Published in final edited form as:
Muscle Nerve. 2013 January ; 47(1): 28–32. doi:10.1002/mus.23496.

Clinical Evolution of Pure Upper Motor Neuron Disease/ Dysfunction (PUMND)

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Abstract

Introduction—PLS is defined as pure upper motor neuron disease/dysfunction (PUMND) beyond 48 months after symptom onset. We know little about its early stages, but such knowledge would help to identify the mechanisms underlying PLS and ALS and determine why PLS patients seem to be protected against lower MND (LMND).

Methods—We reviewed 622 MND cases during a 4-year period and identified 34 patients with PUMND (5.4%).

Results—Among 23 cases with follow-up data/EMGs (2 had only 1 EMG), 13 (57%) remained classified as PUMND, and 8 (35%) developed LMND (mean, 51.4 months after onset). Of these 8, LMND developed in 3 after 48 months from symptom onset. Patients with PUMND and LMND were more functionally impaired (P=.02). Separately, we identified 5 patients with PUMND who developed LMND long after 48 months (range, 50–127 months).

Conclusion—PLS belongs to the ALS spectrum, and perhaps all cases eventually develop LMND.

Keywords

amyotrophic lateral sclerosis; lower motor neuron; upper motor neuron; pure upper motor neuron disease/dysfunction; motor neuron disease

Introduction

Conventionally, motor neuron disease (MND) comprises a clinical spectrum that ranges from exclusively lower motor neuron (LMN) disease (progressive muscular atrophy) to purely upper motor neuron (UMN) disease (primary lateral sclerosis, PLS). In the broad middle exists ALS, which affects both UMNs and LMNs (1). PLS, therefore by definition, manifests as pure UMN disease/dysfunction (PUMND) from onset throughout the disease course. However, as most neuromuscular disease experts know, LMN disease/dysfunction (LMND) sometimes develops in patients with a well-established diagnosis of PLS after many years (2–6). At the earlier stages of the disease, however, accepted diagnostic criteria require that at least 4 years elapse between disease onset and making the diagnosis of PLS,

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No disclosures from E. D'Amico, M. Pasmantier, Y-W. Lee, and L. Weimer.

because if LMND develops, it is more likely to happen during these early stages (7). The development of LMND in previous PUMND may be critical, because it appears to change the diagnosis and even its functional prognosis (8). We reviewed the clinical outcome of PUMND in a single center patient population.

Materials and Methods

IRB approval was obtained from the Columbia University Medical Center for a retrospective chart review of patients newly seen at the Eleanor and Lou Gehrig MDA/ALS Research Center from January 2003 through 2006 (a period of 4 years). We ended the review in 2006, because this allows a sufficient follow-up period (to December 31, 2011) of at least 4 years from onset of PUMND to meet the accepted criteria for determining whether the disease is PLS or has evolved into ALS.

All cases of adult MND of unknown cause were identified through the Eleanor and Lou Gehrig MDA/ALS Research Center Patient Database, which contains over 4,900 MND records. We searched for the cases that we defined as PUMND by reviewing all the clinical, neurological, and laboratory features.

Cases were included if they had PUMND, which is arbitrarily defined as the presence of clinically pure UMN findings and include widespread abnormal hyperreflexia, pathological reflexes, limb spasticity, spastic dysarthria, pseudobulbar affect, minimum or modest muscle weakness, along with no local muscle atrophy and an otherwise normal neurological examination. Furthermore, nerve conduction studies are normal, as are needle electrode examinations [absence of signs of acute and chronic denervation of at least 2 and typically 3 limbs, at least 1 cranial (typically bulbar) muscle, and the thoracic paraspinal muscles at 2 or more levels, according to the El Escorial electromyography (EMG) and Awaji criteria (9, 10)]. Cases with mild, well-defined common entrapment neuropathies were not excluded. Patients who were found to have identifiable causes for degeneration of the corticospinal tracts other than MND on laboratory studies, including neuroimaging examinations, were excluded.

We arbitrarily defined the presence of LMND in this study solely on the basis of EMG findings. When EMG results showed acute denervation (positive waves or fibrillation potentials) in 1 or more muscles with or without chronic neurogenic motor unit potentials and without other evident cause, we concluded that LMND was present. Isolated fasciculation potentials in a few muscles were not considered to be evidence of LMND, unless the findings satisfied the Awaji criteria, specifically signs of chronic neurogenic changes in motor unit action potentials and changes in recruitment not explained by other causes.

Although the EMGs were not always performed by the same electromyographer, most (89%) were completed at the EMG Laboratory at Columbia University Medical Center; therefore, the electrodiagnostic protocol for all patients with PUMND, whether an initial or subsequent study, did not change. Subsequent studies were repeated on the same sides and sites as the previous studies, regardless of electromyographer.

Demographic and clinical data were further reviewed. The age, signs and symptoms at onset, disease duration, the time of PUMND diagnosis, functional status, use of medical assistive devices and the extent of UMN and LMN signs were noted.

Finally, we systematically reviewed the current literature on PLS autopsy studies and specifically searched for any electrophysiological or histological evidence of LMND.

A few of our patients may be the same as those reported in the studies done by Gordon et al (7, 8), particularly the long-standing cases that we identified in 2007. However, we focused on patients with PUMND, and among these patients there was no overlap between the investigations. Also, in this project, we do not use the term UMN-dominant ALS (8). When neurologists describe patients with ALS, we often loosely use UMN-dominant ALS to describe those who have more UMN than LMN signs (11) and *vice versa* in cases of LMN-dominant disease. Gordon et al (7, 8) used UMN-dominant ALS in a specific context, that is, in association with PLS. To avoid any confusion with potential clinical descriptive terminology and emphasize the disease evolution, we have used the term PUMND with LMND to describe cases that initially appear to be PLS, based on the Gordon criteria, but then later develop LMND.

Results

We identified 622 new cases of MND during the 4-year period from January 2003 through December 2006. Among these cases, we identified 34 with PUMND (5.4%). Eleven patients had neither reliable EMG studies nor sufficient clinical follow-up data and thus were excluded from study. Detailed analyses were completed for the remaining 23 cases (Table 1), and 21 cases had at least 2 EMG studies. Among these 23 cases, 8 (34.8 %) developed LMND due to new denervation as seen on EMG (mean, 51.4 ± 28.3 months after symptom onset; range, 24.5 to 102 months). In this group of 8, LMND developed in 3 patients after the 48-month observation period from symptom onset (at 64, 82, and 102 months) required for a diagnosis of PLS (7, 12). PUMND continued to be observed in 13 cases (56.6%), as evidenced by normal EMG studies during follow up (mean, 55 ± 28.5 months from onset). However, 5 of 13 (38.4%) had their final EMG analysis before 48 months after symptom onset (mean, 25.5 ± 5.1), so these cases would require an additional EMG study before we could confirm PLS per the Gordon criteria. The 2 PUMND cases with only 1 EMG remained classified as PUMND based on clinical findings alone. One patient had a period from onset to first negative EMG of 198 months, and the second patient had a period of 37 months. Therefore, using the Gordon criteria (7, 12), 9 of our patients (1.4% of all MND cases) could be classified as definite PLS.

Demographic and clinical features of the 15 patients with PUMND (presumably PLS) and 8 patients with PUMND plus LMND are summarized in Table 1. The 2 groups did not differ in age of onset, age at first evaluation at our Center, or time from onset to the last EMG. However, the functional outcome of the last examination differed significantly between these 2 groups (Fisher exact test, $P = 0.02$). Eight patients in the PUMND group were still fully ambulatory, 6 were using walkers, and 1 patient was in a wheelchair. In contrast, none of the 8 patients with PUMND plus LMND were ambulatory; 5 were using walkers, and 3 were in wheelchairs. The ALS Functional Rating Scale was not available consistently for every patient. A deceased patient in the PUMND with LMND group had already required a wheelchair 2 years before death.

An additional 5 patients newly seen at our Center starting after January 1, 2007 were not included in the analyses; however, we decided to review them, albeit separately, because these patients had PUMND and subsequently developed LMND as detected on EMG long after the accepted 48-month cut off (mean, 77.6 ± 29.5 months; range, 50 to 127 months; Table 2).

Only a few PLS autopsy studies have been reported (4, 13–19) (Table 3). In reviewing them, we found that cases 1, 6, 7, 8, 9 and 10 had some histological changes suggesting anterior horn cell pathology, and EMG findings of cases 3, 5 and 9 showed some LMN involvement.

Cases 1, 3, 6, 7, and 9 had disease duration of less than 4 years. Only cases 2 and 4 suggested no LMND.

Discussion

In our single-center study, we found the frequency of PUMND to be 5.4% of all adult MND cases. Chiò et al (20) found the frequency of PUMND to be 4.0% in 1,332 MND incident cases in a large population-based study. Therefore, PUMND is among the rarest of the ALS subsets.

In this study, we evaluated the evolution of PUMND. We found nearly 40% of patients with PUMND developed EMG evidence of LMND. In 3 patients, LMND developed at 64, 82, 102 months, far after the required 48-month observation period, from symptom onset. Moreover, in all 5 additional patients we identified after the study period, LMND developed long after 48 months (50, 66, 67, 79 and 127 months). Gordon et al (7) also reported 3 patients who also had LMND after 48 months (60, 72, 137 months). It appears that a good proportion of cases still develop LMND after 4 years when it has been concluded that their disease is PLS. Obviously, our study is retrospective, so we cannot state the exact timing of LMND development. The distinction between PUMND (or PLS) and PUMND with LMND appears to be important for prognostication. At our center in 2009, Gordon et al. (8) identified 15 cases of UMN-dominant ALS and found that the patients had focal muscle weakness or bulbar onset of disease. Later in disease, weight loss, reduced forced vital capacity, and limb weakness predicted LMND but not PLS. Our patients with PUMND and LMND, as identified by EMG findings, clearly had significantly greater functional impairment. The presence of LMND seems to increase disease disability.

Moreover, a critical review of the autopsy cases revealed that only a couple of cases did not show clear evidence of LMND (Table 3). This again raises an important question as to whether PLS with absolute PUMND even exists. Furthermore, several cases which were concluded to be PLS had had a short disease duration, less than 4 years, suggesting that the clinical diagnosis of PLS was not established. Because so few autopsy studies are available, making a general statement is difficult. More autopsy studies of presumed PLS cases are essential.

PUMND appears to most often evolve into the ALS phenotype, whereas what appears to be true PLS remains rare, if it exists at all. Survival in PLS is markedly longer than that of all other MND phenotypes in the ALS spectrum. If they are all MNDs, biological factors must exist that prevent LMND from developing in those patients who appear to have PLS. Our task is to identify the clinical and biological factors involved so as to better understand the disease mechanisms to develop treatments for the ALS spectrum diseases.

Acknowledgments

Dr. Mitsumoto gratefully acknowledges the patients, who kindly participated in the study. Grant support from the NIEHS (1R01 ES016348 to Hiroshi Mitsumoto). Also to HM: funding from the MDA (grant number 4350), MDA Wings Over Wall Street, and The Judith and Jean Pape Adams Charitable Foundation, along with donations from the Spina Family, David Marren, the Senerchia family, the Drago family, and others who gave support. Georgia Christodoulou, M.A. assisted with the manuscript preparation. Cassandra Talerico, Ph.D. gave editorial assistance.

Disclosures (past 3 years): Hiroshi Mitsumoto, M.D., has received grant support as stated above. Dr. Mitsumoto also received grants from Avanir, Knopp, Biogen Idec., and Cytokinetics for clinical trials and honoraria for participating in advisory board meetings from Avanir, Sanofi-Aventis, Shionogi, and Biogen Idec. He is now a member of the Data Safety Monitoring Board for the NeuralStem clinical trial. He received honoraria from Sanofi-Aventis Japan for giving seminars at the annual meetings of the Japanese Neurological Society in 2009 and 2010 in Japan. He received a conference grant to Columbia University for 2011 International ALS Conference from

NIDNS, NIH ORDR, MDA, ALS Association, ALS Society of Canada, Adams Foundation, Ride for Life, ALS Hope Foundation, Les Turner Foundation, Sanofi-Aventis, Biogen Idec, Knopp, and Avania.

Abbreviations

ALS	amyotrophic lateral sclerosis
EMG	electromyography
LMN	lower motor neuron
LMND	lower motor neuron disease/dysfunction
MND	motor neuron disease
PLS	primary lateral sclerosis
PUMND	pure upper motor neuron disease/dysfunction
UMN	upper motor neuron

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Table 1

Demographic and Clinical Characteristics in PUMND and PUMND+LMND Groups

Initial disease classification of patient	Gender	Age of onset (years)	First evaluation (age, years)	Time from onset to last EMG (months)	Final disease classification	Functional outcome
PUMND						
1	M	62	62	29	PUMND	WA
2	M	44	44	50	PUMND	FA
3	M	45	47	25	PUMND	FA
4	F	33	33	72	PUMND	FA
5	M	71	72	29	PUMND	WA
6	F	74	76	17	PUMND	WC, NIV
7	F	74	76	95	PUMND	FA
8	M	34	36	28	PUMND	FA
9	F	59	62	90	PUMND	WA
10	M	62	66	51	PUMND	FA
11	F	54	58	57	PUMND	FA
12	M	54	60	76	PUMND	WA
13	F	31	39	97	PUMND	FA
14*	M	38	41	37	PUMND	WA
15*	F	43	60	198	PUMND	WA
Summary, PUMND	**8 M 7 F**	**51.8 (range,33–74)**	**55.5 (range, 33–76)**	**63.4 (range, 17–198)**	**PUMND**	**FA = 8†** **WA = 6†** **WC = 1†** **NIV = 1**
PUMND +LMND						
16	M	48	48	82	PUMND + LMND	WA
17	F	48	49	41	PUMND + LMND	WC (Dec)
18	F	46	49	38	PUMND + LMND	WA

Initial disease classification of patient	Gender	Age of onset (years)	First evaluation (age, years)	Time from onset to last EMG (months)	Final disease classification	Functional outcome
19	M	62	64	86	PUMND + LMND	WA
20	M	45	48	41	PUMND + LMND	WA
21	F	58	61	43	PUMND + LMND	WA
22	F	53	61	102	PUMND + LMND	WC, NIV
23	F	55	66	64	PUMND + LMND	WC, NIV
Summary, PUMND + LMND	**3 M 5 F**	**51.8 (range, 46–62)**	**55.7 (range, 48–66)**	**62.1 (range, 38–102)**	**PUMND + LMND**	**FA = 0** [†] **WA = 5 WC = 3 NIV = 2 Dec = 1**

Dec=deceased, FA=full ambulation, LMND=lower motor neuron disease/dysfunction, NIV=non-invasive ventilation, PUMND=pure upper motor neuron disease, WA=walker, WC=wheelchair.

[*] had only one EMG.

[†] $P = 0.02$ (2 by 3 Fisher Exact Test for the full ambulation, walker, and wheelchair groups).

Table 2

Demographic and clinical characteristics of 5 patients not included in the study

Patient	Gender	Onset of age	Age at First Evaluation	Last EMG from onset (months)	Final Disease Status	Functional Outcome
1	M	51	55	67	PUMND + LMND	WC
2	M	55	65	127	PUMND + LMND	WC, PEG
3	F	64	70	79	PUMND + LMND	WC, NIV, PEG
4	M	41	46	66	PUMND + LMND	WC
5	M	57	64	50	PUMND + LMND	WC

LMND=lower motor neuron disease/dysfunction, NIV=non-invasive ventilation, PEG=percutaneous endoscopic gastroscopy, PUMND=pure upper motor neuron disease/dysfunction, WC=wheelchair.

Table 3

Summary of recent autopsy studies in PLS

Case	Age, gender	LMN Signs, Symptoms	EMG denervation	Disease duration (years)	Neuropathology (LMN involvement)	Comments
Beal 1981 (13)						Hyaline inclusion in AHC
Case 1	66, F	B, A, L	−	3.5	+	
Younger 1988 (14)						
Case 2	71, M	B, A, L	−	5.5	−	−
Case 3	60, M	B, A, L	+	1.0	−	−
Case 4	66, M	B, A, L	−	10.0	−	prior stroke RMCA territory
Pringle 1992 (4)						
Case 5	71, M	B, A, L	+	15.0	−	cortical gliosis
Watanabe 1997 (15)						
Case 6	64, F	B, A, L	−	3.3	+	Hyaline inclusion in AHC
Konagaya 1998 (16)						
Case 7	76, M	B, A, L	−	3.6	+	FTD
Tan 2003 (17)						
Case 8	82 F	B, A, L	−	7.3	+	FTD
Short 2005 (18)						
Case 9	56, F	B, A, L	−	2.6	+	Typical ALS
Kosaka 2011 (19) Case 10	60, F	B, A, L	+	6.0	+	FTD, ubiquitin-positive inclusions in LMNs

A=arms, AHC=anterior horn cells, ALS=amyotrophic lateral sclerosis, B=bulbar, FTD=fronto-temporal dementia, L=legs, LMN=lower motor neuron; RMCA=right middle cerebral artery.