Updates in Pediatric Neuro-immunology

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September 22, 2020

Boston Children's Hospital
Until every child is well™

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Disclosures

- Have received research funding for clinical trial site participation from Biogen, Novartis and Roche
- Have received research funding from Pfizer
- Medications will be off label for indication and/or age except where discussed

Goals

- Correctly apply updated diagnostic criteria for relapsing remitting multiple sclerosis and neuromyelitis optica and be aware of changes in treatment paradigms
- Recognize the exploding significance of anti-myelin oligodendrocyte glycoprotein (MOG) antibodies
- Know the causes of encephalitis and available diagnostic techniques

Diagnostic Categories in Pediatric Neuro-immunology

- Demyelinating
  - Monophasic
  - Chronic relapsing
- Non-demyelinating
  - Encephalitis
    - Autoimmune
    - Infectious
  - Other
    - Rheumatologic
    - Epilepsies

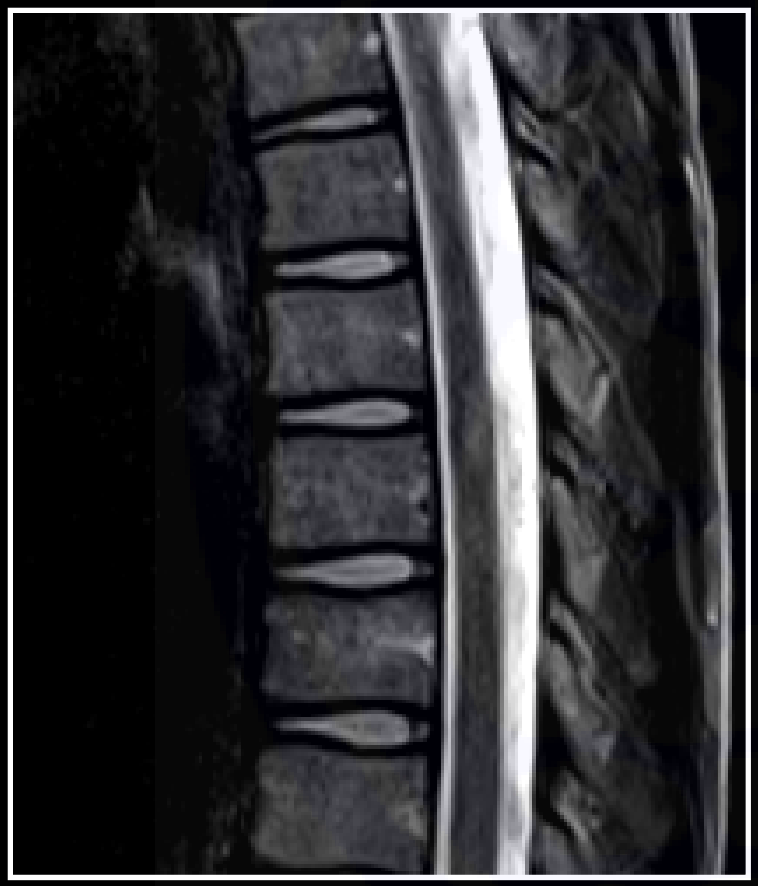
Demyelinating Disorders

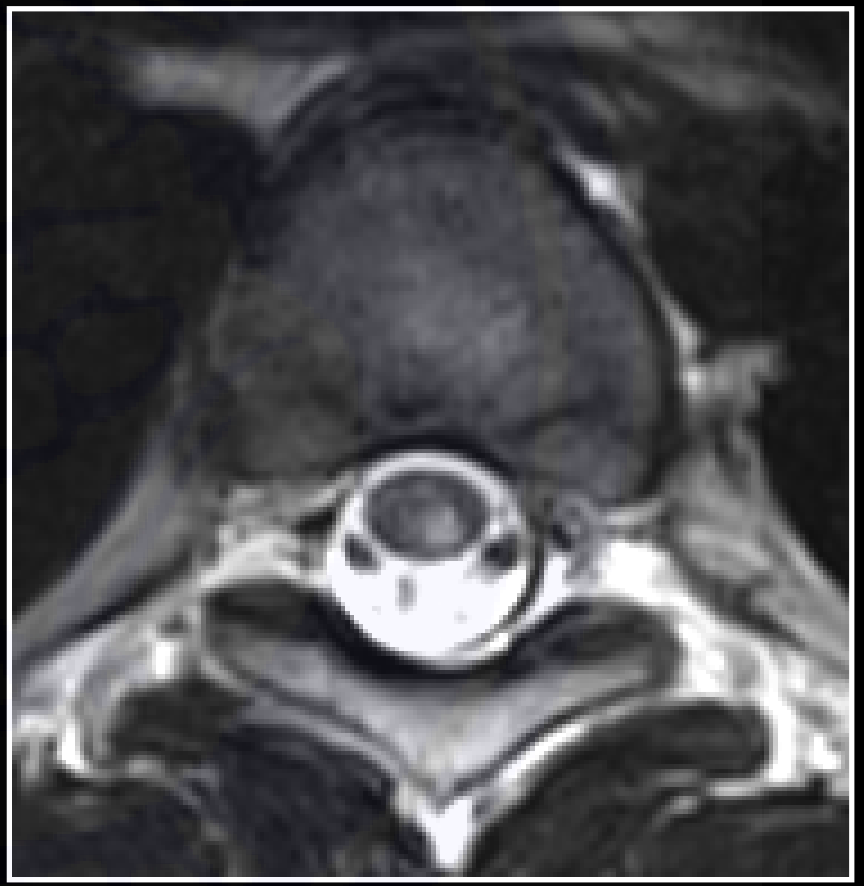
- Monophasic
  - Acute disseminated encephalomyelitis (ADEM)
    - Must have encephalopathy
    - With or without anti-myelin oligodendrocyte (MOG) antibodies
  - Clinically isolated syndromes (CIS)
    - Optic neuritis: +/- anti-MOG antibodies
    - Transverse myelitis: +/- anti-MOG antibodies
    - Other: +/- anti-MOG antibodies
- Chronic relapsing
  - Relapsing remitting multiple sclerosis (RRMS)
  - Neuromyelitis optica spectrum disorder (NMOSD)
  - Relapsing anti-MOG antibody disorders (MOGAD)

Case 1

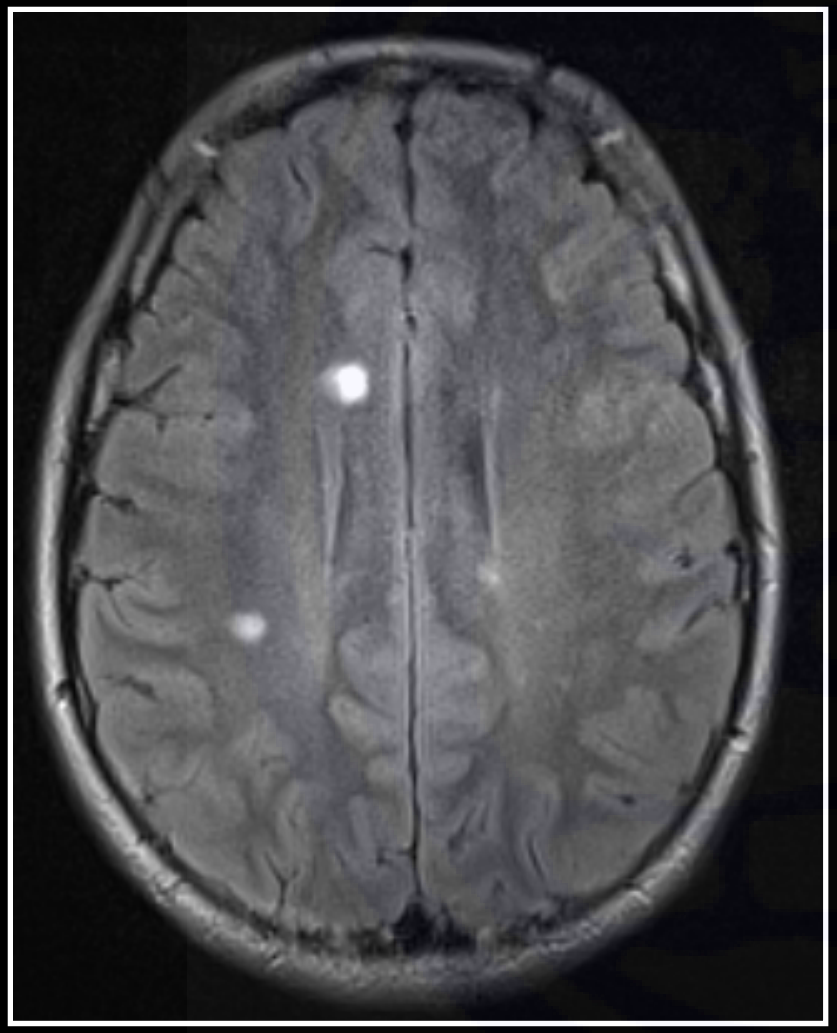
- 14yo girl with numbness and tingling of torso and left leg
- Soon after exercise, developed pins and needles sensation on her left torso above level of umbilicus which spread over 2 days to her left leg
- No prior episodes
- Minimal left leg weakness; no bowel/bladder symptoms
- On exam, 5-/5 left iliopsoas weakness, sensory level to T11 of left torso

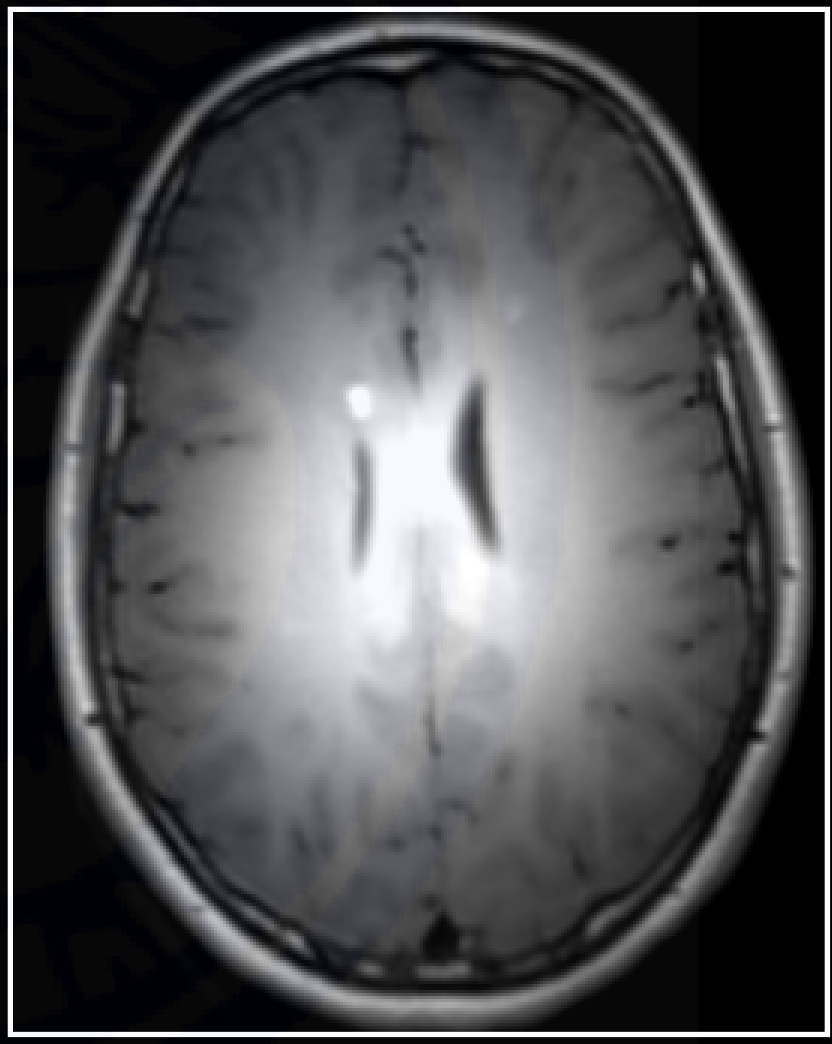
Case 1





Case 1





What is the correct diagnosis?

- Acute disseminated encephalomyelitis
- Acute partial transverse myelitis
- Neuromyelitis optica spectrum disorder
- Relapsing remitting multiple sclerosis

2017 MS McDonald Criteria

- Applies ONLY to patients with clinically isolated syndromes and not to ADEM
  - ADEM diagnosis requires encephalopathy
- Dissemination in space: ≥ 1 T2 lesion in at least 2 of the following 4 areas
  - Periventricular
  - Subcortical
  - Infratentorial
  - Spinal cord

Thompson AJ, et al. Lancet Neurology 2018 Feb;17(2):162-173

2017 MS McDonald Criteria

- Dissemination in time
  - New T2 and/or contrast enhancing lesion at any time
  - Simultaneous presence of asymptomatic contrast enhancing and non-enhancing lesions
  - 2nd clinical attack
- CSF specific oligoclonal bands can substitute for dissemination in time
- Exclusion of other causes!
- Allows for diagnosis of relapsing remitting MS at first attack

Thompson AJ, et al. Lancet Neurology 2018 Feb;17(2):162-173

Case 1

- Rationale for early diagnosis and treatment
  - Delayed time to second clinical attack
  - Reduced annualized relapse rate
  - Reduced formation of new MRI lesions
  - Decreased risk of long term disability
- Which of the 20 (!) disease modifying therapies (DMT) approved for adult RRMS would you prescribe to her?

Treatment options

- Injectables (conventional “first line”)
  - Interferon beta (multiple forms)
  - Glatiramer acetate (multiple forms)
- Oral
  - Dimethyl fumarate (and related medications)
  - Fingolimod (and related medications)
  - Others (teriflunomide, cladribine)
- Infusion therapies
  - Natalizumab
  - B cell depleting agents (rituximab, ocrelizumab)
  - Others (alemtuzumab, mitoxantrone)

Fingolimod vs. interferon beta-1a RCT

- Oral once daily sphingosine-1-phosphate receptor modulator
  - Decreases egress of lymphocytes from nodes
  - Reduces absolute lymphocytes by ≈ 70%
- Randomized double blind trial in patients with MS ages 10-17 years old (mean 15.3)
- 82% reduction in annualized relapse rate in fingolimod (n=107; 0.12) versus interferon beta-1a (n=108; 0.67)

Chitnis T, et al. N Engl J Med 2018 Sept;379:1017-27

Potential adverse events of fingolimod

- Cardiac arrhythmias
  - First dose in supervised setting due to risk of bradycardia
  - 1 case of 2nd degree AV block in trial
- Infections
  - PML (≈ 1/15,000), herpes encephalitis, cryptococcal meningitis
  - No serious infections in trial
- Lymphopenia, leukopenia
- Macular edema (1 case in clinical trial)
- Seizures in 6 (5.6%) in clinical trial

Chitnis T, et al. N Engl J Med 2018 Sept;379:1017-27

Oral and infusion therapies are more effective than injectables in POMS

- In a US Network of Pediatric MS Centers study, 197 patients treated with newer and 544 patients with injectables as initial DMT for a mean of 1.5 to 1.8 years
- Those treated with newer agents had significantly lower relapse rate (0.22 versus 0.49), rate of new T2 lesions and rate of new gadolinium enhancing lesions
- Greater effect of infusion therapies than oral agents on relapse rate

Krysko KM, et al. Ann Neurol 2020; 88:42-55

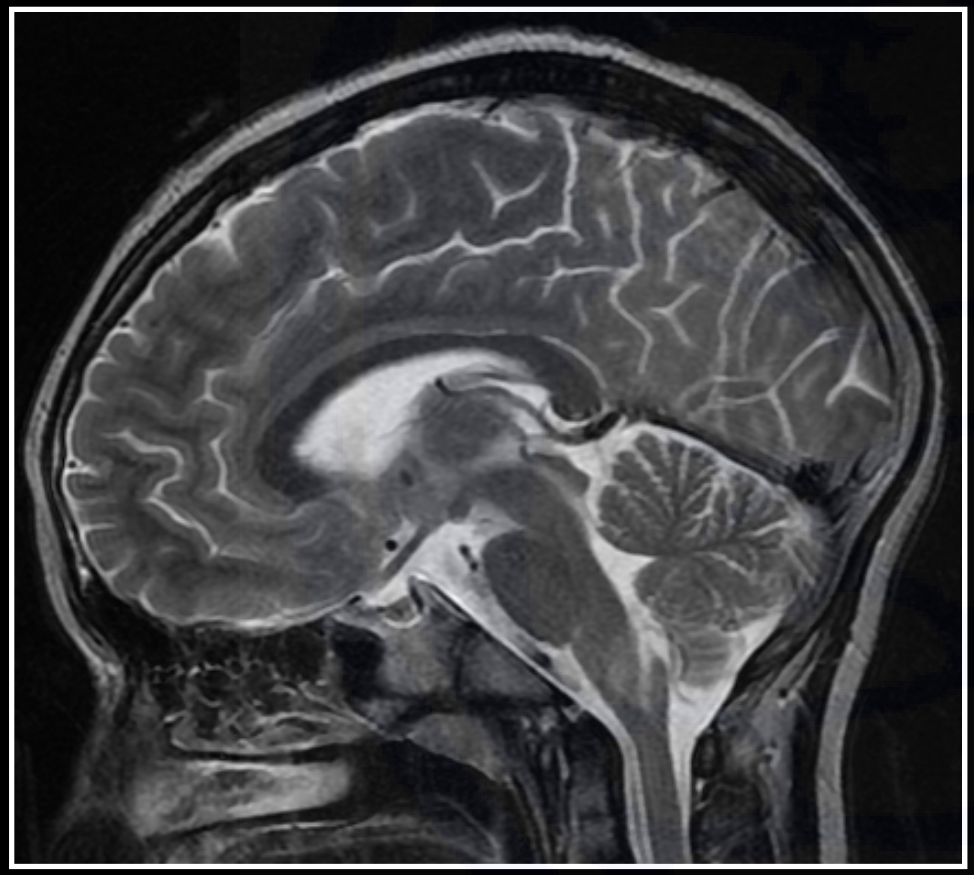
MS – take home points

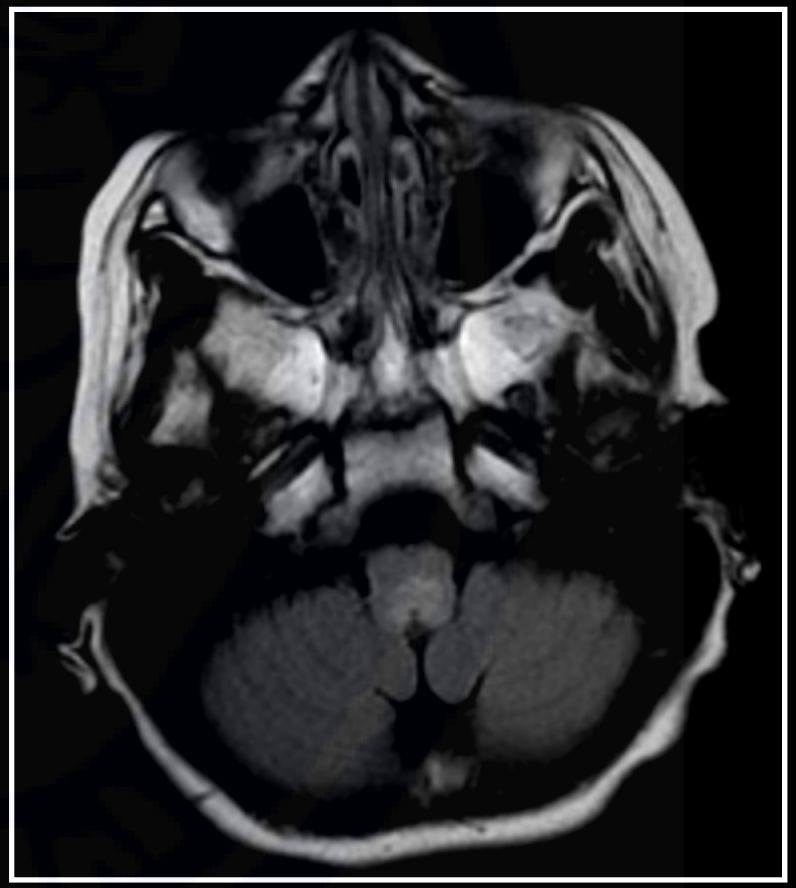
- Correct application of diagnostic criteria for MS can lead to earlier diagnosis and institution of effective treatment
- Many treatment options for MS including 1st FDA approved treatment for ages 10-17
- Newer agents are more effective than injectable agents; with the newer agents, infusion therapies appear more effective than oral agents
- Longer term data are needed to assess potential risks of chronic immunosuppression in POMS with particular focus on infections, immune function and malignancies

Case 2

- 8yo African American girl with vomiting and ataxia
- 1 month prior to admission developed 3-5 episodes of vomiting daily with emergency department visits and admissions; no diagnosis
- 1 day prior to admission developed unsteady gait
- Mother has Grave's disease and Sjogren syndrome
- Exam with upgaze nystagmus and inability to perform tandem gait

Dorsal medulla / area postrema lesion





What is the most likely diagnosis?

- Acute disseminated encephalomyelitis
- Relapsing remitting multiple sclerosis
- Glioma
- Neuromyelitis optica spectrum disorder

Case 2

- Serum positive for antibodies directed against aquaporin 4 (AQP4)
  - Serum is MORE sensitive than CSF for anti-AQP4 antibodies
- Diagnosed with NMO spectrum disorder and started on mycophenolate mofetil
- Has had attacks of myelitis and optic neuritis but has normal gait, bowel/bladder function and vision

Majed M, et al. Neurol Neuroimmunol Neuroinflamm 2016; 3:e231

2015 NMOSD diagnostic criteria applied to pediatric patients

- In US Pediatric MS Network study of 38 patients with NMO diagnosed by expert review panel
  - 97% met revised NMO spectrum disorder criteria
  - Only 49% met 2006 Wingerchuck NMO criteria
  - Serum or CSF NMO IgG positive in 65%; some initially negative and converted on serial testing
  - No significant clinical differences between seropositive and seronegative cases

Chitnis T, et al. Neurology 2016;86:245-252

Relevance of early correct diagnosis

- Initiation of preventive treatment was delayed in NMO relative to MS
  - Preventive treatments for NMO include mycophenolate mofetil and rituximab
  - MS disease modifying treatments may WORSEN NMO
- Patients with NMO had higher attack rates and disability compared to MS

Chitnis T, et al. Neurology 2016;86:245-252

Rituximab most effective treatment in pediatric AQP4 ab positive NMOSD

- European and Brazilian study of 67 children with anti-AQP4 antibody positive NMOSD followed for median of 4 years
- Azathioprine, mycophenolate, and rituximab were associated with reduction in annualized relapse rate with rituximab most effective
  - Azathioprine: 1.69 → 0.59
  - Mycophenolate: 1.04 → 0.72
  - Rituximab: 2.50 → 0.14
- All 14 patients treated with rituximab as first line treatment did not relapse

Paolilo RB, et al. Neurol Neuroimmunol Neuroinflamm 2020;7:e837

Anti-AQP4 NMOSD – take home points

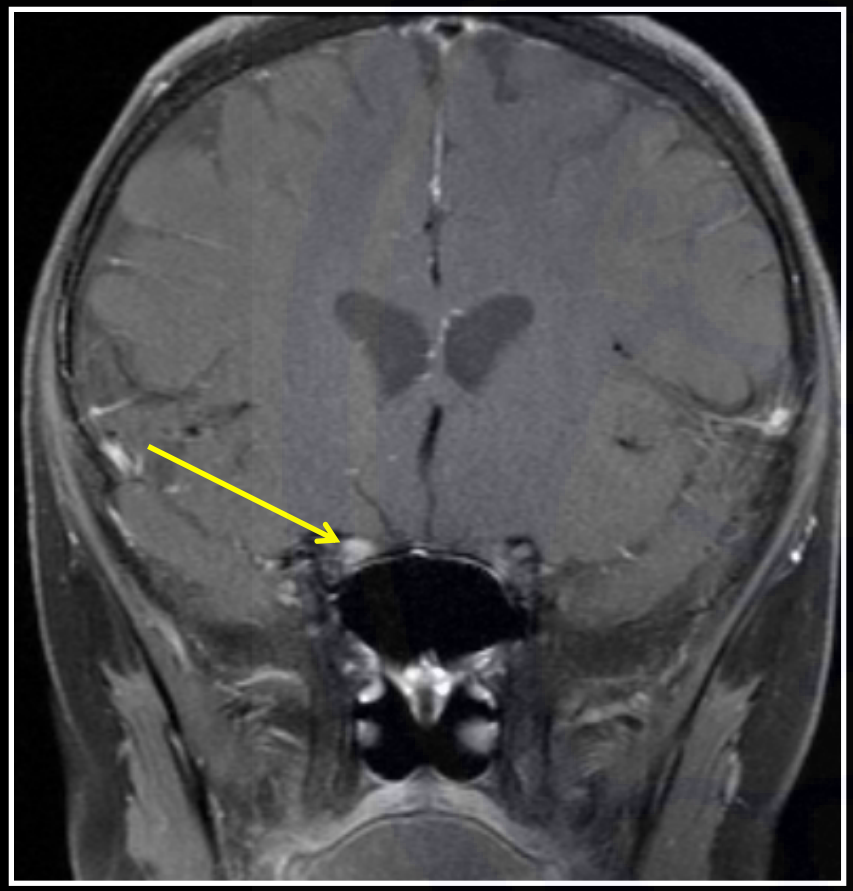
- Anti-AQP4 NMOSD is associated with variety of presentations, not just optic neuritis and transverse myelitis
- NMOSD diagnostic criteria perform well in pediatric patients
- Serum is test of choice for anti-AQP4 antibodies
- Rituximab appears to be most effective treatment for anti-AQP4 NMOSD

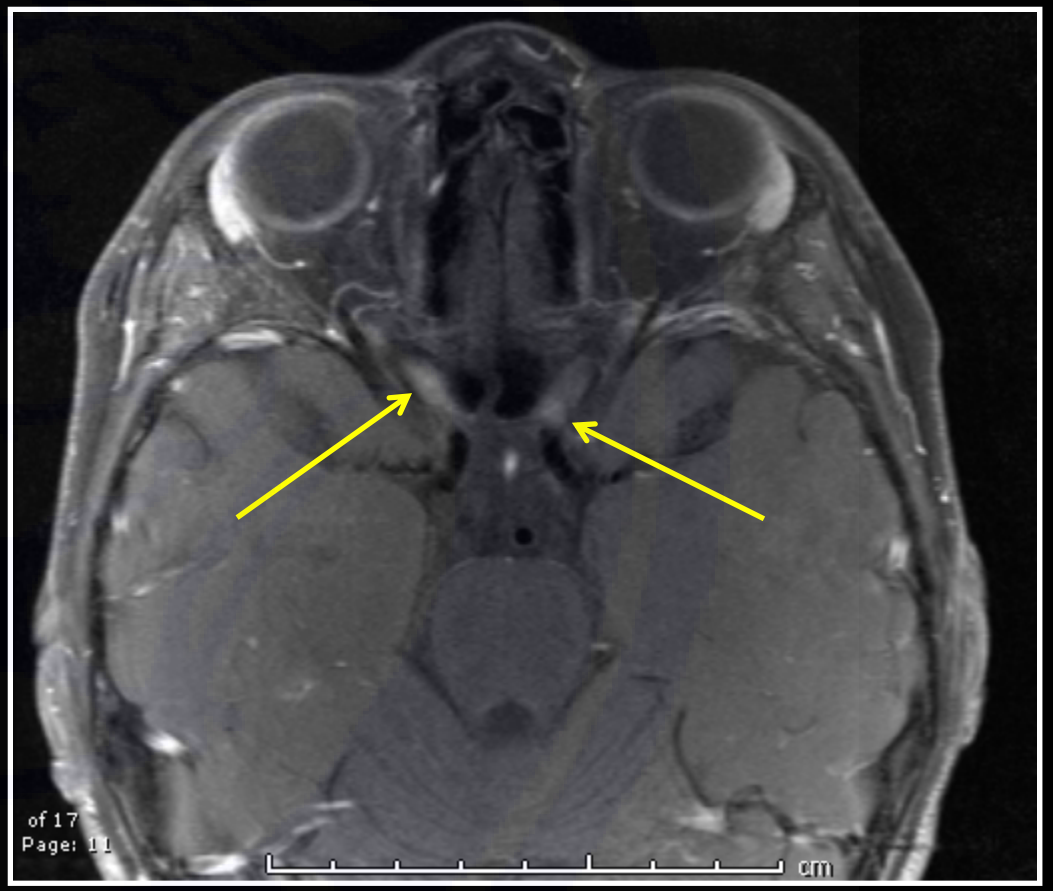
Case 3

- 8yo girl with following history
  - At age 5yo, episode of fever, headache, meningismus, lethargy, behavioral changes, weakness, urinary incontinence, and constipation one week after a febrile URI
  - Brain MRI with multifocal subcortical white matter lesions and CSF with oligoclonal bands
  - Diagnosed with ADEM, treated with IV followed by oral steroids with gradual improvement

Case 3

- Two years later (age 7yo), developed right more than left eye pain, headache, sleepiness, and moodiness then loss of vision in right eye
- MRI with right much greater than left long-segment optic nerve T2 hyperintensity but not affecting the optic chiasm
- Treated with IV then oral steroids with improvement in vision to 20/30
- A few days after steroids ended, developed left optic neuritis

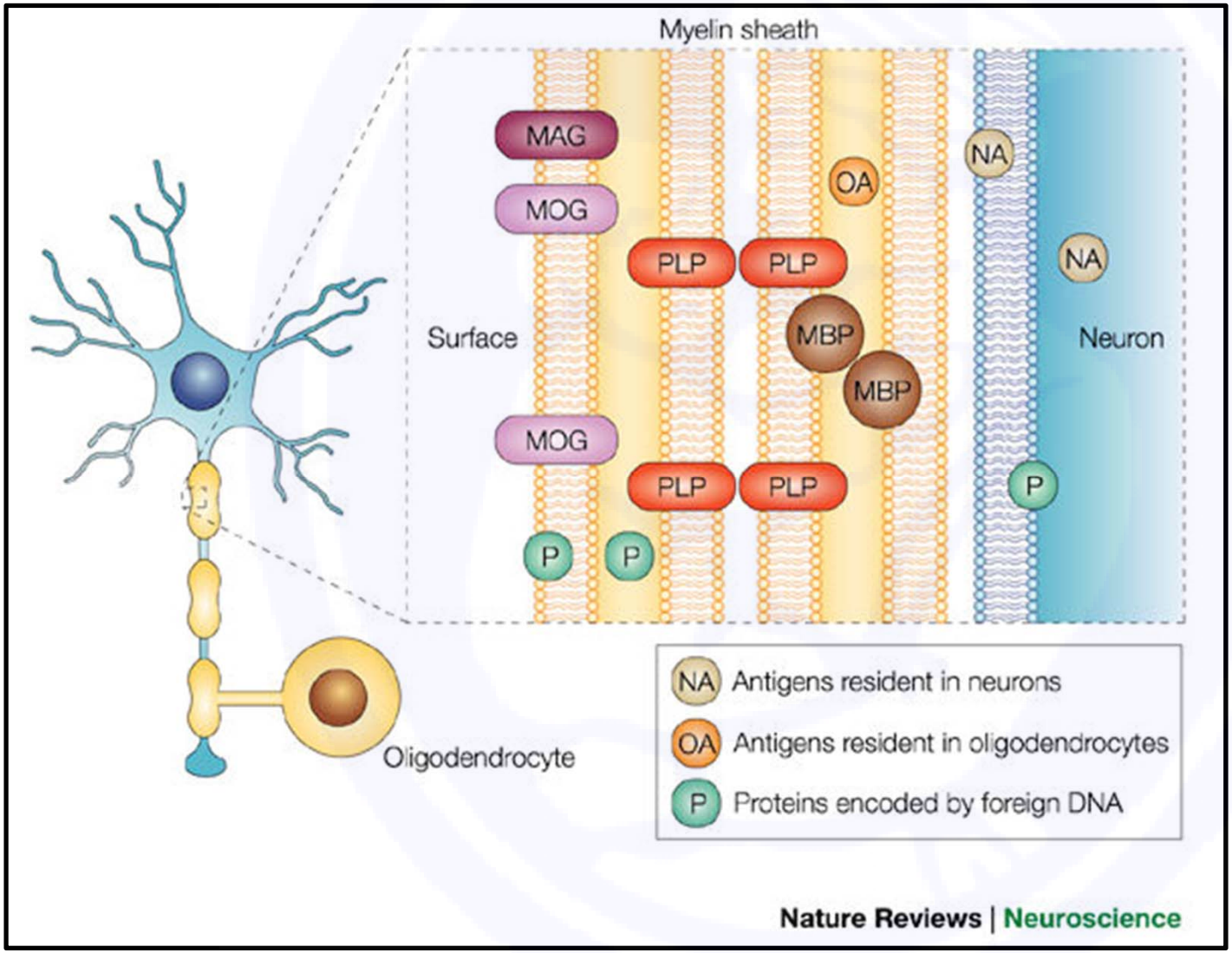




What's the most likely diagnosis?

- Multiphasic ADEM
- Relapsing remitting multiple sclerosis
- Neuromyelitis optica spectrum disorder
- Anti-myelin oligodendrocyte glycoprotein antibody associated disease

MOG = Myelin oligodendrocyte glycoprotein



- Comprises 0.05% of central nervous system myelin

- Preferentially expressed at the extracellular surface of the myelin sheath and oligodendrocyte processes

- Can be used to induce demyelination in animal models

From Hemmer B et al., Nat Rev Neurosci. 2002 Apr;3(4):291-301; slide courtesy of Grace Gombolay MD

Anti-MOG associated demyelinating disease

- Clinical phenotypes include
  - Monophasic and multiphasic ADEM
  - Monophasic and recurrent optic neuritis
  - Monophasic and recurrent transverse myelitis
  - Neuromyelitis optica spectrum disorder
  - Recurrent demyelinating disorder that does not fit well with multiple sclerosis
- In children with 1st demyelinating attack and positive anti-MOG antibodies, approximately 30% of patients have relapses

Jurynczyk M et al., Brain. 2017 Dec 1;140(12):3128-3138

When should I send anti-MOG?

- Two approaches
  - Suggestive clinical phenotype
    - ADEM / multiphasic ADEM / ADEM-ON
    - Recurrent optic neuritis
    - Longitudinally extensive optic neuritis (but not chiasm)
    - Anti-AQP4 antibody negative NMOSD
    - Seizures with demyelination
    - Steroid-dependence
  - All pediatric patients with demyelination
    - About 1/3 of all pediatric patients with demyelination will test positive
- Serum (not CSF) is test of choice

Jarius et al., J Neuroinflammation. 2016 Sep 27;13(1):280; Hennes et al., Neurology, August 29, 2017; 89 (9)

Treatment of MOGAD

- Acute treatment approach
  - Similar to other acute demyelinating disorders
  - Options: IV steroids, IVIg and/or plasma exchange
- Chronic treatment approach
  - Controversial if chronic treatment should be started at onset
    - ≈ 70% of children with anti-MOG antibodies don't relapse
    - Median time to relapse 4.7 months in one large study
    - Persistent presence of anti-MOG antibodies may associated with, but does not guarantee, clinical relapses
  - Typical MS DMTs do not work or may worsen
  - IVIg, mycophenolate mofetil, and rituximab commonly used

Armangue T, et al. Lancet Neurol 2020;19:234-46

How do I treat MOGAD

- In general, after acute treatment, oral steroid taper over 8-12 weeks along with monthly IVIg for 6 months
  - Limited evidence that treatment with immunotherapy for more than 3 months decreases risk of relapse
- Assess need for longer treatment and/or other agents on case-by-case basis

MOGAD – take home points

- Anti-MOG antibodies are very common cause of demyelination in pediatrics; send them (along with anti-AQP4 antibodies) on all patients with demyelination
- Variety of different clinical phenotypes
- Most children with anti-MOG antibodies have a monophasic course
- Treatment paradigms are still emerging

Demyelinating disorders workup

- Brain and spine MRI +/- contrast
  - Orbital MRI if suspected optic neuritis
- Ophthalmology consult
- CSF gram stain, cell counts, glucose, protein, oligoclonal bands, IgG index
- Serum anti-AQP4 and anti-MOG antibodies
  - Available as panel (CDS1) at Mayo Medical Laboratories
- Basic mimics: ESR, CRP, Lyme titers, ANA
- Additional workup on case by case basis
- 25-hydroxy vitamin D

Baseline workup to triage potential risks and guide MS DMT choice

- For all DMT: CBC with differential, liver function tests
- For fingolimod: EKG, ophthalmology exam, VZV titers
- For B cell depleting agents: hepatitis B surface antigen and core antibody, lymphocyte subsets, IgG, IgA, IgM
- For natalizumab: JC virus antibody (available at Quest diagnostics)
- Some providers send testing for hepatitis C and tuberculosis

Case 4

- 5 year old previously healthy boy presents with a complex partial seizure
- Over the next 2 weeks, he had several more seizures, developed a severe movement disorder, and behavioral changes
- CSF contained 44 WBC (all lymphocytes and monocytes), elevated IgG index, and positive oligoclonal bands
- Brain MRI normal

What is the most likely diagnosis?

- Acute disseminated encephalomyelitis
- Autoimmune encephalitis
- Small vessel CNS vasculitis
- Viral encephalitis

Case 4

- Treated with steroids followed by monthly IVIg for 12 months with dramatic improvement
- No tumor identified
- Full scale IQ = 82 one year after onset
- Over 10 year follow up, no relapses
- Has ADHD well treated with stimulant medication
- In age appropriate grade with academic supports, has part time job and driver's license

Anti-NMDAR encephalitis very common identifiable cause of encephalitis

- In California Encephalitis Project, of 761 cases ≤ 30 years old of which 79 (10%) had a cause identified from Sept 2007 to Feb 2011
  - NMDARE (32)
  - Enterovirus (30)
  - HSV-1 (7)
  - VZV (5)
  - WNV (5)

Gable MS, et al. Clinical Infectious Diseases 2012; 54: 899-904

Recognizing anti-NMDAR encephalitis

- Classic triad of seizures, movement disorder and psychiatric symptoms
- Serum is 85% sensitive compared to CSF
- More common in anti-NMDAR encephalitis compared to viral encephalitis
  - Female gender
  - Movement disorders
  - Language dysfunction
  - Autonomic instability
  - Psychosis, hallucinations and personality changes
  - Lower CSF WBC and protein

Dalmau J, et al. Lancet Neurology 2013; 12: 157-165
Gable MS, et al. Clinical Infectious Diseases 2012; 54: 899-904

Anti-NMDAR encephalitis: tumors

- In study of 577 patients, tumor detected in 38%
  - Of these, 97% were female
  - Only 4 girls younger than 12 years old had a tumor
  - 94% of tumors were ovarian teratomas
    - All tumors express NMDA receptor
  - 2% non-ovarian teratoma and 4% other
- Screening CXR and abdominal / pelvic ultrasound
- Depending on age and gender, consider pelvic or body MRI

Dalmau J, et al. Lancet Neurology 2013; 12: 157-165

Anti-NMDAR encephalitis: infections

- Cause of non-paraneoplastic cases unknown in most patients but infections may play a role
  - Typically a non-specific URI
  - Some patients with HSV encephalitis develop anti-NMDAR encephalitis following initial recovery from HSV
    - Always suspect this in patients with “relapses” of HSV encephalitis

Armangue T, et al. Lancet Neurology 2018 Sept;17:760-772

Anti-NMDA receptor encephalitis - treatment

- First line
  - High dose corticosteroids (methylprednisolone 30mg/kg/day max 1g daily for 5 days)
  - Intravenous immunoglobulin 1g/kg/day x 2 days
  - Plasma exchange
- Second line
  - Rituximab (anti-B cell monoclonal antibody)
  - Cyclophosphamide
  - In patients who do not respond to first line treatment, use of second line treatment improves outcomes

Dalmau J, et al. Lancet Neurology 2013; 12: 157-165

Anti-NMDA receptor encephalitis - prognosis

- 85-90% of children and adolescents have a “good” outcome as defined by relatively crude outcome measures
- Patients can have neuropsychological sequelae especially affecting attention
- 15-25% of patients have relapses

BCH Experience

- 13 patients diagnosed over 11 years
- 7 girls, 6 boys
- Epilepsy most common initial misdiagnosis in 5 patients
- Serum only 50% (6/12) sensitive compared to CSF (2 were pre-treated with steroids)
- Median IQ 87 (range 82-125) in 7 patients tested

Anti-NMDARE: Take home points

- Anti-NMDAR encephalitis very common identifiable cause of encephalitis
- Classic triad is psychiatric symptoms, seizures and movement disorder
- Anti-NMDAR antibodies should be sent in the serum and CSF of all patients with encephalitis
  - Serum is about 85% sensitive compared to CSF in published literature but 50% in our experience with 12 patients

Causes of encephalitis

Study	Region	Year	N	Ages	Infectious	Autoimmune	Other	Unknown
1	California	2006	1570	0-92	29%	3%	5%	63%
2*	UK	2010	203	0-87	42%	21%*	0%	37%
3*	Australia	2015	164	0-16	38%	34%*	0%	28%
4*	Spain	2020	296	0-18	34%	22%*	0%	45%

* Included ADEM (2,3) and antibody mediated encephalitis (2-4)

(1) Glaser CA, et al. Clin Infect Dis 2006; 43: 1565-1577, (2) Granerod J, et al. Lancet Infect Dis 2010; 10:835-844, (3) Pillai SC, et al. Pediatrics 2015; 135: e977-984, (4) Armangue T, et al. Lancet Neurol 2020;19:234-46

Diagnostic criteria for autoimmune encephalitis

- Adult and pediatric diagnostic criteria for autoimmune encephalitis have been proposed
  - Take into account clinical features, basic diagnostic test results (MRI, EEG, CSF), and anti-neuronal antibody testing
  - Facilitate initiation of early immunotherapy while awaiting anti-neuronal antibody test results
  - Recognize that many (≈50%) of pediatric patients with clinically defined autoimmune encephalitis do not have detectable anti-neuronal antibodies
- Differential diagnosis and treatment of antibody negative autoimmune encephalitis is challenging

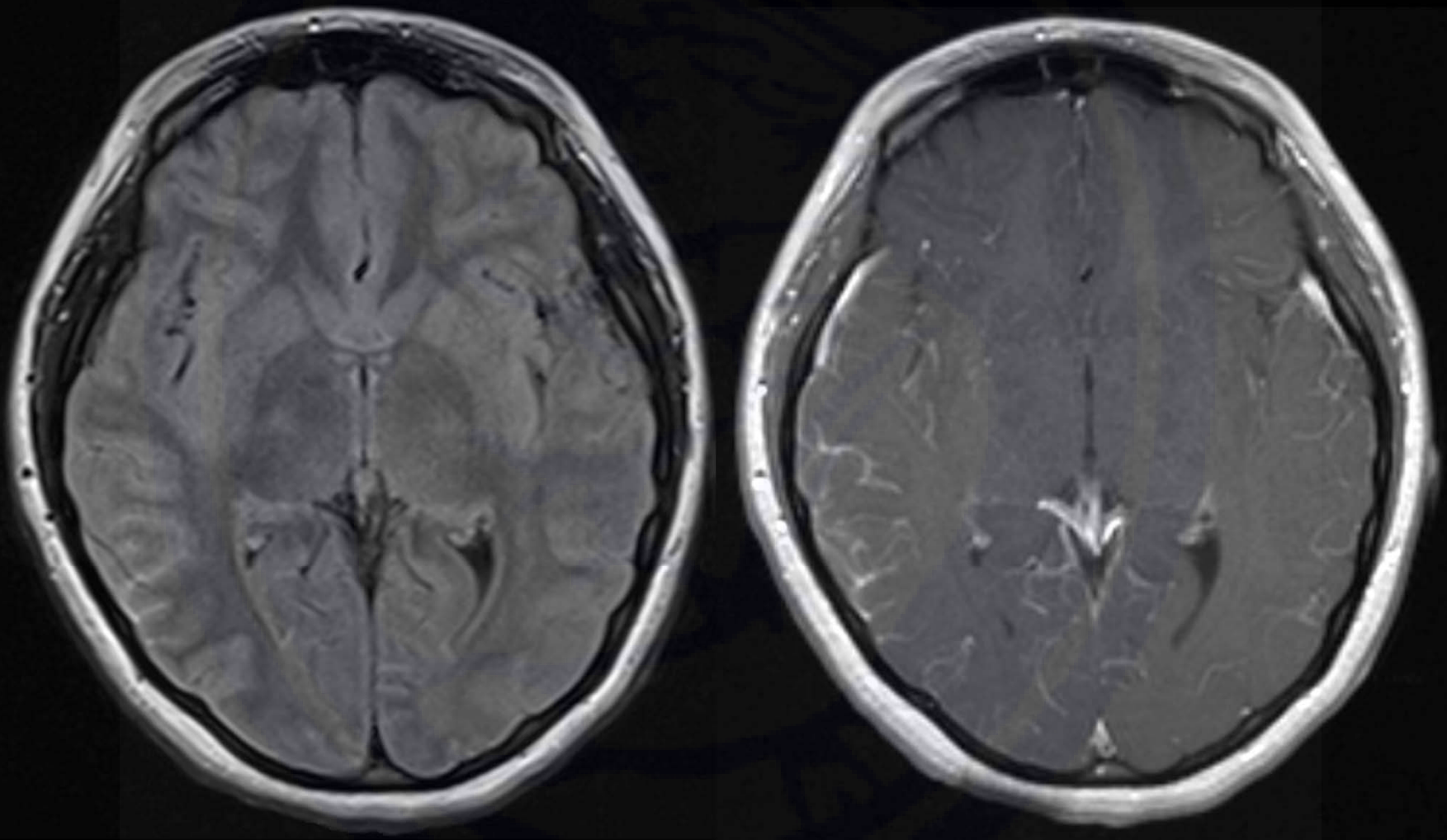
Graus F, et al. Lancet Neurol 2016;15:391-404; Cellucci T, et al. Neurol Neuroimmunol Neuroinflamm 2020;7:e663

Case 5

- 17yo previously healthy girl who developed right temporal headaches, awakening her out of sleep, without other associated symptoms
- A few days later, she had a severe headache in the morning and then had two seizures
  - Left head turn, arms stiff/shaking with post-ictal left facial weakness
- She was admitted with confusion, lethargy, and ongoing R temporal headaches
- LP with 78 WBC (89% lymphocytes), 716 RBC, protein 35 and glucose 60

Case and slides courtesy of Dr. Coral Stredny, MD

Case 5



Case and slides courtesy of Dr. Coral Stredny, MD

What is the most likely diagnosis?

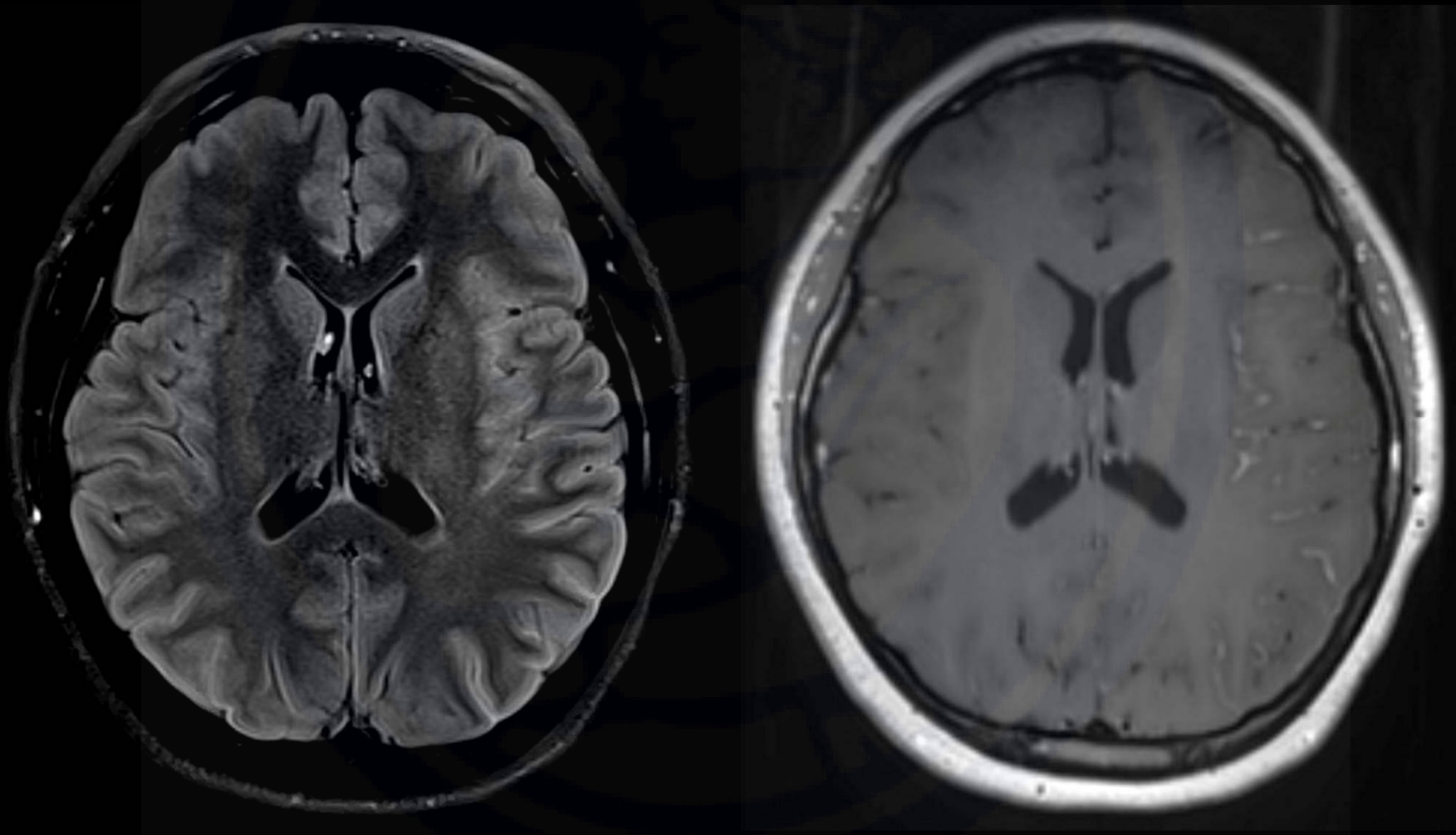
- Acute disseminated encephalomyelitis
- Anti-MOG antibody associated disorder
- Small vessel CNS vasculitis
- Viral encephalitis

Case 5

- Serum anti-MOG antibodies returned positive
- She was treated with intravenous steroids and oral steroid wean
- Upon weaning steroids, she had onset of LEFT temporal headache and RIGHT hand dystonic movements
- Started on IVIg and restarted slower steroid wean. Now symptom free with stable MRI on IVIg q4 weeks
- Anti-MOG antibody remains positive

Case and slides courtesy of Dr. Coral Stredny, MD

Case 5



Case and slides courtesy of Dr. Coral Stredny, MD

Anti-MOG antibodies in pediatric encephalitis

- Prospective Spanish study of 239 children with demyelinating syndromes and 296 with encephalitis
- Anti-MOG antibodies were positive in 39% of demyelinating cohort
- In the encephalitis cohort,
  - 34% infectious (enterovirus, HSV, others)
  - 22% autoimmune
  - 45% unknown cause

Armangue T, et al. Lancet Neurol 2020;19:234-46

Anti-MOG antibodies in pediatric encephalitis

- Of those with autoimmune encephalitis,
  - 34% had anti-MOG antibodies
  - 22% had anti-NMDAR antibodies
  - 11% had other antibodies
  - 33% had other encephalitic syndromes / causes
    - Opsoclonus myoclonus ataxia syndrome (19%)
    - Limbic encephalitis (6%)
    - Rasmussen encephalitis (6%)
    - Small vessel CNS vasculitis (2%)

Armangue T, et al. Lancet Neurol 2020;19:234-46

Anti-MOG antibodies in pediatric encephalitis

- Of 116 children with anti-MOG antibodies, 59% had clinical features of encephalitis
  - 68% fulfilled ADEM diagnostic criteria
  - 32% did not
- Anti-MOG antibodies can be present in children with an encephalitic presentation without ADEM

Armangue T, et al. Lancet Neurol 2020;19:234-46

Antibodies in pediatric autoimmune encephalitis

- Most common
  - Myelin oligodendrocyte glycoprotein (MOG)
  - N-methyl-D-aspartate receptor (NMDAR)
- Less common
  - Glutamic acid decarboxylase (GAD)
  - Glycine receptor

Antibodies in pediatric autoimmune encephalitis

- Uncommon
  - $GABA_A$ receptor
  - Glial fibrillary acidic protein (GFAP)
  - Hu (anti-neuronal nuclear antigen 1)
- Rare
  - Contactin associated protein-like 2 (CASPR2)
  - $GABA_B$ receptor
  - Leucine-rich glioma-inactivated protein 1 (LGI1)
  - Metabotropic glutamate receptor 5 (mGluR5)
- Controversial
  - Dopamine-2 receptor (D2R)

Encephalitis workup

- Brain +/- spine MRI
- EEG
- Lumbar puncture
  - Cell counts, glucose, protein
  - Oligoclonal bands (serum and CSF)
  - Autoimmune encephalopathy antibody panel
  - Neopterin (if WBC normal)
  - Save some!
- Serum antibodies
  - Autoimmune encephalopathy antibody panel
  - ANA
  - Anti-thyroperoxidase and anti-thyroglobulin antibodies

Encephalitis workup

- Infectious testing
  - CSF PCR for enterovirus and HSV
  - Serum Lyme, mycoplasma and EBV titers
  - Additional based on symptoms, season, region
  - Emerging role for metagenomic next generation sequencing for all pathogens
- CBC diff, ESR, CRP, vWF antigen
- TSH
- Urine and serum toxicology screens

Take home point

- Send anti-MOG antibodies!

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