Clinical course, pathological correlations, and outcome of biopsy proved inflammatory demyelinating disease

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Background: A pathological classification has been developed of early active multiple sclerosis (MS) lesions that reveals four patterns of tissue injury: I—T cell/macrophage associated; II—antibody/complement associated; III—distal oligodendroglialopathy, and IV—oligodendrocyte degeneration in the periplaque white matter. Mechanisms of demyelination in early MS may differ among the subgroups. Previous studies on biopsied MS have lacked clinicopathological correlation and follow up. Critics argue that observations are not generalisable to prototypic MS.

Objective: To describe the clinicopathological characteristics of the MS Lesion Project biopsy cohort.

Methods: Clinical characteristics and disability of patients with pathologically confirmed inflammatory demyelinating disease (excluding ADEM) classified immunopathologically (n=91) and patients from the Olmsted County MS prevalence cohort (n=218) were determined.

Results: Most patients who underwent biopsy and had pathologically proved demyelinating disease ultimately developed definite (n=70) or probable (n=12) MS (median follow up 4.4 years). Most had a relapsing remitting course and 73% were ambulatory (EDSS $\leq$ 4) at last follow up. Nine patients remained classified as having an isolated demyelinating syndrome at last follow up. Patients with different immunopathological patterns had similar clinical characteristics. Although presenting symptoms and sex ratios differed, the clinical course in biopsy patients was similar to the prevalence cohort. Median EDSS was <4.0 in both cohorts when matched for disease duration, sex, and age.

Conclusions: Most patients undergoing biopsy, who had pathologically confirmed demyelinating disease, were likely to develop MS and remain ambulatory after a median disease duration of 4.4 years. The immunopathological patterns lacked specific clinical correlations and were not related to the timing of the biopsy. These data suggest that pathogenic implications derived largely from MS biopsy studies may be extrapolated to the general MS population.

The Multiple Sclerosis Lesion Project (MSLP) is an international collaborative effort to study the pathological, clinical, and radiological correlates of the MS lesion. It is based on previous observations describing four different immunopathological patterns of disease with interindividual heterogeneity, but intraindividual homogeneity in early MS lesions, suggesting different pathogenic mechanisms. The four patterns are^{1–3}:

- Pattern I—T cell/macrophage associated
- Pattern II—antibody/complement associated
- Pattern III—distal oligodendroglialopathy
- Pattern IV—oligodendrocyte degeneration in the periplaque white matter.

This may have profound implications for clinical practice since distinct patterns may require distinct therapeutic strategies.⁴

Little is known about the clinical course of patients with inflammatory central nervous system demyelinating disease identified by brain biopsy. The accuracy of the diagnosis of MS has been questioned because of inherent difficulties and limitations associated with biopsy material, and the concern that some of these cases may represent acute disseminated encephalomyelitis (ADEM).⁵

Study of multiple actively demyelinating lesions (≥ 2) from autopsy cases (n=48) and cases of serial biopsy (n=15) or biopsy/autopsy combinations (n=6) has not revealed overlap of immunopathological patterns.⁶ It is unknown whether different immunopathological patterns are associated with

differing disease course and severity. The clinical and pathological data from patients who have undergone biopsy allows us to begin addressing this question. Furthermore, because of the initial presenting clinical and radiological features that lead to biopsy, and the lack of follow up of many MS patients who have undergone biopsy, it has been argued that these are not representative of typical MS as it pertains to a population.^{7,8}

In this report we describe the demographic and clinical characteristics, as well as the disease course in patients who have undergone biopsy and correlate these parameters with immunopathology.

METHODS

This study was approved by the Mayo Clinic institutional review board (IRB # 2067–99). As part of the MSLP, ongoing prospective follow up has located 130 patients who have undergone either stereotactic or open brain biopsies; 107 have been recruited into the study and 23 refused to participate (fig 1). Seven patients were excluded because of prior brain radiation (n=4) or significant comorbidities (n=3; immunopathological pattern II (n=2) and pattern I (n=1)) that impacted on the Expanded Disability Status Scale (EDSS) score estimation.⁹ Nine patients were lost to

Abbreviations: ADEM, acute disseminated encephalomyelitis; EDSS, Expanded Disability Status Scale; FIDS, focal isolated demyelinating syndrome; MSLP, Multiple Sclerosis Lesion Project; PPMS, primary progressive MS; RRMS, relapsing remitting MS; SPMS, secondary progressive MS

Figure 1 MS Lesion Project, patient recruitment. Of 100 patients fulfilling inclusion criteria, 91 were actually included (dashed boxes) as nine either had inadequate clinical information or were lost to follow up.

follow up. We excluded patients with biopsies showing perivenular demyelination consistent with ADEM (as part of MSLP exclusion criteria).¹⁰

The neuropathological and immunocytochemical techniques have been previously described.³ Detailed clinical follow up and EDSS scores were ascertained for all surviving patients who had undergone biopsy ($n = 82$) by medical record review (100%), interview and examination (72%), patient letter or telephone contact (17%), family or physician contact (4%), and clinical record review only (7%).¹¹ For patients who were dead at last follow up, we reviewed death certificates and used the neurological examination recorded in their medical records in the year prior to death to estimate the EDSS. Demographic data, date of symptom onset, date of index attack (attack leading to biopsy), and use of immunomodulatory treatments were recorded. Course of MS was categorised as relapsing remitting (RRMS), secondary progressive (SPMS) or primary progressive (PPMS). PPMS was defined as a progressive course from onset without relapses or remissions. RRMS was defined as full or partial recovery from attacks during the entire observation period. RR patients who subsequently entered a progressive phase were defined as SPMS. The course was categorised as uncertain when it was unclear if an episode represented a discrete attack (for example seizure). Patients were classified as having definite (by Poser's (clinically or laboratory supported) or McDonald's criteria) or probable (clinically or laboratory supported by Poser's criteria) MS.^{5, 12} Those with a single attack who did not fulfil these criteria were classified as having a focal isolated demyelinating syndrome (FIDS).

The population based prevalence cohort consisted of patients with definite (clinically or laboratory supported, $n = 201$) and probable (clinically or laboratory supported, $n = 17$) MS (using Poser's criteria), who were residents of Olmsted County (OMC) on 1 December 2000 (none underwent brain biopsy).^{13, 14} We compared definite and probable MS subjects from the biopsy and prevalence cohorts using Wilcoxon rank sum tests for continuous variables and χ^2 tests for categorical variables. In addition, a linear regression model for most recent EDSS was constructed to compare the biopsy and prevalence cohorts, controlling for sex, age at onset, and duration of disease.

RESULTS

The clinical characteristics of the biopsy cohort are shown in table 1. The biopsy cohort consisted of a total of 91 patients with pathologically proved inflammatory demyelinating disease. Patients sent in from other institutions occasionally lacked an indication for biopsy, but most underwent biopsy to exclude tumor (astrocytoma, lymphoma, or metastases). Some biopsies were performed to exclude vasculitis or infection (progressive multifocal leukoencephalopathy and abscess).

The patients were predominantly Caucasian (98%) and 53% were female. At the time of last follow up, a median of 4.4 years from disease onset, 82/91 patients had developed definite ($n = 70$) or probable MS ($n = 12$). The median age at onset of MS was 36.6 years (range 8.7–69.3), with the index attack representing the first attack in 62% of patients. The remaining 9/91 patients had no additional attacks apart from the attack leading to biopsy and did not fulfil Poser's criteria for probable MS. These patients were classified as having FIDS after a median follow up of 7.1 years.

Clinical course at time of last follow up for the 82 patients with MS was as follows: 47 (57.3%) RRMS, 20 (24.4%) SPMS, 2 (2.4%) PPMS, 8 (9.8%) monophasic (all probable MS by Poser's criteria), and 5 (6.1%) uncertain. Nine (10%) patients died, all of whom had developed definite or probable MS. Seven deaths were MS related (three died within two years of disease onset). Forty one patients used at least one of the disease modifying drugs interferon β -1b (20%), interferon β -1a (18%), glatiramer acetate (12%), and mitoxantrone (5%). At last follow up, median EDSS was 3.0 (range 0.0–10.0). The median time from index attack (attack which led to biopsy) to biopsy was 1.1 (range 0.1–15) months. The index attack symptoms in decreasing order of frequency were hemiparesis (41%), sensory syndrome (36%), truncal ataxia (29%), dysarthria (26%), limb ataxia (25%), cognitive dysfunction (19%), monoparesis (14%), encephalopathy/confusional state (12%), diplopia (12%), aphasia (10%), dysphagia (10%), vertigo (9%), bladder dysfunction (5%), paroxysmal symptoms (4%), optic neuritis (5%), fatigue (3%), quadriparesis (2%), paraparesis (2%), coma (2%), pain (2%), and respiratory failure (1%).

Table 1 Clinical characteristics of the biopsy cohort (n = 91)

	Multiple sclerosis			FIDS	Total biopsy cohort
	Alive	Dead	Total		
No of patients	73	9	82	9	91
Male sex (n (%))	33 (45.2)	2 (22.2)	35 (42.7)	7 (77.8)	42 (46.2)
Age in years at onset (median (range))	36.2 (8.7–69.3)	43.5 (23.3–67.2)	36.6 (8.7–69.3)	45.0 (11.0–69.7)	37.2 (8.7–69.7)
Time in months from onset (first attack) to biopsy (median (range))	2.6 (0.3–331)	5.6 (0.1–360)	2.9 (0.1–360)	0.5 (0.3–2.0)	2.2 (0.1–360)
Time in months from index attack to biopsy (median (range))	1.1 (0.1–15)	2.8 (0.1–5.6)	1.1 (0.1–15)	0.5 (0.3–2.0)	1.1 (0.1–15)
Duration in years of follow up from onset (median (range))	4.4 (0.3–33)	5.3 (0.9–33)	4.4 (0.3–33)	7.1 (0.6–16)	4.4 (0.3–33)
EDSS at most recent follow up (median (range))	3.0 (0.0–9.5)	10.0 (5–10)*	3.0 (0.0–10.0)	2.0 (0.0–3.0)	3.0 (0.0–10.0)
Clinical course (n (%))					
Uncertain	4 (5.5)	1 (11.1)	5 (6.1)	0 (0)	5 (5.5)
RR	46 (63)	1 (11.1)	47 (57.3)	0 (0)	47 (51.6)
PR	3 (4.1)	0 (0)	3 (3.7)	0 (0)	3 (3.3)
SP with superimposed attacks	8 (11)	5 (55.6)	13 (15.9)	0 (0)	13 (14.3)
SP without superimposed attacks	4 (5.5)	0 (0)	4 (4.9)	0 (0)	4 (4.4)
PP	0 (0)	2 (22.2)	2 (2.4)	0 (0)	2 (2.2)
Monophasic	8 (11)	0 (0)	8 (9.8)	9 (100)	17 (18.7)
Use of immunomodulatory drugs† (Yes) (n (%))	39 (53.4)	1 (11.1)	40 (48.8)	1 (11.1)	41 (45.1)
Immunopathological classification (n (%))					
Active	56 (76.7)	5 (56.6)	61 (74.4)	5 (56.6)	66 (72.5)
I	16 (28.6)	1 (20.0)	17 (27.9)	0 (0)	17 (25.8)
II	30 (53.6)	3 (60.0)	33 (54.1)	1 (20)	34 (51.5)
III	10 (17.9)	1 (20.0)	11 (18.0)	4 (80)	15 (22.7)
Inactive (unclassifiable)	17 (23.3)	4 (44.4)	21 (25.6)	4 (44.4)	25 (27.5)

*For patients who died from MS or condition related to MS the EDSS was 10. Patients who died of another cause, unrelated to MS (for example cancer) were assigned EDSS score at last examination prior to death.

†Immunomodulatory drugs include interferon β 1-b and 1-a, glatiramer acetate, and mitoxantrone.

EDSS, Expanded Disability Status Scale; FIDS, focal isolated demyelinating syndrome (monophasic demyelinating disease without other paraclinical evidence of MS); PP, primary progressive; PR, progressive relapsing; SP, secondary progressive; RR, relapsing remitting.

Pathological classification of the biopsy cohort revealed 19% pattern I, 37% pattern II, 17% pattern III, and 0% pattern IV. Actively demyelinating lesions were lacking (that is, only inactive or remyelinated lesions present on tissue block) in 27%, and therefore they could not be classified into any of the four patterns. Of 66 patients for whom data were available regarding initial pathological interpretation, 19 (29%) were initially misdiagnosed by the referring institution (6 low grade astrocytoma, 2 high grade astrocytoma, 2 lymphoma, 1 vasculitis, 2 progressive multifocal leukoencephalopathy (PML), 1 infarction, 1 oligodendroglioma, 1 mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS), and 3 non-diagnostic).

Comparison of patients' clinical characteristics with the different immunopathological patterns (patterns I–III) is shown in table 2. There were no significant differences

Figure 2 Disease severity and duration of the different immunopathological patterns (I–III) of patients in the biopsied cohort. Patterns are represented by different shapes as shown. *Patient with disease duration 22 years.

between the neuropathological patterns and any of the clinical characteristic variables examined at time of last follow up. In particular, there was no correlation between immunopathological patterns and time from index attack to biopsy. There was also no correlation between immunopathological pattern and EDSS at last follow up (fig 2). There was a trend for a greater proportion of women to have pattern I lesions (59%) than pattern II (53%) or pattern III (47%).

Only patients with definite or probable MS by Poser's criteria were included in the OMC MS prevalence cohort (thus excluding patients with FIDS). The clinical course of MS in the patients who had undergone biopsy was similar to that in the population based MS patients (RRMS 47 (61%) v 131 (60%), SPMS in 20 (26%) v 61 (28%), PPMS 2 (3%) v 15 (7%) and monophasic (probable MS by Poser's criteria) 8 (10%) v 11 (5%), respectively). There were significantly more men in the biopsy group (44% v 31%) compared to the prevalence cohort ($p=0.032$). Frequency and type of symptoms of the index attack (onset symptoms in most of the biopsy cohort) differed from onset attack symptoms identified in the population based cohort (motor weakness 59% v 22%, cerebral dysfunction 24% v 2%, optic neuritis 5% v 22% and sensory symptoms 36% v 56%). In the OMC MS prevalence cohort, 50 patients (22.9%) used at least one of the disease modifying drugs (44% on interferon β 1-a; 30% on interferon β 1-b; 10% on glatiramer acetate; and 16% of patients were on two or more drugs). The median duration of treatment was 13.4 months (interquartile range (IQR) 8.7 to 24.2) for interferon β 1-a, 15.6 months (IQR 10.5 to 37.3) for interferon β 1-b, and 14.8 months (IQR 5.0 to 28.9) for glatiramer acetate. Significantly fewer number of patients from the OMC prevalence cohort were receiving treatment compared with the biopsy cohort ($p<0.01$).

Since patients in the biopsy group had a shorter median disease duration than the population based cohort (4.4 v 19 years), we analysed EDSS (at last follow up) stratified by disease duration (fig 3). After correcting for differences in sex (more men in biopsy cohort), disease duration (shorter in the

Table 2 Comparison of clinical characteristics of the different pathological patterns

	Immunopathological classification			
	I (n = 17)	II (n = 34)	III (n = 15)	NA (n = 25)
EDSS at most recent follow up (median)	3.0	3.0	3.0	3.5
Range is 0–10 for all groups				
Duration in years of MS (median (range))	4.1 (1.0–14.1)	4.5 (0.9–33.1)	5.2 (1.2–15.7)	5.2 (0.3–33.1)
Time from onset (first attack) to biopsy in months (median (range))	4 (0–113)	2 (0–331)	1.0 (0–42)	4 (0–360)
Time from index attack to biopsy in months (median (range))	1.1 (0.2–5.6)	1.1 (0.1–7.9)	0.8 (0.2–2.6)	1.5 (0.2–15.0)
Sex (n (%))				
Male	7 (41.2)	16 (47.1)	8 (53.3)	12 (48)
Female	10 (58.8)	18 (52.9)	7 (46.7)	13 (52)
Most recent course classification (n (%))				
RR	9 (52.9)	21 (61.8)	5 (33.3)	12 (48)
PR	0 (0)	1 (2.9)	1 (6.7)	1 (4)
SP with superimposed attacks	3 (17.6)	6 (17.6)	1 (6.7)	3 (12)
SP without superimposed attack	0 (0)	2 (5.9)	1 (6.7)	1 (4)
PP	1 (5.9)	0 (0)	0 (0)	1 (4)
Monophasic	3 (17.6)	3 (8.8)	5 (33.3)	6 (24)
Uncertain	1 (5.9)	1 (2.9)	2 (13.3)	1 (4)

No significant differences were found when comparing patterns I–III for any of the clinical variables described ($p > 0.1$).
NA, non-active; PP, primary progressive; PR, progressive relapsing; SP, secondary progressive; RR, relapsing remitting.

biopsy cohort), and age at onset (older in the biopsy cohort), the prevalence cohort had a statistically significantly lower EDSS score at last follow up compared with the biopsy cohort (estimated average difference 1.64, $p < 0.001$). However, patients from both cohorts with disease duration of > 10 years had similar EDSS scores (fig 3). When comparison was restricted to living patients in the biopsy cohort (since no patients from the prevalence cohort were dead, by definition), the adjusted differences were less (estimated average difference 1.06, $p = 0.005$).

DISCUSSION

Despite a more atypical and aggressive clinical presentation at disease onset, most biopsy patients with pathologically confirmed demyelinating disease went on to develop MS, remained fully ambulatory (73% had an EDSS ≤ 4) with a relapsing remitting course. Only nine of the 91 biopsy patients remained classified as having FIDS and had low levels of impairment (median EDSS of 2.0 (range 0–3.0)) at

last follow up. These patients were more likely to be male and have an older age of onset, factors previously associated with a worse, not better, outcome in MS.¹⁵

Although the accuracy of the MS diagnosis has been questioned in previous smaller MS biopsy studies, none of the patients in our series with a confirmed pathological diagnosis of inflammatory demyelinating disease developed symptoms or signs (clinical or radiological) on follow up (median 4.4 years from onset or median 3.5 years after biopsy) suggesting an alternative diagnosis. Though presenting symptoms and sex ratios differed, the clinical course in the MS patients who had undergone biopsy was similar to a population based prevalence cohort of prototypic MS. When matched for disease duration, biopsy patients had disability that was comparable with prototypic MS (both had median EDSS < 4). Although the median EDSS score in the biopsy cohort was 1.64 points worse than the prevalence cohort (after adjusting for disease duration, sex, and age), EDSS scores in the low range are less reproducible, and a 1 point

Figure 3 Box plot of most recent EDSS by group (Olmsted County MS prevalence cohort (OC) compared with biopsy MS cohort (Bx)) and duration of disease (5, 5–10 and 10+ years). Boxes extend to cover the middle 50% of the data. Median EDSS scores are indicated by the horizontal lines within each box, mean scores by the diamonds. Whiskers extend to cover 95% of the data, with outlying points indicated by individual circles.

increase in EDSS when <4 is of lesser clinical importance than a 1 point rise if EDSS is ≥ 6 .^{16–18} Furthermore the biopsy cohort included deceased patients who were, by definition, not part of a prevalence cohort. This may have further biased the biopsy cohort towards a worse outcome.

These findings indicate that in patients with pathologically proved inflammatory demyelinating disease diagnosed on biopsy, the disease typically evolves into MS, with an overall clinical behaviour similar to a population based MS cohort. Therefore pathological and pathogenic insights derived largely from MS biopsy cohorts are likely applicable to patients with “typical” non-biopsied MS. The biopsy cohort excluded cases of pathologically confirmed ADEM. Although ADEM is also an inflammatory demyelinating disease, it is characterised by restricted periventricular demyelination that can be pathologically distinguished from the more confluent demyelination typical of MS.^{10, 19}

The immunopathological classification of the biopsy cohort in this study revealed a distribution similar to a previous study.³ The demographics, early clinical course, and disease severity of patients with different immunopathological patterns (patterns I–III) were similar. Pattern IV has only been described in autopsies and therefore could not be included in this biopsy series. The small sample size, especially when divided into immunopathological subgroups, may limit our ability to detect modest associations with clinical parameters. Furthermore, because of the limited duration of clinical follow up (median 4.4 years) in this study, longer follow up is needed to determine whether different immunopatterns influence the long term clinical course and cumulative disability in MS.

It has recently been suggested that MS lesions all begin as one pattern characterised by widespread oligodendrocyte apoptosis in the absence of active inflammatory demyelination, and evolve into other patterns associated with complement activation and remyelination.²⁰ In 48 autopsies, 15 serial biopsies, and 6 biopsy/autopsy combinations classified into patterns I–IV as part of the MS Lesion Project, we have not observed an overlap of immunopathological patterns.⁶ Furthermore, immunopatterns were not associated with timing of biopsy relative to the index attack. This lack of temporal association argues against a sequential evolution of immunopathological patterns within a single MS patient.

Recent data on the mechanisms of lesion formation during early MS are largely based on tissue samples obtained from patients who undergo diagnostic brain biopsy typically performed at clinical presentation, or from patients who die either from unrelated events during early disease stages or from fulminant disease. These biopsy and early autopsy samples are more likely to contain actively demyelinating lesions and are therefore better suited to yield information about the earliest events in lesion formation. However, stereotactic brain biopsies are often limited in tissue quantity and do not always contain regions of ongoing active demyelination. Although the detection of actively demyelinating lesions is difficult in the late stage of MS and in patients with chronic progressive disease, the recent use of magnetic resonance imaging (MRI) guided sampling of postmortem tissue may increase the yield of actively demyelinating MS lesions,²¹ and overcome potential limitations in tissue quantity associated with biopsy samples.

We do not have pre-biopsy MRIs or the indication for biopsy on all the patients included in this study. Therefore, we were not always able to determine the indication for the diagnostic biopsy. However, a detailed analysis of MRI data from the biopsy cohort is underway to describe the neuroimaging spectrum of biopsied MS, as well as better define reasons for biopsy. In addition, it will be important to identify immunopathological pattern specific MRI features

which will permit a reliable classification of patients into immunopathological subgroups without the need for a brain biopsy.

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