Paediatric MOG Associated Disease

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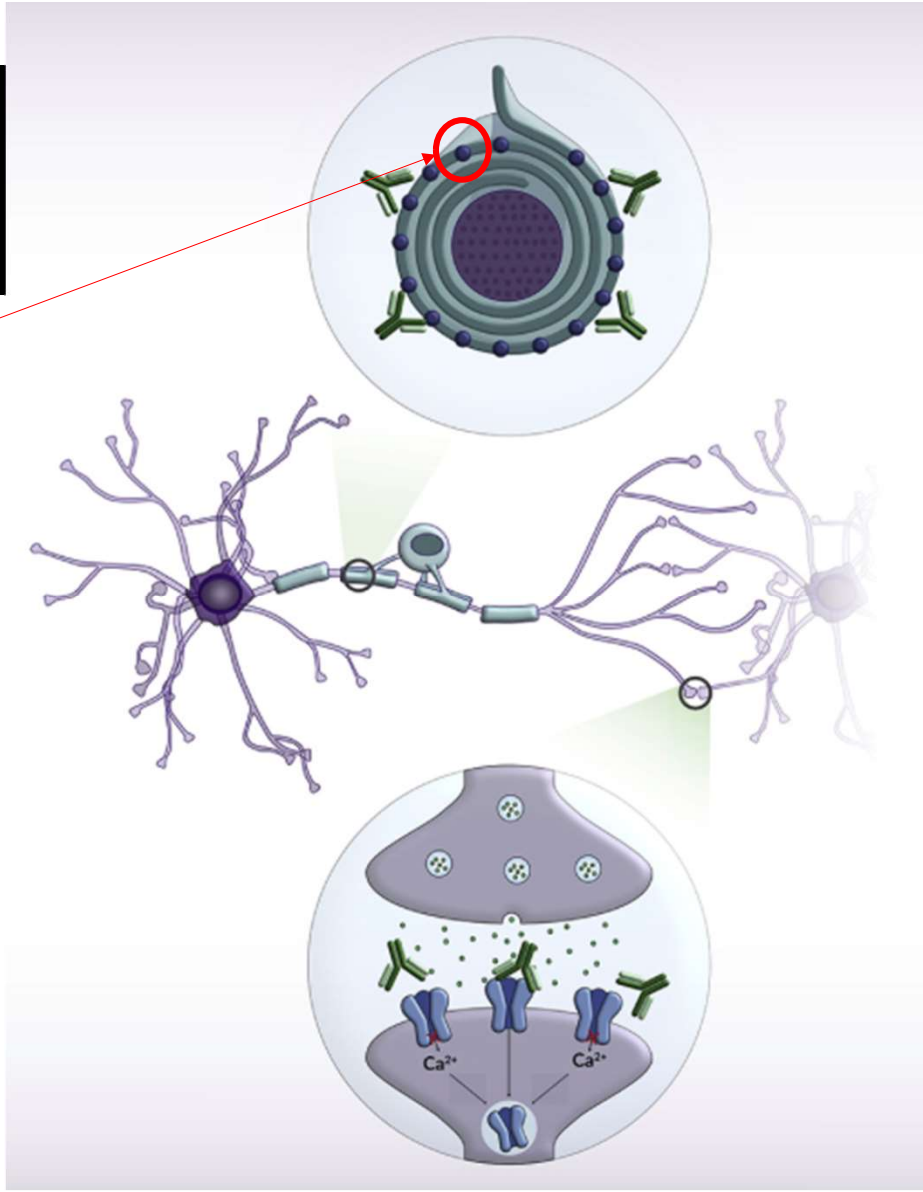
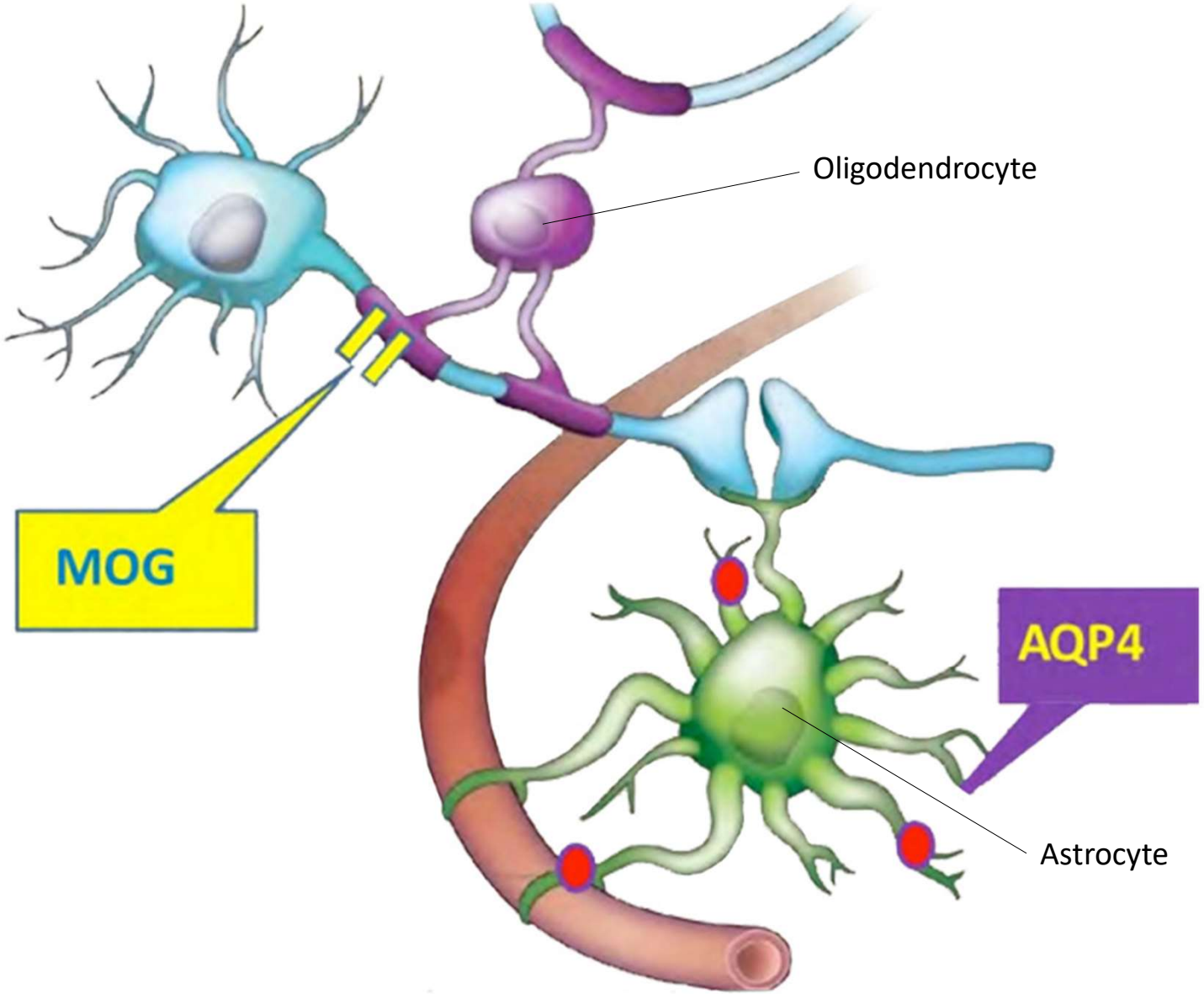
Introduction

- Myelin oligodendrocyte glycoprotein (MOG)
  - myelin transmembrane protein
- Sits on the outer lamella of the myelin sheath
- Contains and extracellular N terminus Ig-like domain onto which antibody can attach
- Position makes it an easy target for immune attack resulting in demyelination




Oligodendrocyte
MOG
AQP4
Astrocyte

History of MOGAD

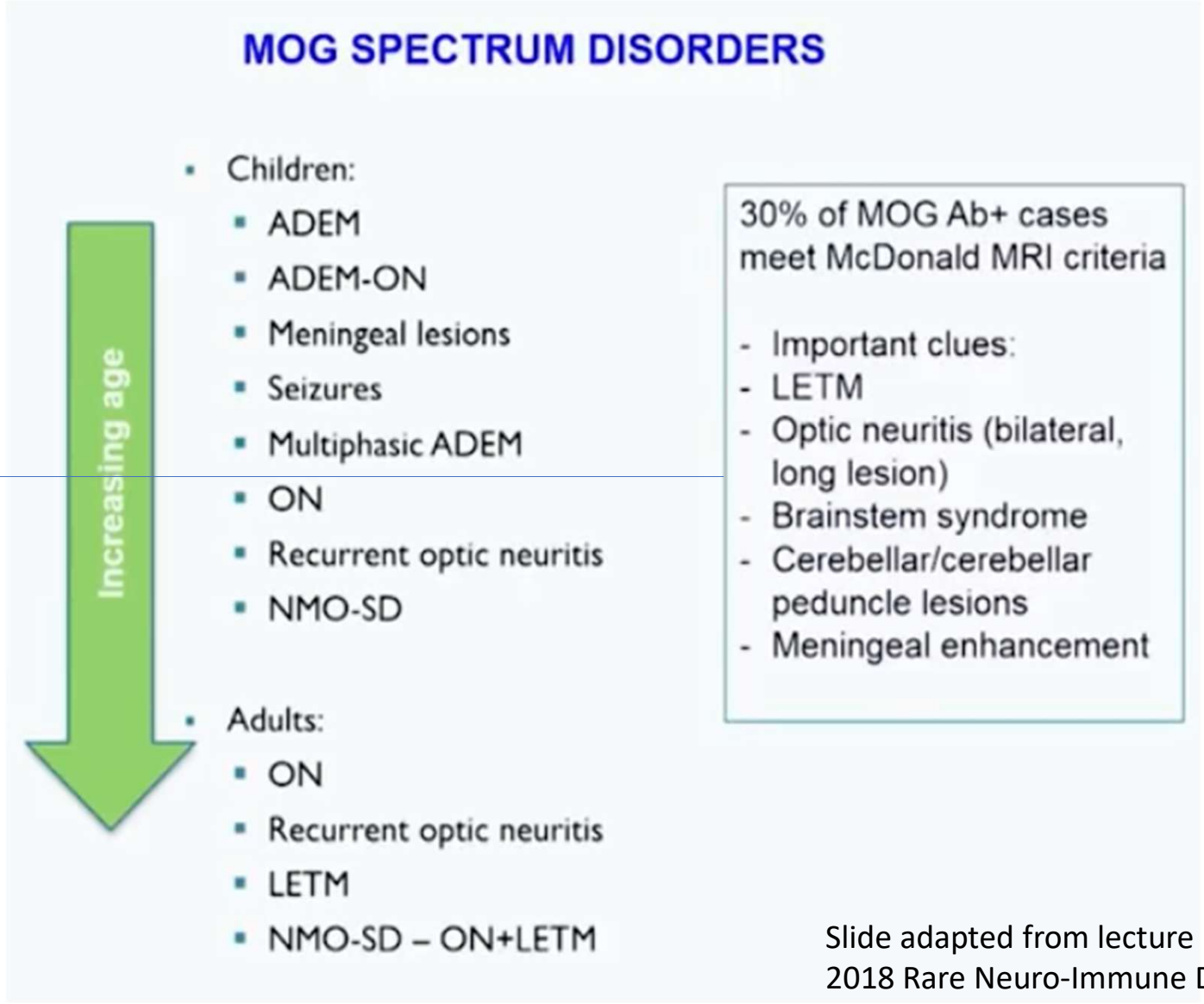
- Emerging disorder
- Discovered during Multiple Sclerosis research – now widely accepted to be distinct from MS
- Previous controversy due to testing methods detecting denatured MOG (present in all forms of non-specific demyelination)
  - Western blot
  - ELISA
- Cell based assays now used – for MOG-Ab IgG1
  - immunofluorescence or fluorescence-activated cell sorting
  - Have been modified and improved to improve sensitivity and specificity
  - Commercialized
- Early reports suggested it was similar to NMOSD
  - ~ 50% of AQ4-Ab-neg NMO test positive for MOG-Ab
- Now increasingly recognized as a distinct demyelinating disorder = MOGAD

MOG- Ab Testing

- Serum testing is most sensitive
- Most studies have used a cut off of ≥1:160
  - Cut off value is important, as low levels of MOG-Ab were also measured in healthy and other neurological controls.
  - Higher cut off (≥1:1280) is increases specificity for non-MS disorders
- MOG-Ab are synthesised systemically (not intrathecally)
  - CSF MOG-Ab have only been shown in patients with high serum Ab titres
  - CSF titres are much lower than serum titres
  - IgG index is generally negative
- Peripheral antibody production is similar to AQ4 Ab production

Clinical Spectrum of MOGAD

- May involve multiple regions simultaneously
  - More so that other causes of CNS demyelination
  - More than half of MOGAD patients have active lesions in more than one region simultaneously
- Some generalizations relate to age
  - No phenotype is restricted to any specific age group
  - MOG antibodies more prevalent in children than adults
- MOG-Ab more frequent in Caucasian (AQ4-Ab more common in non-Caucasian)
- Younger children: boys = girls
- As the population gets older, the proportion of females increases, but it does not reach the female predominance that AQ4-NMO or MS reaches
- Not associated with other autoimmune diseases or malignancy



+/-9 - 11 years

Slide adapted from lecture by: Tanuja Chitnis
2018 Rare Neuro-Immune Disorders Symposium

Neuroanatomic Presentations

- The next part of the discussion divides MOGAD into regional phenotypes
- Comparison will be made between MOG-Ab +ve and MOG Ab –ve:
  - ADEM
  - ON
  - TM
  - (Brainstem, encephalitis)
- Important to remember that these phenotypes are not distinct presentations
- MOGAD may involve multiple regions of the CNS simultaneously (~50%)

MOG-ADEM

- MOGAD frequently presents as ADEM or ADEM-like in young children (50%)
- ON and spinal cord may be concurrently involved with brain features
- MDEM – almost all MOG-Ab +ve
- A lot of overlap in clinical and radiological features at onset of MOG Ab +ve and –ve

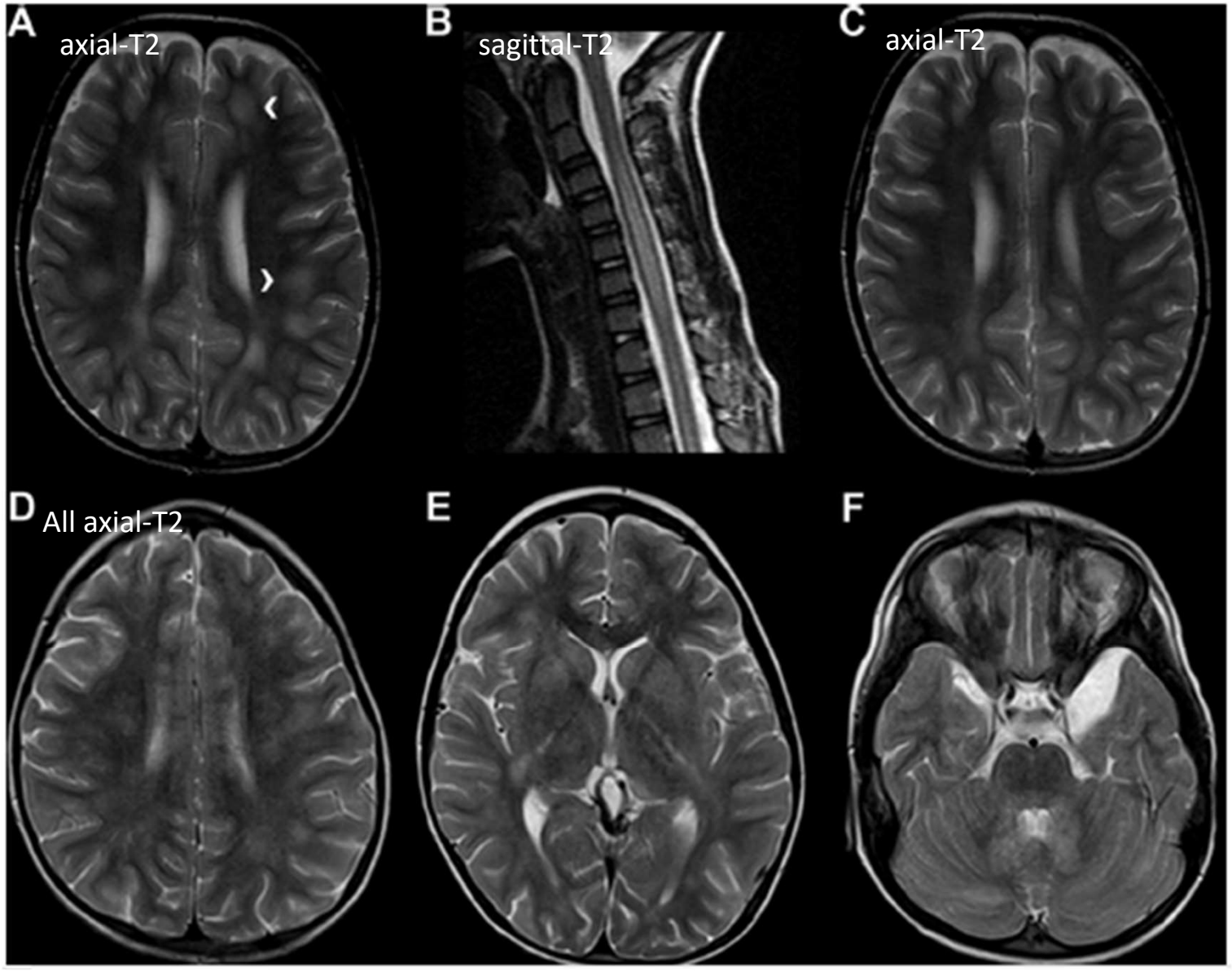
Distinguishing features of MOG-ADEM

	MOG-Ab +ve	MOG –Ab -ve	
Age (years) of presentation	4	7	p= 0.084
Female	50%	40%	p =1.000
Initial clinical presentation and severity	No significant difference		
OCB	6%	7%	p =1.000
CSF cell count / uL	~53	~10	p = 0.038
MRI	Large hazy bilateral lesions No atypical features Involvement of multiple anatomical regions Spinal cord involvement on imaging (92%) - LETM Cerebellum often involved (63%) Fast radiological resolutions (often < 1m)	Large hazy bilateral lesions More atypical lesions (small lesions, well defined lesions, periventricular)	
Relapse	More common (esp when Ab titers stay high)	Less common	
Associated ON	Common	Less common	
Recovery after initial episode	More complete and quicker		

Baumann M, et al. J Neurol Neurosurg Psychiatr, 2015

A: Bilateral hazy lesions
B: LETM
C: Resolution

D: Extensive bilateral hazy lesions
E: BG and thalamus lesions
F: Cerebellar and brainstem lesion

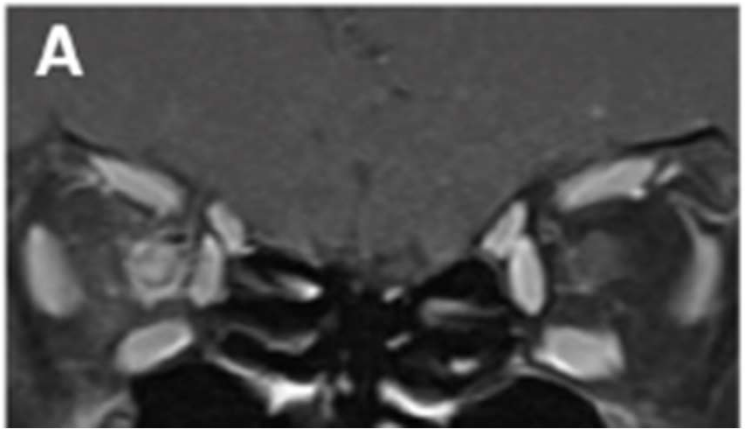


MOG-ON

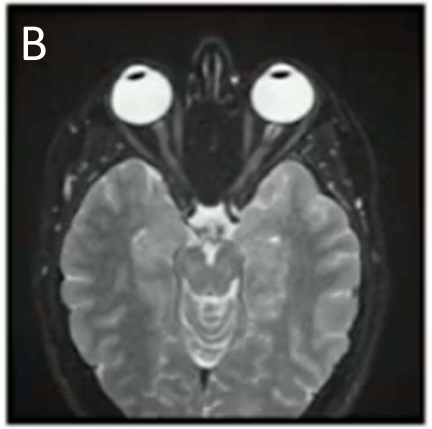
- ON is the most common initial presentation of MOGAD in adolescents and adults
- Frequent in children too
- Higher risk of relapse than other presentations of MOGAD

Distinguishing features of MOG-ON

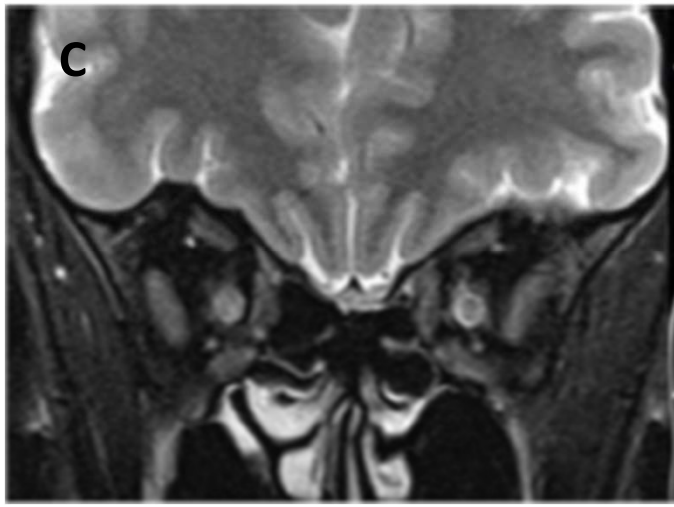
		MOG-Ab +ve	MOG-Ab -ve
Age at presentation		Younger	
Sex Ratio		Less female predominance	Female >> Male in AQ4-NMO and MS
Visual Loss at presentation		Severe	Less severe in all
Bilateral involvement		Common (~80%)	Very uncommon in MS Common in AQ4-NMO
Recovery		Good (20/25 vison @ 6m)	Poor (counting fingers) in AQ4-NMO
Relapse		Very likely	Likely in AQ4-NMO
Optic disc oedema		Common (~86%)	Rare in MS and AQ4-NMO
Peripapillary haemorrhage and “macular star”		Described	Highly atypical in all (can be seen in infx)
MRI	Longitudinally extensive ON enhancement (>2 segments of the ON involved)	Classic	Common in AQ4-NMO Uncommon in MS / isolated ON
	Segment of ON involved	anterior ON	Chiasmal / post chiasmal
	Perineural optic enhancement	~50%	Rare



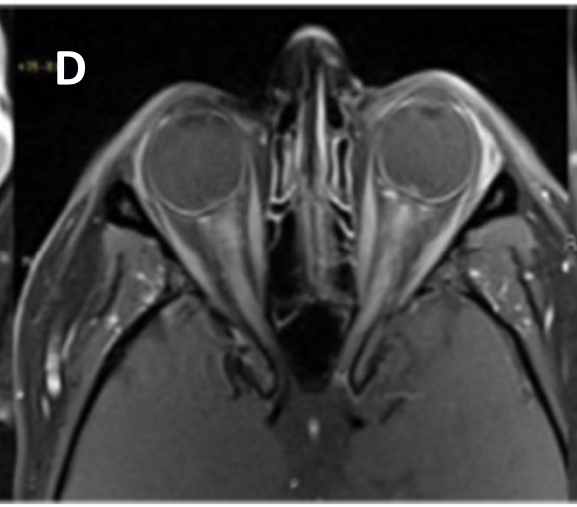
T1 coronal GAD+ : enhancement of optic nerves + R perioptic neuritis



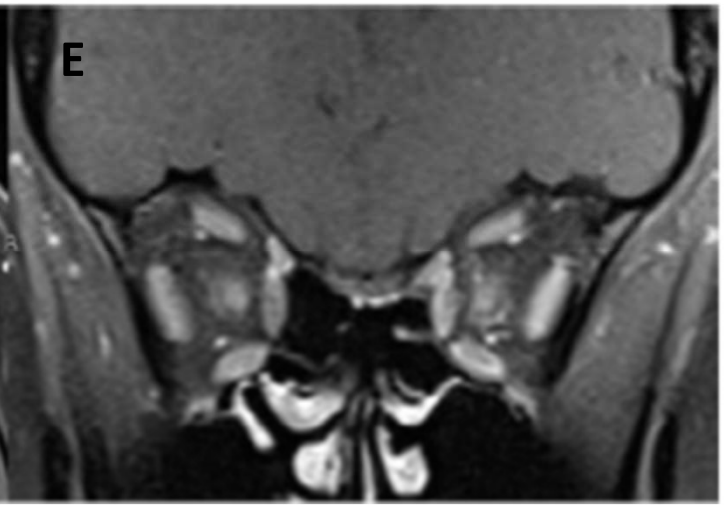
Fat saturated T2 :
LEON and nerve sheath enhancement



Coronal fat saturated T2:
Hyperintensity of the ON



Axial fat saturated GAD+ T1



Coronal fat saturated GAD+ T1

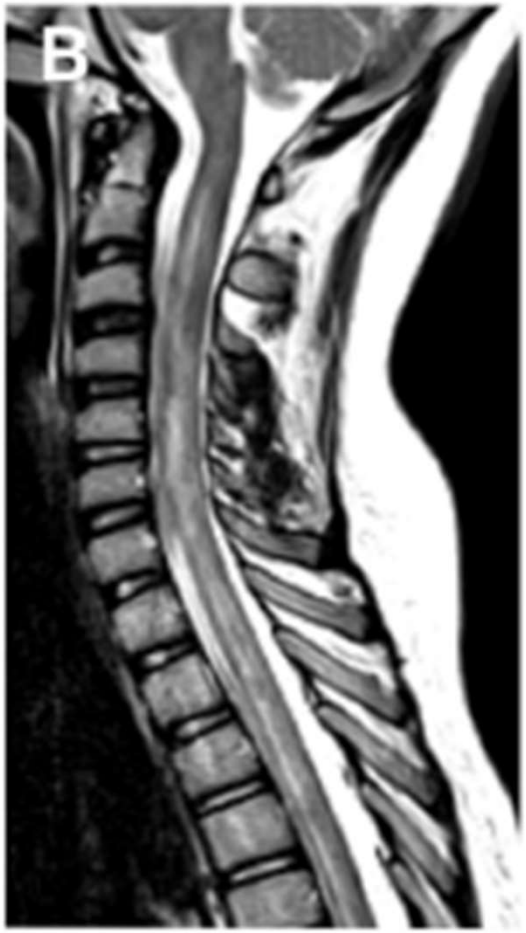
Bilateral LEON – enlargement and contrast enhancement

MOG-TM

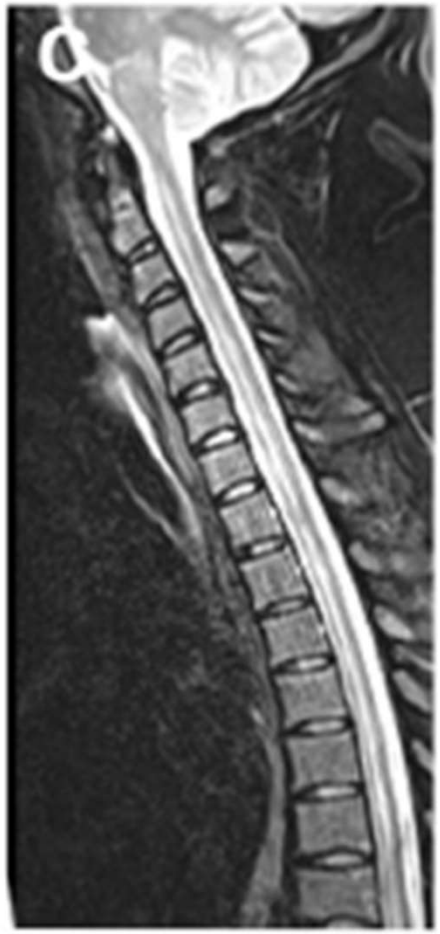
- TM is a relatively common presentation in adults
- Can be seen in children as well
- Can have antecedent infection or vaccination
- Typically steroid responsive with a favorable prognosis
  - ~10% poor prognosis
- MOG-Ab are uncommon in isolated TM

Distinguishing features of MOG-TM

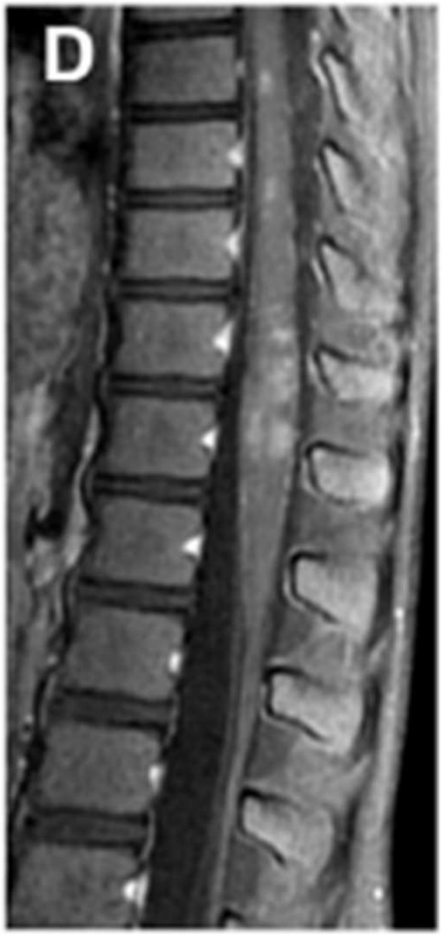
	MOG-Ab +ve	**MOG-Ab -ve**
Clinical severity	Milder, recover quicker and more completely	More severe and residual deficits
Segment involved	Anywhere Predilection for the conus medullaris	AQP4-Ab: Cervico-thoracic MS: Focal
Bladder and bowel involvement	Common	Less common
Longitudinally extensive involvement	Almost always	Common in NMOSD
Gadolinium enchancement (acute)	Much less common (~26%)	Common in NMOSD (~78%)
Multifocal involvement	Common (≥2 noncontiguous lesions ~62%)	Uncommon
Gray matter involvement	Predilection for GM involvement Pseudo-dilation H-sign (~26%)	Less commonly involved H-sign(~6%)



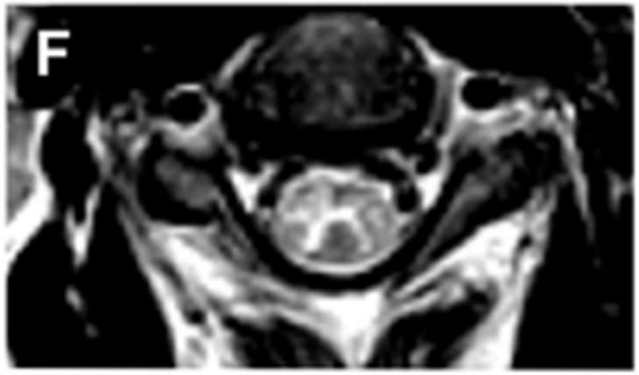
Sagittal STIR:
longitudinal extensive patchy lesion spaning from cervical to thoracic cord.



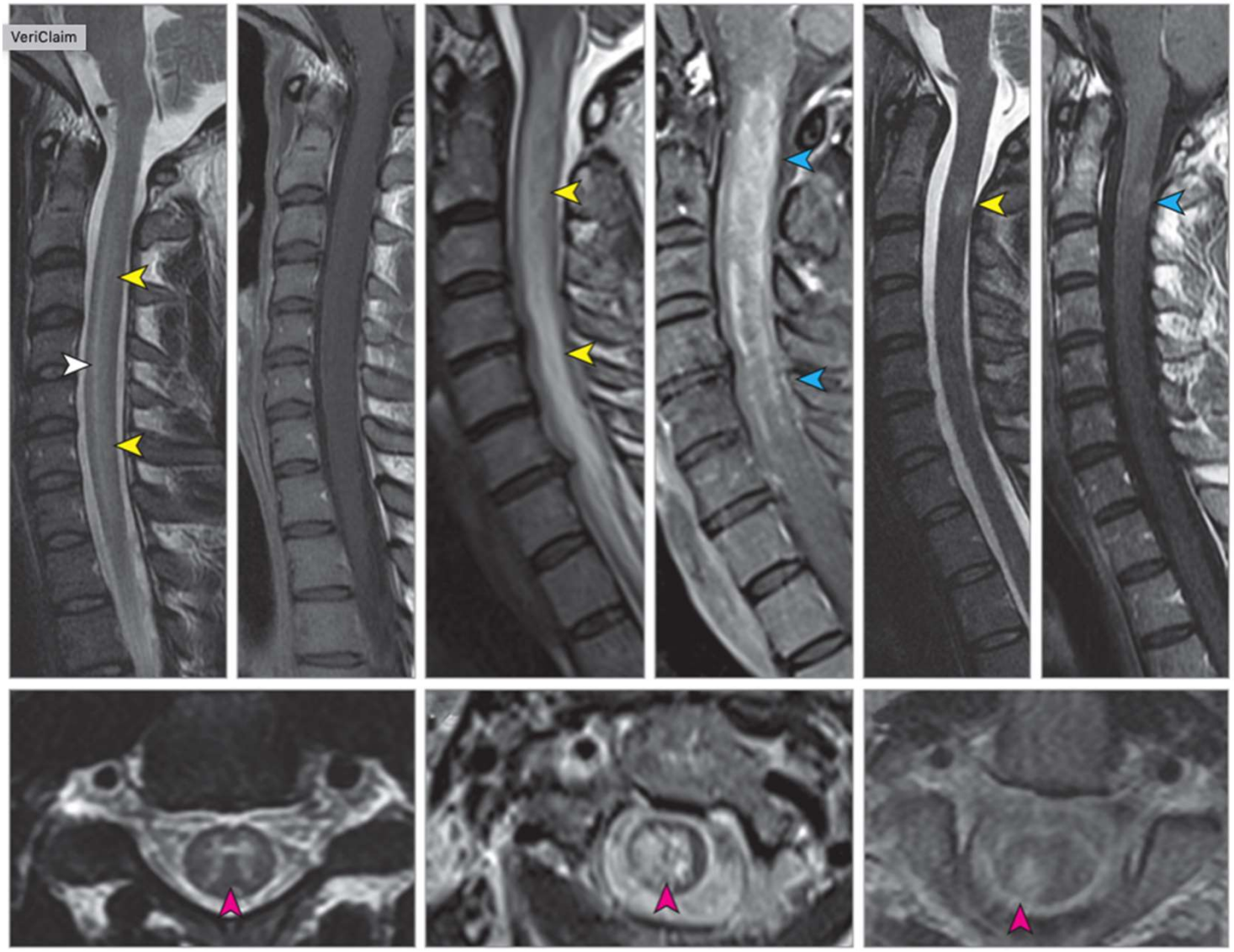
Sagittal T2:
hyperintense longitudinally extensive "pseudo-dilation" of central canal



Sagittal T1 post gadolinium contrast:
showing patchy enhancement of the conus



Axial T2 of upper cervical cord:
Hyperintense "H" sign


VeriClaim
MOG
AQ4
MS

MOG-Brainstem Involvement

- 30% of MOGAD has brainstem involvement
- Poor prognostic indicator for higher disability at long term follow-up
- Usually concomitant with
  - Spinal cord (89%)
  - Cerebral (66%)
  - ON (40%)
  - Isolated
- Most commonly the medulla

MOG Encephalitis / Cerebral involvement

- Encephalopathy without radiological features of ADEM
- Seizures – MRI changes later
- FLAIR-hyperintense lesions, Anti MOG associated encephalitis with seizures (FLAMES) – specific to MOGAD
  - Seizures (focal onset tonic-clonic), headache, fever
  - Respond to high dose steroids
  - Associated with ON (before or after)
- NMDAR encephalitis
  - MOGAD syndrome may precede or follow NMDAR encephalitis
- CNS Vasculitis

MOGAD vs MS

30 % of MOG Ab+ cases meet McDonald MRI criteria

Important clues suggesting MOGAD rather than MS:

- LETM
- ON (esp bilateral, LEON)
- Brainstem involvement
- Cerebellar / cerebellar peduncle lesions
- Meningeal enhancement

Distinction is important as treatment differs

Investigations

Neuroimaging

- Children with MOG-Ab may present with four MRI patterns: (1) multifocal
- hazy/poorly marginated lesions, involving both graymatter and whitematter
- and typically involving the middle cerebellar peduncles; (2) spinal cord and/or
- optic nerve involvement with normal intracranial appearance, or non-specific
- white matter lesions; (3) extensive and periventricular white matter lesions, resembling
- a “leukodystrophy-like” pattern; and (4) cortical encephalitis with
- leptomeningeal enhancement. Dramatic resolution, sometimes within amonth of
- presentation, has been the radiological hallmark of MOG-Ab, perhaps suggesting
- that there is more edema than demyelination

Optical Coherence TomographyOptical coherence tomography (OCT) and electrodiagnostic tests can be useful

- paraclinical parameters in patients with ON [36•]. OCT quantifies retinal nerve
- fiber layer (RNFL) and ganglion cell layer thinning, and the development of
- microcystic macular edema and retinal damage. OCT offers an opportunity to
- monitor disease activity and progression non-invasively.

Treatment

- Acute Phase is responsive to steroids
  - Weaning / cessation – associated with relapses
  - ? Need longer courses or longer weaning (some suggest up to a year)

- Immunosuppression generally not given after first event in MOGAD
  - High rate of monophasic courses
    - (~30% monophasic, ~20% will relapse after many years)
  - In NMOSD – milder phenotype than AQ4-Ab +ve

- Recent reports have highlighted that MOGAD does relapse and accrue disability
  - Raises questions about how maintenance treatment should be managed

Ramanathan et al., J Neurol Neurosurg Psychiatry. 2017 Nov 15

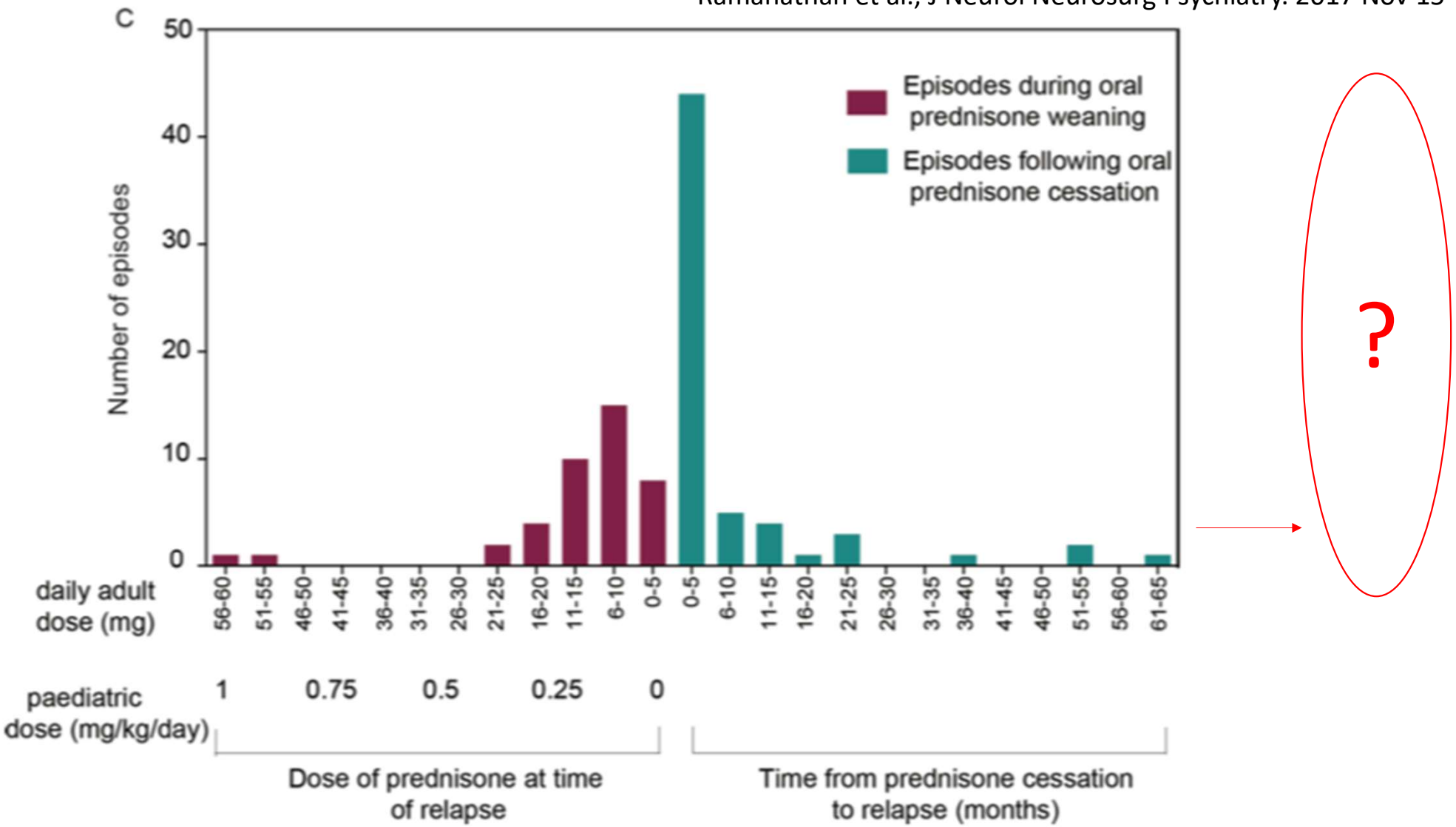
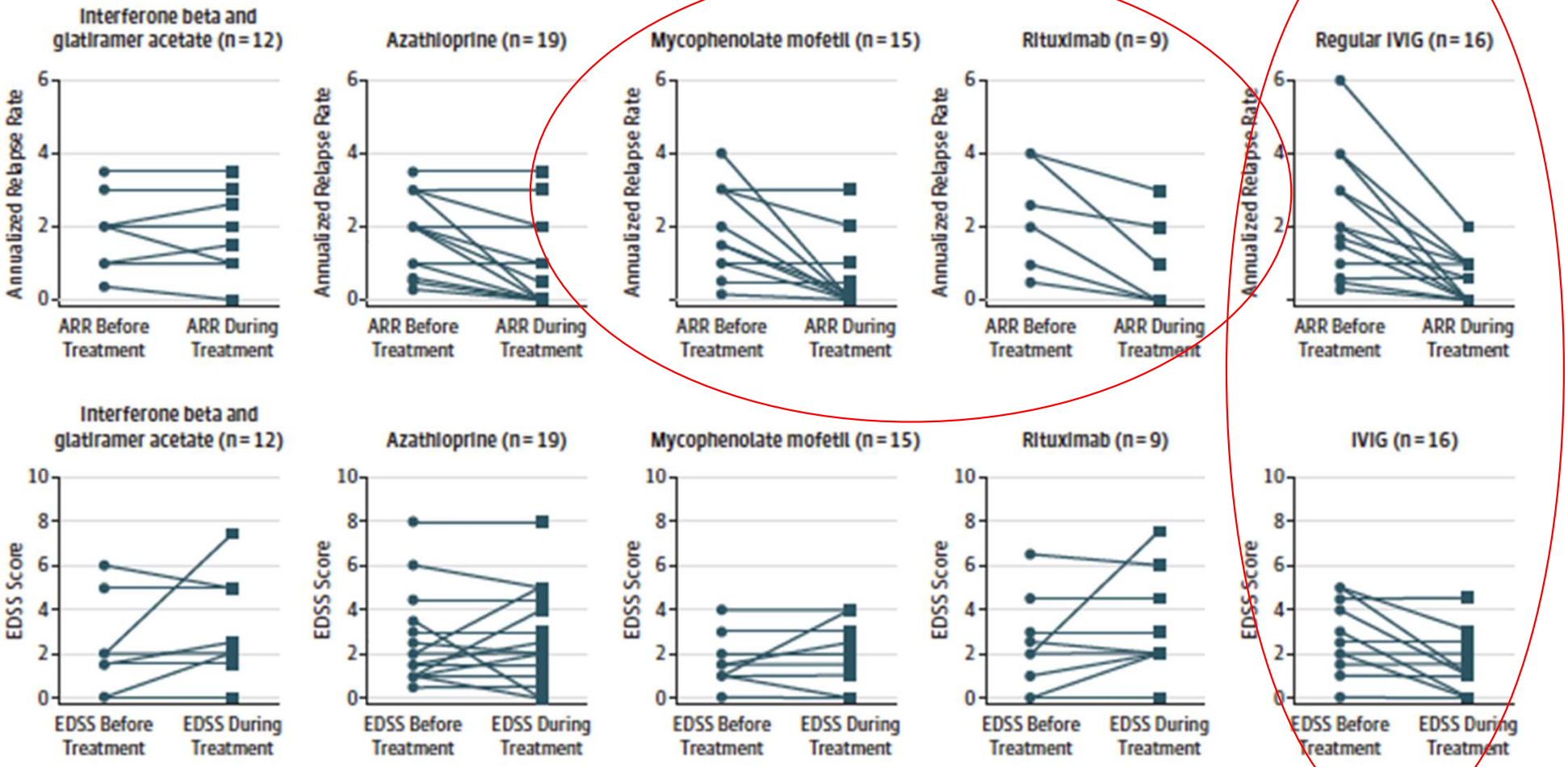


Figure 3. Efficacy of Various Disease-Modifying Therapies in Patients With Myelin Oligodendrocyte Glycoprotein Antibody-Associated Relapsing Demyelination Patients



Hacohen , JAMA neurology, 2018

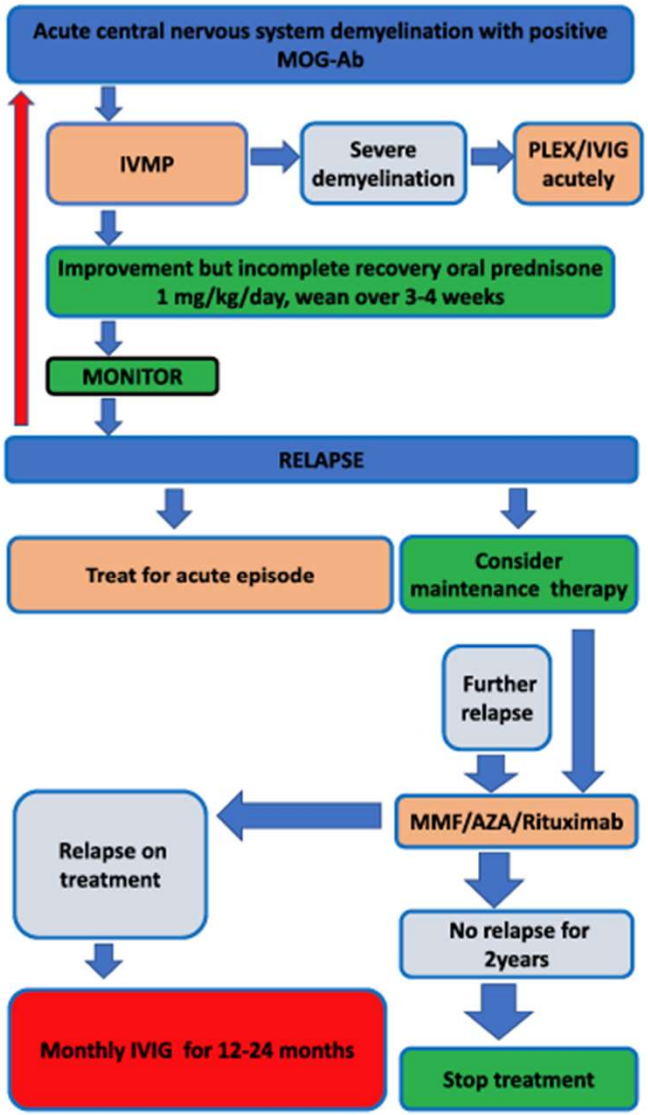


Fig. 2. Treatment algorithm for children with MOG-Ab-associated disease. IVMP intravenous methylprednisolone, PLEX plasma exchange, IVIG intravenous immunoglobulin, AZA azathioprine, MMF mycophenalate mofetil.

Hacohen and Barnwell, Curr Treat Option Neurol 2019.

Relapses

- Identifying patients at risk for relapses and treating relapses is the current focus, as accumulation of disability is thought to be relapse related

- If follow-up Ab testing is still positive – increases the chance of relapse
  - No children are negative at time of relapse, but may become negative in between
  - Not exactly a liner relationship
  - Studies limited by possible extended time to relapse (can be up to 10 years in MOGAD, compared to 1-2 years in AQP4-Ab +ve)
  - Most studies are using a 6 monthly interval for follow-up antibody testing

- Higher titers may be associated with relapses
  - Currently not reliable enough to use for guiding patient management

- Other biomarkers: Neurofilament light chain, glial fibrillary acidic protein and tau are under study

Future Directions

- Diagnostic Criteria for MOGAD
- Better understanding of pathophysiology and triggers
- Reliable biomarkers / predictors for relapse
- Longitudinal follow-up
- Studies of medication efficacy and therapeutic targets

Take home

- MOGAD often involves multiple CNS regions simultaneously or sequentially
- Clinical and radiological features are not specific but constellations are suggestive
- Resolution of acute phase is usually better than MOG-Ab neg
- Relapses are common (up to 70%)

Look out …

EU consortium consensus statements on
Paediatric MOGAD
EJPN

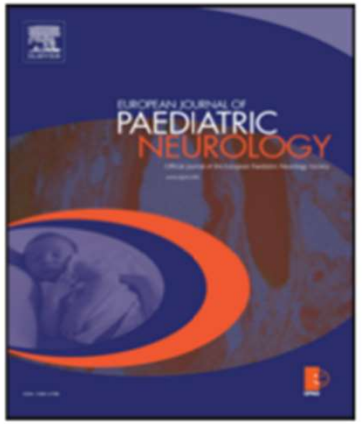
1. Clinical features and a classification

2. Radiological features

3. Diagnostic properties and biomarkers

4. Outcome assessment tools

5. Treatment – acute and maintenance



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Questions