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Incidence and lifetime risk of motor neuron disease in the United Kingdom: a population-based study

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Abstract

Objective—To estimate the incidence and lifetime risk of motor neuron disease (MND) in a population-based sample in the United Kingdom.

Methods—We identified new cases of MND during the period 1990–2005 in the General Practice Research Database, which includes clinical information from more than 3 million Britons enrolled with selected general practitioners. Individuals with a first medical diagnosis of MND recorded in the database were considered incident cases of the disease. The positive predictive value of the computer-based diagnosis was estimated through review of a sample of medical records from potential MND cases.

Results—In the period 1990–2005, 830 new cases of MND were identified. Age-standardized incidence of MND was 2.6 per 100,000 persons per year in women (95% confidence interval (CI) 2.3, 2.8) and 3.9 in men (95% CI 3.6, 4.3). Incidence for both sexes peaked at age 75–79. The rate of MND in men was 54% higher than in women (95% CI 33%, 77%). The lifetime risk of MND, adjusting for competing causes of death, was 1 in 472 (2.1 per 1000) in women and 1 in 350 (2.9 per 1000) in men. No increase in MND incidence over time was apparent.

Conclusion—In this population-based database, we found that MND incidence is higher in men than women, peaking in both sexes at age 75–79.

Keywords

motor neuron disease; incidence; lifetime risk

Introduction

Motor neuron diseases (MND) are a group of neurodegenerative disorders of unknown etiology, characterized by the selective death of upper and lower motor neurons in the central nervous system [1]. Reported incidence rates of MND varies between 0.6 and 2.4 per

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Conflict of interest

We have no conflict of interest

100,000 persons per year in different populations, without displaying a clear geographical pattern [2]. Discrepant rates across studies could be the consequence of different methodological approaches, including variations in case ascertainment and the use of diverse diagnostic criteria [3]. In fact, several population-based studies conducted in Europe using similar methodology have consistently provided incidence rates around 2 cases per 100,000 persons per year [4–8].

Still, significant controversies remain about the epidemiology of MND. Although most studies suggest that MND incidence peaks around age 75–79, decreasing afterwards [9], it is not clear whether this is due to a real decrease in incidence or to underascertainment of MND in older individuals. Additionally, the limited number of cases among the old reduces the stability of incidence estimations in those age groups. Computerized clinical databases including information from large population-based samples for long periods of time, large enough to provide precise incidence estimates, can contribute decisively to clarify this question. No previous studies, however, have evaluated whether MND diagnoses in these databases are of high enough quality for epidemiologic research.

We used data from the General Practice Research Database (GPRD), a large computerized database in the United Kingdom, to provide new insights into these questions. Specifically, our objective was to estimate, in the GPRD, the overall incidence of MND during the period 1990–2005, determine the lifetime risk of developing MND, and assess potential temporal trends in the incidence of this disorder.

Methods

Study population

We used the GPRD, a database containing computerized medical records on over 3 million people in the United Kingdom who are registered with selected general practitioner (GPs) [10–12]. In the United Kingdom, GPs are responsible for primary healthcare as well as for referrals to specialists and for hospital admissions (except in emergency situations). They record information on patient demographics (age, gender, weight, height), diagnoses, drug prescriptions, referrals and hospital admissions as well as some lifestyle information (e.g. smoking status). The recorded information on drug exposure and on diagnoses in the GPRD has been validated repeatedly and proven to be of high quality for pharmacoepidemiologic studies [12–14]. The GPRD is managed by the Medicines and Healthcare Products Regulatory Agency in the United Kingdom. The patients enrolled in the GPRD are representative of the British population with regard to age, gender, geographic distribution and annual turnover rate [11].

Physicians participating in the GPRD have agreed and been trained to record details on computer, in a standard manner, of their patients' health records including clinical and demographic information and to provide this information anonymously for research purposes. In addition, practices involved in the database agreed to provide anonymized copies of their patients' medical records to researchers to supply further clinical details relevant to the study. For the present analysis, only individuals older than 20 with at least one year of follow-up in the GPRD were included in the study population. Younger individuals were excluded since MND in that age group is rare and likely to be confused with neurodevelopmental disorders.

MND ascertainment

We identified all people in the GPRD who had a first diagnosis of MND at any time after the age of 20, during the years 1990 to 2005, in the computerized medical record. MND was defined as any code for amyotrophic lateral sclerosis, motor neuron disease, progressive

bulbar palsy, primary lateral sclerosis, or progressive muscular atrophy. The date of diagnosis was defined as the first occurrence of any of these diagnoses.

To determine the validity of the computer-based diagnosis of MND, we selected a random sample of 81 cases and requested their complete medical records for review. Sixteen records were not available because the patient had died (n=9) or had transferred out of the practice (n=7). One of the authors (GL), a neurologist with clinical experience in MND, reviewed the available medical records for the remaining 65 cases and, based on the available clinical information, decided whether a diagnosis of MND could be made or not. The diagnosis of MND was confirmed in 55 cases (85%, 95% confidence interval 74%–92%). The median difference in the date of diagnosis comparing computer and paper medical records was 0.5 months. Information included in the medical records was insufficient to apply the El Escorial [15] or the Arlie House criteria [16] for MND diagnosis. Among the 10 cases in which the diagnosis of MND could not be confirmed, 4 cases did not provide enough information supporting MND or an alternative diagnosis, 3 had cerebrovascular disease, 1 had siringomyelia, and 2 cases referred respiratory disease in their death certificate, without mention of MND.

We also reviewed the computer records for all MND cases to determine the date of first clinical symptoms compatible with MND. The average time between first symptoms and clinical diagnosis was 7 months.

Statistical analysis

Age and sex-specific incidence rates of MND were computed as the ratio of the number of new cases identified in the GPRD divided by the person-years of follow-up for age and sex-specific groups. Standardized rates were estimated using the European standard population and the 2000 United States (US) Standard population as reference [17]. In a secondary analysis, we estimated separately the incidence of MND variants (progressive bulbar palsy, progressive muscular atrophy, and primary lateral sclerosis) and typical amyotrophic lateral sclerosis. To estimate trends in the incidence of MND over time, we fitted a Poisson model, including age (in 5-year groups), sex and calendar year (first with calendar year treated as a continuous variable and then as a categorical variable with 4 year periods).

We summarized incidence rates separately for men and women by estimating an individual's average probability of being diagnosed with MND during her or his lifetime (lifetime risk). We computed the lifetime risk without adjusting for the existence of competing risks to increase comparability with other studies [18]. However, this measure is an overestimation of the true lifetime risk, since dying from other causes reduces the cumulative probability of developing MND in a population. Therefore, we also computed lifetime risk adjusted for competing risks [19–21], using mortality data in the United Kingdom for the year 2001 from the Office for National Statistics [22]. This methodology allows the estimation of age-conditional probabilities of developing a particular disease taking into account that individuals dying from causes other than the disease of interest cannot develop that disease in the future (as a consequence, the adjusted lifetime risk is lower than the non-adjusted value).

Results

Between 1990 and 2005, the GPRD recorded 830 new cases of MND (360 in women; 470 in men) during 22,492,571 person-years of follow-up (11,572,998 in women; 10,919,573 in men) in individuals older than 20 years.

The crude rate of MND was 3.1 per 100,000 persons per year in women, and 4.3 in men. The European-standardized rates (95% confidence intervals) were 2.6 (2.3, 2.8) in women and 3.9 (3.6, 4.3) in men (age-adjusted rate ratio of MND in men v. women: 1.54, 95% confidence interval 1.33, 1.77). Rates were similar using the 2000 US population as the standard: 2.6 (2.3, 2.9) in women, 4.0 (3.7, 4.4) in men. Age-specific incidence rates increased with advancing age, reaching a peak at age 75–79, both for men and women, and decreasing thereafter (table 1).

Of 830 cases, 105 (13%) were labeled as primary lateral sclerosis, progressive bulbar palsy or progressive muscular atrophy. Separate incidence rates of MND variants and of amyotrophic lateral sclerosis are reported in figure 1. The incidence of amyotrophic lateral sclerosis and variants of MND was higher in the 8th decade of life for both men and women, with an evident decrease of amyotrophic lateral sclerosis incidence later in life but an unclear trend in the incidence of MND variants.

No significant linear trends were found in MND incidence in the GPRD over time (*p* for trend: 0.35), though MND rates were significantly higher after 1994, year of publication of El Escorial diagnostic criteria, compared with the period 1990–1993 (*p*<0.001) (figure 2). Similar trends were observed for MND variants (data not shown).

The unadjusted cumulative lifetime risk of developing MND was 3.0 per 1000 in women and 5.1 per 1000 in men. After adjusting for competing risks, the lifetime risk was 2.1 per 1000 and 2.9 per 1000 in women and men, respectively, corresponding to 1 in 472 women and 1 in 350 men. Table 2 shows the cumulative risk of MND, adjusted for competing risks, at different ages in the GPRD. Most new cases of MND occurred after age 50 as shown by a small cumulative risk of developing MND before age 50 (0.2 per 1000 in both men and women) and a sharp increase afterwards.

Discussion

In this population-based study in the United Kingdom, the incidence of MND peaked at age 75–79, decreasing thereafter. The peak in the age-specific incidence curve suggests that MND is an age-dependent (highest incidence at a particular age) and not aging-dependent disease (higher incidence with increasing age). This finding is consistent with published reports from most population-based studies.

We also found that men had a higher incidence rate of MND than women during the entire study period (54% higher overall). Our findings do not support a recent theory that the traditional sex differences with respect to the incidence of MND may be disappearing [9]. In our population, the proportion of MND variants was 13%, which is similar to population-based registries [7, 8].

The estimated lifetime risk of developing MND was approximately 1 in 350 for men and 1 in 500 for women. These estimates are similar, though not directly comparable, to published MND proportional mortality in the United States population (1 in 350 in men, 1 in 450 in women) [23]. The lifetime risk of MND provides an appropriate summary of the incidence of the disease in a particular population, easily interpreted by policymakers, clinicians and the general public. In spite of having a relatively low incidence, the risk of MND over the lifetime is substantial. To our knowledge, no other estimates of lifetime risk of MND in a population-based sample have been previously published. The (unadjusted) lifetime risk of MND in the GPRD was similar to estimates from population-based studies in Ireland and Scotland [4, 6], though higher than in the Italian registries (see table 3 for a comparison of lifetime risk and incidence rates in the GPRD with previous published reports) [5, 7, 8].

Incidence rates of MND in the GPRD were similar to those reported from previous prospective studies conducted in Europe, including population-based registries (table 3). This provides reassuring evidence that there was not an important degree of misclassification in the ascertainment of MND cases. The estimated rates in the GPRD were comparatively higher for individuals older than 75 years. Two possible mechanisms could explain this finding. First, it is possible that previous studies did not ascertain all cases in older individuals. Second, the computer diagnosis of MND in the GPRD may have a lower specificity among older individuals, which would increase the number of false positives. For example, in the Piemonte and Valle d'Aosta Register for Amyotrophic Lateral Sclerosis, the proportion of false positives for MND among hospitalized patients was higher among individuals 70 and older (47%) than among younger patients (35%) [24]. In the GPRD, we estimated the positive predictive value of the computer-based diagnosis to be 85% both in individuals younger than 70 years and in older individuals.

We observed a decrease in the incidence rates of MND after age 80. This observation suggests that MND could be an age-dependent disease: there is an age of maximal susceptibility with reduced risk before and after that age. Still, our findings cannot exclude the possibility of MND as an aging-dependent disease (higher risk associated with higher age). First, case ascertainment in individuals older than 80 might be incomplete. Comorbidities could mask MND symptoms. Also, individuals with reduced life expectancy could be less likely to be referred to a neurologist and, therefore, receive a diagnosis of MND. Second, competing causes of mortality may result in fewer susceptible individuals attaining age 80 or later. Interventions that improve survival before age 80 could result in increased rates of MND afterwards.

The incidence of MND in the period 1990–2005 remained relatively stable except for lower rates in 1990–1993. This could be an artifact caused by underascertainment of MND cases in the initial years of recording. Nonetheless, the same quality control criteria have been applied through the entire follow-up. Another explanation for this difference could be an increase in the diagnosis of MND following increased awareness among health professionals and the general public, or due to changes in medical practice or diagnostic criteria. In fact, the El Escorial diagnostic criteria for MND were published in 1994 and this event could have led to increased awareness of the disease and better diagnosis. In a study conducted in Scotland, however, there was no comparable change in incidence in the period 1989–1998 [4]. Studies on the mortality of MND in Norway and the United States point to increased rates over time [25, 26], but our results and other incidence studies conducted over long periods of time do not support any trend [4, 27]. Changes in the reporting of MND in death certificates, and not a true increase in incidence, could explain the rise in mortality.

As discussed above, the main concern regarding the use of computerized databases for the study of MND is case ascertainment. We confirmed 85% of identified cases in a validation study. However, the actual validity of the computer diagnosis is expected to be higher because patients with a rapid clinical course towards death were less likely to be included in the validation study (once GPRD patients die, their medical records are no longer available to researchers) and more likely to have MND than other less severe neurological disorders. On the other hand, the characteristics of the British healthcare system (universal access, the GP as gatekeeper to the system and custodian of their patients' entire clinical information) make it unlikely that the frequency of false negatives, i.e. patients with MND not identified as such in the GPRD, is high. When considering the relative advantages and disadvantages of this particular computerized database, the GPRD, versus traditional studies, the probability of diagnostic errors (not large enough to introduce noticeable bias in epidemiologic analyses) needs to be weighed against the possibility of conducting a cost-efficient prospective study in a very large population during a long follow-up period.

In conclusion, our results support the hypothesis of MND as an age-dependent disease, and suggest that computerized medical records in the GPRD are appropriate for the epidemiologic study of MND.

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Figure 1.
Incidence rate of amyotrophic lateral sclerosis and of other motor neuron disease (progressive bulbar palsy, progressive muscular atrophy, and primary lateral sclerosis) in the General Practice Research Database (GPRD), by age and sex, 1990–2005
ALS: amyotrophic lateral sclerosis; PBP: progressive bulbar palsy; PLS: primary lateral sclerosis; PMA: progressive muscular atrophy

Figure 2.
Age-standardized incidence of all types of motor neuron disease by sex and study period,
General Practice Research Database, 1990–2005

Table 1
Age- and sex-specific incidence of amyotrophic lateral sclerosis, General Practice Research Database, 1990–2005

Age groups	Women				Men			
	Cases	Person-years	Incidence rate [†]	95% CI	Cases	Person-years	Incidence rate [†]	95% CI
20–24	1	875773	0.1	0.003, 0.6	0	874336	0	0, 0.4
25–29	1	1027210	0.1	0.003, 0.5	6	1014421	0.6	0.2, 1.3
30–34	2	1138466	0.2	0.02, 0.6	2	1150352	0.2	0.02, 0.6
35–39	3	1127653	0.3	0.05, 0.8	4	1157465	0.3	0.1, 0.8
40–44	5	1058582	0.5	0.2, 1.1	7	1095099	0.6	0.3, 1.3
45–49	18	1002187	1.8	1.1, 2.8	24	1034883	2.3	1.5, 3.5
50–54	26	953004	2.7	1.8, 4.0	26	976358	2.7	1.7, 3.9
55–59	27	859639	3.1	2.1, 4.6	50	872235	5.7	4.3, 7.6
60–65	44	742540	5.9	4.3, 8.0	66	732194	9.0	7.0, 11.5
65–69	52	694035	7.5	5.6, 9.8	74	640235	11.6	9.1, 14.5
70–74	63	653411	9.6	7.4, 12.3	81	540984	15.0	11.9, 18.6
75–79	64	568832	11.3	8.7, 14.4	72	406614	17.7	13.9, 22.3
80–84	32	438791	7.3	5.0, 10.3	40	255840	15.6	11.2, 21.3
85–89	18	270559	6.7	3.9, 10.5	13	119123	10.9	5.8, 18.7
90+	4	162316	2.5	0.7, 6.3	5	49434	10.1	3.3, 23.6
TOTAL	360	11572998	3.1	2.8, 3.4	470	10919573	4.3	3.9, 4.7

CI: confidence interval

[†] Per 100,000 person per year

Probability (per 1000) of developing motor neuron disease (MND) at different ages if free of MND at age in column 1, GPRD, 1990–2005. For example, the probability of developing MND in men before age 70 if free of disease at age 40 is 1.42 per 1000 (shadowed cell). Values are adjusted for competing risks using the method developed by Fay et al [19–21].

Table 2

Age	Risk of MND at age	MEN							
		30	40	50	60	70	80	90	
20		0.03	0.06	0.20	0.60	1.45	2.41	2.86	
30			0.03	0.17	0.58	1.43	2.41	2.86	
40				0.14	0.56	1.42	2.41	2.86	
50					0.42	1.31	2.32	2.79	
60						0.95	2.03	2.53	
70							1.30	1.89	
80								0.99	

Age	Risk of MND at age	WOMEN							
		30	40	50	60	70	80	90	
20		0.01	0.04	0.15	0.44	1.03	1.77	2.12	
30			0.03	0.14	0.43	1.03	1.77	2.11	
40				0.12	0.41	1.01	1.75	2.10	
50					0.30	0.90	1.66	2.02	
60						0.63	1.42	1.79	
70							0.88	1.30	
80								0.57	

Standardized incidence of motor neuron disease (cases per 100,000 person per year) in prospective register-based studies conducted in Europe, age-standardized to the European population. Studies ordered according to period of case ascertainment (from earlier to later).

Table 3

Region (ref.)	Years	Cases*	45–54 yrs M/F	55–64 yrs M/F	65–74 yrs M/F	45–74 yrs M/F	75–84 yrs M/F	Lifetime risk [†] M/F
Scotland [4]	1988–1998	1226	2.6/1.5	6.5/4.4	12.1/8.6	6.0/4.0	14.9/8.5	4.3/2.7
Piemonte, Italy [5]	1995–1996	221	2.3/1.6	7.7/4.6	10.3/8.4	5.9/4.1	9.3/3.0	3.5/2.1
Ireland [6]	1995–1997	231	3.0/2.8	8.7/5.4	11.1/9.9	6.8/5.2	13.3/6.7	4.7/2.7
Puglia, Italy [7]	1998–1999	130	2.2/1.5	5.4/2.3	10.6/5.2	5.0/2.6	5.2/1.8	2.5/1.2
Lombardy, Italy [8]	1998–2002	517	2.7/1.1	6.2/3.5	7.2/6.4	4.9/3.1	6.7/3.8	3.0/1.9
GPRD, UK	1990–2005	830	2.5/2.3	7.2/4.4	13.0/8.4	6.4/4.3	17.0/9.9	5.1/3.0

M/F: male/female. GPRD: General Practice Research Database

* Total number of motor neuron disease cases in the entire population

[†] Cumulative probability of motor neuron disease (per 1000) not adjusted for competing risks, estimated according to Greenland and Rothman [18].