HIGH LIGHT
CME

The natural history of primary lateral sclerosis

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Abstract—*Objective:* To define the syndrome of primary lateral sclerosis (PLS) and disorders that contain features of both ALS and PLS, to determine the time beyond which PLS is less likely to become ALS clinically, and to determine the outcome of people with PLS and those who develop lower motor neuron (LMN) signs. *Methods:* The authors reviewed the records of all 39 patients initially diagnosed with PLS in 1984 to 2004. Diagnostic subgroups were defined based on clinical features. The authors used Kaplan-Meier methods to estimate the time to diagnosis, linear regression analyses to assess function, and a Cox proportional hazard model to assess survival in subgroups. *Results:* Of the 39 patients, 29 had only upper motor neuron (UMN) signs on initial evaluation. Thirteen of the 29 were later classified as having UMN-dominant ALS (UMN-D) because they acquired evidence of denervation by EMG (3.17 years) or examination (3.67 years). Sixteen of the 29 patients, classified as clinically pure PLS, retained only UMN signs and a normal EMG (mean follow-up 8.7 years). Ten patients who met criteria for ALS at the initial visit were used as controls. The UMN-dominant ALS group had lower functional scores ($p = 0.033$) than the PLS group, and similar scores to those with ALS. Survival was longer in both the PLS group ($p = 0.027$) and the UMN-D group ($p = 0.067$) than the ALS group. *Conclusions:* Clinically pure PLS can be defined by isolated UMN signs 4 years after symptom onset, and is a syndrome of slow progression with high levels of function. Prior to the fourth year, the diagnosis of PLS cannot be made with certainty because many patients develop LMN signs. UMN-dominant ALS, defined by predominantly UMN disease with minor LMN signs, has disability similar to ALS, but slower progression.

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Jean-Martin Charcot and Heinrich Erb described the clinical and pathologic features of a disorder with isolated degeneration of the upper motor neuron (UMN), which Charcot termed primary lateral sclerosis (PLS).[1,2] During the 100 years that followed, additional reports described living patients and a few autopsies, but the clinical diagnosis was difficult to make reliably without the modern technology necessary to exclude mimicking conditions such as multiple sclerosis (MS) or vitamin B12 deficiency.

The first report in the era of brain imaging was published in 1988,[3] generating renewed interest in the disorder. Other conditions were identified by neuroimaging and laboratory studies, and three of the cases were confirmed by autopsy. In 1992, clinical diagnostic criteria were proposed[4] that, while widely used, proved to be nonspecific.[5] Subsequent articles included some patients with lower motor neuron (LMN) abnormalities clinically or in the electromyogram (EMG).[6,7] Starting around 1990, the presence of Bunina bodies[8-10] and ubiquitinated inclusions[11-13] became part of the pathologic diagnosis and definition of ALS, rendering the earlier autopsy studies of PLS invalid.[14]

In 2005, the new pathologic criteria, minor LMN signs in some reports, and instances of patients converting to ALS even after 25 years,[15] again raise questions about whether, if modern techniques are applied, PLS and ALS can be distinguished. Is PLS a distinct disease, with sufficiently different clinical outcome from ALS to deserve a separate classification? If so, what is an acceptable time to diagnosis beyond which a patient is likely to retain only UMN signs? Does the prognosis of PLS change when minor LMN signs or EMG denervation appear? And are there distinct disorders with predominant UMN signs but some evidence of LMN degeneration that differ in prognosis from the purely UMN disorder or typical ALS? A more meaningful diagnostic classification accommodating these questions would help systematize future studies.

In this report, we describe patients with a disease of isolated UMN involvement and sufficiently different outcome to justify the clinical diagnosis of PLS,

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define a disorder with findings and prognosis intermediate between that of clinical PLS and typical ALS, report the clinical impact of EMG denervation on the definition and prognosis of PLS, and provide evidence substantiating a diagnostic time for PLS beyond which patients are less likely to develop LMN signs.

Methods. We reviewed the database of motor neuron disease (MND) patients at the Eleanor and Lou Gehrig MDA/ALS Research Center, Columbia University, and reviewed the records of 39 patients given the initial clinical diagnosis of PLS in the years 1984 to 2004. Eligible patients were above age 40, and had no other identifiable cause for degeneration of the corticospinal tracts than MND. Those with incomplete records were excluded. Patients were also excluded who had symptoms suggestive of hereditary spastic paraparesis, including family history of spastic paraparesis, symptom onset before age 40 years, or prominent long tract sensory signs. We contacted, examined, and obtained ALS Functional Rating Scale–Revised (ALSFRS-R) scores from those still living. Although referred with the diagnosis of PLS, on first examination 10 of the 39 patients actually met revised El Escorial Criteria for definite, probable, or laboratory-supported probable ALS[16] and were used as a control group for statistical comparisons. On the basis of clinical features, including outcome, rate of progression, examination, and EMG findings, we grouped patients into the following categories at the time of follow-up: 1) clinically pure PLS (onset after age 40, only UMN signs on examination, normal EMG of three limbs, bulbar muscle, and paraspinal muscles); 2) UMN-dominant ALS (primarily UMN findings on examination, with LMN signs of weakness, wasting, or fasciculation limited to one to two muscles or minor denervation on EMG limited to sparse fibrillation potentials, positive sharp waves, or minor motor unit potential remodeling in one to two muscles); 3) ALS (meeting the WFN El Escorial clinical trial criteria for clinically definite, clinically probable, or laboratory-supported probable ALS). The time from symptom onset to the first EMG or examination with evidence of LMN dysfunction was taken as the time of diagnosis of UMN-dominant ALS.

Our primary aims were to determine whether patients with clinical signs isolated to the UMN have an outcome sufficiently different from that of ALS to justify a separate clinical diagnostic category, to determine if there are disorders with findings and prognosis between those of clinical PLS and typical ALS, to determine the clinical impact of EMG denervation on the prognosis of PLS, and to provide evidence substantiating a time from symptom onset to diagnosis for PLS.

A Kaplan-Meier estimated survival function of the time from symptom onset to development of LMN signs was plotted to determine a diagnostic window period for PLS. Function was assessed using breathing capacity (forced vital capacity, FVC percent predicted) and the ALS Functional Rating Scale revised version (ALSFRS-R).[17] Regression analyses were used to compare differences in function between subgroups, including the 10 control patients with ALS. A Cox proportional hazard model was used to compare the differences in survival time between subgroups. Both analyses were also adjusted for age at symptom onset and sex.

Results. *Clinical.* Of the 29 patients who had only UMN signs on initial evaluation, 17 were men and 12 were women, with mean age at symptom onset of 52 years (table 1). Nineteen first noted symptoms in the legs, three in the arms, and seven in the bulbar region. Seventeen had symmetric onset, and 11 had an ascending pattern of progression. Fifteen patients had pathologic emotional lability, 11 had bladder symptoms, and 1 had symptomatic cognitive deterioration. The average disease duration at time of follow-up was 93 months (7.75 years). None had similarly affected family members.

Primary lateral sclerosis. Sixteen patients, 10 men and 6 women, had only UMN signs and a normal EMG after repeated evaluation (mean follow-up 104.4 months [8.7 years]) (tables 1 and 2). The average age at symptom onset was 51 years. The site of onset was in the legs in 13, bulbar in 2, and the arms in 1. One died of cardiac disease after 9 years of MND symptoms; 15 were still living.

Eleven of these patients who had only UMN signs and a normal EMG 4 years after symptom onset, the determined time to diagnosis (see below), were classified as clinically pure PLS. Their average ALSFRS-R score was 38.5 after 11.6 years of follow-up, and the average FVC was 102%. Six were still employed or attending school regularly. Two others reached retirement age and stopped working after 2.3 and 21 years of symptoms. One with progressive symptoms of stiffness in all limbs and dysarthria starting at age 44 had a normal EMG and examination showing only UMN signs 30 years after his symptoms began. The Cox proportional hazard model, after adjusting for age at symptom onset and sex effects, showed strong statistical evidence ($p = 0.027$) that the hazard rate for the PLS group is approximately 0.68% of the hazard rate for the ALS group. Five of 16 patients who had isolated UMN signs for less than 4 years from symptom onset were labeled as classification uncertain (see tables 1 and 2).

UMN-dominant ALS and the time to transition. Thirteen patients, later classified as having UMN-dominant ALS, acquired EMG evidence of denervation in a median of 3.17 years after symptom onset, and clinical LMN signs 6 months later (median 3.67 years) (see tables 1 and 2). This group comprised six women and seven men, with an average age at onset of 53 years. Six had onset in the legs, five had bulbar onset, and two had onset in the arms.

Of those who developed LMN signs, 46% did so by 3 years and 77% did so by 4 years from symptom onset. The figure shows that the chance that a patient converted to UMN-dominant ALS after 4 years from symptom onset is only 23%, justifying 4 years after symptom onset as a screening window period for the diagnosis of PLS. While the majority (77%) developed LMN signs within 4 years, three did not make the transition until 60, 72, or 137 months from symptom onset. The last one died of ALS after an additional 23 months, a total of 160 months from symptom onset. Four patients eventually developed clinical signs and EMG abnormalities sufficient for the WFN diagnosis of ALS, while nine retained evidence of denervation in only a few muscles. The prognosis of at least 6.4 years for the group overall was better than the ALS group. The Cox proportional hazard model, after adjusting for age at symptom onset and sex effects, showed moderately strong statistical evidence ($p = 0.067$) that the hazard rate for the UMN-dominant group is approximately 15% of the hazard rate for the ALS group.

Electrophysiology. Patients who developed UMN-dominant ALS showed EMG evidence of denervation in a median of 3.17 years after symptom onset. EMG changes were consistent with acute denervation (fibrillation potentials, positive sharp waves, or both), chronic denervation (increased amplitude or duration of motor unit potentials), or motor unit irritability (fasciculation potentials). These findings preceded or were concurrent with the development of LMN signs (UMN-dominant ALS) in all but one instance, and the EMG changes preceded the development of LMN signs by 6 months on average. Those patients with prolonged course, mild to moderate disability, and no LMN signs (clinically pure PLS) all had normal EMG.

Table 1 *Classification of patients referred for diagnosis of primary lateral sclerosis (PLS)*

ID	Group	Age, y	Sex	Time to UMN-D, y	LMN sign seen	FVC	ALSFRS-R	Died	Follow-up duration, y
1	PLS	52	M	NA	N	93	41	N	9.00
2	PLS	44	F	NA	N	103	37	N	16.00
3	PLS	45	M	NA	N	105	41	N	10.83
4	PLS	71	F	NA	N		29	N	6.00
5	PLS	48	F	NA	N			N	12.25
6	PLS	44	M	NA	N		35	N	30.00
7	PLS	60	M	NA	N			Y	9.00
8	PLS	42	M	NA	N	105	39	N	9.83
9	PLS	60	M	NA	N			N	4.92
10	PLS	48	M	NA	N		43	N	8.00
11	PLS	40	F	NA	N		43	N	12.08
12	UKN	55	F	NA	N	103	41	N	2.58
13	UKN	41	F	NA	N	88	44	N	2.42
14	UKN	52	M	NA	N			N	1.33
15	UKN	62	M	NA	N	120	29	N	1.92
16	UKN	54	M	NA	N		45	N	3.17
17	UMN-D	69	M	1.83	Y	81	31	N	2.33
18	UMN-D	63	F	6.00	Y			Y	12.00
19	UMN-D	50	M	3.33	Y		28	N	3.42
20	UMN-D	56	F	3.17	Y	96	37	N	5.00
21	UMN-D	42	M	4.00	Y	81	32	N	4.67
22	UMN-D	64	F	3.83	Y	74	37	N	6.25
23	UMN-D	59	F	1.25	Y	42	21	N	7.58
24	UMN-D	46	M	2.00	Y	104	34	N	3.58
25	UMN-D	41	F	3.67	Y	63	41	N	3.67
26	UMN-D	50	M	1.50	Y	71	24	N	2.00
27	UMN-D	54	F	11.42	Y	70	35	Y	13.33
28	UMN-D	52	M	2.08	Y	73	24	N	2.08
29	UMN-D	49	M	5.00	Y			N	8.00
30	ALS	55	F	NA	Y	25	19	Y	1.67
31	ALS	68	M	NA	Y	96	42	Y	1.50
32	ALS	54	F	NA	Y			Y	4.92
33	ALS	70	F	NA	Y	62	30	N	5.58
34	ALS	55	M	NA	Y	95	42	Y	2.00
35	ALS	69	F	NA	Y			Y	3.00
36	ALS	71	M	NA	Y			Y	5.08
37	ALS	67	M	NA	Y	85		N	5.00
38	ALS	54	M	NA	Y	95	28	N	0.58
39	ALS	51	F	NA	Y	53	24	N	4.50

UMN-D = upper motor neuron dominant ALS; LMN sign = lower motor neuron abnormalities detected on examination or in electromyogram; FVC = forced vital capacity; ALSFRS-R = ALS Functional Rating Scale revised version; NA = not applicable; UKN = classification uncertain (isolated upper motor neuron signs for <4 years).

Functional outcome: ALSFRS-R, FVC, and time to disability. The ALSFRS-R, FVC, and employment history were obtained at the most recent evaluation (see tables 1 and 2). Formal regression analyses showed strong differences in function among the patient subgroups (see table 2). The patients with PLS had higher ALSFRS-R scores ($p = 0.033$) and FVC ($p = 0.056$) than the UMN-dominant ALS group. As a group, patients with UMN-dominant ALS had more disability than those with clinically pure PLS and had ALSFRS-R scores and FVC similar to the most recently obtained in the ALS control group. These findings were unchanged after excluding those who ultimately met criteria for the diagnosis of ALS. Eight of 10 living patients with pure PLS are still working, in school, or retired at a defined age; all but one of the patients with UMN-dominant ALS are now retired or unable to work.

PLS plus. One patient had a family history of neurodegenerative disease (clinically diagnosed AD in the mother), and one patient had symptomatic cognitive impairment (memory loss) (table 3). Two patients had hypomimia, bradykinesia, and slow stride, suggesting mild parkinsonism, but neither had postural instability or responded to levodopa therapy. No patient had abnormal ocular movements.

Excluded diagnoses. More common causes of UMN disease were prominent in the differential diagnosis of

Table 2 *Description of patients by subgroup*

	PLS	UKN	UMN-D	ALS	*p* Value
N	11	5	13	10	
Age, y	50.36 (9.55)	52.80 (7.60)	53.46 (8.51)	61.40 (8.15)	0.02*
Sex					0.93†
F	4 (10.26)	2 (5.13)	6 (15.38)	5 (12.82)	
M	7 (17.95)	3 (7.69)	7 (17.95)	5 (12.82)	
FVC	101.50 (5.74)	103.67 (16.01)	75.50 (17.10)	73.00 (27.28)	0.04*
ALSFRS-R	38.50 (4.75)	39.75 (7.67)	31.27 (6.36)	30.83 (9.43)	0.05*

Data shown as mean (SD) or n (%); forced vital capacity (FVC) based on 24 observations; ALS Functional Rating Scale revised version (ALSFRS-R) based on 29 observations.

* From analysis of variance F-test.
† From chi-square test.

PLS = primary lateral sclerosis; UKN = classification uncertain (isolated upper motor neuron signs for <4 years); UMN-D = upper motor neuron dominant ALS.

MND with predominantly UMN signs. Patients were excluded from the study because of inadequate records (5), refused participation (1), or diagnosis of polyneuropathy (4), MS/myelitis (3), stroke (2), gene-positive familial ALS (1), Charcot–Marie–Tooth disease type V (1), Friedreich ataxia (1), multiple system atrophy (1), progressive supranuclear palsy (1), and cerebral palsy (1).

Discussion. It is still debated whether PLS and ALS are distinct disorders or manifestations of a single disorder. The clinical syndrome of PLS is rare, accounting perhaps for 1 to 3% of all patients with MND.[18] Because there is currently no defining test, PLS is a clinical diagnosis in living patients. Different conditions can cause isolated UMN signs and need to be excluded in the diagnostic evaluation of PLS. Prior to 1980, technology was inadequate to exclude the more common causes of the syndrome, and so early case reports are difficult to interpret.

By 1988, advances in neuroimaging and laboratory analyses made it possible to exclude mimicking conditions. A publication that year[3] described six living patients with no clinical or physiologic signs of LMN disease, and six patients with purely UMN signs clinically but who also showed EMG signs of denervation. Three other cases had autopsies show-

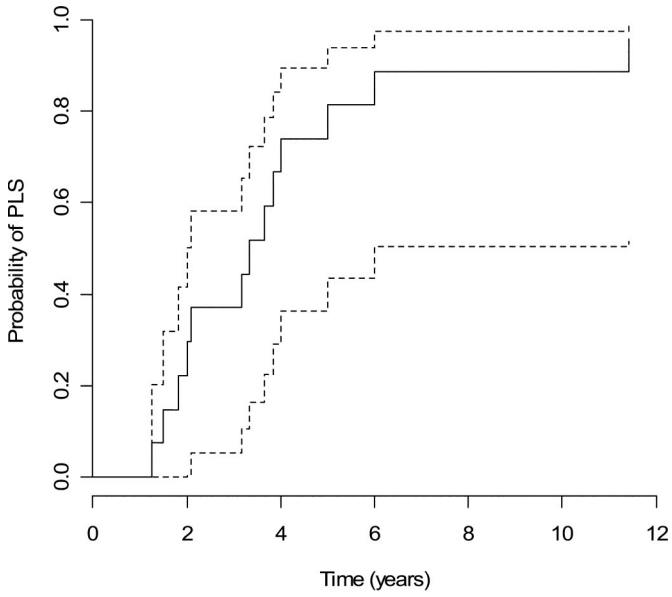

Figure. Estimated survival function (with 95% confidence band) of time to diagnosis of primary lateral sclerosis (PLS).

Table 3 *Diagnostic categories of UMN predominant MND*

Autopsy proven PLS
Clinically diagnosed PLS with degeneration in motor cortex and corticospinal tracts, no loss of motor neurons, no gliosis in anterior horn cells, and no Bunina or ubiquitinated inclusions.
Clinically pure PLS
Evident upper motor neuron signs, no focal muscle atrophy or visible fasciculation, and no denervation in EMG 4 years from symptom onset. Age at onset after 40. Secondary and mimicking conditions excluded by laboratory and neuroimaging.
UMN-dominant ALS
Symptoms less than 4 years, or disability due predominantly to UMN signs but with minor EMG denervation or LMN signs on examination, not sufficient to meet diagnostic criteria for ALS.
PLS plus
Those with predominant UMN signs who also have clinical, laboratory, or pathologic evidence of dementia, parkinsonism, or sensory tract abnormalities. Note: If cerebellar signs, urinary incontinence, or orthostatic hypotension are evident, multiple system atrophy could be considered.
Symptomatic lateral sclerosis
Clinically diagnosed PLS with evident possible cause (HIV, paraneoplastic syndrome).

UMN = upper motor neuron; MND = motor neuron disease; PLS = primary lateral sclerosis.

ing degeneration and loss of motor neurons in the precentral gyrus and degeneration of the corticospinal tracts without loss of motor neurons or gliosis in brainstem or spinal cord.[3] The notion of PLS as a syndrome of diverse etiology, or secondary PLS, arose from two additional cases with positive HIV serology, and also from other reports of the syndrome in women with breast cancer.[19] One patient in the current series had a history of breast cancer.

In 1992, based on the clinical features of eight cases and one autopsy, Pringle et al. proposed diagnostic criteria.[4] These criteria, used in many subsequent reports, have proven uncertain because of low specificity; some of their patients later turned out to have other disorders.[5] Additionally, the criteria do not discriminate between patients with minor EMG changes or LMN signs and those with only UMN signs, and the inclusion of an observation period of 3 years before diagnosis now appears unreliable.

A major inconsistency in subsequent reports of PLS involves evidence of lower motor neuron disease clinically or in the EMG.[6,7,20] In a 2001 report of 20 patients,[6] all exhibited a slowly progressive course, but 14 of 20 patients developed insidiously progressive weakness, 12 developed asymmetric atrophy of the intrinsic muscles of the hand, 16 showed EMG evidence of denervation, and only six remained with purely UMN findings after follow-up EMG. Further, 11 of 20 showed definite evidence of denervation and reinnervation on muscle biopsy. However, some of these patients may not have had a pure disorder of the UMN initially. Nine of the 20 patients described cramps or fasciculations at symptom onset, and six had abnormalities on the first EMG. Even with minor LMN findings, however, the overall prognosis was more benign than that of ALS, suggesting that predominant UMN syndromes, with or without minor LMN signs, may include patients with different clinical manifestations and possibly different outcomes. Another report[21] also identified two clinical forms of PLS; in the more common type, symptoms ascend from the legs, while the other type begins in the arms, hands, or bulbar regions. Our experience is similar.

The distinction between PLS and ALS has been further complicated by the paucity of modern autopsy studies of patients with clinical PLS. In an influential 1970 ALS autopsy series,[22] three possible cases of PLS showed ″minimal cell loss with severe pyramidal tract degeneration and well-marked changes in the brain.″ All three showed thinning of ventral roots. Other autopsies based upon traditional concepts of histopathology, depending on evidence of degeneration, neuronal cell loss, and astrogliosis, appeared after 1977.[23-26]

By 1990, however, new pathologic criteria, including Bunina bodies and ubiquitinated inclusions, became accepted hallmarks of ALS.[8-14] These findings rendered outdated the earlier autopsy reports of PLS, again raising the question of whether, with modern techniques, PLS and ALS can be distinguished pathologically. There have been six autopsy reports of UMN syndromes since 1997.[27-32] In all but one,[29] ubiquitinated inclusions or Bunina bodies were seen; these patients may have had ALS, not PLS. Failure to find inclusions does not mean they were absent and the single case of clinical PLS without identified inclusions (autopsy proven PLS) also had dementia.[29] In contrast to most clinically diagnosed cases of PLS, four of these six autopsied patients had evidence of multisystem degeneration in life, including LMN signs, dementia, or parkinsonism. In one report with dementia and inclusions at autopsy, the authors used the term ″upper motor neuron predominant form of ALS.″[30] Others later described UMN-dominant ALS with EMG changes.[7]

We chose symptom onset after age 40 to avoid overlap with hereditary spastic paraparesis (HSP). Spastic paraparesis is a common early manifestation of PLS, making it similar to HSP; unfortunately, gene identification is not always possible in HSP, and some may not have a family history. Bulbar and arm onset would also exclude HSP. Our patients had no family history of MND, and overt dementia occurred in only one patient, although one report[33] described cognitive decline on formal testing. We suggest that the terms PLS plus and symptomatic lateral sclerosis can be used for those with UMN signs and dementia or parkinsonism, or those with associated possible causes such as paraneoplastic syndrome or HIV (see table 3). Symptoms usually started in the legs, but as in other reports[21,34] some began in bulbar and arm muscles. The population was not large enough to reach meaningful conclusions about the impact of site of onset on prognosis.

We chose 4 years as the time to diagnosis of clinically pure PLS because the probability of developing LMN signs after 4 years is only about 0.23 (see the figure). Seventy-seven percent of our patients who developed LMN signs did so within 4 years, either clinically or in the EMG. Four patients did so between 3 and 4 years. Using the Pringle criteria of 3 years, 31% of our patients would have been incorrectly labeled as having PLS. The figure also shows other choices of window periods. The probability of developing LMN signs after 6 years is about 0.1, for example. We did not define the time to diagnosis later (i.e., 5 years) because of the clinical practicality of leaving a patient without a diagnosis so long, and because no patients made the transition between years 4 and 5. Erb noted that one of his original cases developed amyotrophy after 6 years.[35] Three of our patients (23%) developed LMN signs 5, 6, and 11 years after symptoms began. One is still alive at 12 years, one died of bladder cancer 21 months after LMN signs appeared, and one died of ALS 23 months after LMN signs appeared. Most patients who retain only UMN signs for 4 years seem likely to continue having slow progression for years, but LMN signs may appear even after many years.

We do not believe pure PLS should be diagnosed if fasciculation or other features of LMN disease are

visible. Once LMN signs developed, our patients became more disabled than those with pure PLS as measured by the ALSFRS-R and FVC, and the degree of disability became similar to that of ALS. However, even though one patient eventually died of ALS, and several others later met criteria for the diagnosis of ALS, the overall prognosis of 6.42 years was better than the ALS control group, suggesting that the rate of progression of UMN-dominant ALS lies between that of PLS and ALS. Onset with isolated UMN signs and disability due predominantly to UMN disease, even if LMN signs develop, seems to carry a better prognosis. Patients with initial and prolonged disability due to UMN dysfunction who developed visible LMN signs or EMG evidence of denervation were classified as "upper motor neuron-dominant ALS,"[14,30] a term used to signify both the presence of LMN signs and the different prognosis from our patients with typical ALS.

EMG proved to be a reliable predictor of impending clinical appearance of LMN signs, and therefore could identify UMN-dominant ALS. Those patients with prolonged course, mild-moderate disability, and no LMN signs (clinically pure PLS) had normal EMG. In UMN-dominant ALS, EMG signs of denervation occurred on average 6 months prior to clinical appearance of LMN signs. Any EMG evidence of denervation portended the clinical transition; whether or not the changes sufficed to meet El Escorial criteria for ALS, patients still developed clinical LMN signs.

Overall, UMN-dominant syndromes seem to have a distinct outcome, with those retaining only UMN signs for at least 4 years having a more benign prognosis; most of these patients with clinically pure PLS have a prolonged course with high levels of independence for years or decades. Prior to the 4th year from symptom onset, the diagnosis of PLS cannot be made with confidence, and it may be imprudent to reassure patients of the prolonged, less disabling course of PLS before that time. The label UMN-dominant ALS may be more appropriate during this evaluation phase, and for those who develop minor LMN signs. EMG should be performed periodically in those with only UMN signs to document those destined for transition. The majority with UMN-dominant ALS have outcome in between that of pure PLS and classic ALS, though some will develop rapidly progressive ALS even after years of having only UMN signs.

This study cannot answer the question whether PLS, UMN-dominant ALS, and typical ALS are separate disorders neuropathologically or in pathogenesis. There is only one modern report of a patient with clinical PLS that did not contain the inclusions of ALS at autopsy. While our data indicate that these clinical disorders are sufficiently distinct to merit separate classifications, only new neuropathologic or molecular studies can determine their point of biologic separation. The possibility remains that PLS is one extreme of the clinical spectrum of motor neuron diseases, or that disorders with more or less severe LMN findings will have corresponding findings at autopsy. Patients with LMN signs, even those with typical ALS, have a wide range of presentations and outcome; further subcategorization based on the current data would likely be inaccurate because of the small sample size. Given the current state of knowledge, it seems appropriate to use the clinical classifications of PLS and UMN-dominant ALS during life, with the understanding that they may be variants of ALS, as determined by autopsy.[36]

Large-scale, prospective, systematic studies and more autopsies are needed to better estimate disease frequency and prognosis based on clinical subtype (see table 3), including clinically diagnosed pure PLS and UMN-dominant ALS, and to determine whether subcategories may exist within each subtype. Use of exactly defined clinical subtypes may facilitate study of etiology and prognosis, as well as lead to treatment trials.

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