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An all-Ireland epidemiological study of MND, 2004–2005

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Background and methods: We conducted an all-Ireland population-based prospective epidemiological survey of motor neurone disease (MND) using the Northern Ireland and Republic of Ireland MND registers to examine the incidence and prevalence of the disease over the period 2004–2005. *Results and conclusions:* Incidence of MND was 1.9 per 100 000 person-years and rates were comparable in both the north and south of Ireland. Prevalence of MND was 5.0 per 100 000 population. When compared with previous published surveys of MND performed in the Republic of Ireland over the last 10 years, rates of disease have remained relatively constant. When standardized to the 1990 US population, the incidence of MND in Ireland was found to be consistent with other European prospective surveys of MND.

Introduction

Motor neurone disease (MND) is a relatively uncommon neurodegenerative condition, and data generated from small populations may yield imprecise estimates of disease. Until recently, most epidemiological studies of MND have been prevalence-based. Disparate methodologies have prevented accurate comparisons to be made between countries and regions. To date, only eight prospective studies of MND exist in the literature [1–8]. However, the recent development of population-based registries in the Republic of Ireland, Scotland and parts of Italy and England [1–4,6–8] ensures that ongoing prospective data collection is maintained. In this study, we examined the incidence and prevalence of MND over the entire island of Ireland by combining the data from the prospective MND registers of both Northern Ireland (NI) and the Republic of Ireland (ROI) for the period 2004 to 2005. We compared these data with those of previous epidemiological surveys of MND in the ROI and with other population-based prospective surveys.

Methods

The populations of NI and the ROI are similar. The ROI has a younger population, with 39% less than 25 years and 11% more than 65 years compared with 35% and 13% for NI, respectively [9,10]. The large majority of both populations are white, 99% in NI and 94% in the ROI, as indicated by 2001 and 2005 data, respectively [9,10]; 2004 mid-year estimates for NI and the ROI found the total population to be 1 710 322 and 4 043 800, respectively [9,10]. Prevalence day for this survey was taken as 30 June 2005 and incidence was measured from 1 August 2004 to 31 July 2005. This study was approved by local ethics committees.

Cases were ascertained from the NI and the ROI MND registers. Six sources of potential ascertainment were used. These include: (a) the neurology departments, (b) the motor neurone disease associations (MNDA), (c) acute hospital trust coding system lists, (d) the regional pharmacy unit in the Royal Victoria Hospital, (e) general practitioners (GPs) and (f) neurophysiology departments. Once potential cases were identified from any source, medical notes were reviewed to confirm the diagnosis of MND. Patients were then approached for their consent. Before entry onto the disease register, patients were assessed clinically, where possible, in order to confirm their diagnosis and to assign a diagnostic category using the El Escorial Criteria (EEC). The original EEC [11] were used to classify patients into definite, probable, possible and suspected MND/amyotrophic lateral sclerosis (ALS). Patients with diagnoses of progressive bulbar palsy (PBP) and primary lateral sclerosis (PLS) were included and are categorized as 'possible' under the original EEC. Patients from all four EEC categories were included in the study.

The denominator for the calculation of prevalence and incidence was the 2004 mid-year estimates for the resident populations of NI and the ROI [9,10], as 2005 population data were not available for the ROI. Disease rates were also measured for the population greater than 15 years, as this group was considered to be the 'at-risk' population. MND is considered a disease of adult onset and excluding cases 15 years or younger reduces the likelihood of inclusion of genetic motor

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neurone diseases resembling MND; 95% confidence limits were calculated using the normal approximation of the Poisson distribution. Age- and gender-specific rates were also calculated. Employing the direct standardization method, comparison was made between other prospective incidence surveys of MND using the 1990 US population as the standard, as most of the studies were based on data from the 1990s. The search strategy used to collect relevant prospective articles of MND incidence is described in the Appendix.

Results

There were 32 incident cases ascertained in NI and 77 ascertained from the ROI, providing a total of 109 incident cases for all-Ireland. The age-adjusted male:female (M:F) ratio was 0.7:1 for NI, 1.7:1 for the ROI and 1.3:1 for all-Ireland. Incidence rates are presented in Table 1 and were comparable for both NI and the ROI. Mean age at onset was 63.2 (SD 11) years and was greater in females, 64.6 (SD 9.5) years, than in males, 62.1 (SD 12) years. Mean age at onset was lower in the ROI, 62 (SD 12) years, compared with NI, 66 (SD 8) years, but this was not statistically significant ($P = 0.2$). The mean age at diagnosis was 65.4 (SD 10.9) years and was greater in females, 66.1 (SD 9.4) years, compared with males, 64.6 (SD 12.8) years, but was not statistically significant ($P = 0.5$).

There were 83 prevalent cases ascertained in NI and 204 in the ROI, providing a total of 287 incident cases for all-Ireland. The age-adjusted M:F ratio was 1.2:1 for NI, 1.6:1 for the ROI and 1.5:1 for all-Ireland. Prevalence rates are presented in Table 1 and were almost identical for NI and the ROI. Mean age at onset was 58.1 (SD 14) years, being similar in females, 58.2 (SD 14.3) years, and males, 58.0 (SD 13.8) years, and with no difference noted between the ROI and NI. The mean age at diagnosis was 60.1 (SD 10.9) years and was similar in females, 60.4 (SD 13.8) years, and males, 59.9 (SD 13.5) years.

Table 1 Disease rates for MND

	NI	ROI	All-Ireland
Total IR (CI)	1.9 (1.2 to 2.5)	1.9 (1.5 to 2.3)	1.9 (1.5 to 2.3)
Female IR (CI)	2.2 (1.2 to 3.2)	1.4 (0.9 to 2.0)	1.7 (1.2 to 2.1)
Male IR (CI)	1.6 (0.7 to 2.4)	2.4 (1.7 to 3.0)	2.1 (1.6 to 2.7)
IR >15 years (CI)	2.4 (1.6 to 3.2)	2.4 (1.9 to 2.9)	2.4 (1.9 to 2.8)
Total PR (CI)	4.9 (3.8 to 5.9)	5.0 (4.4 to 5.7)	5.0 (4.4 to 5.6)
Female PR (CI)	4.5 (3.1 to 5.9)	3.8 (3.0 to 4.7)	4.0 (3.3 to 4.7)
Male PR (CI)	5.4 (3.8 to 7.0)	6.3 (5.2 to 7.4)	6.0 (5.1 to 6.9)
PR >15 years (CI)	6.1 (4.8 to 7.5)	6.4 (5.5 to 7.3)	6.3 (5.6 to 7.0)

CI, 95% confidence interval; IR, incidence rate per 100 000 person-years; PR, prevalence rate per 100 000 population.

Age- and gender-specific incidence rates were found to increase with age up to a peak, before falling off in the older age groups. Incidence rates peaked in males in the 65–69-year age group, with a second peak in the 80–84-year age group, while those of females peaked in the 75–79-year age group (see Table 2 and Fig. 1). Age- and gender-specific prevalence rates were also found to increase with age. However, prevalence rates in females peaked in the 70–74-year age group while those of males continued to rise (see Table 3 and Fig. 2). When standardized to the 1990 US population, the incidence rate for the 45–74-year age group in all-Ireland increased from 5.2 to 5.7 per 100 000 person-years and was found to be similar to other prospective population-based studies (see Table 4).

Discussion

The incidence of 1.9 per 100 000 person-years and prevalence of 5.0 per 100 000 population for all-Ireland is consistent with figures quoted in the literature over the last 30 years. However, prevalence figures are a less useful epidemiological marker of disease frequency in MND because of the short survival of patients with the disease. Incidence and prevalence are similar in both the north and south of Ireland, with no evidence of a north–south gradient. Traynor *et al*. [7] noted a higher incidence in the north-western counties of the ROI; however, the findings in this study do not support this. Unfortunately, cluster analysis software such as the spatial scanning statistic [13] could not be employed to further investigate this previous finding by Traynor *et al*. [7] because of the small numbers. As would be expected from the relatively small numbers, no obvious geographical trends were observed in this study, and although there was a notable reversal in the usual male to female ratio in the NI population, this may also be a consequence of the small size of the study cohort.

No change in incidence was observed in the ROI over a 10-year period from 1995 to 2005 when our results (1.9 per 100 000 person-years) were compared with those of Traynor *et al*. [7], who found an incidence of 2.1 per 100 000 person-years for the period 1995–1997. A stable secular trend of MND incidence for the ROI was also found by O'Toole *et al*. [6]. No change in prevalence was found in the ROI over the 10-year period when our results (5.0 per 100 000 population) were compared with those of Traynor *et al*. [7] who found a prevalence of 4.7 per 100 000 person-years. Similarly, a recent epidemiological study of MND by Forbes *et al*. [3], found that incidence had not changed over the period 1989–1998 in Scotland.

As might be anticipated, the mean age of onset of MND in patients in the incidence cohort was higher

Table 2 Age- and gender-specific incidence rates of MND, all-Ireland 2004–2005

Age ranges (years)	*N*	Females IR per 100 000	95% CI	*N*	Males IR per 100 000	95% CI	*N*	Total IR per 100 000	95% CI
0–14	0	0	0	0	0	0	0	0	0
15–19	0	0	0	1	0.45	0.01 to 2.5	1	0.23	0.01 to 1.28
20–24	0	0	0	0	0	0	0	0	0
25–29	0	0	0	0	0	0	0	0	0
30–34	0	0	0	0	0	0	0	0	0
35–39	1	0.46	0.01 to 2.58	1	0.47	0.01 to 2.60	2	0.47	0.06 to 1.68
40–44	0	0	0	1	0.49	0.01 to 2.75	1	0.24	0.01 to 1.36
45–49	1	0.54	0.01 to 3.0	5	2.72	0.88 to 6.36	6	1.63	0.60 to 3.54
50–54	6	3.59	1.32 to 7.81	1	0.59	0.01 to 3.29	7	2.08	0.83 to 4.28
55–59	3	1.94	0.4 to 5.68	8	5.15	2.22 to 10.15	11	3.55	1.77 to 6.36
60–64	8	6.43	2.77 to 12.68	10	8.13	3.90 to 14.96	18	7.28	4.31 to 11.50
65–69	8	7.49	3.23 to 14.75	16	16.03	9.16 to 26.05	24	11.61	7.44 to 17.28
70–74	11	11.76	5.87 to 21.04	9	11.18	5.11 to 21.24	20	11.49	7.01 to 17.76
75–79	10	12.41	5.96 to 22.84	4	6.95	1.89 to 17.79	14	10.14	5.54 to 17.01
80–84	0	0	0	5	13.82	4.48 to 32.37	5	5.17	1.67 to 12.07
85+	0	0	0	0	0	0	0	0	0
Total	48	1.65	1.22 to 2.19	61	2.14	1.64 to 2.75	109	1.89	1.56 to 2.29

IR, incidence rate; CI, confidence interval.

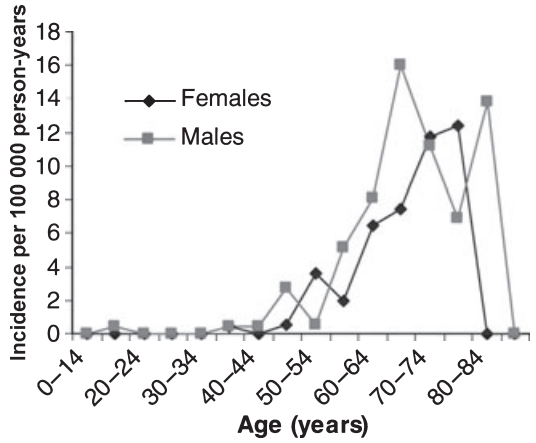

Figure 1 Line graph of age- and gender-specific incidence of MND for all-Ireland, 2004–2005.

than that in the prevalence cohort. This is consistent with the observation that that an older age of onset is associated with a poor prognosis [14]. By extension, a higher proportion of less severely affected patients with an earlier age of disease onset would be expected to be found in the prevalence study.

Consistent with the majority of epidemiological studies of MND, age-specific incidence was noted to decline in the older age groups and does not directly support the 'ageing theory' for MND. With the exception of studies from the Mayo Clinic (Rochester, MN, USA) [15,16], age-specific incidence and mortality rates in published studies repeatedly show a decline in MND after approximately 75 years in both males and females. It is noteworthy that the Rochester studies were retrospective and drawn from a relatively smaller population, and that the study did not disaggregate the age groups beyond 75 years. Moreover, a further study using Mayo Clinic records for Olmsted County, Minnesota in 2002 [17] suggested that age-adjusted incidence peaked in the seventh decade. Nonetheless, there is a theoretical risk in the elderly of poorer ascertainment. A study, based in Scotland, assessing MND patients over 80 years [18], found that these patients received fewer riluzole prescriptions and specialist neurological consultations. Bulbar-onset disease, which has a poorer prognosis [19], was also considerably more common among the elderly. It is possible therefore that these factors could contribute to reduced ascertainment in older age groups. However, the consistent finding of a decline in disease incidence in the very old in all published population-based studies suggests that the observation is robust. The decline in incidence in the very old may be explained by the death of the susceptible population, as MND is generally fatal in 3–5 years. Interestingly, peak incidence in both this study and that by Traynor *et al.* [7] occurred in the 65–69-year age group, suggesting no change over the last 10 years.

Prevalence was noted to decline sharply in females after the age group 70–74 years, while continuing to rise in males. Other studies have demonstrated that females are more likely to present with progressive bulbar palsy (PBP) [7,20,21] and that survival in this clinical subtype of MND is associated with a poorer prognosis [20]. It is possible that the decline in age-specific prevalence among older females is due to increased mortality from PBP, as has been also shown in a previous Irish study [7].

Table 3 Age- and gender-specific prevalence rates of MND, all-Ireland 30 June 2005

Age ranges (years)	*N*	Females PR per 100 000	95% CI	*N*	Males PR per 100 000	95% CI	*N*	Total PR per 100 000	95% CI
0–14	0	0	0	0	0	0	0	0	0
15–19	0	0	0	1	0.45	0.01 to 2.50	1	0.23	0.01 to 1.28
20–24	0	0	0	0	0	0	0	0	0
25–29	2	0.92	0.11 to 3.31	0	0	0	2	0.46	0.06 to 1.65
30–34	2	0.9	0.11 to 3.24	4	1.82	0.50 to 4.65	6	1.36	0.50 to 2.95
35–39	1	0.46	0.01 to 2.58	3	1.4	0.29 to 4.09	4	0.93	0.25 to 2.38
40–44	4	1.93	0.53 to 4.95	7	3.46	1.39 to 7.12	11	2.69	1.34 to 4.81
45–49	8	4.31	1.86 to 8.50	8	4.36	1.88 to 8.58	16	4.33	2.48 to 7.04
50–54	11	6.58	3.28 to 11.77	14	8.28	4.53 to 13.90	25	7.43	4.81 to 10.97
55–59	10	6.48	3.10 to 11.91	23	14.82	9.39 to 15.13	33	10.66	7.34 to 14.95
60–64	10	8.04	3.85 to 14.79	35	28.46	19.83 to 39.59	45	18.2	13.27 to 24.34
65–69	20	18.72	11.44 to 28.91	21	21.04	13.03 to 32.16	41	19.84	14.24 to 26.91
70–74	29	30.1	20.76 to 44.52	16	19.88	11.37 to 32.39	45	25.86	18.86 to 34.59
75–79	13	16.13	8.59 to 27.59	15	26.06	14.60 to 42.99	28	20.27	13.47 to 29.32
80–84	3	4.95	1.02 to 14.48	16	44.24	25.30 to 71.84	19	19.64	11.79 to 30.67
85+	3	6.22	1.29 to 18.18	8	38.9	16.78 to 76.64	11	15.99	7.98 to 28.61
Total	116	3.99	3.62 to 4.72	171	6	5.10 to 6.90	287	4.99	4.41 to 5.56

PR, prevalence rate; CI, confidence interval.

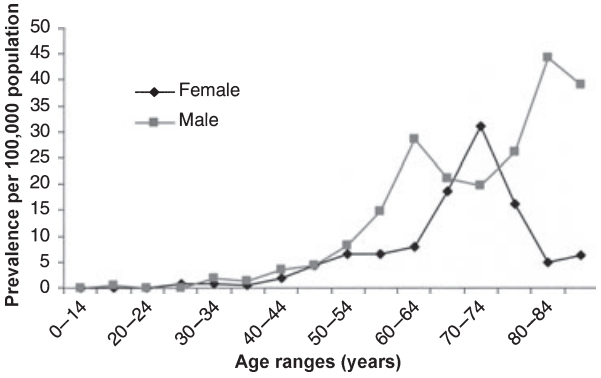

Figure 2 Line graph of age- and gender-specific prevalence of MND for all-Ireland, 30 June 2005.

Our results were similar to other prospective studies, providing no evidence of a latitudinal gradient within populations of European extraction. Standardizing rates from eight studies to the 1990 US population, it was found that rates tended to be lowest in southern European countries; however, the range of standardized rates was reasonably narrow and confidence intervals overlapped across studies, implying no significant difference. The original EEC [11] were employed in all studies except two, including all four diagnostic categories as well as cases of primary lateral sclerosis. The study from Western Washington state [5] excluded cases of primary lateral sclerosis while the study from north-western Italy [8] was most restrictive, including only

Table 4 Incidence (per 100 000) of MND from prospective published surveys 1990–2004

Country/region	Study period	No. cases	Crude incidence rates (95% CI)	Adjusted incidence for the 45–74-year age group[a]	Male:female ratio	Ref.
Ireland	1995–1997	231	2.1 (1.8–2.4)	6.3 (4.6–7.9)	1.4:1	[7]
Ireland	2002–2004	465	2.0 (1.9–2.2)	5.7 (4.2–7.2)	1.4:1	[6]
Scotland	1989	114	2.2 (1.8–2.7)	5.2 (4.0–6.3)	1.2:1	[1]
Scotland	1989–1998	1226	2.4 (2.2–2.6)	5.5[b] (5.0–6.0)	1.2:1	[3]
Nova Scotia, Canada	2003	21	2.2	n/a	2.0:1	[12]
North-western Italy	1995–1996	221	2.5 (2.2–2.9)	5.4[b] (4.6–6.3)	1.2:1	[8]
Southern Italy	1998–1999	130	1.6 (1.2–1.9)	4.1[b] (2.6–5.7)	1.6:1	[4]
Lombardy, Italy	1998–2002	517	2.1 (1.2–3.2)	4.2[b] (3.4–5.1)	1.3:1	[2]
Western Washington State, USA	1990–1995	235	1.8 (1.3–2.4)	5.6 (3.7–7.4)	1.2:1	[5]
All-Ireland (current study)	2004–5	109	1.9 (1.6–2.3)	5.7 (4.5–7.0)	1.3:1	

[a]Adjusted to the 1990 US population.
[b]Taken directly from published article.
n/a, not available.

definite and probable cases and excluding primary lateral sclerosis and primary muscular atrophy. It can therefore be noted that compared with the other studies, MND incidence from the north-western Italian study [8] is likely to be an underestimate.

From current prospective epidemiological data it appears that MND frequency is stable within European populations. It is important that further epidemiological surveys adhere to robust methodologies, employing prospective incidence-based disease registers. The newly developed European incidence-based registry of MND (EURALS) [22] will facilitate the collation of data on European patients with MND. The provision of a pan-European registry will not only help provide large-scale accurate epidemiological data, but will also enhance recruitment for observational studies of risk and for enrolment in therapeutic trials.

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Appendix

Search strategy

Databases MEDLINE and EMBASE were chosen and a search was performed for all articles relevant to the topic 'prospective studies of incidence in MND'. Within MEDLINE, three separate searches were performed. The first set of searches pertained to the population under study. A search was made using the medical subject heading (MeSH) terms 'Amyotrophic lateral sclerosis' and 'Motor Neurone Disease' with subheading 'epidemiology'. Secondly, 'Amyotrophic lateral sclerosis', 'Motor neuron$ disease' and their abbreviations (ALS, MND) were searched for as keywords. All six separate searches were combined using the boolean operator 'OR'. The second set of searches pertained to the measurement of incidence. The MeSH term 'incidence' was searched for as was 'incidence' as a keyword. Both these searches were combined using 'OR'. Thirdly, a search was performed for the MeSH term 'prospective studies' as well as 'prospective' as a keyword and both were combined with 'OR'. Finally, all three sets of searches were combined with 'AND'. Because of reference searches of already acquired articles it was discovered that a small number of relevant articles were missing because the term 'prospective' had not been indexed or used in the title or abstract. The search was then redesigned excluding the use of 'prospective studies' or 'prospective' as a keyword. This yielded significantly more articles, all of which had to be searched separately. Nine articles that described prospective incidence studies of MND were found. A similar search strategy was employed for the EMBASE database and no further articles were found.

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