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Primary Lateral Sclerosis and Early Upper Motor Neuron Disease: Characteristics of a Cross-Sectional Population

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Abstract

Objectives—The goals of this study were to characterize clinical and electrophysiologic findings of subjects with upper motor neuron disease and to explore feasibility of clinical trials in this population.

Methods—Twenty northeast ALS consortium (NEALS) sites performed chart reviews to identify active clinical pure upper motor neuron disease patients. Patients with hereditary spastic paraplegia (HSP) or meeting revised El Escorial electrodiagnostic criteria for ALS were excluded. Patients were classified into two groups according to the presence or absence of minor electromyography (EMG) abnormalities.

Results—233 subjects with upper motor neuron disease were identified; 217 had available EMG data. Normal EMGs were seen in 140 subjects, and 77 had minor denervation. Mean disease

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duration was 84 (±80) months for the entire cohort with no difference seen between the two groups. No difference was seen in clinical symptoms, disability, or outcome measures between the two groups after correcting for multiple comparisons.

Conclusions—Minor EMG abnormalities were not associated with phenotypic differences in a clinical upper motor neuron disease population. These findings suggest that subtle EMG abnormalities can not necessarily be used as a prognostic tool in patients with clinical upper motor neuron disease. This study also demonstrates the availability of a large number of patients with upper motor neuron diseases within the NEALS network and suggests feasibility for conducting clinical trials in this population.

Keywords

primary lateral sclerosis; upper motor neuron disease; amyotrophic lateral sclerosis; registry; corticospinal motor neurons

Introduction

Primary lateral sclerosis (PLS) is an idiopathic motor neuron disorder that causes degeneration of upper motor neurons, leading to progressive weakness, spasticity, and functional disability. Motor neuron diseases as a whole are considered rare [1], and pure upper motor neuron disease typically represents only 5% of the total motor neuron disease population [2], [3], [4].

It is unclear whether PLS and amyotrophic lateral sclerosis (ALS) represent different phenotypes within the same disease process or if PLS is a distinct entity with a unique pathogenesis. Studies have shown that in patients who clinically appear to have pure upper motor neuron disease, electrophysiological studies [1] and muscle biopsy histopathology [2] often demonstrate lower motor neuron disease. These findings suggest that PLS could represent a subtype within the ALS continuum, and over time many cases that start as upper motor neuron disease could progress to ALS. However, there is clearly a group of patients with longstanding PLS that demonstrate only upper motor neuron disease for many years without developing signs of lower motor neuron dysfunction [3], and these patients are clinically quite different from ALS. Upper motor neuron-predominant disease can be distinguished from typical ALS based on younger age of onset, female predominance in older patients, different patterns of spread, and significantly longer survival with mean duration of disease in PLS estimated at 5-20 years [3].

When a patient initially presents with upper motor neuron disease, clinicians do not have adequate predictors to determine which patients will continue as PLS and which patients will go on to meet criteria for ALS [6]. In fact, because early upper motor neuron disease can develop into an ALS phenotype over time, current diagnostic criteria requires pure upper motor neuron disease to be present for 4 years before a diagnosis of PLS can be made [5], [6], [7]. This uncertainty not only limits the clinician's ability to adequately counsel the patient, but also impedes upper motor neuron disease research progress. If PLS and ALS share the same underlying pathophysiology, patients with early upper motor neuron disease could benefit from inclusion into ALS clinical trials. Conversely, if PLS is a distinct

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disorder, then it is crucial to identify these patients earlier in their disease course and correctly diagnose them for targeted disease-specific research efforts. Studies that better characterize upper motor neuron disease are therefore crucial to facilitate research progress in this area.

Previous clinical studies of upper motor neuron disease were often based on small sample sizes because of low disease prevalence. The aim of this study was to better characterize the clinical and electrophysiologic features of a large cross-sectional cohort of patients with upper motor neuron disease. We hypothesized that among patients with clinical pure upper motor neuron disease, minor EMG abnormalities could be predictive of phenotypic differences or a higher level of disability, as mild EMG abnormalities could be an early indicator of an eventual transition to ALS. Another goal of this study was to develop a registry of active upper motor neuron disease patients seen in United States motor neuron disease clinics over a one-year period to explore the feasibility of multicenter clinical trials in this patient population. Understanding the demographic and clinical features of these patients will provide valuable insight into the available population for future upper motor neuron disease research efforts.

Materials and Methods

Twenty member sites of the Northeast ALS Consortium (NEALS) participated in this retrospective study. Institutional Review Board approval was obtained from each participating site. Each site performed a retrospective chart review to identify patients with upper motor neuron disease who were seen in clinic within the past 12 months.

Subjects were eligible for inclusion in the registry if they were age 18 or older, had signs and symptoms of an upper motor neuron disorder, and were seen at the site between September 1, 2011 and December 31, 2012. Subjects were excluded if they had lower motor neuron signs on their last neurologic exam, had a family history of Hereditary Spastic Paraplegia (HSP), had genetic testing positive for HSP, or had an EMG satisfying the revised El-Escorial electrodiagnostic criteria for ALS (Figure 1). Electrodiagnostic El Escorial criteria for ALS requires that needle electromyography (EMG) examination show evidence of active and chronic denervation in at least two of four regions (brainstem, cervical, thoracic, or lumbosacral). For the cervical and lumbosacral regions, EMG abnormalities must be present in more than two muscles innervated by two different nerve roots and peripheral nerves [8],[9]. Subjects were classified as having a normal EMG if they had fasciculation potentials in no more than two muscles, had no fibrillations, and had no motor unit changes; otherwise they were classified as having minor denervation on EMG.

For each subject, a data collection form included date of form completion, age, gender, time from last clinic visit, time from symptom onset to completion of form, location of upper motor neuron signs at onset and at last visit, time since last EMG and EMG findings, level of physical disability (including walking with any assistance or use of a cane, walker or wheelchair), clinical symptoms, revised ALS functional rating scale (ALSFRS-R) [10], vital capacity, use of noninvasive ventilation, and use of a feeding tube.

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Descriptive statistics were performed for the total cohort and comparing the group with normal EMG findings to the group with minor denervation on EMG. Categorical variables (gender, site of symptom onset, sites of upper motor neuron involvement, disability variables, symptom variables, use of non-invasive positive pressure ventilation, and use of a feeding tube) were assessed with logistic regression, and continuous variables (age, time since symptom onset, ALSFRS-R, and vital capacity) were assessed with linear regression. For all outcomes of interest except for gender and site of onset, tests of significance were adjusted for disease duration, measured as months from since symptom onset to time of last visit. All tests were performed at the 0.05 significance level. The Bonferroni correction was applied to control for multiple comparisons.

Results

Data were collected on 233 subjects from 20 NEALS sites, with each site contributing data on 2-32 subjects. Sixteen out of 233 subjects were excluded because of missing EMG data, leaving 217 patients for analysis. Of those, 140 subjects had normal EMGs, and 77 had minor denervation on EMG (Figure 1). Mean time from symptom onset to most recent EMG was 38 months (±42). Mean disease duration for the group was 84 (±80) months and did not differ between patients with normal EMGs compared to patients with minor denervation ($p = 0.777$). One hundred and thirty two had disease duration of 48 months or more, meeting criteria for a diagnosis of PLS [5-7]. The mean age of patients was 61 (±11) years, and 50% of patients were male (Table 1).

Upper motor neuron dysfunction was most prevalent in the lower extremities at the time of symptom onset (85%) and at time of the last visit (98%) for the total cohort and for both groups (patients with normal EMG and patients with minor denervation on EMG). When comparing the 2 groups, no difference was seen in site of upper motor neuron involvement at symptom onset (84% for normal EMG, 86% for minor denervation, $p = 0.763$). When comparing groups and adjusting for time since symptom onset, upper extremity involvement was more common at the time of last visit in the group with minor EMG abnormalities. This difference did not remain statistically significant after applying a correction for multiple comparisons (Table 1).

The majority of subjects in the total cohort and in each group (patients with normal EMG and patients with minor denervation on EMG) required assistance for walking. No differences were seen between groups in use of a cane, walker, or walking without assistance. More patients in the group with minor EMG abnormalities required use of a wheelchair when compared to the normal EMG group after adjusting for disease duration, but this difference did not remain statistically significant after applying a correction for multiple comparisons (Table 2).

The most common symptoms for the entire cohort were spasticity (95%), abnormal gait (94%), dysarthria (68%), dysphagia (55%), and pain (43%). When comparing subjects with no EMG abnormalities to subjects with minor denervation on EMG after controlling for disease duration, no differences were seen in symptom frequency between groups (Table 3).

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Revised ALS Functional Rating Scale (ALSFRS-R) data were available for 95 subjects, with a mean ALSFRS-R total score of 33 (±9). No differences were seen in ALSFRS-R when comparing subjects with normal EMG to subjects with minor denervation on EMG after controlling for disease duration ($p = 0.331$).

Vital capacity measurements were available for 110 subjects, with a mean vital capacity of 73% predicted (±22%) for the group. No differences were seen in vital capacity when comparing the two groups after adjusting for disease duration ($p = 0.312$).

Non-invasive positive pressure ventilation (NIPPV) was used by 17% of subjects, with no difference between groups after controlling for disease duration ($p = 0.991$). Feeding tubes were used in 8% of subjects in the cohort; 5% of subjects with normal EMG and 13% of subjects with minor denervation had feeding tubes. This difference was significant after controlling for disease duration ($p = 0.036$), but did not remain significant after correcting for multiple comparisons.

Discussion

When comparing clinical pure upper motor neuron disease patients with normal EMG findings to those with minor EMG abnormalities, no differences were seen in site of onset, frequency of clinical symptoms, ALFRS-R, vital capacity, or use of non-invasive positive pressure ventilation. In a previous study where patients with UMN disease self-reported their most bothersome symptoms [11], abnormal gait, dysarthria, and spasticity were most frequent, similar to the findings in this study. The group with minor EMG abnormalities had more upper extremity involvement at last clinic visit, more frequently required use of a wheelchair, and were more likely to have a feeding tube. However, these differences did not survive a correction for multiple comparisons. Overall, minor EMG abnormalities in subjects with clinical upper motor neuron disease were not associated with a specific phenotype or disease severity. These findings suggest that subtle EMG abnormalities can not necessarily be used as a prognostic tool in patients with clinical upper motor neuron disease. The only clear predictor of disease severity in upper motor neuron disease subjects in this cohort was disease duration, which we expect given the progressive nature of motor neuron disease.

This study represents one of the largest databases of upper motor neuron disease and PLS patients to date. This registry of over 230 active patients from 20 United States sites within the NEALS network demonstrates the feasibility of upper motor neuron disease clinical research, both based on the number of potentially eligible active patients and the number of investigators that showed interest in upper motor neuron disease research efforts by contributing data.

This study has several limitations. The retrospective nature of the registry could result in the underreporting of symptoms if documentation in the clinic notes was inadequate. Data were obtained in a cross-sectional manner from the most recent clinic visit for each patient, which limits the analysis of disease progression. EMG data and protocols for genetic testing were not standardized across all sites given the retrospective nature of this study. Although we

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excluded patients with family history of motor neuron diseases and patients how have known positive genetic testing for HSP, genetic testing for HSP was not performed on many of the registry participants, so it is possible that some HSP patients were misclassified in this registry. EMGs were performed at the discretion of the treating clinician at variable time intervals, so many of the patients do not have follow-up electrodiagnositc studies later in their disease course. Therefore, future prospective studies are warranted to validate these results. Additionally, performing multiple comparisons could result in falsely identifying significant differences between groups, but by correcting for multiple comparisons, this study could be underpowered to detect subtle differences between groups, particularly in less common symptoms.

Ultimately, additional research is needed to unveil the underlying pathogenic mechanisms for upper motor neuron disorders to ensure accurate classification and diagnosis of motor neuron disease patients. Future studies with longitudinal data collection and incorporation of biofluid and genetic analyses are needed to verify that upper motor neuron disease patients with similar phenotypes do indeed share biologic commonalities. This type of study will allow for a better understanding of disease pathogenesis and could lead to a more accurate classification system for upper motor neuron disease. Plans to add longitudinal data and biofluid sample collection to the NEALS Upper Motor Neuron Disease Registry are underway.

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Abbreviations

ALS	Amyotrophic Lateral Sclerosis
ALSFRS-R	revised Amyotrophic Lateral Sclerosis Functional Rating Scale
EMG	electromyography
HSP	hereditary spastic paraplegia
NEALS	Northeast Amyotrophic Lateral Sclerosis consortium
PLS	primary lateral sclerosis

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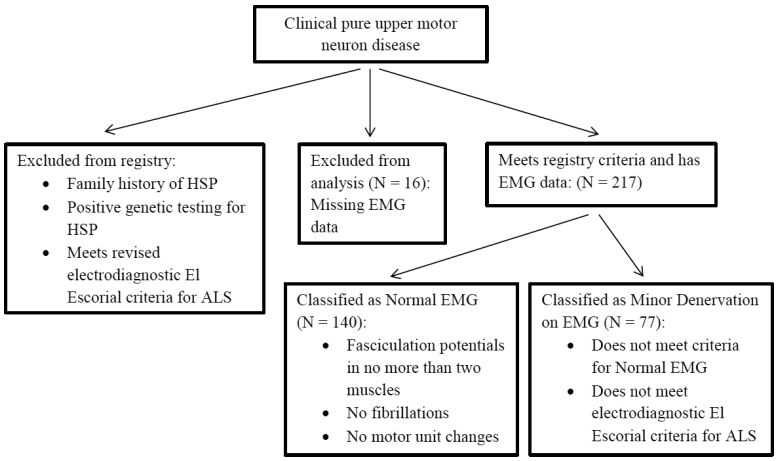

Figure 1.
Inclusion and Exclusion Criteria for the NEALS Upper Motor Neuron Disease Registry

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Table 1

Description of Upper Motor Neuron Disease Registry Subjects

	Normal EMG n=140	Minor Denervation on EMG n=77	Total n=217	p-value
Time since onset in months	82 (82)	86 (78)	84 (80)	0.777
Age in years	60 (11)	63 (11)	61 (11)	0.137
Gender (% male)	51%	49%	50%	0.848
Upper motor neuron involvement at onset (%)				
Lower extremities (%)	84%	86%	85%	0.763
Upper extremities (%)	40%	31%	37%	0.221
Bulbar (%)	24%	30%	26%	0.388
Upper motor neuron involvement at last visit (%)				
Lower extremities (%)	98%	99%	98%	0.841
Upper extremities (%)	84%	95%	88%	0.018*
Bulbar (%)	62%	64%	63%	0.736

Continuous variables are displayed as: mean (standard deviation).

Models were adjusted for time since symptom onset for upper motor neuron involvement at last visit

Significant P-values marked with an asterisk (*)

EMG, Electromyography

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Table 2

Level of disability

	Normal EMG n=140	Minor Denervation on EMG n=77	Total n=217	p-value
Use of any walking assistance	74%	77%	75%	0.482
Use of cane	21%	16%	19%	0.338
Use of walker	37%	34%	36%	0.675
Use of wheelchair	34%	47%	38%	0.047*
Walking unassisted	29%	26%	28%	0.551

Significant p-values marked with an asterisk (*)

Models were adjusted for disease duration for all variables above

EMG, electromyography

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Table 3

Symptoms reported by registry subjects

	Normal EMG n=140	Minor Denervation on EMG n=77	Total n=217	p-value
Spasticity	97%	92%	95%	0.097
Abnormal gait	94%	95%	94%	0.853
Dysarthria	68%	67%	68%	0.994
Dysphagia	51%	62%	55%	0.059
Pain	43%	43%	43%	0.839
Sleeping Difficulty	36%	33%	35%	0.851
Fatigue	30%	41%	34%	0.108
Depression	32%	34%	33%	0.727
Pseudobulbar Affect	33%	31%	32%	0.86
Sialorrhea	28%	32%	30%	0.45
Shortness of Breath	26%	30%	28%	0.504
Anxiety	23%	19%	21%	0.666

Models were adjusted for disease duration for all variables above

EMG, electromyography