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Risk factors for motor neuron disease: a case-control study based on patients from the Scottish Motor Neuron Disease Register

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Abstract

In order to identify risk factors for the subsequent development of motor neuron disease (MND) we have carried out a case-control study of incident patients in Scotland, identified using the Scottish Motor Neuron Disease Register. A standard questionnaire was given to 103 patients and the same number of community controls matched on a one to one basis using the general practitioner's (GP) age and sex register. Recall bias was minimised by using GP records to verify the subject's report. There was an overall lifetime excess of fractures in patients, odds ratio (OR) = 1·3 (95% confidence interval (CI), 0·7–2·5) and this was highest in the 5 years before symptom onset (OR = 15, 95% CI, 3·3–654). There was no association with non-fracture trauma but the OR for a manual occupation in patients was 2·6 (95% CI, 1·1–6·3). Both occupational exposure to lead (OR = 5·7, 95% CI, 1·6–30) and solvents/chemicals (OR = 3·3, 95% CI 1·3–10) were significantly more common in patients. No consistent association was found between MND and factors reflecting socioeconomic deprivation in childhood; childhood infections or social class. Our results identify a number of different factors which may contribute to the aetiology of MND.

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Environmental factors, which might be temporally remote from the onset of clinical disease, may be important in the aetiology of motor neuron disease (MND).[1–3] This case-control study was planned to examine the following controversial issues concerning environmental exposures and the subsequent development of MND.

TRAUMA

Kurtzke wrote:

"*. . . trauma — and particularly major trauma to the limbs, is in fact a risk factor for amyotrophic lateral sclerosis . . . it seems a lead worth pursuing in this otherwise hopeless disorder*".[4]

This statement is based on evidence which includes the close temporal relationship of physical trauma with the development of MND reported in numerous anecdotal cases,[5–12] and evidence from case-control studies, some of which have suggested a possible link with blunt trauma, electric shock, surgical procedures, or hard physical labour.[13–19]

The interpretation of many previous reports is limited by methodological problems which risk introducing important sources of bias, particularly when patients are a selected group,[17] or the investigators cannot avoid the recall bias inherent in obtaining information from patients with a vested interest in explaining their disease.[15] Associations with MND based on death certificate diagnoses, such as superficial injury, are almost certainly the consequence of MND.[20] The question of a possible relation of MND to trauma is not only important for aetiological hypotheses but has implications for medicolegal claims which may arise when MND apparently follows physical trauma. Therefore we sought to examine this potential relation further, attempting to improve on previous methodology.

OCCUPATION AND ENVIRONMENTAL TOXINS

A patient who developed MND following intoxication by the insecticide pyrethrum,[21 22] led Williams *et al* to suggest that some toxic substances may have the capacity to produce MND because genetically determined biochemical differences combine with the "wrong" environmental factor(s) (ecogenetic/xenobiotic hypothesis).[23] It has been suggested that leather,[24 25] textile,[26] and agricultural[27 28] occupations or exposure to metallic toxins[29–31] may be risk factors for MND. Accordingly we sought differences in potential occupational hazards between cases and controls.

SOCIAL CLASS AND THE ENVIRONMENT IN CHILDHOOD

Late deterioration after poliomyelitis is well recognised[32–35] but the majority of case-control studies which have examined the frequency of preceding poliomyelitis in patients or their relatives do not support a causal association.[14–16] Two possible predictions with respect to poliomyelitis and MND can be made: either (1) if conditions were of a high standard of hygiene in childhood then later exposure to poliovirus might result in greater, albeit subclinical, nervous system damage because of greater vulnerability of motor neurons in later childhood, and therefore childhood affluence should correlate with increased risk of MND[36 37]; or (2) if childhood was spent in circumstances of poor domestic

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hygiene then the number of individuals exposed to poliovirus infection would be greater, thereby increasing the subsequent risk of MND, if the two are related.[38]

Therefore, as suggested by Martyn,[39] our case-control study also sought any difference in the childhood environment with respect to standard of housing, domestic amenities, overcrowding, and social class of the patient's father.

Patients and methods

PATIENTS

Patients with MND were identified from the Scottish Motor Neuron Register (SMNDR) which is a prospective, population-based, collaborative study which aims to identify *all* incident patients in Scotland diagnosed after 1 January 1989 and employs multiple sources of case ascertainment and standardised diagnostic criteria.[40] Only sporadic patients with a combination of multiple spinal level upper *and* lower motor neuron signs (amyotrophic lateral sclerosis), with or without progressive bulbar palsy were included in this case-control study. Of 147 such patients diagnosed between 1 May 1990 and 31 October 1991, 39 had died before approach was possible. In each instance permission for inclusion was obtained from the patient's consultant neurologist or physician and the general practitioner (GP) but was declined in five, leaving 103 study patients.

CONTROLS

Because of the distances involved in travelling to interview subjects all over Scotland, controls were identified in advance of the visit, so that, whenever possible, both patient and control could be seen on the same day. Following a written explanation of the general nature of the study, the patient's GP or practice manager was telephoned and asked if they would be prepared to identify the individual of the same sex with the date of birth nearest to the patient, either forwards or backwards, using the practice age and sex register—a complete record of all patients in the practice and usually computerised. The only potential reason for exclusion of a control was dementia or psychological problems of such an extent that cooperation with a questionnaire would be difficult; in fact, in no instance was this necessary. It was stressed that no other selection criteria (for example, current illness) were to apply. The GP was asked to contact both patient and control to confirm their willingness to participate and then inform the investigators so that a visit could be arranged. As a check on the selection process for controls, after the completion of the study, a random sample (every fifth participating practice) was recontacted to perform the match for a second time. Only three out of 20 requests produced a different match from that used for the study (in two the first control had refused and in one a subject had been inappropriately excluded on the basis of residence outside the GP's usual boundary).

DATA COLLECTION

The case and then the corresponding control were visited in their respective homes by AMC. For patients, details of the history collected by the SMNDR were verified and modified if discrepancies existed. Great care was taken in establishing the dates of symptom onset so that fractures which might have been a consequence of limb weakness were ignored. Case and control were treated in an identical fashion as far as the questions pertaining to antecedent factors were concerned; for example, an equivalent date was assigned to controls when considering factors, such as trauma, which antedated the development of first MND symptoms. Involving the subject's spouse in the interview was also matched as far as possible.

The standard questionnaire recorded the dates, anatomical location, and nature of all trauma requiring medical consultation including fractures, blunt trauma, operations, and any electric shocks. Following the interviews all the GP's practice notes, which should include reports from accident and emergency departments and results of *x* rays, for the case and control, were scrutinised to confirm the patients' report and ascertain any injuries or operations requiring medical consultation which may have been omitted during the subject's interview. Systematic GP records began with the introduction of the National Health Service (NHS) around 1948 and are transferred to the new GP when a patient moves to a different area and so represent a valuable source of unbiased information with respect to events before the development of MND. In one case-control pair access to the notes was withheld by the GP but information regarding trauma was provided by letter.

A detailed lifetime employment history was obtained and classified according to the Office of Population and Censuses and Surveys (OPCS).[41] Highest social class was derived from this classification, using husband's occupation for married women, own occupation for spinsters. The following direct questions were also asked: "Have you ever had an occupation with exposure to solvents or chemicals?"; "Have you ever worked in the extraction of minerals, ores, or the manufacture of metals?"; "Have you ever worked with lead/used insecticides or pesticides, as part of your occupation?": quantification of this exposure was difficult but a period of *regular* contact over 12 months or more was recorded as positive and details recorded. Structured questions about cigarette smoking and a history of atherosclerotic disease were also included.

A lifetime residential history was recorded of residences of more than 2 years' duration (limited to a maximum of the six of greatest duration if there were more than this number but always including residential details for the first 10 years of childhood). For each residence information was collected on its location whether urban (city or town), or rural (village or isolated house); the availability of

Table 1 Matched case-control analysis, all subjects lifetime history of fractures before symptom onset, yes or no. The totals column indicates those fractures recalled by patient, GP records (*) and best combined information

	Male (best estimate available)	Female	Totals (patient, GP, best estimate)
Case and control	21	5	26,12,26
Case only	11	17	27,26,28
Control only	15	6	19,21,21
Neither	14	14	31,44,28
Total	61	42	103
OR (95% CI)	0·7(0·3–1·7)	2·8(1·1–8·8)	1·3(0·7–2·5)
OR based on GP records only			1·2(0·7–2·3)
OR based on patient recall only			1·4(0·8–2·7)

*Difference between real fracture rate and GP records is accounted for mostly by patient recall of pre-1948 fractures (before NHS records began). OR = odds ratio.

Table 2 Matched case-control analysis of all fractures within 5 years of first symptom onset

	Male	Female	Totals best estimate (GP records)
Case and control	0	0	0 (0)
Case only	7	8	15*(14)
Control only	0	1	1 (1)
Neither	54	33	87 (88)
Total	61	42	103 (103)
OR (95% CI)	∞(1·87-∞)	8 (1·1-348)	15 (2·3-654)

*One fracture which occurred overseas explains the difference between patient (or best estimate) and GP records only.

domestic amenities (a garden, separate bathroom with a fixed bath, running hot water, and flush lavatory); and residence size (number of occupants per room and per bedroom). The father's social class, based on his occupation at the time of the subject's birth, was derived according to the OPCS.

STATISTICAL ANALYSIS

Data were entered, as they were collected using dbase IV, a database for microcomputers, for subsequent analysis by SPSS-X statistical package, using χ^2 for categorical data and rank test for continuous data. Confidence intervals were calculated using a computerised analysis program, applying a matched case-control study method.[42 43]

Results

The age and sex distribution of the patient group was representative of incident patients with MND in Scotland in 1989–90. However, the mean survival from symptom onset of patients who died before they could be included was shorter than those included in the case-control analysis (difference in the means of 6·4 months, 95% CI, -0·1–12·9). The check for non-participation rate of first choice controls was 15% (8–21%). The age and sex of cases and controls were identical, a result of the matching process. There were 61 men (mean age 63, range 35–85 years) and 42 women (mean age 67 range 28–86 years).

TRAUMA

With matched case-control analysis there was an overall non-significant excess of fractures in patients (table 1) and a significant excess of fractures (with a very wide confidence interval) occurring within 5 years before symptom onset (table 2). Patients were as good as controls (κ = 0·8) in recalling the true number of fractures (that is, the best estimate of the total number of fractures based on both sources) so that analysis of the results based on the patients' account alone did not produce further positive associations. Figure 1 shows the distribution of all fractures by interval before the onset of MND (or equivalent time for controls) and figure 2 the odds ratio for a fracture occurring at any given time. An occupational history which included manual work was more common in MND patients (OR = 2·6, 95% CI, 1·1–6·3), which may have resulted in physical trauma not otherwise reported. There was no correlation between the site of fracture and the anatomical area in which the weakness began.

No significant difference was found between cases and controls in the number of non-bony traumatic events requiring medical attention; total number of operations or electric shocks.

OCCUPATION AND ENVIRONMENTAL TOXINS

No single occupational group except for manual as opposed to non-manual (see above)

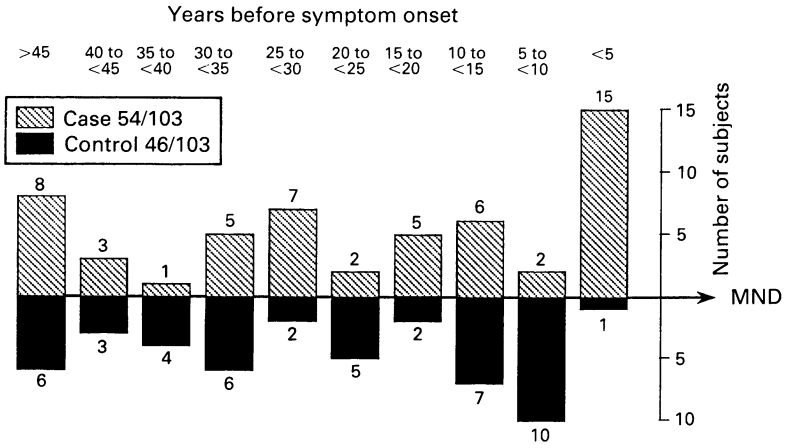

Figure 1 Distribution of fracture frequency by interval before the onset of motor neuron disease

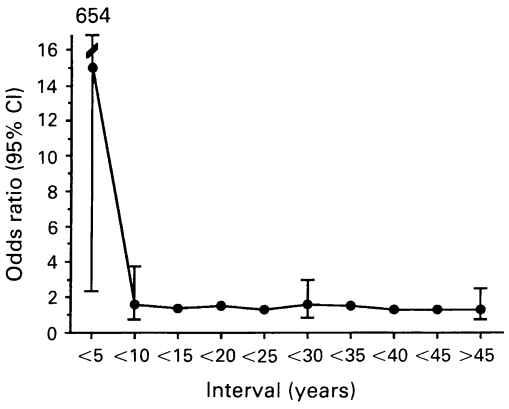

Figure 2 Cumulative odds ratios and 95% confidence intervals for a fracture occurring before the onset of symptoms due to motor neuron disease

Table 3 Matched case-control analysis of subjects' occupational exposures. Table records regular exposure over a period of 12 or more months

	Lead M, F, total	*Chemicals/solvents M, F, total*	*Pesticides M, F, total*	*Minerals Ores M, F, total*
Case and control	2, 0, 2	5, 0, 5	9, 1,10	3, 0, 3
Case only	16, 1,17	13, 7,20	16, 2,18	6, 1, 7
Control only	3, 0, 3	5, 1, 6	13, 0,13	2, 0, 2
Neither	40,41,81	38,34,72	23,39,62	50,41,91
Odds ratio (95% CI)	[for total, male and female]			
	5·7 (1·6–30)	3·3 (1·3–10)	1·4 (0·6–3·1)	3·5(0·7–34)

Table 4 Matched case-control analysis of domestic amenities in the first 10 years of life table records if amenity ever absent

	No garden	*No bath*	*No hot water*	*No flush toilet*
Case and control	24	49	45	11
Case only	25	25	27	17
Control only	28	19	17	19
Neither	26	10	14	56
Odds ratio (95% CI)	0·9 (0·5–1·6)	1·3 (0·7–2·5)	1·6 (0·8–3·1)	0·9 (0·4–1·8)

was significantly overrepresented, although the numbers in each of the 16 categories defined by the OPCS were small. The highest odds ratio was in unskilled and labouring occupations. There was an excess of patients who reported an occupational exposure for which inquiry was made (table 3). If the figures for all the substances in table 3 are combined then the OR for an exposure of potential toxicity = 3·2 (95% CI, 1·5–7·3).

THE ENVIRONMENT IN CHILDHOOD AND SOCIAL CLASS

There was a non-significant trend for patients to have had no hot water or a fitted bath (table 4). However, this was not supported by any difference in the availability of a flush toilet, home space, as judged by the presence of a garden or the number of individuals per room in the house or rural versus urban living. No patient gave a history of paralytic poliomyelitis, although four patients and six controls had had contact with a family member with poliomyelitis (OR 0·7; 0·1–2·8). The frequency of the common childhood infections was the same in patient and control groups. The patients' highest social class and the patients' fathers' social class at the time of birth did not differ from that of controls. There were no associations with vascular disease or tobacco use.

Discussion

SOURCES OF BIAS

The case-control method as a technique for establishing aetiology is subject to many potential sources of bias and rather than explain all cases, may only identify associations rather than causal relationships.[44–46]

In this study clinical homogeneity was achieved with predetermined specific diagnostic criteria for inclusion—that is, a mixture of multilevel spinal involvement with or without bulbar palsy. Selection bias was minimised by using incident, rather than prevalent, population-based patients. Despite attempts to include all incident patients in a given time period and achieving a representative group in terms of demographic variables, there was a non-significant trend towards longer survival in those included in the case-control study. However, it seems unlikely that factors associated with a longer survival are systematically related to the premorbid issues being examined.

Recall bias is a major problem. This was reduced by not providing specific information to subjects about the hypothesis under examination. In addition, as far as trauma was concerned, we were able to verify events by the use of GP records. These are unbiased for the knowledge of subsequent development of MND, and are a complete medical history, at least for events after 1948 when the NHS was introduced. Recall bias (for trauma) did not appear to be influencing the account obtained from patients, as all subjects, whether case or control, approximated the true trauma rate (that is, best information combining both sources) equally well.

There was no reliable way of verification of information relating to environmental toxins so recall bias cannot be excluded in the same way. On the other hand, the problem of overmatching (certain large employers in small towns engaged both patient and control) will tend to reduce the number of discordant pairs and the power of the study.

Non-respondent bias among patients—for example, that resulting from a mailed questionnaire,[17 47] was avoided by a personal approach to as many incident patients as possible, as was membership bias, a problem for some studies,[16 47] by using multiple sources of case ascertainment. Our first choice control participation rate was high.

Exposure suspicion (interviewer) bias was possible but a standardised questionnaire was used; prespecified hypotheses were tested; every effort was taken to avoid eliciting a biased account from patients; and results were analysed after data collection was complete. By recording only those events before first symptom onset, any associations were likely to represent primary rather than secondary phenomena. We were very careful to exclude fractures where the site of MND onset may have been related to the fracture (for example, wrist fracture in a patient presenting with footdrop). None of the fractures within 3 months of symptom onset could have been due to weakness—for example, wrist fracture in a patient presenting with bulbar palsy or fracture following an assault. However, despite these measures, subclinical weakness, and, therefore, a tendency to injury cannot be excluded with absolute certainty.

Inadequate sample size may have resulted from the numbers it was possible to include (103 cases matched one to one), thereby reducing the statistical power of the analysis. However, any study has constraints in terms of time and resources. Some factors, which occur in low frequency, may be important if the aetiology of MND is multifactorial but would not have been detected.

Finally, insensitive measure bias may be operating if the questions asked are only an indirect reflection of the putative exposure or mechanism under examination.

RISK FACTORS

Trauma

This study lends some further support to the cumulative evidence which claims an association of physical trauma, particularly fractures, with MND. An overall non-significant trend was mainly due to the much higher fracture rate in the 5 years before symptom onset. However, these findings are not supported by any relationship of MND to non-fracture or operative trauma.

One of the largest case-control studies,[14] in two parts, identified patients from (i) death certificates (with antecedent information from the spouse), and (ii) cases known to the ALS research group (selected collaborating neurologists) versus a mixture of hospital and neighbourhood controls. This study was vulnerable to selection bias, recall bias, and potential non-standardised data collection. However, the two different methodological approaches were consistent in their conclusion, that mechanical injuries were two to three times more frequent, in both sexes, in MND. A further study claiming a relationship of MND to trauma was limited to males, cases were ascertained from death certificates, and used military records collected before the development of MND as the source of information on trauma, thereby avoiding the major problem of recall bias. Lifetime operations, injuries, and fractures were more than twice as common in cases.[13] A recent study, which made a concerted effort to achieve patient homogeneity, used a selection of control groups, tested specific hypotheses, and attempted to minimise recall bias, failed to demonstrate any such relationship.[2]

When considering the cause of, or associations with, disease, some lines of evidence are more convincing than others.[48] Associations on the basis of case-control studies are generally less persuasive than cohort studies but prospective follow-up of a group of patients with fractures to the development of MND would require such enormous numbers as to make such a study impracticable. How specific is the association? Trauma has a potential role in Parkinson's disease,[49] Alzheimer's disease,[50] and dystonia[51] and so this may weaken the argument. However, the association of MND and trauma is consistent, almost all studies have been positive, whether or not statistically significant,[52] but the interpretation of literature reports is complicated by publication bias which may mean that positive associations are more likely to be submitted and published. There does not appear to be any clear biological plausibility to connect trauma with MND, unless tissue damage in some way influences motor neuron function, perhaps mediated by trophic factors. It has not been possible to demonstrate an exposure-response relationship (for example, in those patients with fractures that MND developed earlier) or any anatomical relationship of trauma to the commencement of weakness. On the other hand, it could be argued that there is a temporal relationship, of fractures with MND (clustered in the years before symptom onset).

Occupation, environmental toxins

All the potential environmental toxins for which information was sought resulted in an OR of more than 1·0 and 95% CIs did not overlap with unity for exposure to lead and solvents/chemicals. This result must be interpreted with caution as there was no way to avoid recall bias (see above).

The major nervous system effects of lead intoxication are encephalopathy and motor neuropathy. The descriptions of selective motor involvement and amyotrophy date from Aran[53] but upper motor neuron signs have also been described in patients with lead poisoning.[54] Lead is widespread in the environment, with large increases in deposits (for example, in quiescent Greenland ice caps) which correspond to the onset of industrialisation in the mid-eighteenth century and this has accelerated since the use of leaded petrol.[55] Individuals are likely to have quite variable exposures[56]—for example, owing to occupation or dietary habits.[57] The evidence for an association of lead and MND[55 58–62] and the possibility of interactions of lead and other minerals in MND is controversial.[29 63 64] Other case-control studies have also suggested that lead exposure may be important in the aetiology of MND,[65 66] the most recent study from the Mayo group[2] also reported a significant exposure in men, OR = 5·5 (95% CI, 1·44–21·0).

Some solvents are neurotoxic and may produce a peripheral neuropathy, pyramidal signs, toxic encephalopathy,[67] or extrapyramidal effects.[68] The case reports of MND associated with insecticide use[21 22] and a possible association with solvents[69] or toluene use in Sweden[70] and with textile[26] and leather workers[25] make it conceivable that occupational exposures are important in increasing the risk for MND.

The environment in childhood and social class

No association was found with highest social class of the patient or the patient's father. Although some factors related to socioeconomic deprivation in early childhood (the absence of hot water or a bath) showed a trend towards patients being relatively deprived, the evidence based on this study is weak and does not favour a role of other factors related to deprivation, particularly communicable diseases, including poliomyelitis. There is no further support, from this study, for the possible correlation of MND mortality with affluence[37] or deprivation.[39] These findings are consistent with others that have also failed to show any relationship to home space,[14] or poliomyelitis.[14–16 71]

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