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ORIGINAL ARTICLE

Acute multiple sclerosis lesion pathology does not predict subsequent clinical course—a biopsy study

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Abstract

Background Knowledge of the clinical outcome in tumefactive demyelination remains limited.

Aims This study aims to characterise the natural history of biopsy-proven, pathogen-free, cerebral demyelination in an adult Irish population.

Methods We identified all patients with biopsy-proven demyelination in a single neuropathology centre between 1999 and 2017. A baseline, and at least one follow-up MRI scan was available in each instance (mean of 3 scans per patient), together with both the presenting and most recent clinical details including disability level and disease-modifying drugs.

Results In 21 patients, white matter biopsies showed the following: macrophages with myelin debris, myelin-axonal dissociation, reactive astrocytes and occasional lymphocytes. During a mean follow-up time of 8 years (± 4.4), 17 patients developed MS, confirmed both clinically and on MRI, using the 2010 McDonald criteria: 11 relapsing remitting (RR) MS, four secondary progressive and two primary progressive MS. Four patients had a monophasic illness with lesion regression, without clinical or radiological evidence of any further disease activity on follow-up. The patients with progressive MS had significantly higher levels of physical disability than either the RRMS or monophasic patients.

Conclusion Uniform white matter subacute demyelination is associated with a diverse clinical course ranging from a monophasic illness to progressive MS, suggesting that extraneous factors distinct from the basic pathology significantly influence the clinical course in MS.

Keywords ADEM · Demyelination · MRI · Multiple sclerosis

Introduction

The pathology of an acute multiple sclerosis (MS) plaque displays a number of characteristic findings, including a heavy infiltrate of macrophages containing myelin debris, reactive astrocytes (including Creutzfeldt-Peters cells), a variable number of lymphocytes and oligodendroglia [1, 2]. Whilst active MS plaques are not commonly identified at post mortem, they may be seen in biopsies obtained where there was a suspicion of a neoplastic mass lesion but which later was shown to be demyelinating in nature [3].

Radiologic tumefactive demyelination is a single T2-weighted lesion exceeding 2 cm in lesion diameter, although lesions may be up to 12 cm in maximal diameter [4], although Hardy et al. have proposed a management pathway for such tumefactive cases [5]. Nevertheless, biopsy may still be performed, usually if there is clinical suspicion of tumour [6]. In the absence of robust evidence of the natural history of biopsy-proven demyelination, re-biopsy may take place without benefit and with increased risk to the patient [7].

Biopsy-proven demyelination may give rise to the clinical consideration of acute disseminated encephalomyelitis (ADEM) [8]. Pathologically, ADEM is characterised by perivenular inflammation, with limited 'sleeves of demyelination'. In some cases, larger areas of demyelination may occur secondary to coalescence of numerous smaller lesions and appear to be tumefactive. Whilst in children, ADEM may be

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confidently diagnosed and managed without recourse to biopsy, this may not be the case in adults, when an encephalopathic presentation with confluent white matter abnormalities on imaging may lead to greater diagnostic uncertainty.

This study aimed to identify any neuropathological features of biopsy-proven demyelination, identified in a routine diagnostic workup, that may (i) discriminate between subgroups of MS or (ii) predict the future clinical course.

Patients and methods

This study is a retrospective review of all biopsy-proven cases of tumefactive inflammatory demyelination identified from a single clinical neuropathology database; without a priori knowledge of the clinical or radiological details, these were subsequently obtained in each instance. Patients were referred from different centres following an acute encephalopathic presentation; however, the biopsies were performed and analysed in our centre only.

We included any cases of demyelination from 1999 to 2017; we chose 1999 to begin the search as radiological records are in electronic format in our centre from that date, thus facilitating a comprehensive review of all patient imaging at our centre, to ensure an MS diagnosis. Brain scans were performed in each referral centre at 1.5 T; however, due to differences in manufacturer, the scanning parameters differed between centres; nonetheless, a T2-weighted and T1-weighted scan with contrast was available in each instance. Informed written consent was obtained at the time of the neurosurgical procedure from each patient, in line with routine clinical practice at our centre.

All biopsies were reviewed without knowledge of the presenting complaints, or any underlying medical or neurologic disorder, and in the absence of clinical outcome. Each biopsy satisfied the diagnostic criteria, for pathologically confirmed subacute demyelination, as set out by van der Valk et al. [9]. Separately, one of us obtained and reviewed the clinical findings and radiologic and other investigations.

Study inclusion criteria following confirmation of pathogen-free demyelination were (i) availability of an initial diagnostic MRI brain and at least one follow-up MRI, to determine if there was radiological evidence of dissemination in both time and space [10] and (ii) clinical details from the referring neurologist on the current disability status of the patient using the expanded disability status scale (EDSS) [11]. Exclusion criteria included underlying immune deficiency and prior cranial irradiation [12].

We obtained the final diagnosis of either MS or monophasic demyelinating illness, from the clinician's patient record. For MS patients, subgroups were classified as relapsing remitting (RR), secondary progressive (SP) or primary progressive (PP) using current consensus criteria [13]. In cases of relapse-onset MS (i.e. RRMS and SPMS), we obtained details of the disease modifying drug (DMD) being prescribed by the treating physician. Due to the multicentre referrals for biopsy, we were unable to obtain accurate information on the presence or absence of oligoclonal bands in the cerebrospinal fluid (CSF) in each case.

Results

In total, we identified 84 cases of biopsy-proven demyelination but radiology was available in only 43 cases (either a single scan at presentation without a follow-up, or no imaging at presentation could be retrieved); of these 43 cases, clinical information was not available for 20, leaving 21 cases which fulfilled the study criteria.

Neuropathology

Microscopic examination of the 21 cases revealed abnormal white matter; dominated by large lipid-filled macrophages, some of which were aligned alongside intact axons. Axonal varicosities were evident in some areas. The abundant myelin-containing macrophages did not display any atypia. Occasional perivascular lymphocytes were also present. Rare cells with large nuclei were also present but these appeared to be either of astrocytic or macrophagic origin. Atypical astrocytes suggestive of progressive multifocal leukoencephalopathy (PML) were not identified. The proliferative index as assessed by MIB1, where mitoses or atypical reactive astrocytes were observed, was invariably zero.

Immunohistochemistry demonstrated the presence of CD3-positive T-lymphocytes in the parenchyma with accumulation of infrequent perivascular CD20-positive B-lymphocytes. CD68 confirmed an intense macrophage infiltrate. GFAP demonstrated large hypertrophied reactive astrocytes.

Myelin basic protein (MBP) was present, predominantly along intact axons within the centre of the lesion but also in the form of MBP-positive debris in macrophages. We observed extensive Luxol fast blue-positive debris with residual intact myelin sheaths in the centre of the lesions. Neurofilament confirmed relative axonal preservation in the centre of most of the observed lesions, together with occasional axonal varicosities. Examples of the histopathological abnormalities observed are displayed in Fig. 1.

Clinical details

There were ten women and seven men identified, who fulfilled the McDonald 2010 criteria (based on a retrospective review of the MRI abnormalities) for an MS diagnosis [10], with a mean age of 47.6 years (± 16.1). However, as the reason

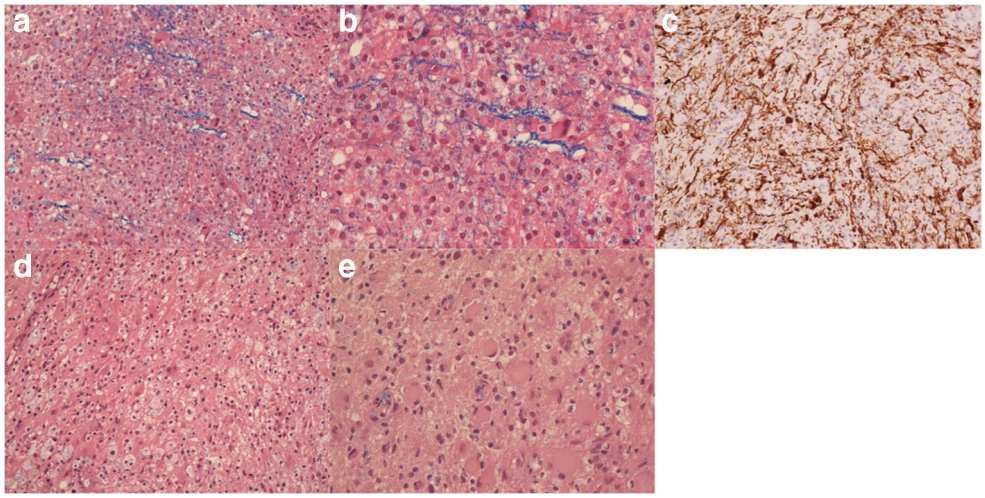

Fig. 1 **a** Low power view of area of active demyelination taken from close to lesion edge and showing myelin coated axons surrounded by large macrophages some containing myelin debris (Luxol Fast Blue – Haematoxylin & Eosin × 20). **b** Medium power view of area of active demyelination taken from close to lesion edge and showing myelin coated axons surrounded by large macrophages some containing myelin debris (Luxol Fast Blue – Haematoxylin & Eosin × 40). **c** Medium power view of area of demyelination (parallel section to area shown in Figs. 1 and 2) stained with neurofilament antibody to show relative axonal sparing but with axonal varicosities and spheroids clearly visible (Neurofilament × 20). **d** Medium power view of centre of area of demyelination showing increased numbers of astrocytes (Haematoxylin & Eosin × 20). **e** High power view of plaque centre to show large reactive gemistocytic reactive astrocytes, without any atypia (Haematoxylin & Eosin × 40)

for referral for biopsy was based on diagnostic uncertainty, due to the atypical presentation, none of these cases were diagnosed as MS by their clinician ab initio. At the time of referral by each clinician, this represented the first manifest clinical episode of demyelination for each patient included.

The mean duration of clinical follow-up from the time of biopsy was 8 years (±4.4). In the follow-up period, relapsing remitting MS was established in 11 patients, four patients had developed secondary progressive MS, and two cases had primary progressive MS. The four patients with SPMS were classified as RRMS at the time of biopsy, and a progressive disease course emerged in the ensuing clinical follow-up. The demographics of the patients included are summarised in Table 1.

Clinical presentation was diverse, although 14 of the 17 cases later shown to have developed MS were documented to be encephalopathic at presentation. Three had seizures, and two had both headache and meningism. Nine of the patients with RRMS fulfilled the Association of British Neurologists criteria for highly active RRMS on the basis of frequent disabling relapses with concurrent MRI activity after the diagnostic biopsy [14].

The two PPMS cases presented with a history of exclusive cognitive impairment and subsequently developed a more prototypic progressive myelopathy; unlike the cases of relapse-onset MS, we did not observe tumefactive lesions in the two PPMS cases. The reason for biopsy was again based on diagnostic uncertainty: in the context of rapidly evolving

Table 1 Summary of the demographic details of patients with biopsy-proven demyelination

	RRMS *n* = 11	SPMS *n* = 4	PPMS *n* = 2	Monophasic demyelination *n* = 4
Age (years)	39.5 ± 11.9	64.8 ± 8.6	61.5 ± 16.3	54.3 ± 18
Gender	Male = 3 Female = 8	Male = 2 Female = 2	Male = 2 Female = 0	Male = 3 Female = 1
Follow-up (years)	6.3 ± 3.7	12.5 ± 4.2	8.5 ± 0.7	5 ± 3.3
Median EDSS (range)	2 (1–3.5)	5.8 (5–7.5)	5 (4–6)	N/A
Disease-modifying drugs	Natalizumab: *n* = 6 Interferon-β: *n* = 3 Alemtuzumab: *n* = 1 Fingolimod *n* = 1 Dimethyl fumarate: *n* = 1	None	None	None

EDSS expanded disability status scale, *RRMS* relapsing remitting multiple sclerosis, *SPMS* secondary progressive multiple sclerosis, *PPMS* primary progressive multiple sclerosis, *N/A* not available

cognitive impairment, rather than concerns regarding neoplasia or other disorders as in the RRMS cases.

The 17 confirmed MS cases all fulfilled the McDonald criteria for dissemination in space (DIS) on the baseline MRI, 14 of the 17 cases exhibited dissemination in time (DIT) radiologically on the baseline scan and all 17 had confirmation of DIT on a subsequent MRI brain [10]. In the two cases of PPMS, spinal cord MRI scans were available for confirmation of the presence of at least two T2-weighted lesions. An example of the tumefactive lesions seen in a RRMS case is displayed in Fig. 2, and the imaging abnormalities seen in one of the PPMS cases presenting with cognitive impairment is shown in Fig. 3.

The median EDSS of all MS patients is 3 (range 1–7.5). In the patients with relapse-onset MS, none of the SPMS patients were prescribed a DMD. In the RRMS cases, DMD use is as follows: natalizumab: $n = 6$, interferon-β: $n = 3$, alemtuzumab: $n = 1$, fingolimod (following an adverse reaction to natalizumab): $n = 1$, dimethyl fumarate: $n = 1$.

Four patients had a strictly monophasic demyelinating disease; in common with the cases that were to be later clinically diagnosed as MS, these cases were all encephalopathic at presentation. The four patients, three men and one woman, had a mean age of 54.3 years (± 18). One man presented at the age of 78, which accounts for the standard deviation of 18 years. Overall, the four patients had a mean follow-up of 5 years (± 3.3).

In contrast to the MS patients, none of the patients had a second clinical episode or further radiological activity evident during follow-up; indeed in all four cases follow-up imaging demonstrated lesion regression. None of the four patients fulfilled criteria for DIS at presentation and over the course of follow-up, none fulfilled the criteria for DIT. Regarding the clinical presentation, all four patients were encephalopathic at the time of presentation. One patient had seizures, two were hemi-paretic and one had a visual field deficit. All four patients had a number of investigations performed by their referring clinical to exclude other disorders, such as paraneoplastic demyelination.

All four patients currently have sequelae of their prior neurological illness including headache and arm pain, hemiparesis and cognitive impairment, dysphasia, refractory epilepsy and persistent visual field deficit. In each of these four patients, the clinical diagnosis based on the absence of relapse or of progression was one of ADEM by their referring clinician. On review of these four biopsies, we were unable to confidently separate the neuropathology findings from the findings in the 17 patients in whom a diagnosis of MS was established. Furthermore, perivascular lymphocytes were more prominent but this was entirely subjective and in no instance was their correlation between the pathology observed and the clinical diagnosis of ADEM, in contrast to the MS cases.

Discussion

There are three novel findings in this study; firstly, demyelination identified pathologically was similar irrespective of the clinical diagnosis and was not predictive of future clinical course—therefore, the practicing neurologist needs to cognisant of the fact that when there is recourse to biopsy in MS, other external features (other than the pathology) have greater influence on the clinical course. Secondly, in those patients who had developed relapse-onset MS, the majority had a 'highly active' disease course, four of whom developed a secondary progressive disease course. Lastly, we were unable to confidently establish a pathologic diagnosis of ADEM, in those with a strictly monophasic illness—highlighting the absence of robust biomarkers in routine clinical practice to discriminate between a diverse range of demyelinating

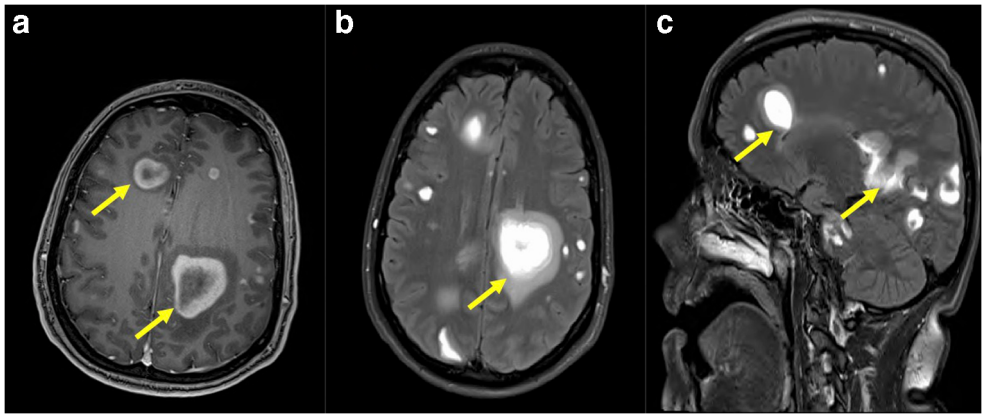

Fig. 2 MRI brain scan from a patient with relapsing remitting MS and an encephalopathic presentation. **a** Axial T1-weighted image with gadolinium enhancement, showing ring enhancing lesion, **b** axial fluid attenuated inversion recovery (FLAIR) image demonstrating corresponding T2-weighted abnormalities, **c** sagittal FLAIR image demonstrating 'Dawson's fingers' with demyelinating lesions orthogonal to the long axis of the corpus callosum

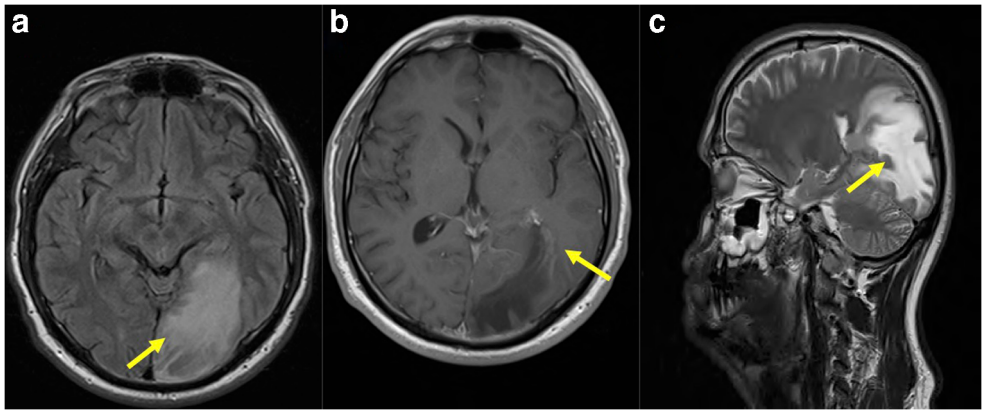

Fig. 3 MRI brain scan from a patient presenting with a monophasic illness consisting of visual field loss, seizures and encephalopathy. **a** Axial fluid attenuated inversion recovery (FLAIR) image demonstrating high signal intensity abnormality in the occipital lobe, **b** T1-weighted image post gadolinium contrast administration demonstrating faint contrast enhancement at the edge of the lesion, **c** sagittal T2-weighted image demonstrating the longitudinal extent of the hyper-intense lesion

disorders that may lead to diagnostic uncertainty, as in this case series.

It is estimated that tumefactive MS cases have a prevalence of 1–2 per 1000 [15], whilst not all cases proceed to biopsy, it is often the presence of 'red flags' for an MS diagnosis, such as encephalopathy or headache, that prompt the physician to exclude alternative causes based on pathology [16]. This was the case in our series, as the majority of the cases were encephalopathic at the time of presentation. Our series also included two cases of PPMS, whilst the lesions were not deemed to be tumefactive in nature, a phenotype consisting solely of cognitive impairment, as previously described [17], led to diagnostic uncertainty, although subsequently a more classical progressive myelopathy picture emerged.

A prior study of MS lesions, obtained either from biopsy or autopsy, has reported on the heterogeneity that may be seen in lesions, depending on activity [2]. In this study by Lucchinetti et al., active lesions were characterised by an infiltration of macrophages and activated microglia, containing intracytoplasmic granules of myelin debris. Pathologic abnormalities consistent with active demyelination were observed in our cohort, as the pathology in the MS cases was dominated by abundant macrophages with myelin debris. However, whilst we observed occasional lymphocytes, they were not nearly as prominent as macrophages. The striking finding in our cohort was the similarity of the histopathological abnormalities in all cases (MS or monophasic), irrespective of the future clinical course. This is similar to our previous observations and the paucity of lymphocytes may possibly be due to their engulfment by macrophages [3]. However, in contrast to the work by Lucchinetti et al., the white matter biopsy samples in this series were processed using routine laboratory methods, and so it was not possible to classify the lesions into subtypes based on the level of inflammatory activity.

The clinical course of the relapse-onset patients in our study consisted primarily of 'highly active' cases of RRMS with subsequent frequent disabling relapses, which is in contrast to previous earlier reports [6, 18, 19], where either the minority of patients converted to MS following presentation, or those that did, remained at a low level of physical disability. We hypothesise that a number of factors may have led to clinician's referral of only the most 'aggressive' MS cases [20].

Firstly, a proposed management algorithm may be implemented by clinicians [5], thereby leading to a less frequent referral to neurosurgery. This is evident in our cohort given that over half were prescribed a second-line DMD to manage their highly active disease. However, the use of a DMD may in fact have a deleterious effect on the progression of MS in some instances, as highlighted by cases involving the emergence of new tumefactive lesions following treatment with either fingolimod or natalizumab [21, 22]. Expert guidelines have suggested that treatment should not be initiated following a single clinical event with a tumefactive demyelinating lesion, unless either clinical or radiological evidence of both DIS and DIT can be established [5]. Such an approach may mitigate the potential for harmful effects of DMTs where an MS diagnosis is not definite.

Secondly, advances in imaging [23], including spectroscopy [24] or better identification of spinal cord lesions [25], may aid in a diagnosis of MS, even in an atypical clinical presentation. Thirdly, a combination of imaging modalities, such as hypo-attenuation on CT, when a tumefactive lesion is seen on MRI [26], may be predictive of demyelination and may obviate the requirement for biopsy even in an atypical presentation of MS.

In our study, we identified four cases of SPMS with a high level of physical disability, with an EDSS ranging from 4.5 to 7.5. Whilst the two cases of PPMS we identified had similar levels of physical disability (EDSS 6 and 4) at follow-up, there were distinct differences in clinical presentation and the observed radiologic abnormalities. Previously, it has been

suggested that the pathology in SPMS may have a greater inflammatory component [27]. The biopsy specimens reviewed in all progressive MS cases in our study did not reveal any differences in their respective histopathology. Nonetheless, the clinical outcomes were in keeping with the known natural history of progressive MS [28].

As a point of comparison, we also included the pathology from patients with what eventually became a monophasic demyelinating illness, diagnosed as ADEM at presentation by the referring clinician. Controversy remains as to whether one can make such a diagnosis in an adult, rather than that of a clinically isolated syndrome [29, 30]. The autopsy pathological findings of ADEM have been previously described and include 'sleeves of demyelination' rather than a more complete pattern of demyelination as seen in MS [31, 32]. In our biopsy study, none of the four cases had pathology consistent with ADEM, nor were we able to discriminate between these monophasic cases and the MS cases based on the histopathology alone. The absence of clinic-pathological correlation in this series, in relation to the monophasic demyelinating disorders observed, highlights the diagnostic uncertainty that may arise for the clinician when faced with an atypical demyelinating disorder. Also, that recourse to biopsy may not provide any additional diagnostic clarification beyond confirmation of a demyelinating pathology.

The cohort in our study diagnosed clinically (but not pathologically) with ADEM had a mean clinical follow-up of 5 years. In the study by Pittock et al., 10% of tumefactive cases were monophasic in nature [6], and similarly in the study by Lucchinetti et al., one quarter of patients had a monophasic course [4]. Whilst this may reflect similar cases to our series, it may equally be that the follow-up times of 4 years in both studies and 5 years in our group of four may have been insufficient for a second MS-defining relapse to occur [33]. Lesion regression had occurred in each of our patients.

A number of limitations in our study need to be considered. Firstly, due to the multicentre nature of our data, it was not possible to obtain accurate information on the presence of unmatched oligoclonal bands in each case. These have been reported to be less often detected in ADEM [8], and with variable frequency in cases of tumefactive demyelination [4, 6]. This could be addressed in a future study through the use of a nationalised laboratory results system which is currently under development in Ireland. Furthermore, the unavailability of either accurate clinical information or MRI brain scans limited the sample number to 21 from a possible 84 cases where neuropathological data were available. The limited number of scans relates in part to older images stored on microfilm that could not be retrieved and in keeping with laboratory data, clinical data may be readily available nationally through the use of an integrated national electronic health record.

Secondly, the cases of progressive MS had conventional MRI scans available but did not have quantitative MRI measures or assessments of brain or spinal cord atrophy, in order to investigate the relationship between neuroinflammation and neurodegeneration in this cohort [34]. This could be addressed in a future prospective study with patients recruited from the onset of consideration for biopsy.

Thirdly, the biopsy specimens in our cohort were derived solely from hemispheric white matter lesions and did not include cortex or meninges. A prior biopsy study has demonstrated cortical demyelination and meningeal inflammation [35]. This may be addressed in future biopsy cases in our centre, through modification of the neurosurgical approach, in order to systematically preserve both meninges and grey matter sampled on approach to the white matter lesion. Furthermore, as the biopsy samples were analysed in the course of a routine clinical diagnostic service, we did not perform a quantitative analysis on the samples. Such an analysis would permit quantification of axon density, plasma cells or the extent of demyelinating activity [2], which may provide useful prognostic features in terms of prediction of the clinical course.

Finally, a number of genetic and environmental risk factors have been proposed to influence the clinical outcome in MS [36]. Due to the retrospective nature of our study, it was not possible to study the influence of vitamin D, smoking or other potential risk factors on the rate of disability progression. This would be of interest in a future prospective study in which more deeply phenotyped subjects are enrolled for inclusion.

Conclusions

In conclusion, our study identified 21 cases of biopsy-proven demyelination, four of whom were monophasic, whilst the remaining 17 developed clinically definite MS. Despite the homogenous pathology, consisting of macrophages and reactive glial cells in all cases, the diverse clinical outcomes confirm other extraneous factors have a significant influence on the clinical course in MS. Thus, in summary, we were unable to predict the future clinical behaviour of biopsy-proven, pathogen-free demyelination.

Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest.

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