Journal of Clinical Neuroscience 28 (2016) 97–101

Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

Clinical Study

Disability profile of multiple sclerosis in New Zealand

Sridhar Alla [a,b,*], John F. Pearson [b], Bruce V. Taylor [c], David H. Miller [a,b,d], Glynnis Clarke [b], Ann Richardson [e], Ernie Willoughby [f], David A. Abernethy [g], Clive E. Sabel [h], Deborah F. Mason [a,b,i]

[a] New Zealand Brain Research Institute, 66 Stewart Street, Christchurch 8011, New Zealand
[b] University of Otago, Christchurch, New Zealand
[c] Menzies Research Institute, University of Tasmania, Hobart, Australia
[d] Queen Square MS Centre, UCL Institute of Neurology, London, UK
[e] School of Health Sciences, University of Canterbury, Christchurch, New Zealand
[f] Auckland District Health Board, Auckland, New Zealand
[g] University of Otago, Wellington, New Zealand
[h] School of Geographical Sciences, University of Bristol, Bristol, UK
[i] Christchurch Public Hospital, Christchurch, New Zealand

ARTICLE INFO

Article history:
Received 3 June 2015
Accepted 6 September 2015

Keywords:
Age
Disability
Disease duration
Multiple sclerosis
New Zealand
Prevalence

ABSTRACT

New Zealand is a high risk region for multiple sclerosis (MS). The aim of this study was to investigate demographic, clinical and temporal factors associated with disability status in the New Zealand National Multiple Sclerosis Prevalence Study (NZNMSPS) cohort. Data were obtained from the 2006 NZNMSPS with MS diagnosis based on the 2005 McDonald criteria. Disability was assessed using the Expanded Disability Status Scale (EDSS). Disability profiles were generated using multiple linear regression analysis. A total of 2917 persons with MS was identified, of whom disability data were available for 2422 (75% females). The overall disability was EDSS 4.4 ± standard deviation 2.6. Higher disability was associated with older age, longer disease duration, older and younger ages of onset, spinal cord syndromes with motor involvement at onset, and a progressive onset type. Lower disability was associated with sensory symptoms at onset and a relapsing onset type. Overall, the factors studied explained about one-third of the variation in disability, and of this, about two-thirds was accounted for by age, age of onset and disease duration and one-third by the nature of first symptoms and type of disease onset (progressive or relapsing). Current age, age at onset and disease duration all had independent associations with disability and their effects also interacted in contributing to higher disability levels over the course of the disease.

1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disorder of the central nervous system that commonly has its onset in young adults aged between 20 and 35 years of age. A relapsing-remitting onset of disease is seen in about 85% of cases, and a progressive onset occurs in about 15%. In 2006 the New Zealand National Multiple Sclerosis Prevalence Study (NZNMSPS) [1] confirmed New Zealand (NZ) as a high risk population for MS with an overall age and sex standardised prevalence rate of 73.1 per 100,000 population, although in Māori, the indigenous population of NZ, the prevalence was substantially lower at 24.2 per 100,000 population [1–3].

After prolonged follow up (typically spanning several decades), the majority of people with MS will have developed substantial and irreversible locomotor disability. However, there is a great deal of inter-individual variability in the disease course and for a significant proportion of subjects there is little or no disability for many years. At present, there are no tools that can reliably predict an individual's progression over time. Natural history and longitudinal studies [4–11] have succeeded to a certain extent in defining the course and the prognostic value of certain demographic and clinical characteristics of patients at disease onset. These studies have shown a number of demographic (for example, age, sex) and clinical factors (for example, type of MS, age at onset, symptoms at onset) associated with disability evolution [7,10,12,13]. However, most of these studies have derived disability data from northern hemisphere populations; data from the southern hemisphere are sparse with little or no countrywide data available.

* Corresponding author. Tel.: +64 3 378 6076; fax: +64 3 378 6080.
E-mail address: allsr357@gmail.com (S. Alla).

http://dx.doi.org/10.1016/j.jocn.2015.09.020
0967-5868/

Furthermore, disability levels of the MS population and factors associated with disability status have not been previously studied throughout NZ. The aim of this study is to describe the disability profile, including demographic, clinical and temporal factors associated with disability status, among persons with MS in the NZ population.

2. Methods

Data were obtained from the NZNMSPS, a cross-sectional study that identified all persons diagnosed with MS (2005 McDonald criteria) [14] resident in NZ on national census day, 7 March 2006. Patients with clinically isolated syndromes, possible MS, neuromyelitis optica and neuromyelitis optica spectrum disorders [15] were excluded. Multiple sources of case ascertainment were used including neurologists and MS society databases, hospital discharge records, public advertising, Māori health workers and NZ government health information statistics. A capture-recapture analysis of multiple sources of ascertainment estimated between 95.2% and 98.8% capture with 95% confidence. Ethical approval for the study was obtained from the NZ multi-region ethics committee. For detailed information of study methodology, see Taylor et al. [1].

The NZNMSPS used a self-administered survey questionnaire to obtain demographic data including age, sex and ethnicity. In keeping with NZ census ethnicity definitions [16], only those who self-identified Māori ethnicity on the questionnaire were included as Māori for this analysis [3]. Those who did not have a positive response for Māori ethnicity are referred to as "non-Māori". Clinical information, including age at symptom onset, disease duration, onset type (relapsing or progressive onset) and nature of symptoms at onset, were obtained from the person's medical record by their treating neurologist or by direct review by a study neurologist. Disability was assessed using the Expanded Disability Status Scale (EDSS) [17]. A majority of patients (75%) had a telephone EDSS [18] and in 25% of cases disability was obtained from a clinical EDSS [17] performed either by the patient's neurologist or study neurologists.

Disability was modelled by linear regression of EDSS on demographic (sex, ethnicity), clinical (type of onset, nature of first symptoms at onset) and temporal (age, age at onset, disease duration) variables. To disentangle the effects of age on age at onset and disease duration, the analysis was conducted in two pairs, that is age and age at onset or age and disease duration as in Johnson and Melzer [19]. Analysis of variance showed significant two-way interaction between age and disease type at onset ($p < 0.001$), age and age at symptom onset ($p < 0.001$), age and disease duration ($p < 0.001$), thus these interactions were added in models. The disability profiles (Fig. 1) were generated by calculating the predicted disability from the regression model at medians for age, age at onset and disease duration and the curves were further smoothed using the locally weighted scatterplot smoothing LOESS procedure [20]. Model assumptions were assessed graphically with no evidence of lack of fit. Correlation coefficients are Pearson product moment correlations. All statistical tests were two-sided with type 1 error rate of 5%, analysis carried out in R version 3.2.0 (Vienna, Austria).

3. Results

A total of 2917 persons with definite MS were identified on census day in 2006. Of these, disability data were available for 2422 (1,824 females, 598 males) including 58 Māori. The demographic and clinical characteristics of the cohort are presented in Table 1. The majority (2023 patients, 83.5%) had relapsing onset MS and 399 (16.5%) progressive onset MS (primary progressive MS). The relapsing onset cases consisted of 1200 (49.5%) patients with relapsing remitting MS and 823 (34%) with secondary progressive MS on census day.

As expected, persons with progressive onset symptoms had higher disability levels compared with relapsing onset cases. Disability levels (EDSS) stratified by type of onset are presented for sex, ethnicity and nature of onset symptoms in Table 2.

Linear modelling showed that temporal variables (age, age at onset of symptoms, and their interactions) (Table 3) or age, disease duration and their interactions (Table 4) explained 22–23% of the variation in EDSS, while onset type (relapsing or progressive) and onset symptoms, explained 10–11%, with no significant contribution from sex or ethnicity. The models also demonstrated that age has a significant effect on disability independent of age at onset of symptoms and disease duration ($p < 0.001$). Overall, the results indicated that disability increased with increasing age ($p < 0.001$) and disease duration ($p < 0.001$), and decreased with intermediate ages of onset ($p < 0.001$). Those with sensory only symptoms at the onset had milder disability compared with those with spinal motor symptoms at onset ($p < 0.05$).

The profiles of disability by age, age at onset and disease duration are presented for relapsing and progressive onset MS in Figure 1. The profiles show average disability generally increasing with increasing age and disease duration for typical combinations of age, disease duration and age of onset. The profile of average disability by age of onset appears more complex, being higher at younger and older ages of onset.

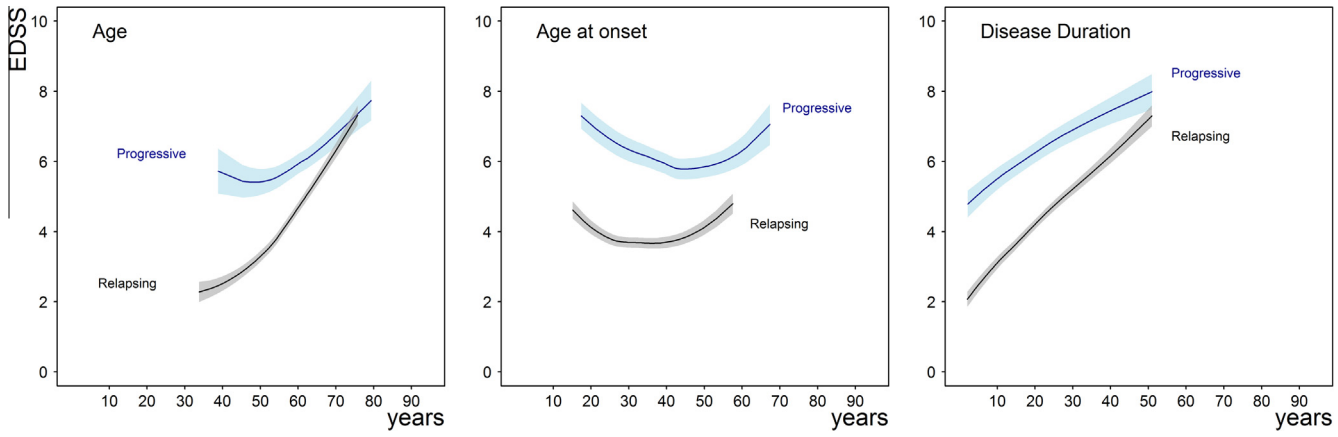

Fig. 1. Profiles of disability by (left) age, (centre) age at onset and (right) disease duration are presented for relapsing and progressive onset multiple sclerosis. EDSS = Expanded Disability Status Scale.

Table 1
Demographic and clinical characteristics of the 2006 New Zealand multiple sclerosis cohort

Characteristic	Relapsing onset	Progressive onset	Total
Patients	2023 (83.5)	399 (16.5)	2422
Sex			
Male	443 (21.9)	155 (38.8)	598
Female	1580 (78.1)	244 (61.2)	1824
Age, years	49.6 ± 12.7	58.0 ± 11.5	51.0 ± 12.9
Age at symptom onset, years	33.7 ± 10.0	42.3 ±11.3	35.1 ± 10.7
Disease duration, years	17.2 ± 12.0	17.1± 11.2	17.2 ± 11.9
EDSS	4.0 ± 2.6	6.3 ± 2.0	4.4 ± 2.6
Nature of first symptoms			
Optic nerve	402 (19.9)	4 (1.0)	406
Spinal cord	618 (30.5)	289 (72.4)	907
Brain stem/cerebellar	394 (19.5)	43 (10.8)	437
Sensory only	330 (16.3)	15 (3.8)	345
Polysymptomatic and other	233 (11.5)	35 (8.8)	268
Missing	46 (2.3)	13 (3.3)	59

Data are presented as mean ± standard deviation or count (%) where appropriate.
EDSS = Expanded Disability Status Scale.

Table 2
Disability levels in the New Zealand multiple sclerosis population

Characteristic	Relapsing onset (n = 2023)	Progressive onset (n = 399)
Sex		
Male	3.8 ± 2.4	6.2 ± 1.9
Female	4.1 ± 2.6	6.3 ± 2.0
Ethnicity		
Māori	4.0 ± 2.8	6.6 ± 1.6
Non-Māori	4.0 ± 2.6	6.3 ± 2.0
Nature of first symptoms		
Optic nerve	4.2 ± 2.7	7.0 ± 1.4
Spinal cord syndrome	4.3 ± 2.5	6.3 ± 1.9
Brainstem/Cerebellar	3.9 ± 2.5	6.2 ± 2.3
Sensory only	3.5 ± 2.4	6.1 ± 2.1
Polysymptomatic and other	3.9 ± 2.7	6.2 ± 2.0

Values represent mean ± standard deviation of Expanded Disability Status Scale scores.

4. Discussion

This nationwide study of MS in NZ, a country with a high prevalence of the disease, provides a disability profile of a prevalence cohort that was studied at a time when few patients were receiving disease modifying treatments. Overall, approximately 60% of the MS population experienced moderate or severe disability (EDSS 3.5 or greater). The study identified demographic, clinical and temporal factors associated with disability. Overall, these factors explained about one-third of variation in disability (Table 3, 4). Age, age of onset and disease duration together accounted for 22–23% of the disability variation; this included both their individual and interacting effects. The nature of first symptoms and type of clinical onset (progressive or relapsing) explained another 10–11%. While it is recognised that two-thirds of disability variation was unexplained by our models, the associations that were observed are of interest and are now discussed.

For those aged over 50 years, increasing age was clearly associated with increasing disability, the association being most strongly evident in those with relapsing onset MS (Fig. 1). This association could reflect a number of factors. One factor might be age-related changes in pathogenic mechanisms, for example a shift from adaptive to innate immune-mediated tissue damage with older age as patients evolve from a relapsing remitting to secondary progressive disease course [21]. There may also be an adverse effect on disease course of age-related comorbid disorders such as hypertension and hyperlipidaemia [22]. Increasing survival of older people with MS [23] may also enhance the association of age with disability.

Interestingly, our model of age of onset *versus* disability shows a non-linear pattern with higher disability at younger and older ages of onset and lower disability when onset was at intermediate ages (Fig. 1). The higher disability with younger age of onset may reflect longer disease duration amongst subjects seen during a single time-point prevalence study. Higher disability at older age of onset has been previously reported [24,25] and may reflect the greater likelihood of a progressive course in older age groups. However, caution is needed when interpreting the relationship of age of onset with disability when data is collected in the context of a single time point prevalence study as reported here. Age of onset may be spuriously increased by incomplete recall of past clinical events, especially when they are more remote in time. For the same reason, disease duration may also be underestimated. Although time of symptom onset was confirmed using available clinical records, it is still possible that past events have not been recalled by patients, which could limit the interpretation of study results. Notwithstanding, we observed a clear relationship of increasing disability with increasing disease duration (Fig. 1).

Consistent with previous studies patients with the relapsing onset type of MS had less disability than those with a progressive onset [6,7,10,12,13,26], the latter also having an older age of onset as previously well documented [26,27]. Our observations are in accordance with a number of studies reporting sensory only and spinal motor symptoms at onset of disease being associated with

Table 3
Regression coefficients from the Expanded Disability Status Scale model on age and age at onset

	Per decade	Standardized			R^2
	β	β	95% CI	p value	Total
Demographic					<0.01%
Male		−0.01	(−0.21, 0.20)	0.94	
Māori		0.02	(−0.55, 0.59)	0.95	
Clinical					10.5%
Progressive onset		1.98	(1.69, 2.26)	<0.0001	
Symptoms at onset					
Spinal (including motor)		0.22	(0.02, 0.42)	0.033	
Sensory only		−0.27	(−0.53, 0.00)	0.048	
Temporal					22.7%
Age	1.24	1.65	(1.53, 1.77)	<0.0001	
Age at onset	−0.74	−0.79	(−0.90, −0.68)	<0.0001	
Age × Age at onset	0.002	0.22	(0.13, 0.30)	<0.0001	
Age × Progressive onset	−0.54	−0.72	(−1.00, −0.44)	<0.0001	
Total R^2					33.2%

Temporal variables scaled by mean and standard deviation, mean age 51 years and mean age at onset 35 years.
CI = confidence interval.

Table 4
Regression coefficients from an Expanded Disability Status Scale model on age and disease duration

	Per decade	Standardized			R^2
	β	β	95% CI	p value	Total
Demographic					<0.01%
Male		−0.01	(−0.22, 0.19)	0.91	
Māori		0.01	(−0.56, 0.58)	0.97	
Clinical					10.5%
Progressive onset		1.90	(1.62, 2.19)	<0.0001	
Symptoms at onset					
Spinal (including motor)		0.21	(0.01, 0.41)	0.036	
Sensory only		−0.30	(−0.56, −0.03)	0.028	
Temporal					22.3%
Age	0.47	0.62	(0.49, 0.75)	<0.0001	
Disease duration	0.73	0.88	(0.74, 1.01)	<0.0001	
Age × Disease duration	−0.001	−0.14	(−0.23, −0.05)	0.002	
Age × Progressive onset	−0.32	−0.43	(−0.69, −0.17)	0.001	
Total R^2					32.8%

Temporal variables scaled by mean and standard deviation, mean age 51 years and mean disease duration 18 years.
CI = confidence interval.

better and poorer disability status, respectively [7,28,29]. Male sex has sometimes been reported to be associated with higher disability [30,31], however on careful scrutiny this may in part reflect a higher proportion of males with a primary progressive course [7,32]. In our large population based study, sex did not differentiate disability after correction for all other predictors including the type of onset (progressive or relapsing onset). Our results are in accordance with some studies [32–34] that have also reported no sex effect on disability outcome. Ethnicity has been associated with rapid disability progression in Canadian First Nation peoples [35] and African Americans [36]. However, we did not find such differences in disability profiles between NZ indigenous Māori and non-Māori.

This study used multiple sources of case ascertainment with an estimated capture rate of 96.7% of the entire cohort of people with MS in NZ on census day 2006. Disability scores are not available for the entire prevalence cohort; however the available scores (83%) were uniformly distributed throughout the country, across sexes and ethnicity. Furthermore, the proportions of telephone to clinical EDSS assessments were uniform throughout the country and mean EDSS scores were similar between the telephone and clinically assessed groups, thus limiting any geographical or methodological bias in the type of disability assessments. The possible effect of disease modifying therapies on disability was not ascertained. The NZNMSPS did not collect information on the number of patients on disease modifying therapies, however considering the first available, modestly effective disease modifying therapies with a stringent eligibility criteria had only been recently introduced (2000) [37], it is estimated that a small number (<20%) [37] of patients were treated with these drugs with limited benefit by 2006, and thus are likely to have had no material effect on the clinical features of our cohort in 2006.

In summary, our modelled analysis of data obtained in a national prevalence cohort has identified several clinical and temporal features that were associated with disability in MS. While there are limitations interpreting such associations in a point prevalence study, it may be informative to undertake further investigation to understand the basis of such associations. The mechanisms that underlie the strong association of older age with increasing disability in relapsing onset MS may be of particular interest.

Conflicts of Interest/Disclosures

The authors declare that they have no financial or other conflicts of interest in relation to this research and its publication.

Acknowledgements

We thank the National Multiple Sclerosis Society of New Zealand and the New Zealand Brain Research Institute for supporting the first author's research position. D.H.M. is supported by the UCL-UCLH Biomedical Research Centre. The New Zealand National Multiple Sclerosis Prevalence Study was funded by a joint partnership grant from the New Zealand National Multiple Sclerosis Society and the New Zealand Health Research Commission (grant no: HRC MS 05524).

References

[1] Taylor BV, Pearson JF, Clarke G, et al. MS prevalence in New Zealand, an ethnically and latitudinally diverse country. Mult Scler 2010;16:1422–31.
[2] Alla S, Mason DF. Multiple sclerosis in New Zealand. J Clin Neurosci 2014;21:1288–91.
[3] Pearson JF, Alla S, Clarke G, et al. Multiple sclerosis in New Zealand Maori. Mult Scler 2014;20:1892–5.
[4] Confavreux C, Vukusic S. Natural history of multiple sclerosis: a unifying concept. Brain 2006;129:606–16.
[5] Cottrell DA, Kremenchutzky M, Rice GP, et al. The natural history of multiple sclerosis: a geographically based study. 5. The clinical features and natural history of primary progressive multiple sclerosis. Brain 1999;122:625–39.
[6] Debouverie M, Pittion-Vouyovitch S, Louis S, et al. Natural history of multiple sclerosis in a population-based cohort. Eur J Neurol 2008;15:916–21.
[7] Runmarker B, Andersen O. Prognostic factors in a multiple sclerosis incidence cohort with twenty-five years of follow-up. Brain 1993;116:117–34.
[8] Sayao AL, Devonshire V, Tremlett H. Longitudinal follow-up of "benign" multiple sclerosis at 20 years. Neurology 2007;68:496–500.
[9] Scalfari A, Neuhaus A, Degenhardt A, et al. The natural history of multiple sclerosis, a geographically based study 10: relapses and long-term disability. Brain 2010;133:1914–29.
[10] Tremlett H, Zhao Y, Rieckmann P, et al. New perspectives in the natural history of multiple sclerosis. Neurology 2010;74:2004–15.
[11] Weinshenker BG, Bass B, Rice GP, et al. The natural history of multiple sclerosis: a geographically based study. I. Clinical course and disability. Brain 1989;112:133–46.
[12] Confavreux C, Vukusic S, Adeleine P. Early clinical predictors and progression of irreversible disability in multiple sclerosis: an amnesic process. Brain 2003;126:770–82.
[13] Renoux C. Natural history of multiple sclerosis: long-term prognostic factors. Neurol Clin 2011;29:293–308.
[14] Polman CH, Reingold SC, Edan G, et al. Diagnostic criteria for multiple sclerosis: 2005 Revisions to the "McDonald Criteria". Ann Neurol 2005;58:840–6.
[15] Wingerchuk DM, Hogancamp WF, O'Brien PC, et al. The clinical course of neuromyelitis optica (Devic's syndrome). Neurology 1999;53:1107–14.
[16] Statistics New Zealand. Profile of New Zealander Responses, Ethnicity Question: 2006 Census. http://www.stats.govt.nz. (consulted January 2013). Available from: http://www.stats.govt.nz.
[17] Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 1983;33:1444–52.
[18] Lechner-Scott L, Kappos L, Hofman M, et al. Can the Expanded Disability Status Scale be assessed by telephone? Mult Scler 2003;9:154–9.

[19] Johnson SB, Meltzer LJ. Disentangling the effects of current age, onset age, and disease duration: parent and child attitudes toward diabetes as an exemplar. J Pediatr Psychol 2002;27:77–86.
[20] Cleveland WS. Robust locally weighted regression and smoothing scatterplots. J Am Stat Assoc 1979;74:829–36.
[21] Lassmann H, Van Horssen J, Mahad D. Progressive multiple sclerosis: pathology and pathogenesis. Nat Rev Neurol 2012;8:647–56.
[22] Marrie RA, Cohen J, Stuve O, et al. A systematic review of the incidence and prevalence of comorbidity in multiple sclerosis: overview. Mult Scler 2015;21:263–81.
[23] Brønnum-Hansen H, Koch-Henriksen N, Stenager E. Trends in survival and cause of death in Danish patients with multiple sclerosis. Brain 2004;127:844–50.
[24] Liguori M, Marrosu MG, Pugliatti M, et al. Age at onset in multiple sclerosis. Neurol Sci 2000;21:S825–9.
[25] Trojano M, Liguori M, Bosco Zimatore G, et al. Age-related disability in multiple sclerosis. Ann Neurol 2002;51:475–80.
[26] Confavreux C, Vukusic S. Age at disability milestones in multiple sclerosis. Brain 2006;129:595–605.
[27] Andersson PB, Waubant E, Gee L, et al. Multiple sclerosis that is progressive from the time of onset: clinical characteristics and progression of disability. Arch Neurol 1999;56:1138–42.
[28] Phadke JG. Clinical aspects of multiple sclerosis in north-east Scotland with particular reference to its course and prognosis. Brain 1990;113:1597–628.
[29] Koch M, Kingwell E, Rieckmann P, et al. The natural history of primary progressive multiple sclerosis. Neurology 2009;73:1996–2002.
[30] Bergamaschi R, Berzuini C, Romani A, et al. Predicting secondary progression in relapsing-remitting multiple sclerosis: a Bayesian analysis. J Neurol Sci 2001;189:13–21.
[31] Kantarci O, Siva A, Eraksoy M, et al. Survival and predictors of disability in Turkish MS patients. Turkish Multiple Sclerosis Study Group (TUMSSG). Neurology 1998;51:765–72.
[32] Tedeholm H, Skoog B, Lisovskaja V, et al. The outcome spectrum of multiple sclerosis: disability, mortality, and a cluster of predictors from onset. J Neurol 2015;262:1148–63.
[33] Amato MP, Ponziani G, Bartolozzi ML, et al. A prospective study on the natural history of multiple sclerosis: clues to the conduct and interpretation of clinical trials. J Neurol Sci 1999;168:96–106.
[34] Trojano M, Avolio C, Manzari C, et al. Multivariate analysis of predictive factors of multiple sclerosis course with a validated method to assess clinical events. J Neurol Neurosurg Psychiatry 1995;58:300–6.
[35] Saeedi J, Rieckmann P, Yee I, et al. Characteristics of multiple sclerosis in aboriginals living in British Columbia, Canada. Mult Scler 2012;18:1239–43.
[36] Cree BA, Khan O, Bourdette D, et al. Clinical characteristics of African Americans vs Caucasian Americans with multiple sclerosis. Neurology 2004;63:2039–45.
[37] Byrne S, Mason D. A review of interferon use in patients with relapsing remitting multiple sclerosis in the canterbury region, New Zealand: 2000–2006. NZ Med J 2012;125:37–44.