Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration

ISSN: 2167-8421 (Print) 2167-9223 (Online) Journal homepage: https://www.tandfonline.com/loi/iafd20

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To cite this article: Renée Walhout, Esther Verstraete, Martijn P. van den Heuvel, Jan H. Veldink & Leonard H. van den Berg (2018) Patterns of symptom development in patients with motor neuron disease, Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 19:1-2, 21-28, DOI: 10.1080/21678421.2017.1386688

To link to this article: https://doi.org/10.1080/21678421.2017.1386688

Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2018; 19: 21–28

ORIGINAL ARTICLE

Patterns of symptom development in patients with motor neuron disease

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Abstract

Objective: To investigate whether symptom development in motor neuron disease (MND) is a random or organized process. *Methods*: Six hundred patients with amyotrophic lateral sclerosis (ALS), upper motor neuron (UMN) or lower motor neuron (LMN) phenotypes were invited for a questionnaire concerning symptom development. A binomial test was used to examine distribution of symptoms from site of onset. Development of symptoms over time was evaluated by Kaplan-Meier analysis. *Results*: There were 470 respondents (ALS = 254; LMN = 100; UMN = 116). Subsequent symptoms were more often in the contralateral limb following unilateral limb onset (ALS: arms $p = 1.05 \times 10^{-8}$, legs $p < 2.86 \times 10^{-15}$; LMN phenotype: arms $p = 6.74 \times 10^{-9}$, legs $p = 6.26 \times 10^{-6}$; UMN phenotype: legs $p = 4.07 \times 10^{-14}$). In patients with limb onset, symptoms occurred significantly faster in the contralateral limb, followed by the other limbs and lastly by the bulbar region. Patterns of non-contiguous symptom development were also reported: leg symptoms followed bulbar onset in 30%, and bulbar symptoms followed leg onset in 11% of ALS patients. *Conclusions*: Preferred spread of symptoms from one limb to the contralateral limb, and to adjacent sites appears to be a characteristic of MND phenotypes, suggesting that symptom spread is organized, possibly involving axonal connectivity. Non-contiguous symptom development, however, is not uncommon, and may involve other factors.

Keywords: *Motor neuron disease*, *amyotrophic lateral sclerosis*, *symptom development*, *upper motor neuron*, *lower motor neuron*

Introduction

Mechanisms underlying the ongoing degeneration of motor neurons in amyotrophic lateral sclerosis (ALS) are still unknown. The question remains whether ALS is a multifocal disease with degeneration of independent vulnerable regions, or one focus of disease with subsequent propagation throughout the nervous system. It has been suggested that ALS spreads in a prion-like fashion, with cell-to-cell transmission of misfolded protein aggregates (1–3). If this is true, spread of disease is likely to be guided by axonal connectivity, which might be reflected by the pattern of symptom development.

Degeneration of lower motor neurons (LMN) is thought to differ from upper motor neuron (UMN) degeneration, due to differences in somatotopic organization: LMN degeneration would preferentially spread at one level of the spinal cord to the other side of the spinal segment, while degeneration of UMNs would spread preferably along the cortex to neighboring areas of the ipsilateral motor cortex (4). Based on this concept of neurodegeneration, different patterns of symptom development would be expected in UMN degeneration compared to LMN degeneration. Studies disentangling UMN and LMN involvement in ALS are, however, hampered by the fact that UMN signs can be difficult to measure (5) and a reliable objective marker of UMN involvement is not available. While most of the studies thus far have focused on symptoms in ALS (6–8), patterns of symptom development in pure upper or lower MND have been explored to a lesser

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(Received 1 May 2017; revised 14 September 2017; accepted 25 September 2017)

ISSN 2167-8421 print/ISSN 2167-9223 online
DOI: 10.1080/21678421.2017.1386688

extent. These MND subtypes, however, offer opportunities to disentangle UMN versus LMN spread.

In this study, therefore, symptom development was investigated in a large cohort of patients with ALS, as well as UMN and LMN phenotypes, looking for specific patterns of disease spread that might provide insight into the underlying mechanism of motor neuron degeneration.

Methods

Patient selection

Patients were identified from a database of a prospective population-based study of MND in the Netherlands (9). At the time of diagnosis, ALS patients were classified as having definite, probable or possible ALS using the revised El Escorial criteria (10). In patients initially diagnosed with possible ALS, diagnosis was confirmed by progressive deterioration. Patients with an LMN phenotype ('LMN patients') had no UMN findings on clinical examination (11), while patients with a UMN phenotype ('UMN patients') did not have any LMN findings on clinical examination or electromyography and were diagnosed with a suspected PLS (12,13). As early stages of hereditary spastic paraparesis (HSP) can mimic PLS, patients were checked for a family history of HSP, genetically tested for genes known to be associated with HSP and they were clinically followed up.

Data collection

A questionnaire was designed to evaluate symptom development in patients with MND, consisting of a schematic representation of the body, including six anatomical sites (bulbar region, right/left arm, trunk, right/left leg). Patients were asked to order these sites by number, according to the onset of symptoms. Symptoms were defined for the limbs and trunk as weakness or loss of function, and for the bulbar region as difficulties with speech or swallowing. Symptoms of the trunk were exemplified as difficulty getting up or walking upright. Because the respiratory muscles are innervated by both cervical and thoracic segments of the spinal cord, symptoms of dyspnea were not asked for specifically. If symptoms had started at multiple sites at the same time, patients were asked to assign the same number to those sites. In addition, for each site, patients were asked to report the date of symptom onset. If possible, patient responses were validated against medical records.

To investigate the spread of symptoms after onset at a particular site, body sites were defined relative to the side of onset as ipsilateral and contralateral. Contiguous spread was defined as spread of symptoms to adjacent anatomical sites (e.g. right arm to left arm), while non-contiguous spread was defined as spread to distant sites, thereby skipping adjacent anatomical sites (e.g. bulbar region to legs).

Standard protocol approvals, registrations, and patient consents

The study was approved by the medical ethics committee of the University Medical Center Utrecht. Written informed consent was given by all patients participating in the study.

Statistical analysis

Calculations were performed using SPSS (version 17.0, SPSS, Chicago, IL) and R (www.R-project.org). The binomial test of proportions was used to examine whether symptom development from site of onset to any other site was random. Under the null hypothesis (independent foci), site of onset and involvement of subsequent symptomatic sites should be independent and therefore, symptoms should be equally distributed to subsequent sites. The Bonferroni method was used to correct for multiple testing. A statistical threshold of $p < 0.05$ was considered statistically significant. Corrected p values are reported.

Kaplan-Meier analysis was performed to evaluate symptom development over time. Using the reported dates of symptom onset, time to progression from the initial site of onset to any site could be calculated in months. If patients did not report a site as being symptomatic, the time of censoring (1 January 2011) was used to calculate the symptom-free period. The percentage of patients reporting symptoms at a specific site after one and two years was calculated (including confidence intervals, CI) and compared. If dates of symptom onset were not reported at all, the patient was excluded from the analysis.

Results

The questionnaire was sent to 600 patients. Nineteen patients were reported to be deceased and of the remaining 581 patients, 470 returned the questionnaire (total response, 81%; UMN patients, 87%, ALS and LMN patients, 79%). Baseline characteristics are listed in Table 1.

At the time of censoring, 103 UMN patients had a disease duration longer than four years, without any LMN involvement, fulfilling the diagnostic criteria for PLS (14,15). Sixty-eight LMN patients had a disease duration longer than four years with no signs of UMN involvement.

Site of onset

In total, 367 out of 470 patients reported a focal site of onset (Table 2): 216 ALS patients, 70 LMN patients and 81 UMN patients. Multifocal onset of

Table 1. Demographic and clinical characteristics of respondents per diagnosis.

	ALS	LMN phenotype	UMN phenotype
Diagnosis, *n* (%)	254 (54)	100 (21)	116 (25)
Gender, *n* (%)			
Male/Female	163/91	76/24	71/45
Age at diagnosis, median (range), y	59.5 (23–81)	63.0 (25–80)	58.0 (20–81)
Age at onset, median (range), y	58.0 (23–80)	59.0 (18–77)	53.0 (16–77)
Site of onset, *n* (%)			
Bulbar	59 (23)	0 (0)	17 (15)
Cervical	91 (36)	53 (53)	6 (5)
Thoracic	3 (1)	6 (6)	0 (0)
Lumbosacral	101 (40)	41 (41)	93 (80)
Disease duration, median (range), months	37 (7–378)	68 (11–451)	109 (20–462)
ALS type			
Sporadic/familiar	240/14		
ALS-FTD, *n* (%)	3 (1)		
El Escorial classification at diagnosis			
Definite ALS	30 (12)		
Probable ALS	113 (45)		
Probable ALS lab supported	49 (19)		
Possible ALS	62 (24)		

ALS = amyotrophic lateral sclerosis; LMN = lower motor neuron; UMN = upper motor neuron. FTD = frontotemporal dementia.

Table 2. Site of onset reported by patients with MND.

Site of onset	ALS ($n=254$)	LMN phenotype ($n=100$)	UMN phenotype ($n=116$)
Focal onset (%)	(85%)	(70%)	(70%)
Bulbar	55	0	16
Right arm	41	21	3
Left arm	39	14	2
Right leg	38	11	20
Left leg	40	18	40
Trunk	3	6	0
Multifocal onset (%)	(15%)	(30%)	(30%)
Contiguous, contralateral	31	25	33
Contiguous, ipsilateral	1	1	
Contiguous other	4	2	
Non-contiguous	1		1
More than two regions	1	2	1

ALS = amyotrophic lateral sclerosis; LMN = lower motor neuron; UMN = upper motor neuron. Contiguous = spread of symptoms to adjacent anatomical site; non-contiguous = spread of symptoms to non-adjacent, distant sites (skipping adjacent anatomical site); contralateral = spread of symptoms to the other side of the body; ipsilateral = spread of symptoms to the same side of the body.

symptoms was reported by 103 patients with ALS, UMN and LMN phenotypes (Table 2). Of these patients, 89 reported simultaneous onset in both legs or both arms.

Spread of symptoms

The site of onset and the subsequent second site patients appeared not to be random. Table 3 shows the number of times a site was reported as subsequently being symptomatic. From each focal region of onset, spread to more than one region was possible, and symptom development in each region was calculated as a separate event. The thoracic region was disregarded in the analysis, as patients reported few symptoms in this area, probably due to the fact that symptoms in this region are difficult to recognize.

The preferential second affected site in ALS, LMN and UMN phenotypes was the contralateral limb in patients with unilateral limb onset (arms: ALS $p=1.05\times10^{-8}$, LMN $p=6.74\times10^{-9}$; legs: ALS $p<2.86\times10^{-15}$, LMN $p=6.26\times10^{-6}$, UMN $p=4.07\times10^{-14}$). In addition, ALS patients with bulbar onset reported more frequently subsequent involvement of the arms, compared to the legs (63.6% vs. 36.4%, $p=0.006$).

ALS, LMN and UMN patients with arm onset reported relatively more subsequent symptoms in the ipsilateral leg compared to the contralateral leg; this was not, however, significant. The same pattern was seen in patients with leg onset, the contralateral arm being less frequently reported as subsequent symptomatic site than the ipsilateral arm (ALS $p=0.001$, LMN $p=0.005$, UMN $p=0.03$).

Spread of symptoms was further analyzed by subdividing the body into the regions of the El Escorial criteria (10) (bulbar, cervical, thoracic, lumbosacral) – instead of including right and left limbs as separate sites (Supplementary Table 1). In ALS patients with bulbar onset, there was preferential spread to the anatomically adjacent cervical region compared to the lumbosacral region ($p=0.002$). In ALS and LMN patients with a lumbosacral onset, the cervical region was more frequently reported as subsequent symptomatic region compared to the more distant bulbar region (ALS $p=6.14\times10^{-3}$, LMN $p=0.001$). ALS and LMN patients with cervical onset reported subsequent involvement of the lumbosacral region more often than the bulbar region (ALS $p=2.93\times10^{-6}$, LMN $p=0.001$), suggesting a preferred rostrocaudal direction of symptom development.

Table 3. Spread of symptoms from site of onset.

	ALS		LMN phenotype		UMN phenotype	
First site → second site	n (%)	*p* value	*n* (%)	*p* -value	*n* (%)	*p* -value
Bulbar region	55			0		15
arm	35 (63.6)	0.006 ↑			4 (26.7)	NS
leg	20 (36.4)	NS			11 (73.3)	NS
Arm	81		35		6	
contralateral arm	41 (50.6)	$1.1x10^{-8}$ ↑	24 (68.6)	$6.7x10^{-9}$ ↑	1 (16.7)	NS
ipsilateral leg	26 (32.1)	NS	7 (20.0)	NS	3 (50.0)	NS
contralateral leg	7 (8.6)	NS	2 (5.7)	NS	1 (16.7)	NS
bulbar region	7 (8.6)	NS	2 (5.7)	NS	1 (16.7)	NS
Leg	76		26		50	
contralateral leg	55 (72.4)	$< 2.9x10^{-15}$ ↑	17 (65.4)	$6.3x10^{-6}$ ↑	36 (72.0)	$4.1x10^{-14}$ ↑
ipsilateral arm	11 (14.5)	NS	7 (26.9)	NS	12 (24.0)	NS
contralateral arm	3 (3.9)	0.001 ↓	0 (0.0)	0.005 ↓	2 (4.0)	0.03 ↓
bulbar region	7 (9.2)	NS	2 (7.7)	NS	0 (0.0)	$2.9x10^{-4}$ ↓

Sites that showed significantly more subsequent involvement are marked by (↑). Sites with significantly less subsequent involvement are marked by (↓). The results are corrected for multiple testing by the Bonferroni method; corrected *p* values are shown. *n* = number of times a site was reported as subsequently being symptomatic. From each focal region of onset, spread to more than one region was possible, and symptom development in each region was calculated as a separate event. ALS = amyotrophic lateral sclerosis; LMN = lower motor neuron; UMN = upper motor neuron; NS = not significant.

Symptom spread appeared to be more likely to adjacent anatomical sites or regions, but patterns of non-contiguous symptom development were also reported. In 55 ALS patients with a bulbar onset, subsequent symptom development was reported by 50 patients: 15/50 reported a non-contiguous pattern of symptom development, with subsequent involvement of one or both legs (30%). In 97 patients with leg onset, 92 reported symptoms in a subsequent region. Ten of these 92 patients reported a non-contiguous pattern (11%): nine reported involvement of the bulbar region following leg onset and one patient reported involvement of the right arm following left leg onset. In 16 UMN patients with bulbar onset, subsequent symptom development was reported by 15 patients. Of these 15 patients, nine reported leg involvement following bulbar onset (60%), a pattern that has been previously reported in PLS (15). In 91 UMN patients with leg onset, 80 reported symptoms in a subsequent region: 10/80 patients reported a non-contiguous pattern of bulbar involvement following leg involvement (13%). In 40 LMN subjects with leg onset, subsequent symptom development was reported by 34 patients, two of whom reported subsequent involvement of the bulbar region (6%). Clinical characteristics of ALS patients with non-contiguous symptom development compared to patients with contiguous symptom development are shown in Supplementary Table 2.

Symptom development over time

Reported dates on symptom development were available for 188 ALS patients, 64 LMN patients and 76 UMN patients (89% of patients with a focal onset). Involvement of body regions over time according to site of onset is illustrated with Kaplan-Meier curves (Figure 1). The numbers of UMN patients with bulbar onset ($n = 14$) and arm onset ($n = 4$) were insufficient to produce meaningful curves, as was thoracic onset for all MND subtypes. The Kaplan-Meier curves were used to compare involvement of specific sites after disease onset. Differences in frequency of involvement one and two years after disease onset are shown in Supplementary Table 3.

Bulbar onset

For ALS patients who initially had bulbar symptoms ($n = 46$), the time to develop arm symptoms was compared with the time to develop leg symptoms (panel A). After one year, the percentage of ALS patients reporting arm symptoms was 46.7% (95% CI 29.8–59.6), while the percentage reporting leg symptoms was 34.3% (95% CI 18.5–47.1). After two years, the percentage of ALS patients having arm symptoms was 62.1% (95% CI 44.1–74.3), while the percentage having leg symptoms was 51.4% (95% CI 32.7–64.9). The difference in development of arm symptoms compared to leg symptoms was not significant.

Arm onset

Among ALS patients with arm onset ($n = 74$), additional involvement of the contralateral arm developed significantly faster compared to any other site (panel B). After one year, the percentage of patients reporting symptoms in the contralateral arm was 52.0% (95% CI 39.3–62.1); after two years, this percentage was 72.0% (95% CI 59.7–80.5). Following the contralateral arm, symptoms seemed to develop

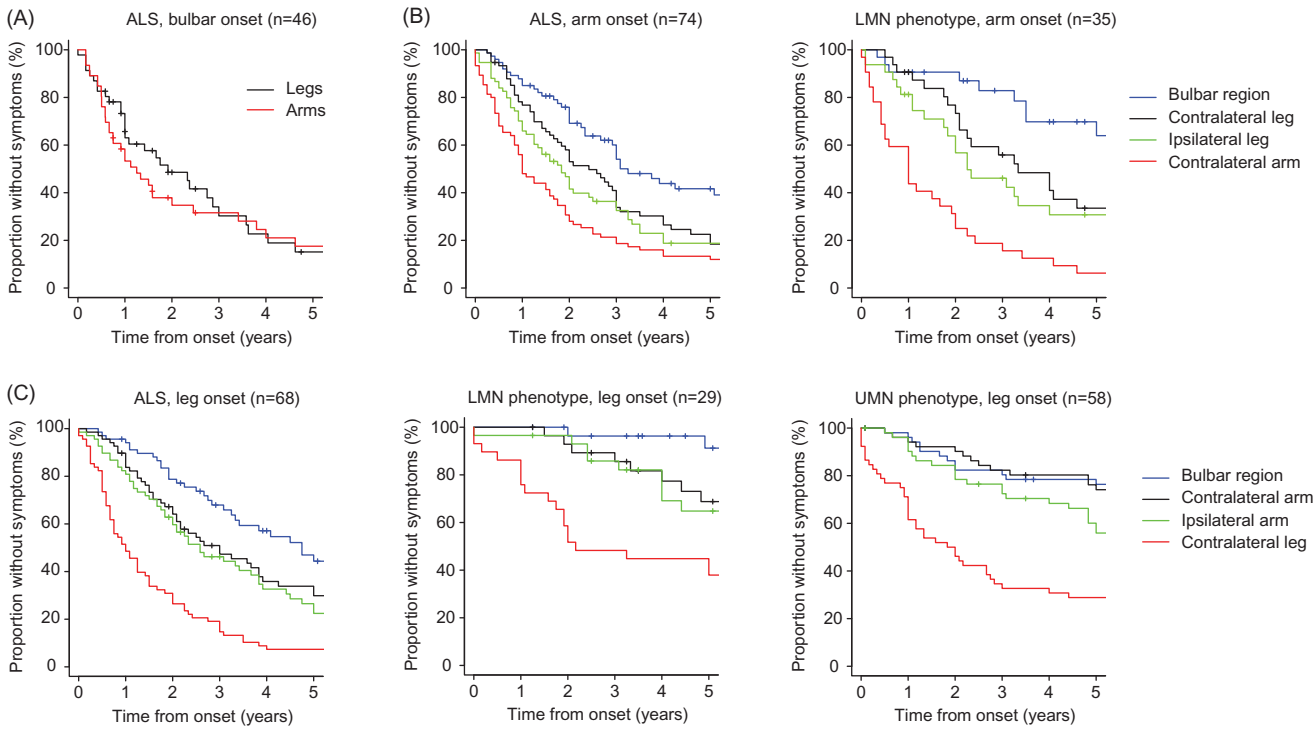

Figure 1. Symptom development over time in MND patients according to site of onset. Kaplan Meier curves showing involvement of sites over time according to site of onset in patients with MND. (A) Bulbar onset in ALS patients. There was no significant difference in subsequent development of arm symptoms compared to leg symptoms (B) Arm onset. Both in ALS and lower motor neuron (LMN) patients, symptoms in the contralateral arm were reported faster compared to the legs and bulbar region. (C) Leg onset. In ALS patients, symptoms in the contralateral leg were reported significantly faster than involvement of the arms and bulbar region, respectively. A similar pattern was seen in patients with a lower motor neuron phenotype and in patients with an upper motor neuron (UMN) phenotype.

more rapidly in the ipsilateral leg than in the contralateral leg but this difference was not significant. Bulbar involvement was reported by 30.9% of the patients after two years. In the case of arm onset in LMN patients ($n = 35$), symptom development also occurred faster in the contralateral arm.

Leg onset

In ALS patients with leg onset ($n = 68$), symptoms in the contralateral leg occurred significantly faster than involvement of the arms and bulbar region, respectively (panel C). After one year, the percentage of ALS patients having symptoms in the contralateral leg was 51.5% (95% CI 38.0–62.0); after two years, this percentage was 73.5% (95% CI 60.7–82.2). There was no significant difference in involvement of the ipsilateral arm compared with the contralateral arm. Again, involvement of the bulbar region was relatively less frequent (21.3% after two years). For LMN patients ($n = 29$) and UMN patients ($n = 58$) with leg onset, the Kaplan-Meier curves show a pattern similar to ALS patients, with earlier involvement of the contralateral leg compared to other sites.

Discussion

In this study, we investigated symptom development in MND, looking for patterns of disease spread. Disease progression was characterized by a non-random spread of symptoms from site of onset to subsequent body regions. The results suggest that disease progression in MND is an organized process, with preferred and most rapid symptom development to the contralateral limb in ALS, UMN and LMN phenotypes. Following limb onset, the bulbar region is relatively spared, being less frequently the next symptomatic site and showing late involvement. This organized development of symptoms to contiguous anatomical regions is similar throughout the spectrum of MND.

In 1991, Brooks et al. were the first to suggest that symptoms develop most often in adjacent anatomical sites during disease progression (16,17), and this was confirmed by more recent neuropathological (18) and clinical (6–8,19) studies. While several studies investigated symptom development in ALS at the level of UMN and LMN involvement, studies on the natural disease course of pure upper or lower MND are scarce. In PLS, symptoms have been reported to begin unilaterally in one leg, before developing in the contralateral leg (20), whereas there is also evidence supporting progression by local cortical spread (21). Pure LMN phenotypes have previously been characterized by a diffuse symmetric weakness and atrophy usually starting in the distal limb regions (22,23). By combining the variety of MND phenotypes in one

study, the results of this study support the hypothesis of orderly progression and propagation of UMN and LMN neurodegeneration.

The results of our study also demonstrate a non-contiguous pattern of symptom development in a substantial proportion of the ALS patients, shown by symptom development in the legs after bulbar onset (30%) and vice versa (11%). Non-contiguous patterns were even more frequently reported in patients with a UMN phenotype, with leg involvement following bulbar onset in 60% of the patients. These patterns of disease progression cannot be related to the somatotopic organization of the motor cortex, or the spinal cord, suggesting more factors may be contributing to spread of disease. The non-contiguous progression has been described in other clinical studies on symptom development (7,8). As symptoms might have gone unnoticed by patients, the retrospective design might have contributed to the finding of non-contiguous symptom development. A study with prospective, clinical assessment of ALS patients found that symptom development rarely skipped regions (6). However, a needle EMG study in ALS also revealed that involvement of motor neuron pools was distributed non-contiguously (24), suggesting that degeneration of LMNs might occur independently and supporting the notion that non-contiguous patterns of symptom development might be present. Mechanisms other than neural connectivity have, therefore, been proposed as contributing to this pattern of symptom development, including multifocality of onset and selective vulnerability.

This study shows that preferred distribution of symptoms from one limb to the contralateral limb is a uniform feature of MND, reported in both UMN and LMN phenotypes. For the LMN, this pattern of symptom development suggests that the disease process is likely to spread locally to the contralateral side of the spinal segment, before propagating along the spinal cord. Recently, a resting state network was identified in the ventral part of the spinal cord (25,26). This network was present bilaterally, suggesting a connectivity between the left and right motor columns of the anterior horn that might account for local propagation to the contralateral side in LMN disease. For the UMN phenotype, our results suggest an interhemispheric spread of disease, potentially guided by the corpus callosum as the main interconnecting white matter tract between the left and right motor cortices (Figure 2). Degenerative changes within this tract have been consistently reported in imaging studies (27,28) and post mortem studies in ALS (29,30) as well as PLS (31). Alternatively, rather than interhemispheric spread, the observed pattern in patients with a UMN phenotype could also be due to selective vulnerability of motor neurons. Overall, our findings may support spread of disease along axonal connections, facilitating propagation to and from structurally and functionally related body regions (32–34). Spread of disease from neuron to neuron is potentially a uniform feature in neurodegenerative diseases that requires further exploration (35,36).

This study has a number of limitations. We opted for a questionnaire as an efficient and patient-friendly method to gain insight into the disease course. However, the retrospective design might have introduced selection bias and recall bias. Patients with a more progressive disease course

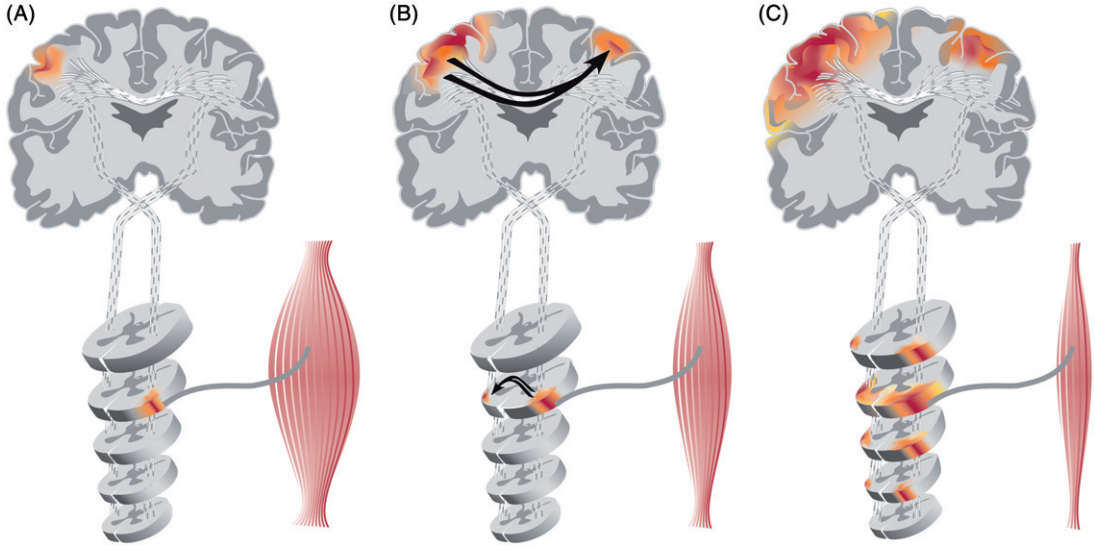

Figure 2. Schematic hypothesis of upper and lower motor neuron degeneration, underlying symptom development in MND. (A) Motor neuron degeneration starts with a focal site of onset in the brain and spinal cord, leading to regional symptoms. (B) From this focal site of onset, spread of disease is guided by axonal connectivity to highly connected regions of the neural network. For the upper motor neuron, this involves early interhemispheric spread via the corpus callosum; at the level of the spinal cord, disease spreads to the contralateral site of the spinal segment. The result is a pattern of symptom development with subsequent symptoms in the contralateral side of the body, both in upper and lower motor neuron phenotypes. (C) Neurodegeneration continues to adjacent regions of the motor cortex and spinal cord, reflected by generalization and progression of muscle atrophy and weakness.

might have been excluded from the analysis, and symptoms might have been under-reported. Also, symptoms might have gone unnoticed if weakness did not result in a functional change. Moreover, clinical follow-up data of respondents were partly available, rendering the verification of clinical phenotypes during the disease course and the temporal order of symptoms limited. As a final point, the clinical diagnosis of MND phenotypes remains challenging, taking into account the lack of objective upper motor neuron markers to differentiate pure LMN phenotypes from ALS. Taking into account these limitations, prospective data collection with clinical assessment of UMN and LMN dysfunction and repeated electromyography for detection of early, subclinical LMN involvement would certainly be of great value to validate the results of this study.

In conclusion, symptom development in MND seems to be an organized process, with preferred spread of symptoms from a single site of onset towards highly connected anatomical regions in UMN as well as LMN phenotypes. The results might suggest that axonal connectivity is involved in guiding the ongoing motor neuron degeneration underlying symptom development in MND.

Declaration of interest

This study was supported by the ALS Foundation Netherlands, Prinses Beatrix Spierfonds, the European Community's Health Seventh Framework Programme (grant agreement n° 259867), and the SOPHIA project (funded through the EU Joint Programme – Neurodegenerative Disease Research, JPND).

R. Walhout reports no disclosures. E. Verstraete received a consultancy fee from Biogen Idec. MPvdH received a grant from The Netherlands Organization for Health Research and Development (Veni scheme), from the ALS Foundation Netherlands and from MQ. J.H. Veldink reports no disclosures. LHvdB received a grant from The Netherlands Organization for Health Research and Development (Vici scheme), travel grants and consultancy fees from Baxalta; serves on scientific advisory boards for Prinses Beatrix Spierfonds, Thierry Latran Foundation, Cytokinetics and Biogen.

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