Pathologic Features of CNS Demyelinating Disease: *Can Pathology Lead to a Specific Diagnosis?*

Claudia F. Lucchinetti, MD
Professor of Neurology
Mayo Clinic, Rochester MN

**Prototypic MS**

- RR → SP

**Benign MS**

- RIS

**Fulminant**

- Marburg MS
- ADEM/AHLE
- BCS

**Restricted Distribution**

- NMO/NMOSD
- Relapsing Myelitis
- Relapsing ON

**Isolated**

- ON
- Transverse myelitis

**Progressive**

- Chronic myelopathy
- Cerebellar syndrome

**Chronicity**

**Severity**

Courtesy: Brian Weinshenker
Spectrum of CNS Inflammatory Demyelinating Diseases (IDDs)

• May mimic or be mimicked by brain tumors, infectious encephalitides, granulomatous disorders, and other inflammatory disorders
• May present with focal, multifocal, or non-localizing neurological deficits
• Differentiation between specific inflammatory demyelinating diseases can be challenging
• Clinical and Therapeutic Implications
• Pathology Can Aid in Diagnosis

Prototypic MS
Pathological Hallmarks of MS

MS Plaque Types

ACTIVE  SMOLDERING  INACTIVE  SHADOW
Patient Dependent Heterogeneity

Pattern I
- T cell/macrophage associated

Pattern II
- Antibody/complement associated

Pattern III
- Distal oligodendrogliopathy

Pattern IV
- Primary oligodendrocyte degeneration


Focal White Matter Lesion in Early MS
Heterogenous Mechanisms of Demyelination

- T cells/Macrophages (Cytokines, radicals)
- Antibody/Complement
- Increased CNS vulnerability
# Distinguishing Pathological Features

<table>
<thead>
<tr>
<th>Feature</th>
<th>Pattern I</th>
<th>Pattern II</th>
<th>Pattern III</th>
<th>Pattern IV</th>
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<tbody>
<tr>
<td>Perivenous</td>
<td>+++</td>
<td>+++</td>
<td>+/-</td>
<td>NA</td>
</tr>
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<td>Sharp borders</td>
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<td>NA</td>
</tr>
<tr>
<td>Complement</td>
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<td>++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>MAG loss</td>
<td>-</td>
<td>-</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>OG apoptosis</td>
<td>+/-</td>
<td>+/-</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>RM</td>
<td>+++</td>
<td>+++</td>
<td>+/-</td>
<td>NA</td>
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<tr>
<td>T cells/MOs</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+/-</td>
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**Cortical Demyelination Extensive in Progressive MS**  
Subpial Demyelination Only Observed in MS
Bruck et al.

• 251 tissue blocks/122 cases/20 different diseases
  - Viral encephalitis (herpes, measles, CMV, PML),
  - Bacterial meningitis (pneumococcus, staphylococcus, haemophilus influenzae, syphilis, tuberculosis),
  - Neoplastic disorders (lymphoma, carcinoma)
  - Metabolic disorders (central pontine myelinolysis)

➢ 180 tissue blocks from 33 MS cases
➢ SUBPIAL DM ONLY SEEN IN MS

Radiologically Isolated Syndromes
Case History

- Healthy asymptomatic subject volunteered to undergo research MRI
- MRI: numerous periventricular WM lesions, large tumefactive ring enhancing lesion left frontal lobe
- Normal Neurological Examination
- Normal CBC, Lyme, Toxo antibodies, anti-cardiolipin antibodies, ACE, ESR, RPR, ANA, ENA, HIV and CSF
- Brain biopsy at two sites; “Gliosis in site #1 and ganglioma in site #2.

Case History

- Despite no Sxs, treated with 3 days of IVMP and Copaxone for two years
- Followup MRIs revealed resolution of enhancement and reduced size of the tumefactive lesion
- 2007-2013: developed single new non-enhancing T2 lesion left hemisphere
- Clinically stable; on no Tx and asymptomatic
- Biopsy sent for re-review
RIS Take Home Messages

- Pathology does not differentiate asymptomatic RIS from RRMS
- Active demyelination can be seen in asymptomatic RIS
- Axonal injury is evident in RIS despite asymptomatic onset
- RIS can involve both WM and Cortex
Spectrum of CNS Inflammatory Demyelinating Diseases

- Marburg variant of acute MS
- Balo’s Concentric Sclerosis
- Acute Disseminated Encephalomyelitis
- Acute Hemorrhagic Leukoencephalitis
- Tumefactive Demyelinating Lesions
- Neuromyelitis Optica/NMO Spectrum Disorders
Marburg MS

- 1906 Marburg described 3 cases of fulminant demyelinating disease
- Malignant course
- Rapid progression with death within 1 year
- Hemiplegia, hemianopsia, aphasia, seizures, confusion
- Pathology
  - Active Confluent Demyelination
  - Admixture of astrocytes/myelin-laden macrophages
  - Inflammation with variable T cells
  - More destructive than classic MS

Marburg MS: 30 yo F; 3 wk hx of rapidly progressive left hemiparesis and neglect; raised ICP

12/24/1994

1/08/1995
Pathology: Marburg MS

Marburg MS

- Classification in literature confusing as clinical and radiographic phenotype can be seen in:
  - ADEM, TDL, NMO
  - Brain Tumor
  - Abscess

- 18.5 kDa isoform of MBP is less cationic than the MBP of normal and classic MS due deamination of arginyln residues generating citrulline.
  - May cause structural instability of central myelin sheath (Wood et al. 1996; Beniac et al. 1999)
Balo’s Concentric Sclerosis

- Josef Balo (1929): Hungarian neuropathologist
- “leuko-encephalitis periaxialis concentrica”
- Course: Benign to Fulminant
- Young adults: 34 yrs (3-62)
- Predilection for SE Asian ancestry
- Lesions in cerebral hemispheres, optic chiasm, cerebellum, brainstem, spinal cord
- HA, cognitive/behavioral, hemiparesis, ataxia, dysarthria, aphasia, seizures
- Mimics ADEM or tumor
Balo’s Concentric Sclerosis

- Unique Concentric pathology

LFB/PAS

Bielschowsky

Myelin

CD68

Antemortem dx possible via MRI

Rovira et Al, Neuroradiology 2007
BCS Lesions Show MAG Loss-Pattern III

HYPOXIC-PRECONDITIONING

Stadelmann et al, Brain 2005
CADASIL MUTATION AND BALO CONCENTRIC SCLEROSIS: A LINK BETWEEN DEMYELINATION AND ISCHEMIA?
Chitnis et al. Neurology 2012
Balo’s Concentric Sclerosis

- Concentric lesions described in MS, Marburg MS, and NMO/NMOSD

|-----------------|------------------------|----------------------|----------------------|-----------------|

ADEM/AHLE
ADEM: Clinical Definitions


- Rare, typically monophasic; favorable prognosis
- Children > Adults (age < 10 yrs); M>F
- First event: acute/subacute; polyfocal; “encephalopathy”
- Relapsing forms: MDEM
- Post-infection or vaccination (+/-)
- CSF: generally absent OCBs
- MRI
  Multifocal (WM / cortical / deep GM)
  Large lesions
  Fuzzy-borders
  Similar age (All enhancing)
- Diagnosis of Exclusion (overlap with NMO, MS, BCS)

PeriVenous Demyelination in ADEM

(Prineas 2002; Greenfield’s Neuropathology)
ADEM: 30 F; HA, N, V, encephalopathy and gait impairment over 4 weeks

CSF: WBC 8; PRO 248; OCB -
Patterns of Perivenous DM

Perivenous DM
- n=13

Coalescent DM
- n=7

Confluent DM
- PV / CON: n=1
- PV / CL / CON: n=2

Pattern of Demyelination and Course

<table>
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<tr>
<th>Pattern</th>
<th>n</th>
<th>Monophasic</th>
<th>Relapsing</th>
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<tr>
<td>PV alone</td>
<td>4</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>PV + CL</td>
<td>6</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>PV + CON</td>
<td>3</td>
<td>1 (fatal)</td>
<td>2</td>
</tr>
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</table>
Clinical Correlates of Perivenous DM

- Compared with the Confluent DM cohort (n=91; 90% MS), the Perivenous DM cohort was more likely to present with:
  - Encephalopathy (p < 0.004)
  - Depressed level of consciousness (DLC) (p < 0.001)
  - Headache (p < 0.001)
  - Meningismus (p < 0.005)
  - CSF pleocytosis (p < 0.02)

- Depressed LOC distinguishes ADEM from MS
  - Broadly defined “encephalopathy” does not

Broad Spectrum of MRI Findings Associated with Perivenous DM
Cortical Pathology in ADEM

- Subpial and intracortical DM
- Unique pattern of cortical microglial activation and aggregation
  - Only in PVD patients w/ decreased LOC (n=10)
  - None in Confluent DM cohort.
- ? Substrate of ADEM encephalopathy

Histology ADEM & MS

<table>
<thead>
<tr>
<th>Pathology</th>
<th>ADEM</th>
<th>MS</th>
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<tbody>
<tr>
<td>Macrophages</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Granulocytes</td>
<td>++</td>
<td>+/-</td>
</tr>
<tr>
<td>Perivenous (WM) DM</td>
<td>++</td>
<td>--</td>
</tr>
<tr>
<td>Coalescence</td>
<td>+/-</td>
<td>--</td>
</tr>
<tr>
<td>Confluence</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Perivenous (GM) DM</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Microglial Cortical aggregate (GM)</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>Subpial DM</td>
<td>++</td>
<td>+++</td>
</tr>
</tbody>
</table>
**ADEM Take Home Messages**

1. Pathology helpful in diagnosis of ADEM
2. The presence of PV +/- coalescence DM is associated with a monophasic course (survival or fatal)
3. ADEM demonstrates a unique cortical pathology associated with ↓ LOC
4. PV DM cases can be associated with confluent DM (? ADEM and MS share Pathogenic Spectrum)
5. Confluent DM in association with PV DM may be associated with a greater risk of recurrence: ? MDEM versus MS

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**Acute Hemorrhagic Leukoencephalitis**

- Hurst 1941: Rare
- Viral prodrome
- Demyelination w/ hemorrhage (usually small, petechial)  
  (Prineas 2002; Greenfield’s Neuropathology)
- Severe, often fatal
AHLE: 21 M; paresthesias; diplopia, gait ataxia, L facial weakness, dysarthria; respiratory compromise; refractory to steroids/plasma exchange; died 1 mo

2/2/2009

CSF: WBC 25 pro 70 mg/dL, 0 OCB

2/28/2009

Early and widespread injury of astrocytes in the absence of demyelination in acute haemorrhagic leukoencephalitis

CASE REPORT
MOG-Associated Encephalomyelitis
(Spadaro et al. 2015)

- 66 yo Caucasian woman
- 2011: Transverse Myelitis
- AQP4-IgG and NMDA Abs negative
- 2012: TM; brainstem syndrome
- MOG Abs positive
- Rituximab with complete B cell depletion
- Massive brain lesions
- Brain Biopsy: Type II pathology
MOG-Ab Associated Pathology

- First pathological case of MOG-Ab associated demyelinating disease
- MOG Ab may be pathogenic
  - MOG Ab binds to extracellular domain
  - Abs can access CNS via open BBB
  - MOG Abs have a complement activating isotype
  - Histopathology resembles MOG-EAE; Type II pathology
Tumefactive Demyelinating Lesions

- MS may present as a mass lesion(s) indistinguishable clinically and radiologically from a tumor
- Clear definition lacking
- Present with cerebral symptoms
- Uni/multifocal; edema; mass effect
- Diagnostic difficulty; brain biopsy may be necessary
- Biopsy specimen may resemble a tumor (Creutzfeldt cells)

Open ring sign (Masdeu 1996)
**TDLs**

**Histological Features of Inflammatory Demyelination**

- Presence of foamy macrophages, particularly in the absence of coagulative necrosis
- Intimate admixture of macrophages and astrocytes
- Even distribution of reactive astrocytes
- Creutzfeldt cells ("granular mitoses")
- Sharply circumscribed white matter lesions

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**Clinical Courses Associated with Tumefactive Demyelination**

1. Fulminant course to death—*Marburg variant*
2. Monophasic attack with recovery
3. Tumefactive presentation followed by typical RRMS
4. Typical MS course with subsequent tumefactive attack
5. RR course with strictly tumefactive attacks
Pt. #1: Monophasic to Death “Marburg MS”

Pt. #2: Monophasic Course with Recovery
#3 Tumefactive presentation followed by RRMS

1988

1992  Disease duration 17yrs  EDSS=3

2001

Pt. #4: RRMS followed by tumefactive relapses

8/18/1993

2/15/1994
#5 RR course with tumefactive attacks

Disease duration=13yrs
EDSS=1

1990

1996

2001

2cm L parietal + satellite (x2) lesions

Bx: *grade III glioma*

Rx: whole brain XRT
subsequent radiosurgery

Re-review of slides: active demyelination

Progressive deterioration

Died 6.25 yrs after onset

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38 yo F: subacute onset L arm and face paresthesias

2cm L parietal + satellite (x2) lesions

Bx: *grade III glioma*

Rx: whole brain XRT subsequent radiosurgery

Re-review of slides: active demyelination

Progressive deterioration

Died 6.25 yrs after onset

Radiation Necrosis
Diagnostic Pitfall
Misdiagnosis as Astrocytoma

Effect of brain irradiation on demyelinating lesions

K. Peterson, MD, J. K. Roentz-Hutt, MD, J. M. Powers, MD, E. Alford, MD, R. W. Walker, MD, and J. B. Ponten, MD

**Article abstract**—Demyelinating lesions, such as those in multiple sclerosis, may resemble primary or metastatic brain tumors on CT or MRI, and even be mistaken for neoplasms on biopsy. We encountered five such patients in whom an incorrect diagnosis of CNS neoplasm was made on the basis of radiologic appearance (five) and biopsy (four). All five received radiation therapy, and three chemotherapy treatment. Review of the pathological findings indicated that the original lesions were not neoplastic but demyelinating. The four patients who received radiation in full tumor-cidal doses had unexpectedly poor clinical outcome, suggesting that radiation is especially injurious in patients with demyelinating disease.

NEUROLOGY 1995;45:2105-2112
Radiographic Features of TDLs

- Large lesion size (0.5-7.5 cm)
- Mass effect (45%)
- Edema (77%)
- Gadolinium enhancement (95%)
- Ring-enhancement pattern common
- Butterfly configuration involving corpus callosum (7%)

Common Prebiopsy TDL Enhancement Patterns

- Ring, arc, open ring 42.5%
- Heterogenous 32%
- Open ring cortex
- Homogenous 8%

Lucchinetti et al., 2008
Uncommon Prebiopsy TDL Enhancement Patterns

- Punctate 3%
- Concentric 1%
- No enhancement 15%
- Nodular >2mm 0.5%
- Diffuse/patchy 4%
- Diffuse/patchy 4%
- Fluffy 1%

OTHER
- Punctate 3%
- Concentric 1%
- No enhancement 15%

Lucchinetti et al., 2008

The Spectrum of Biopsied Tumefactive MS

1. Detailed clinical F/U of 168 cases: > 90% patients develop clinically definite MS
2. Despite atypical MRI at presentation, most are multifocal on MRI prior to biopsy
3. 20% develop recurrent TDLs
4. Often good prognosis
   - Disability at last f/u better than MS prevalence cohort matched for disease duration >10 yrs
   - Longer interval to second attack (median 4.8 years)

Lucchinetti et al. Brain 2008
Diffusion Weighted Imaging Characteristics of Biopsy-Proven Demyelinating Brain Lesions (AbouZeid et al. 2012)

- 40 ADC maps reviewed from 30 patients
- 93% of lesions were enhancing
  - 52% ring-enhancement pattern
- Compared to cohort of ring-enhancing tumors/abscess
- Variable ADC map in IDD
  - 7% normal diffusion
  - 33% restricted
  - 60% increased
- Features to suggest IDD
  - 57% had change in pattern on serial imaging
  - Peripheral restriction

Variable ADC Patterns in TDLs
Pattern of Diffusion Restriction
Abscess vs TDL

- Abscess
  A) ADC map showing central restriction
  C) post-gad ring enhancement

- Demyelinating Lesion
  B) ADC map showing peripheral restriction
  D) post-gad enhancement

Rapid DW/ADC Changes in TDLs
TDLs Take Home Messages

• Classification of TDLs in literature confusing
• TDLs can be found in:
  • Prototypic MS
  • Marburg MS
  • Balo’s Concentric Sclerosis
  • NMO/NMOSD
  • ADEM/AHLE
• Both pattern II and pattern III immunopathologies can be assoc with TDLs

NMO/NMOSD
What is NMO?

- Relapsing > Monophasic
- Any interval between attacks
- ON — unilateral or bilateral
- Longitudinally extensive myelitis in active disease
- Brain Involvement described
- AQP4-IgG: Specific and sensitive pathogenic auto-antibody

Pathological Hallmarks

- Destructive lesions
- Eosinophils
- Perivascular immune complex deposition
- Humoral immunity targeting perivascular space

Lucchinetti; Brain, 2002
Lesion Types in NMO

**Destructive, Demyelinated**

- Myelin AQP4
- C9neo
- AQP4

**Non-Destructive, Non-Demyelinated**

- Myelin
- C9neo
- AQP4

**Active MS shows Increase AQP4**

- Myelin
- C9neo
- AQP4

- Active demyelination
- No perivascular rosettes; Myelin debris in macrophages
- Perivascular AQP4 enhanced

**NMO lesions show AQP4 loss**

- Myelin
- C9neo
- AQP4

- Myelin preservation
- Perivascular rosettes; Macrophages negative
- AQP4 loss
NMO and the BRAIN

“NMO-typical” Brain Lesions are in AQP4-rich Sites

Arch Neurol. 2006;63(7):964-8

NMO BRAIN LESIONS

Myelin  C9neo  AQP4
Supraspinal Neuromyelitis Optica (NMO) lesions may show complement deposits in combination with MAG loss and oligodendrocyte apoptosis. This mimics an overlap of pattern II and pattern III.

NMO Brain Lesions Can Mimic Immunopattern Overlap

Spectrum of early non-lytic astrocytic abnormalities: early stress response in NMO
Early Perivascular Astrocytic Loss in NMO but Preserved in MS

Granulocytic Infiltration Prominent in NMO Rare in MS
Early Eosinophil Recruitment in Vacuolated Perivascular Regions

Early astrocyte responses drive early granulocytic recruitment: complement deposition not required

- 23.5% of regions examined had mild or marked granulocytic infiltration in the absence of complement deposition

| 23 patients | 337 blocks | 1048 regions examined |
Creutzfeldt-Peters Cell Present in MS but Absent in NMO

Astrocyte Death in Advanced NMO Lesion

PLP, 4x  AQP4, 4x

GFAP  GFAP  GFAP
Cortical DM is Absent in NMO
Popescu et al. Neurology 2010

Meningeal Inflammation Differs in MS vs MNMO

MS: Lymphocytic
NMO: Plasma cell/Granulocytic
Meningeal Lymphoid Follicles
“PRESENT” in MS/ABSENT in NMO

**MS**

**NMO**

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**Case**

65 year old Female Presenting with Tumefactive Brain Lesion

- **2/2006**: subacute onset right lower quadrantanopsia
- MRI brain: enhancing left occipital lesion later involved both occipital lobes. MRI spine negative
- **8/2006**: Brain biopsy “active demyelination”; dx MS
- CSF normal; VERs prolonged bilaterally
- **2007-2009**: Glatiramer acetate started and courses of IVMP for exacerbations of visual dysfunction and cognitive impairment
Follow-up

- Pt seen back 4 years after onset, with new Gad-enhancing lesions on brain MRI
- Copaxone stopped and pt began IV steroids and pulse cyclophosphamide
- Re-review of original brain biopsy showed changes consistent with NMO (neuromyelitis optica)
Followup

• NMO-IgG testing recommended; serum was positive
• Patient treated with Cytoxan
• Relapse LETM 3/2010 (first “typical” NMO relapse); 4 years AFTER onset
• Brain Lesions can be presenting symptoms in NMO
• Brain biopsy was “diagnostic”; prompted NMO-IgG testing
Diagnostic Utility of AQP4 in Active Demyelinating Lesions (Popescu et al. 2015)

- Retrospective analysis of 20 surgical biopsies (19 pts; 11 brain/9 spinal cord)
- Inclusion Criteria: 2 of 3 AQP4 associated neuropathological findings

AQP4 Immunohistochemistry

NMO Spinal Cord n=9
NMO Brain n=9
MS Brain n=2
Pathological Features on Biopsy

- Dystrophic astrocytes
- GFAP + macrophages
- AQP4+ in PPWM
- Creutzfeldt cells
- Myelin vacuolation
- Vascular hyalinization
- Granulocytes

Clinical Outcomes

- NMO/NMOSD
- LETM/LETM
- RRMS
- NMO-IgG+

AQP4 Loss

AQP4 Increase

Patient

Pathological Features on Biopsy

Clinical Outcomes

Brain biopsy

Spinal cord biopsy

Biopsy  ON  Brain syndrome

TM  Bilateral ON  N/V  Death

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Summary

• AQP4 Immunohistochemistry useful in identifying cases of NMO/NMOSD
• NMOSD should be considered in DDx of tumefactive brain or spinal cord lesions
• AQP4-IgG testing may avert biopsy and avoid ineffective therapies if treated erroneously for MS
Can Pathology Lead to a Specific Diagnosis?

<table>
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<th>PATHOLOGY</th>
<th>DIAGNOSIS</th>
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<tr>
<td>Confluent Demyelination</td>
<td>MS/Marburg/TDLs</td>
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<tr>
<td>Perivenular Demyelination</td>
<td>ADEM/AHLE</td>
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<td>AQP4 loss in active DM</td>
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Thank you for your attention!
Collaborators

Mayo Clinic: B. Popescu; Y Guo, C Howe, M Caulfield; Parisi JE; B Weinshenker; S Pittock; V Lennon; A McKEon; D Wingerchuk; P Zeimer; L Linbo; S. Weigand

Univ of Gottingen: W. Bruck; I Metz

Univ Vienna: H. Lassmann; J Frisher

CNS Inflammatory Demyelinating Syndromes

CNS-IDS

NMO/NMOSD BCS Anti-MOG CRION TMIrTM ADEM/AHLE Marburg

CIS → MS ← RIS

Relapses

Chronic progression

Active DM plaque heterogenous patterns

I II III IV

Tcells/MΦ Ab/C Hypoxia/mitochondrial Primary 0G degeneration

Smoldering WM plaque CDM “NAWM”