APERTURE: What have we learned about ADEM?

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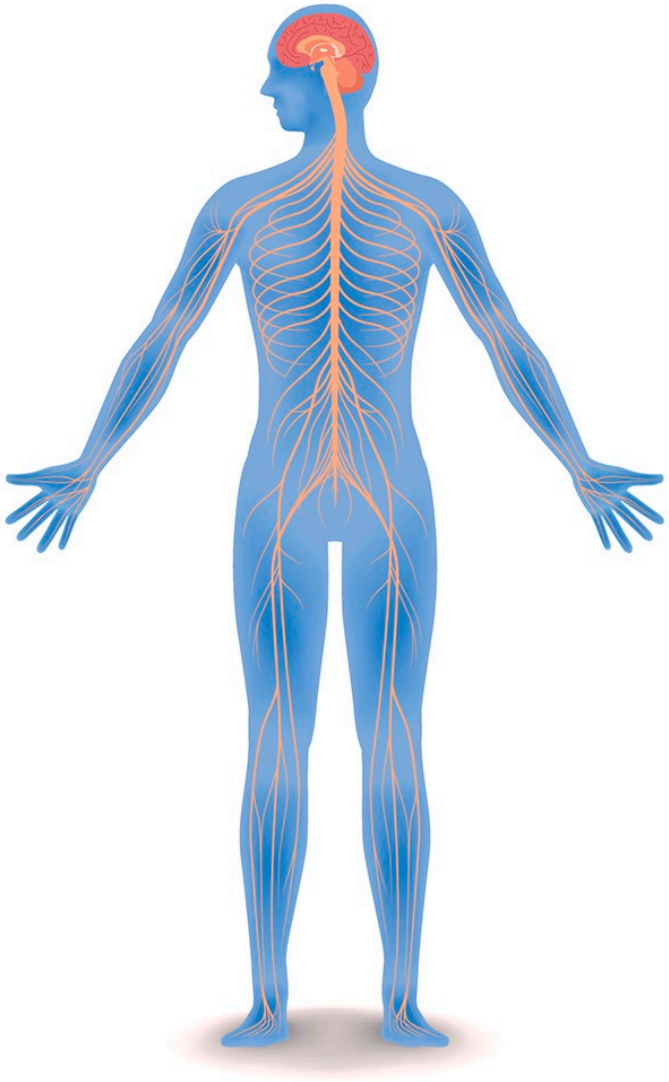
October 10, 2021

2021 Rare Neuroimmune Disorders Symposium

Disclosures

- I received the James T. Lubin Clinician-Scientist Fellowship Award from the Siegel Rare Neuroimmune Association
- I will be discussing off-label use of therapies

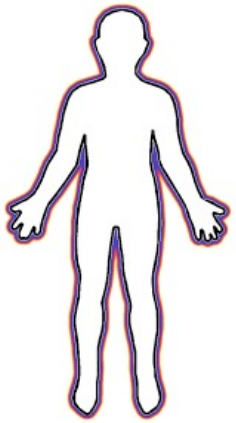
What is ADEM?



- Acute disseminated encephalomyelitis
- Sudden and widespread inflammation of the brain and spinal cord
- Leads to myelin injury within the central nervous system and abnormal functioning of brain (encephalopathy)

Disease process

Vulnerable individual



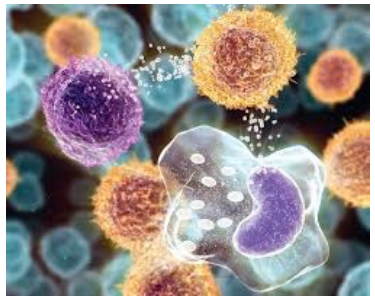
- Personal or family history of autoimmune disease
- Low vitamin D

Environmental trigger

- Infection
- Tumor

Hours, days, weeks

Abnormal immune response



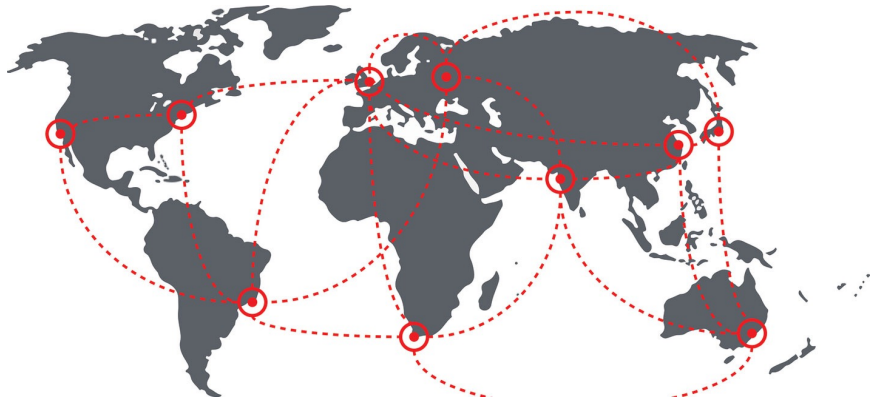
- Blood brain barrier breakdown
- Molecular mimicry
- Recognize self as foreign

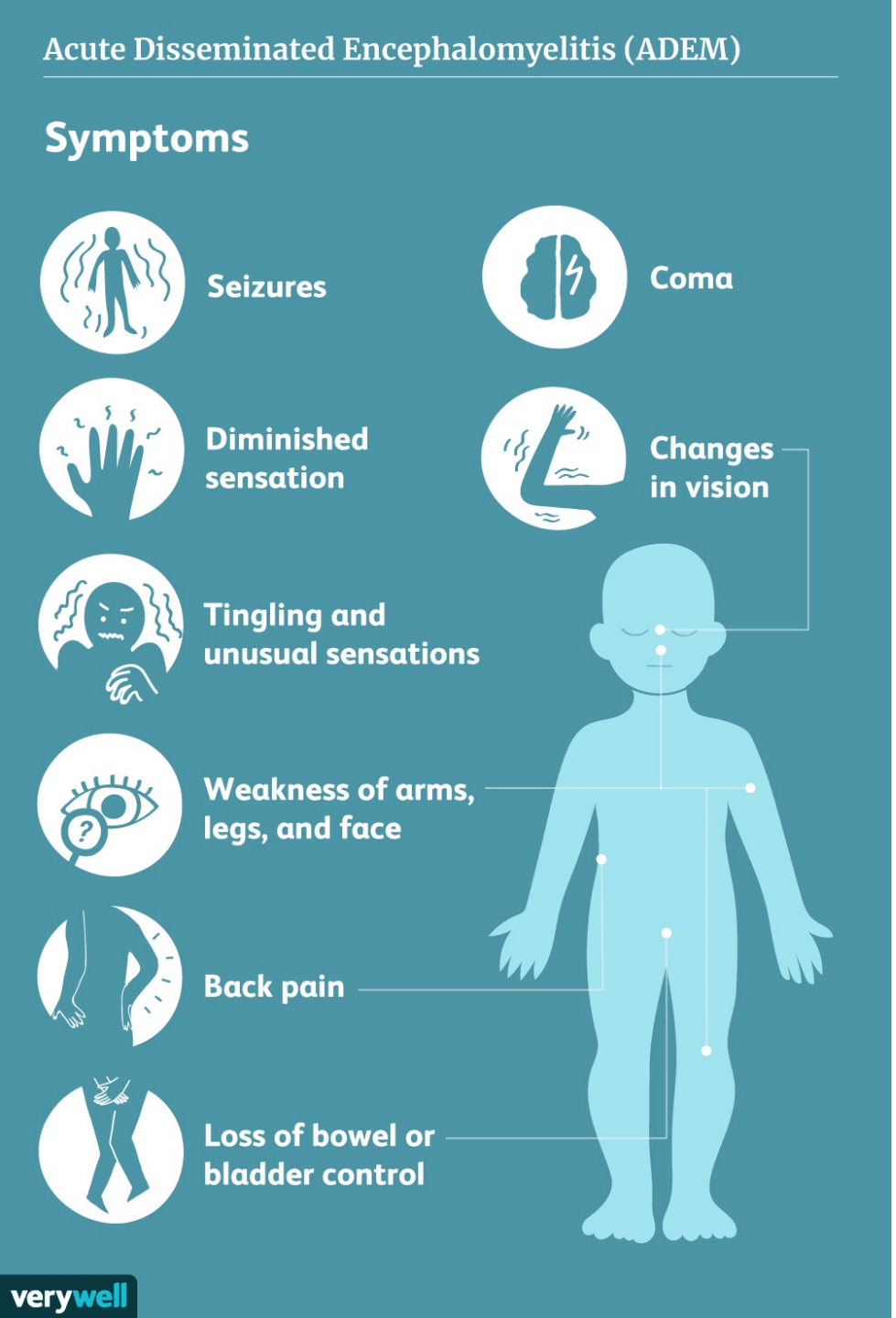
Neurological symptoms

- Confusion
- Weakness
- Numbness
- Vision change
- Bowel and bladder dysfunction

Epidemiology

- Primarily affects children
- Average age of onset around 4-8 years
- 3-6 cases per million children a year
- Slight male predominance
- More common in winter and in locations further from the equator



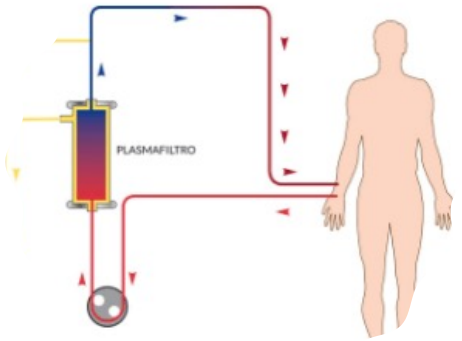


Clinical Presentation

- Acute illness 1-2 weeks before (50-80%)
- Can have fever, headache, nausea 3-4 days before neurological symptoms
- Common presenting symptoms:
  - Brain → Irritability, sleepiness, incoordination, gait problems
  - Spinal cord→ Weakness, numbness, bowel and bladder dysfunction
  - Optic nerve→ eye pain, blurry vision

Acute Treatment

- No large scale, prospective, randomized controlled clinical trials
- High dose intravenous steroids
- Therapeutic plasma exchange (PLEX)
- Intravenous immunoglobulin (IVIG)
- Oral corticosteroid taper



Hospital course

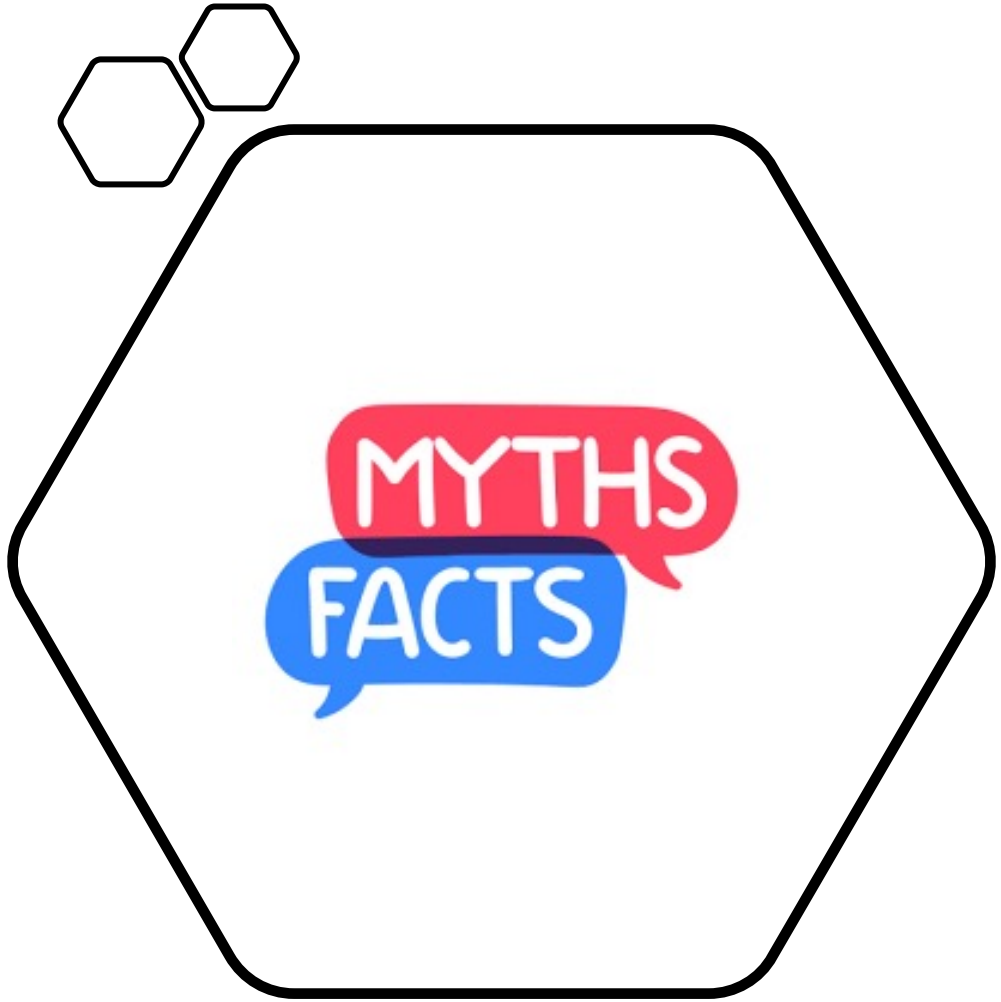
- May spend 1-3 weeks in the hospital and rehabilitation
- 25% will require ICU level care (75% of whom are on ventilator)
- Supportive care for breathing, seizures, cerebral edema
- Once able to tolerate, can initiate therapy (PT, OT, ST) to help with neurological recovery

Prognosis

- Often marked improvement within 30 days
- Follow-up MRI can show normal or near normal
- Cognitive and mood related symptoms can persist after the acute period
- Children may not have normal rates of white matter and gray matter growth
- Up to 1/3 with recurrent attacks
- Up to 3% may succumb to the illness

Our changing understanding of ADEM

- “ADEM doesn’t relapse”
- “ADEM is a benign illness”
- “ADEM is primarily a white matter disease”



ADEM classifications

- Monophasic ADEM
  - A single ADEM episode with no further demyelinating events or new MRI lesions outside the acute three-month period after onset

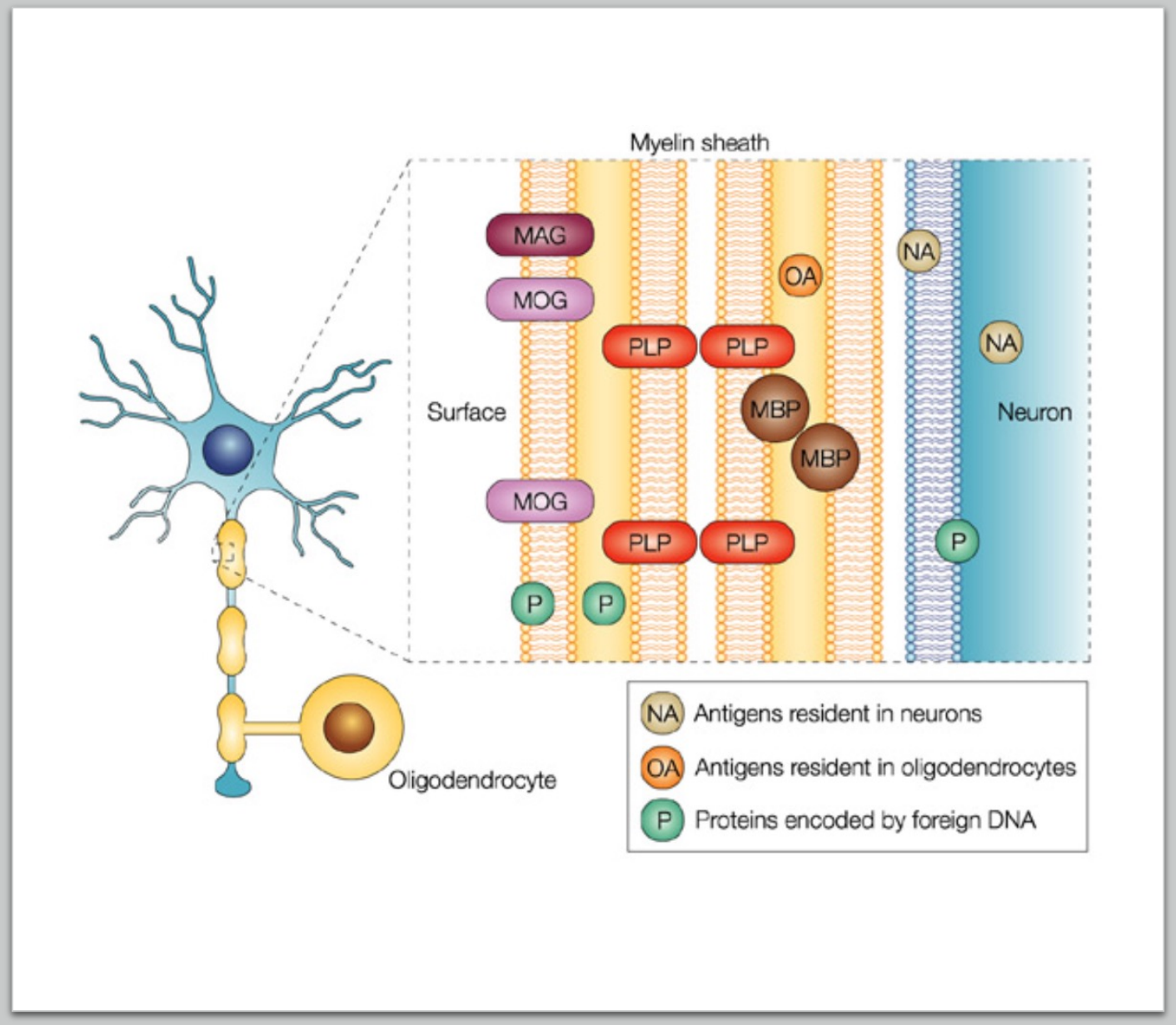
- Multiphasic ADEM
  - Two episodes of ADEM separated by at least three months in time.
  - The second event can involve the same or new symptoms, signs or MRI lesions compared with the first event.
  - This diagnosis is limited to two episodes of ADEM.
  - Three or more suggest ultimate diagnosis of MS, NMO, or other disorder

MOG antibody disease (MOGAD)

- Frequently present in children with acquired demyelinating syndromes other than MS
  - ADEM
  - AQP4 neg NMOSD
  - Bilateral and recurrent optic neuritis
  - Myelitis (often longitudinally extensive)
- Clinically can overlap with other demyelinating conditions such as MS and NMO but is a distinct disease entity
- Relapses can occur

Myelin Oligodendrocyte Glycoprotein

- Myelin protein expressed in the central nervous system
- Produced by oligodendrocytes late in myelination
- First identified in 1984 using a mouse monoclonal antibody
- Testing for MOG antibodies as become more accurate and widely available



Other MOG syndromes

- Encephalitis with seizures
- Aseptic meningitis
- Leukodystrophy-like
- Gray matter predominant longitudinally extensive TM
- Increased intracranial pressure from cerebral edema

Multiple Sclerosis and Related Disorders 27 (2019) 30–33

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Case report

Atypical Anti-MOG syndrome with aseptic meningoencephalitis and pseudotumor cerebri-like presentations

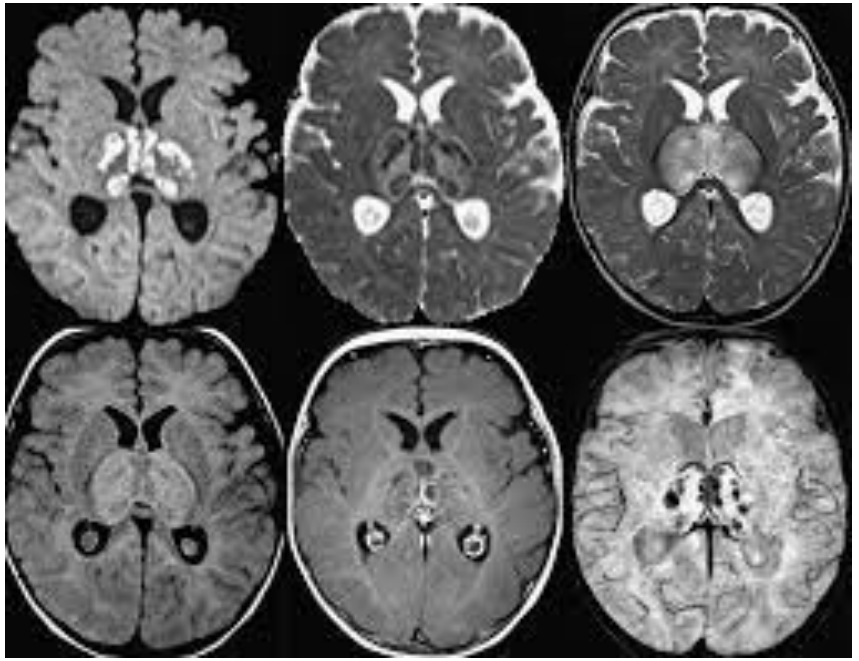
Ram N Narayan*, Cynthia Wang, Peter Sguigna, Khalil Husari, Benjamin Greenberg

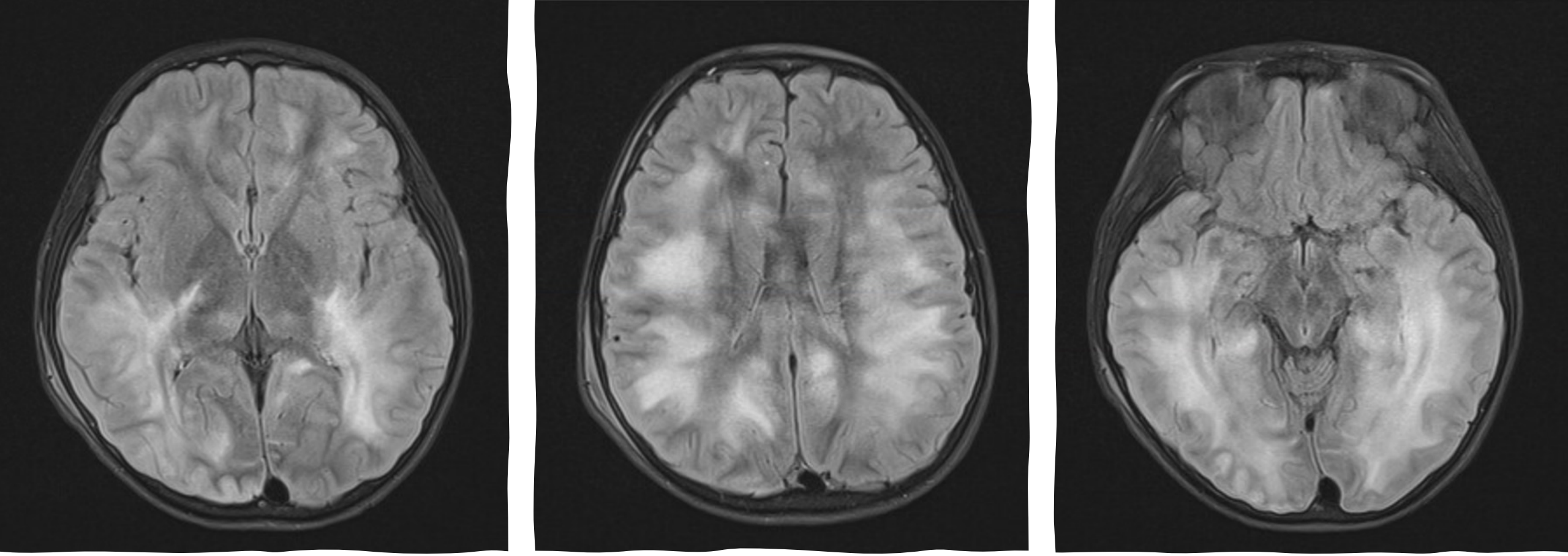
UT Southwestern Medical Center, 5323 Harry Hines Blvd Dallas, Texas, TX 75235, United States

“ADEM is a benign condition”

Severe syndromes with features overlapping ADEM

- Acute hemorrhagic encephalomyelitis or leukoencephalitis (AHEM, AHLE), Weston-Hurst syndrome
  - A very severe presentation of ADEM with rapid worsening and often death
  - Associated with multifocal hemorrhages and necrosis
- Acute Necrotizing Encephalopathy of Childhood (ANEC)
  - Deep gray matter injury with viral respiratory infections such as influenza
  - Sometimes associated with RANBP2 mutation



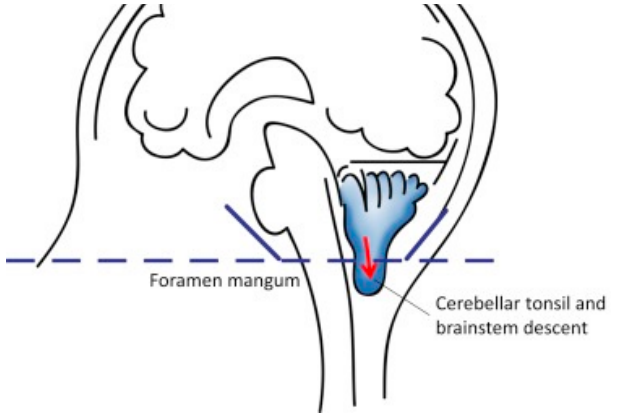


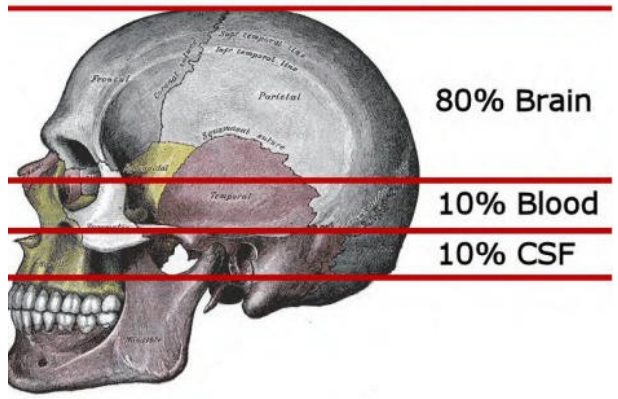
Case of life-threatening ADEM

- 5-year-old boy presents with fever, lethargy, and seizures
- 3 days later, had worsening of mental status and required intubation to protect airway
- MRI brain showed lesions consistent with ADEM and diffuse cerebral edema
- An intervention to divert cerebrospinal fluid was needed

Severe swelling of the brain can cause irreversible injury

- Swelling and increased pressure in the brain can be seen in ADEM
- The space inside the skull is fixed
- When one component increases, others are pushed out
- Heart has to do more work to supply blood and oxygen to the brain





Pediatric Neurology 99 (2019) 64–68

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Clinical Observation

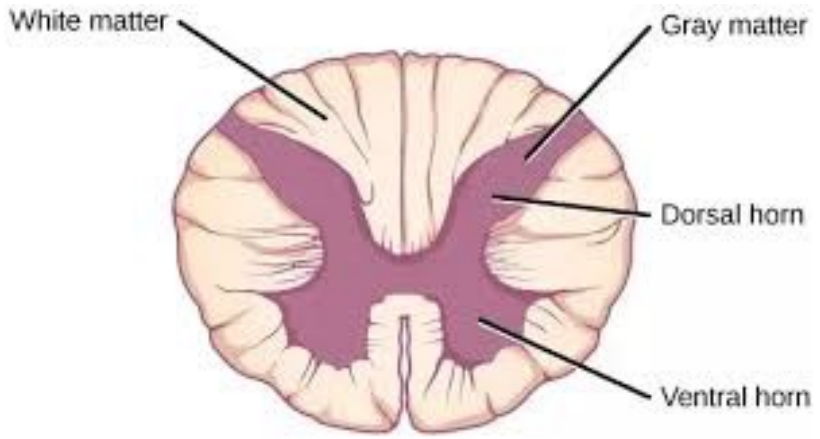
Acute Disseminated Encephalomyelitis (ADEM) and Increased Intracranial Pressure Associated With Anti–Myelin Oligodendrocyte Glycoprotein Antibodies

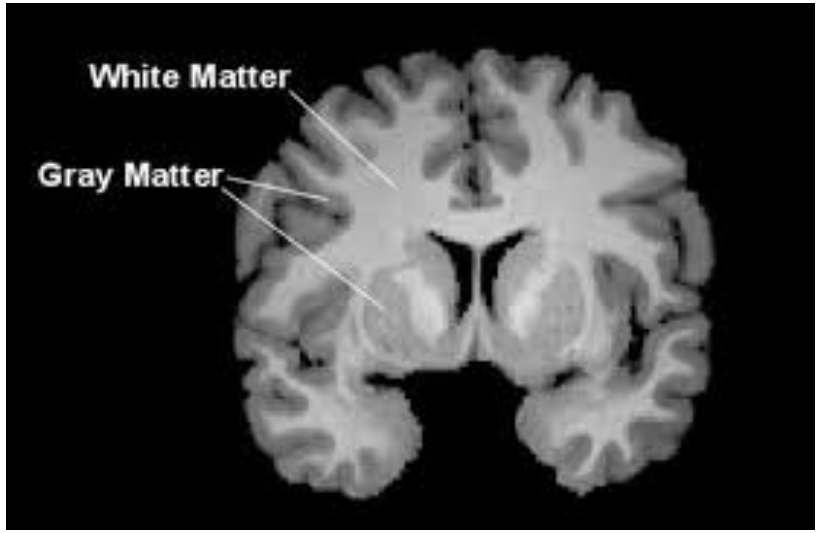
Ram N. Narayan, MBBS *, Cynthia Wang, MD, Benjamin M. Greenberg, MD, MHS

Department of Neurology, University of Texas Southwestern, Department of Neurology and Neurotherapeutics, Dallas, Texas

“ADEM is a white matter disease”

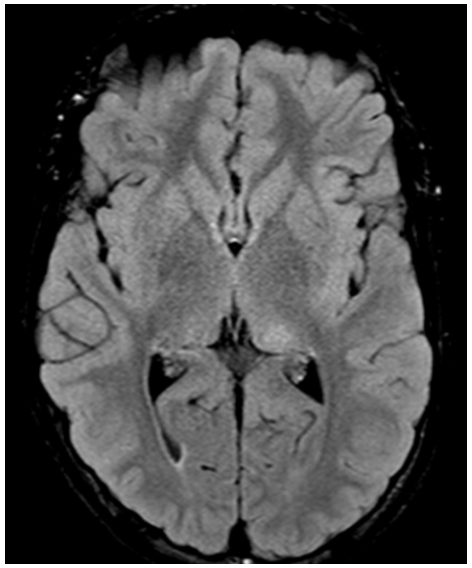
- ADEM is classified as an acute demyelinating syndrome
- Myelin exists primarily in the white matter
- Brain lesions in ADEM often occur in deep white matter
- Gray matter involvement in the brain has been described with ADEM
- Involvement of the gray matter and anterior horns of the spinal cord is often attributed to acute flaccid myelitis (AFM)

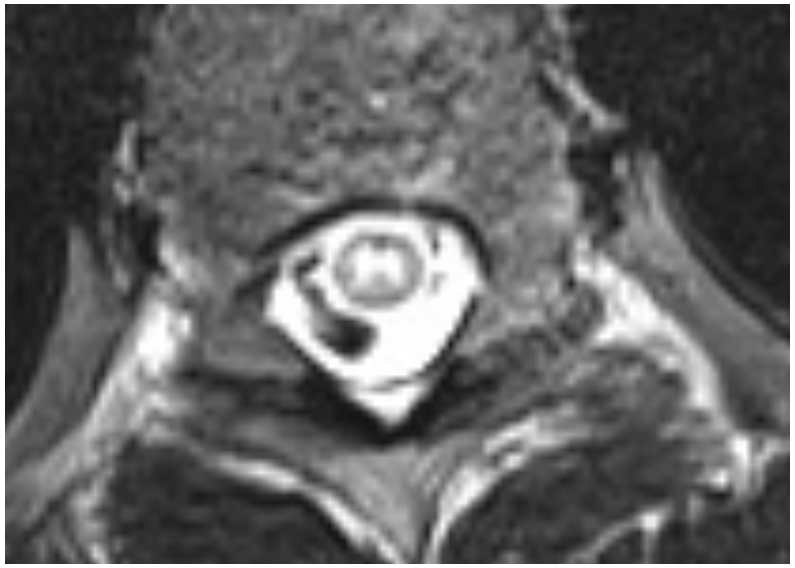




Cases of gray matter predominant ADEM

- 13-year-old boy develops difficulty with walking, poor balance, and urinary retention follow a viral illness
- On examination, he has bilateral leg weakness, a sensory level, and brisk deep tendon reflexes
- MRI brain shows lesion in thalamus and MRI spine shows involvement of gray matter of spinal cord
- MOG antibody testing returned positive





Pediatric Neurology 000 (2018) 1–4

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Original Article

Anti-Myelin Oligodendrocyte Glycoprotein Antibody Associated With Gray Matter Predominant Transverse Myelitis Mimicking Acute Flaccid Myelitis: A Presentation of Two Cases

Cynthia Wang, MD *, Ram Narayan, MD, Benjamin Greenberg, MD, MHS

University of Texas Southwestern Medical Center, Dallas, Texas

Hypothesis that what we call ADEM is composed of different disorders

Goal of evaluating relationship of patient's initial features to their long-term outcomes

Neuropsychological testing to discover cognitive deficits related to ADEM

aperture

Assessment of pediatric and adult encephalomyelitis related outcomes: understand, reveal, educate

Demographic features of the cohort

- 37 children
- Average age: 5.5 years
- Sex: 65% male, 35% female
- Race/ethnicity:
  - 78% White
    - 59% Caucasian
    - 19% Hispanic
  - 14% Black
  - 8% Asian

Clinical features of the cohort

Initial presentation of ADEM:

- 8% with simultaneous optic neuritis
- 41% with simultaneous myelitis

MOG positivity

- 50% overall (17 of 34 tested)
- 59% when limited to those tested at time ADEM presentation

Relapse rate

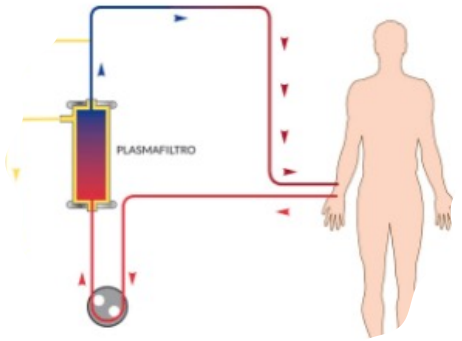
- 24% at average follow-up time of 5.7 years

Alternative diagnoses

- 4/37 (11%) did not meet ADEM criteria and/or had a better alternative diagnosis (acute flaccid myelitis x2, cerebellitis, multiple sclerosis)

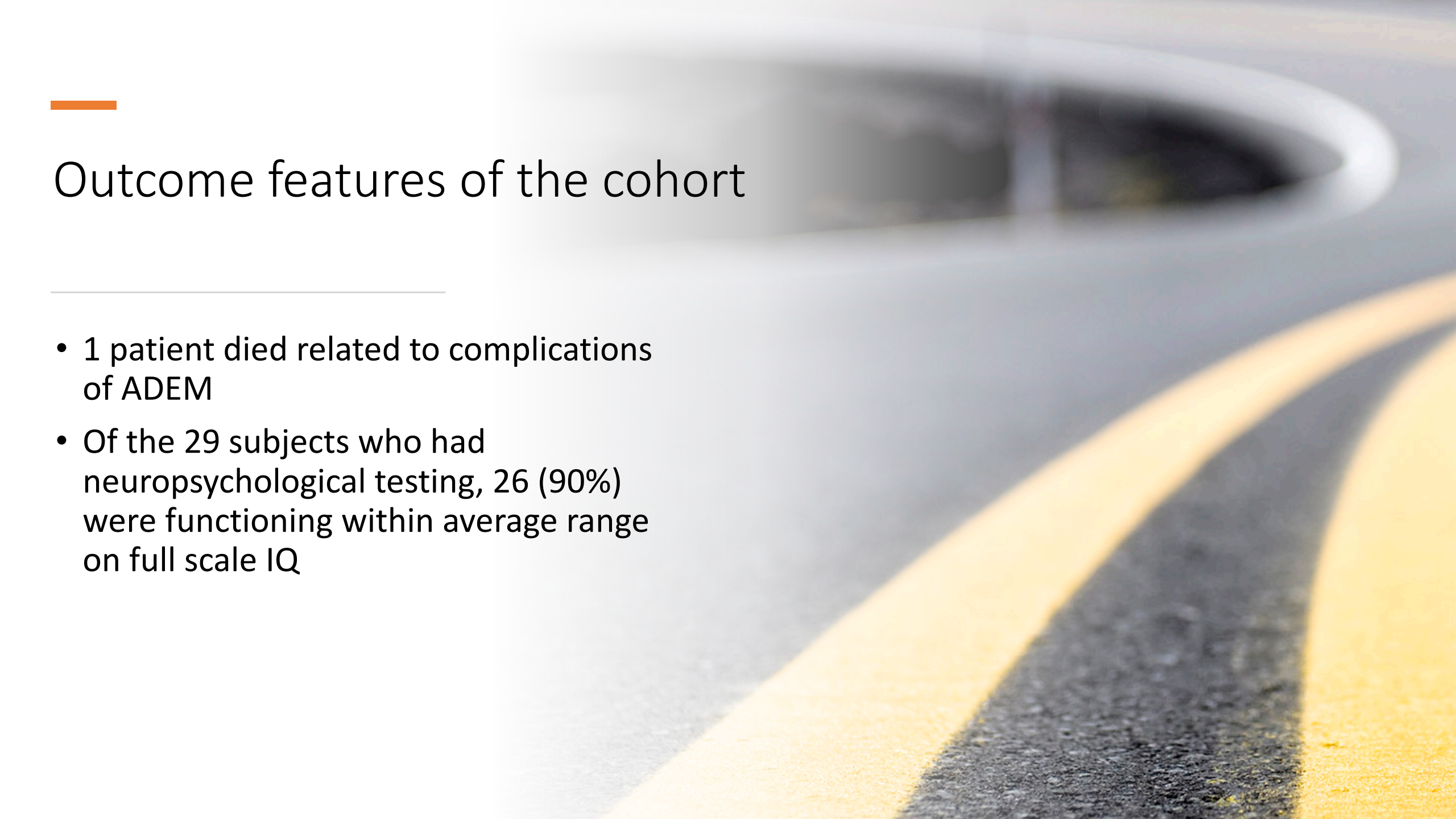
Treatment features of the cohort

- 73% of patients were treated at UTSW/Children's Dallas
- Acute therapies
  - IV steroids alone - 38%
  - IV steroids and IVIG – 19%
  - IV steroids and PLEX – 32%
  - IV steroids, PLEX, and IVIG – 11%
- Chronic therapies
  - 9/37 or 24% received chronic immunotherapies
  - Rituximab (7), mycophenolate (4), IVIG (3), natalizumab (1)



Outcome features of the cohort

- 1 patient died related to complications of ADEM
- Of the 29 subjects who had neuropsychological testing, 26 (90%) were functioning within average range on full scale IQ



Summary

- ADEM is currently defined by clinical and imaging criteria but moving toward more specific diagnoses based on cause
- Outcomes are generally favorable, but some cases can be life-threatening, lead to long-term disability, or be associated with relapses
- Understanding the specific types of ADEM will help develop more effective and targeted treatments

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