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Research Paper

The aetiology of acute neurological decline in multiple sclerosis: Experience from an open-access clinic

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Abstract

Background: Multiple sclerosis (MS) relapses contribute to disability and influence treatment decisions. Many centres now provide open access to specialist services for patients with new symptoms. However, there is scarce literature on the spectrum of presentations encountered in this setting.

Objective: The objective of this paper is to characterise presentations to an open, rapid-access MS relapse clinic and the impact on disease management.

Methods: A retrospective review of outpatient episodes over a three-year period was conducted. Demographic and service data, symptoms, disability, diagnosis and management were recorded according to a standardised proforma.

Results: A total of 371 attendances were analysed. A new MS relapse was diagnosed in 216 (58%) episodes, of which 56 (26%) patients had an additional diagnosis which had also contributed to their presentation. Of 266 reports of non-relapse-related symptoms, 73 were unrelated to MS. Treatment interventions were made in almost all relapsing patients and in 70% of patients presenting with acute, non-relapse-related symptoms of MS. Changes to disease-modifying therapies were considered in 28% of consultations.

Conclusion: Diagnosing MS relapses is crucial for disease management and yet remains challenging. Clinicians should be aware of differential diagnoses and confounding factors. The high incidence of therapeutic interventions observed suggests that rapid-access clinics represent an effective platform for responsive disease management.

Keywords: Multiple sclerosis, relapse, acute, symptomatic treatment, rapid-access, clinic

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Introduction

Acute relapses are a characteristic clinical feature of multiple sclerosis (MS). They occur at disease onset in 80%–90% of patients, contribute significantly to short-term disability,[1] remain an essential component of establishing the clinical diagnosis[2] and guide decisions on therapeutic interventions.[3] Clinical relapses are thought to represent foci of acute inflammation and demyelination occurring within clinically eloquent areas of the central nervous system (CNS).[4] Anatomically they are commonly located in the optic nerve, brainstem and spinal cord and rarely are multifocal.[2] Relapse frequency is variable and unpredictable but peaks in the third and fourth decades at around 0.3 per year and reduces gradually with age and disease duration.[5] Temporal patterns of relapse may also be influenced by infections,[6] seasonality[7] and pregnancy.[8]

The onset of neurological symptoms during relapse is usually acute or sub-acute. Complete or partial recovery usually occurs within two to three months but can continue for up to one year[1] and is thought to reflect resolution of inflammation, remyelination and redistribution of axonal sodium channels. The impact of relapse on individual patients is difficult to predict

and is modified by anatomical site, pre-existing disability and environmental factors, but affects not only physical ability but also financial and social circumstances.[9] Although many relapses may be considered mild, around 30% are severe (≥1.0 increase in Expanded Disability Status Scale (EDSS)[1] score), which may result in physical dependence and can occasionally be life threatening. Conventional management of MS relapse includes administration of oral or intravenous corticosteroids which are recognised to shorten the duration of symptoms[10] but do not influence longer-term outcome. Symptomatic treatments are also provided and there is evidence that multi-disciplinary therapy interventions improve short-term recovery.[11] However, the clinical identification of MS relapse remains challenging. New signs and symptoms can be obscured by pre-existing deficits, disease progression, psychosocial influences and short-term factors including infection and heat which may require alternative management.

A growing drive towards patient-centred, responsive health care has increasingly shaped recommendations for the provision of care for patients experiencing relapse. As a result contemporary guidance suggests patients should be afforded rapid access to specialist MS care in an outpatient setting including access to therapists, equipment and social support.[12–14] This has prompted many specialist centres to develop open, rapid-access services which may vary in design, but allow patients with new symptoms to receive prompt expert assessment. Typically patients self-refer and are seen within a dedicated rapid-access clinic, fitted into a routine clinic or on an ad hoc basis within inpatient facilities. The subsequent consultation may be led by a specialist MS nurse, a specialist MS physician or trainee, all of whom need to be aware of confounding factors influencing clinical presentation. In addition they must be able to make a rapid decision on the aetiology of new symptoms or signs and provide acute management and make modifications to longer-term treatment where appropriate. Whilst rapid-access services are now commonplace, there remains scarce literature on the nature of patients seen in this setting, the spectrum of their complaints or outcomes. In addition whilst the main purpose of these clinics may be to identify patients in acute relapse and provide appropriate intervention, it is clear that relapse is not the sole reason for acute neurological deterioration in patients with MS, although the description of these confounding factors in the clinical setting has not been widely explored.

In this study we systematically reviewed data from a weekly rapid-access MS clinic, in order to determine the nature of attendances and the impact on subsequent disease management. It is hoped that results will inform on the acute needs of patients with MS and how these can be best met using current or new service models.

Methods

The University Hospital of Wales (UHW) in Cardiff is a tertiary referral centre for neurology and serves a cohort of approximately 1900 people with MS[15] within a population base of 1.2 million. During each encounter between a patient and the MS service, data are recorded prospectively in a secure electronic database. Data from 8589 clinical encounters (patient seen in person) were recorded during 2010 to 2012. Demographic and clinical data are routinely recorded using minimum datasets including relapse status, EDSS, and site and timing of relapses since last review.

A rapid-access clinic was instigated as a regional service from January 2004 in order to assess acute neurological dysfunction in patients with MS. Contact details of this clinic are provided to all patients on first review. Patients self-refer by telephone and are triaged according to an established proforma. If relapse is considered possible or likely, patients are offered an outpatient appointment and assessment is undertaken by a multidisciplinary team comprising a specialist MS physician or trainee, an MS nurse ± a physiotherapist and occupational therapist. The anatomical site and nature of any relapses are recorded as well any planned interventions.

A retrospective review was undertaken of all patients presenting to the rapid-access MS clinic at UHW between January 2010 and December 2012. All data were obtained from entries that were made in electronic or paper records at the time of the index consultation. Follow-up data were collated from the MS electronic database during August 2013, ensuring that all patients had at least six months of follow-up after the index consultation. Data available for analysis comprised demographic information including age and sex, socioeconomic status (using post code to determine the Welsh Index of Multiple Deprivation,[16] which is then ranked as low, medium and high) and geographical location (post code). The electronic database was also used to calculate the number of previous relapses each patient had experienced at the time of presentation. Relapse data are collected both systematically during clinic visits and by annual postal questionnaire and also opportunistically at other points of clinical contact. In addition a range of

service data including time from telephone referral to consultation, and time from consultation to first follow-up was examined. Clinical data comprised the MS disease duration, disease course, date of onset of symptoms and the nature of symptoms. The presenting symptoms were classified according to a modified European Database for Multiple Sclerosis (EDMUS) classification which has been shown to allow a consistent clinical description of MS using a common language.[17] Current EDSS, clinical diagnosis reached at the time of consultation and any management decisions made as a result of the consultation were also recorded.

The database was also used to compare demographic and clinical variables between patients who had ever been telephone-triaged to rapid-access clinic between 2010 and 2012 versus any patients known to the service who had accessed the UHW MS service over the same time period in order to determine any barriers to access. In the latter group patient age, disease duration and MS disease course were calculated from most recent contact and EDSS data were used only if recorded within 12 months. Where available, EDSS scores recorded for rapid-access attendees within a 12-month, relapse-free period prior to clinic (baseline) and during a three- to 12-month, relapse-free period after clinic (follow-up) were employed to determine change in EDSS associated with acute presentation.

Continuous variables are expressed as a mean value with range and/or standard deviation and non-continuous variables as median with interquartile range (IQR). Comparison between rapid-access clinic patients and all other patients who accessed the MS service during the study period were made using unpaired *t*-tests (age, disease duration), chi-squared (MS disease course) and Mann-Whitney *U* test (EDSS). Symptom duration in relapse and non-relapse groups was compared using an unpaired Student's *t*-test. Median changes in EDSS were compared using Mann Whitney *U* tests. Referral rates to paraclinical specialist services were compared depending on the presence or absence of a therapist in the clinic using Fisher's exact test.

Results

A total of 241 patients were seen on 376 occasions during the three-year study period. One patient (who made a single attendance) was excluded from the analysis as clinical documentation relating to the consultation was unavailable. Four further attendances were excluded as a rapid-access appointment had been erroneously used to book a routine appointment for a patient who had not presented with new symptoms ($n = 3$) and a patient with clinically isolated syndrome ($n = 1$). The study population therefore comprised 238 patients presenting on 371 occasions. Service data (date of referral/ follow-up) were available for attendances dating from January 2011 ($n = 247$). The 238 patients attending rapid-access clinic represented 23% of the 1027 patients contacting the telephone-triage service during the study period (2010–2012). Comparisons of the demographic and clinical features between these groups are shown in Table 1. Of all the attendees at rapid-access clinic, 100 (27%) were recorded as taking disease-modifying therapy (DMT) at the time of attendance (interferon 57 (15.4%), glatiramer acetate nine (2.4%), monoclonal antibody therapy 33 (8.9%), and mitoxantrone one (0.3%)). Of 272 patients attending with relapsing–remitting MS, 80 (29%) were documented to be on DMT at the time of attendance.

Median delay from first contact to patient review was three days (range 0–14, IQR two to four days) (Figure 1(a)). Seventy-nine per cent of patients were seen within one week of self-referral. Mean symptom duration was 26 days (range 0–540; SD 49) at time of review. Patients found to have a new relapse presented more rapidly than patients with non-relapse symptoms ($p < 0.01$, Figure 1(b)). Of patients diagnosed with a new relapse, 4% were first relapses, 34% had experienced two to four prior relapses, 35% between five and seven and 27% > 8.

The most common presenting symptoms were limb sensory (47%), limb motor (43%), pain (35%) and balance/incoordination (27%) (Figure 2). Diagnoses reached at the time of review are illustrated in Figure 3. In 96 out of 371 cases (26%), more than one diagnosis was assigned, either because the clinician could not discriminate between differential diagnoses with certainty, or because two or more conditions were felt to coexist and these were proportionally equal both in relapse and non-relapse patients. The most frequent diagnosis reached during clinic attendance was of a new relapse (216 cases, 58%). In 99 cases (27%), non-relapse symptoms of MS, including pain, spasticity or fatigue, were felt to be contributing to the acute presentation. In the remaining patients a broad range of conditions was diagnosed. In 73 out of 371 consultations (20%), a 'non-MS' condition was suspected to explain the acute symptoms and these included: musculoskeletal conditions, migraine, ophthalmological conditions or medical conditions such as thyrotoxicosis or pulmonary embolus. In 26 of the 73 non-MS presentations (36%), patients were referred to

Table 1. Comparison of the demographic and clinical features of patients who had ever been telephone triaged to rapid-access clinic between January 2010 and December 2012 (n = 238) versus any other patients who accessed the UHW MS service during the same period (n = 789).

	Rapid access clinic (RAC) patients	Non-RAC patients	Statistical significance
Sex	n = 238	n = 778	p = 0.071
Female	177 (74%)	538 (69%)	
Male	61 (26%)	240 (31%)	
Mean Age	n = 238	n = 784	p < 0.001
	40.8 years (SD 10.1)	52.1 years (SD 13.2)	
Mean Disease duration	n = 234	n = 228	p < 0.001
	10.1 years (SD 8.0)	13.6 years (SD 11.4)	
EDSS	n = 238	n = 655	p = 0.001
Median (Interquartile range)	4.5 (3.0-6.0)	6.0 (2.0-6.5)	
EDSS < 4.0	84 patients (35.3%)	224 patients (35.3%)	
EDSS 4.0 – 6.0	113 patients (47.5%)	202 patients (30.8%)	
EDSS > 6.0	41 patients (17.2%)	229 patients (35.0%)	
Disease course	n = 236	n = 693	p < 0.001
Relapsing-remitting	176 (74.6%)	330 (47.6%)	
Secondary progressive	46 (19.5%)	283 (40.8%)	
Primary progressive	10 (4.2%)	67 (9.7%)	
Clinically isolated syndrome	3 (1.3%)	13 (1.9%)	
NMO	1 (0.4%)	0	
Socioeconomic status	n = 210	n = 616	p = 0.89
Low	57 (23.9%)	169 (27.4%)	
Medium	66 (27.7%)	183 (29.7%)	
High	87 (36.6%)	264 (42.9%)	

Patient age, disease duration and MS disease course were taken to be that most recently recorded during the study period. EDSS data for non RAC patients was used only if it had been recorded within 12 months of the clinical contact. The number of patients for which data was available is represented by "n=" in each row. MS: multiple sclerosis; EDSS: Expanded Disability Status Scale; UHW: University Hospital of Wales; NMO: neuromyelitis optica.

alternative hospital specialities for further review. In 66 attendances (18%), documentation was made of concurrent symptoms of infection. In 64 of those 66 cases (97%), the infection was considered to be contributing to the acute neurological presentation. Infection coincided with acute relapse in 21 (10%) episodes but in 43 (12%) presentations, patients were thought to be experiencing an infective exacerbation of old symptoms rather than new relapses.

Baseline EDSS data were available for 331 patient attendances (277 related to an MS problem, of which 167 related to a relapse). Follow-up EDSS data were available for 154 patient attendances (130 related to an MS problem of which 73 related to a relapse). For 113 patient attendances, both baseline and follow-up EDSS data were available (93 related to an MS problem of which 51 related to a relapse). Median baseline EDSS was 4.0 (IQR 2.0–6.0), median clinic EDSS was 5.0 (IQR 3.5–6.0) and median follow-up EDSS was 3.5 (IQR 2.0–6.0). Changes in EDSS according to the presence of a new MS problem and according to the presence of an acute relapse are shown in Table 2.

Clinical management decisions or interventions as a result of the consultation are illustrated in Figure 4. Of the 216 patients diagnosed with a new relapse, 205 were given steroids (typically oral methylprednisolone). Of the 99 patients who presented with worsening, non-relapse symptoms of MS, 69 (70%) received an intervention, either of medication alteration or referral for therapy. In 105 of the 371 consultations (28%), a discussion regarding DMT (implementation, escalation or withdrawal) was documented in the case records. Twenty-five per cent of patients were referred for therapy (physiotherapy, occupational therapy, speech and language

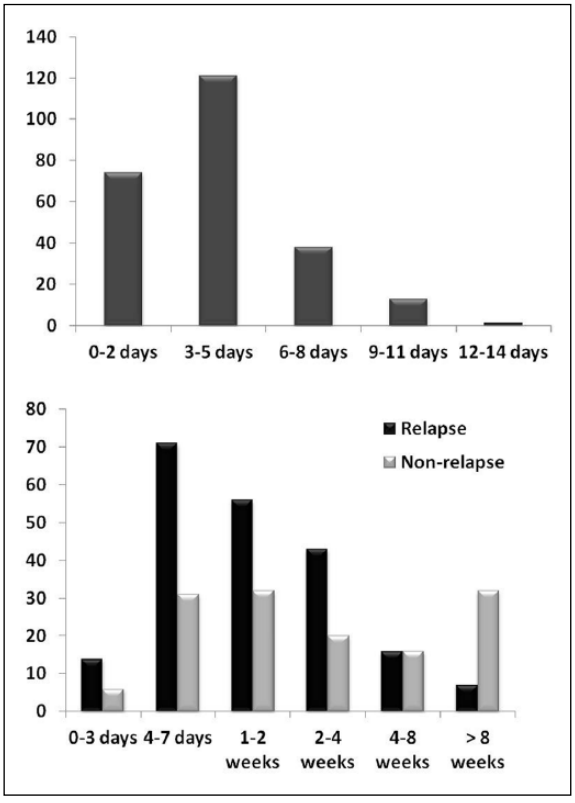

Figure 1. (a) Time between self-referral and consultation at a multiple sclerosis (MS) rapid-access clinic. (b) Duration of symptoms at the time of attendance at MS rapid-access clinic, according to whether the patient was thought to be experiencing an MS relapse.

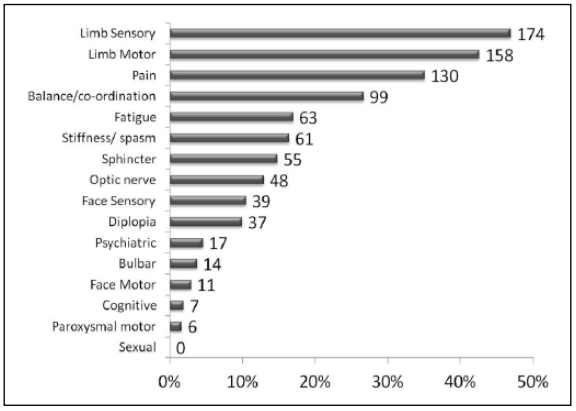

Figure 2. Nature of presenting complaint expressed during 371 attendances at a multiple sclerosis (MS) rapid-access clinic. Numbers relate to patient attendance with corresponding percentages shown on the horizontal axis. Patients often presented with several concurrent symptoms so total exceeds 371 (100%).

therapy or continence services). Referral rates to physio- or occupational therapy were considerably higher when the relevant therapist had been present during the consultation (18% when therapist present vs. 5% therapist not present; $p = 0.004$). Seven patients (four relapse; three non-relapse) required direct admission to the ward, while the remainder of the cohort were managed as outpatients.

Mean time to follow-up was 62 days (range 0–748 days), most commonly by telephone (70%). Mean time to follow up in person was 3.3 months (range 0–25.3 months, SD 3.6). At the time of study completion, only 1% of patients had not had any follow-up and 3% had not had any follow-up in person.

Discussion

The principal aim of this study was to review attendances at a clinic designed to provide rapid access to specialist, multi-disciplinary care for patients experiencing acute symptoms of MS. This service primarily aims to meet the needs of patients experiencing a relapse of MS employing a system of self-referral and telephone triage. While acute relapse accounted for 58% of presentations, a high proportion of patients had acute problems unexplained by relapse.

The most common acute symptoms were of motor and/or sensory disturbance of the limbs, pain and balance and coordination difficulties. The relatively low incidence of optic nerve presentations compared with prior relapse studies may be explained by preferential attendance at ophthalmological services. In addition the frequency of symptoms such as fatigue, cognitive or mood disturbance and sexual dysfunction may reflect under-reporting by the patient or under-documentation by the clinician. This may be exacerbated by a multi-disciplinary setting where the patient faces an audience of several health professionals, detracting from discussion of sensitive issues. In order to address these concerns some clinics have utilised standardised symptom questionnaires which may be suited to capturing a broader range of symptoms,[18] but were not employed in this study.

The majority of patients attending clinic had a relapsing disease course, many of whom were receiving DMT, and almost all those in relapse were offered oral or intravenous steroid treatment. However, a significant minority of patients with relapsing disease reported acute symptoms that were not felt to be attributable to MS relapse. More than a quarter of patients attending the clinic had progressive MS or advanced disease. In these patients, progression of disease or exacerbation of non-relapse symptoms of MS rather than relapse was commonly thought to

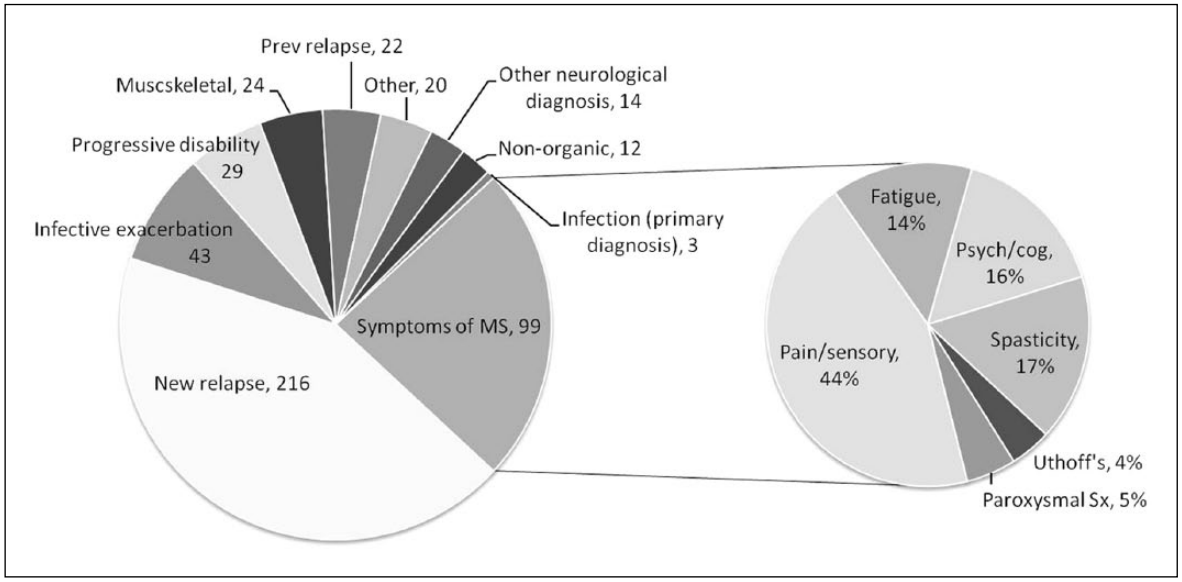

Figure 3. Diagnosis of acute symptoms made during 371 attendances at a multiple sclerosis (MS) rapid-access clinic (left). Clinicians may have assigned more than one diagnosis (see text) so the total exceeds 371. The smaller pie chart (right) shows the breakdown of non-relapse-related symptoms of MS.

account for the acute presentation. In consultations where acute symptoms were not considered to be directly attributable to MS (20%), the underlying diagnosis varied widely and included neurological conditions such as migraine as well as non-neurological conditions such as thyrotoxicosis or uveitis. The relatively high frequency with which patients were assigned multiple diagnoses in the clinic serves to illustrate the challenge of confidently characterising acute symptoms in MS and emphasises the importance of remaining vigilant for other medical conditions in a disease with a mean duration exceeding 35 years.

A widely accepted definition of a relapse is: patient-reported symptoms or objectively observed signs typical of an acute inflammatory demyelinating event in the central nervous system (CNS), current or historical, with duration of at least 24 hours, in the absence of fever or infection.[2] Our study shows that in normal clinical practice, even after detailed review within a specialist service, MS clinicians often found it difficult to discriminate confidently between an acute relapse and an alternative explanation such as disease progression or fluctuations of the chronic symptoms of MS. These data underline the importance of patients being reviewed in person during acute exacerbations by health professionals with adequate experience and raises questions about the validity of employing historical patient-derived relapse data on which longer-term interventional therapeutic decisions are made.

Coexistent infection was perceived to be a common contributor to the acute presentation. Most often the patient was felt to have recurrence of pre-existing symptoms of MS in the context of recent infection (often termed a pseudo-relapse). However, 10% of patients thought to be experiencing a new relapse were also felt to have concurrent infection. Infection is known to be a potent precipitant of MS relapses, with an at-risk period that stretches some two to four weeks either side of an infection.[6,19–23] Crucially, relapses associated with infection appear to be more severe and sustained.[6,20] Most clinicians would advocate treating any underlying infection before prescribing steroids to a patient with infection-related relapse. However, these studies do support robust mechanisms for early follow-up of patients with coexistent relapse and infection in order to identify persistent neurological disability that may warrant subsequent treatment with steroids.

Treatment interventions were made in over two-thirds of non-relapsing patients. A quarter of all cases were referred to therapists allied to neurology, and the clinic frequently prompted referral for other specialist opinions including ophthalmology, rheumatology or psychiatry. The clinic visit also prompted a discussion regarding DMT in over a quarter of cases, highlighting the utility of this clinic in guiding long-term as well as short-term management.

This study outlines a model of rapid-access outpatient clinics to facilitate care of patients with MS. The

Table 2. Change in EDSS observed in patients attending the rapid-access MS clinic according to whether they were diagnosed with a problem related to MS and whether they were diagnosed with an acute relapse.

	Overall		MS		Non-MS			Relapse		Non-relapse		
	n	Change EDSS	*n*	Change EDSS	*n*	Change EDSS	*p* value	*n*	Change EDSS	*n*	Change EDSS	*p* value
Baseline to clinic	331	0.5	277	0	54	0	0.124	167	1	164	0	0.000
Clinic to follow-up	154	0	130	0	24	–1	0.180	73	–1	81	0	0.000
Baseline to follow-up	113	0	93	0	20	0	0.730	51	0	62	0	0.915

Baseline EDSS scores were recorded within a 12-month, relapse-free period prior to clinic. Follow-up EDSS scores were recorded during a three- to 12-month, relapse-free period after clinic. Statistical comparisons were made using Mann-Whitney *U* tests. EDSS: Expanded Disability Status Scale; MS: multiple sclerosis.

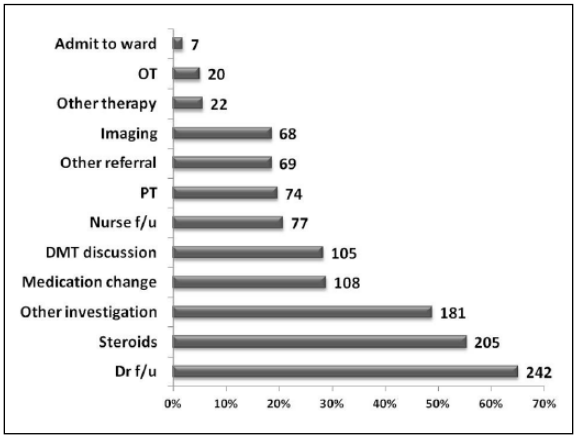

Figure 4. Management decisions made during for 371 patient attendances at a multiple sclerosis (MS) rapid-access clinic. Numbers relate to patient attendance with corresponding percentages shown on the horizontal axis. Patients may have had more than one outcome so total exceeds 371 (100%). OT: occupational therapy referral; PT: physiotherapy referral; nurse f/u: follow-up plans documented for nurse-led clinic; doctor f/u: follow-up plans documented for doctor-led clinic.

challenge of diagnosing MS relapses along with the high incidence of treatment and therapy interventions even in patients not experiencing a true MS relapse suggest that specialist, multidisciplinary resources may be justified in all MS patients with acute symptoms. MS specialist nurses and therapists can play a crucial role in this setting by offering continuous outpatient and community care and by providing detailed personal knowledge of individual patient histories. However, the wide ranging diagnoses encountered in the clinic suggests that access to physicians with expertise beyond MS is also necessary. The overwhelming trend towards successful outpatient management of acute exacerbations seen in this study supports the rapid-access intervention as one which may avert hospital admissions and associated costs to the patient and health services.

A limitation of this study is that we have not been able to compare patients managed in the rapid-access clinic with those patients with acute MS problems who are managed in other settings. A single rapid-access clinic, seeing up to five patients per week, appears adequate to meet the current demand of an MS population approaching 2000; access to the clinic within a week of referral was achieved in over three-quarters of cases and clinics often did not run to full capacity. However, estimates from local retrospective recording suggest that around 80% of patients who feel they are experiencing a relapse do not request access to the rapid-access clinic service. This

has implications for patient care as specialist assessment at the time of acute exacerbation informs both immediate and long-term management of the individual. Our data suggest that patients wait an average of 26 days before self-referral. It is possible that patients with short-lived relapses choose not to consult this service or feel that their needs are adequately met by their family doctors. However, another consideration is whether attendance at the clinic is being limited in some cases by lack of awareness or other barriers such as problems with accessibility or perceived lack of benefit. Our comparison of patients attending the rapid-access clinic with all patients in contact with the MS service during the same period revealed that patients attending rapid-access clinic were younger, had lower disease duration and were more likely to have relapsing–remitting MS and lower disability than the MS population who access the service by telephone as a whole. This is unsurprising given that we are aiming to select out a subpopulation with active, relapsing disease. The similarities in socioeconomic status between those who attend clinic and those who do not provides some reassurance that social deprivation does not appear to be an obvious barrier to attendance. A prospective trial to evaluate the benefit of rapid-access clinics compared with other models of care in patients who consult the MS service would be useful to determine the true benefit of this model. Further retrospective work to address the reasons why some patients who suspect a relapse do not engage with the MS service at all is equally important.

In summary, these data characterise the nature of acute symptoms encountered by patients with MS and illustrate a model of rapid-access multidisciplinary care for acute neurological deterioration in patients with MS.

Conflict of interest

None declared.

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References

1. Hirst C, Ingram G, Pearson O, et al. Contribution of relapses to disability in multiple sclerosis. *J Neurol* 2008; 255: 280–287.
2. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol* 2011; 69: 292–302.
3. National Institute for Health and Clinical Excellence. Natalizumab for the treatment of adults with highly active relapsing–remitting multiple sclerosis. London: National Institute for Health and Clinical Excellence, 2007.
4. Ludwin SK and Raine CS. The neuropathology of multiple sclerosis. In: Raine CS, McFarland HF and Hohlfeld R (eds) *Multiple sclerosis: A Comprehensive text*. Philadelphia, PA: Saunders Elsevier, 2008; Philadelphia, USA.
5. Tremlett H, Zhao Y, Joseph J, et al. Relapses in multiple sclerosis are age- and time-dependent. *J Neurol Neurosurg Psychiatry* 2008; 79: 1368–1374.
6. Correale J, Fiol M and Gilmore W. The risk of relapses in multiple sclerosis during systemic infections. *Neurology* 2006; 67: 652–659.
7. Iuliano G, Boz C, Cristiano E, et al. Historical changes of seasonal differences in the frequency of multiple sclerosis clinical attacks: A multicenter study. *J Neurology* 2013; 260: 1258–1262.
8. Confavreux C, Hutchinson M, Hours MM, et al. Rate of pregnancy-related relapse in multiple sclerosis. Pregnancy in Multiple Sclerosis Group. *N Engl J Med* 1998; 339: 285–291.
9. Oleen-Burkey M, Castelli-Haley J, Lage MJ, et al. Burden of a multiple sclerosis relapse: The patient's perspective. *Patient* 2012; 5: 57–69.
10. Beck RW, Cleary PA, Anderson MM Jr, et al. A randomized, controlled trial of corticosteroids in the treatment of acute optic neuritis. The Optic Neuritis Study Group. *N Engl J Med* 1992; 326: 581–588.
11. Craig J, Young CA, Ennis M, et al. A randomised controlled trial comparing rehabilitation against standard therapy in multiple sclerosis patients receiving intravenous steroid treatment. *J Neurol Neurosurg Psychiatry* 2003; 74: 1225–1230.
12. National Institute for Health and Clinical Excellence. *Multiple sclerosis: National clinical guideline for diagnosis and management in primary and secondary care*. London: National Institute for Health and Clinical Excellence, 2004.
13. Leary SM, Porter B and Thompson AJ. Multiple sclerosis: Diagnosis and the management of acute relapses. *Postgrad Med J* 2005; 81: 302–308.
14. Porter B, Matheson F, Chataway J, et al. Key steps to delivery of a person centred relapse service. Letchworth Garden City: Multiple Sclerosis Trust, 2010.
15. Harding KE, Liang K, Cossburn MD, et al. Long-term outcome of paediatric-onset multiple sclerosis: A population-based study. *J Neurol Neurosurg Psychiatry* 2013; 84: 141–147.

16. The Welsh Index of Multiple Deprivation. Welsh Government. 2011. http://wales.gov.uk/statistics-and-research/welsh-index-multiple-deprivation/?lang=en (accessed 2011).
17. Amato MP, Grimaud J, Achiti I, et al. European validation of a standardized clinical description of multiple sclerosis. *J Neurol* 2004; 251: 1472–1480.
18. Perrin Ross A, Williamson A, Smrtka J, et al. Assessing relapse in multiple sclerosis questionnaire: Results of a pilot study. *Mult Scler Int* 2013; 2013: 470476.
19. Andersen O, Lygner PE, Bergström T, et al. Viral infections trigger multiple sclerosis relapses: A prospective seroepidemiological study. *J Neurol* 1993; 240: 417–422.
20. Buljevac D, Flach HZ, Hop WC, et al. Prospective study on the relationship between infections and multiple sclerosis exacerbations. *Brain* 2002; 125: 952–960.
21. Edwards S, Zvartau M, Clarke H, et al. Clinical relapses and disease activity on magnetic resonance imaging associated with viral upper respiratory tract infections in multiple sclerosis. *J Neurol Neurosurg Psychiatry* 1998; 64: 736–741.
22. Panitch HS. Influence of infection on exacerbations of multiple sclerosis. *Ann Neurol* 1994; 36 (Suppl): S25–S28.
23. Sibley WA, Bamford CR and Clark K. Clinical viral infections and multiple sclerosis. *Lancet* 1985; 1: 1313–1315.