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The Clinical Spectrum of Isolated Peripheral Motor Dysfunction

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Abstract

Introduction—Isolated peripheral motor dysfunction due to lower motor neuron or peripheral nerve disorders presents an interesting challenge to clinicians because of the diverse differential diagnosis with a broad range of prognoses.

Methods—We retrospectively reviewed clinical data of adults who presented over 12 years with muscle weakness, atrophy, or fasciculations, but without hyperreflexia or sensory involvement.

Results—In 119 patients, 52% had a motor neuron disease (MND), 13% had immune neuropathies, 11% had genetic neuronopathies, 10% had residual or post-polio syndrome, 5% had benign fasciculation, 1% had an infectious etiology, and 8% were not given a final diagnosis. Only MND patients had cognitive dysfunction or frontal release signs. Bulbar and respiratory symptoms virtually excluded consideration of immune neuropathy.

Conclusions—Only half of the patients were diagnosed with MND. A significant minority have treatable conditions. Cognitive involvement, frontal release signs, and bulbar or respiratory symptoms are strongly suggestive of MND.

Keywords

amyotrophic lateral sclerosis; isolated peripheral motor dysfunction; motor neuron disease; multifocal motor neuropathy; progressive muscular atrophy

Patients who present with isolated dysfunction of the peripheral motor system pose an interesting challenge to the clinician. The simultaneous combination of upper and lower motor neuron (UMN and LMN) signs has a relatively narrow differential diagnosis, which is dominated by amyotrophic lateral sclerosis (ALS), the most common form of motor neuron disease (MND). Isolated peripheral motor dysfunction (IPMD), by contrast, has a much broader differential diagnosis, encompassing a diversity of pathophysiologic mechanisms and a wide range of prognoses. IPMD may localize to the LMN, neuromuscular junction, or muscle. In this study, we focused on disorders that affect anterior horn cell bodies, axons, or

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Additional Supporting Information may be found in the online version of this article.

These findings have been presented in abstract form at the following meetings: the 35th annual Carrel-Krusen Neuromuscular Symposium, February 2013, Dallas, TX; the 65th annual meeting of the American Academy of Neurology, March 2013, San Diego, CA; and the 60th annual meeting of the American Association of Neuromuscular and Electrodiagnostic Medicine, October 2013, San Antonio, TX.

myelin sheaths in relative isolation. These include neurodegenerative, autoimmune, genetic, infectious, toxic, and idiopathic conditions.¹

Previous reports have offered a focused picture of this clinical spectrum as it relates to MND. Two studies reported the prevalence of mimic syndromes in MND patient registries, where patients had been misdiagnosed with either ALS² or progressive muscular atrophy (PMA),³ and found that multifocal motor neuropathy (MMN) was the most common disorder to be mistaken for MND. We conducted a broader survey of this clinical spectrum by reviewing all patients referred to our tertiary academic neuromuscular clinic with IPMD considered to be caused by an LMN or peripheral nerve disorder. Our goal was to determine which clinical features and diagnostic tests are most useful for distinguishing between treatable and untreatable conditions.

Methods

We conducted a retrospective chart review of patients seen at our institution over the years 2000–2011. To identify patients with IPMD we performed a systematic search of billing and clinic records using the following list of diagnoses: anterior horn cell disease; motor neuron disease; spinal muscular atrophy; amyotrophic lateral sclerosis; progressive muscular atrophy; progressive bulbar palsy; Kennedy disease (X-linked spinal and bulbar muscular atrophy); acute poliomyelitis; post-polio syndrome; West Nile virus infection with neurologic manifestation; hexosaminidase deficiency; Charcot–Marie–Tooth disease; radiation neuronopathy; chronic inflammatory demyelinating polyneuropathy; and multifocal motor neuropathy. We included patients who were ≥18 years of age at the time of symptom onset. All patients had at least 1 encounter in the neuromuscular outpatient clinic. We defined IPMD as weakness, atrophy, or fasciculations (or a combination of these findings) in the absence of hyperreflexia, Babinski signs, or significant sensory complaints or findings. Patients were allowed to have minimal vibratory or pinprick sensory loss at the toes. We excluded patients who were diagnosed with disorders primarily affecting muscle or the neuromuscular junction. The study protocol was reviewed and approved by the institutional review board of The Ohio State University Wexner Medical Center.

For subjects who met the inclusion criteria, the following data were collected from available charts: gender; age at symptom onset; number, chronicity, localization, and symmetry of symptoms at the time of presentation; past medical and family history; examination findings at 3 time-points (initial presentation, the time of diagnosis, and last follow-up); electrodiagnostic (EDx) findings; selected laboratory values (serum creatine kinase, GM1 antibodies, hexosaminidase activity, Lyme antibodies, and any genetic testing); cerebrospinal fluid tests; MRI results; and muscle biopsy results. The final diagnosis assigned by the treating physician was recorded. The time-point at diagnosis was defined as the first office visit in which the clinician stated the final diagnosis as the overall impression without giving other considerations in a differential diagnosis. If a diagnosis was revised over time, only the final diagnosis was recorded. When available, the referring diagnosis was also recorded.

Data Analysis

Data were collected and analyzed using LibreOffice Calc, Microsoft Excel, and Microsoft Access. Except when indicated, data are presented as median (25th percentile, 75th percentile). A 2-tailed Student *t*-test assuming unequal variance was used to compare categories with >10 values. $P < 0.05$ was considered statistically significant.

Results

Our initial search identified 942 potential subjects, 119 of whom met inclusion criteria. Demographic and clinical data for these subjects are presented in Tables 1 and 2. There was a slight male predominance, and the median age at the time of symptom onset was in the sixth decade. Patients had been symptomatic for a median of 2 years before their first visit to our clinic. All patients were seen by a neuromuscular trained physician and were followed-up for a median of 9.5 (0, 30) months (maximum 132 months), with 24% ($n = 28$) having only 1 visit. The time from first encounter to final diagnosis ranged from 0 to 42 months, and approximately half were diagnosed at the first visit.

MND made up the largest category, with the majority diagnosed with ALS or PMA. Seven patients were not assigned a specific subcategory of MND (referred to as “MND-uncategorized”). There were also 2 patients with monomelic amyotrophy. Other diagnostic categories included immune-related motor neuropathies, genetic disorders [including adult-onset spinal muscular atrophy (SMA), Kennedy disease, and other hereditary neuropathy], residual polio or post-polio syndrome, benign fasciculations, or cramp–fasciculation syndrome. One patient had motor neuronopathy related to human immunodeficiency virus (HIV) infection. This patient presented with asymmetric bilateral proximal upper extremity weakness, which had been insidiously progressive for about 8 months, and was diagnosed with HIV/acquired immunodeficiency syndrome within 2 weeks after his initial visit based on positive serology and low CD4 count. He was placed on highly active anti-retroviral therapy and, after 12 months, his weakness stopped progressing and remained stable for the ensuing 5 years of follow-up. Due to multiple diagnostic possibilities his clinicians did not state his diagnosis with certainty until 18 months after his initial visit, when his strength had clearly stabilized.

Ten patients (8% of the cohort) remained undiagnosed. Half had only a single encounter in the neuromuscular clinic. The clinical information for these subjects is listed in the Supplementary Material (available online).

Clinical Features Distinguishing Treatable from Untreatable Conditions

At the initial clinic visit, 33 patients (28% of total) had evidence of central nervous system (CNS) or bulbar involvement. Thirteen had symptoms or signs of CNS involvement (cognitive decline, pseudobulbar affect, snouting, or palmomental reflexes), and 92% were diagnosed with MND ($n = 12$, 19% of MND). One patient who had a snouting reflex was not given a final diagnosis. Bulbar symptoms or signs (dysarthria or dysphagia) were seen in 22% of subjects ($n = 26$). Of these, 85% were diagnosed with MND ($n = 22$, 35% of MND), 8% with Kennedy disease ($n = 2$, 50% of Kennedy), 1 with post-polio syndrome, and 1

undiagnosed. Five additional patients who developed signs of CNS or bulbar involvement during follow-up were diagnosed as having MND. Gynecomastia was observed in all subjects with Kennedy disease.

Although patients with MND had the highest median onset age of any category, 23% ($n = 14$) had onset before age 50 years, and 8% ($n = 5$) had onset before age 40 years. Patients with MMN were significantly younger than those with MND ($P = 0.003$). Genetic conditions as a category tended to begin younger, with most of this difference attributable to the 6 patients with adult-onset SMA, all but 1 of whom reported symptom onset before age 30 years.

The majority of patients had a chronic and progressive course prior to the first clinic encounter. Four percent ($n = 5$) were noted to have a mono-phasic or nonprogressive course; 2 were never given a final diagnosis (subjects 20 and 91), and the remainder were diagnosed with benign fasciculations or cramp–fasciculation syndrome. A waxing-and-waning course was noted in 1 patient with benign fasciculations and 1 patient with CIDP. Another patient initially reported a relapsing–remitting course, but later developed progressive symptoms and was ultimately diagnosed with “atypical MND.”

As per inclusion criteria, no patients had brisk reflexes at the time of initial evaluation. At the time of final diagnosis, however, 12 MND patients had developed hyperreflexia and were diagnosed with ALS. The hyperreflexia was noted at a median of 6 months from the initial examination and was present by 9 months in all but 1 patient. This outlier was diagnosed initially with cramp–fasciculation syndrome and was clinically stable for a period of 42 months, after which he developed hyperreflexia and weakness and was subsequently diagnosed with ALS. About two-thirds of patients who were assigned a diagnosis of ALS never had documented hyperreflexia ($n = 27$, 69% of ALS). Eight only had a single encounter in our clinic, so it is not known whether they later developed hyperreflexia.

Utility of Diagnostic Testing

Ninety-three percent of patients ($n = 111$) had EDx studies performed either at our center or by referring physicians. Ninety patients had EDx studies performed at our center, and reports were available for detailed review. The remainder had either missing reports or outside studies that were not reviewed. Motor conduction block was observed in 9% of studies ($n = 8$). Seven of these patients were diagnosed with MMN (64% of MMN) and retained this diagnosis, but the eighth patient did not respond to a trial of immunoglobulin and the treating physician was unsure of the correct diagnosis at the last follow-up. Fasciculations were seen by electromyography (EMG) in 47% of patients with MND ($n = 29$) and were absent in all patients with immune neuropathies ($P < 0.001$). Bulbar or thoracic abnormalities on needle EMG were seen in 62% of patients with MND ($n = 28$) and in 33% of patients who remained undiagnosed ($n = 3$). Only 2 patients with immune neuropathies had bulbar or thoracic muscles examined, and neither had abnormal findings.

Anti-ganglioside antibodies were tested in 18% of patients ($n = 21$) and were positive in 3 with MMN (27% of MMN). The diagnostic yield of ganglioside testing was 14%. Hexosaminidase A activity was normal for all 17 patients who were tested. Creatine kinase

(CK) levels were measured in 54 patients, and were elevated in 33. The median CK value in MND patients was 2.6 times the upper limit of normal for our laboratory, and the median value for immune neuropathies was 0.6 times the upper limit of normal ($P = 0.005$). Genetic testing results were available for 24 patients, including 15 tested for SMA, 7 tested for Kennedy disease, and 1 who had a *TRPV4* mutation. Three of the 6 patients diagnosed with SMA had identified genetic abnormalities in the survival motor neuron 1 gene (*SMN1*), and the remaining 3 SMA patients had negative genetic testing. The latter 3 all had chronic and progressive symmetric proximal lower extremity weakness beginning in the third or fourth decade of life and were evaluated in our clinic 12–29 years after symptom onset. The oldest had a family history of similar symptoms in her father. These clinical features were indistinguishable from those found in patients with *SMN1* mutations. Patients with negative SMA genetic testing who were diagnosed with MND tended to be clinically distinct, with asymmetric upper extremity or respiratory involvement. Three of the 4 patients with Kennedy disease had expanded CAG repeats in the androgen receptor gene (*AR*); the fourth patient's results were not available in the chart. No other genetic testing results were positive.

Discussion

We surveyed an entire clinic population to describe the spectrum of patients with IPMD related to LMN or peripheral nerve disorders. We were surprised to find that only about half of the patients had MND. The remaining half consisted of disorders with relatively better prognoses. One of our objectives was to identify treatable entities, and we found that immune neuropathies were the next most common diagnostic category after MND, with a prevalence of 13% in our cohort.

A few clinical features were helpful for distinguishing between MND and other disease categories. All patients in this cohort who had a palmomental sign, cognitive decline, or pseudobulbar affect were diagnosed with MND. These findings suggest central neurodegeneration and have actually been used to exclude PMA in some studies.⁴ Dysphagia and speech changes were similarly prevalent in patients with MND, but were somewhat less specific.

Immune neuropathies made up 13% of our population, which is similar to the 10% prevalence found as mimic syndromes in the Dutch PMA registry.³ Anti-ganglioside antibody testing had a poor sensitivity and low diagnostic yield. About one third of our patients who remained undiagnosed had clinical presentations that were compatible with MMN. Adding these groups together, about 15% of our cohort could be considered candidates for immunotherapy. This figure is similar to that of Tan *et al.*,⁵ who treated 65 patients with various motor neuron syndromes, including 30 with isolated LMN dysfunction, with high-dose glucocorticoids and cyclophosphamide. Nine percent of their study participants responded to therapy, all of whom had LMN syndromes ($n = 6$, 20% of LMN syndromes). More recently, Burrell *et al.*⁶ treated 42 patients with undifferentiated IPMD with intravenous immunoglobulin. A surprisingly high 73.8% of their subjects responded to therapy. The clinical phenotype of these responders resembled typical MMN, with most patients having unilateral upper extremity involvement. Differences between these studies

may be accounted for by different selection criteria and biases, as well as different outcome measures.

The median age of 60 years for subjects with MND in this study is consistent with previous reports.⁷ There was an overall tendency in this study for younger patients to be diagnosed with relatively benign or even treatable conditions, although the clinical usefulness of this relationship is tempered by the fact that MND may also present in the third or fourth decades of life, which was the case in nearly 10% of patients in our study.

The sometimes challenging nature of this clinical spectrum is reflected in the fact that 8% of our cohort remained undiagnosed despite intensive evaluation. Review of the clinical information for these patients (refer to Supplementary Table 1 available online) suggests that some may have had early or atypical forms of MND, and that a few had clinical presentations compatible with possible MMN.

Limitations of the study include its retrospective design, which complicates data interpretation due to heterogeneity of documentation styles and introduces the potential for recall bias, particularly for conditions with a long disease course. For example, it would be of interest to note which diagnostic tests were crucial for making each individual diagnosis. Unfortunately, the retrospective approach makes these data problematic to record with accuracy, thus rendering any resulting analysis questionable. We also acknowledge that our sample size is somewhat smaller than we had anticipated, and we suspect that the study had incomplete case ascertainment. This is most likely a reflection of inconsistent coding and billing practices during the earlier years of the study period. Perhaps a more accurate way to identify this specific cohort would be to keep a prospective case log of clinic patients and to flag all individuals who present with IPMD. This approach would also make it easier to identify patients with neuromuscular junction disorders or muscle diseases that may mimic LMN syndromes. Notwithstanding the small sample size, we believe that this cohort is a representative sample of our clinic population. Based on these limitations it is not possible to estimate the sensitivity or specificity of CNS or bulbar involvement for the diagnosis of MND in IPMD.

Finally, we acknowledge that the case definitions and categorizations had a significant impact on the results. For instance, it could be argued that benign fasciculations and fasciculation/cramp syndrome should not be included among LMN disorders, because they are not associated with weakness or atrophy. This category was included because MND is often the chief concern of referring physicians or patients with these conditions. It could also be argued that SMA, Kennedy disease, and poliomyelitis could be considered “motor neuron diseases,” because they have direct pathologic effects on anterior horn cells and, conversely, that some forms of MND may be categorized as genetic syndromes. Our classification system was based on the conceptual and clinical approach used most commonly at our institution. The case definitions were also limited by heterogeneity among clinicians regarding usage of diagnostic terms, particularly among the MNDs. Two-thirds of patients categorized as having ALS did not have hyperreflexia and thus may have been labeled as having PMA. Clinicians often used the terms “MND” and “ALS” interchangeably in clinic

notes without regard to formal diagnostic criteria used for ALS research.⁸ For this reason we did not attempt to analyze the MND subcategories separately.

In conclusion, approximately half of patients who presented to our tertiary neuromuscular clinic with IPMD from LMN disorders were diagnosed with MND. Any evidence of central neurodegeneration was highly suggestive of MND in this clinical setting, and this observation should be evaluated prospectively to determine its sensitivity and specificity. We recommend that clinicians who evaluate these patients perform a careful examination for subtle signs of central involvement. Treatable entities made up the second largest diagnostic category, with approximately 15% of patients being potential candidates for immunotherapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ALS	amyotrophic lateral sclerosis
CIDP	chronic inflammatory demyelinating polyradiculoneuropathy
CNS	central nervous system
CK	creatine kinase
EDx	electrodiagnostic

EMG	electromyography
HIV	human immunodeficiency virus
IPMD	isolated peripheral motor dysfunction
LMN	lower motor neuron
MMN	multifocal motor neuropathy
MND	motor neuron disease
PMA	progressive muscular atrophy
SMA	spinal muscular atrophy
UMN	upper motor neuron

Table 1

Diagnoses and demographic characteristics.

Category/disease	Number (% of total per category)	Men/women (% men)	Onset age, years (first, third quartiles)
Motor neuron disease	62 (52)	46/16 (74)	60 (50, 68)
ALS	39 (63)	29/10 (74)	61 (53, 71)
PMA	14 (23)	12/2 (86)	54 (50, 60)
MND (uncategorized)	7 (11)	3/4 (43)	64 (56, 73)
Monomelic amyotrophy	2 (3)	2/0 (100)	43
Immune neuropathy	15 (13)	8/7 (53)	43 (36, 56)*
MMN	11 (73)	4/7 (36)*	38 (31, 49)*
CIDP	4 (27)	4/0 (100)	56 (53, 59)
Genetic	13 (11)	9/4 (69)	43 (26, 65)*
SMA	6 (46)	3/3 (50)	25.5 (22, 27)
Kennedy disease	4 (31)	4/0 (100)	55 (44, 65)
hereditary neuropathy	3 (23)	2/1 (67)	65 (57, 68)
Polio/post-polio	12 (10)	7/5 (58)	40 (38, 52)*
Fasciculations	6 (5)	5/1 (83)	43 (40, 47)
Benign fasciculations	4 (67)	3/1 (75)	43 (37, 45)
Fasciculation/cramp	2 (33)	2/0 (100)	45
Infectious	1 (1)	1/0 (100)	35
Undiagnosed	10 (8)	4/6 (40)	60 (55, 63)
Total	119	80/39 (67)	54 (41, 63)

ALS, amyotrophic lateral sclerosis; MND, motor neuron disease; PMA, progressive muscular atrophy; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; MMN, multifocal motor neuropathy; SMA, spinal muscular atrophy; LGMD, limb-girdle muscular dystrophy.

* P < 0.05 (P-values calculated relative to MND).

Table 2

Time course of symptoms and diagnosis.

Category/disease	Symptom duration (months)	Months from initial visit	Number diagnosed on first visit (% category)
Motor neuron disease	18 (9, 36)	1 (0, 6)	30 (48)
ALS	12 (8, 24)	0.5 (0, 6)	18 (46)
PMA	33 (12, 57)	2.5 (0, 9)	6 (43)
MND (uncategorized)	36 (36, 36)	0 (0, 1)	4 (57)
Monomelic amyotrophy	132	0	2 (100)
Immune neuropathy	18 (10, 48)	0.5 (0.5, 4.75)	5 (33)
MMN	18 (12, 54)	2.5 (0, 5.75)	4 (36)
CIDP	21 (5.5, 39)	0 (0, 0.75)	1 (25)
Genetic	96 (60, 183) *	0 (0, 2)	6 (46)
SMA	222 (144, 336)	0.5 (0, 4.75)	3 (50)
Kennedy disease	66 (48, 84)	0.5 (0, 1.25)	2 (50)
hereditary neuropathy	45 (38, 53)	0 (0, 12)	1 (33)
Polio/post-polio	180 (96, 294) *	0 (0, 0) *	11 (92)
Fasciculations	42 (9, 77)	0 (0, 0)	5 (83)
Benign fasciculations	45 (11, 89)	0 (0, 0)	4 (100)
Fasciculation/cramp	40	18	1 (50)
Infectious	8	18	0 (0)
Undiagnosed	12 (12, 29)	NA	NA
Total	24 (12, 60)	0.5 (0, 6) †	57 (48)

ALS, amyotrophic lateral sclerosis; MND, motor neuron disease; PMA, progressive muscular atrophy; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; MMN, multifocal motor neuropathy; SMA, spinal muscular atrophy; LGMD, limb-girdle muscular dystrophy; NA, not applicable. Values expressed as median (first, third quartiles) unless indicated otherwise.

* P < 0.05 (P-values calculated relative to MND).

† Calculations include undiagnosed patients.