

Comparison of sporadic and familial disease amongst 580 cases of motor neuron disease

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SUMMARY A review of 580 hospital case notes of patients with motor neuron disease (MND) revealed 20 families in which more than one case had been reported. For 27 of the cases in these families full medical records were available, and a history of a further 37 affected family members were obtained. The cases in these 20 families are termed familial and the remainder sporadic. Parent to child transmission occurred in 16 of the 20 families of the familial cases, suggesting autosomal dominant inheritance. In three families there was involvement of siblings only, and in one family two cousins were affected. The sex ratio for the documented familial case records seen was 0.8:1 (M/F = 12:15), for the total (documented and historical) it was 1.06:1 (33:31), but in sporadic cases it was 1.6:1 (341:212) and more frequent occurrence of sensory features at presentation was reported in the familial cases (15% in the familial cases and 5% in the sporadic cases). However, none of these differences reached statistical significance. Familial cases also differed from sporadic cases in having a younger age of onset (a mean of 52 years in the familial cases compared with 56 years in the sporadic) and in the shorter median reported duration of illness (1.1 year in the familial cases; 2.6 years in the sporadic). However, in only one fifth of sporadic cases was the age at onset and death known, although this was known for 22 of the 27 familial cases, so that the data on survival and age of onset are too incomplete to test formally.

Motor neuron disease (MND) is usually classified into three diagnostic subsets, amyotrophic lateral sclerosis, progressive muscular atrophy and progressive bulbar palsy. These definitions have been made more precise by excluding the so-called heredo-familial spinal muscular atrophies, in which the pyramidal tracts are never involved, and also the secondary neuronal diseases such as Creutzfeldt-Jakob disease, carcinomatous and diabetic amyotrophies and syringomyelia.

It seems that each of these clinical types of MND include familial forms^{1,2} with different patterns of inheritance.^{1,3,4} In some families, in which only siblings were affected, parental consanguinity has been encountered more often than expected, suggesting autosomal recessive inheritance. Autosomal dominant patterns of inheritance have also been reported.^{1,2,5,6} However, there is still too little

information to be sure about the classification and characteristics of these inherited forms of MND.

In this paper we describe those cases with a family history found amongst 580 consecutive sets of case notes of patients with motor neuron disease in three teaching hospitals.

Methods and patients

The source of cases were medical records of all patients with MND diagnosed between 1965 and 1982 at The London Hospital; between 1970 and 1984 at the Radcliffe Infirmary, Oxford and between 1976 and 1984 at The National Hospital for Nervous Diseases, London. In these hospitals the diagnostic index was searched for cases with ICD 356.3 (1964-1969), 348.9 (1970-1978) and 335.2 (1977-1984) (see table 1). The diagnosis of MND was established in each case only after full in-patient investigation which usually included blood tests, radiological studies, CSF examinations and electrophysiological studies, mainly for ruling out other disease entities. In some cases results of muscle biopsy and post mortem examinations were available.

An analysis of these clinical and diagnostic procedures to test their effectiveness in distinguishing diseases reported as being MND from those reported as being multiple sclerosis,

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Table 1 Sources of the study patients

		Number of cases		
		London Hospital 1965-1982	Radcliffe Infirmary Oxford 1970-1984	National Hospital Queen Square 1976-1984
SMND	M	72	70	199
	F	52	30	130
FMND	M	1	1	10
	F	3	3	9
Total	M	73	71	209
	F	55	33	139
	Total	128	104	348
London Hospital selected by ICD codes:			356 1965-1967 348-9: 1968-1978 335-2: 1979-1982	
Radcliffe Infirmary:			Personal collection	
National Hospital selected by ICD codes:			348-9: 1976-1978 335-2: 1979-1984	

cervical spondylosis and stroke was carried out.⁷ This showed that 96% (362 out of 378) of cases from three hospitals could be correctly classified by the computer analysis as having MND using a discriminant analysis procedure, so that for these hospitals and conditions there was good agreement between the diagnostic criteria in use.

Results

Twenty families were identified in which two or more cases had been reported. Sixty four cases in all were referred to but full medical notes were available for only 27 (documented cases) included in the series. For the remainder (historical cases) the medical history, or very limited information, had been obtained from the *propositi* (table 2). Observed differences between groups were tested using chi-squared and *t* tests as appropriate.

Genetic background

Only the 5% documented cases (27 out of 580) could be confidently regarded as familial. However, if cases described in the family histories are included the proportion increases to 10% (64 out of 617 including the historical cases).

There were 16 families of the 20 in which there was a reported involvement of a parent and her (his) children; 3 families in which involvement only of siblings was reported; and one family in whom there were two affected paternal cousins involved (table 2).

Details of the familial cases are shown in table 2, and two examples of pedigrees are illustrated in figs 1 and 2. Family 1 has been reported previously by Hawkes *et al*² but the pedigree has been modified to include additional information which has become available.

Clinical characteristics

These are summarised in table 3. The sex ratio for the documented familial cases was 0.8:1 (M/F = 12:15), for the total familial (documented + historical) was 1.06:1 (33:31), but in sporadic cases it was 1.6:1 (341:212). Familial cases were clinically atypical with a younger mean age of onset (52 years in familial MND; 56 years in sporadic MND) and a shorter median duration of illness (1.1 years in familial MND; 2.6 years in sporadic MND). There was a more frequent presentation with sensory features, four familial cases out of 27 with pain and temperature disturbance in a glove and stocking distribution. This was reported in only 5% of the sporadic cases. The site of onset of the disease in the two groups was similar; in 44% of sporadic and 48% of familial cases the clinical onset was in an arm; in 37% of each the clinical onset was in a leg. In 19% of sporadic and 15% of familial cases the clinical onset was bulbar. None of these differences however reached statistical significance, although as shown below they are in agreement with previous reports.

Discussion

Sex ratio

There have been frequent reports of preponderance of male to female patients with sporadic MND, with a tendency to the opposite finding in familial cases. Sex ratios of 1.22 to 2.5 or more^{9,10} for sporadic cases, and of 1:1¹¹ for familial cases have been reported. A 1:1 ratio has been calculated for sporadic cases older than 65 years.¹² The female preponderance of 1:0.8 in our cases of familial MND is compatible with the observation of Hawkes even after excluding the families he described.² This difference in the sex incidence has not been explained. Both endocrine differences and differences in environmental contacts must be considered.

Past reports also suggest differences in age of onset. In one report¹³ the age of onset was 51 years for familial and 61 years for sporadic cases. In our series of 580 cases the mean age of onset was 52 years for familial and 56 years for sporadic cases. This difference in age of onset might reflect earlier diagnosis of familial MND in patients acquainted with the disease in their parents or siblings. However, the apparently shorter duration in such cases suggests that it is a real phenomenon.

The duration of all MND cases from onset to death is usually 3 to 5 years although it may be as brief as 1 year or as long as 15 years.¹ From our data the mean survival of familial cases was only 1.1 years, (derived from 22 of 27 cases) while in sporadic cases it was 2.6 years, but unfortunately information was available on only 98 out of 535 cases (table 1).

Table 2 Continued

Family	Type of cases	Case No & Generation	Sex	Age at onset	Age at death (yr)	Duration of illness	Mother	Father	Daughter	Son	Patterns of inheritance												
											Vertical				Horizontal								
											Grand mother	Grand father	Aunt	Uncle	Cousin								
											M	F	M	F	M	F							
5	Doc	II	M	61	?	?																	
	Hist	I	M	48	50	2 yr															1/?	1/?	
5	Doc		F	60	?	?																	2/?
	Hist		M	55	57	2 yr																	2/?
7	Doc	II	M	41	43	2 yr	+																1/?
	Hist	I	F	75	78	5 yr					1/?												1/?
5	Doc		F	70	70	3 mth																	2/?
	Hist		M	54	54	2 mth																	2/?
5	Doc	II	F	60	60	4 mth		+															1/?
	Hist	I	M	65	67	2 yr					1/?												1/?
5	Doc		F	73	74	5 mth																	2/?
	Hist		F	52	54	2 yr																	2/?

7: fifth generation.
 grandfather (father side) had the disease.
 1/3 one of the three siblings had the disease.
 = case of MND.

It has been suggested that sensory pathways are more often involved in familial cases.^{2,3,14} This is compatible with our finding that 4 of 20 familial cases had sensory features at presentation, whereas only 5% of sporadic cases had sensory features. Posterior column involvement is well recognised in familial MND.² The issue of sensory features in MND is contentious in view of the possibility of a co-existing disorder such as polyneuropathy or cord compression, and since the coexistence of sensory features in a patient thought to have MND is usually held to exclude the diagnosis.

The proportion of cases in which the presenting symptoms involved the legs in the present series is consistent with previous reports and was the same in both sporadic and familial MND. In two previous studies, the disease began with weakness in the legs in 40%¹⁵ and 48%¹⁶ of patients with familial MND. In our series the disease presented with weakness of the legs in 37% in both groups. In an earlier study of sporadic MND 37% (94 out of 255) began in the legs and 28% (72 out of 255) began in the bulbar area.¹⁷ In the present study only 19% in the sporadic cases had a bulbar onset, and the comparable figure for familial cases was 15%.

Table 3 Comparison of clinical features in sporadic and documented familial MND

	Sporadic MND	Familial MND
Sex ratio*	1.6:1	0.8:1
M/F	(341/212)	(12/15)
Age at onset (yr)† range:	13-87	19-74
Mean, (SD)	56, (12.4)	52, (14.3)
(n = 535)		(n = 27)
Age at death (yr)† range:	33-88	27-84
Mean, (SD)	62.3, (11.02)	52.4, (14.6)
(n = 98)		(n = 22)
Duration of illness† (yr)		
Mean, (SD)	2.6, (3.09)	1.1, (1.74)
(n = 98)		(n = 22)
Sensory symptom* and/or sign	5.2% (n = 553)	14.8% (n = 27)
Site of Onset*: Arm	43.6% (241/553)	48.1% (13/27)
Leg	37.3% (206/553)	37.0% (10/27)
Bulbar	19.0% (105/553)	14.8% (4/27)

*None of the differences shown here reached statistical significance.
 †The information was too incomplete to test.

Pattern of inheritance

A major problem in genetic studies of MND is that the late age of onset of the disease makes it likely that the familial nature of many cases is not ascertained, as many of those theoretically at risk have not reached the usual age of onset at the time of reporting,⁸ so that it is likely that the estimate of the proportion of familial cases is always low.

In approximately 10-15% a familial occurrence of MND has been reported.^{1,18,19} Based on our documented cases the proportion in the present study is 5% (27 out of 580), but if cases described in the family histories are included, the proportion increases to 10% (64 out of 617).

In 24 families with 124 cases of typical amyotrophic lateral sclerosis reported by Kurland and Mulder¹¹ inheritance was autosomal dominant. In the present series parent to child transmission occurred in 80%,

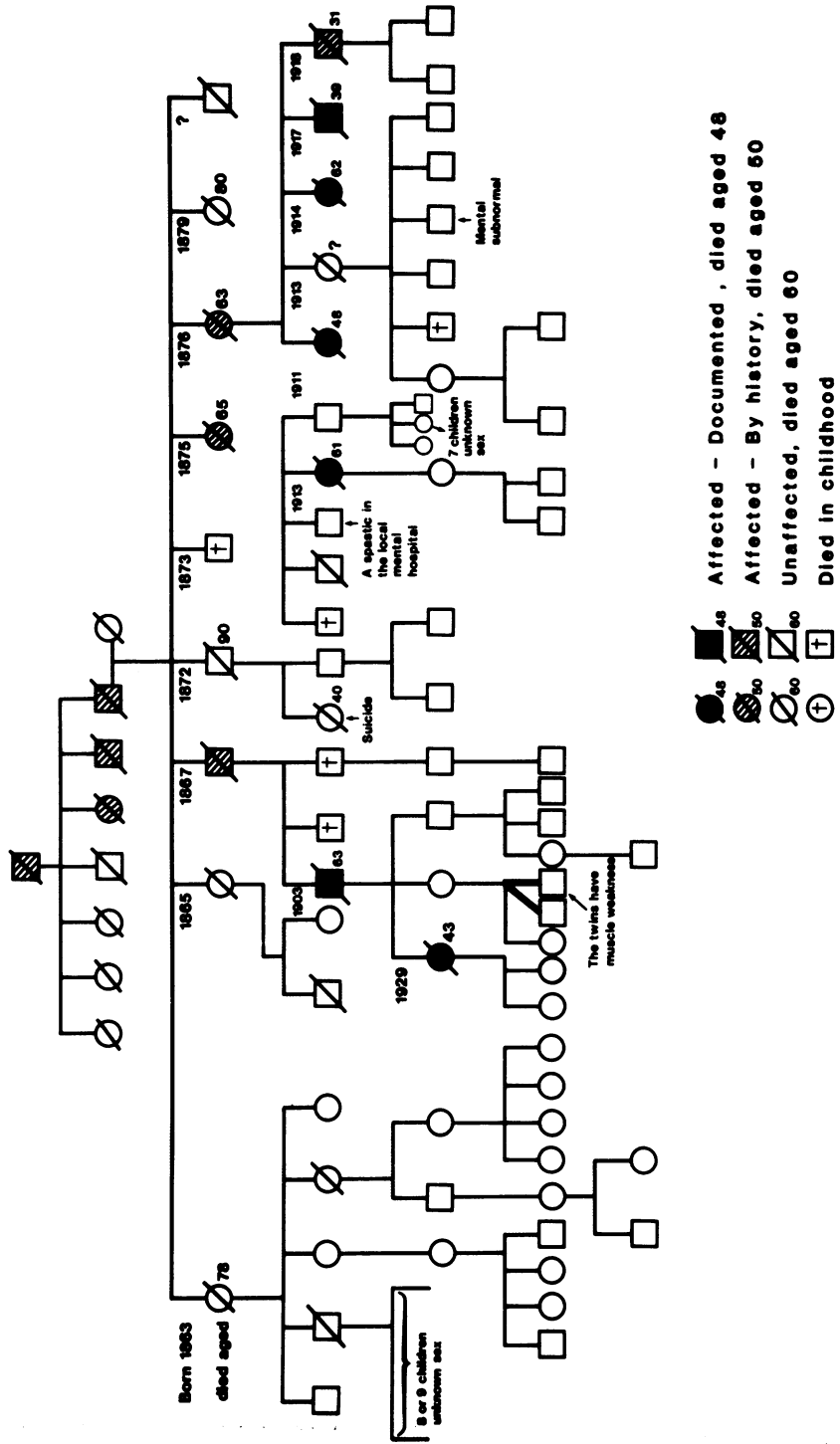


Fig 1 A pedigree of family I.

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