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Original article

The epidemiology of multiple sclerosis in the Scottish Highlands: Prevalence, incidence and time to confirmed diagnosis and treatment initiation

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ABSTRACT

Introduction: Although multiple sclerosis (MS) is frequent in the northern hemisphere, there have not been recent epidemiological studies in the Scottish Highlands about MS.
Objectives: To get updated data regarding MS prevalence, incidence and mortality in the Highlands. Time between symptom onset and MS diagnosis was also evaluated in incident MS cases and the pattern of use of disease-modifying therapies (DMTs) was analysed.
Methods: Study population was people with MS under the care of the Highland Health and Social Care Partnership. The catchment area included North area (Wick, Thurso, Brora, Invergordon), Center (Inverness, Aviemore, Nairn, Fort William), and West coast (Ullapool, Skye). Data were obtained from the MS database at Raigmore hospital (prevalence, midyear 2017) and the prospective hospital-register based study (diagnosis) that was carried out over a 12-month period, in 2016. The 2010 McDonald criteria for diagnosis of new MS cases were used. Crude prevalence and incidence and 95% confidence interval (CI) were calculated for the MS adult onset population, and data was standardised to the European standard population 2013; cause-specific mortality rate was analysed. Pattern of use of DMTs during the first year of diagnosis was also registered.
Results: 745 patients were registered in the MS database. 75.4% (562 cases) were females, and female/male ratio was 3:1. Mean age of population was 54.1 ± 14.1 years (range: 15-95 years). Mean number of years since diagnosis was 8.5 ± 4.6 years. Estimated prevalence for the population aged 15 and older was 376 cases per 100,000 inhabitants (95% CI: 354-399). 36 incident MS cases were registered in 2016 (88.8% females; mean age 40.4 ± 12.1 years). Annual incidence in Highlands was 18.2 per 100,000 inhabitants (95% CI: 14-24). The mean period of time from symptom onset to diagnosis was 38.8 ± 43.2 months. 47.2% (17/36) did not take any DMT during the first year after the diagnosis.
Conclusion: Prevalence and incidence of MS in the Scottish Highlands is high. Although the gap period between symptom onset and diagnosis is moderate, a significant proportion of recently diagnosed MS patients were not keen to start a DMT the first year after the diagnosis.

1. Introduction

Multiple sclerosis (MS) is the most frequent cause of neurological disability in young people, and quality of life and other aspects such as mood, cognition, and family and society financial burden are significantly affected (Thompson et al., 2018).

MS is more common in the Northern Europe and among Northern European ancestry people. In the UK, it has been estimated that around 130,000 people are living with MS (Mackenzie et al., 2014). Although MS is frequent in Scotland, there have not been updated epidemiological studies in the Scottish Highlands about MS prevalence.

The Scottish Highlands is a cultural and geographical region localised in the north of Scotland and is home to astonishing scenery, including the renowned Loch Ness. This area is very sparsely populated, and is the largest region in Scotland and covers nearly 10,000 sq miles. The Highland council with capital in Inverness is the administrative body for much of the region. There are two distinct operational units providing services in NHS Highlands: Highland Health and Social Care Partnership and Argyll and Bute Health and Social Care Partnership.

In 1981, the reported MS prevalence was 97.3 cases per 100,000 in the Outer Hebrides (Dean, 1981); however, no data was available for the Highlands. Existing data from the North-East (Aberdeen and Orkney

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areas) showed an increase in prevalence since the 80s of the 20th century, from 144 cases per 100,000 inhabitants (Sheperd and Downie, 1980) to 248 cases per 100,000 (Visser et al., 2012).

There is also limited data about MS incidence in the Scottish Highlands and the pattern of use of disease-modifying therapies (DMTs) in treatment-naive patients. In order to get a full picture of MS burden in the Highlands, epidemiological studies including prevalence, incidence and mortality are needed. Accurate data may be helpful to make decisions about development and implementation of new services for MS as well as the need to establish the requirement for more staff for MS care (NHS Quality Improvement Scotland (QIS) 2009; www.healthcareimprovementscotland.org).

2. Objectives

The main purpose of this audit was to get updated data about the prevalence and incidence of multiple sclerosis in the Scottish Highlands, an area felt to be of high incidence. Secondary aim was to analyse diagnostic delay and treatment which has not been well studied in Scotland. It was hypothesized that repeated studies in small and homogeneous populations such as the Highlands may probably show an increased MS prevalence over time through the years.

Time is brain, and delays in both MS diagnosis and the time to start a DMT may be prognostic factors in the long-term. So, the secondary purpose of this audit was to calculate time to MS diagnosis and to start a DMT. The time between symptom onset and MS diagnosis was evaluated in incident MS cases, and the pattern of use of DMTs is described.

3. Material and methods

3.1. Study design

For the MS prevalence research project, a cross sectional observational study was carried out with the MS database available in 2017.

For the MS incidence project, a prospective hospital-register based study was carried out over a 12 month period, from 1st January 2016 to 31st December 2016.

3.2. Study population

Study population was the people with MS living in the catchment area covered by the Highland Health and Social Care Partnership. The Partnership is made up of two areas: North and West Operational unit and the inner Moray Firth Operational Unit. Highland Health and Social Care Partnership cover the same area as the Highland Council.

Raigmore hospital is the only tertiary reference centre of NHS Highlands and is localised in Inverness (latitude 57°47′N), and has been based on the site since 1941. People with MS get neurological speciality care from Neurology service only at Raigmore hospital. The MS service covers most of areas in the Highlands including North area (Wick

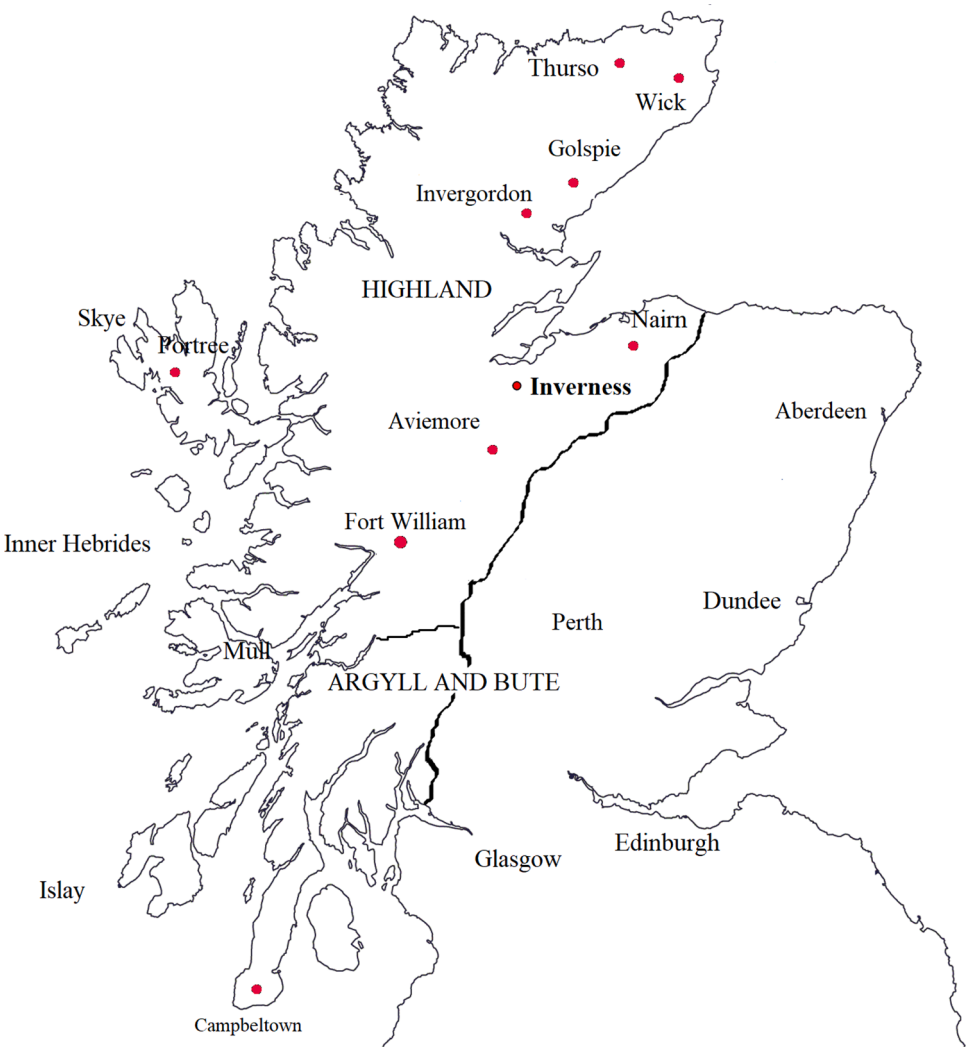

Fig. 1. Map of the Highlands.

58°44′N, Thurso, Brora, Invergordon), Center (Inverness, Aviemore, Nairn, Fort Augustus, Fort William), and West coast (Ullapool, Sky Isle), as shown in the Highlands map (Fig. 1).

For the purpose of analysing the crude prevalence and incidence, it was considered only the population covered by the Highland Health and Social Care Partnership (https://www.nrscotland.gov.uk). Midyear 2017 population estimates for Highlands's council was 235201 inhabitants (115113 men and 120088 women) and were included in the prevalence analysis (Mid-Year Population Estimates Scotland 2017). The 2016 population was 234770 inhabitants (114846 men and 119924 women) and was used for the incidence analysis (Mid-Year Population Estimates Scotland 2017). For the purpose of this study prevalence and incidence data were calculated for the adult onset MS population aged 15 and above. In the Highland council, people aged 0-14 comprised 15.7% of total population (37044), so including those people in the analysis could lead to an underestimation of the adult-onset MS prevalence and incidence.

The Argyll and Bute region (population: 87130 inhabitants; 43811 women) was not included in this epidemiological study because this area is covered by Glasgow and Clyde health board. As there is a Health and Social Care Partnership between Argyll and Bute Council and Glasgow area, those patients are not routinely referred to Raigmore hospital.

3.3. Ascertainment and recruitment method

Prevalence data was obtained from the MS database available at Raigmore hospital. Incidence data was obtained from the prospective hospital MS register and compared with the Scottish incidence MS register. Diagnosis was verified by reviewing medical records and the list of recently diagnosed MS patients.

3.3.1. Prevalence

Prevalence data were used for case ascertainment of patients alive and resident in the study area on the prevalence day (1st June 2017). The Raigmore Hospital MS database is usually used by the MS specialist nurses to register the whole MS population under the care of the MS service. The database has been used for clinical and assistance purposes for several years since 2001. Data included in the database are name, Community health index (CHI) number, date of birth, sex and year of diagnosis of MS patients, among other variables. However no clinical data was available regarding MS subtypes. This database was the first approach to estimate the prevalence of MS in the NHS Highlands. The MS database also included information about deceased patients and for those MS patients who moved to/from other NHS areas in the last years.

3.3.2. Incidence

Data sources used to ascertain new cases included neurologist and rehabilitation outpatient clinics, MS clinical nurse specialist clinics, Raigmore hospital MS database, hospital records and laboratory and Pharmacy data. Incidence data was from MS diagnosis.

The Scottish Multiple Sclerosis Register National Report 2017 collected MS incidence data from Scotland (http://www.msr.scot.nhs.uk) and was used to identify the number of new MS cases seen in Argyll and Bute. This report provided information on all patients who were diagnosed by a Neurologist and had a confirmed diagnosis of MS from January to December 2016.

The MS Specialist Nurse registry from Raigmore hospital was used as the internal source of data. Each year, all new MS patients diagnosed at NHS Highlands are included in the MS register. Hospital incidence data was compared with the data available at the Scottish MS register. Demographic data about new MS patients is available, and prospective data can be analysed. However, no data was available regarding the number of paediatric MS cases seen below the age of 15 years.

3.4. Data collection

Community health index was used to identify each new MS patient. The CHI is a code composed by 10 digits, and the first 6 digits represent day, month and year of birth. For the prevalence study, collected data included age, sex, area of residence, and also mortality data. Collected data for incident new MS patients included date of birth, sex, dates of symptom onset, first clinical assessment and diagnosis; time to diagnosis, nature of first symptoms, and the type of DMT used in the first year of diagnosis. Time to diagnosis was calculated in months.

3.5. Diagnostic criteria

The 2010 McDonald criteria for the diagnosis of MS (Polman, 2011) were used for those incident patients diagnosed between 1st January and 31st December 2016.

3.6. Statistical methods

Crude prevalence and age/sex specific prevalence were calculated for MS population aged 15 and older for 2017. Crude incidence and age/sex specific incidence for 2016 and the 95% confidence intervals (CI) were also calculated. The incidence was defined as the number of new MS cases per population at risk in a given time period (2016).

Mortality rate and cause-specific mortality rates were estimated. Cause-specific mortality rate was defined as the number of deaths attributable to a specific disease (MS) in a population over a given time period (usually expressed per 100,000 persons per year).

Quantitative variables were described using mean ± standard deviation; range and median was also calculated. ANOVA and t-tests were also performed to evaluate differences by sex, when needed. Statistical analysis was done by using EXCEL and EpiInfo (EpiInfo 2020;http:www.cdc.gov/epiinfo).

3.7. Ethics

A formal research ethics approval was not required as this project was an audit project and audit data were de-identified.

4. Results

4.1. Prevalence of multiple sclerosis in the NHS Highlands

In total, 745 MS patients were registered in the MS hospital database and were actively followed up at the Neurology and/or MS Nurse Specialist clinics. People on the database that were recorded as deceased included 120 patients.

4.1.1. Prevalence analysis

Regarding the 745 patients, the 75.4% (562 cases) were females, and 24.5% (183) were males. Female to male ratio was 3:1 and there were 307 females per 100 MS males. The mean age of the population was 54.1 ± 14.1 years [range: 15-95 years], and there were no significant differences in the mean age by sex.

The mean age at diagnosis was 45.45 ± 13.27 years [range: 14-84 years]. The mean number of years of evolution since the diagnosis was 8.5 years ± 4.6 years [range: 1-18 years; median, 9 years].

The estimated crude prevalence of MS for the Highland council total population was 316.7 cases per 100,000 inhabitants (95% CI: 295 to 340). However this may be an underestimation, as the population aged 14 and lower were 37,044 and no cases of childhood MS were included in this study. A more accurate estimation is the crude prevalence for adult-onset MS population aged 15 and above which was 376 per 100,000 population (95% CI: 354-399). Crude and age/sex specific prevalence of multiple sclerosis in the Highland Health and Social Care Partnership area for 2017 is shown in **Table 1**.

Table 1
Crude and age/sex prevalence of multiple sclerosis in the Highland Health and Social Care Partnership area, 2017.

	Women			Men			Total		
Age, years	Cases, n	Population, 2017	Crude prevalence per 100,000 (95% CI)	Cases, n	Population, 2017	Crude prevalence per 100,000 (95% CI)	Cases, n	Population, 2017 CCriu	
15-19	2	5944	33.6 (11-102)	1	6634	15 (3-68)	3	12578	23.8 (10-60)
20-29	21	11612	180 (118-276)	4	12444	32 (13-83)	25	24056	104 (70-153)
30-39	79	13722	575 (462-717)	23	13210	174 (116-261)	102	26932	378 (312-460)
40-49	122	15987	763 (640-910)	36	14444	249 (180-345)	158	30431	519 (444-606)
50-59	137	18777	729 (618-862)	53	17881	296 (227-387)	190	36658	518 (450-597)
60-69	114	16339	697 (581-837)	39	15941	244 (179-334)	153	32280	473 (405-555)
70-79	64	11953	585 (307-5000)	22	10634	206 (137-313)	86	22587	380 (308-470)
80-89	19	6186	307 (197-479)	5	4387	114 (49-267)	24	10573	226 (153-338)
90-99	4	1429	280 (109-718)	0	612		4	2041	196 (79-503)
TOTAL	562	101949	551 (514-591)	183	96187	190 (169-215)	745	198136	376 (354-399)

After direct standardisation to the European Standard Population (ESP, 2013), prevalence of MS in adults aged 15 and older in the Highland Health and Social Care Partnership area was 363.6 per 100,000 population (95% CI: 339.4-392.4. The Age-sex standardised prevalence for women aged 15 and older was 551.26 (95% CI: 491.12-580.60), and for men aged 15 and older 183.82 (95% CI: 156.45-210.70).

4.1.2. Mortality

Mortality data was available from the historical database section of 120 MS deceased patients. 70.8% (85 cases) were females. Regarding annual mortality data, there were 7 death cases in 2014; 10 in 2015; and 9 cases in 2016.

The estimated mortality rate for the year 2016, and as per the MS population, was 8 cases per 1000 MS patients. Cause-specific mortality rate was 3.6 MS deaths per 100,000 inhabitants in 2016.

4.2. Incidence of multiple sclerosis in the Highlands

4.2.1. Incidence data

During the year 2016, 490 new patients having a confirmed diagnosis of MS were included in the MS Register in Scotland. Approximately 10% (47 cases) were patients diagnosed in the whole Highlands region. 36 incident cases corresponded to the Highland geographical area covered by Highland Health and Social Care Partnership and were analysed specifically.

In the whole Highlands region in the year 2016, the MS Scottish register reported an overall MS annual incidence per 100,000 inhabitants of 11.6. However, the overall annual incidence in the Highland Health and Social Care Partnership area was even higher: 14.4 cases per 100,000 inhabitants (95% CI: 10.08-19.94); and the incidence in the group of population aged 15 and above was 18.2 per 100,000 inhabitants (95% CI: 14-24). The 2016 crude incidence in Argyll and Bute Health and Social Care Partnership region was lower 12.6 (95% CI: 7-22).

Annual incidence was compared with the overall annual incidence per 100,000 population in Scotland which was 8.6. The highest incidence in Scotland was 18.56 and was recorded in Orkney and the lowest incidence was 6.14 in the NHS Borders.

The age-specific distribution regarding the number of new cases and the age/sex specific incidence in the Highland Health and Social Care Partnership area in 2016 is shown in **Table 2**. After direct standardization to the ESP, 2013, standardised incidence in the Highland Health and Social Care Partnership area including age 0-14 was 16.61 (95% CI: 11.1-22.1), whereas standardised incidence in the population aged 15 and older was 19.58 (95% CI: 13.1-26).

Table 2
Age-sex specific crude incidence per 100,000 inhabitants in the Highland Health and Social Care Partnership area, 2016.

Women			Men		Total	
Age, years	Cases	Incidence (95% CI)	Cases	Incidence (95% CI)	Cases	Incidence (95% CI)
15-19	1	16.6 (3-65)	0		1	7.8 (0-30)
20-29	6	50.9 (21-105)	0		6	24.8 (10-51)
30-39	9	66.6 (33-122)	1	7.7 (1-36)	10	37.8 (19-67)
40-49	10	60.9 (31-108)	2	13.4 (3-43)	12	38.3 (21-65)
50-59	4	21.6 (7-51)	1	5.63 (1-26)	5	13.7 (5-30)
60-69	2	12 (2-39)	0		2	6.1 (1-20)

4.2.2. Demographic and clinical data of incident cases

36 incident new MS cases were registered in 2016 in the Highland Health and Social Care Partnership area. There were 32 females (88.8%) and 4 males (11.1%). The mean age at diagnosis was 40.5 ± 12.1 years [range: 15-67] and no differences were detected by sex. Regarding MS subtypes, 82.4% (32) were categorized as relapsing MS, and 17.6% (4) as progressing forms (1 primary progressive MS and 3 secondary progressive MS patients) of MS at the time of the diagnosis.

Initial symptoms/syndrome at presentation were: poor balance and gait ataxia, 1 case (2.7%); fatigue and poor balance, 1 case (2.7%); hemisensory syndrome, 2 cases (5.5%); lower limb weakness, 9 cases (25%); optic neuritis, 7 cases (19.4%); and sensory symptoms, 16 cases (44.4%).

4.2.3. Time to diagnosis

The mean period of time from symptom-onset to diagnosis of multiple sclerosis was 38.8 ± 43.2 months [range: 2-193 months; median: 22 months]. The mean period of time between first symptom onset and the assessment at the Neurology clinic was 28.3 ± 44.4 months [range: 1-192 months; median: 9 months]. The mean period of time between the first assessment at Neurology clinic and the diagnosis was 10.5 ± 13.7 months [range: 1-49 months; median: 4 months].

A significant correlation (Spearman coefficient: 0.34; $p = 0.04$) between age and time to MS diagnosis from onset was observed. No

significant differences were observed in the period of time "initial symptoms-to-diagnosis" by sex; however there was a trend to a shorter period of time to get the diagnosis in females (36.5 vs 54.2 months).

4.2.4. Use of DMTs

19 patients (52.8%) started a DMT during the first year of diagnosis: dimethyl fumarate, 9 cases (25%); glatiramer, 4 cases (11.1%); interferon, 4 cases (11.1%); natalizumab, 1 case (2.7%); alemtuzumab, 1 case (2.7%). Three patients switched medication due to tolerability issues during the first year of follow up. 47.2% of incident patients (17/36) did not take any DMT during the first year after the diagnosis, and the reasons are summarised in **Table 3**.

5. Discussion

The 2017 Highland Health and Social Care Partnership area prevalence data is higher than the prevalence found in 2009 in Shetland (305 cases per 100,000 inhabitants), and Aberdeen (237 per 100,000 inhabitants), and slightly lower than the reported prevalence data in Orkney for 2009 (421 per 100,000 inhabitants) (Visser et al., 2012).

An increase in the number of MS cases has been seen in comparison with previous studies performed in other Scottish geographical settings (North-East and South) in the previous decades. In comparison with the Outer Hebrides prevalence study in the 80s (Dean, 1981), the Highlands's MS prevalence was 4 times higher in 2017. The overall prevalence in the area of Greater Glasgow in 2004 was 145 per 100,000 inhabitants (Murray et al., 2004). In the Lothian and Border Health Board regions of south east Scotland, epidemiological studies from 1998 showed a prevalence of 203 per 100000 population in Lothian region and 219 in the Border region (Rothwell and Charlton, 1998).

In the General Practice Research database (GPRD) study, the estimated prevalence of MS in UK in 2010 was 203.4 per 100,000 population and 6003 new cases were diagnosed that year (9.64 per 100,000/year) (Mackenzie et al., 2014). The prevalence of MS cases recorded in the GPRD database increased by about 2.4% per year reaching 285.8 per 100,000 in women and 113.1 per 100,000 in men by 2010. These data support the message that MS services should be expanded with more MS nurses, neurologists, and physiotherapy and neuropsychology specialists.

The average age at diagnosis in the Highlands incident MS cases is comparable to that reported in UK; however the incidence was higher than the observed in the whole UK. Indeed latitude has been associated with higher MS incidence, and a linear regression model recently predicted an increase in the average incidence of MS of 1.31 cases/100,000 person years per increase in degree latitude in Scotland (McDonald et al., 2019).

It is also noticeable an increase in the number of new MS patients diagnosed in the Highlands through the years (Kearns et al., 2019). Data from the Scottish MS register showed that there has been an increased trend regarding the number of people with a new diagnosis of MS in the Highlands from 2010 to 2016, and the number of incident cases ranged from 23 (2011) to 45 (2014), and 46 (2016) (http://www.msr.scot.nhs.uk). This fact can be explained by several factors including a true increase in MS incidence, and also other factors such as an increase in early diagnosis rate, an easy access to MRIs and the establishment of a regular MS service. However an evaluation over longer periods of time is needed before starting to look at changes in diagnostic capacity. The increase in cases over time probably reflects a gradually better detection and diagnosis as occurred in other health boards in Scotland (Donnan et al., 2005).

Table 3
Reasons for not taking DMTs in new MS patients – 2016 incident cases.

Causes	n	%
Not keen to use traditional pharmacological therapy	4	23.5
Progressive MS in absence of identified relapses	4	17.6
Planning pregnancy	3	17.6
Mild MS symptoms	3	17.6
Active neoplasia	1	5.8
Interested in autologous stem cell transplantation	1	5.8
Waiting list	1	5.8

The time gap between symptom onset and diagnosis was moderate, and a window opportunity to reduce delayed time to diagnosis was identified. Differences in MS subtypes and presentation may explain in part the wide range of time observed. Plans to increase awareness and a quicker referral system from GPs to Neurology service are potential ways to reduce diagnostic delays.

The proportion of patients taking DMTs was slightly lower than observed by O'Connell (2017) in Northern Ireland; there, two thirds of MS patients were on DMTs. However in a British Columbia review from an older cohort (1991-2008) around one third of incident MS patients filled a prescription for MDT within 3 years of diagnosis (Kingwell, 2015).

The decision-making process for starting, switching, and/or stopping DMTs have become more complex as the number of DMTs has increased in clinical practice. The field of MS treatment is rapidly changing and new DMT guidelines are being published (Rae-Grant et al., 2018). "Time matters in multiple sclerosis" is a therapeutic strategy based on proactive monitoring and shared decision-making in MS. Important key components include early diagnosis and early access to treatment (Giovannoni et al., 2016). Data from the Danish MS registry showed that patients who started treatment with DMTs later reached an EDSS score of 6 more quickly compared with patients who started early (Chalmer et al., 2018).

Therapeutic inertia is another aspect to be improved. This concept has been defined as the lack of treatment initiation or escalation when there is evidence of disease activity, based on clinical course and neuroimaging markers (Saposnik et al., 2016). Physician and patient–based therapeutic inertia should be identified and addressed. In this paper we report valuable information regarding patient-based therapeutic inertia within the first year of MS diagnosis, although the small size of our sample may limit the generalisation of these findings. A group of patients declined DMT due to volition, either because they had mild symptoms or did not want to use a pharmacological intervention; however the rest did not start a DMT for other reasons (contraindication in pregnancy or cancer or because of being ineligible for a DMT at the time the study was done). Other factors underlying declining to start DMT that need further elucidation in the future include the onset type and clinical presentation, age, sex, and education level of the patients.

The revised McDonald clinical criteria for the diagnosis of MS have been recently published in 2018 (Thompson et al., 2018). Patients with a previous diagnosis of clinical isolated syndrome who had positive oligoclonal bands are now considered as having MS according to the new MS diagnostic criteria. This fact may have an impact regarding a potential increase in MS incidence that should be addressed in future studies. As a consequence of changes in diagnostic methods, people with MS may be diagnosed earlier if gaps in referrals are adequately addressed. However, heterogeneity in symptoms presentation may lead to differences in how the diagnostic pathway proceeds.

Further MS prevalence studies should cover all surgeries and GPs in the Highlands. There are some concerns about the fact that MS patients with advanced disease or secondary progressive MS are not routinely followed up at MS clinics, and the real prevalence could be even higher than found. Letters requesting information about MS patients (and MS subtypes) will be sent to all surgeries and GPs in a second MS prevalence project. This will give us probably a more accurate census of the prevalence of MS in the Highlands. There is also a lack of information regarding infantile MS, and paediatric cases should be included in prospective incidence and prevalence studies.

Conclusions

Prevalence and incidence of MS in the Highlands has increased in the last 50 years. This fact reflects several factors including differences in studies over time, improved diagnostic methods (routine use of MRI and CSF analysis for oligoclonal bands), and also a true increase in prevalence due to improved survival, higher incidence or a result of migration. There is an increasing population living longer with MS, and this fact has important implications for resource allocation for MS in the NHS Highlands. A significant proportion of recently diagnosed MS patients were not keen to start with a DMT in the first year of diagnosis.

Credit author statement

Francisco Javier Carod Artal's individual contributions:

Conceptualization; Data curation; Formal analysis; Methodology; Roles/Writing - original draft preparation; Writing - review & editing.

Declaration of Competing Interest

Dr Carod-Artal has participated in advisory boards and/or received travel grants from Biogen, Genzyme-Sanofi, Merck, Novartis, Roche, and Teva.

However Author does not have any specific conflict of interest related to this specific paper and research.

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