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Clinical-radiological-pathological spectrum of CNS idiopathic inflammatory demyelinating disease in the elderly

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Abstract

Background—The spectrum of CNS idiopathic inflammatory demyelinating disease (CNS-IIDD) in the elderly is uncertain.

Objective—To describe the clinical, radiological, and pathological features of a cohort of 30 pathologically proven CNS-IIDD patients ≥ 65 years.

Methods—Elderly MS/CIS patients were compared to a cohort of 125 patients with pathologically proven MS/CIS and symptom onset <65 years.

Results—Median age at symptom onset was 69 years (IQR 68–75). Median follow-up was 1.9 years (IQR 1.0–5.6). Diagnoses were MS (14/30), CIS (11/30), NMO (4/30), and ADEM (1/30). Disability was higher in patients with MS/CIS ≥ 65 compared to patients <65 (median EDSS 4 [IQR 2.5–7] vs. 2.5 [IQR 1.5–4]; $p=0.002$). When compared to patients <65, there was no difference in the lesion size, number of patients fulfilling Barkhof's criteria, edema or mass effect. Confluent demyelination was observed in 27 patients [MS/CIS (23/25), NMO (4)], two had a mixed perivenular/confluent pattern [MS (1), ADEM(1)] and one patient with MS had a mixed confluent/perivenular/coalescent pattern. Early active lesions were found in 19/30 patients ([MS 4, CIS 13, NMO 2], 53%). Cortical demyelination was present in 7/12 (58%) patients [MS(3), CIS(3), ADEM (1)].

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Drs. Tobin, Costanzi, Guo and Mr. Weigand report no disclosures.

Author contributions

Dr. Tobin designed the study, collected and analyzed the data, wrote the first draft of the manuscript.

Dr. Costanzi designed the study, collected and analyzed the data and reviewed the manuscript for important intellectual content.

Dr. Guo supplied critical reagents and testing, collected and analyzed data and reviewed the manuscript for important intellectual content.

Dr. Parisi supplied critical reagents and testing, collected and analyzed data reviewed the manuscript for important intellectual content.

Mr. Weigand performed statistical analysis of the data and reviewed the manuscript for important intellectual content.

Dr. Lucchinetti conceived and designed the study, collected and analyzed the data, and reviewed the manuscript for important intellectual content.

Conclusions—A spectrum of CNS-IIDD can develop in the elderly, with presenting symptoms similar to younger patients. Early diagnosis of CNS demyelinating disease is essential to avoid invasive and disabling procedures.

Search Terms

demyelination; elderly; neuromyelitis optica; acute disseminated encephalomyelitis; brain biopsy; autopsy

Introduction

The onset of CNS idiopathic inflammatory demyelinating disease (CNS-IIDD) typically presents in young adults, but can begin in the elderly with an incidence similar to that of children (1.4/100,000).^{1, 2} It is often misdiagnosed, and can be mimicked by other phenomena.^{2, 3}

CNS-IIDD encompasses a variety of entities including clinical isolated syndrome (CIS), typical multiple sclerosis (MS), fulminant or tumefactive multiple sclerosis (MS), acute disseminated encephalomyelitis (ADEM) and neuromyelitis optica (NMO). A late onset of CNS-IIDD is relatively uncommon and little is known about its clinical, radiological, or pathological features.

Previous cohort studies have focused mainly on late MS and fixed an average threshold for symptom onset at 50 years old.^{4–7} Roughly 3–10% of MS patients have onset after age 50.^{3, 8–10}

There are few reports of patients experiencing their first symptoms of demyelinating disease 65 and two case reports of disease onset in an 82 and 87-year-old patient.^{11, 12} The prognosis in patients with late onset MS is uncertain, with some studies demonstrating a worse prognosis when compared to younger patients^{2, 6, 7} and some reporting no difference.¹⁰ There is no large series of patients with pathologically proven CNS-IIDD of onset after the age of 65.

Our primary aim was to describe the clinical, radiological and pathological features of a series of elderly patients with pathologically proven CNS-IIDD with symptom onset after the age of 65 years. Our secondary aim was to compare elderly MS/CIS patients to a pathologically defined cohort of MS/CIS patients whose onset was <65 years.

Methods

This study, approved by the Mayo Clinic Institutional Review Board (IRB#2067-99), is a retrospective review of clinical, radiological and pathological material collected from patients with biopsy or autopsy proven CNS-IIDD. Patients were identified from an original cohort of 760 patients belonging to the Multiple Sclerosis Lesion Project (MSLP)-US cohort.¹³ The Multiple Sclerosis Lesion Project (MSLP) is an international collaborative effort to study the pathological, clinical, and radiological correlates of the MS lesion. Patients are identified through the MS clinical practice Clinic, and Neuropathology

Department at Mayo Clinic, including both local patients, and patients referred for evaluation. All patients undergo detailed pathological studies on tissue sampled for clinical purposes, and have clinical records and neuroimaging reviewed and abstracted. A subset of patients undergo a detailed face to face clinical evaluation by an MS trained neurologist.

Inclusion criteria for the current study were: (i) brain biopsy or autopsy performed as part of the diagnostic evaluation in order to exclude other etiologies; (ii) pathological evidence of CNS-IIDD confirmed by a certified neuropathologist (J.E.P., Y.G.); (iii) first attack symptom at age 65 years; and (iv) sufficient clinical information regarding the attack leading to biopsy or autopsy obtained by a certified neurologist (C.F.L., C.C.).

Exclusion criteria included patients with a pathological diagnosis of non-demyelinating disease such as a neoplasm or vascular disease; limited available tissue; absence of sufficient clinical data, as well as history of adjuvant chemotherapy with 5-fluorouracil and levamisole due to an association between these agents and a multifocal inflammatory leukoencephalopathy.¹⁴

Clinical Evaluation

All patients were assessed for age at symptom onset, age at index attack prompting biopsy or autopsy, index and other attack symptoms, estimated EDSS at index attack, along with date and EDSS at last follow-up. Clinical course at time of biopsy and at last follow-up was categorized as isolated demyelinating event, monophasic, relapsing-remitting, primary or secondary progressive. Patients meeting the pathological criteria for MS were classified as having CIS or MS (definite or probable) by revised McDonald criteria.¹⁵ Clinical course of multiple sclerosis was based on Lublin and Reingold criteria for relapsing-remitting, primary or secondary progressive.¹⁶ ADEM was diagnosed pathologically based on the presence of perivenular demyelination.¹⁷ NMO was diagnosed based on the revised 2006 criteria,¹⁸ along with identification of NMO-IgG in serum or loss of aquaporin-4 reactivity in active demyelinating brain or spinal cord lesions.¹⁹

Radiological Evaluation

MRI data were collected and analyzed retrospectively. Lesions identified on each brain MRI study were defined as either the initially biopsied lesion ("index lesion"), or as other lesions. Lesions were classified as enhancing or non-enhancing based on high signal in the lesion on T1 weighted imaging following gadolinium administration. The following radiological features of lesions were analyzed: location, number, size (0.3–2 cm, 2.1–5cm, >5cm) of both the T2 weighted margin to margin signal abnormality and the discernible lesion borders from the surrounding edema and the presence of T2W hypointense rim (defined as a discernible smooth complete thin border of T2W hypointensity relative to the hyperintensity of both the lesion center and surrounding edema). Brain MRI data were scored for radiological evidence of multiple sclerosis using Barkhof criteria.²⁰

Neuropathological Assessment

Histopathology was available in all patients. Initial diagnostic pathological evaluation involved histochemical staining of formalin-fixed paraffin-embedded sections with

hematoxylin and eosin and Luxol-fast blue/periodic acid–Schiff. Immunohistochemistry were performed using the avidin–biotin technique.²¹ Primary antibodies were: Myelin proteolipid protein (PLP, 1: 500, SEROTEC, USA), myelin associated protein (MAG, 1: 1000, abcam, USA), myelin oligodendrocyte glycoprotein (MOG, 1:1000, abcam, USA), Kim1p (1:5000, Dr. Bruck, Berlin, Germany), CNPase (1:2000, Sternberger, USA) polyclonal rabbit anti-human AQP4 (1:250, Sigma-Aldrich, USA), polyclonal anti C9 neoantigen (C9neo, 1:2,000, Dr. Paul Morgan, Cardiff, UK), and monoclonal mouse anti-human C9neo (1:400; Dr. Paul Morgan, Cardiff, UK).

Demyelinating activity was classified as: 1) no demyelination, 2) early active, 3) late active, 4) inactive, and 5) remyelination.²² The pattern of demyelination was further categorized into three types: perivenous (demyelination restricted around blood vessels), coalescent (perivenous demyelination overlapped between adjacent vessels) and confluent (large demyelinating lesions beyond blood vessels). Early active lesions were classified into four immunopathological patterns (I–IV) according to previously published criteria.²¹ Among patients with sufficient cortex available, cortical demyelination was evaluated and classified as leukocortical, intracortical, or subpial.²³

All cases were assessed for senile plaques and neurofibrillary tangles with Bielschowsky silver stain.

Comparison with a non-elderly cohort

A subset of patients from this cohort with a diagnosis of MS/CIS only were compared to a cohort of patients younger than 65 years from a previously published cohort of patients with biopsy proven MS/CIS, also collected as part of the MSLP.²⁴ Patients were included in that study if they had pathological evidence of confluent inflammatory demyelination consistent with multiple sclerosis. Patients with ADEM or neuromyelitis optica were excluded. Clinical, radiological and pathological features were compared between the cohorts to determine if there were differences between patients older than 65 years with CNS-IIDD and younger patients.

Statistics

Group-wise comparisons on numeric variables were made with Wilcoxon rank-sum tests while categorical variables were compared using chi-squared tests. In particular, we used the “N-1” chi-squared method for analyzing 2×2 tables unless expected cell counts were below 1 in which case we used Fisher’s exact test.²⁵ We analyzed imaging features using an approach described previously.²⁴ Briefly, to account for patients having multiple scans, the patient rather than the scan was the unit of analysis. During a period of interest (e.g., pre-biopsy or post-biopsy), we assessed whether an imaging (e.g., ring enhancing lesions) feature was ever present. For ordered variables such as lesion size, we recorded the maximum value during the period. Because not all patients had an appropriate imaging study available during each interval of interest, the denominator in percentage calculations depended upon the variables being analyzed. All analyses were performed using R statistical software version 3.0.2.

Results

Case ascertainment

Seven hundred and sixty patients were reviewed from the Multiple Sclerosis Lesion Project (MSLP)-US cohort. Ninety patients had their biopsy or autopsy performed at or after age 65 and ultimately 30 patients met the inclusion criteria and were analyzed (Supplementary Figure 1). Clinical details were obtained via medical record review (100%) and telephone contact with the patient or family (7/30, 23%). For the comparison cohort of patients <65 years, 125 patients were identified from the MSLP-US cohort.²⁴

Demographic details of the cohort are shown in Table 1. Median age at symptom onset was 69 years (IQR 68–75). Median time from symptom onset to biopsy/autopsy was 39 days (IQR 18–149 days). The oldest patient with new onset CNS-IIDD was 83 years at onset. The majority of patients were female (21/30; 70%). Patients were followed for a median of 1.9 years (IQR 1.0–5.6). Thirteen patients had died at last follow-up (43%).

Clinical Features

The spectrum of diagnoses is shown in Table 1. Overall, 83% of patients had a diagnosis of MS (n=14) or CIS (n=11). One patient had a diagnosis of ADEM and four patients had a diagnosis of NMO.

Half of patients developed cognitive dysfunction either at onset or during the study follow-up, with the majority of those patients having a diagnosis of clinically isolated syndrome or multiple sclerosis. The range of symptoms developed by patients studied is shown in Figure 1.

Most (18/30, 60%) patients had a monophasic clinical illness, five of whom died at follow-up. Autopsy was performed on 4 patients who died in the context of the acute demyelinating event of whom 2 had multiple sclerosis, 1 had NMO and 1 had ADEM. The cause of death could not be determined in 3 patients. One patient died of complications of metastatic colon cancer, one from a cardiac arrest in the context of Stage IIIA adenocarcinoma of the lung and one from ventricular fibrillation in the context of metastatic pancreatic cancer. Median EDSS at follow-up was 4 (IQR 3–8). For 27 patients who had an EDSS available at baseline, 41% had an EDSS >4, meaning that they were restricted in their activities of daily living on account of their illness. Spinal fluid analysis was performed in 15 patients and oligoclonal band testing was negative in all 12 for whom results were available.

Treatment information was available on 23 patients. Of these, 19 (83%) received short term steroid treatment during the index attack. Long term preventative treatment consisted of steroids (4, 18%), Betaseron (2, 9%), Avonex (2, 9%), azathioprine (2, 9%) and methotrexate (1, 4%).

MRI Imaging

The median time from symptom onset to pre-biopsy MRI was 17 days (IQR 6–82) and the median time from onset to last MRI was 1.6 years (IQR 1.1–2.5 years)(Table 1). The majority of patients with pre-biopsy MRI (15/19, 79%) had multifocal white matter lesions

on MRI brain at the time of biopsy. The locations of index brain lesions for 15 patients with MS/CIS are shown in Figure 2. Note that although the distribution of the lesions was typical of CNS-IIDD, 3 of 15 (20%) patients had so-called “butterfly lesions” of the corpus callosum (Figure 3). For MS/CIS patients, lesions of a size greater than or equal to 2 cm in diameter, margin to margin, as measured on T2 weighted imaging, were common (11/14, 79%). Most MS/CIS patients had a T2 rim (10/15, 67%). Of MS/CIS patients with a T1 post gadolinium brain MRI brain available, all but one (14/15, 93%) had gadolinium enhancing lesions prior to biopsy or autopsy. Eight of those patients had ring enhancing lesions. Only one patient had the classically described “open ring sign” pattern.^{26, 27}

Of patients ultimately diagnosed with MS/CIS who had baseline MRI available, 8/15 (53%) fulfilled modified Barkhof criteria for a radiological diagnosis of MS prior to biopsy, and 9/16 (56%) fulfilled modified Barkhof criteria by their last MRI following biopsy.²⁰ All of these patients who had MRIs available following biopsy had multifocal lesions, indicating dissemination in space and time.

MRI spine performed prior to biopsy was available in 3 patients, two of whom demonstrated features consistent with demyelination. Post biopsy MRI spine was available in 5 patients (two of whom had pre biopsy MRI spine available). Of those patients, 4 ultimately demonstrated features consistent with demyelination.

Pathological findings

Pathological review was performed on 75 tissue blocks from 26 biopsy and 4 autopsy patients (Supplementary Table 1). Confluent demyelination alone was present in 90% (27/30) of patients (23/25 MS or CIS; 4/4 NMO). Two patients had coexistent confluent and perivenular demyelination (one MS and one ADEM). One patient with MS had perivascular, coalescent, and confluent demyelinating lesions. The spectrum of pathological changes in this cohort is shown in Figure 4. Early active demyelination was present among 63% (19/30) of patients. Active demyelination with ongoing remyelination was common. Among patients of MS/CIS with active demyelination, the immunopattern was not evenly distributed ($p=0.002$). The majority demonstrated immunopattern II (11/14; 79%), followed by immunopattern I (2/14, 14%) and immunopattern III in a single case. Cortex was available for review in 12 patients. Cortical demyelination was present in 58% (7/12) of patients overall, including in six of ten (60%) patients diagnosed as MS/CIS at last follow-up and in the single case of ADEM. Lesion location was subpial among five patients (MS 2, CIS 2, ADEM 1), also intracortical in the patient with ADEM, and leukocortical in four patients (MS 3, CIS 1). Although some senile plaques were seen, no cases were found to have neurofibrillary tangles.

Comparison with <65 year Cohort

Patients with an ultimate diagnosis of MS/CIS from this cohort were compared to a previously published cohort of 125 biopsy/autopsy proven MS/CIS patients <65 years. The median age of the younger cohort was 37 years (IQR 26–45). For the <65 year cohort, symptom onset to biopsy was 7.1 weeks (IQR 3.7–28.6) and symptom onset to last follow-up was 3.9 years (IQR 2.0–9.0). There were no significant differences in demographics or

MRI lesion location between patients with MS or CIS. Patients ≥65 years more frequently reported visual field defects ($p=0.03$), headache ($p=0.04$) and bowel, bladder or sexual dysfunction ($p=0.04$) than younger patients (Supplementary Figure 2). The ≥65 years MS/CIS cohort had a higher EDSS at last follow-up compared to patients <65 years (4 [IQR 2.5–7] vs. 2.5 [IQR 1.5–4], $p=0.002$), despite a shorter follow-up time in the ≥65 year group.

A comparison of imaging findings is summarized in Supplementary Table 2. Elderly patients ≥65 years were more likely to have a corpus callosal lesion ($p=0.007$) (Figure 3). There was no difference in T2 lesion size or the presence of mass effect or edema between the cohorts. Ring enhancement on brain MRI was relatively common in both cohorts (57% vs 61%). There was no difference between the cohorts for disease duration prior to biopsy, or the proportion of patients who fulfilled Barkhof criteria prior to biopsy or at last follow-up.

Discussion

We describe a cohort of incident CNS-IIDD, with onset ≥65. The full spectrum of CNS-IIDD, including MS, CIS, ADEM, and NMO, was observed among this pathologically confirmed cohort, demonstrating that the onset of CNS demyelination can occur at any age. The spectrum of CNS-IIDD in elderly patients was similar to that of younger patients. The majority of patients had clinically isolated syndrome or multiple sclerosis. Although this cohort has some similarities to younger patients, they differ in important ways. Older patients were more likely to present with visual field defects, headache or and bowel, bladder or sexual dysfunction ($p=0.04$) than younger patients. It is true that the younger cohort may not be entirely representative of typical MS, given that they were also included in a biopsy cohort, and that they included few cases of myelitis or optic neuritis as presenting features. The clinical outcomes in the MSLP study have previously been reported to be similar or better than a population based MS cohort, contrary to intuition.¹³ In addition, older patients accumulated more disability and were more likely to have a monophasic clinical course. One patient in the cohort had a final diagnosis of ADEM demonstrating that even in elderly patients who present with an encephalopathy and who have diffuse white matter disease on MRI brain, ADEM should be considered in the differential diagnosis.

Cognitive dysfunction was a common clinical feature in our older cohort in a frequency similar to CNS-IIDD pathological patients presenting at < 65 years of age.²⁸ Although Alzheimer pathology can co-exist with demyelination, none of our patients demonstrated pathological findings of Alzheimer's disease supporting the view that cognitive dysfunction was due to CNS-IIDD. Biopsy specimens are prone to sampling error, meaning that some AD pathology could have been missed. However, the majority of patients with available cortex demonstrated cortical demyelination. Cortical demyelination preferentially affects the cingulate gyrus, insular cortex and temporobasal cortex making it a credible substrate for cognitive decline.²⁹ Detailed neuropsychometric assessments were not performed in this cohort, so the affected cognitive domains cannot be outlined.

Patients with multiple sclerosis diagnosed later in life have a higher likelihood of having progressive disease from onset.^{2–6} However, a monophasic clinical course was more common than recurrent relapses in the older cohort, with 60% of patients experiencing only one episode. This may represent the high mortality rate or limited follow-up.

Older patients ≥ 65 years tended to accumulate more disability than younger patients < 65 years of age, despite a shorter duration of follow-up. Patients who recover early from an initial relapse tend to have a better outcome than patients who are slow to recover and older patients have been found to have worse disability outcomes in prior studies.^{30, 31} Whether this relates predominantly to failure of remyelination, more extensive axonal loss, or a combination of the two is unclear.

The imaging findings prior to biopsy of the elderly patients in this study were consistent with multiple sclerosis in over half of patients ultimately diagnosed with MS/CIS, and patients commonly had more than one lesion on MRI. Furthermore, the radiological features resembled those described among pathologically confirmed CNS-IIDD patients < 65 years of age with respect to lesion size, presence of mass effect and edema, as well as enhancement pattern.

Corpus callosal lesions were overrepresented among patients > 65 years when compared to those < 65 years. In these patients it is not surprising that malignancy was the primary concern, particularly since the incidence of multiple sclerosis over the age of 65 years is lower than that of brain malignancy.³² A majority of patients had multifocal lesions or fulfilled Barkhof criteria for demyelination even prior to biopsy, including among those with corpus callosal lesions. Therefore, it is important to consider demyelinating disease in the differential diagnosis of tumefactive and corpus callosal brain lesions presenting in the elderly. The evaluation for other features suggestive of demyelination, such as past history consistent with an MS relapse, oligoclonal bands in spinal fluid or rapidly evolving diffusion weighted changes on brain imaging, may delay or obviate the need for a brain biopsy. A therapeutic trial of intravenous steroids or therapeutic plasma exchange should also be considered prior to biopsy. If CNS lymphoma is forms part of the differential diagnosis, a trial of intravenous steroids should be avoided, as this may confound subsequent biopsy interpretation.

All stages of demyelinating activity were evident in the elderly cohort, including frequent early remyelination, suggesting that reparative processes are not exhausted despite late-onset disease. All immunopathological patterns (I, II, III) were identified among the elderly MS/CIS cohort of patients with early active lesions, with a higher frequency of pattern II versus patterns I and III.

We also observed all cortical lesion types among the MS/CIS cohort, in a frequency even greater than that seen among a younger published MS/CIS cohort.²³ These findings underscore that cortical demyelination is an early event in MS disease evolution/pathogenesis regardless of age of disease onset.

Conclusions

The full clinical and pathological spectrum of CNS-IIDDs was observed. Presenting symptoms were similar to published series on biopsied demyelinating disease in younger patients, but disability was greater. A monophasic clinical course was more common in the elderly, possibly reflecting limited follow-up. Although mass lesions in the elderly are most often neoplastic, CNS-IIDD such as MS, NMO, and ADEM should be considered in the differential diagnosis. Early diagnosis of CNS demyelinating disease is essential to avoid invasive and disabling procedures.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

LFB/PAS Luxol fast blue stain and Periodic Acid Schiff

PLP IHC Proteolipid protein immunohistochemistry

AQP4 IHC aquaporin 4 immunohistochemistry.

Figure 1.
Presenting symptoms overall and by diagnosis at last followup. Some patients presented with more than one symptom at the index attack.

Figure 2.

Bar plot showing the index lesion location, overall and by diagnosis at last follow-up, in the young and elderly cohorts (MS and CIS only). Index lesion can appear at more than one location. Corpus callosum lesions were more common in the elderly cohort, while frontal lesions were more common in the young cohort.

Figure 3. T2 FLAIR (A and C) and post contrast T1 (B and D) images from two patients from the elderly cohort with “Butterfly lesions” involving the corpus callosum and the white matter of both hemispheres (arrows).

Figure 4. The pathological changes of CNS demyelinating diseases in elderly patients

(A–F): **Multiple Sclerosis**. Brain surgical biopsy from a patient with MS shows extensive demyelination in the subcortical white matter (arrows) [(A) LFB/PAS; (B) PLP IHC]. (C) Extensive white matter macrophage infiltration, forming a sharp border at the lesion edge (triangles). (D) An enlarged view from the boxed region in panel B demonstrating subpial cortical demyelination (asterisk). (E) Extensive cortical microglial reaction and subcortical macrophage infiltration demonstrated by Kim1p staining. (F) Myelin degradation products within foamy macrophages (enlarged inset view) suggest active demyelination [PLP IHC]. (G): **ADEM**. Perivascular demyelination in brain white matter (arrowheads), characteristic of ADEM [PLP IHC]. (H and I): **NMO** (H) Confluent demyelination in the spinal cord white matter [PLP IHC]. Myelin laden macrophages (inset high power view) suggesting active demyelination. (I) AQP4 IHC on the consecutive section highlighted extensive aquaporin 4 loss in this active lesion. (Bar in A–C=5 mm, Bar in D, E and G–I= 200 μ m, bar in F=100 μ m)

Table 1

Demographics. Values shown are n (%) or median (IQR) [range]

Clinical features	All patients (n=30) [*]
Gender ratio, Female: Male	21:9
Age at symptom onset, years	69 (68 – 75) [65 – 83]
Clinical course prior to biopsy/autopsy, n (%) [†]	
First neurological event	22 (73%)
Relapsing-remitting	5 (17%)
Progressive	2 (7%)
Uncertain	1 (3%)
Disease duration	
Onset to biopsy, days	39 (18 – 149) [3d – 5.6y]
Onset to pre-biopsy MRI, days	17 (6, 82) [2d – 3.3y]
Onset to pre-biopsy MRI, days (MS/CIS only)	17 (6, 48) [2d – 3.3y]
Onset to last MRI, years	1.6 (1.1, 2.5) [0.3 – 7.5]
Onset to last MRI, years (MS/CIS only)	1.6 (1.3, 3.1) [0.6 – 7.5]
Diagnosis at last follow-up, n (%)	
Multiple sclerosis	14 (47%)
Clinically isolated syndrome	11 (37%)
Neuromyelitis optica	4 (13%)
Acute disseminated encephalomyelitis	1 (3%)
Expanded Disability Status Scale score	
At time of index attack	3.5 (3.0 – 6.5) [1.5 – 9.5]
At last follow-up	4.0 (2.8 – 8.0) [1.0 – 10]

^{*} 20 patients had MRI with 19 of 20 patients having a pre-biopsy MRI and 14 of 20 having a post-biopsy MRI

[†] Four of 30 patients were autopsy only