ASN Annual Meeting

New insights into ADEM: Unraveling a complex disease

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Joshua P. Klein, MD, PhD

Vice Chair, Clinical Affairs, Department of Neurology
Brigham and Women's Hospital
Associate Professor of Neurology and Radiology
Harvard Medical School

I have no disclosures or conflicts of interest relevant to the content of this presentation.

- Board of Directors, *American Society of Neuroimaging*
- Board of Directors, *Neurohospitalist Society*
- Editor-in-Chief of *The Neurohospitalist* (SAGE)
- Co-Author of *Principles of Neurology*, 10th and 11th Ed. (McGraw Hill)
- Chair & Scientific Director of *Neurology Board Review* Course (Audio Digest Foundation)
- Section Chair, Director, Lecturer, Author, Committee member (AAN Institute)
- Consultant, *Best Doctors*
- Consultant, *Advance Medical*
- Medical expert for law firms

Acute Disseminated Encephalomyelitis (ADEM)

What is the clinical syndrome?

What is the epidemiology?

What is the pathophysiology?

What is its relationship to other demyelinating conditions?

What are the current diagnostic criteria?

What is the prognosis?

ADEM

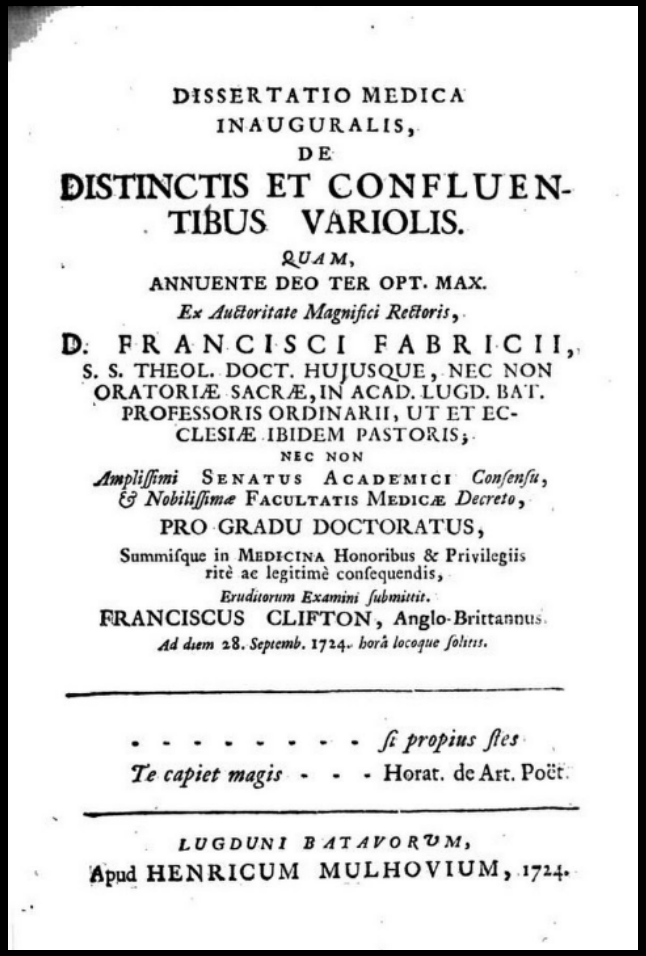
What is the clinical syndrome?

- *Rapidly progressive encephalopathy with poly-focal neurological deficits*
- *Often post-infectious or post-vaccinal*
- *Monophasic course with clinical and radiographic resolution*
- *More common in children, male:female incidence is ~1.3:1*

But… there is a lot of variability.

ADEM – early concepts

What is the clinical syndrome?



DISSERTATIO MEDICA
INAUGURALIS,
DE
DISTINCTIS ET CONFLUEN-
TIBUS VARIOLIS.
QUAM,
ANNUENTE DEO TER OPT. MAX.
Ex Auctoritate Magnifici Rectoris,
D. FRANCISCI FABRICII,
S. S. THEOL. DOCT. HUJUSQUE, NEC NON
ORATORIÆ SACRÆ, IN ACAD. LUGD. BAT.
PROFESSORIS ORDINARII, UT ET EC-
CLESIÆ IBIDEM PASTORIS;
NEC NON
Amplissimi SENATUS ACADEMICI *Consensu,*
& Nobilissimæ FACULTATIS MEDICÆ *Decreto,*
PRO GRADU DOCTORATUS,
Summisque in MEDICINA Honoribus & Privilegiis
ritè ac legitimè consequendis,
Eruditorum Examini submittit.
FRANCISCUS CLIFTON, Anglo-Brittannus.
Ad diem 28. Septemb. 1724. horâ locoque solitis.

. . . . . *si propius stes*
Te capiet magis . . . Horat. de Art. Poët.

LUGDUNI BATAVORUM,
Apud HENRICUM MULHOVIUM, 1724.

"There also occurs severe headaches, inflammation of the eyes, deceptive and inconsistent impressions, disrupted separations, convulsions, jumping of the tendons, very great weakness and eventually death itself."

Clifton F. A dissertation on distinct and confluent smallpox, 1724

ADEM – early concepts

Multiple nicht eitrige Encephalomyelitis und multiple Sklerose.

Von

Prof. Dr. **G. Anton** und Dr. **Fr. Wohlwill,**
Assistenzarzt der Klinik.

(Aus der Kgl. Universitäts-Psychiatrischen- und Nervenklinik zu Halle a. S.)

"Multiple non-purulent encephalomyelitis and multiple sclerosis"

"The hemispheres are affected as well as the cerebellum…

…lesions are usually quite large by confluence of smaller lesions, round or oval, with irregular borders, often at gray-white matter interfaces…

…a small vessel in the center [of each lesion] is recognizable."

Z Neurol 1912;31-98

ADEM – early concepts

Multiple nicht eitrige Encephalomyelitis und multiple Sklerose.

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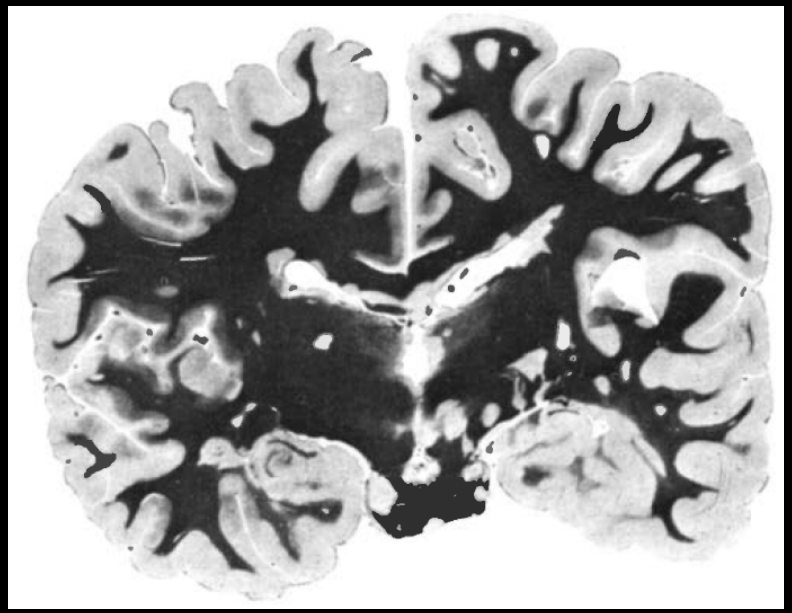
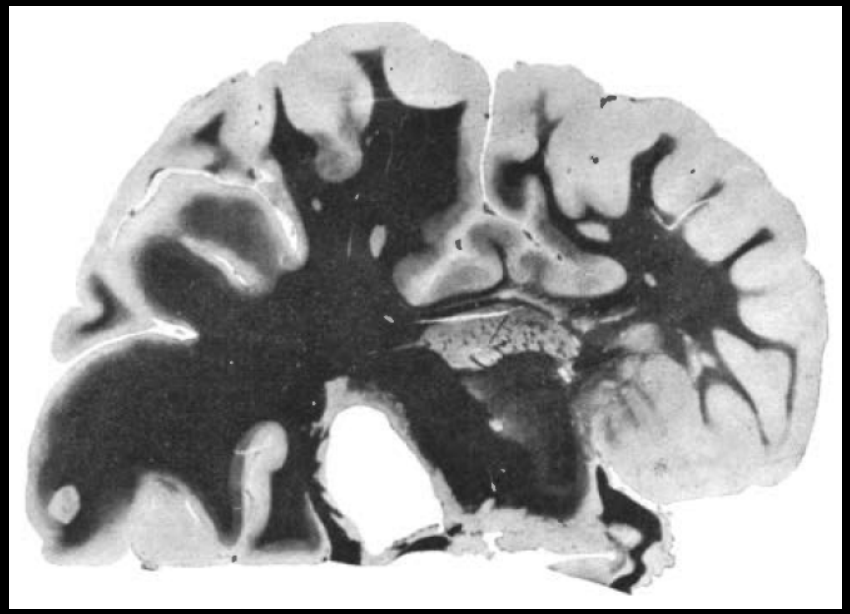
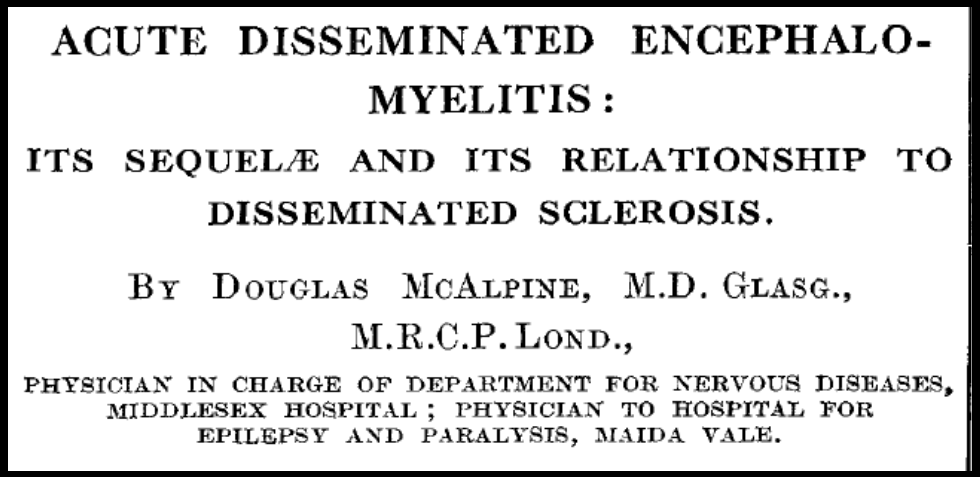
Gross pathology





Z Neurol 1912;31-98

ADEM – early concepts



ACUTE DISSEMINATED ENCEPHALO-MYELITIS:

ITS SEQUELÆ AND ITS RELATIONSHIP TO DISSEMINATED SCLEROSIS.

By Douglas McAlpine, M.D. Glasg., M.R.C.P. Lond.,

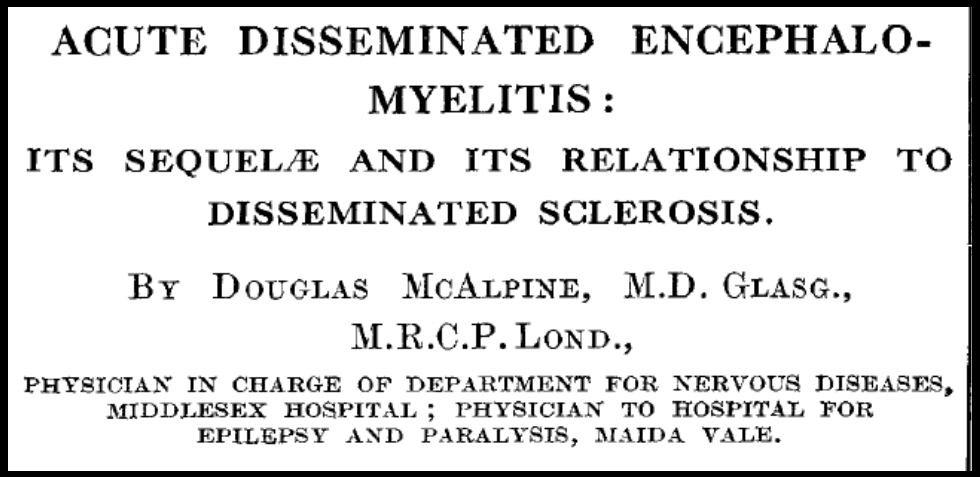
PHYSICIAN IN CHARGE OF DEPARTMENT FOR NERVOUS DISEASES, MIDDLESEX HOSPITAL; PHYSICIAN TO HOSPITAL FOR EPILEPSY AND PARALYSIS, MAIDA VALE.

Three groups of cases: 1) *post-vaccinal, 2) following infectious fevers, and 3) spontaneous*.

Abrupt and severe onset … fever often present … headache, meningeal signs … rapid recovery in most but not all cases.

Lancet 1931;217(5616):846-52

ADEM – early concepts



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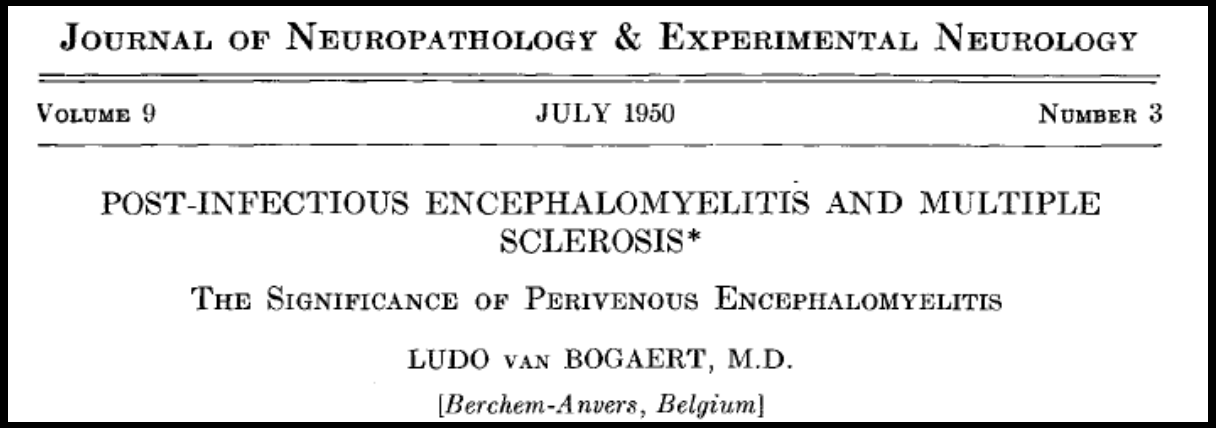
"Disseminated encephalomyelitis, both in its acute phase and in its sequelae, may closely resemble disseminated sclerosis."

"It is suggested, but without any proof, that a different virus is responsible for these two diseases, and that in [ADEM] immunity is usually conferred by the first attack, whereby relapses are prevented."

Lancet 1931;217(5616):846-52

ADEM – early concepts



JOURNAL OF NEUROPATHOLOGY & EXPERIMENTAL NEUROLOGY

VOLUME 9 JULY 1950 NUMBER 3

POST-INFECTIOUS ENCEPHALOMYELITIS AND MULTIPLE SCLEROSIS*

THE SIGNIFICANCE OF PERIVENOUS ENCEPHALOMYELITIS

LUDO VAN BOGAERT, M.D.

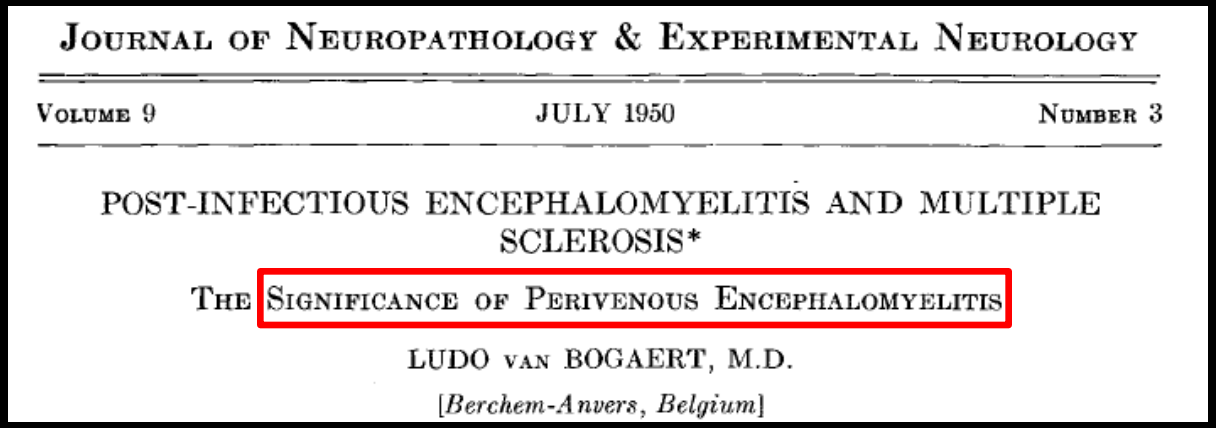
[*Berchem-Anvers, Belgium*]

"The predilection for children, the variability in the symptoms, etiology, and clinical course, as well as the almost miraculous recoveries point to close clinical similarity of ADEM with those afflictions of the nervous system which follow the exanthematous or other infections."

"The criterion of either complete recovery or of non-progressive or phasic sequela is essential for differentiating ADEM from the common instances of MS."

JNNP 1950;9:219-49

ADEM – early concepts



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THE SIGNIFICANCE OF PERIVENOUS ENCEPHALOMYELITIS

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[*Berchem-Anvers, Belgium*]

"Perivenous encephalitis gets its special character from the *nature of the 'terrain'* in which the noxious agent operates and *not from the causative agent itself*, which is too variable and often not specific. The exact name of this 'allergic' or 'hyperergic' disposition is of little importance."

"*Perivenous encephalitis* is only one of the pathologic pictures resulting from participation of the CNS in non-specific infections; *meningoencephalitis* and *cerebral purpura* are two other types."

JNNP 1950;9:219-49

ADEM – early concepts

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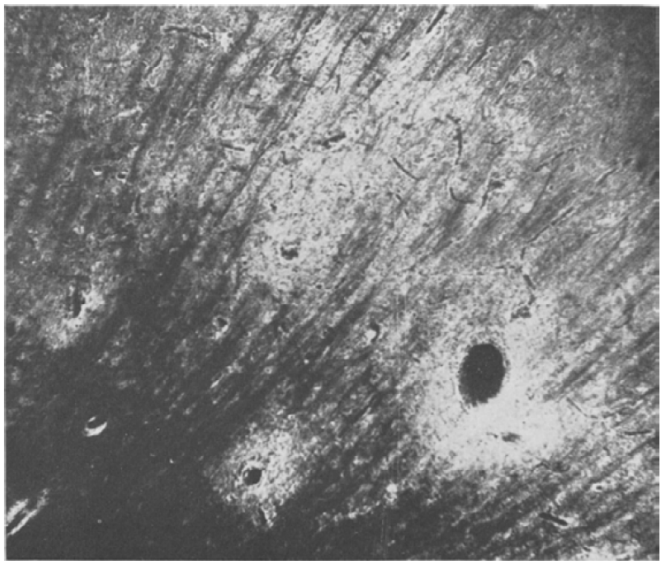


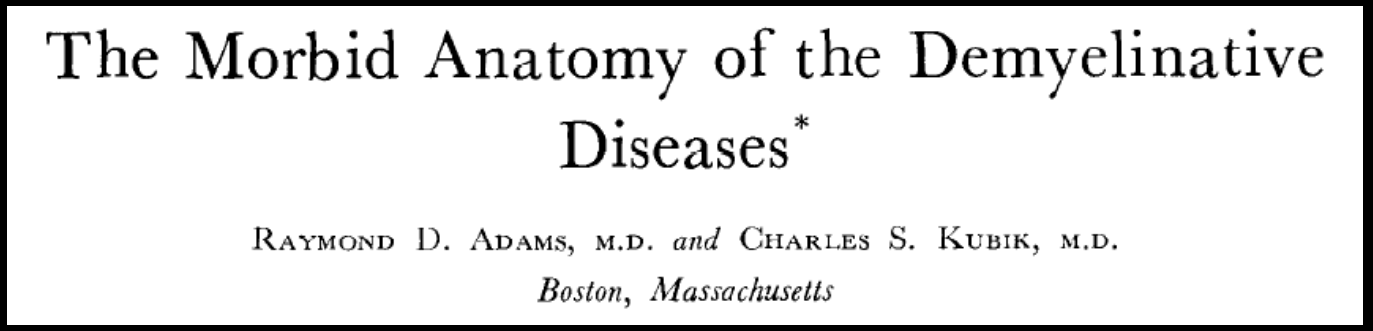
FIG. 3. (*Case 2.*) Parietal cortex. Perivascular infiltration with accompanying rarefaction of the myelinated fibers. (Frozen section; Spielmeyer stain.)

Perivascular infiltration with demyelination

A pathognomonic lesion?

JNNP 1950;9:219-49

ADEM



The Morbid Anatomy of the Demyelinative Diseases*

RAYMOND D. ADAMS, M.D. *and* CHARLES S. KUBIK, M.D.
Boston, Massachusetts

1. *MS (disseminated sclerosis, acute or relapsing)*
2. *ADEM (infectious and vaccine encephalomyelitis)*
3. *Cerebral sclerosis (Schilder, metachromatic leukodystrophy)*
4. *Hemorrhagic leukoencephalitis (Hurst, brain purpura)*

Am J Med 1952;12(5):510-46

ADEM

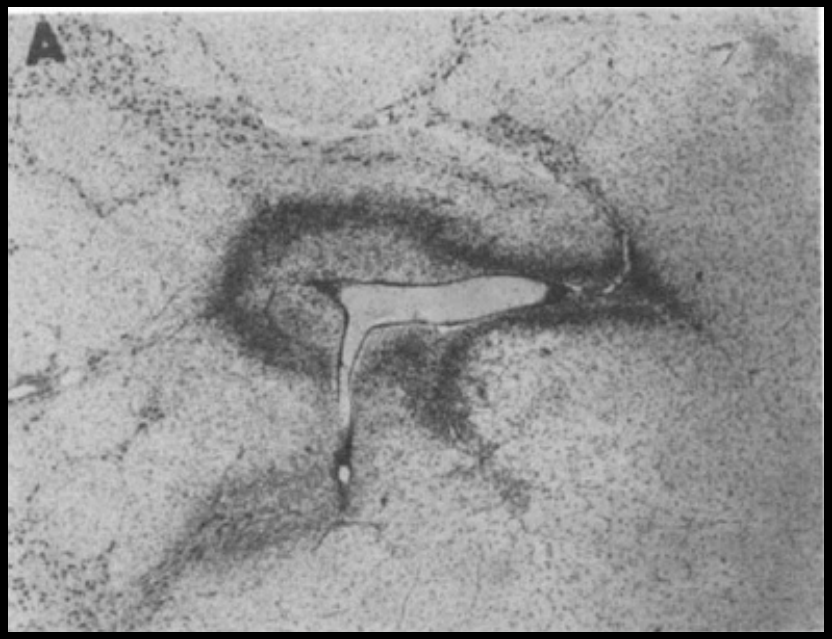
The Morbid Anatomy of the Demyelinative Diseases*

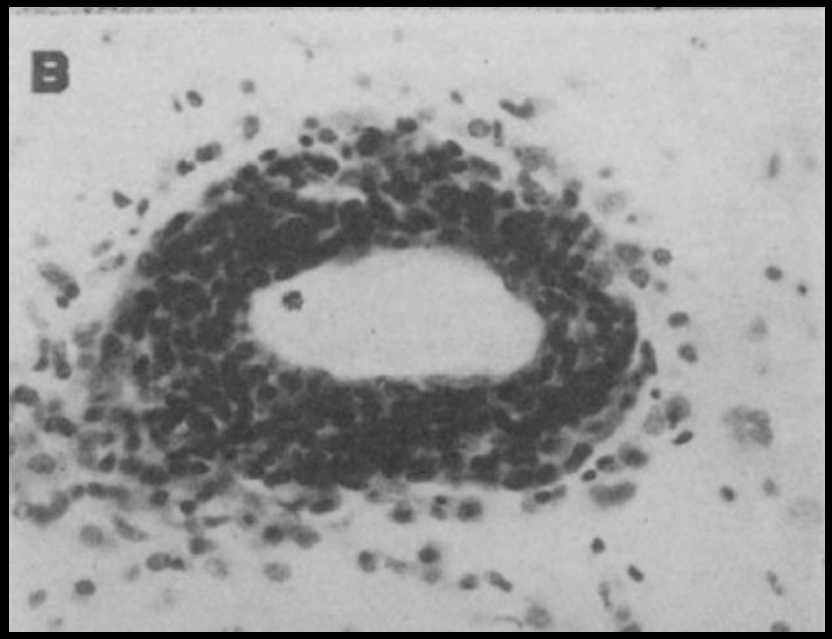
RAYMOND D. ADAMS, M.D. *and* CHARLES S. KUBIK, M.D.
Boston, Massachusetts

"The essential process in these [demyelinative] diseases is a focal necrobiosis of nervous tissue which varies in degree from degeneration of myelin sheaths with sparing of the axis cylinders to an almost complete degeneration or necrosis of all elements of nervous tissue."

Am J Med 1952;12(5):510-46

MS – lesion pathology

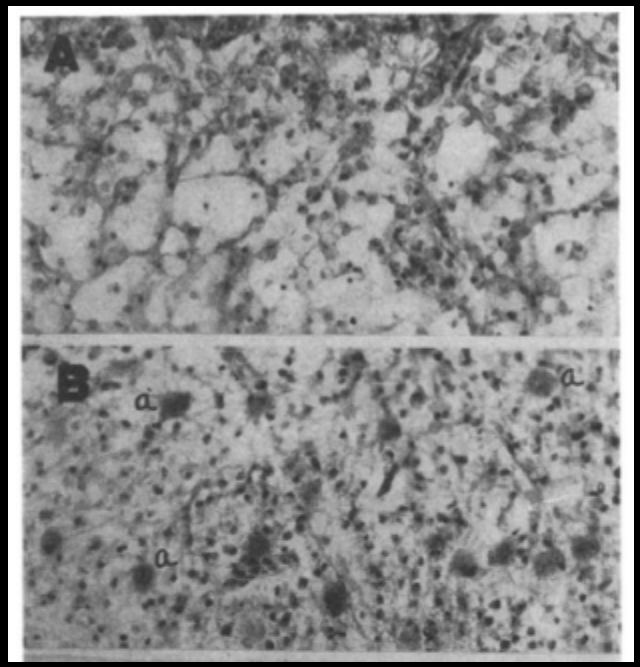


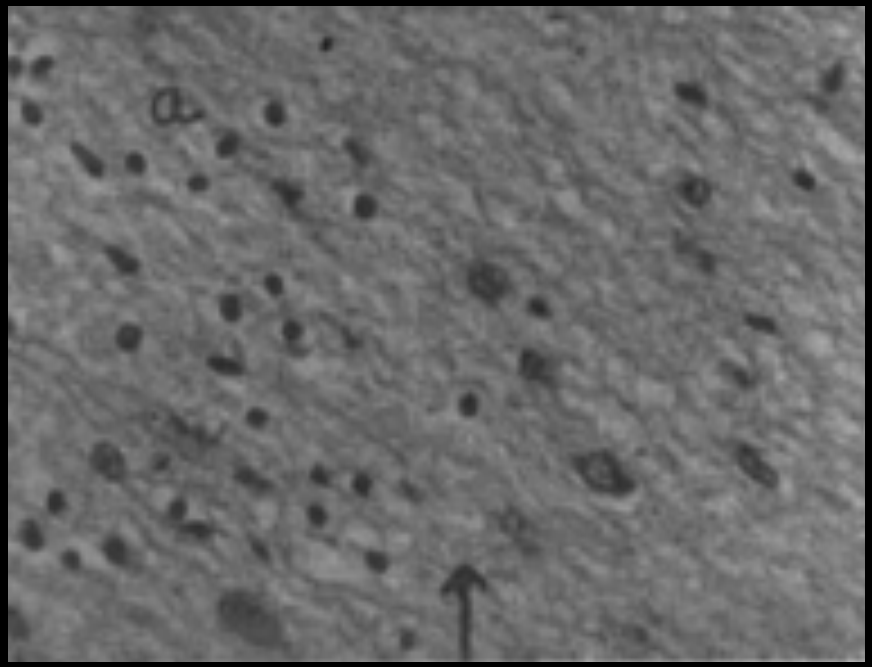


Acutely, perivascular inflammation with microglial reaction within an area of demyelination.

Am J Med 1952;12(5):510-46

MS – lesion pathology

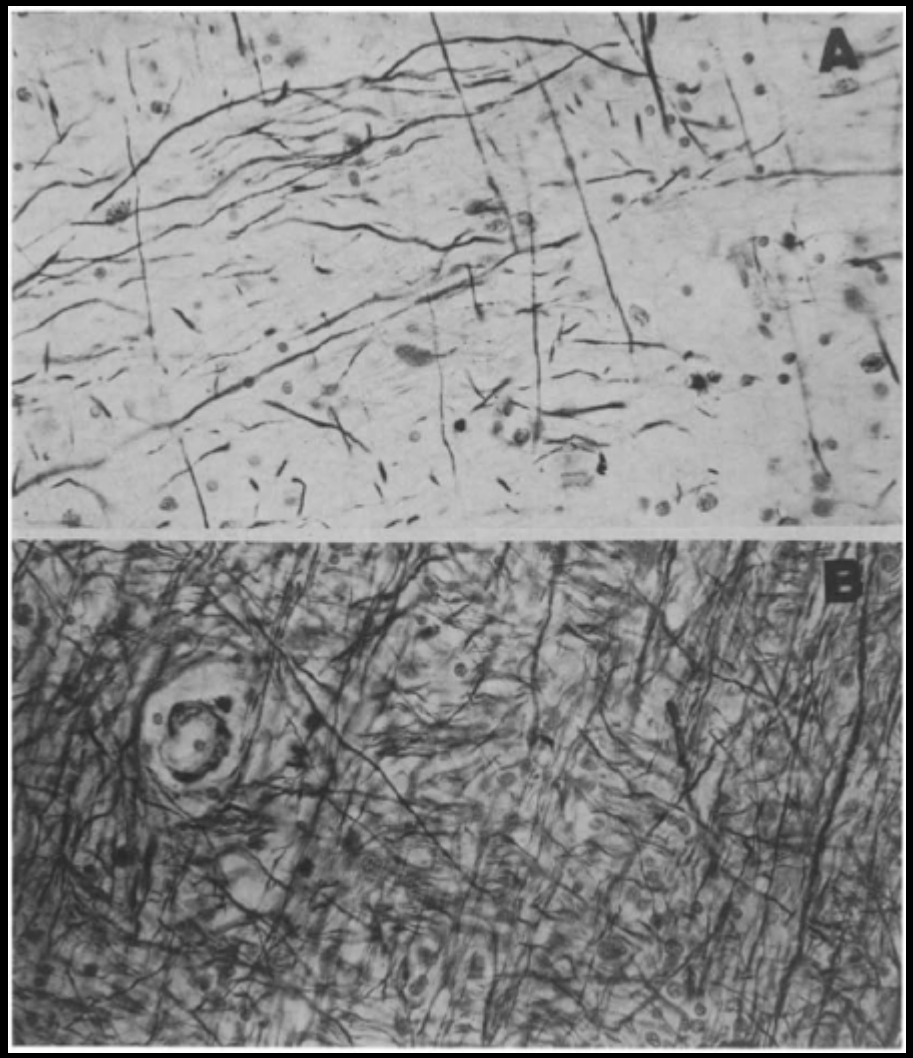




The extent of macrophage, astrocyte, and microglial infiltration and activity depends on age of lesion.

Am J Med 1952;12(5):510-46

MS – lesion pathology

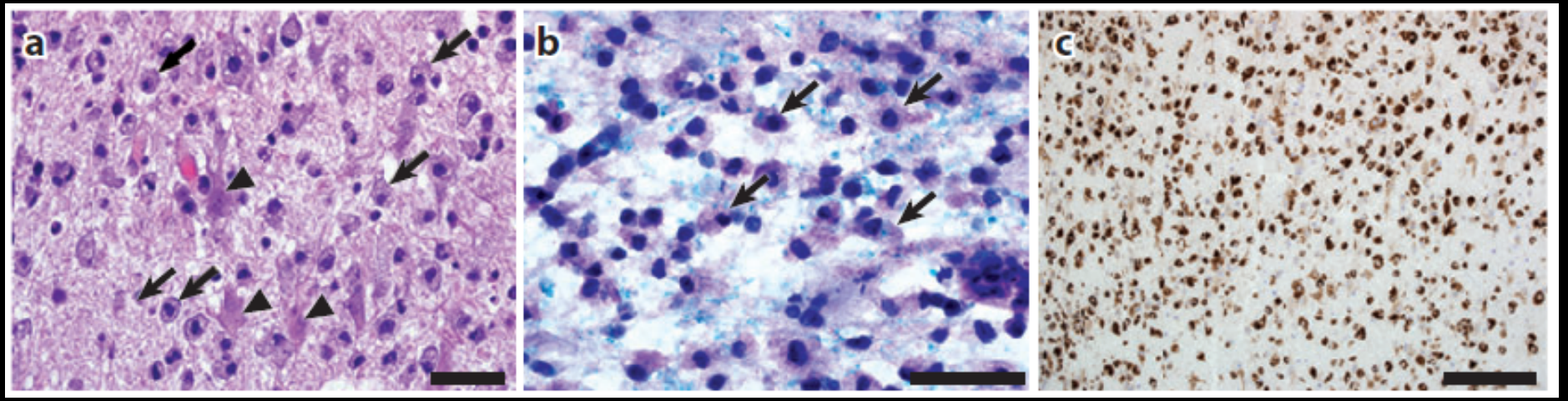


Remyelination and axonal injury is variable; here there is loss of axons.

Here there is destruction of myelin with preservation of axon cylinders.

Am J Med 1952;12(5):510-46

MS – lesion pathology



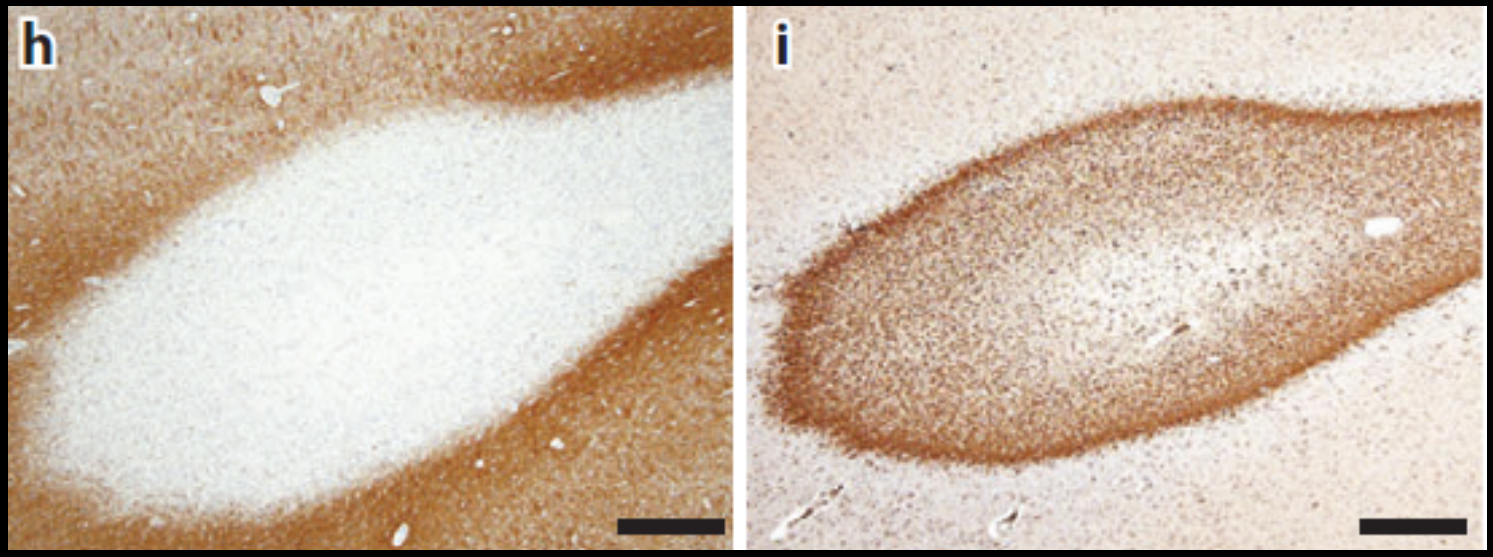
Left - hypercellular inflammatory infiltration

Center - a ‘sea’ of myelin-laden macrophages

Right - lesion infiltration with activated macrophages and microglia

Ann Rev Pathol Mech Dis 2012;7:185-217

MS – lesion pathology

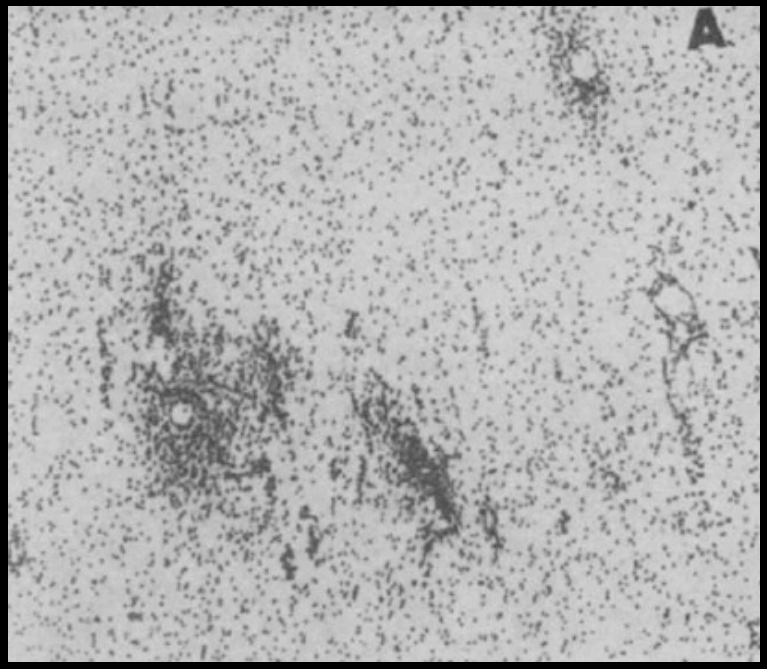


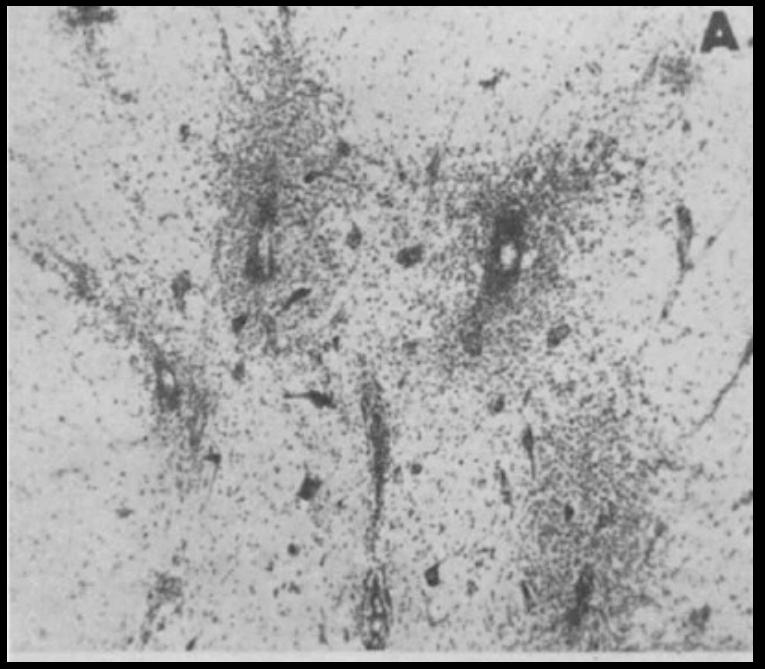
Left - sharply demarcated, confluent plaque

Right - myelin-laden macrophages accumulate at the expanding plaque edge and diminish toward the hypocellular center

Ann Rev Pathol Mech Dis 2012;7:185-217

ADEM – lesion pathology

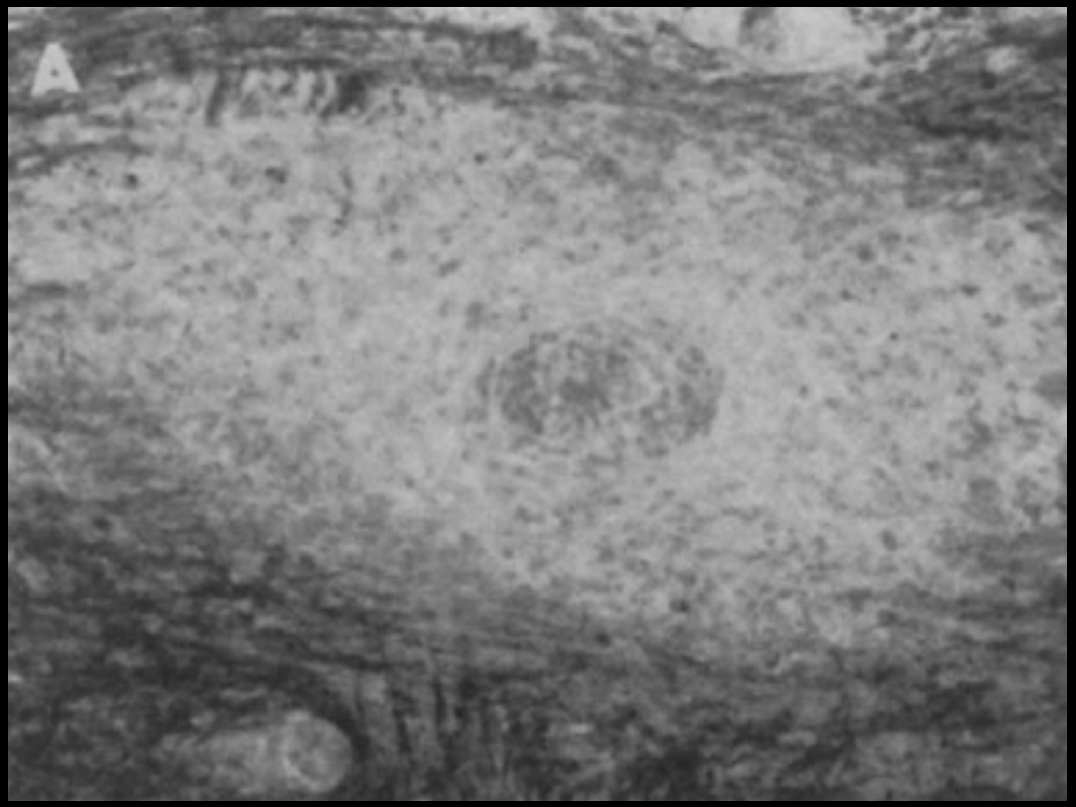




Disseminated perivascular inflammation with lymphocytic infiltration and microglial proliferation

Am J Med 1952;12(5):510-46

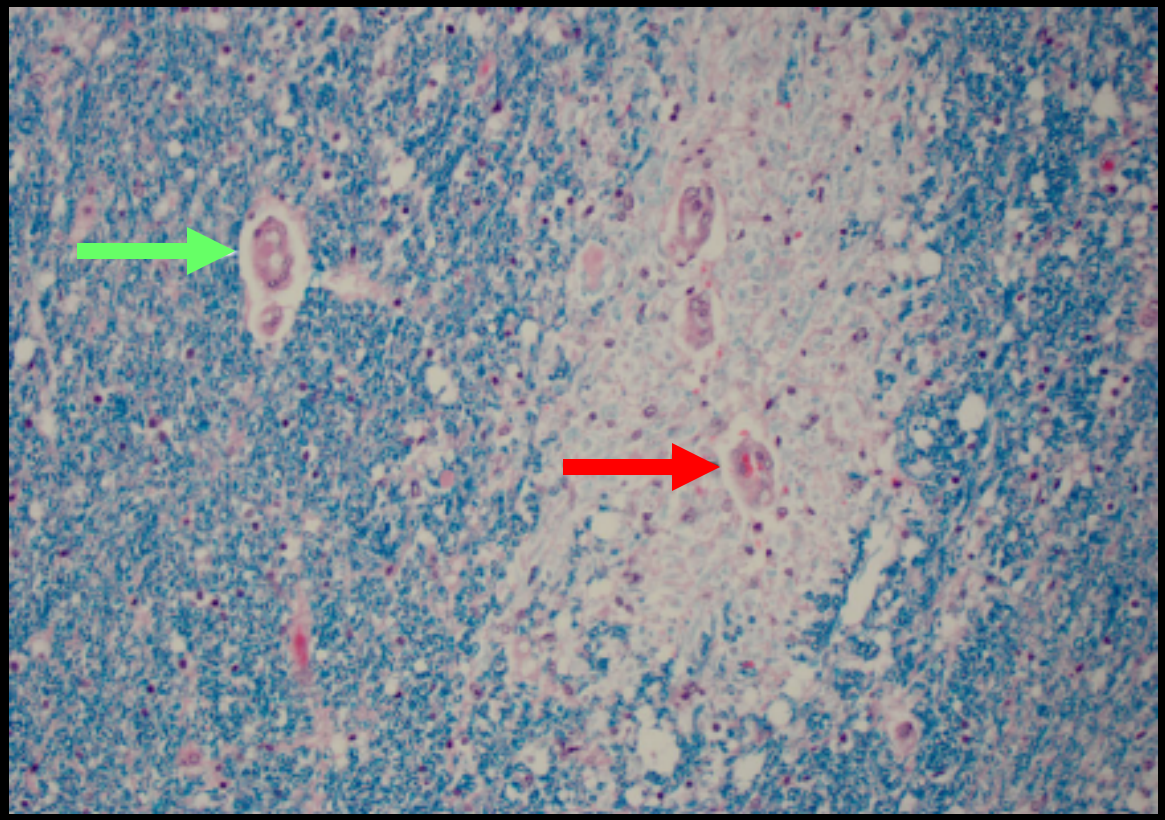
ADEM – lesion pathology



Perivenous ‘sleeves’ of demyelination with indistinct margins

Am J Med 1952;12(5):510-46

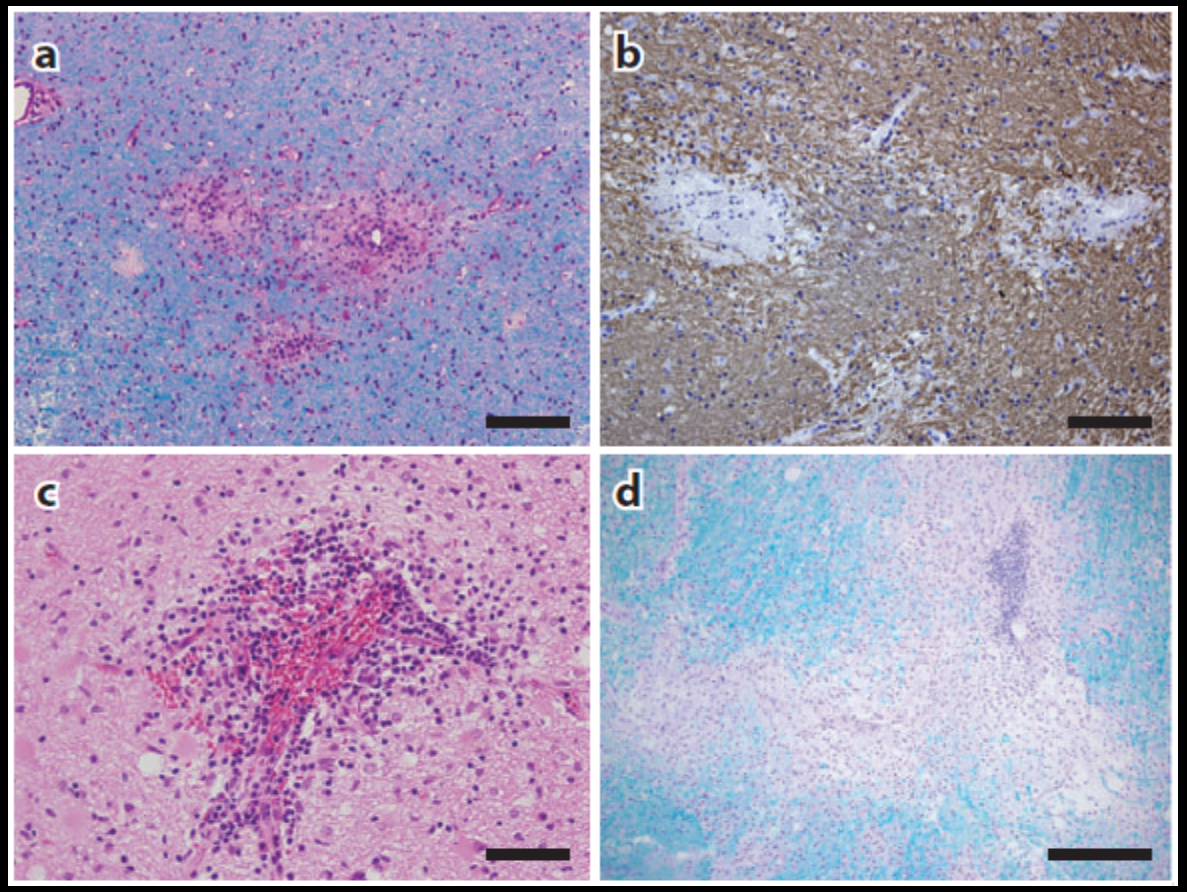
ADEM – lesion pathology



Perivenous ‘sleeves’ of demyelination with indistinct margins

J Neurol 2015;262:2013-24

ADEM – lesion pathology

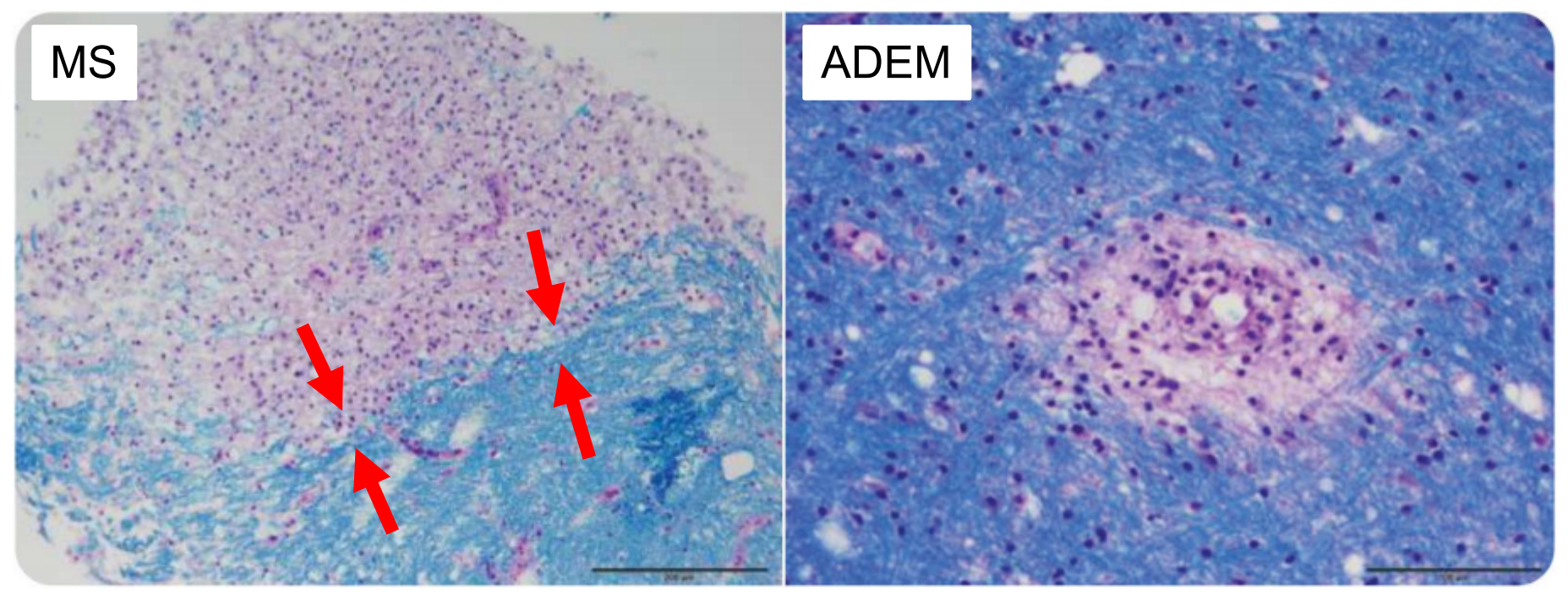


Perivenular inflammation and demyelination

Coalescence of small lesions into larger confluent lesion with irregular borders

Ann Rev Pathol Mech Dis 2012;7:185-217

Summary – lesion pathology



MS: confluent demyelinated plaque, sharp border

ADEM: multifocal perivascular demyelination, indistinct border

Neurology 2016;87:S12-19

Summary – lesion pathology (as of 1952)

Lesion	Acute MS	Chronic MS	ADEM
Distribution of lesions	patchy, irregular	patchy, irregular	diffuse
Age of lesions	mixed	mixed	uniform
Number of lesions	variable	variable, numerous	variable, innumerable
Relationship to veins	prominent	variable	always
Relationship to pia	rare	rare	common
Meningitis	none to slight	none to slight	variable

Am J Med 1952;12(5):510-46

MS versus ADEM – lesion pathology

A study of two cohorts from Mayo Clinic in 2010:

13 with biopsy showing perivenous demyelination

91 patients with biopsy showing confluent demyelination

Compared sensitivity and specificity of these *pathologic findings* to *clinical diagnostic features*…

Brain 2010;133:333-348

Clinical diagnostic features (as of 2010)

	Encephalopathy	Focality	Brain imaging
Monophasic ADEM	Present	Polysymptomatic	Large and multiple white and gray matter lesions
Recurrent ADEM	Present	Recurrence of initial symptoms and signs at >3 months	Large and multiple white and gray matter lesions
Multiphasic ADEM	Present	New anatomic involvement at >3 months	Large and multiple white and gray matter lesions
Clinically-isolated syndrome	Absent	Mono- or poly-symptomatic	McDonald criteria: focal lesion(s) not DIS&DIT
Relapsing-remitting MS	Absent	Polysymptomatic	McDonald criteria: focal lesions DIS&DIT

Neurology 2007;68:S7-S12

MS versus ADEM – lesion pathology

Back to the Mayo 2010 study…

Of the 13 patients with perivenous demyelination (PVD):

10 had only PVD

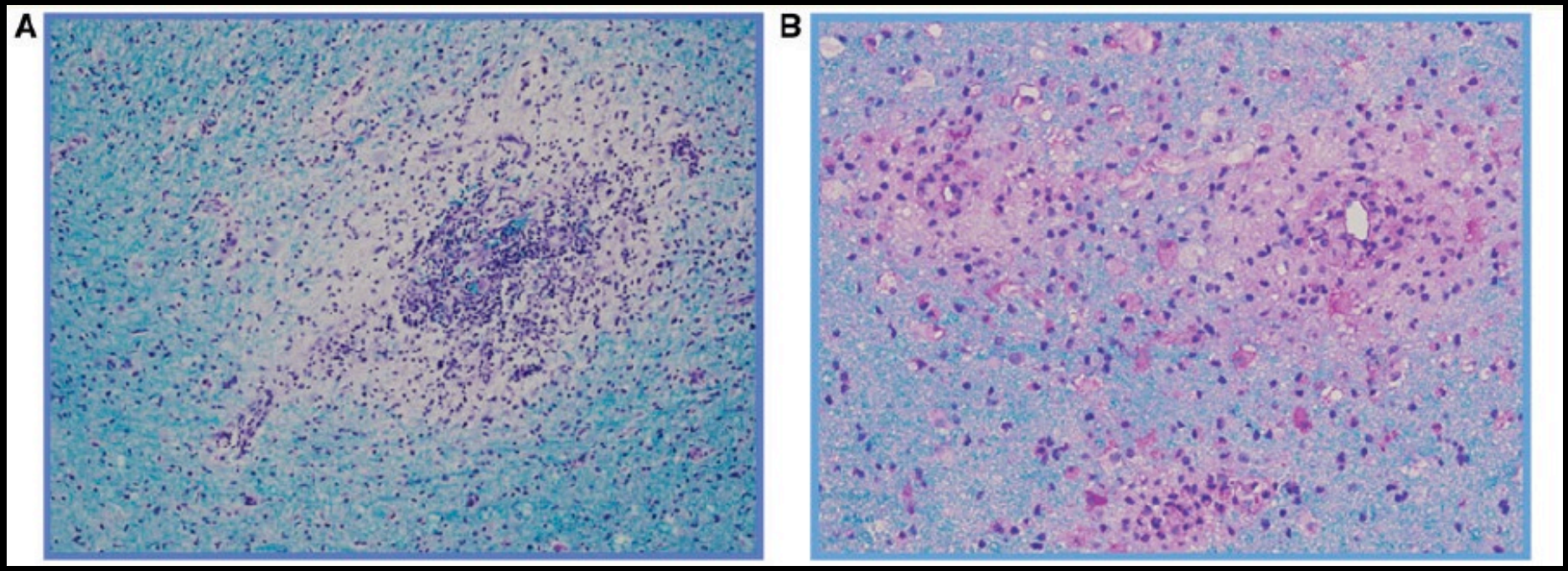
Of these 10 patients, 9 had a monophasic course

3 had mixed pathology (PVD & confluent demyelination)

Of these 3 patients, 2 had a relapsing course

Brain 2010;133:333-348

MS versus ADEM – lesion pathology

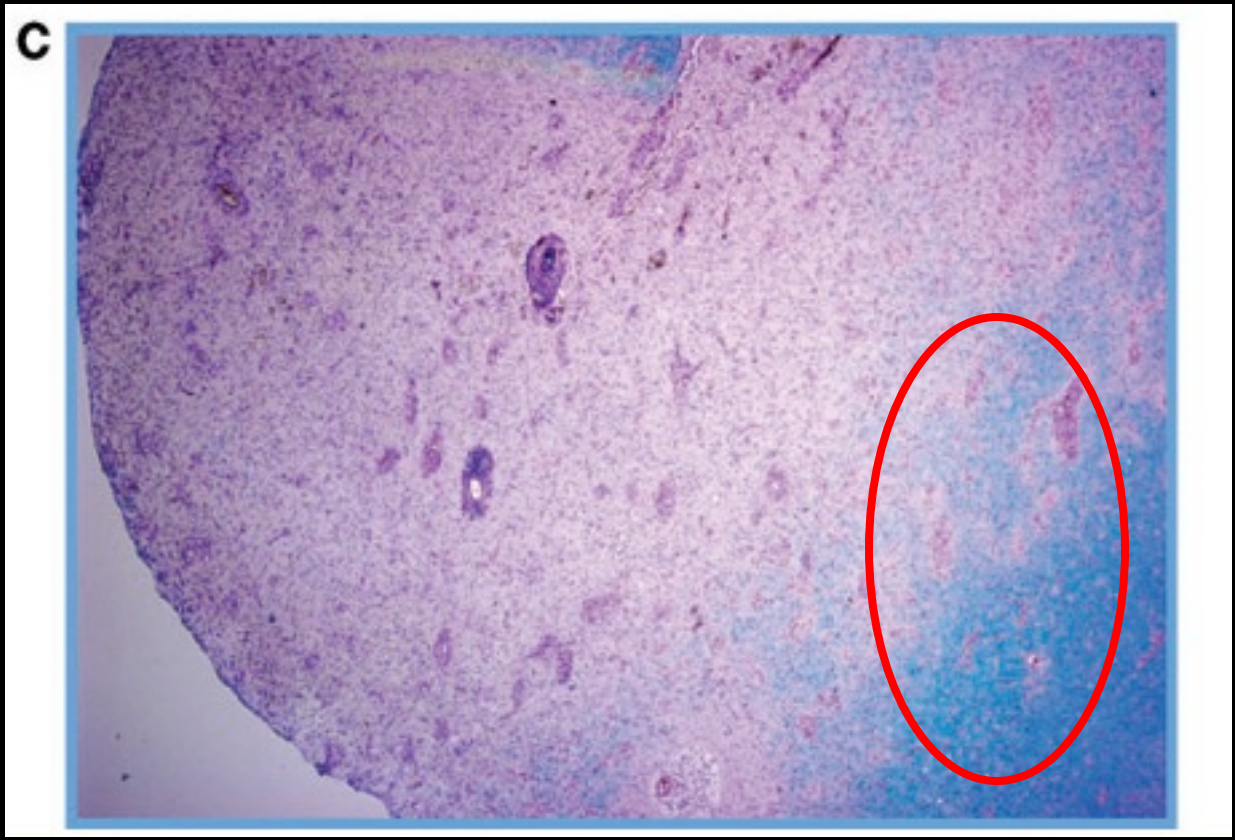


a) ADEM: Perivenous inflammation and demyelination

b) ADEM: Coalescence of three perivenous lesions

Brain 2010;133:333-348

MS versus ADEM – lesion pathology



c) Mixed pathology: confluent demyelination with perivenous demyelination at the periphery of the plaque

Brain 2010;133:333-348

Conclusions of Mayo study…

On the one hand, **pathology matched clinical findings**

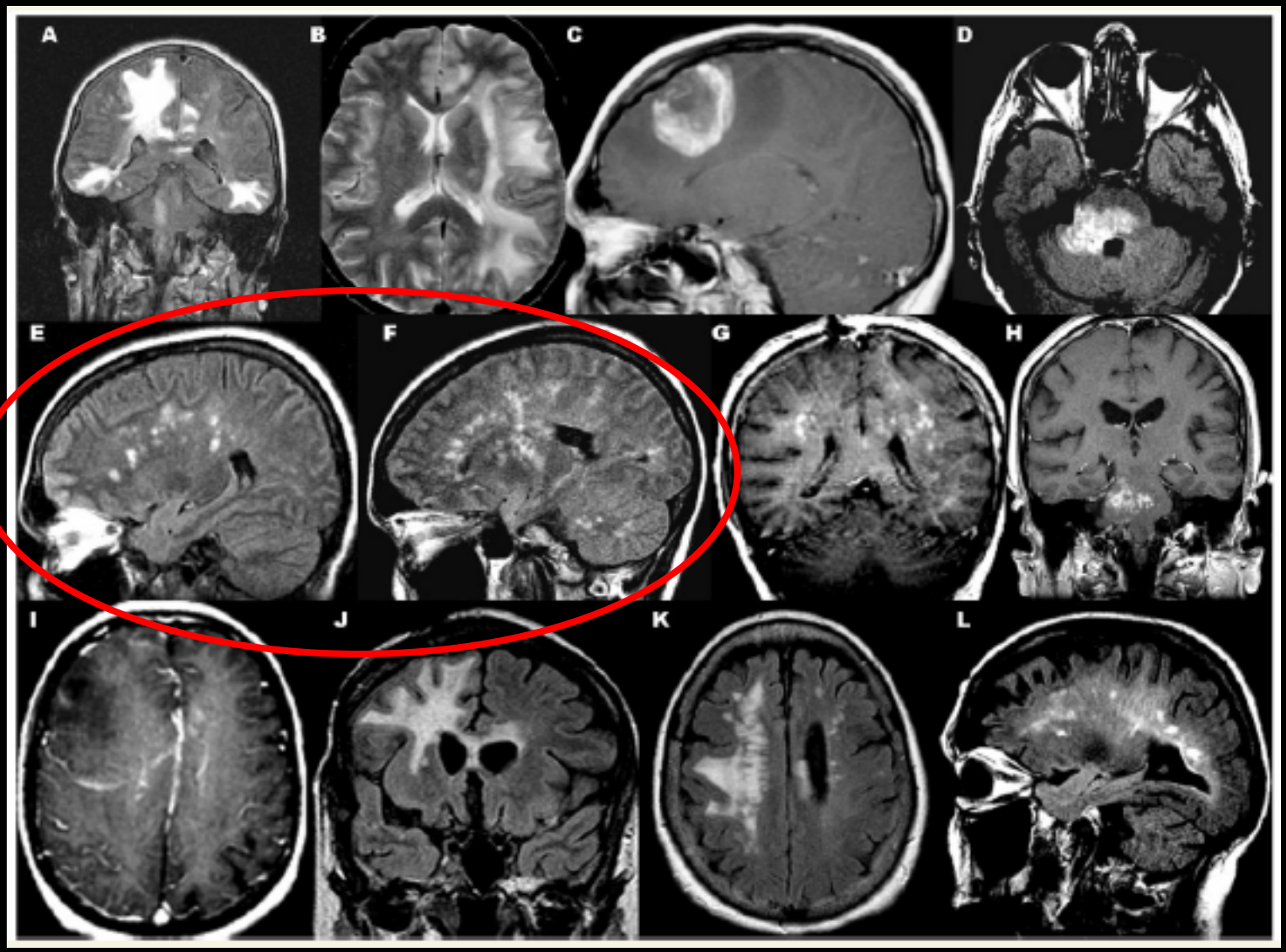
patients with perivenous demyelination were more likely to satisfy ADEM clinical diagnostic criteria

On the other hand, **pathology was sometimes non-specific**

patients with confluent demyelination often initially satisfied criteria for diagnosis of ADEM

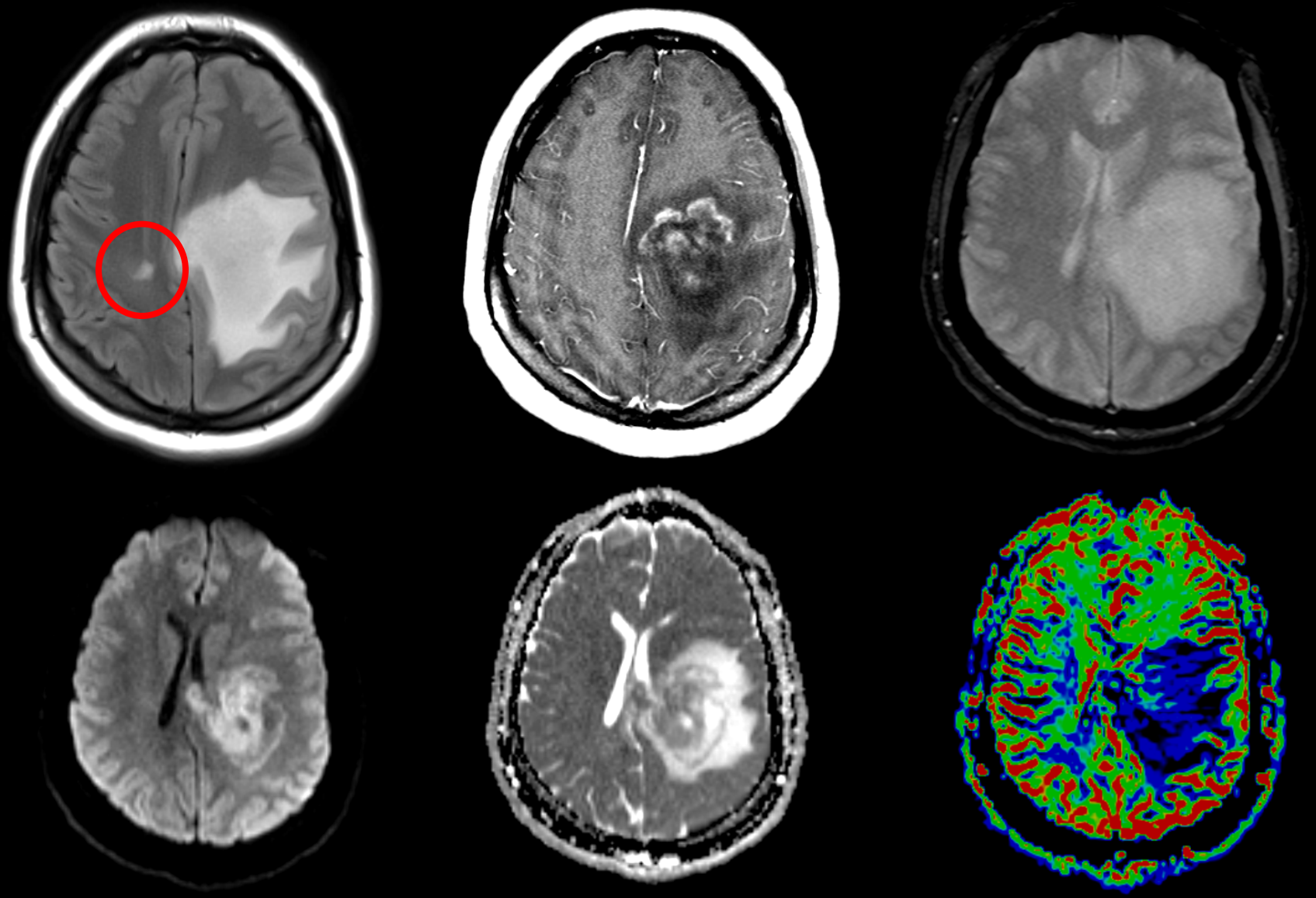
Brain 2010;133:333-348

Imaging correlates of perivenous demyelination



Brain 2010;133:333-348

Imaging correlates of perivenous demyelination



Klein JP. Youmans and Winn Neurological Surgery, 7th edition

Imaging correlates of perivenous demyelination

Table 2 MRI characteristics in ADEM vs MS

MRI characteristics	ADEM: Typical	MS: Typical
Deep gray matter and cortical involvement	Yes	No
Bilateral diffuse lesions	Yes	No
Poorly marginated lesions	Yes	No
Large globular lesions	Yes	No
Periventricular pattern of lesions	No	Yes
Lesions perpendicular to long axis of corpus callosum	No	Yes
Ovoid lesions	No	Yes
Lesions confined to corpus callosum	No	Yes
Sole presence of well-defined lesions	No	Yes
Black holes (on T1 sequence)	No	Yes

Neurology 2016;87:S38-S45

Imaging correlates of perivenous demyelination

Open questions:

Are there imaging determinants

…of clinical prognosis?

…of future relapsing disease?

Is there a role for surveillance imaging?

Acute disseminated encephalomyelitis in 228 patients

A retrospective, multicenter US study

Diederik L.H. Koelman, BSc
Salim Chahin, MD, MSCE
Soe S. Mar, MD
Arun Venkatesan, MD, PhD
George M. Hoganson, MD
Anusha K. Yeshokumar, MD
Paula Barreras, MD
Bittu Majmudar, MD
Joshua P. Klein, MD, PhD
Tanuja Chitnis, MD
David C. Benkeser, PhD
Marco Carone, PhD
Farrah J. Mateen, MD, PhD

ABSTRACT

Objective: To analyze the range of demographic, clinical, MRI, and CSF features of acute disseminated encephalomyelitis (ADEM), a rare, typically monophasic demyelinating disorder, and analyze long-term outcomes including time and risk factors for subsequent clinical events as well as competing diagnoses.

Methods: We performed a retrospective, multicenter study in 4 US academic medical centers of all patients clinically diagnosed with ADEM. Initial presentation of pediatric and adult ADEM and monophasic and multiphasic disease were compared. The Aalen-Johansen estimator was used to produce estimates of the probability of transitioning to a multiphasic diagnosis as a function of time since initial diagnosis, treating death and alternative diagnoses as competing risks.

Results: Of 228 patients (122 children, age range 1–72 years, 106 male, median follow-up 24 months [25th–75th percentile 6–67], 7 deaths), approximately one quarter (n = 55, 24%) experienced at least one relapse. Relapsing disease in children was more often diagnosed as multiphasic ADEM than in adults (58% vs 21%, $p = 0.007$), in whom MS was diagnosed more often. Encephalopathy at initial presentation (hazard ratio [HR] 0.383, $p = 0.001$), male sex (HR 0.394, $p = 0.002$), and increasing age at onset (HR 0.984, $p = 0.035$) were independently associated with a longer time to a demyelinating disease relapse in a multivariable model. In 17 patients, diagnoses other than demyelinating disease were concluded in long-term follow-up.

Conclusions: Relapsing disease after ADEM is fairly common and associated with a few potentially predictive features at initial presentation. Age-specific guidelines for ADEM diagnosis and treatment may be valuable, and vigilance for other, mostly rare, diseases is imperative.

Neurology 2016;86:2085

Large cohort of patients with ADEM

Retrospective multicenter study of all patients clinically diagnosed with post-infectious and non-postinfectious ADEM.

Inclusion: ADEM diagnosed by neurologist.

Exclusion: normal brain and spine MRI, or alternative diagnosis at first assessment.

Neurology 2016;86:2085

Large cohort of patients with ADEM

228 patients identified

54% pediatric, 46% adult

Average age 17 (range 1-72)

46% male, 54% female

Neurology 2016;86:2085

Large cohort of patients with ADEM

Table 4 Final diagnosis of patients initially diagnosed with ADEM

Final diagnoses	No. (%)
Monophasic ADEM[a]	156 (68)
MS	24 (11)
Multiphasic ADEM	23 (10)
NMOSD	8 (4)
Susac syndrome	2 (1)
Lupus cerebritis	2 (1)
CNS lymphoma	2 (1)
Astrocytoma grade 3 anaplastic	1
Primary brain tumor	1
CNS Lyme disease	1
CLIPPERS	1
Mitochondrial disorder involving the CNS	1
Glioblastoma multiforme	1
PANS/autoimmune encephalitis	1
CNS vasculitis	1
Rabies myeloencephalitis	1
Chronic relapsing inflammatory optic neuritis	1
Recurrent encephalitis	1

Most cases of ADEM had a history of preceding infection or vaccination.

Neurology 2016;86:2085

Large cohort of patients with ADEM

25% of patients had a relapse, which diagnostic criteria did not predict.

Competing diagnoses were common.

Some features of initial presentation helped predict relapsing disease (*female sex, absence of encephalopathy*).

Some features helped distinguish between pediatric and adult ADEM (*relapses in adults were MS > multiphasic ADEM*).

Neurology 2016;86:2085

J Neurol
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ORIGINAL COMMUNICATION

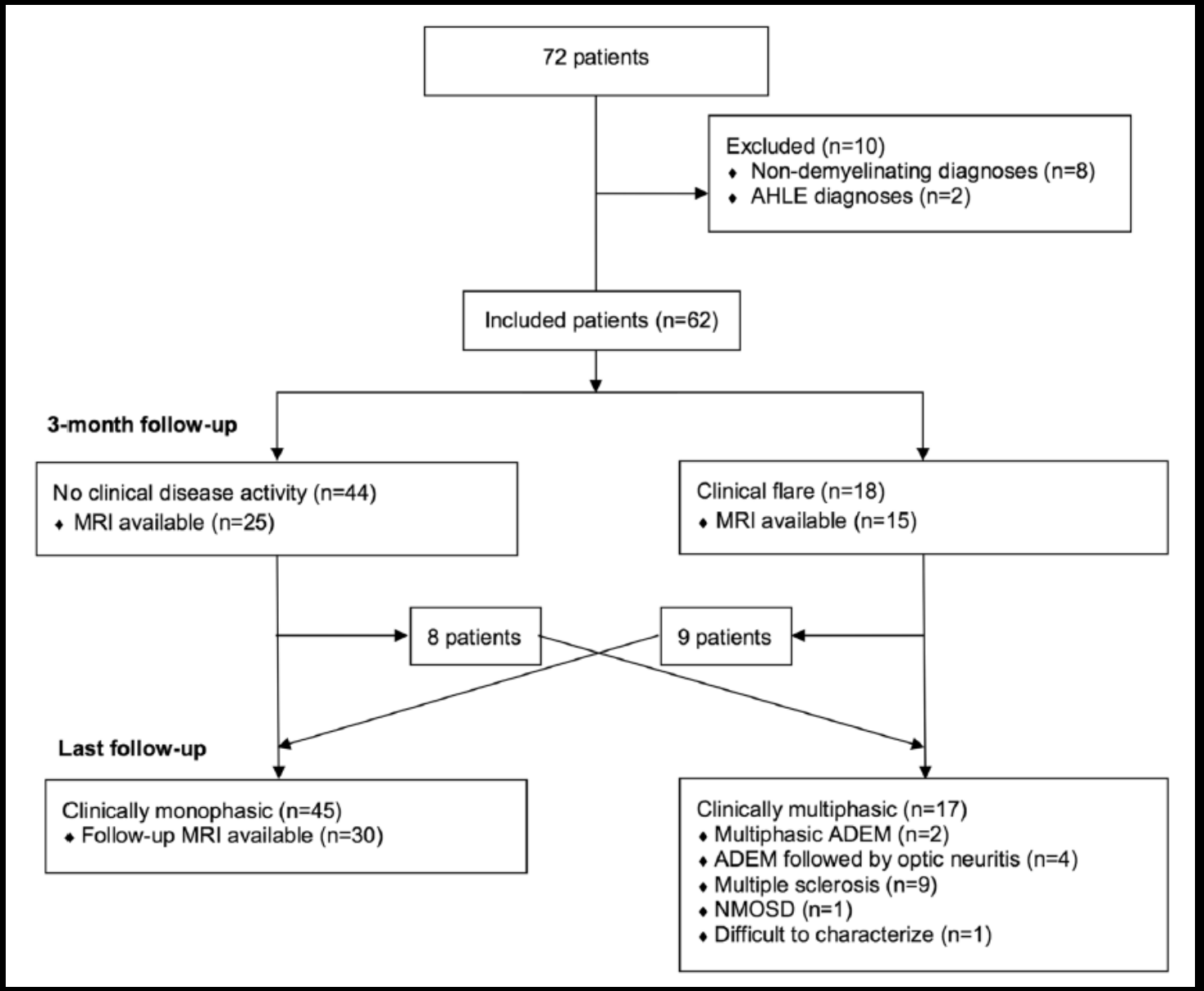
Acute disseminated encephalomyelitis: prognostic value of early follow-up brain MRI

Diederik L. H. Koelman[1,2] · David C. Benkeser[3] · Joshua P. Klein[4,5,6] · Farrah J. Mateen[1,6]

Patients with ADEM are presumed to have a monophasic course...

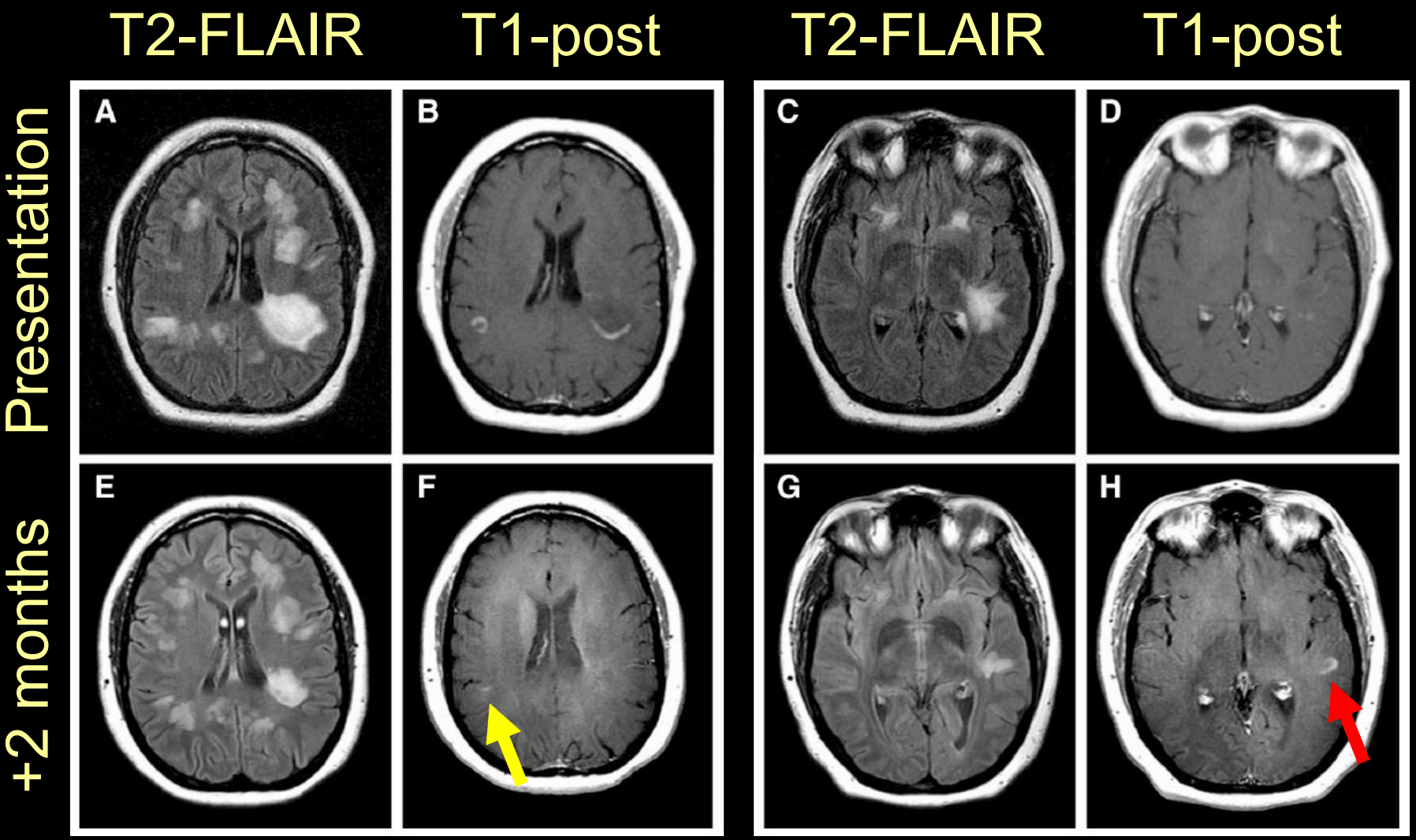
but this is uncertain because follow up imaging is not routinely performed.

J Neurol 2017;264(8):1754



J Neurol 2017;264(8):1754

ADEM: new lesions on early follow-up MRI



J Neurol 2017;264(8):1754

New and persistent lesions on early follow up MRI, as well as clinical flares, were more common in clinically multiphasic vs monophasic patients.

Performing early follow up brain MRI in ADEM patients can aid in predicting multiphasic disease (including MS) and may stratify patients who would benefit from initiation of disease-modifying therapy.

J Neurol 2017;264(8):1754

ADEM

Table 1 ADEM and its convergence with relapsing demyelinating disorders

Diagnosis	Clinical criteria
ADEM, monophasic[7]	Single polyfocal CNS event with encephalopathy and presumed inflammatory demyelination and no new disease activity (clinical or MRI) >3 months after onset
ADEM, multiphasic[7]	ADEM followed at >3 months by second ADEM episode, but no further ADEM or non-ADEM demyelinating events
ADEM-MS[7]	ADEM followed at >3 months by non-ADEM demyelinating relapse and new MRI lesions meeting criteria for dissemination in space[8]
ADEM-NMOSD[9]	ADEM followed at >3 months by events including optic neuritis, longitudinally extensive transverse myelitis, or area postrema syndrome, meeting MRI requirements according to revised NMOSD criteria[9]
ADEM-ON	ADEM, MDEM, or multiple ADEM attacks followed by optic neuritis

Neurology 2016;87:S38-S45

Summary

ADEM is an inflammatory central nervous system syndrome with immune-mediated demyelination.

ADEM unlikely a single distinct disease.

There is significant and incompletely described clinical, radiographic, and pathological overlap with MS and NMO-spectrum disorders.