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Abstract

Introduction

Multiple sclerosis is a chronic inflammatory disorder of the central nervous system, characterised by acute episodes of neurological dysfunction thought to reflect focal areas of demyelination occurring in clinically eloquent areas. These symptomatic relapses are generally considered to be random clinical events occurring without discernable pattern. We have investigated the hypothesis that relapses may follow a predetermined sequence and may provide insights into underlying pathological processes.

Methods

Employing a prospective clinical database we analysed data from 1482 patients who had experienced two or more consecutive relapses. Using regression analysis, we compared site and symptom of index event with those of first relapse.

Results

We demonstrate that following disease ignition subsequent relapses may not be random events but dependent on characteristics of the index event. All anatomical sites were more likely to be affected in the first relapse if that site had been involved in the index event with a similar association observed when comparing by symptoms.

Conclusion

These findings have importance in understanding the evolution of disease, predicting individual disease progression and may aid with patient counselling and management.

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Introduction

Multiple Sclerosis (MS) is a complex inflammatory disorder of the central nervous system (CNS) and represents a major cause of chronic neurological disability in western societies. Understanding the natural history of the disease is important for patient counselling, as well as impacting on clinical trial design and influencing clinical practice. Relapses are a characteristic clinical feature of MS presenting at disease onset in approximately 85% of affected individuals and remain an essential component of contemporary clinical diagnosis as well as an important factor in informing treatment strategies.[1]

Relapses are defined as 'the occurrence of a symptom or symptoms of neurological dysfunction with or without objective confirmation, lasting more than 24 hours.[2] They are most apparent during the early phases of disease before the appearance of major fixed disability and are generally considered to represent focal areas of inflammatory demyelinating pathology affecting clinically eloquent areas of the CNS.[3] Individual relapses can have a widely variable impact depending on the severity of the event, site affected, pre-existing disabilities and the degree of subsequent recovery. Clinical features of relapse are diverse and although there remains disagreement on the exact frequency of symptoms and mode of presentation they will commonly involve combinations of sensory change, visual impairment and motor deficit. Age specific patterns of presentation are also observed since lower limb motor symptoms, sphincteric symptoms and sexual symptoms are all associated with increasing age at first presentation, whereas optic neuritis is more likely to occur at a younger age.[4] Recovery from relapse, which occurs in the majority of patients over a period of 2 months,[5] is thought to happen as a result of resolution of oedema and inflammation, lesion repair through axonal sodium channel redistribution and remyelination, and functional reorganisation.[6]

Although relapse onset for an individual patient is unpredictable, observational studies of large patient cohorts with MS have identified some important temporal patterns. The most prominent of which is a relationship to age with relapse frequency peaking at around 0.8 per year in the 3rd and 4th decades of life and declining thereafter with disease duration [1]. In addition, environmental factors have also been shown to influence relapse frequency including seasonality,[7] systemic infections(8) and high levels of airborne particulate matter.[9] Biological factors thought to influence relapse frequency include pregnancy and vitamin D levels.[10] Furthermore disease modifying therapies also have a significant impact in reducing not only the frequency but also the severity of relapse. Relapse pattern within individual patients can also provide important prognostic information concerning disease trajectory and may influence longer term disease management since a high number of relapses occurring within the first two years of disease onset as well as short inter-attack intervals are associated with poorer long-term outcome.[11]

Despite the existing knowledge on the natural history of relapses, information regarding the anatomical distribution of relapses within the same patient remains limited. Inflammatory lesions causing relapse are currently thought to be a largely random phenomena and there are limited published data regarding relapse pattern with respect to the site of initial presentation.[12] Here, we have investigated the hypothesis that subsequent relapses in MS are not random, but may be related to the first (index) event. Evidence for pre-determined clinical relapse patterns would offer further information about disease pathogenesis and may aid clinical decision-making.

Materials & Methods

The Neurology Department at the University Hospital of Wales operates a regional neuro-inflammatory clinic for South East Wales serving a population of approximately 1.3 million people. It provides dedicated, consultant-led, multidisciplinary neuroinflammatory clinics and rapid-access

relapse assessment supplemented by a network of community-based MS nurse-led clinics. Data from patients are collected prospectively and stored in a secure database, and include demographic details, a full medical history including comprehensive history of disease onset and course, examination findings including dated Expanded Disability Status Scale (EDSS) assessments, details of investigations and pedigree details. Data collection started in 1985 with a series of cross-sectional studies and has continued prospectively since 1999. The MS database currently contains records on 2654 patients with MS, of whom 2063 have prospectively collected detailed longitudinal data from disease onset. All patients are consented for information to be held (South East Wales Local Research Ethics Committee Panel C/REC reference number 05/WSE03/111).

Symptoms from index event and first relapse were characterised according to an expanded EDMUS system[13] into 13 symptomatic subcategories (arm motor, ataxia, bulbar, cognitive, diplopia, face motor, face sensory, leg motor, limb sensory, optic nerve, sexual, sphincter and vestibular) and 5 anatomical sites (optic nerve, cerebellum, long tracts, brainstem and cortex). Logistic regression was performed to explore the relationship between symptomatic system and anatomical site involved in each event, corrected for age at onset and sex with association expressed as a β value. When there was more than one site of relapse at index or subsequent event, results were corrected for multiple testing.

Results

Prospectively collected relapse data from 1482 MS patients with detailed clinical information from the disease onset event and at least one sequential relapse were identified for analysis and included 409 males and 1073 females (M1: 2.6F) (Table 1). The remaining patients in our cohort either have primary progressive disease, have not suffered a relapse (i.e. clinically isolated syndrome), have only ever had an index event before secondary progression or have been lost to follow-up. Care was

taken to exclude episodes of neurological dysfunction related to deterioration of pre-existing deficits or transient infection related events. Mean age of disease onset was 31 years and mean interval between index and 1st relapse was 4 years, and is similar to previously published data.[14] Long tracts were the most commonly recurrently affected anatomical site, involved in both index event and 1st relapse in 654 (71.8%), followed by brainstem relapses (126 (33.6%).

All sites were more likely to be affected in the first relapse if that site had been involved in the index event (optic nerve: $\beta=0.65$, $p=0.0019$; cerebellum: $\beta=0.93$, $p=1.3\times10^{-5}$; long tracts: $\beta=0.74$, $p=2.3\times10^{-6}$; brainstem: $\beta=0.88$, $p=3.9\times10^{-8}$; cortex: $\beta=3.77$, $p=9.8\times10^{-5}$) (Table 2). In addition, cerebellar involvement at first relapse was associated with brainstem involvement at index event ($\beta=0.71$, $p=0.00028$), and long tract involvement in the first relapse was associated with optic neuritis ($\beta=0.48$, $p=0.01$) and brainstem involvement ($\beta=0.46$, $p=0.004$) at index event.

When analysed by symptom, first relapses (etable 1) also demonstrated a pattern of concordant association with those experienced at index event (arm motor: $\beta=0.75$, $p=2\times10^{-9}$; ataxia: $\beta=0.94$, $p=2.1\times10^{-5}$; cortical: $\beta=4.5$, $p=0.0002$; diplopia: $\beta=0.77$, $p=0.003$; leg motor: $\beta=0.81$, $p=1.8\times10^{-9}$; limb sensory: $\beta=1.03$, $p=1.6\times10^{-9}$; optic nerve: $\beta=0.59$, $p=0.0017$; vestibular: $\beta=1.51$, $p=1.3\times10^{-7}$). Only bulbar, face motor, face sensory, sexual and sphincteric symptoms showed no association. In addition, two discordant associations were identified: optic nerve at index event with arm motor symptoms at first relapse ($\beta=0.52$, $p=0.0007$) and leg motor (index) with sphincteric symptoms (first) ($\beta=0.62$, $p=0.0026$). No sites or symptoms were found to be negatively associated.

Discussion

This study, performed in a large, well characterised population-based cohort of patients with MS, suggests that relapses may not occur in a random fashion but, at least in the initial stages of disease, tend to follow a pattern of anatomical system involvement. Combining conventional with advanced imaging measures also shows that the formation of enhancing lesions occurs in sites of subtle but consistent changes in brain tissue integrity,[15–18] supporting the evidence that MS lesions and consequent clinical events tend to develop close to or in sites of previous damage. The reasons for this are unclear but may represent a pattern of epitope spreading [19] with a perpetuating inflammatory cascade provoked by an initial site of disease ignition expanding into neighbouring sites. Alternatively neighbouring sites may acquire subclinical damage as a result of the index event, which makes them more susceptible to the impact of further anatomically random inflammatory events.

Although our results suggest a predetermined pattern of clinical events, the pattern and spread of pathology and its relationship to relapses is difficult to characterise in detail. Serial conventional magnetic resonance imaging (MRI) scans may help clarify this pattern, although lesions visible on MRI do not clearly fit the pattern of clinically expressed disease.[20] Beyond variable levels of clinical expression in different anatomical locations, the inability to detect disease in normal appearing white or grey matter with conventional sequences, as well as adaptive functional reorganisation that limits the clinical impact of damage, makes conventional MRI alone of limited use in understanding the spread of pathology. As a result, it may be difficult to prove with conventional imaging alone whether new lesions develop outwards from a common starting point. Studies at high field strengths may shed light on the spread of MS pathology, suggesting that new lesions do appear to develop outwards from a common starting point, lending some biological support to our findings.[21]

Some observers have also suggested that tissue hypoxia makes a significant contribution to neuro-inflammation in the context of demyelinating disorders such as MS. The exact mechanism by which this occurs is unclear but may result from insufficient arterial supply due to flow restriction from local cerebral oedema, vessel constriction, compromised venous drainage or excess oxygen demand from the collective inflammatory cells present.[22] These factors can all contribute to the characteristic distribution of brain and spinal cord lesions seen in MS. Intrinsic variability in human vasculature may also lead to pathology occurring preferentially within selected or neighbouring sites for a single individual and may also help to explain the site and symptom concordance observed in our study.

However, one important caveat of our study is that only relapses associated with new symptoms and/or signs were recorded and, although these are likely to represent new areas of pathology in clinically eloquent regions, sites of subclinical inflammation would have remained undetected [23]. These data are therefore only relevant to clinically expressed disease. In addition, although care has been taken to exclude causes of pseudo-relapses such as deterioration in pre-existing symptoms, any inadvertent inclusion of patients exhibiting these symptoms cannot be excluded.

Overall our results are of value in understanding the natural history of MS, suggesting that relapse pattern may reflect a predetermined trajectory of pathological progression and spread. As well as adding to knowledge about pathogenesis of the disease, an understanding of the potential site of first relapse may also influence decisions concerning subsequent disease management.

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Table 1

Demographics of patient population.

Total patients	1482
Female	1073 (72.4%)
Relapsing onset	1420 (95.8%)
Progressive onset	62 (4.2%)
Mean age at disease onset	31 years (SD 9.7 years)
Mean inter-attack interval	4 years (SD 5.3 years)
Mean annualised relapse rate	0.5 (SD 0.58)
Mean follow-up	18 years (11.6 years)

Table 2

β value estimates (p values) for a site being affected at first relapse (R1), given the site of index event.

	R1: Optic nerve		R1: Cerebellum		R1: Long tracts		R1: Brainstem		R1: Cortex	
Index event	β (p)	n	β (p)	n	β (p)	n	β (p)	n	β (p)	n
Optic nerve	**0.65 (<0.01)**	91	0.22 (0.38)	34	**0.48 (0.01)**	212	0.02 (0.91)	54	-1.72 (0.13)	1
Cerebellum	-0.26 (0.33)	19	**0.93 (<0.01)**	44	0.08 (0.68)	109	0.18 (0.36)	45	-0.63 (0.44)	2
Long tracts (motor and sensory)	0.03 (0.88)	154	0.22 (0.26)	116	**0.74 (<0.01)**	654	0.31 (0.06)	206	-0.25 (0.69)	10
Brainstem	-0.31 (0.96)	48	**0.71 (<0.01)**	77	**0.46 (<0.01)**	265	**0.88 (<0.01)**	126	0.52 (0.40)	8
Cortex	0.04 (0.06)	2	-0.14 (0.86)	2	0.15 (0.83)	8	-0.02 (0.99)	3	**3.77 (<0.01)**	2

After correction for multiple testing, significant p values are <0.01 (highlighted in bold)