The Scottish motor neuron disease register: a prospective study of adult onset motor neuron disease in Scotland. Methodology, demography and clinical features of incident cases in 1989

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Abstract
The Scottish Motor Neuron Disease Register (SMNDR) is a prospective, collaborative, population based study of motor neuron disease (MND) in Scotland. The register started in January 1989 with the aim of studying the clinical and epidemiological features of MND by prospectively identifying incident patients. It is based on a system of registration by recruitment from multiple sources, followed by the collection of complete clinical data and follow up, mainly through general practitioners. In this report the register's methodology and the demography and incidence data for the first year of study are presented. One hundred and fourteen newly diagnosed patients were identified in 1989 giving a crude incidence for Scotland of 2·24/100 000/year. Standardised incidence ratios showed a non-significant trend towards lower rates in north eastern regions and island areas.

The motor neuron diseases (MND) occur at any age but most of the childhood forms (spinal muscular atrophies) are familial, and a result of a mutation on the long arm of chromosome 5.[1] In contrast, although some forms of adult onset MND have a genetic basis,[2] with linkage to chromosome 21,[3] the vast majority are sporadic. Numerous diverse theories of aetiology have been summarised in recent reviews[4–6] but there is still no universally accepted cause or effective treatment. Amyotrophic lateral sclerosis (ALS), progressive bulbar palsy (PBP), and progressive muscular atrophy (PMA), the principal subtypes, are almost certainly clinical variants of a single disease[6] with the common underlying pathological finding of anterior horn cell degeneration. Primary lateral sclerosis (PLS), a much debated but probably true entity, may be a separate disorder.[7]

The incidence of MND may not be as static or as uniform as was once believed.[8] If the distribution of the disease in time and place is changing then this might provide clues to its cause. There is evidence for an environmental influence in the Western Pacific forms of MND which has largely been derived from epidemiological studies,[9][10] and together with the low concordance in twin studies,[11] suggests that factors other than genetic might be important in sporadic MND in developed countries.

A study design ensuring complete case ascertainment is of major importance when seeking putative environmental factors by studying variation of incidence in time and place. Clinical surveys from specialised centres are likely to be biased and death certificate data inaccurate. The Scottish Motor Neuron Disease Register (SMNDR) was established in January 1989 with the aim of prospectively studying the epidemiology of this disease in Scotland by registering and following up all incident cases presenting to medical attention. Scotland is a suitable country because it is geographically and demographically well defined; few patients are likely to get health care outside the country; almost all individuals are registered with a general practitioner (GP); a centralised medical records system means that medical records are transferred if the patient moves between areas or can be traced in the United Kingdom with the National Health Service Register; population denominators are well defined and, importantly, the number of cases coming to our attention every year is such that complete and detailed documentation is possible in all cases.

Scotland is in the north of the United Kingdom and covers an area of roughly 78 772 km^2.[12] The population estimate for 1989 was 5 090 700, 18% of whom were over 65 years.[13] The country is divided into nine regions, three island areas, 53 districts and 1211 postcode sectors and is served by 3041 GPs. Neuromedical services are provided by 19 consultant neurologists and four consultant clinical neurophysiologists who are likely to see most, but not all, patients with MND.

Methods
1) All consultant neurologists and neurophysiologists in Scotland agreed to collaborate and were the main source of case notification. They were requested to complete a simple registration form (table 1) which was forwarded to the study coordinators based at the Western General Hospital, Edinburgh, for inclusion on a centralised database. Collaborators were encouraged to register patients when the diagnosis of MND was first made so that suspected, as well as definite cases, could be followed up. The threshold of individual col-

Table 1 Registration form details

(Responses: yes, no, uncertain)
General principles:
Muscular weakness
Progressive history
Absence of sensory signs
Seen by a neurologist
Anatomical classification:
Bulbar signs
UMN bulbar signs
LMN bulbar signs
Limb signs
UMN limb signs
LMN limb signs
EMG performed?
Is there any suggestion of an alternative diagnosis?
Is there any associated disorder?
Is the patient aware of the diagnosis?
Date of onset
Date of diagnosis
Is the diagnosis definite/probable/suspected?

laborators with respect to the registration of suspected cases varied.

2) The two family care officers employed by the Scottish Motor Neurone Disease Association (SMNDA) offered patients the option of self-referral to the register.

3) In 1990 a letter was sent to all GPs in Scotland asking for details of any patients in their practice diagnosed with MND after 1 January 1989.

4) The information and statistics division of the Common Service Agency for the Scottish Health Service provided a list of all patients discharged from Scottish hospitals in 1989 coded by International Classification of Diseases (ICD) 9 as code 335 (anterior horn cell disease). The records of all patients older than 15 years, not already included on the register, were obtained and reviewed before inclusion.

5) A request was made to neuropathology departments for any patients diagnosed with MND at postmortem examination.

6) All death certificates for 1989 identified from the General Register Office for Scotland were examined when ICD-9 335 was recorded as the underlying cause of death or as a contributing factor. GP practice records with letters and summaries from hospital consultations were then requested from health boards.

After registration clinical details included in discharge summaries or outpatient correspondence and the reports of neurophysiological investigations were obtained to allow classification of MND subtypes based on clinical features (see below). After a patient's death the complete hospital and GP records were scrutinised and pathology reports obtained where available.

Patients were included on the register if the diagnosis of MND had been made or suggested for the first time after 31 December 1988. At registration, the patient's GP was informed of the aims of the study. Follow up of all patients was achieved mainly through GPs using a six monthly questionnaire. The questionnaire highlighted any revision of the diagnosis, any change of GP (to allow transfer of follow up), and simple clinical features such as difficulty with speaking or swallowing, limb weakness and the date of death. Collaborators,

informed of the study's progress by a monthly newsletter, were encouraged to send copies of follow up correspondence from hospital clinics. A paper file is maintained for each patient. A dBase IV computer system was used to construct a database for compiling features of key interest and permitting organised retrieval of data.

The 1989 population estimate for Scotland and its regions[13] (derived from the last population census in 1981) was used for the calculation of rates and standardised incidence ratios. Age specific incidence was calculated using age at diagnosis, usually in relation to the first admission to hospital for investigations. The significance of differences between the means for ages according to sex was examined using the Students t test. Age adjusted standardised incidence ratios (of observed to expected cases) were calculated for each of the nine regions and three island areas using the indirect method.[14] Confidence intervals (CI) were calculated using the confidence intervals analysis programme.[15]

DIAGNOSTIC CRITERIA

There are no universally accepted criteria for the diagnosis of MND. A subcommittee of the World Federation of Neurology (WFN) proposed a set of criteria for the diagnosis of ALS but these criteria are too complicated for general epidemiological use as they are difficult to follow and depend on very detailed correlation of clinical, electrophysiological and laboratory data. We devised a set of simple but specific criteria suitable for applying to this study, and other large scale studies, using aspects of the WFN approach. The criteria for diagnosis are as follows: the term "motor neuron disease" is used to encompass any adult (> 15 years) onset progressive motor system disorder (sporadic or familial). The following categories are identified:

1) *Clinically definite MND*

A combination of lower motor neuron (LMN) signs, clinically or by electromyography (EMG), and upper motor neuron (UMN) signs (table 2), not due to longstanding neurological disease, involving the brainstem and one or more spinal regions (cervical, thoracic, lumbosacral). If signs were limited to the brainstem and only one spinal region, then both UMN and LMN signs were required in that region, otherwise it was not considered necessary for both UMN and LMN signs to be present in all involved regions. This was qualified further by the following mandatory criteria: a progressively deteriorating course of the disease; absence of sensory signs (including visual abnormalities) apart from mild vibration sense loss in the elderly; absence of sphincteric disturbance; Parkinsonism; dementia and causes of syndromes which may mimic MND, after appropriate investigations and follow up. Normal or brisk reflexes in the presence of a clearly wasted limb were used as evidence of UMN involvement.

Patients in this group were assigned a category which gave an indication of the

Table 2   Physical signs by region used in the classification of patients

Region	Upper motor neuron (UMN) signs	Lower motor neuron (LMN) signs
Bulbar	Dysarthria (may be LMN) Dysphagia (may be LMN) Spastic, clumsy tongue Exaggerated jaw jerk/facial jerks Spastic tetraparesis Extensor plantar response(s)	Wasted tongue or cranial musculature Fasciculation of the tongue Dysphonia/weak cough Palatal weakness/nasal escape Wasting/weakness/fasciculation of sternomastoid
Cervical	Reflexes present in a wasted limb Finger jerks Spastic tetraparesis/extensor plantar(s),without bulbar signs	Wasting/fasciculation C2-T1 Paradoxical breathing/diaphragmatic palsy Absent upper limb reflexes
Thoracic	Spastic paraparesis Extensor plantar response(s)	Paraspinal/abdominal fasciculation Paraspinal wasting, truncal weakness Intercostal weakness/reduced vital capacity
Lumbo/sacral		Wasting/fasciculation L2-S2 Absent lower limb reflexes

clinical pattern of the MND as follows:

(*1–1*) *ALS/PBP* Clinically definite MND which began with limb symptoms but later developed bulbar features.

(*1–2*) *PBP/ALS* Clinically definite MND which began with bulbar symptoms and later developed limb symptoms or began with bulbar and limb symptoms simultaneously.

2) Clinically probable MND

(*2–1*) *PBP* A syndrome in which dysarthria and dysphagia of UMN or LMN origin are the predominant features (but which may be accompanied by sternomastoid weakness) in the absence of LMN limb signs but which may be accompanied by UMN limb signs (for example extensor plantar response) but not symptoms (for example difficulty in walking).

(*2–2*) *Spinal ALS (3 regions)* and (*2–3*) *Spinal ALS (2 regions)* Three and two regions (cervical, thoracic and lumbosacral) involved respectively with a combination of UMN and LMN signs, not necessarily both in the same region but without bulbar features and given the above qualifications, in particular exclusion of cervical spondylotic myelopathy. Patients registered with monomelic atrophy were not included in the calculation of incidence data.

(*2–4*) *PMA* An exclusively LMN motor disorder affecting at least two regions and with a clearly progressive course supported by consistent neurophysiological investigations (see below).

(*2–5*) *PLS* An exclusively UMN motor system disorder (after at least two EMG examinations separated by at least six months) affecting all four limbs with or without involvement of the brainstem; in the absence of a family history of gait disturbance and with no evidence of multiple sclerosis or MND mimic syndromes after CSF immunological studies; visual evoked responses and MRI of the brain or cervical cord. Patients with unspecified spastic paraparesis were explictly excluded.

The above classification was applied firstly, either at registration based on the documented features of the illness when patients first came to medical attention, or, if patients were identified through hospital discharge or mortality data, retrospectively, again based on the features at medical presentation. Secondly, when the full extent of the disease was established after follow up, or all available data had been reviewed after death, whichever came first.

Criteria for neurophysiological diagnosis were not established prospectively and are difficult to apply rigorously given the variation in clinical practice between neurophysiologists. Particular attention was paid to the results of nerve conduction studies and EMG where available to:

1) Exclude other causes of LMN disease, particularly polyneuropathies, compressive neuropathies or radiculopathies, multifocal motor neuropathy[16] and myopathies.

2) Identify LMN involvement which was not evident on clinical examination and which could therefore be used to assist subgroup classification. Equal weight was given to the finding of LMN abnormalities on EMG as to the clinical LMN signs (table 2) when determining the extent of regional involvement.

3) A means of documenting the spread of LMN abnormalities and therefore the progressive nature of the disease.

Myelography was usually performed when the diagnosis was probable rather than definite. Most patients had a CSF examination. In some instances support for the diagnosis was obtained with swallowing tests (barium cine swallow) and muscle biopsy. Antiganglioside antibodies were not routinely performed.

The diagnosis was considered proven by postmortem examination if this showed: LMN and UMN neuronal loss in the brainstem or spinal cord and neuronal atrophy with loss of Nissl substance, corticospinal tract degeneration and the absence of extensive central chromatolysis, active neuronophagia, neurofibrillary tangles, abnormal storage material, spongiform change and extensive inflammation.

Results

Initially, a total of 123 patients were registered but nine patients were not included in the incidence analysis because the diagnosis did not fulfil the above criteria. Either MND coexisted with other neurological disease or the diagnosis was subsequently shown not to be MND. One hundred and fourteen patients with definite or probable MND were diagnosed in 1989. Many patients were notified from multiple sources but the first source of referral was as follows: 68 patients by collaborating neurologists and neurophysiologists; 24 from hospital discharge data; 10 by SMNDR family care officers; nine by GPs; two from

Table 3 Clinical classification at presentation and based on data as of May 1991

|	At presentation Men	Women	Total	May 1991 Men	Women	Total
Clinically definite MND						
1–1 Beginning in the limbs (ALS/PBP)	10	15	25	21	17	38
1–2 Beginning in the bulbar muscles(PBP/ALS)	8	16	24	8	21	29
Clinically probable MND						
2–1 Progressive bulbar palsy (PBP)	1	7	8	1	2	3
2–2 Spinal amyotrophic lateral sclerosis (ALS) (3 regions)	28	9	37	23	7	30
2–3 Spinal ALS (2 regions)	11	4	15	7	4	11
2–4 Progressive muscular atrophy (PMA)	4	1	5	2	1	3
2–5 Primary lateral sclerosis (PLS)	0	0	0	0	0	0
Total	62	52	114	62	52	114
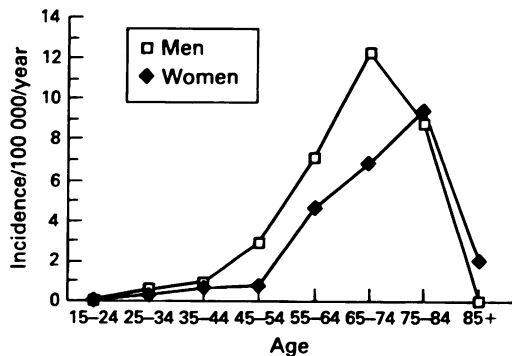
Figure 1   Age-sex specific incidence rates for motor neuron disease (Scotland 1989).
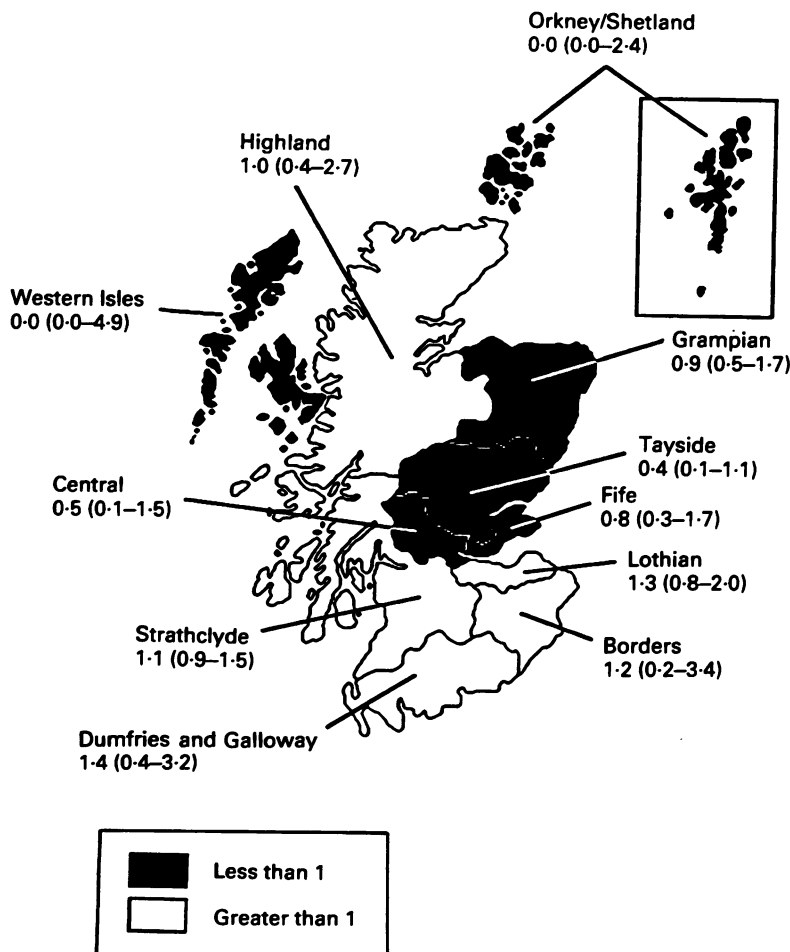

Figure 2   Distribution of motor neuron disease (Scotland) 1989. Standardised incidence ratios (95% confidence intervals).

mortality records; and one from pathology records. Ninety two patients (81%) had been seen at some time by a neurologist and 95 (83%) had had an EMG.

Sixty two patients (54%) were men [mean (SD) age at diagnosis 62·5 (12·4) range 27–84 years], 52 (46%) were women [mean (SD) age at diagnosis 68·0 (12·1) range 31–91 years], giving a male to female ratio of 1·2:1. The difference in ages was significant (5·5 years, 95% CI 0·9–10·1).

The classification of the patients' clinical status, is given in table 3. Patients with PBP and PMA only at onset were in the minority and most individuals presenting with PBP evolved into the PBP/ALS group. Six patients (5%) had a family history of MND but none was related to each other.

The crude incidence for Scotland was 2·24/100 000/year (95% CI 1·83 to 2·65). Age and sex specific incidence rates (presented in table 4) continued to rise to a peak between 75–84 years for women and 65–74 years for men (fig 1). The number of patients older than 85 years was very small making interpretation of rates in the very elderly difficult. The age adjusted standardised incidence ratios for individual regions showed some variation (fig 2). Ninety five per cent confidence limits overlapped with unity, however, indicating none was significantly different from the expected at the p < 0·05 level, although lower standardised ratios were observed in the north east and island areas.

Discussion

The epidemiological method may provide important clues to the causes of MND by demonstrating temporal and geographical trends in distribution. Difficulties arise in delineating the optimum size for such a study: under-reporting and error in diagnosis will bias mortality studies based on very large populations, whereas random variation will lead to imprecise estimates if a sample used is too small. In this study, which will continue to accrue registrations, the size has not compromised diagnostic accuracy because data can be sought prospectively. The population base is such that a useful number of patients can be registered within a few years and thereby offers the opportunity to provide a valuable long term study of MND in Scotland. In addition, the methods of the SMNDR are unique with

Table 4 Age-sex specific incidence rates for MND in Scotland (1989). The numbers of patients are given in five year age bands, incidence and 95% confidence interval (CI) is calculated for 10 year age bands for the mid-decades.

Age band	Population	n	Men Incidence/100 000/yr (95% CI)	Population	n	Women Incidence/100 000/yr (95% CI)	Population	n	Total Incidence/100 000/yr (95% CI)
15–24	407 1870	(0)	0·00 (0·00–0·73)	391 983	(0)	0·00 (0·00–0·76)	799 853	(0)	0·00 (0·000·37)
25–29	210 796	(2)		201 758	(0)		412 554		
30–34	184 169	(0)		182 061	(1)		366 230		
25–34	394 965	(2)	0·51 (0·10–1·50)	383 819	(1)	0·26 (0·10–1·20)	778 784	(3)	0·38 (0·19–0·90)
35–39	167 833	(0)		168 056	(1)		335 889		
40–44	172 561	(3)		172 776	(1)		345 337		
35–44	340 394	(3)	0·88 (0·27–2·10)	340 832	(2)	0·59 (0·27–1·70)	681 226	(5)	0·73 (0·09–1·38)
45–49	144 006	(5)		149 071	(1)		293 077		
50–54	136 881	(3)		145 717	(1)		282 598		
45–54	280 887	(8)	2·85 (0·87–4·80)	294 788	(2)	0·68 (0·31–1·97)	575 675	(10)	1·74 (0·60–2·81)
55–59	131 201	(11)		144 283	(6)		275 484		
60–64	123 114	(7)		141 079	(7)		264 193		
55–64	254 315	(18)	7·08 (3·81–10·30)	285 362	(13)	4·56 (2·10–7·03)	539 677	(31)	5·74 (3·72–7·77)
65–69	113 212	(14)		141 953	(9)		255 165		
70–74	73 196	(9)		106 321	(8)		179 517		
65–74	186 408	(23)	12·30 (7·30–17·40)	248 274	(17)	6·85 (3·60–10·10)	434 682	(40)	9·20 (6·35–11·21)
75–79	59 099	(6)		99 573	(10)		158 672		
80–84	31 927	(2)		70 064	(6)		101 991		
75–84	91 026	(8)	8·79 (2·70–14·90)	169 637	(16)	9·43 (4·81–14·10)	260 663	(24)	9·20 (5·52–12·90)
> 85	14 979	(0)	0·00 (0·00–20·00)	50 306	(1)	1·99 (0·80–8·90)	65 285	(1)	1·50 (0·60–6·90)
Total	2 460 373	(62)	2·52 (1·89–3·15)	2 630 327	(52)	1·90 (1·37–2·43)	5 090 700	(114)	2·24 (1·83–2·65)

its prospective, collaborative design recruiting incident patients from multiple sources to achieve complete case acertainment with detailed clinical records and follow up of an unbiased sample. In this way accurate data will be obtained over several years concerning temporal trends, demography and prognosis in MND.

Some studies of incidence or clinical features in MND have relied on data collected from tertiary referral centres,[17] [20] but generally, such studies give a lower incidence or a lower mean age or both than those which make a more concerted effort in case finding. One of the most comprehensive, but retrospective, studies was conducted in Rochester, Minnesota.[21] [22] Forty four patients were included in that population based study between 1925–84 giving a crude incidence of 2·0/100 000/year (95% CI 1·4 to 2·7). The incidence of MND has been examined in a number of other countries but in only two, both from Scandinavia,[23] [24] the crude incidence was higher than our study. The denominators, however, were not provided so it is difficult to make a satisfactory comparison because of possible differences in age structure of the population at risk. A previous study of the incidence of MND in Scotland[25] based on unverified hospital discharge data (1968–77), and therefore likely to be contaminated with diseases other than MND, gave a high crude average first discharge rate of 4·7/100 000/year and 3·01/100 00/year for men and women respectively. Mortality statistics collected over the same period gave average rates of 1·57/100 000/year and 1·18/100 000/year respectively. A further incidence study confined to the Lothian region[26] was incomplete in tracing case records and reported a range of incidence over 1968–75 of 1·0 to 1·9/100 000/year.

All studies that have examined age specific

incidence, except the Rochester study, found a decline in rates in the elderly age group. Our data show that the highest age specific incidence of 9·2/100 000/year for men and women combined (see table 4) was maintained into the 75–84 year age group. The decline in rates over 85 years is difficult to interpret due to the small numbers but may be due to failure to diagnose the illness in this age group rather than poor ascertainment of diagnosed patients. If rates really do continue to rise into old age rather than decline, as is generally reported, then senescence must make a major contribution to the development of MND.

Mortality data reflect incidence. MND is recorded as a cause of death in about 80% of clinically diagnosed patients[27] [28] and therefore may be a useful method for following trends in this disease. There is always a concern, however, that changing diagnostic practices, changes in the ICD, or increasing case ascertainment may be responsible for any observed changes. In addition, this method may not reflect true rates in the elderly and does not allow the study of clinical features and prognostic variables or case control studies.

Apart from the conspicuous exception of the south Pacific varieties of MND,[29] [30] which may have a separate aetiology to that observed in Western countries,[31] [32] it has been claimed that the distribution of MND is uniform worldwide.[33–36] This concept has recently been challenged[8] but the low incidence observed in developing countries might relate to poor case ascertainment rather than any true difference in incidence.[37] [38] There is some tentative evidence from the use of small area statistics, that clustering of cases within populations may occur,[39] supporting numerous anecdotal reports of clusters.[40–44] We have started examining the distribution of patients in Scotland but have no clear evidence of non-random distribution. Failure to demonstrate non-uni-

formity may be due to the inadequate statistical power of our sample so far and it remains to be seen if the tendency for lower rates in the northeast and island areas will be confirmed as the years go by and more patients are recruited.

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