TEACHING COURSE: TC25: AUTOIMMUNE NEUROLOGIC DISORDERS:
IMMUNE MEDIATED DISORDERS OF THE CNS:
PHENOTYPES, TREATMENT AND PATHOPHYSIOLOGY

Autoimmune Spinal Cord Disorders

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MAYO CLINIC

DISCLOSURE

- Dr. Pittock receives no royalties from the sale of tests performed in the NeuroimmunologyLaboratory at Mayo Clinic; however, Mayo Collaborative Services Inc. does receive revenue for conducting these.
- Dr. Pittock reports grants, personal fees, non-financial support and other from Alexion Pharmaceuticals, Inc., grants from Grifols, grants from AEA (Autoimmune Encephalitis Alliance), grants, personal fees, non-financial support and other from MedImmune/Viele Bio, Inc..
- Dr. Pittock has a patent Patent# 8,889,102 (Application#12-678350) - Neuromyelitis Optica Autoantibodies as a Marker for Neoplasia issued, and a patent Patent# 9,891,219B2 (Application#12-573942) - Methods for Treating Neuromyelitis Optica (NMO) by Administration of Eculizumab to an individual that is Aquaporin-4 (AQP4)-IgG Autoantibody positive issued.
- Patents pending for MAP1P, Septin5, Kelch11.

- <u>Off Label Usage</u>
  - I will mention use of a variety of immunotherapies.

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Learning Objectives

- To highlight neural antibodies and their association with myelopathy
- To identify MRI patterns that associate with the different types of myelopathy
- To highlight the differential diagnosis of autoimmune myelopathy

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Time to nadir is critical

- Acute/hyperacute <12 hrs to nadir
  - Spinal cord infarct
    - Severe deficit (paraplegia/quadriplegia)
- Time to nadir: 1-21 days
  - Inflammatory/transverse myelitis/MS/NMOSD
    - Tonic spasms may follow (NMOSD>MS)
- Progression >21 days
    - Spondylosis
    - Tumor
    - Dural AVF
    - Nutritional
    - Sarcoid

MAYO CLINIC

Wingerchuk and Frohman. NEJM 2010
Kim et al. Arch Neurol 2012
TM consortium working group. Neurology 2002

Cerebrospinal fluid myelopathy pearls

- Non-inflammatory (WBC normal; no OCB)
  - Infarct, Dural AVF, Spondylosis, tumor, B12
  - Inflammatory may be normal
- Inflammatory (↑WBC; +/- OCB's)
  - MS, NMOSD, ITM, infectious, sarcoid
  - Occasionally seen in non-inflammatory
- Markedly ↑CSF protein; normal cell count
  Spinal block (tumor/spondylosis); Guillain Barre
- ↓Glucose
  - Meningo-myelitis

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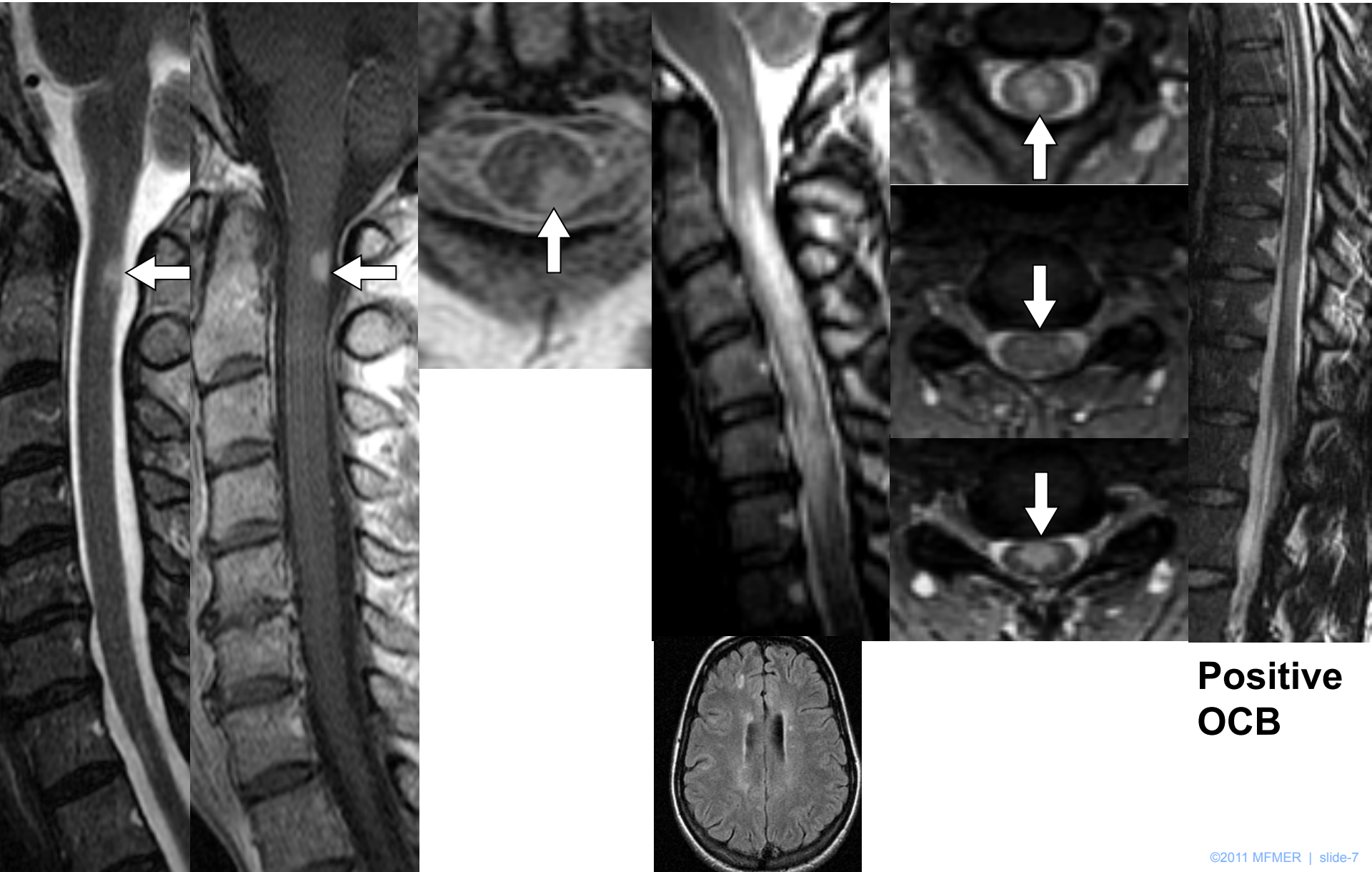
Transverse Myelitis - Lesion Length

- **Short TM (MRI T2 lesion <3 vertebral segments)**
  - MS is commonest cause (adults) – peripheral
    - Children may have LETM
  - Under-recognized in AQP4-IgG + NMOSD
- **LETM (MRI T2-lesion ≥3 vertebral segments)**
  - Hallmark of AQP4-IgG pos NMOSD - central
  - **Caution!** AQP4-IgG seronegative LETM
  - Many other causes of long lesions

Frohman & Wingerchuk et al. NEJM 2015
Banwell, Lennon and Pittock et al. Neurology 2008
Katz Sand and Lublin. Continuum 2013
Wingerchuk et al. Neurology 1999
Tobin, Weinshenker and Lucchinetti. Curr opinion Neurol 2016

MRI of STM in MS; Coalescence of short MS lesions may resemble LETM (axial helps)



Positive OCB

Neuromyelitis Optica Spectrum Disorders (NMOSD)

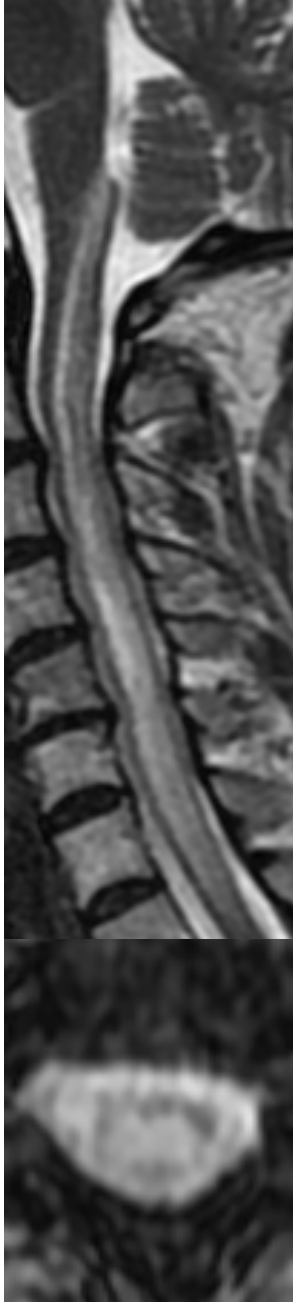
- Autoimmune channelopathy (predominantly astrocytopathy)
- Serum biomarker aquaporin-4-IgG
  - ≈80% sensitive; 99-100% specific
- Predilection for:
  - Spinal cord
  - Optic nerve
  - Area postrema

MAYO CLINIC

Wingerchuk & Weinshenker et al. Neurology 2015
Lennon et al. Lancet 2004

LETM in AQP4-IgG + NMOSD

- Severe; paraplegia common
- Central on axial images
- Length distinguishes NMOSD from MS
- LETM prompts AQP4-IgG testing
- **Caution!** AQP4-IgG seronegative LETM
  - Other causes of LETM exist
  - Dx criteria for seronegative NMOSD require dissemination in space

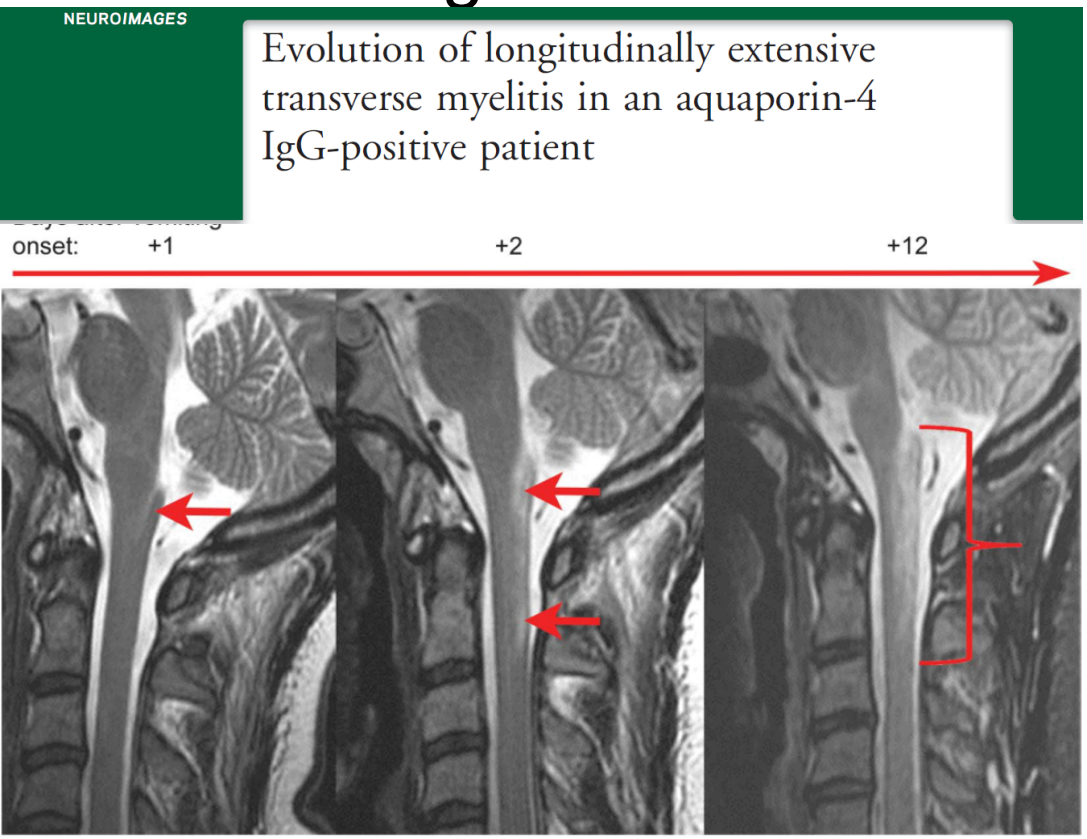


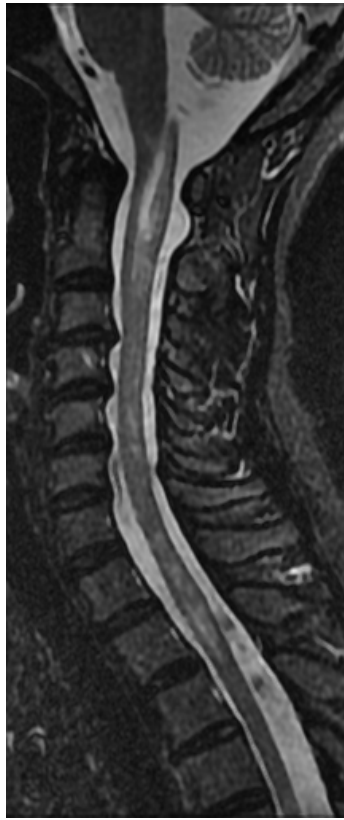
MAYO CLINIC

Wingerchuk et al. Neurology 1999
Wingerchuk & Weinshenker et al. Neurology 2015
Tobin, Weinshenker and Lucchinetti. Curr opinion Neurol 2016
Graham, McCarthy, Kavanagh, O'Rourke and Lynch. Neurology 2016

Factors Influencing Lesion Length in NMOSD

- Timing of MRI in relation to symptoms:
  - Imaged too early – short
  - Imaged too late – short/discontinuous/resolved





Short myelitis lesions represents 14-15% of AQP4+ NMOSD myelitis

Original Investigation

Short Myelitis Lesions in Aquaporin-4-IgG–Positive Neuromyelitis Optica Spectrum Disorders

Eoin P. Flanagan, MBBCh; Brian G. Weinshenker, MD; Karl N. Krecke, MD; Vanda A. Lennon, MD, PhD; Claudia F. Lucchinetti, MD; Andrew McKeon, MBBCh; Dean M. Wingerchuk, MD; Elizabeth A. Shuster, MD; Yujuan Jiao, MD; Erika S. Horta, MD; Sean J. Pittock, MD

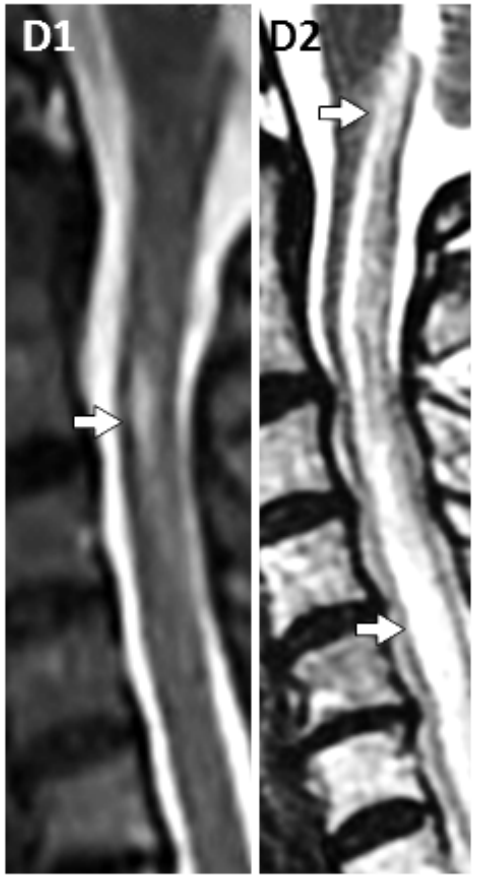
Original Research Paper

Short segment myelitis as a first manifestation of neuromyelitis optica spectrum disorders

So-Young Huh, Su-Hyun Kim, Jae-Won Hyun, In Hye Jeong, Min Su Park, Sang-Hyun Lee and Ho Jin Kim

Multiple Sclerosis Journal

2017, Vol. 23(3) 413–419



- Distinction of AQP4-IgG pos NMOSD from MS important as MS medications may worsen NMOSD

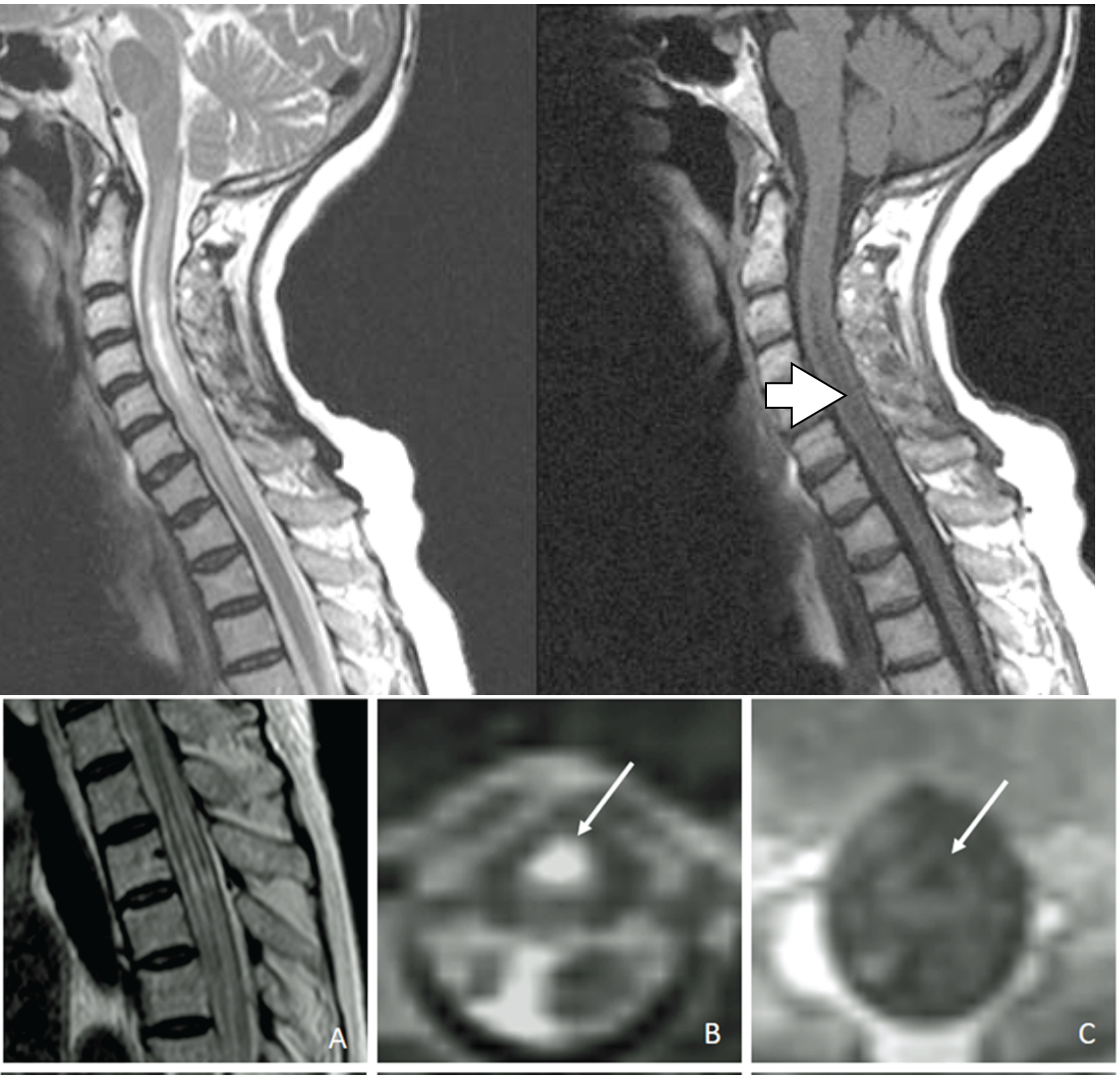
STM in AQP4+ NMOSD

- Predictors of AQP4-IgG (+) in STM:
  - Nonwhite race
  - Tonic spasms
  - Coexisting autoimmunity (e.g., lupus)
  - MRI (central cord, ≥2 segments, MS brain lesions absent)
  - CSF lacking oligoclonal bands
- MS prevalence in region
  - CNS demyelinating episode 50 times more likely MS than NMOSD in Minnesota

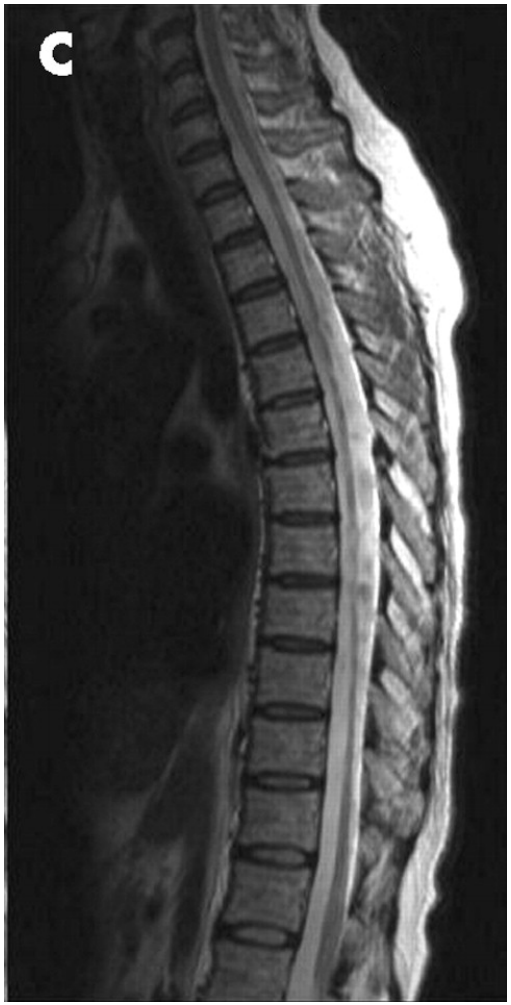
Flanagan et al. JAMA Neurol 2015
Flanagan et al. Ann Neurol 2016
Huh et al. MSJ 2017

Differential Diagnosis of Longitudinally Extensive Spinal Cord Lesions

NMOSD: T1 Hypointense & bright-spotty T2 lesions

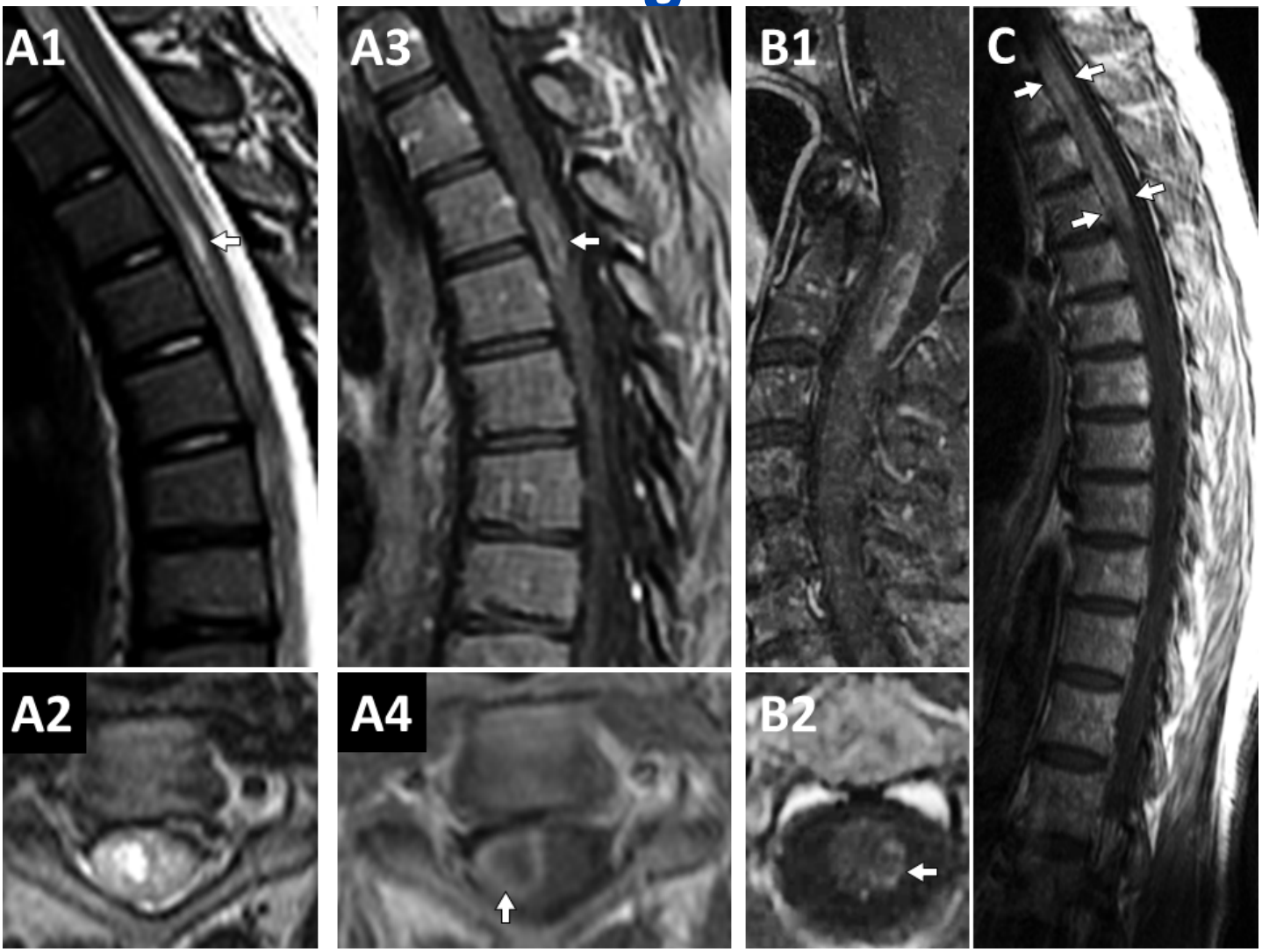


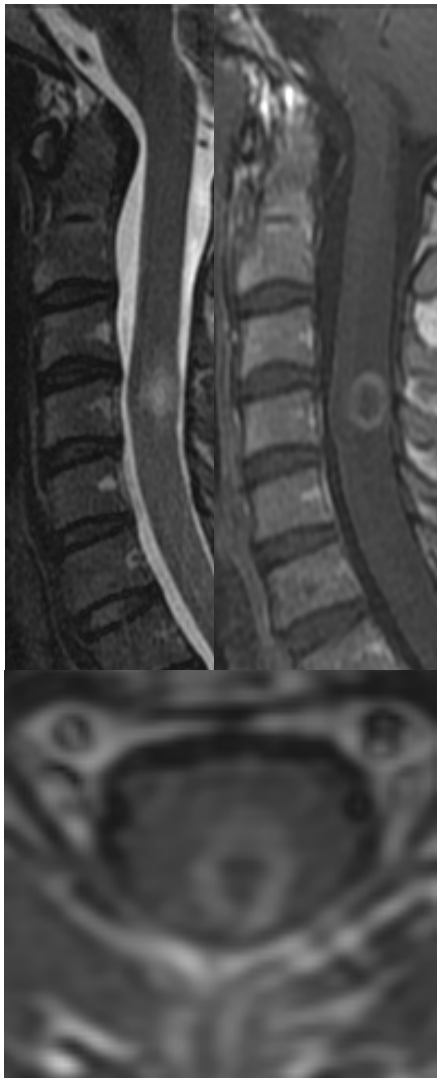
Segmental cord atrophy



Downer et al. Neuroradiology 2011
Yonezu et al. MSJ 2014
Pekcevik et al. MSJ 2016
Tanaka et al. JNNP 2007

Ring enhancement distinguishes NMOSD from other LETM etiologies but not MS



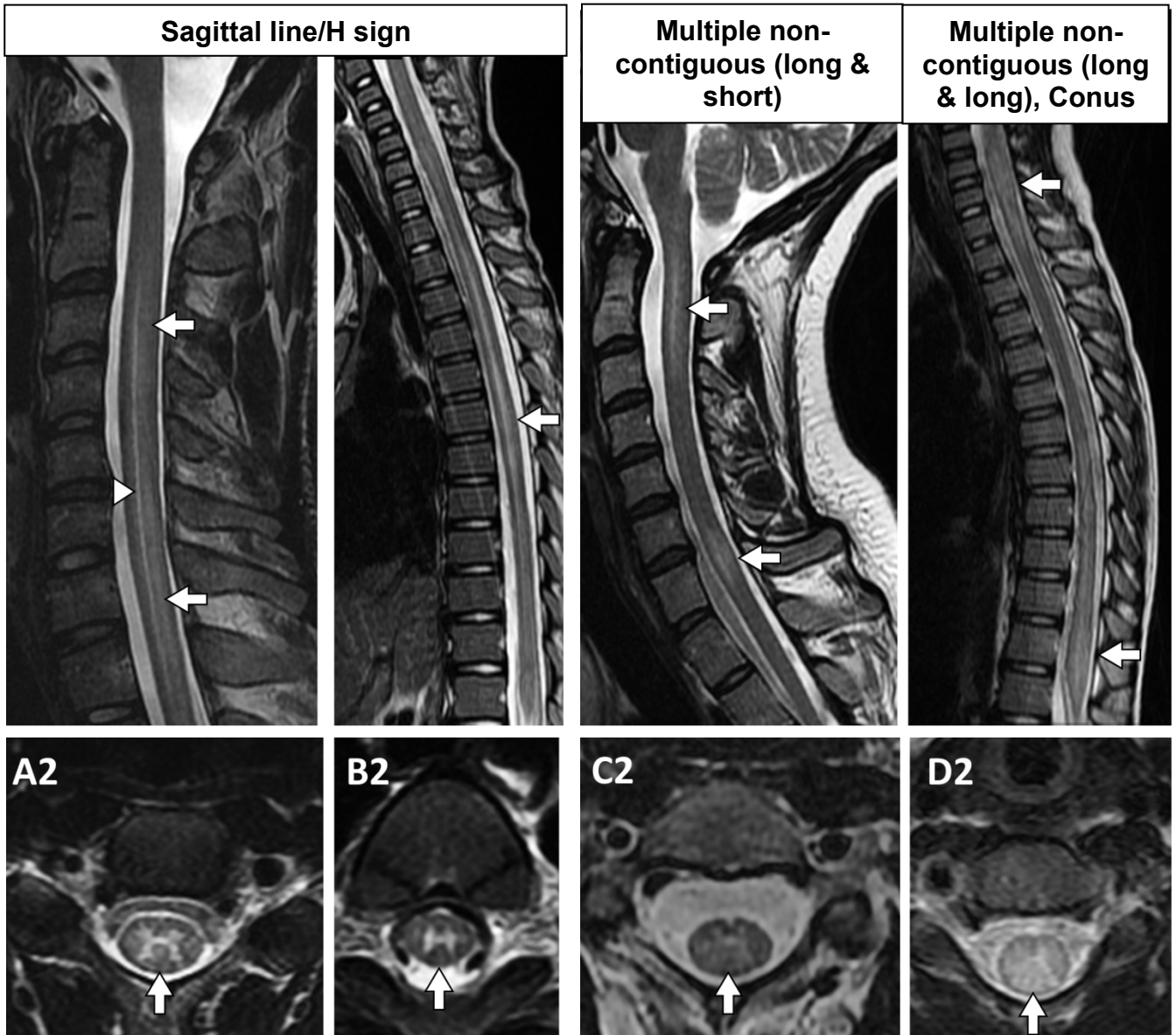


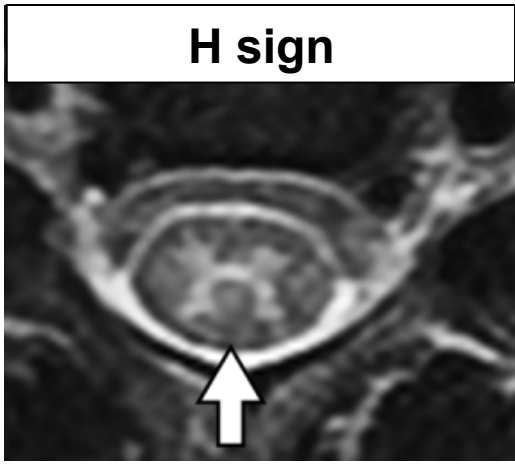
AQP4+ NMOSD

MS

Yokote et al. Acta Neurol Scan 2015
Zalewski et al. JNNP 2017

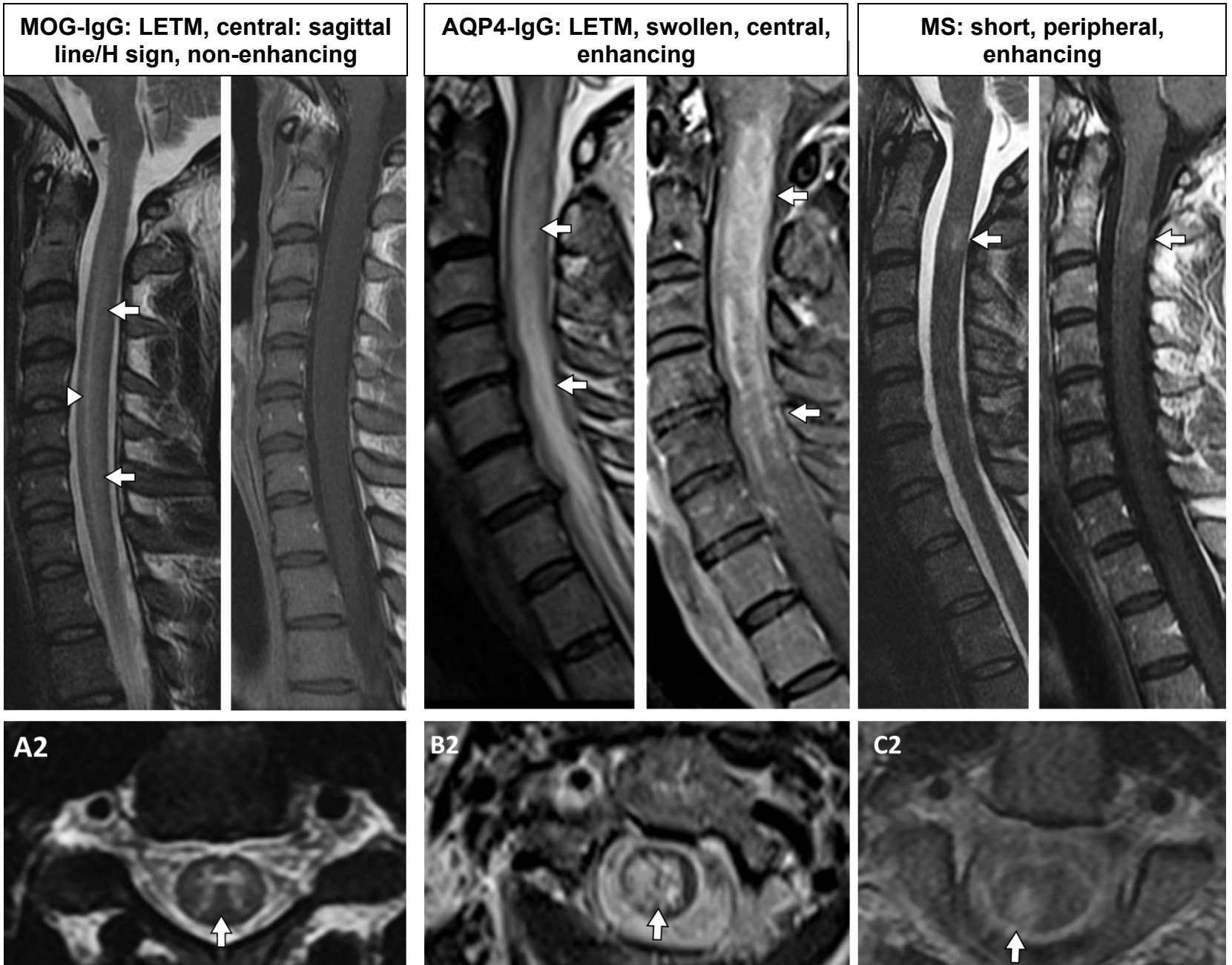
MOG-IgG myelitis – may mimic viral post-viral acute flaccid myelitis





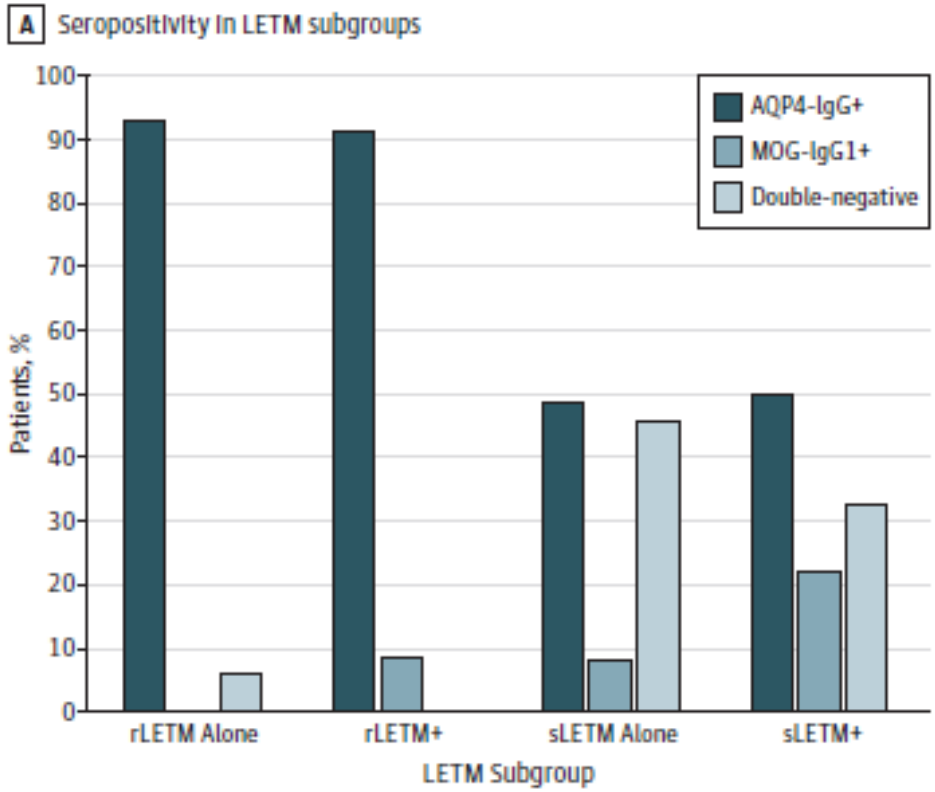
Dubey et al. JAMA Neurol 2019
Kitley et al. JAMA Neurol 2014
Jarius et al. J Neuroinflamm 2016

MRI Comparison: MOG-IgG, AQP4-IgG & MS



AQP4-IgG much more likely in Recurrent LETM than MOG-IgG

- AQP4-IgG accounts for 93% of patients with recurrent LETM
- MOG-IgG accounts for 3% of recurrent LETM



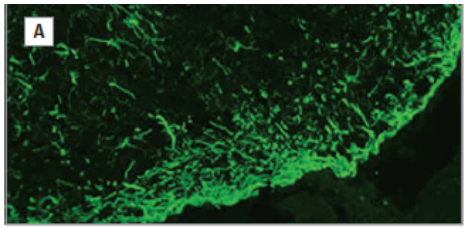
Jitprapaikulsan et al, JAMA Neurology, 2018

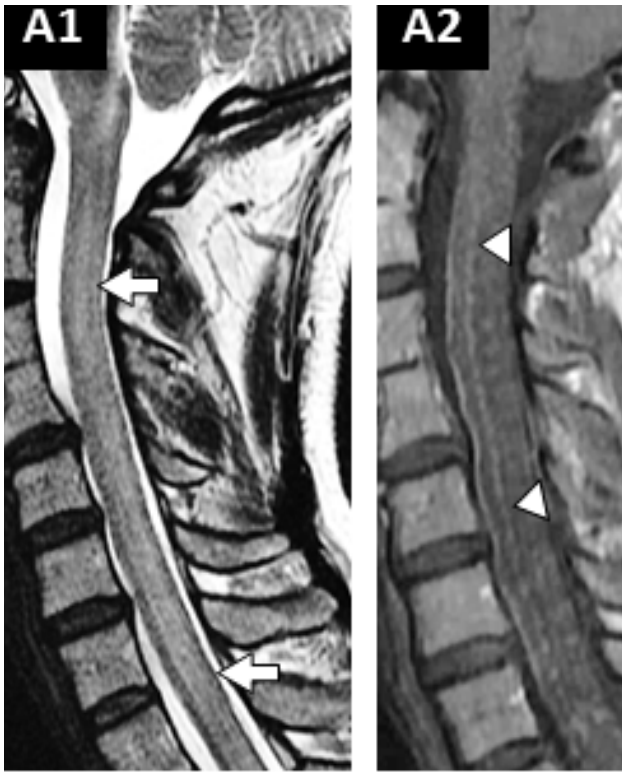
JAMA Neurology | Original Investigation

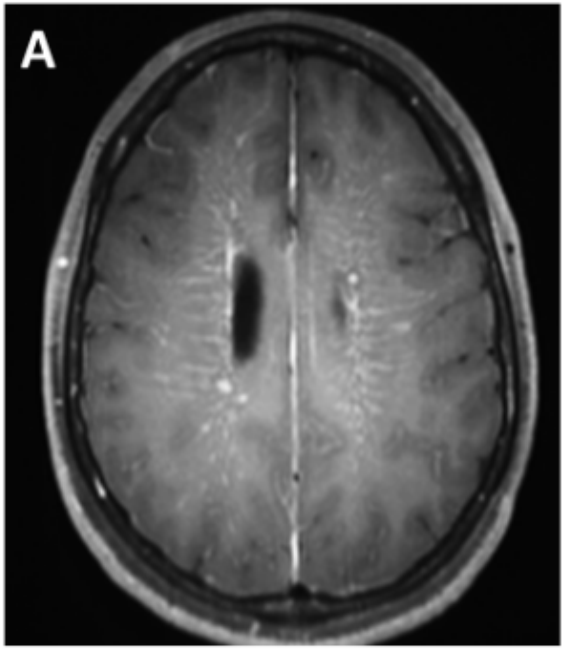
Autoimmune Glial Fibrillary Acidic Protein Astrocytopathy
A Novel Meningoencephalomyelitis

Boyan Fang, MD, PhD; Andrew McKeon, MD; Shannon R. Hinson, PhD; Thomas J. Kryzer, AA; Sean J. Pittock, MD; Allen J. Aksamit, MD; Vanda A. Lennon, MD, PhD

- Tremor, optic disc edema clinical clues
- CSF testing most sensitive & specific
- NMDA, AQP4 antibodies may coexist
- Myelitis coexists with encephalitis
- Teratoma
- Steroid-responsive

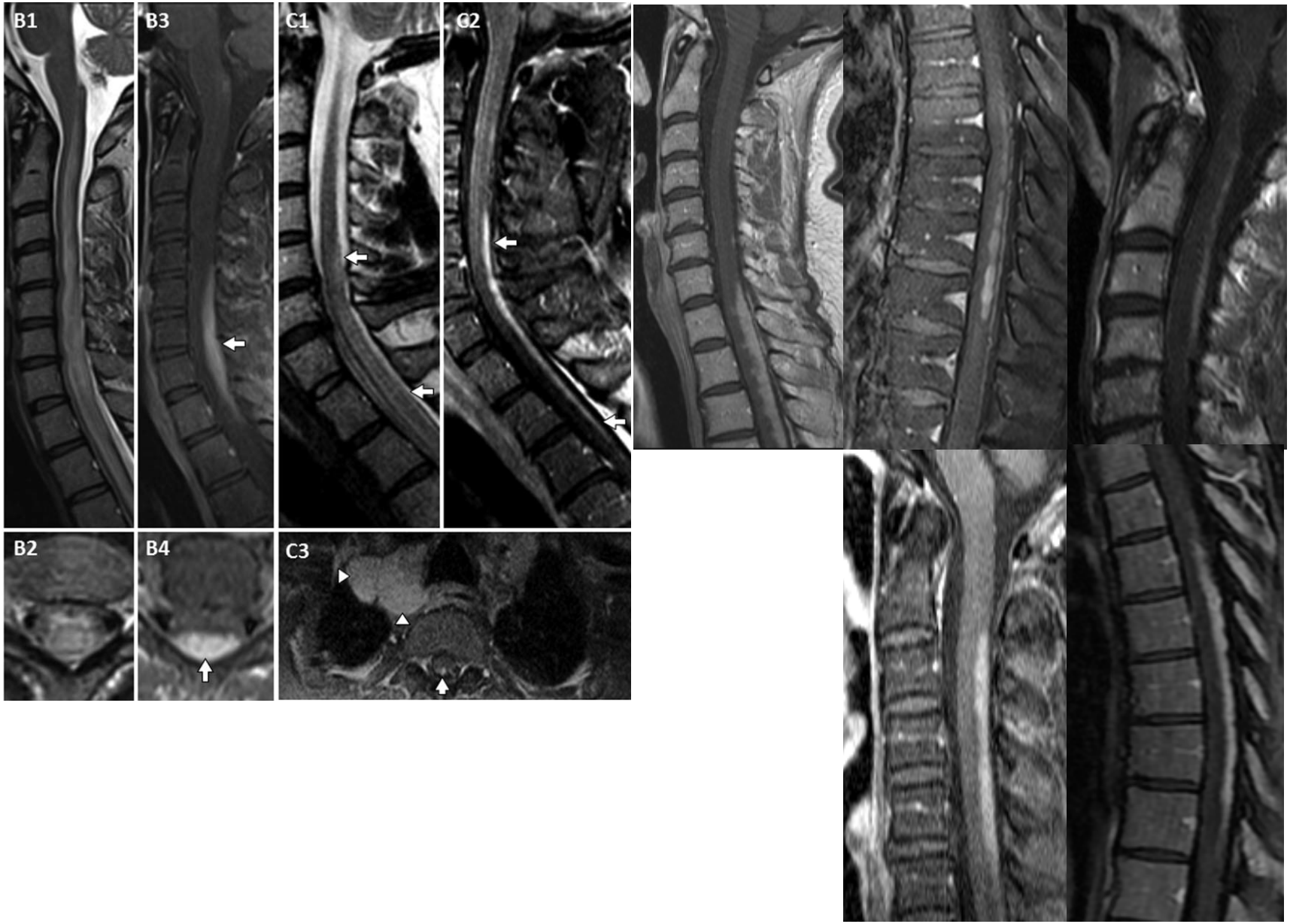






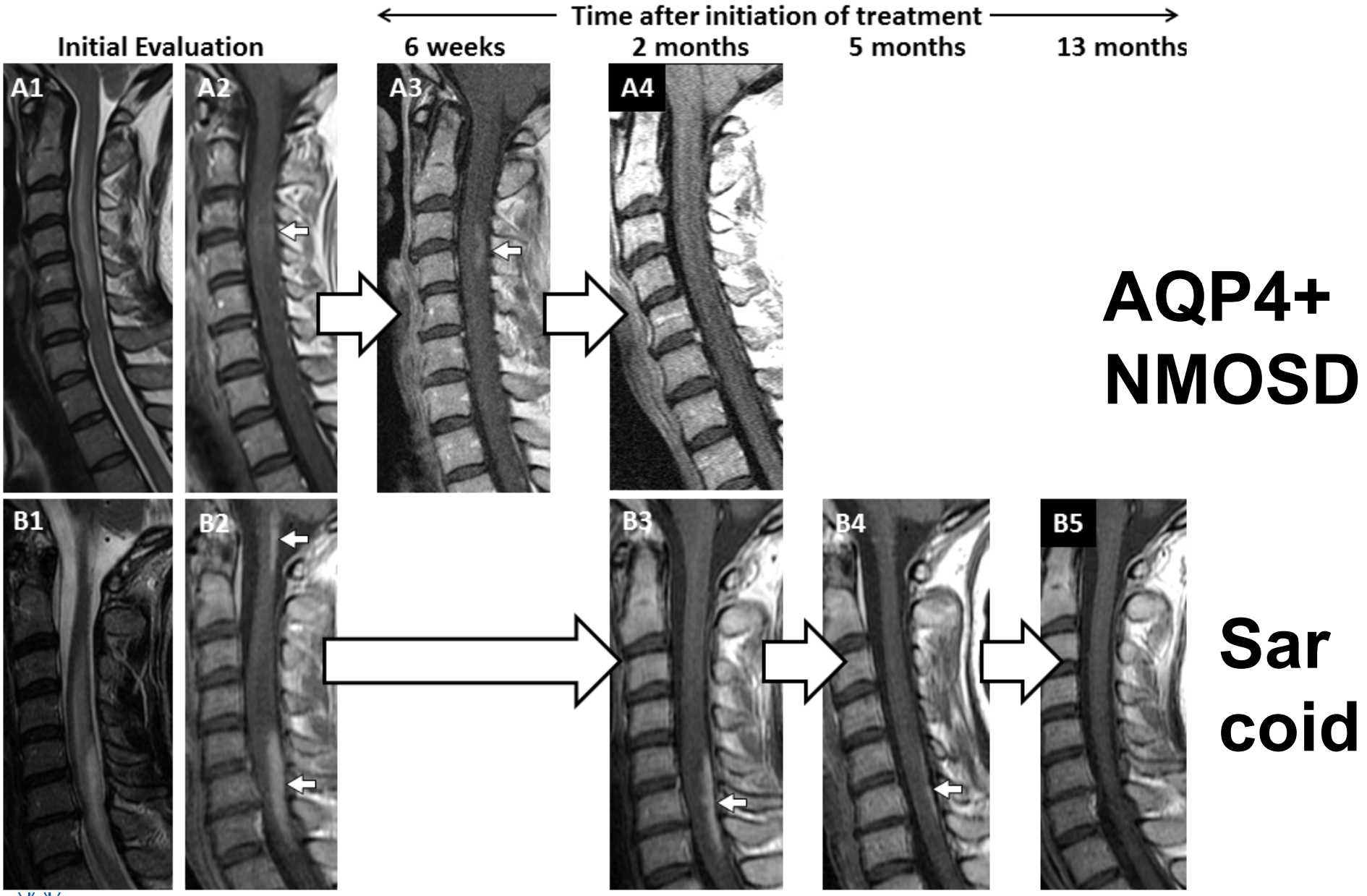
Aksamit et al, ANA 2012
Flanagan et al. Ann Neurol 2017
Sechi et al, JNNP, 2018

Linear dorsal subpial enhancement predicts spinal cord sarcoidosis over AQP4+ NMOSD



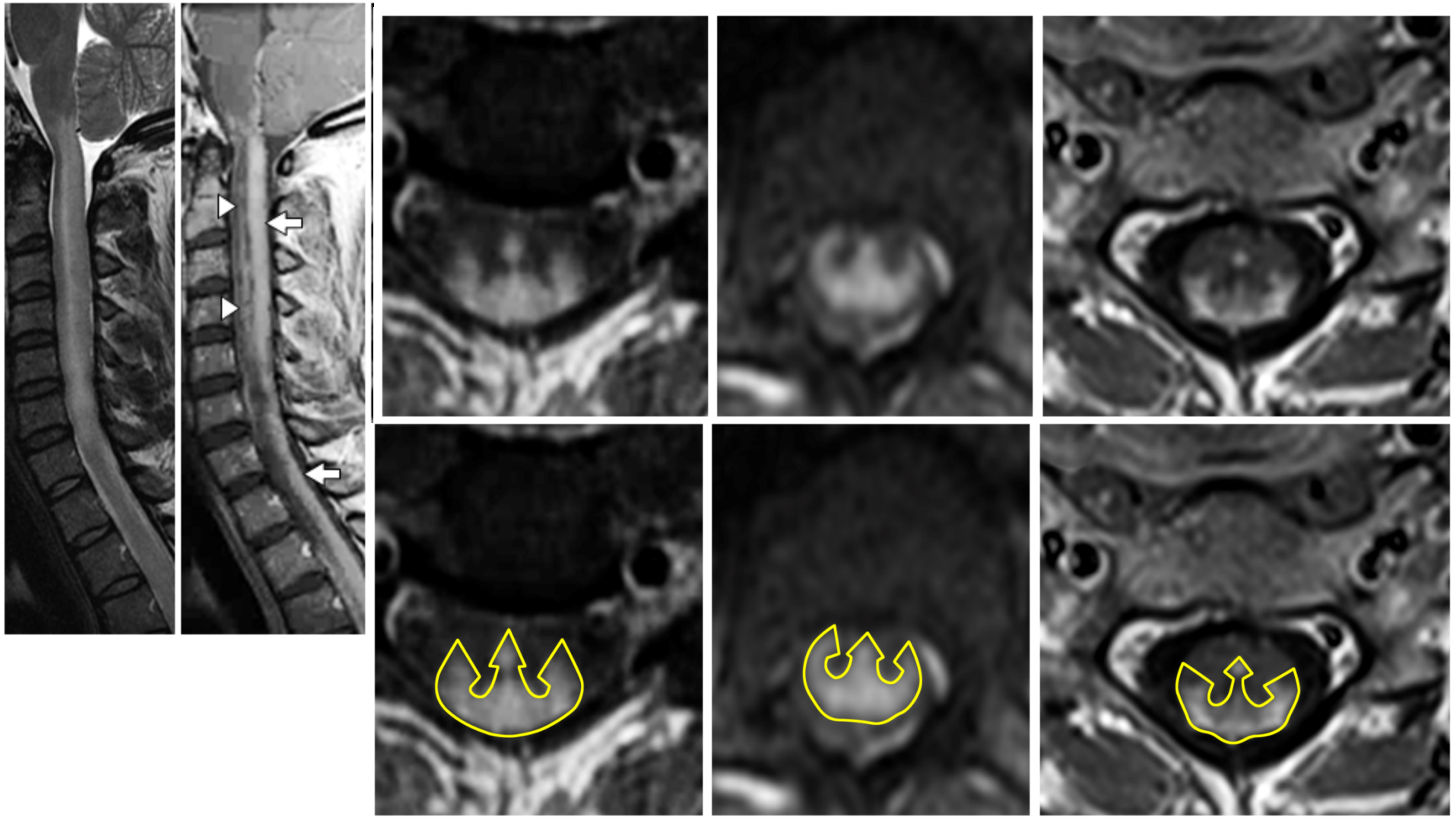
Flanagan et al. Ann Neurol 2016

Persistent enhancement predicts sarcoid over NMOSD



Flanagan et al. Ann Neurol 2016

Central canal enhancement in spinal cord sarcoidosis and the ‘trident sign’ on axial post gad images



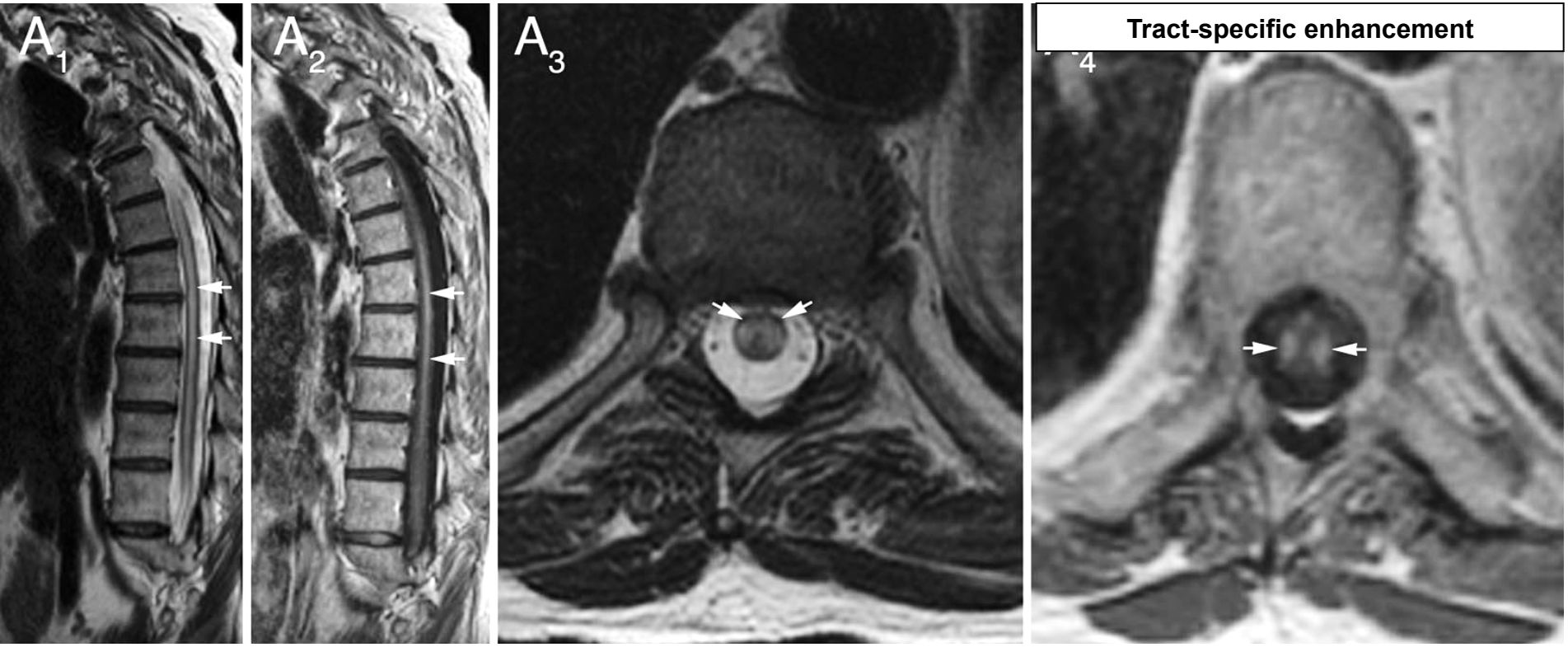
Zawlewski et al. Neurology 2016

E.P. Flanagan, MBBCh
A. McKeon, MBBCh
V.A. Lennon, MD, PhD
J. Kearns, MBBCh
B.G. Weinshenker, MD
K.N. Krecke, MD
M. Matiello, MD
B.M. Keegan, MD
B. Mokri, MD
A.J. Aksamit, MD
S.J. Pittock, MD

Paraneoplastic isolated myelopathy

Clinical course and neuroimaging clues

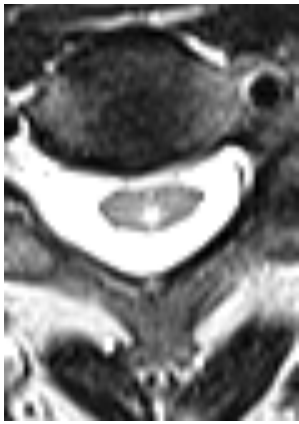
Neurology® 2011;76:2089-2095



CRMP5-IgG & Amphiphysin IgG

Tractopathy (dorsal/lateral columns)

- Deficiency Copper/B12 (N_2O), Vit E
- Paraneoplastic myelopathy
- Mitochondrial (DARS2, Leber's, ADLD,)
- Toxic (intrathecal mtx, cytarabine, heroin, pyridoxine excess; Cbl-c deficiency)
- Infectious (syphilis, HIV, HTLV-1)
- Hereditary (Friedreich's, SCA, CTX, HSP Mitofuscin)
- Sensory ganglionopathy (e.g., sjogren's, paraneoplastic)
- Sarcoid, posterior spinal artery infarct

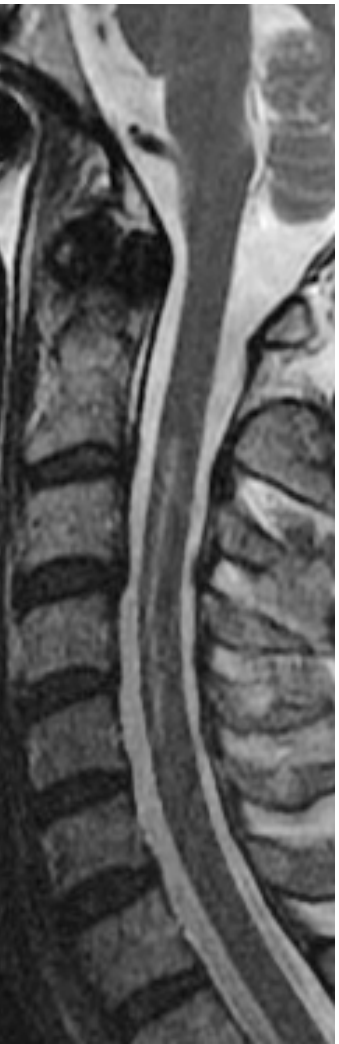


JAMA Neurology | Original Investigation

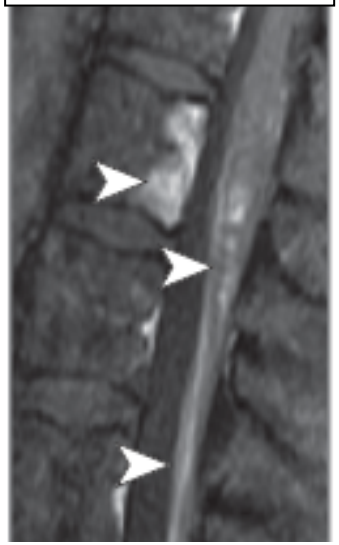
Characteristics of Spontaneous Spinal Cord Infarction and Proposed Diagnostic Criteria

Nicholas L. Zalewski, MD; Alejandro A. Rabinstein, MD; Karl N. Krecke, MD; Robert D. Brown Jr, MD; Eelco F. M. Wijdicks, MD; Brian G. Weinshenker, MD; Timothy J. Kaufmann, MD; Jonathan M. Morris, MD; Allen J. Aksamit, MD; J. D. Bartleson, MD; Giuseppe Lanzino, MD; Melissa M. Blessing, DO; Eoin P. Flanagan, MBBCh

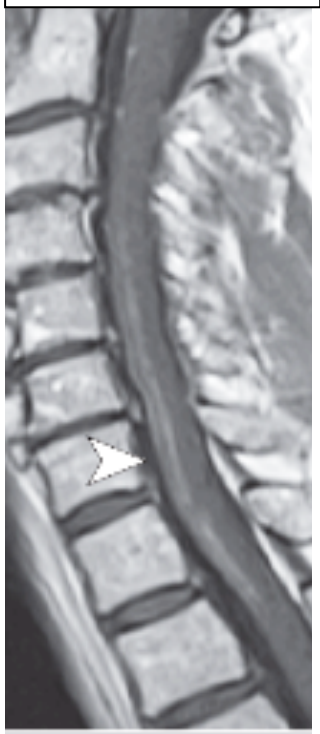
JAMA Neurol. doi:10.1001/jamaneurol.2018.2734



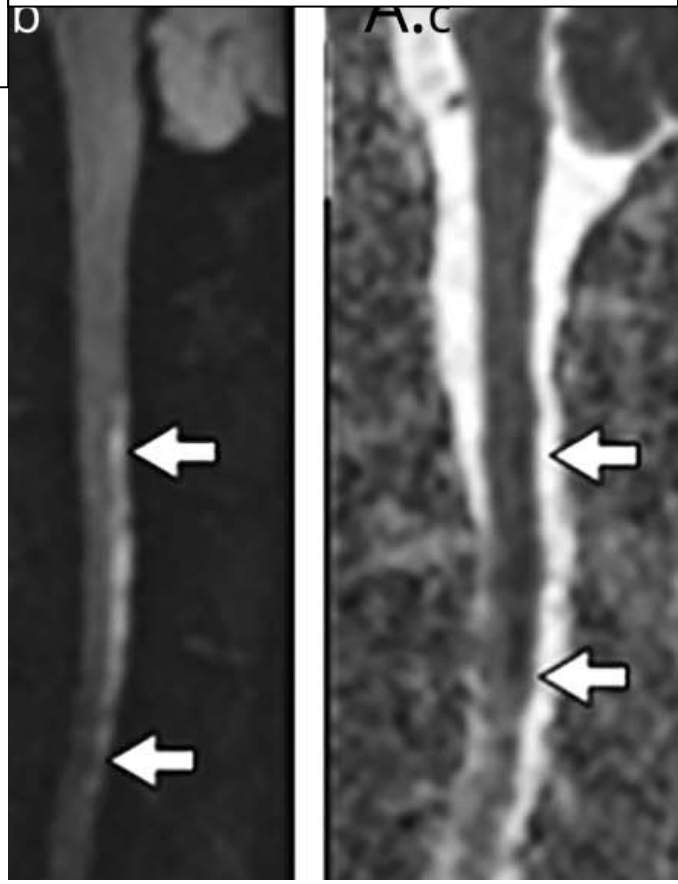
Vert body infarct



Linear strip of enhancement in anterior cord

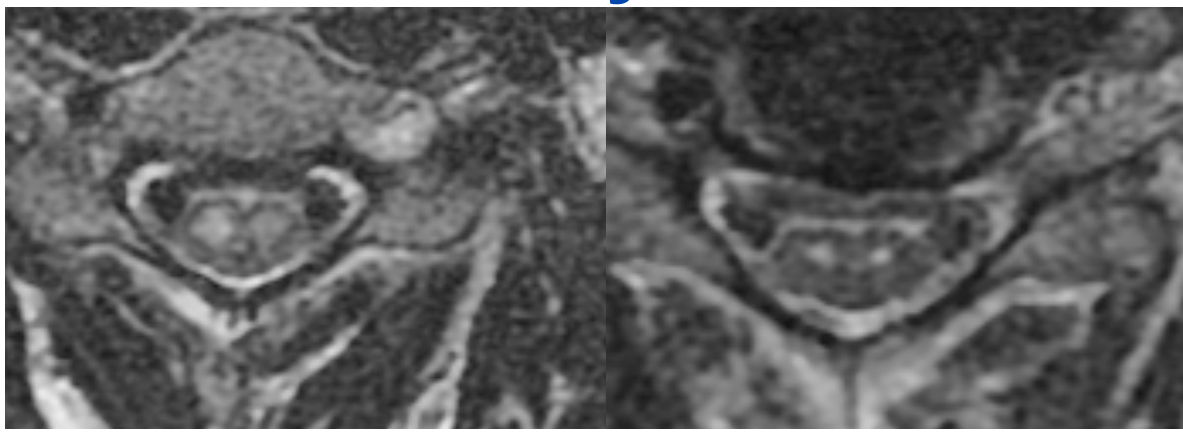


Restricted Diffusion



Zawlewski et al. Neurology 2018

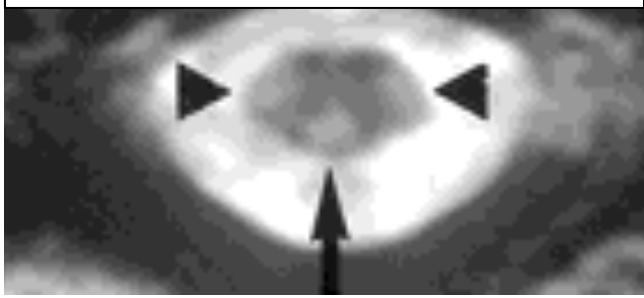
Owl or snake eyes?



Causes

- Vascular (primary or secondary)
- Inflammatory/ autoimmune (eg, AQP4, MOG)
- ALS
- Hirayama's disease
- Hopkins syndrome
- Infectious (polio, west nile virus, enterovirus)

Tractopathy



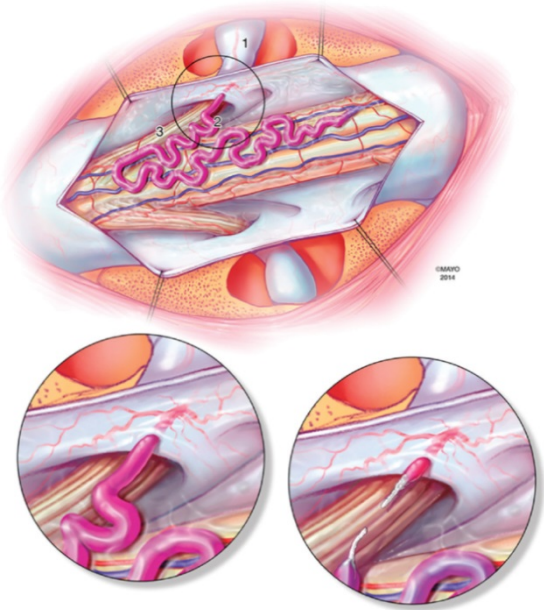
A cluster of acute flaccid paralysis and cranial nerve dysfunction temporally associated with an outbreak of enterovirus D68 in children in Colorado, USA

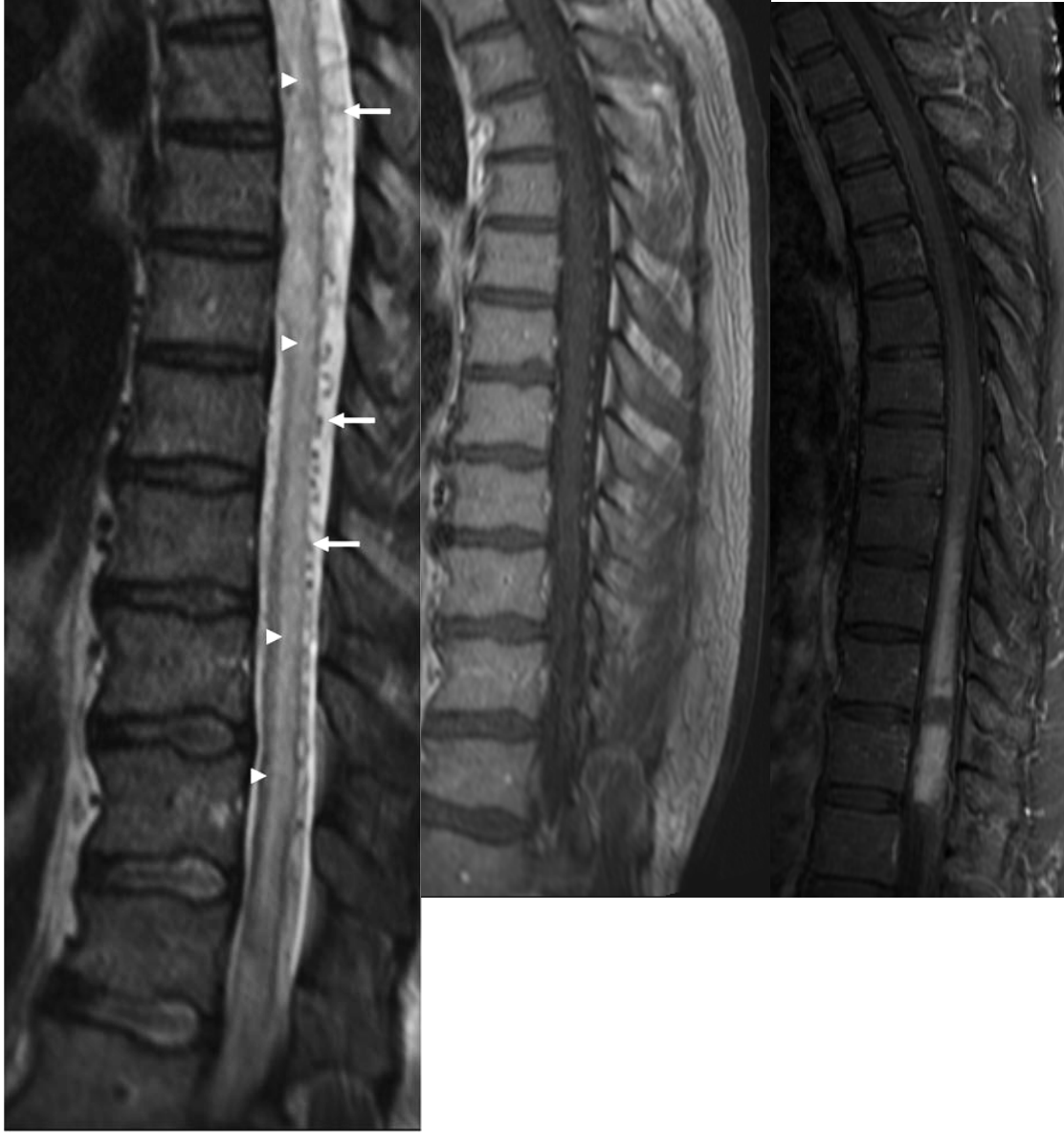
Kevin Messacar, Teri L Schreiner, John A Maloney, Adam Wallace, Jan Ludke, M Stephen Oberste, W Allan Nix, Christine C Robinson, Mary P Glodé, Mark J Abzug, Samuel R Dominguez

www.thelancet.com Published online January 29, 2015 http://dx.doi.org/10.1016/S0140-6736(14)62457-0

Dural AV fistula

- Progressive or stepwise myelopathy
- Valsalva/exertion
- Worse with steroids
- Dx: spinal angio





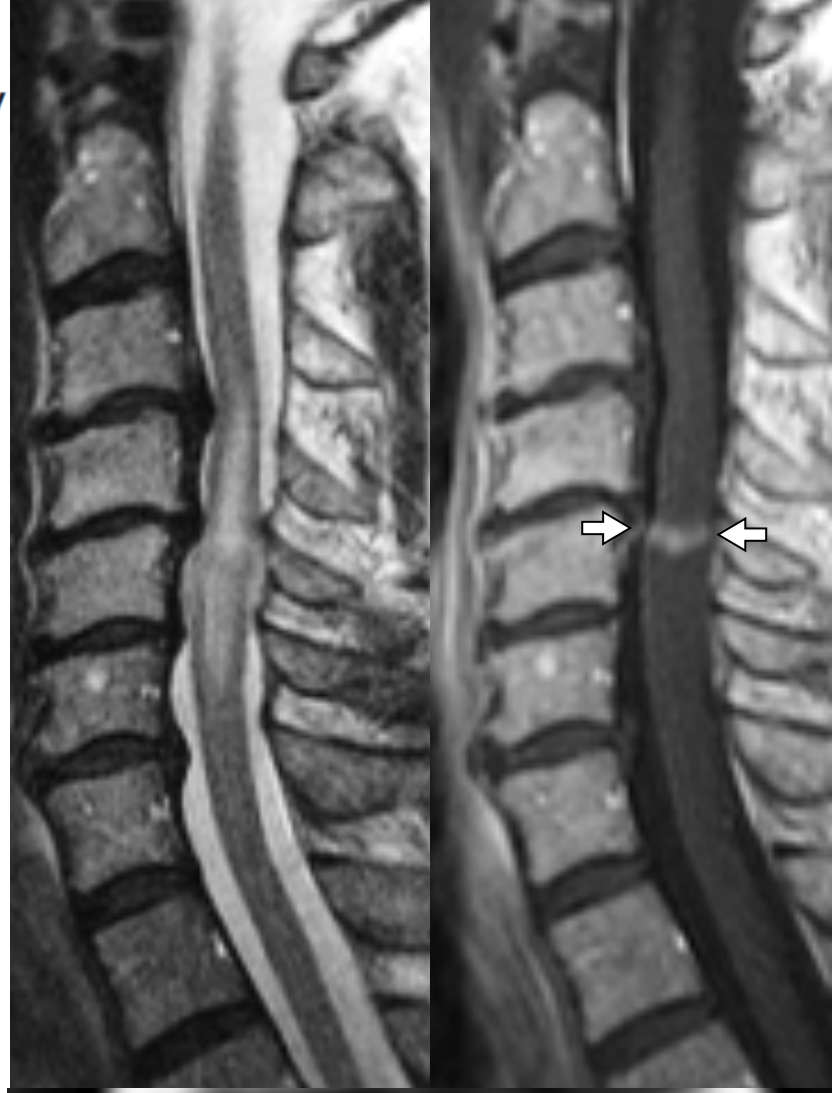
Rabinstein. Continuum 2015
McKeon et al. Neurology 2011
Zalewski et al. JAMA Neurol 2018

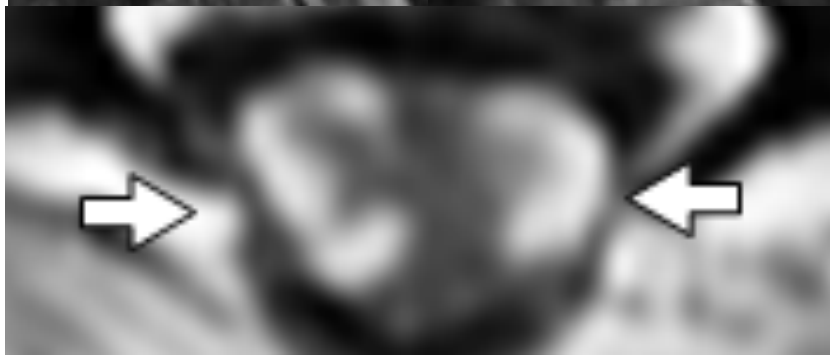
Specific Pattern of Gadolinium Enhancement in Spondylotic Myelopathy

Eoin P. Flanagan, MBBCh,[1] Karl N. Krecke, MD,[2] Richard W. Marsh, MD,[3] Caterina Giannini, MD, PhD,[4] B. Mark Keegan, MD,[1] and Brian G. Weinshenker, MD[1]

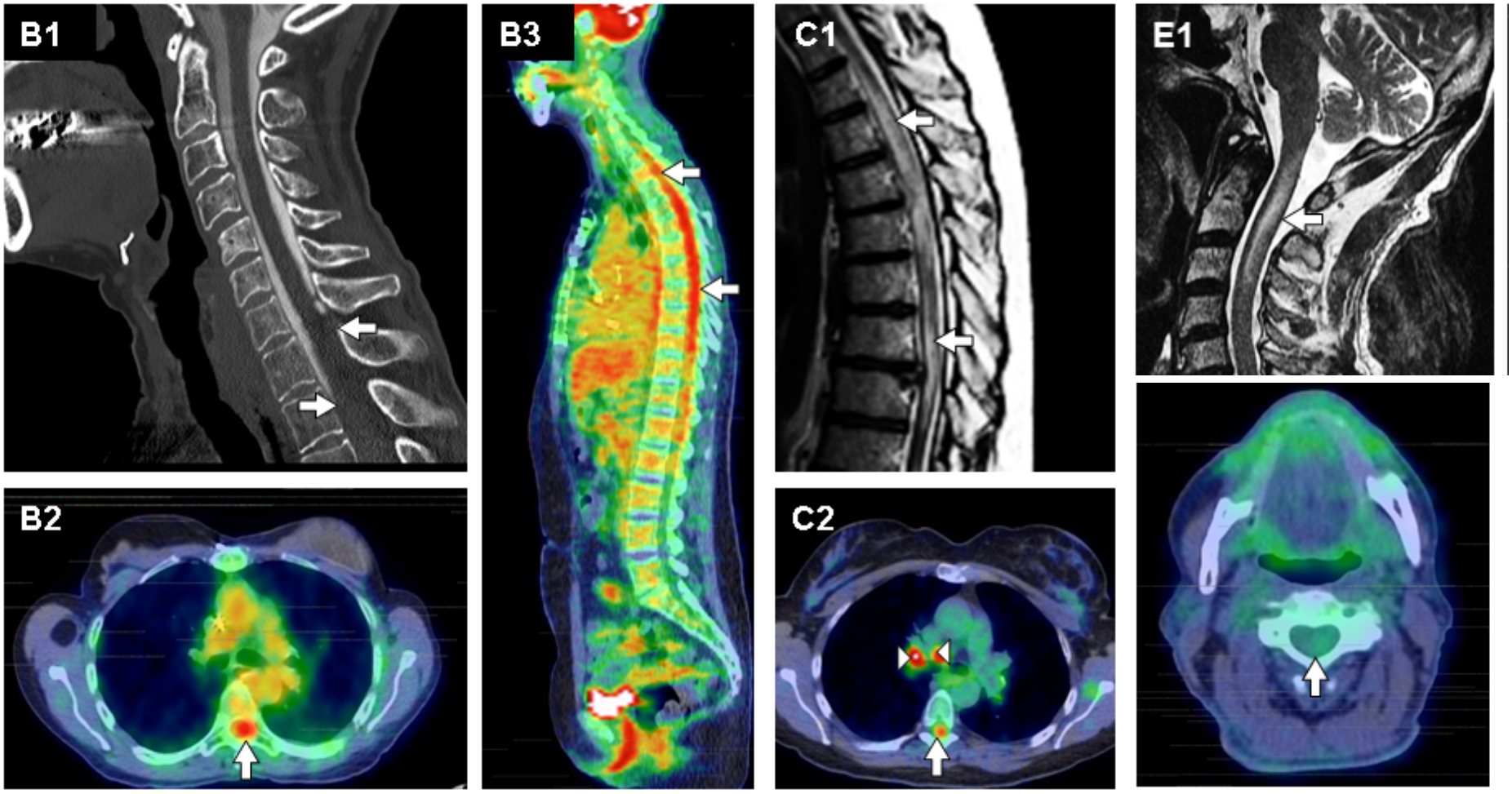
ANN NEUROL 2014;76:54–65

1. Pancake like or transverse band (width>height)
2. Location:
   - Just below max stenosis
   - Middle of T2-lesion
3. Axial circumferential sparing gray matter
4. Persists months up to 2 yrs after successful surgery





Neoplastic & Sarcoid have greater PET-FDG uptake than other inflammatory myelitis



Astrocytoma | Sarcoid | NMOSD

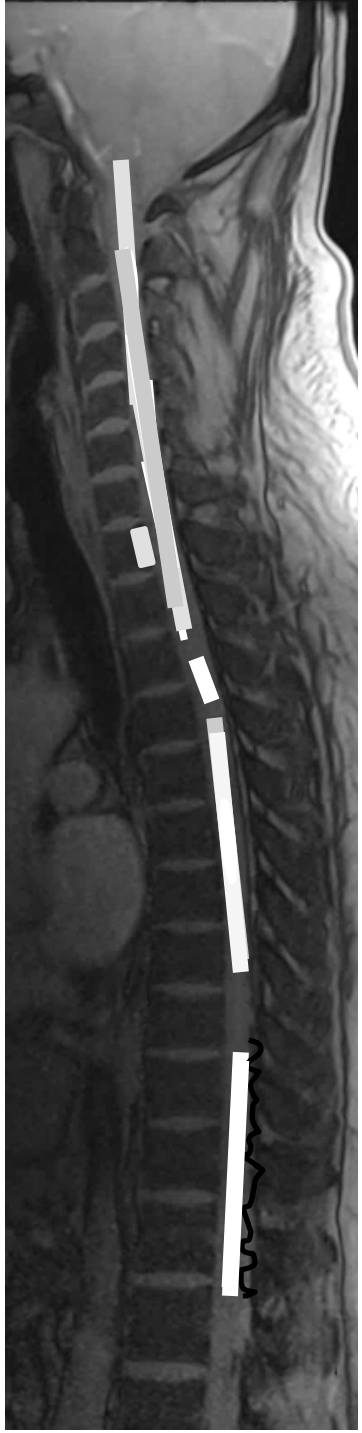
MAYO CLINIC

Flanagan et al. Mayo Clin Proc 2013

Other antibody associated myelopathy

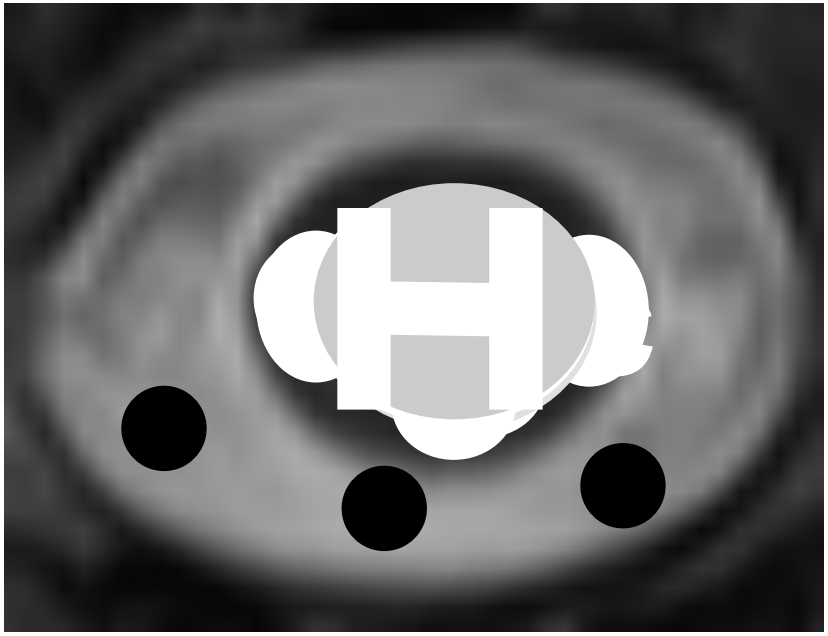
- GAD 65 & Glycine receptor antibody
  - MRI may be normal
  - May occur:
    - In isolation
    - As a component of PERM
    - As a component of stiff person syndrome

MAYO CLINIC



Eoin Flanagan MD, Mayo Clinic

Summary of T2 patterns



other tractopathy

Flanagan EP. Handb Clin Neurol 2016

Eoin Flanagan MD, Mayo Clinic

Summary of Enhancement Patterns

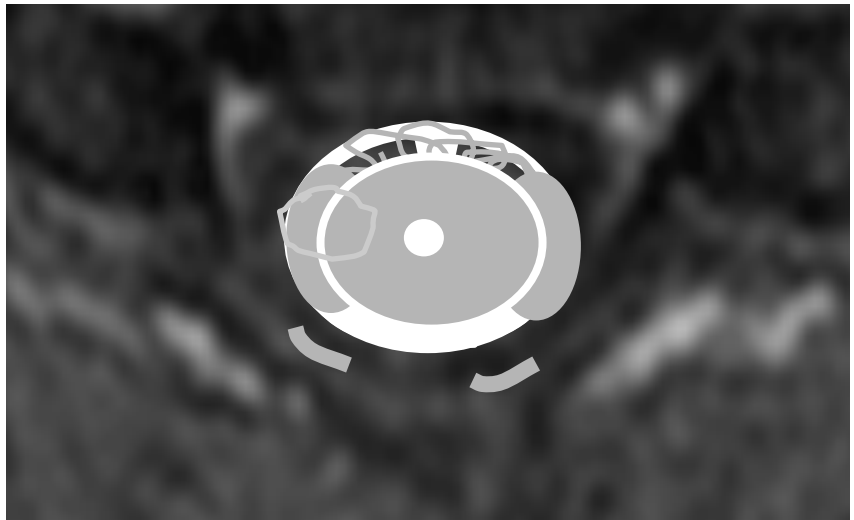
Spondylosis

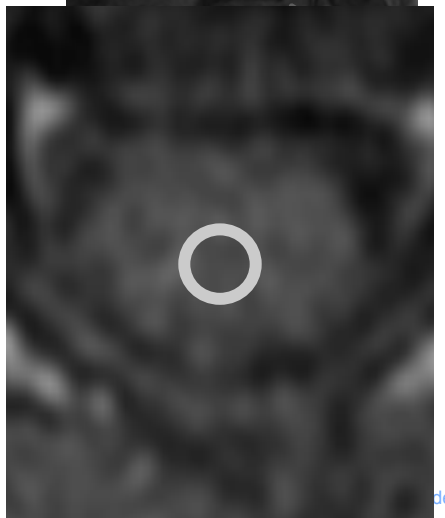
[redacted]

Dural AVF

Intramedullary metastasis

Paraneoplastic myelopathy





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