Motor Neuron Disease in the Rocky Mountain Region

LAURANCE D. SMITH, MD, *Norristown, Pennsylvania;* CATHERINE E. KENNY, MD, *Colorado Springs, Colorado;* STEVEN P. RINGEL, MD; *and* HANS E. NEVILLE, MD, *Denver*

We saw 166 patients with motor neuron disease over a ten-year period, 116 with amyotrophic lateral sclerosis—111 sporadic and 5 familial—and 50 with progressive muscular atrophy. The age at onset varied widely, with the youngest mean onset occurring in the familial group. The most common presenting symptoms were leg or arm weakness and difficulty speaking or swallowing; fewer patients reported cramping, fasciculation, or fatigue. Mean survival time was less in familial cases, women, older patients, and in those with difficulty speaking and swallowing. A total of 50% of all patients were alive after four years; 13% were alive after ten years. Previous reports on the natural history of motor neuron disease may be overly pessimistic in suggesting that survival time rarely exceeds two years.

(Smith LD, Kenny CE, Ringel SP, et al: Motor neuron disease in the Rocky Mountain region. West J Med 1988 Apr; 148:430-432)

The adult motor neuron diseases are a group of hereditary or acquired disorders characterized pathologically by progressive degeneration of the motor neurons required for voluntary movement. Loss of motor neuron innervation leads to atrophy and weakness of the cranial, trunk, or limb muscles, while intellect and perception are spared.

Motor neuron disease includes several major subcategories.[1,2] In amyotrophic lateral sclerosis (ALS) muscle atrophy is combined with signs of pyramidal tract dysfunction, including spasticity, hyperreflexia, or Babinski's signs; the majority of cases occur sporadically, although some are familial. Progressive muscular atrophy (PMA) is a sporadic adult illness where muscle atrophy and weakness are prominent. There are no clinical signs of pyramidal tract dysfunction, although pyramidal lesions may be present pathologically. Spinal muscular atrophies (SMA) are recessively inherited disorders with onset from infancy through early adulthood. Spinal muscular atrophy resembles the progressive disorder, except for its purely familial occurrence and more favorable prognosis.[3]

There is a cumulative loss of motor neurons, increasing disability, and death in all forms of motor neuron disease,[4-6] although the rate of progression varies widely. In this report we review the clinical characteristics and course of these disorders in 166 patients seen in a major tertiary medical facility in the Rocky Mountain region and compare the results with previous reports.

Patients and Methods

Inclusion Criteria

Patients were selected from a retrospective chart review of new cases seen at the University of Colorado Neuromuscular Clinic between 1976 and 1986. All fulfilled the clinical criteria of motor neuron disease[5] and had confirmation of neurogenic muscle disorder by electromyogram or muscle biopsy.

Patients were classified into three groups based on clinical findings: 111 patients in the sporadic ALS group had no family history of the disease and had pyramidal signs at some point during their illness; 5 patients with autosomal-dominant ALS had a family history consistent with autosomal-dominant transmission and had pyramidal signs; 50 patients in the group with progressive muscular atrophy had no family history of motor neuron disease and never had pyramidal signs. Patients with a family history of spinal muscular atrophy and without pyramidal signs were excluded. Patients with pyramidal signs unaccompanied by muscle atrophy, a prior history of polio, significant sensory loss, or other atypical neurologic signs, or any patients who improved were also excluded. Two patients with a history of ALS in other family members but without an autosomal dominant pattern of inheritance were excluded.

Analysis of Clinical Data

Age, sex, family history, presenting symptoms, and abnormal physical signs present at the first and subsequent evaluations were tabulated. All patients were given repeat examinations or follow-up status was determined by telephone contact. Duration of illness was defined as the time from the onset of symptoms to the time of death or to the latest follow-up.

Results

The mean age at onset in the three clinical groups of motor neuron disease is listed in Table 1. In the autosomal-dominant ALS group the illness developed at a slightly younger mean age. ALS developed in women at an older mean age in all three groups, as it did in patients presenting with bulbar

ABBREVIATIONS USED IN TEXT

ALS = amyotrophic lateral sclerosis
PMA = progressive muscular atrophy
SMA = spinal muscular atrophy

From the Neurology Group, Norristown, Pennsylvania (Dr Smith); the Neuromuscular Section, Department of Neurology, University of Colorado School of Medicine (Drs Ringel and Neville); and the Department of Neurology, Veterans Administration Medical Center (Dr Neville), Denver. Drs Smith and Kenny are now in private practice.

Reprint requests to Hans E. Neville, MD, Department of Neurology, Box B185, University of Colorado School of Medicine, 4200 E Ninth Ave, Denver, CO 80262.

TABLE 1.—*Age at Onset of Motor Neuron Disease (N=166)*

	Sporadic ALS				Autosomal-Dominant ALS				Progressive Muscular Atrophy			
		Age at Onset,				Age at Onset,				Age at Onset,		
	(No.)	Years	(range)	SD	(No.)	Years	(range)	SD	(No.)	Years	(range)	SD
All patients	(111)	56.2	(17-85)	14.0	(5)	50.6	(35-67)	14.4	(50)	54.8	(17-83)	16.5
Men	(54)	54.2	(17-85)	14.6	(2)	44.5	(37-52)	10.6	(25)	54.5	(17-83)	17.4
Women	(57)	58.1	(24-83)	13.3	(3)	54.5	(35-67)	17.2	(25)	55.2	(22-72)	16.0

ALS=amyotrophic lateral sclerosis, SD=standard deviation

TABLE 2.—*Presenting Symptoms of Motor Neuron Disease in All Categories (N=166)*

Complaint	%
Leg weakness	33
Arm weakness	21
Difficulty with speech or swallowing	20
Cramping	4
Fasciculation	3
Fatigue	2
Multiple symptoms	17
	100

symptoms (data not shown). There was no difference in the mean age at onset between patients presenting with arm or leg weakness or for patients with bulbar signs—weakness, fasciculation of cranial musculature, hyperactive gag, or jaw jerk—but free of bulbar symptoms (data not shown).

The most common presenting symptom was leg or arm weakness (Table 2). Occasionally patients reported two symptoms beginning simultaneously at the onset of illness. The relative frequency of these symptoms was similar among the three groups with the exception that bulbar symptoms and cramping were more common in patients with sporadic ALS.

Survival figures for the 166 patients are shown in Figure 1: half the patients survived at four years. The longest individual survival for each group occurred in patients who are still alive—sporadic ALS, 19 years; autosomal-dominant ALS, 3 years; PMA, 24 years.

Table 3 outlines the mean duration of illness in 75 patients who have died—55 with sporadic ALS, 3 with autosomal-dominant ALS, and 17 with PMA. The longest mean duration of illness was in the PMA group, while the shortest was in the autosomal-dominant ALS group. In all three clinical groups the mean survival was shorter in women, patients over the age of 55 years at the start of illness, and patients presenting with bulbar symptoms. There was no difference in the mean duration of illness between patients presenting with arm or leg

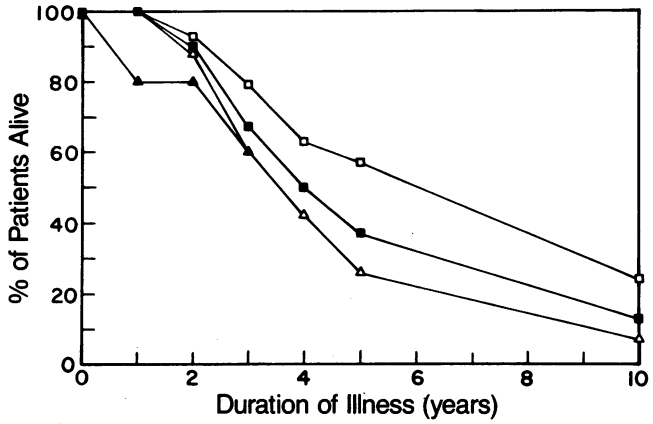

Figure 1.—The graph summarizes the duration of illness and patient survival in motor neuron disease. △ = sporadic amyotrophic lateral sclerosis; ▲ = autosomal-dominant amyotrophic lateral sclerosis; □ = progressive muscular atrophy; ■ = all patients

weakness, or for patients with signs of bulbar dysfunction but free of symptoms at the time of first evaluation (data not shown). Esophagostomy or gastrostomy had no effect on the duration of illness (data not shown).

Discussion

Previous reports of the natural history of motor neuron disease have reached disparate conclusions depending on whether the cases are selected solely from death certificates, from autopsy records, or from a population of living patients. Reports based on death certificates are more likely to select older patients,[7] while autopsy reports may reflect the most rapidly progressive cases.[6] Conversely, younger, more mobile patients and those with relatively indolent disease are more likely to receive care in a regional center and thereby be overrepresented in clinical reports.[8,9]

The referral population in our study is similarly biased but includes all patients, whether alive or dead, and we analyzed outcome according to clinical differences among the various

TABLE 3.—*Duration of Illness in Patients With Motor Neuron Disease Who Have Died (N=166)*

	Sporadic ALS				Autosomal-Dominant ALS				Progressive Muscular Atrophy			
		Duration of Illness,				Duration of Illness,				Duration of Illness,		
	(No.)	Years	(range)	SD	(No.)	Years	(range)	SD	(No.)	Years	(range)	SD
All dead patients	(55)	3.0	(1-18)	2.9	(3)	1.9	(0.8-3)	1.1	(17)	3.5	(1-11)	2.6
Men	(26)	3.7	(1-18)	3.9	(1)	3.0	...	...	(9)	4.1	(1-11)	3.2
Women	(29)	2.4	(1-5)	1.2	(2)	1.4	(0.8-2)	0.7	(8)	2.8	(2-6)	1.4
Age at onset <55 yrs	(17)	4.6	(1-18)	4.6	(2)	1.9	(0.8-3)	1.4	(3)	4.7	(1-11)	5.5
Age at onset >55 yrs	(38)	2.3	(1-7)	1.2	(1)	2.0	...	...	(14)	3.2	(1-6)	1.7
Difficulty with speech or swallowing at presentation	(18)	2.7	(1-7)	1.4	(1)	2.0	...	...	(3)	2.7	(1-5)	2.1

ALS=amyotrophic lateral sclerosis, SD=standard deviation

forms of motor neuron disease. The distinction between ALS and PMA is imperfect inasmuch as the division in some cases must be made on the basis of transient clinical signs. Some authors have not made the distinction at all,[4,7,10] and so may have unknowingly included isolated cases of adult spinal muscular atrophy, a disorder with a much longer survival time. Such patients may be included in our study, thereby increasing the number of patients with long survival. We feel confident that such patients are restricted to the group with progressive muscular atrophy, with onset before the age of 55 years.[3]

The presence of hyperreflexia or other signs of pyramidal tract dysfunction accompanied by muscle atrophy is strongly suggestive of ALS. We found this combination in more than half our patients during the initial evaluation. Pyramidal signs may develop later in the illness[4] and may disappear due to severe muscle atrophy; this occurred in eight of our patients. The proportion of our patients with progressive muscular atrophy (30%) is similar to that in previous reports,[1,11,12] as is the low incidence of familial ALS.[6,11,13,14]

Most (90%) of our patients presented with the well-recognized symptoms of limb weakness, bulbar dysfunction, or both,[5,10,11,15] although a few reported symptoms that have not been emphasized, such as cramping, fasciculation, or fatigue. As we mentioned before,[12] bulbar symptoms and cramping were particularly common in the sporadic ALS group.

Motor neuron disease is thought to be slightly more common in men than in women, with men numbering as high as 71% of the total in one report.[14] We encountered a nearly equal number of men and women for all varieties of motor neuron disease, which others have attributed to the excess number of women in the age group at risk for these disorders.[16]

The mean age at onset varied little among our clinical groups, while the range in age at onset was older than 60 years. In other studies, the mean age at onset has varied widely due to biases inherent in selection and ascertainment—from 52 years reported in a prevalence study enumerating only living patients[7] to 66 years in a review of death certificates.[16,17] Our findings agree with those in previous reports in that the youngest mean age at onset was in the autosomal-dominant ALS group,[13] and the older mean age at onset occurred in women and in all patients presenting with bulbar symptoms.[1,4,10,11]

A short survival following the onset of motor neuron disease has been emphasized in the past based on reviews of autopsy findings or death certificates.[1,16] These reports probably underrepresent younger patients and those with a long survival, since we were able to show a shorter survival by analyzing data on dead patients separately (Table 3). In contrast to the often quoted survival time of two years or less, we found that half our patients were alive four years after the start of illness (Figure 1), in agreement with other studies that included living as well as dead patients.[10,15] Most of our patients with prolonged survival times were in the PMA group,[6,12] while the shortest duration of illness occurred in the autosomal-dominant ALS group.[13]

We confirmed the poor prognosis for older patients,[10,15,16] which may result from several factors, and for patients presenting with bulbar symptoms.[4,10,14] We noted a relatively poor prognosis for women, which is perhaps due to the older mean age at onset. Older patients may ignore initial symptoms or attribute them to aging, delaying diagnosis and leading to a shorter calculated survival time.[8] In addition, medical complications may contribute to shorter survival in a population expected to have more illness than the young. Patients with bulbar involvement are predisposed to dysphagia, malnutrition, or aspiration pneumonia. The most significant factor in the poor prognosis associated with bulbar symptoms may relate to the older mean age at onset in this group, however, because patients presenting with bulbar symptoms had the same mean age at onset as the entire group and no worse a prognosis in one study.[16]

There was no difference in prognosis between patients presenting with arm or leg weakness.[6] Interestingly, we found that patients with signs of bulbar dysfunction but free of bulbar symptoms did not differ in mean age at onset and had no worse prognosis than the whole group, despite what appears to be an ominous physical abnormality.

Esophagostomy or gastrostomy were offered to those patients with severe dysphagia, malnutrition, or at risk for aspiration. Surgical modification improved the quality of life in these selected patients but did not extend life.

A few patients had prolonged survival, including those with poor prognostic features. Previous studies have noted the great variation in natural history, with 10% alive after 10 years[5] and patients rarely surviving as long as 35 years.[4] At the time of initial evaluation, these patients may be clinically indistinguishable from others who will succumb rapidly, further emphasizing the prognostic uncertainty in any individual case of motor neuron disease.

REFERENCES

1. Brownell B, Oppenheimer DR, Hughes JT: The central nervous system in motor neuron disease. J Neurol Neurosurg Psychiatry 1970; 33:338-357

2. Brain WR, Croft P, Wilkenson M: The course and outcome of motor neuron disease, *In* Norris FH, Kurland LT (Eds): Motor Neuron Diseases—Research on Amyotrophic Lateral Sclerosis and Related Disorders. New York, Grune & Stratton, 1969, pp 20-27

3. Kugelberg E: Chronic proximal (pseudomyopathic) spinal muscular atrophy, chap 2, *In* Vinken PJ, Bruyn GW (Eds): Handbook of Clinical Neurology, Vol 22. New York, American Elsevier North-Holland, 1975, pp 67-80

4. Bonduelle M: Amyotrophic lateral sclerosis, chap 13, *In* Vinken PJ, Bruyn GW (Eds): Handbook of Clinical Neurology, Vol 22. New York, American Elsevier North-Holland, 1975, pp 281-338

5. Mulder DW, Howard FM: Patient resistance and prognosis in amyotrophic lateral sclerosis. Mayo Clin Proc 1976; 51:537-541

6. Rowland LP: Motor neuron diseases: The clinical syndromes, chap 2, *In* Mulder DW (Ed): The Diagnosis and Treatment of Amyotrophic Lateral Sclerosis. Boston, Houghton Mifflin, 1980, pp 7-34

7. Jokelainen M: Amyotrophic lateral sclerosis in Finland: I & II. Acta Neurol Scand 1977; 56:185-204

8. Juergens SM, Kurland LT: Epidemiology, chap 3, *In* Mulder DW (Ed): The Diagnosis and Treatment of Amyotrophic Lateral Sclerosis. Boston, Houghton Mifflin, 1980, pp 35-52

9. Mulder DW: Introduction, chap 1, The Diagnosis and Treatment of Amytrophic Lateral Sclerosis. Boston, Houghton Mifflin, 1980, pp 1-6

10. Rosen AD: Amyotrophic lateral sclerosis: Clinical features and prognosis. Arch Neurol 1978; 35:638-642

11. Kristensen O, Melgaard B: Motor neuron disease—Prognosis and epidemiology. Acta Neurol Scand 1977; 56:299-308

12. Norris FH Jr: Adult spinal motor neuron disease, chap 1, *In* Vinken PJ, Bruyn GW (Eds): Handbook of Clinical Neurology, Vol 22. New York, American Elsevier North-Holland, 1975, pp 1-56

13. Emery AE, Holloway S: Familial motor neuron diseases, *In* Rowland LP (Ed): Human Motor Neuron Diseases, Vol 36, Advances in Neurology. New York, Raven Press, 1982, pp 139-147

14. Mackay RP: Course and prognosis in amyotrophic lateral sclerosis. Arch Neurol 1963; 8:117-127

15. Boman K, Meurman T: Prognosis of amyotrophic lateral sclerosis. Acta Neurol Scand 1967; 43:489-498

16. Juergens SM, Kurland LT, Okazaki H, et al: ALS in Rochester, Minnesota, 1925-1977. Neurology (NY) 1980; 30:463-470

17. Zack MM, Levitt LP, Schoenberg B: Motor neuron disease in Lehigh County, Pennsylvania: An epidemiologic study. J Chronic Dis 1977; 30:813-818