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Focality of upper and lower motor neuron degeneration at the clinical onset of ALS

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ABSTRACT Objective: To localize and analyze the anatomic distribution of upper motor neuron (UMN) and lower motor neuron (LMN) loss in patients with ALS early in their disease when motor manifestations were still relatively focal using clinical examination signs. **Methods:** We reviewed records of 100 patients with ALS who were evaluated when the diagnosis was first established or suspected. From the patient history, we ascertained the body region of first symptoms and the time course. From the physical examination, we separately graded severity of UMN and LMN signs in each body region, indexed these to the body region of first symptoms, and sorted and analyzed the data. **Results:** Motor manifestations began in one body region in 98% of patients. UMN and LMN signs were both maximal in these same body regions, but they were independent of each other in severity and their outward distribution, which conformed to neuronal anatomy. The outward distribution of both UMN and LMN signs seemed more directed to caudal body regions than to rostral ones. **Conclusions:** Motor neuron degeneration in ALS is a focal process at both upper and lower motor neuron levels of the motor system. At each level, it begins corresponding to the same peripheral body region and then advances contiguously and separately to summate over time. **NEUROLOGY 2007;68:1571-1575**

Motor manifestations of ALS are focal and discrete at the clinical onset and then progress contiguously outward over time to become diffuse and complex.¹⁻⁶ Because motor manifestations are caused by simultaneous and progressive degeneration of upper motor neurons (UMNs) and lower motor neurons (LMNs), analysis of motor focality should start with localization of the underlying pathologic anatomy. This can be done through the physical examination of the motor system and motor signs,^{7,8} which probably localizes more easily, reliably, comprehensively, and evenly balanced between UMN and LMN than other methods.⁹ We used the clinical examination as the basis for evaluation of early motor manifestations, early being the first symptoms noted by patients and the first physical examination signs noted by neurologists, because that is when they are still relatively focal and discrete. We found that motor neuron degeneration may be an orderly and sequential process at both levels of the motor system.

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Supplemental data
at www.neurology.org

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Table Composite severity scores showing distribution of motor neuron deficits indexed to region of onset

Body region of onset	Body region evaluated	Composite LMN severity scores	Composite UMN severity scores
Bulbar (n = 29)	Bulbar*	102	94
	Both arms	40	40
	Both legs	8	41
Arms (n = 34)	Onset arm (focus)	85	38
	Contralateral arm	41	13
	Ipsilateral leg	14	25
	Contralateral leg	6	20
	Bulbar	6	4
Trunk (n = 6)	Trunk*	24	NA
	Both arms	17	4
	Both legs	8	7
Legs (n = 29)	Onset leg (focus)	66	34
	Contralateral leg	37	24
	Ipsilateral arm	19	17
	Contralateral arm	16	14
	Bulbar	4	3

*Scores are doubled to normalize with limbs.

LMN = lower motor neuron; UMN = upper motor neuron; NA = not applicable.

METHODS General methods, patient selection, and excluded patients.

We chose charts from patients followed up serially through their disease in the ALS Neuro-Rehabilitation Clinic at Virginia Mason Medical Center until we reached 100 patients who met inclusion criteria. The inclusion criteria were that patients had been seen within 6 months of suspected diagnosis and met the modified El Escorial criteria for probable or definite ALS at the time or in the course of their disease.¹⁰ The exclusion criteria were patients who had major nonmotor or atypical ALS features, patients who had other diseases that could cause motor deficits, and patients 6 months beyond diagnosis. All patients had been examined by the same neurologist who specialized in ALS (J.R.), and all received similar initial evaluations that consisted of a history routinely ascertaining first symptoms and the time course of these first symptoms and a physical examination routinely seeking, grading, and recording motor signs. UMN signs routinely evaluated were spastic dysarthria, jaw jerk, hyperactive gag, emotional incontinence, limb reflexes > 2 on a four-point scale,¹¹ spread of limb reflexes, Hoffmann sign, increased muscle tone, and clonus. LMN signs routinely evaluated were atrophy, fasciculation, and weakness. EMG data were not used for determination of LMN involvement because needle examination was not performed on all regions or standardized for all patients. UMN or LMN signs of the truncal and axial muscles were not analyzed. Although LMN signs could potentially mask UMN signs, determining their coexistence is routine for ALS clinicians. Charts were reviewed with an Investigational Review Board and Health Insurance Portability and Accountability Act-compliant process (BRI IR3029600).

Indexing disease topography, severity, and duration.

We used both nominal and ordinal scales.¹² Motor manifestations were focal when one particular region or side was clearly noticed to have had early (or first) motor symptoms, and we determined this by patient history. These regions or sides established the index region, and the other body regions were then arranged relative to this as ipsilateral or contralateral and as

rostral or caudal. Bulbar or truncal/respiratory index regions were not themselves lateralized. The duration of symptoms was the interval from the first symptoms to the time of the initial evaluation. UMN and LMN signs were determined by physical examination as described above. The severity of UMN and LMN signs was established by retrospective grading severity of UMN and LMN signs in each body region from review of the recorded physical examination and the severity of motor signs by the following scale: 0 = no involvement; + = definite but trace involvement; ++ = moderate involvement; and +++ = significant and severe involvement.

Data processing and disease indices. The UMN and LMN scores in each body region as indexed to the body region of first symptoms were entered into a database (Excel:mac, Microsoft® Excel 2004, Microsoft, Redmond, WA) and were sorted to analyze the anatomic distribution signs. UMN and LMN severity indices were UMN or LMN severity scores summated by body regions; total severity index was the sum of both of these indices; %LMN index was LMN severity index divided by total severity index expressed as a percent. One-third of the charts were reviewed twice, and abstracted data were highly reproducible.

RESULTS Demographics and overall data.

The mean age was 62 years (range 26 to 85 years). Fifty-eight percent of patients were men and 42% were women. Ninety-two percent were sporadic and 8% were familial, including 2 unrelated patients with SOD1 gene mutations (A4V and G93A). The average time from onset of symptoms to the examination was 11 months (range 2 to 35 months). The average Functional Rating Scale score in the 77 patients for whom it was available within 4 months of the initial evaluation was 32.5 out of 40 (range 22 to 40).¹³ The composite data are presented in table, and the full

data separated by region of onset and sorted by severity of UMN deficits and of LMN deficits are presented in the tables E-1 through E-7 on the *Neurology* Web site at www.neurology.org. Twenty-nine patients had onset in the bulbar muscles, usually predominant in one specific muscle group such as masticatory or pharyngeal or laryngeal or tongue muscles. Thirty-four patients had onset in the arms, 24 in right arm and 10 in left arm. Twenty-nine patients had onset in the legs, 13 in right leg, 15 in left leg, and 1 in both. Six patients had onset primary in truncal or respiratory muscles, usually with respiratory and postural problems at the outset. Two patients had nonlocalizable onset. In ascertainment, we excluded 18 patients for the following reasons: neuropsychiatric impairment (3 with frontotemporal dementia and 4 with schizoaffective disorder), medical problems (2 with diabetes, 1 with alcoholism, 1 with multiple sclerosis, and 1 with chronic pain syndrome), and disease beyond 6 months of diagnosis.

Bulbar onset patients. Distribution of UMN signs (table E-1). Twenty-four of 29 bulbar onset patients had evidence of UMN deficits (5 had pure LMN deficits). Four of these 24 had UMN deficits confined to bulbar muscles, 7 also had UMN deficits in the arms, and 13 also had UMN deficits in arms and legs. Severity of deficits was greater rostral than caudal and often asymmetric.

Distribution of LMN signs (table E-2). Twenty-seven of 29 bulbar onset patients had LMN deficits (2 had pure UMN deficits or pseudobulbar palsy). Twelve had LMN deficits confined to bulbar muscles, 11 also had LMN deficits in the arms, and 4 also had LMN deficits in arms and legs. Severity of deficits was generally greater rostral than caudal and asymmetric.

UMN and LMN severity. There was no correlation between severity of UMN and LMN involvement.

Arm onset patients. Distribution of UMN signs (table E-3). Twenty-three of 34 arm onset patients had UMN deficits (1 other had suspected but not definite UMN deficits, and 10 had pure LMN deficits). Six had UMN deficits confined to arm of onset; 16 also had UMN deficits in the ipsilateral leg—12 of whom also had it in the contralateral leg and one of whom had it in the contralateral arm. Severity of deficits was generally worse in the arm of onset.

Distribution of LMN signs (table E-4). All 34 arm onset patients had LMN deficits (none had pure UMN deficits). Five had LMN deficits confined to the arm, 18 also had LMN deficits in the contralateral arm, 4 also had LMN deficits in the ipsilateral leg without deficits in the contralateral arm, 1 also had LMN deficits in both the contralateral arm and

the ipsilateral leg, 4 also had LMN deficits in all other limbs, 2 also had LMN deficits in bulbar muscles as well as all other limbs, and no patients had LMN deficits in the contralateral leg without deficits in the ipsilateral leg. Severity of deficits was generally worse in the arm of onset. In the legs, it was usually asymmetric, always worse ipsilateral.

UMN and LMN severity. There was no correlation between severity of UMN and LMN involvement.

Leg onset patients. Distribution of UMN signs (table E-5). Nineteen of 29 leg onset patients had UMN deficits (10 had pure LMN deficits). Seven had UMN deficits in the contralateral leg but not in the ipsilateral arm, 2 had UMN deficits in the ipsilateral arm but not in the contralateral leg, and 10 had diffuse UMN deficits. UMN deficits were never seen in the contralateral arm without concurrent deficits in contralateral leg and ipsilateral arm. Severity of deficits was generally worse in the leg of onset.

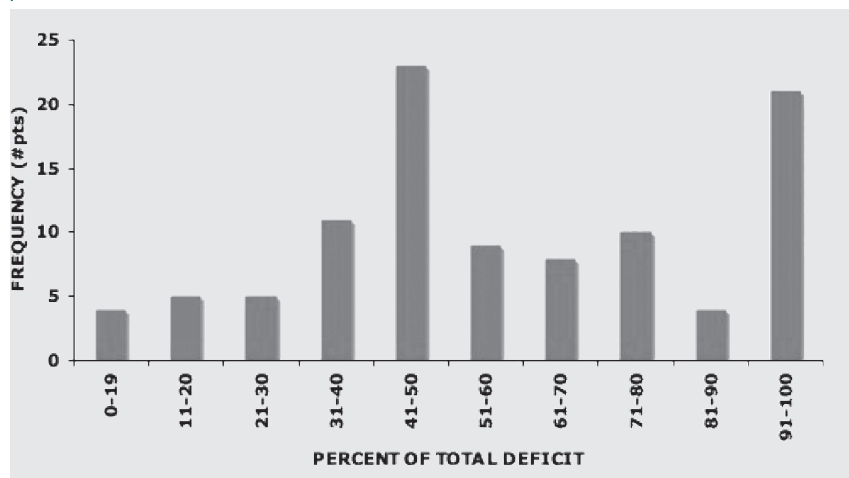
Distribution of LMN signs (table E-6). Twenty-seven of 29 leg onset patients had LMN deficits (2 had pure UMN deficits). Four had LMN deficits confined to the index leg, 8 also had LMN deficits in the contralateral leg, 2 also had LMN deficits in both the contralateral leg and the ipsilateral arm, none had LMN deficits in the ipsilateral arm without deficits in the contralateral leg, 1 also had LMN deficits in the contralateral arm but not in the ipsilateral arm, 8 also had LMN deficits in all limbs, and 4 also had LMN deficits in bulbar muscles as well as all or most limbs. Severity of deficits was generally worse in the leg of onset. When LMN deficits were in the arms, it was often asymmetric, usually worse ipsilateral.

UMN and LMN severity. There was no correlation between severity of UMN and LMN involvement.

Truncal or respiratory and diffuse onset patients (table E-7). Of the 6 patients with truncal or respiratory onset symptoms, 3 had LMN deficits in the arms and 3 had LMN deficits in arms and legs. None had bulbar deficits. Two had no UMN deficits in the limbs, and 4 had various patterns of UMN deficits in the limbs. Two patients had “diffuse onset” in that they were unable to localize a region of onset. Their clinical examinations showed diffuse LMN and UMN deficits, but one had a pattern of deficits suggesting bulbar onset.

Severity indices, progression indices, and survival. The frequency histograms of UMN, LMN, and total severity indices had essentially normal distributions (data not shown). The frequency histogram of percent of deficits due to LMN deficits showed “pure” LMN deficits in 25%, “pure” UMN deficits in 9%, and a variable mix of UMN and LMN with a

Figure Frequency histogram of the percent of overall deficit attributable to lower motor neuron deficit



The relative contributions of lower motor neuron and upper motor neuron deficits to the overall deficits are highly variable and not likely related to each other. The slight preponderance of lower motor neuron deficits is likely explained by their masking of upper motor neuron deficits.

normal distribution in the remaining 66% (figure). There was no correlation between UMN severity and LMN severity.

DISCUSSION In 98% of patients, the early motor manifestations were focal and involved virtually any body region and sometimes discrete sites within those regions. They frequently had progressed to involve contiguous body regions where they appeared with decreasing severity. When they began in the limbs, they were virtually always unilateral. In the arms, the right side predominated over the left side, whereas in the legs, they were equally divided, suggesting use may be a risk factor, an observation that has not been made by others who have reported on this.^{3,14} The distribution of body regions was approximately equal in bulbar, arm, and leg regions, and there was a small percent that began in truncal or respiratory muscles, a distribution that suggests a relationship either to the number of motor neurons or to their use.

Both UMN and LMN signs of these early focal motor manifestations were maximal in the same peripheral body region and had spread outward into contiguous body regions. The outward spread of signs, however, was different between UMN and LMN, either to different peripheral body regions or to the same peripheral body region but to different extents. This incongruity may be explained by the observation that they each seemed to conform to underlying neuronal anatomy, which is somatotopically arranged, rather than to body region anatomy. Three of the important differences between UMN and LMN anatomy are 1) arms are contiguous at the LMN level but not at the UMN level; 2) bulbar regions are relatively contiguous at the LMN level but not at the UMN level, and bilaterality at the UMN level is required for signs; and 3) anatomic

distances between body regions are different for UMN and LMN: UMNs span 11 to 12 cm along the motor cortex, and LMNs span 50 cm along the brainstem and spinal cord.^{15,16} This likely also explains the complexity of motor manifestations as disease progresses, manifestations resulting from summation of the outward spread of motor neuron degeneration at both levels over time.

Outward spread of both UMN and LMN signs seemed to be weighted toward caudal body regions over rostral ones, suggesting underlying motor neuron degeneration had preferential directions of outward spread rather than simple radial or centrifugal directions. This suggests that there may be differences in motor neuron vulnerability, a possibility previously raised by Swash^{17,18} and by Brooks et al.^{6,14} Although the study by Brooks et al. evaluated this longitudinally, in contrast to our cross-sectional study, and found symptom accrual with similar preferential directions of spread, their data are based on patient questionnaires and therefore tracked functional change of body region, not UMN and LMN anatomic change.^{6,14}

The severity of UMN and LMN signs were essentially independent of each other except for a slight predominance of LMN signs over UMN signs, likely explained by LMN signs masking UMN signs. Charcot named ALS based on his belief that lateral sclerosis is amyotrophic, i.e., UMN degeneration causes LMN degeneration.^{19,20} But Gowers believed that UMN and LMN degenerations are simultaneous and independent.¹ Most²¹⁻²³ but not all²⁴ neuropathologic studies that have sought correlation have found none, supporting Gowers' view of UMN and LMN independence. Our findings suggest that in early disease, there is linkage between UMN and LMN degenerations in terms of the corresponding body region that manifests motor deficits but independence between them in terms both of severity of involvement and of outward spread.

Because the clinical phase of ALS is a continuation of a latent preclinical phase,²⁵⁻²⁹ progressive motor neuron degeneration might have a highly discrete true onset and might be a focally advancing and summing process. If so, advancement would be *within* UMN and LMN anatomic levels and also possibly *between* UMN and LMN anatomic levels, the latter possibly advancing by *convergence* (one LMN receiving input from many UMNs) and *divergence* (one UMN innervating many LMNs).³⁰ In this regard, it is reasonable at least to consider that the shared focal peripheral body region,³¹ as well as its UMN^{32,33} and LMN³⁴ innervations, may be significant in the initiation of disease because it too defines onset anatomy, before degeneration becomes dif-

fuse and complex. It may be that the focality and contiguity that are observed in the three dimensions of the motor system are not as simple as presented here, but nonetheless, they are both remarkable phenomena and require study.

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