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Incidence of multiple sclerosis in the Republic of Ireland: A prospective population-based study

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ABSTRACT

Background: Multiple sclerosis (MS) incidence and prevalence is increasing worldwide, with a disproportionally higher rate in women. Recent studies have questioned the presence of a latitudinal gradient in Europe. Ireland is a high prevalence country for MS with a previously reported North-South gradient making it ideal to further explore this concept.

Objectives: In this study we prospectively determined the incidence rate of newly diagnosed MS in Ireland over a 12-month period and demonstrated the presence of a North-South gradient.

Methods: A national prospective population-based observational study was performed to ascertain all new cases of MS diagnosed from 1st March 2014 – 28th February 2015 in the Ireland. Within the main study there was a smaller nested cohort study to explore clinical outcomes with a view to future prospective follow-up of this cohort. Sources of case ascertainment included neurologists, MS nurse specialists and MS support services. The Irish census 2011 was used to obtain population statistics and the incidence rate was age-standardized to a European Standardised Population (ESP 2011). The North-South gradient was assessed, by comparing incidence rates between northern and southern counties.

Results: 292 patients fulfilled the inclusion criteria equating to an age-standardised incidence rate (A-SIR) of 6/100,000 (95% CI: 5.3–6.6); for women the rate was 8.7/100,000 (95% CI: 7.7–9.6) and for men 3.3/100,000 (95% CI: 3.0–3.7). The female to male sex ratio was 2.7:1. Mean age at diagnosis amongst the RRMS group was 37 years (SD: 9.6) and 55 years (SD: 7.7) in the PPMS group; there were no gender differences associated with age of diagnosis. Onset was progressive in 10% of cases. A significant difference was seen in incidence rates between the northern region (A-SIR: 9.6×10^{5}, CI: 6.9–12.3) and the southern region (A-SIR: 5.1×10^{5}, CI: 3.8–6.3) (Z-score =3.34, $p < 0.05$). Amongst the nested cohort (n=113) mean age at symptom onset in the RRMS group (n=106) was 34 years (SD: 8.7) and 50 years (SD: 11.8) in the PPMS group (n=7). The female to male sex ratio was 3.5:1. Eighty percent had started or were due to start disease modifying therapy at time of review and 77% were taking supplemental vitamin D. Using the hospital depression and anxiety scale (HADS) mild to severe depressive symptoms were reported in 34% with no prior history of depression. Seventy-five percent were in full or part-time employment with 8% not working due to disability arising from their MS.

Conclusions: This is the first study to prospectively assess the incidence rate of MS in Ireland and shows that Ireland has a high incidence rate, comparable with the rest of the British Isles, with a persistent North-South gradient. The age of onset of relapsing remitting multiple sclerosis appears to be increasing over the last 20 years. It will be of interest to re-assess this population over time to see if increasing incidence rates, as well as improved survival, are driving the reported increases in MS prevalence.

1. Introduction

Multiple sclerosis (MS) is the commonest cause of non-traumatic neurological disability in young adults (Compston and Coles, 2008). It significantly affects quality of life and imposes a financial burden on patients, family and society (Karampampa et al., 2012). Epidemiological studies have informed our understanding of the interplay between genetic and environmental factors in disease pathogenesis (Ramagopalan et al., 2010). Secular temporal trends show evidence of an increasing incidence and prevalence of MS with disproportionate increase in women (Koch-Henriksen and Sorensen, 2010). Understanding the temporal dynamics of the epidemiology of

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MS is important, both for the delineation of potential aetiological factors, and for the planning of future service provision.

Ireland is a northern European country with a genetically relatively homogenous population. Consecutive epidemiological studies in Ireland dating back to the 1950's (Allison and Millar, 1954; McDonnell and Hawkins, 1998; McGuigan et al., 2004; Gray et al., 2008; Lonergan et al., 2011) have shown increasing prevalence over time and a persistent North-South gradient. To date incidence rates have been based on retrospective estimates from these prevalence studies and, as such, are open to recall bias. Thus the aim of our study was to carry out a prospective observational study to establish the incidence rate of MS in the Republic of Ireland for the first time. We wished to establish if this rate was comparable to other recently published studies from the British Isles (Mackenzie et al., 2014; Balbuena et al., 2016; Simpson et al., 2015) and if there was a persistent North-South gradient.

2. Materials and methods

2.1. Study design

This was a prospective, population-based, observational study carried out in the Republic of Ireland over a 12-month period from the 1st March 2014 to 28th February 2015. Within this main study there was a smaller nested cohort study, in which participants provided more detailed clinical data with a view to a prospective follow-up of this cohort.

2.2. Study population

The Republic of Ireland, situated between latitude 51°5 and 55°5 north, covers an area of 70,283 km^2. In the 2011 census (http://www.cso.ie), Ireland's population was 4,581,269 (2,268,698 men and 2,312,571 women), a population increase of 1.6% since the prior census of 2006. There are a relatively few neurologists (1/140,000 population) in Ireland with a long record of collaborative research in the epidemiology of a number of neurological conditions.

2.3. Ascertainment & recruitment methods

Multiple data sources were used to ascertain cases including all consultant neurologists, MS clinical nurse specialists (CNS), MS Ireland (a patient support organisation), MS support nurses (pharmaceutical sponsored) and participant self-referral. Letters and e-mails were regularly sent to all consultant neurologists and MS CNS in both public and private hospitals throughout the country and presentations were given regularly at local meetings. The study was advertised on the MS Ireland webpage and written information was sent out to each local MS society branch. Full written informed consent was obtained from each participant prior to any study procedures.

2.4. Data collection

Data collected for each participant included a unique code composed of date of birth, sex, initials and county of residence (to avoid duplication of cases from multiple sources), diagnosis and preferred method of contact by the study team. If a patient wished to be included, but not contacted by the study team, the case had to be confirmed and referral completed by their treating consultant neurologist to ensure they met with the inclusion/exclusion criteria.

2.5. Inclusion Criteria

Participants were included in the study if they met with the 2010 McDonald (Polman et al., 2011) criteria for diagnosis of MS made between 1st March 2014 and 28th February 2015. Referrals were also accepted for patients diagnosed with clinically isolated syndrome (CIS) who agreed to be contacted at the end of the study period to assess if they had converted to MS by the 2010 McDonald criteria.

2.6. Exclusion criteria

Participants were excluded if they did not meet the McDonald 2010 criteria over the study period or if the diagnosis could not be confirmed by the study team or their treating neurologist. The clinical course of participants' MS was defined using the recently published clinical course guidelines (Lublin et al., 2014).

2.7. Nested cohort study

In a nested cohort study, all consenting participants had a more detailed clinical assessment including full medical history and examination. A questionnaire aimed to determine family history and potential environmental factors including smoking history, and preceding illnesses was completed. Neuropsychiatric assessment included the Hospital Anxiety and Depression Scale (HADS) (Snaith, 2003; Honarmand and Feinstein, 2009). Quality of life and disease impact was assessed by the Multiple Sclerosis Impact Scale (MSIS-29) (Hobart et al., 2001). If it was not possible to carry out an assessment in person, relevant questionnaires were posted out to the patient and detailed history was gathered over the phone after the patient had provided informed consent in writing. The telephone EDSS (Lechner-Scott et al., 2003) was used to assess level of disability.

2.8. Statistical methods

The most recent Irish census of 2011 was used to obtain population statistics (http://www.cso.ie). The incidence rate was age-standardized to a European Standardised Population (ESP 2011) with 95% confidence intervals. North-South differences in population were compared using a Z value, where Z is a standard normal deviate. Quantitative variables were described using mean ± standard deviation (SD) or median and range. All tests were carried using SPSS version 20.

2.9. Ethical approval

Full ethical approval was received from the St Vincent's University Hospital Ethics and Medical Research Committee.

3. Results

3.1. Study population

Of the 391 patients referred over the 12-month study period, 278 (71%) were from hospital sources, 27 (7%) from MS Ireland, 71 (18%) from pharmaceutical sponsored support nurses and 15 (4%) were self-referrals. Ninety-nine referrals were excluded (48 patients were referred by more than one source, 27 had clinically isolated syndrome, 8 had a diagnosis other than MS and 16 were outside the study time window). There remained 292 unique incident MS cases fulfilling all the inclusion & exclusion criteria. Of the whole cohort (n=292) onset was progressive in 29 (10%) cases. Mean age at diagnosis amongst the RRMS group was 37 years (SD: 9.6) and 55 years (SD: 7.7) in the PPMS group; there were no significant differences in age at diagnosis by sex.

3.1.1. Incidence rates

Age and sex-specific crude incidence rates are outlined in Table 1. The MS age-standardized incidence rate (A-SIR) was 6.0/100,000 (95% CI: 5.3–6.6); for women the rate was 8.7/100,000 (7.7–9.6) and for men 3.3/100,000 (3.0–3.7). The female: male incident case ratio was 2.7:1. The geographical regions within Ireland and incidence rates per region are outlined in Fig. 1 and Table 2. A significant