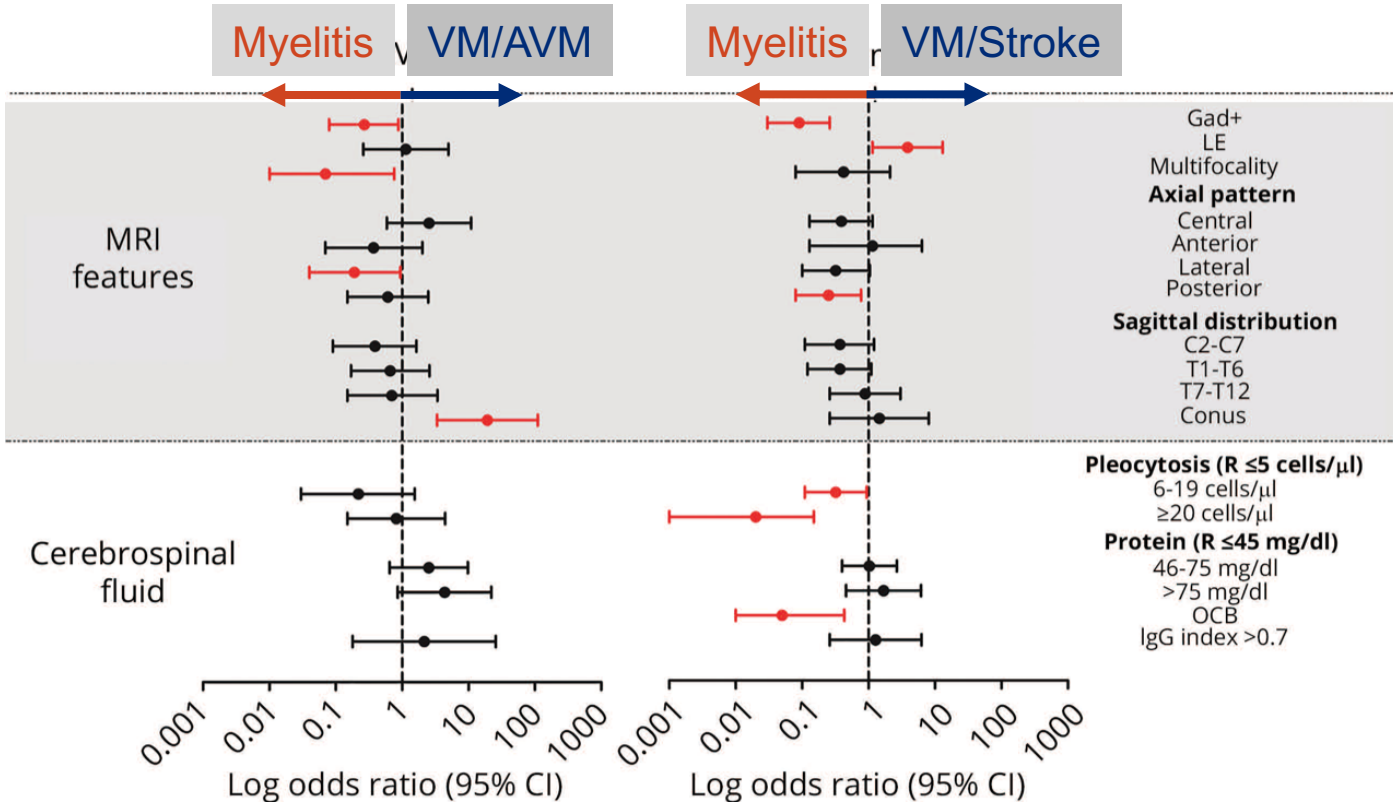
Clinical Biomarkers and Predictors of Vascular Myelopathy



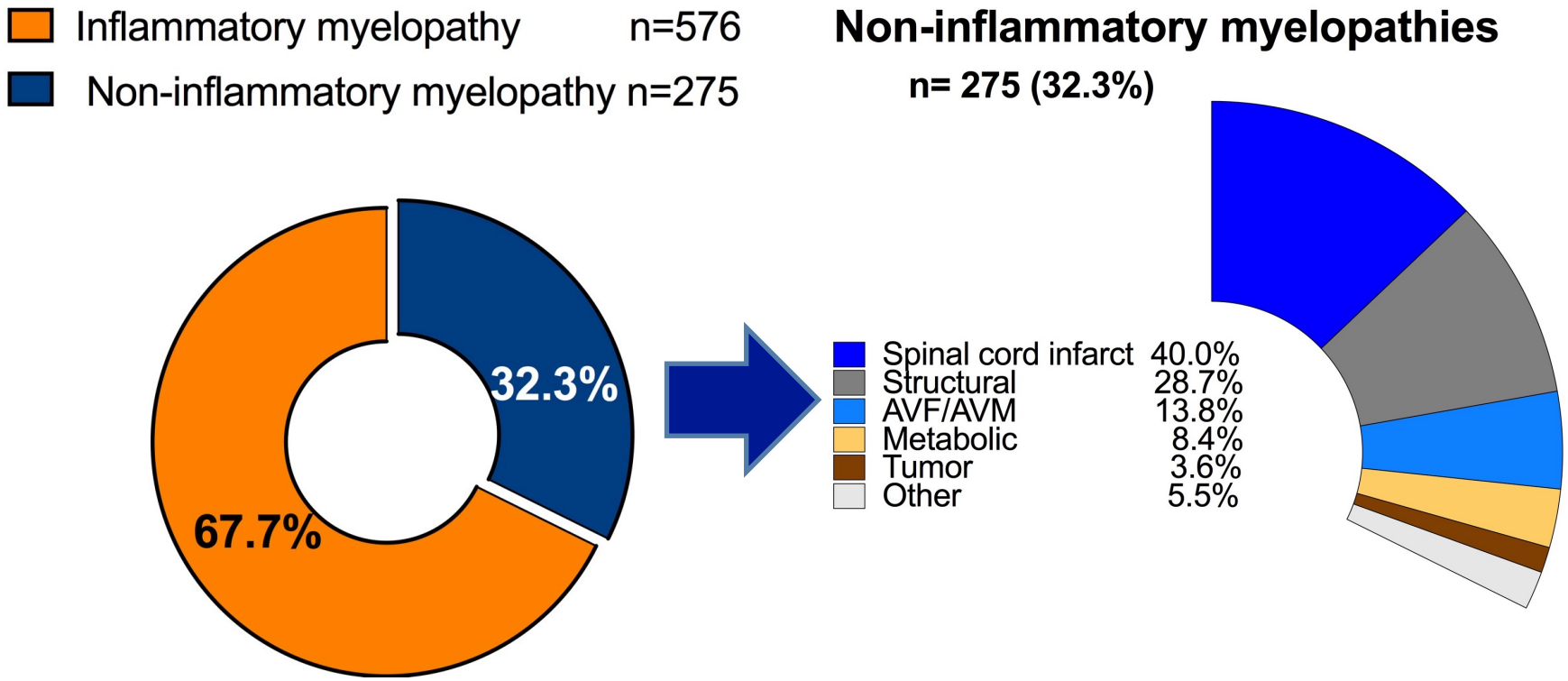
Take home messages

- Posterior location and Gad (+) MRI lesions favor the diagnosis of myelitis vs stroke
- MRI lesion in strokes and dAVF are frequently unenhanced (Gad-) at early stages
- CSF in ischemic/strokes of the spinal cord lacks pleocytosis and markers of neuroinflammation such as OCBs
- Chronic vascular lesions in venous hypertension lesions (e.g., dAVF) frequently involve lumbar cord and conus

Barreras P, Fitzgerald KC, Mealy MA, et al. Clinical biomarkers differentiate myelitis from vascular and other causes of myelopathy. Neurology. 2018;90(1):e12-e21. doi:10.1212/WNL.0000000000004765

Patients referred to the JHTMC with diagnosis of TM 2010-2018

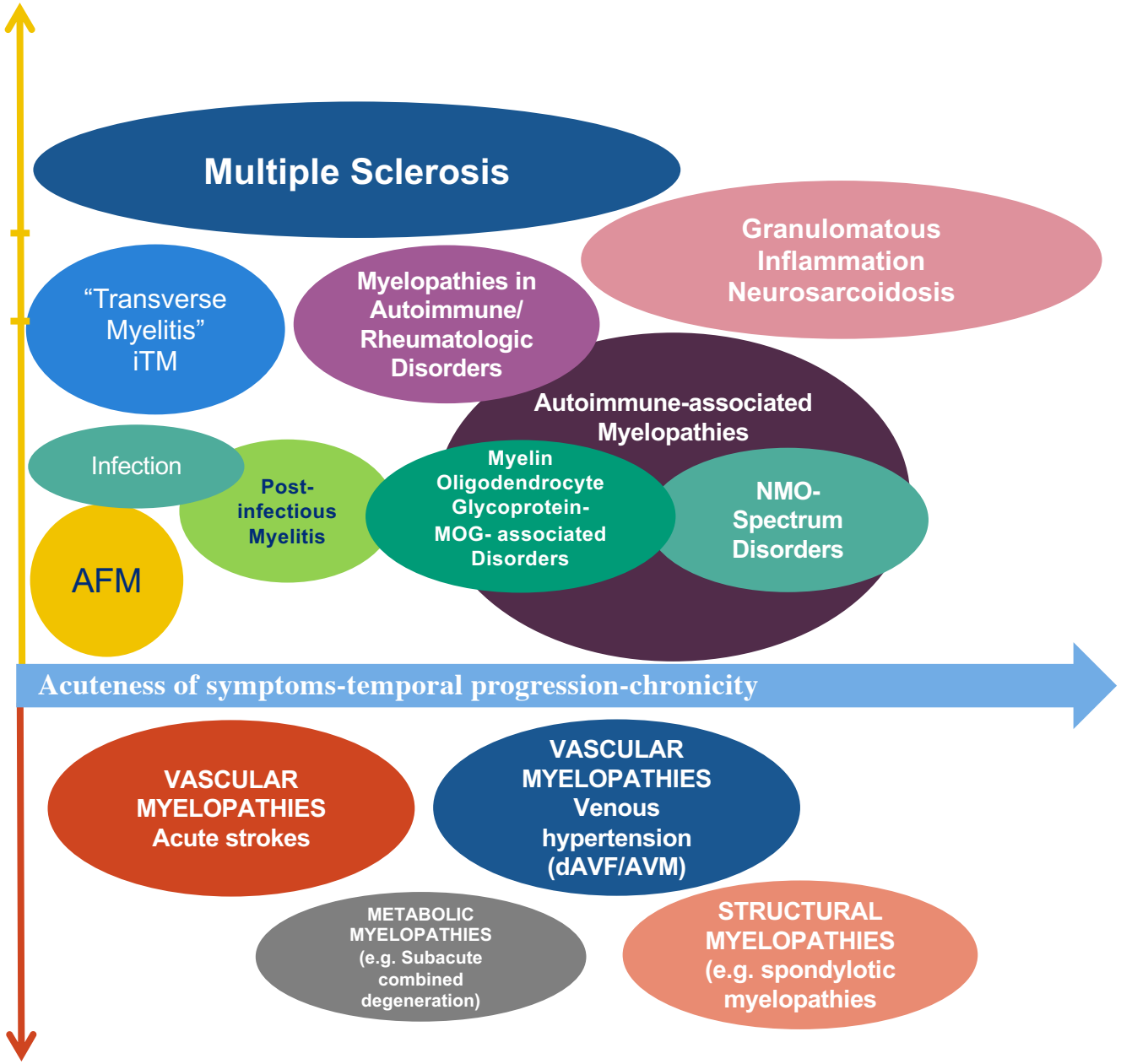
- Almost 18% referred to the JHTMC with diagnosis of TM had a vascular myelopathy!



The spectrum of Myelopathies in 2020

Inflammatory Myelopathies Aka “myelitis”

Non-Inflammatory Myelopathies



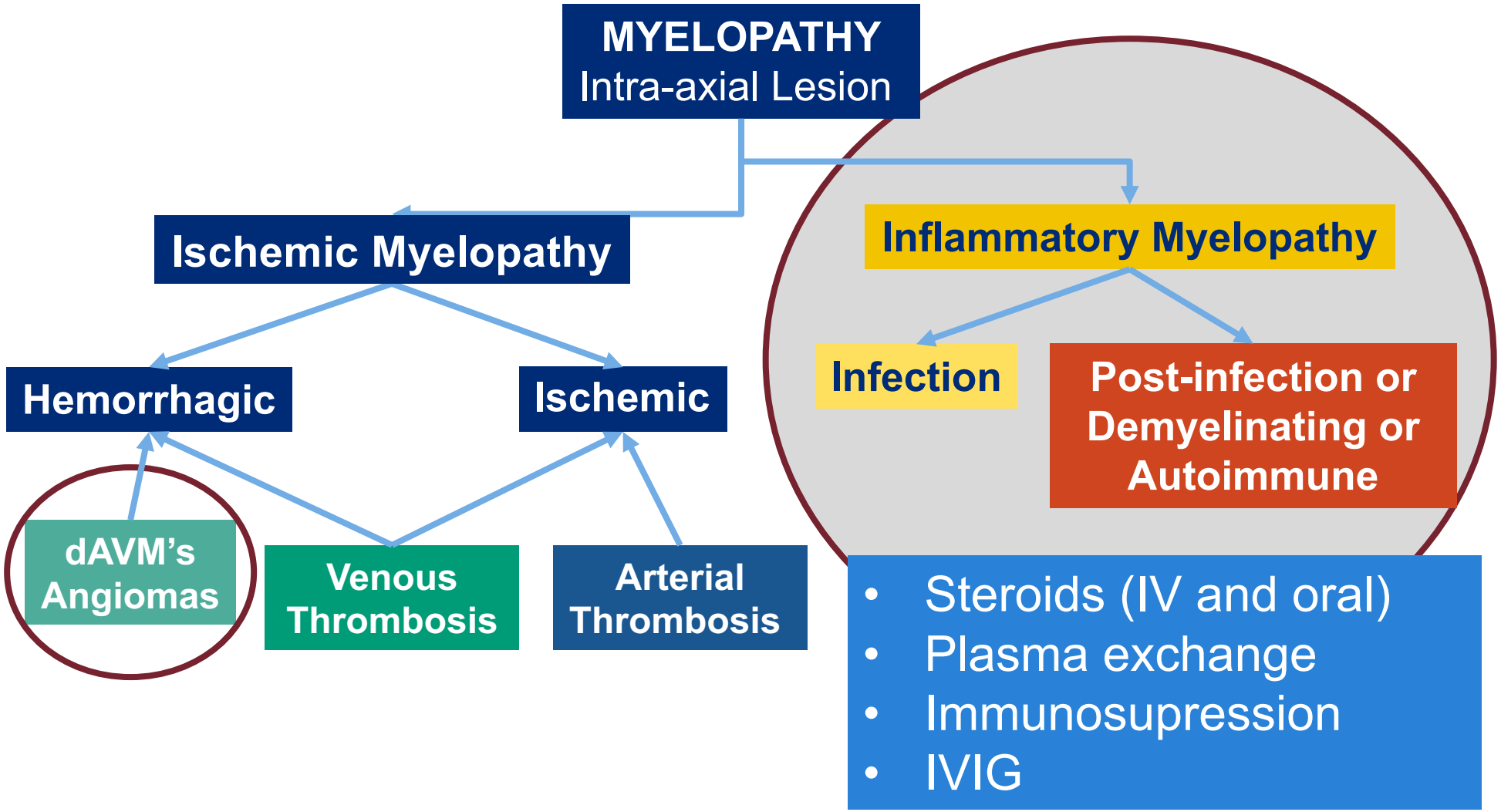
Vascular Myelopathy Related to Ischemic Disease (Strokes)

Vascular Myelopathy related to ischemic disease (Strokes)	**Definite**	• Myelopathy • MRI hyperintense lesion in a defined vascular territory or watershed area[a] on T2W images. • Vascular abnormality demonstrated on spinal angiogram explanatory of the clinical presentation. • Exclusion of other etiologies
	Probable	• Myelopathy • MRI hyperintense lesion in a defined vascular territory or watershed area on T2W images. • Spinal angiogram negative or not available • Positive diffusion weighted imaging OR • Known stroke risk factors or mechanism explanatory of the clinical presentation (ie severe hypotension, hypercoagulable state). • Exclusion of other etiologies
	Possible	• Myelopathy • MRI hyperintense lesion in a defined vascular territory or watershed area on T2W images. • Spinal angiogram and DWI negative or not available. • No identifiable risk factor or mechanism. • Exclusion of other etiologies

[a] Arterial territory supplied by sources flowing in opposite directions, includes the upper thoracic region, isolated gray matter and the posterior lumbosacral watershed area

Barreras P, Fitzgerald KC, Mealy MA, et al. Clinical biomarkers differentiate myelitis from vascular and other causes of myelopathy. Neurology. 2018;90(1):e12-e21. doi:10.1212/WNL.0000000000004765

The right diagnosis will direct the right management of myelopathies



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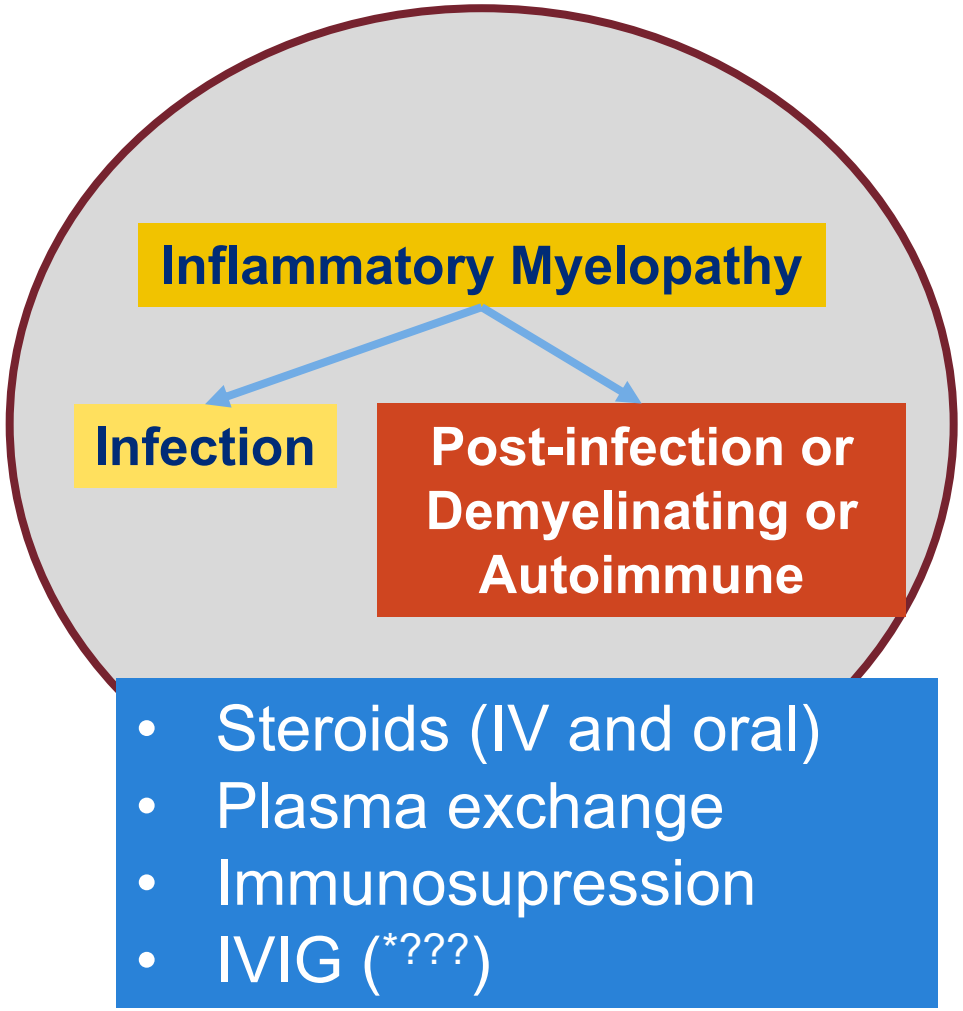


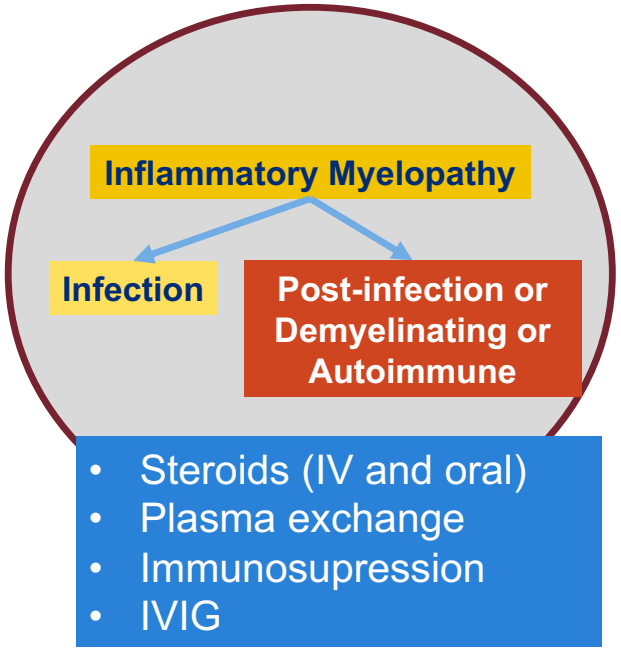
B-cell depletion therapies
- Demyelinating myelopathies
- NMOSD, MOG-related,
- Autoimmune myelopathies

Complement-inhibition therapies
- NMOSD

TNF-inhibitors
- Sarcoidosis associated myelitis

Cytotoxic/immunosuppressive
- Recurrent immune-mediated myelopathies

The right diagnosis will direct the right management of myelopathies



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Cytotoxic/immunosuppressive
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Rx:

1-Physical therapy and rehabilitation

2-Physical therapy and rehabilitation

3-Physical therapy and rehabilitation

4-Physical therapy and rehabilitation

5-Physical therapy and rehabilitation

6- Resilience!

7- Vitamin P !!

MYELOPATHIES 2021

Stop using the diagnosis of ”Transverse Myelitis”

Start using etiological diagnosis in myelopathies!!