Upper motor and extra-motor neuron involvement in recent-onset motor neuron disease

van der Graaff, M.M.

Citation for published version (APA):
General Discussion
PERSPECTIVE OF THE PROJECT

The term motor neuron disease (MND) encompasses several clinical phenotypes along a spectrum of a pure "lower motor neuron" phenotype at the one end (progressive muscular atrophy (PMA)), via a mixed phenotype (amyotrophic lateral sclerosis (ALS)) to a pure upper motor neuron phenotype (primary lateral sclerosis (PLS)) at the other end of the spectrum. In recent years cognitive and behavioral disturbances are observed in patients with motor neuron disorders which further expand the spectrum. It has become increasingly clear that there is more overlap between the clinical phenotypes than previously thought. For example, in PMA degeneration of the corticospinal tract was found in a post mortem study and PLS patients may develop lower motor neuron signs in the course of the disease. In terms of prognostication, ALS can be divided into a "classical phenotype" and an "upper motor neuron predominant" phenotype, the latter phenotype carrying a better prognosis than the first, somewhat similar to but not as good as that of PLS.

We felt that there were several reasons to focus our research on the role of the upper motor neuron in ALS. Firstly, the clinical subclassification of phenotypes suggests that upper motor neuron (UMN) signs and lower motor neuron (LMN) signs can readily be assessed in daily practice. However, it has been shown that the interpretation of tendon reflexes or plantar reflexes are subject to considerable interobserver disagreement. Moreover, in patients with a paralysis of the extensor hallucis longus muscle the plantar response is equivocal even in the case of upper motor neuron degeneration. Secondly, clinical trials are still mainly focused on ALS patients. PLS (and PMA) patients are usually excluded, in order to obtain a homogeneous study population. This approach hampers the extrapolation of trial results to phenotypes other than ALS.

The perspective of our study was two-fold. First, in an attempt to find reliable clinical measures to detect upper motor neuron symptoms that can be used in the clinical examination, we focused on identification of the type of dysarthria, and on finger- (FiTS) and foot (FoTS) tapping speed. Second, we conducted a (longitudinal) neuro-imaging study on four subtypes of MND, i.e. PMA, ALS with bulbar onset (ALS-B), ALS with limb onset (ALS-L) and PLS. We investigated ALS-L and ALS-B separately as there are substantial epidemiological differences between these two phenotypes when it comes to age at onset, male/female ratio, response to riluzole and prognosis. It is as yet unknown whether there are significant differences in the extent to which the
UMN is involved in both phenotypes. All patients, except for the patients with PLS, had symptoms less than one year, thus representing a relatively early stage of disease. With MR spectroscopy we sought for changes in the motor cortex, with MR diffusion tensor imaging and tractography we sought for changes in white matter tracts, motor and extra-motor. The combination of these neuro-imaging modalities enabled a spatiotemporal profiling of the process of neurodegeneration in the brain for each phenotype.

In summary the aims of this thesis were
- To evaluate the reliability of clinical tests to detect UMN signs in patients with MND, one test for the bulbar region and one test for the extremities.
- To search for differences and similarities in the pattern and spread of degeneration of upper motor neurons and extra-motor neurons in the brain in the various phenotypes at an early stage of disease.
- To evaluate correlation between surrogate markers for UMN degeneration and clinical measures of disease
- To evaluate the properties of the various MR modalities to pick up longitudinal changes, thus making them suitable to be applied in intervention studies to monitor disease progression.

RELIABILITY OF TWO CLINICAL TESTS TO DETECT UMN SIGNS

Clinical bulbar UMN signs and symptoms

Background
When we started the study we looked for simple and reliable tests to score upper motor neuron sign in the bulbar, cervical and lumbosacral region without the use of ancillary investigation such as electrodiagnostics. Bulbar subscales on ALS specific rating scales do not rate upper motor and lower motor neuron signs separately. The clinical use of brainstem reflexes as a measure for bulbar UMN involvement is unclear. The palmomenatal reflex for example may be present in healthy people and absent in disease states and is therefore neither sensitive nor specific. The snout reflex is usually absent in healthy individuals but may occur in elderly people, being related to aging of the brain, and is therefore not specific. The corneomandibular reflex is usually absent in healthy individuals and found in a higher frequency in patients with ALS than in patients with cerebrovascular disease and thus may be useful. However, the corneomandibular reflex should not be mistaken for the corneomenatal reflex which occurs in many healthy...
Chapter 8

Subjects. Excessive yawning occurs, especially in the bulbar onset form of ALS but has not been studied systematically in cohorts of patients and controls. Pseudobulbar affect may occur in patients with ALS, but to a lesser extent also in healthy individuals, though a combination of pathological laughter and crying in the same individual did occur only in patients with ALS.

In summary, clinical bulbar signs or symptoms suggestive of UMN pathology are either unspecific for disease or not systematically investigated in the MND population. Therefore, we performed a reliability study on the clinical identification of dysarthria type in several categories (flaccid, spastic, “mixed” flaccid and spastic, cerebellar and hypokinetic) among neurologists as findings of these study could be directly applied in clinical practice as well as in rating clinical parameters in our imaging study.

Clinical identification of type of dysarthria

Our study proved that the clinical identification of dysarthria types by neurologists without the use of additional validated instruments or rating scales is not reliable. Neurologists identified 40% of the dysarthria samples correctly, for interrater agreement the kappa was 0.26, for intrarater agreement 0.46. Residents in neurology and speech therapists performed likewise. When provided with clinical information, correct identification improved for neurologists and residents, but not for speech therapists. Zyski et al. found slightly better scores: in their study speech/language pathologists correctly identified dysarthria type in approximately 50% of all cases.

Assessment in their study was more structured as their raters used an adapted checklist with 16 perceptual dimensions of the original 38 dimensions of the Mayo clinic rating system for analysis. Our study reflected daily clinical practice in which neurologists rely on their skills to identify the type of dysarthria just by listening, as there is no validated clinical rating scale at hand that is developed for neurologists to identify the type of dysarthria.

Given the results of our study we refrained from using type of dysarthria as a clinical parameter in our imaging study.

Implications

The revised El Escorial Criteria describe clinical bulbar UMN features as follows: clonic jaw reflex, gag reflex, exaggerated snout reflex, “pseudobulbar features”, or forced yawning. However, many of these features are rather subjective, and sometimes only noted on self report (yawning). Based on our study, the type of dysarthria (more specifically a pseudobulbar dysarthria) was not used as a clinical bulbar UMN parameter in our neuro-imaging studies.
As there is some evidence that the clinical examination of the corneomandibular reflex and assessment of pseudobulbar affect are potentially simple and reliable parameters, the sensitivity and specificity of these two parameters deserve to be subjected to further study in the future. We did not formally study pseudobulbar affect in our imaging study. However, at baseline, we documented self-report of either pathological crying, laughter or yawning. If one or more of these three were present, the individual scored a “yes” on pseudobulbar symptoms. Each of the cohorts in our imaging studies consisted of 12 individuals at baseline. In PLS, 10 out of 12 individuals scored positive on pseudobulbar symptoms at baseline, in patients with ALS-L 5 out of 12, in patients with ALS-B 6 out of 12, in patients with PMA 3 out of 12, and in the control group 0/12 individuals. Therefore, these symptoms seemed to occur only in the presence of disease. The fact that pseudobulbar symptoms may also be present in PMA may be suggestive of supranuclear bulbar involvement in these patients. The systematic use of reliable clinical bulbar UMN parameters might in itself cause a shift from the clinical syndrome of PMA towards ALS.

Clinical UMN signs and symptoms in the extremities

Background

In ALS studies several parameters are used, varying from clinical hyperreflexia, preserved reflexes in weak and atrophic limbs, to the Modified Ashworth Spasticity scale, plantar responses, and to a UMN “burden” score. This UMN “burden” score is a composite score, adding up a number of pathological UMN signs (pathologically brisk biceps, supinator, triceps, finger, knee and ankle reflexes, and extensor plantar responses, assessed bilaterally and brisk facial and jaw jerks) on examination. However, many of the clinical parameters have considerable interobserver variability as was demonstrated for the rating of briskness of tendon reflexes and for the plantar response. For the same reason we did not use the Modified Ashworth Scale as its reliability and validity have been questioned.

Finger and foot tapping speed (FiTS and FoTS) have been used in ALS studies as a parameter for upper motor neuron function. Decreased FiTS has also been described after closed head injury, in stroke, and in Parkinson’s disease. FoTS is less widely used but its application is comparable to that of FiTS. Interrater reliability of FoTS as a marker for UMN impairment was shown to be better than that of the Babinski sign. FiTS and FoTS have two advantages: (1) these measures are very easy to perform without the use of any equipment; (2) they are a continuous variable, and
chapter 8

therefore suitable to monitor disease progression over time. In our MR spectroscopy study the FiTS proved to be a better parameter to differentiate patients from controls, and to differentiate patients with ALS from patients with PMA, than MRS metabolite concentrations. Reliability of the measurement of FiTS has been studied, but in these studies equipment such as a counter with a lever mounted on a board \(^{51}\) or a counter with two levers with individuals instructed to perform an alternate tap with the index finger were used.\(^{52}\) Reliability data of FiTS and FoTS without any devices were not available, neither were normative data. Inspired by our MR spectroscopy study showing the potential importance of the measurement of FiTS and FoTS (without devices, except for a stopwatch) we initiated a study on its reliability and we provided normative data.

Reliability and normative values of finger and foot tapping speed

In the reliability study we found a good agreement of the two raters with the gold standard, which was a video recording, and with each other. However, agreement of one of the raters with the gold standard seemed to be dependent on the speed of tapping, with agreement in the range of a FiTS of > 50 taps/sec improving in a second trial. The intraclass correlation coefficient in the second trial was 0.97 (p< 0.001) for rater 1 and 0.95 (p< 0.001) for the rater 2. Agreement of both raters with de gold standard for FoTS was good, with an intraclass correlation coefficient of 0.98 (p< 0.001) for both raters on both sessions. We therefore conclude that measurement of FITS and FoTS without the use of equipment such as a mechanical counter, (mouse) button, keyboard or dynamometer, or alternatively electronic, infrared or magnetic markers or sensors, is very reliable especially when two trials are registered and the results of the second trial are used.

We also provided normative data related to age, gender and dexterity. FiTS was inversely related to age. With every year increase in age, FiTS decreased with 0.2 taps/sec (CI: 0.1-0.3, p= 0.001). This is in line with previous studies.\(^{53-55}\) FoTS and age were not significantly associated (p=0.70). Studies on normative values for FoTS and relation with age are lacking. However, it was demonstrated that fine motor skills are more affected by age than course motor skills, which may be an explanation for our finding.\(^{56}\) In contrast to other studies we did not find a significant difference of FiTS between males and females.\(^{21,62}\) However, FiTS in those studies was measured with devices and therefore comparison with our study is cumbersome. We found a significant difference of FoTS between males and females, females tapping slower. Data from other studies on this effect of gender on FoTS are not available. We found a strong relation of FITS
and dexterity. It was very rare for a healthy right-handed individual to tap slower with the dominant hand than with the non-dominant hand. Therefore a FITS being slower in the dominant hand may be suggestive of pyramidal or extrapyramidal pathology. This may be relevant especially in the clinical setting, when searching for upper motor neuron signs in the extremities.

In our imaging studies some patients selectively could not tap with their index finger due to a paresis/paralysis of the extensor indicis muscle, but they could tap with either their thumb or their middle finger. We therefore decided to provide normative data also for the thumb and the third finger, to be used in those cases.

Implications
Our reliability study of the measurement of FITS and FoTS without the use of any devices except for a stopwatch convincingly showed that it is cheap, easy and reliable, and can readily be used in a research setting as well as in clinical practice. It enables detection and longitudinal monitoring of UMN signs in the extremities. In light of this good reliability and the fact that it is a continuous variable, FITS and FoTS deserve to be a standard parameter in cross sectional as well as longitudinal intervention trials. Future studies comprising larger numbers of individuals might provide cut-off points related to age, gender and dexterity, enabling to decide whether a certain FITS or FoTS in an individual indicates pathology.

UPPER AND LOWER MOTOR NEURON INVOLVEMENT IN VOCAL CORD DYSFUNCTION

Case study and review of the literature
Whilst conducting the research for this thesis we came across several patients with ALS suffering from acute stridor due to vocal cord abduction paralysis (VCAP) or laryngospasm in clinical practice. These were not end-stage disease patients. When screening PubMed this complication seemed to be very rare. However, specific otolaryngology publications on ALS suggest a much higher frequency. Hoarseness was noted as initial manifestation in 3.9% of 441 ALS patients being seen by an otolaryngologist. A large cohort study including more than 100 bulbar onset ALS patients visiting a specialized otolaryngology clinic found bilateral VCAP in as much as 30%. Hoarseness may be attributed to decreased vital capacity, but also to vocal
Vocal cord paresis may be a result of upper and of lower motor neuron degeneration, or of a mixture of these two mechanisms. As it is thought to be a very rare condition, it is usually not actively sought for.

Implications
Probably vocal cord abduction paresis and laryngospasm occur much more frequently than previously thought. A study in which all newly diagnosed ALS, PLS and PMA patients undergo laryngoscopy and needle myography of the vocal cord abductors and adductors would be of great interest, especially as this condition may lead to sudden death if not recognized.

NEURO-IMAGING STUDIES

MR spectroscopy
Background
MR spectroscopy can be used to study involvement of the UMN at the level of the motor cortex. Metabolites measured with MR spectroscopy provide information on the composition of brain tissue in the selected region. N-acetyl aspartate (NAA) is primarily present in (motor) neurons and a decreased level reflects a dysfunction or loss of neurons. Several cross-sectional MR spectroscopy studies of the motor cortex in patients with advanced ALS showed abnormally low levels of NAA. Increased levels of myo-inositol (mI) indicate increased membrane turnover and are considered to represent glial (hyper)activity. There is accumulating evidence that glial (hyper)activity may be responsible for spreading of the disease after the initial neuronal damage. Glutamate (Glu) would be of great interest given its role in the pathogenesis of ALS but its spectroscopic measurement is hampered by technical shortcomings. None of the above referenced studies were conducted in patients at an early stage of disease, and many did not study well defined phenotypes separately. We studied levels of NAA, mI and Glu in the primary motor cortex, in search of early corticomotoneuron involvement and early signs of glial (hyper)activity in the various phenotypes.

MR spectroscopy study of the primary motor cortex: baseline findings
With respect to NAA levels in PLS, our findings suggesting neuronal degeneration of corticomotoneurons were in line with previous studies. There are no data on mI levels
in PLS available. We found that, despite the longer disease duration in PLS compared to the other patient groups, the increase in mI levels is not specific enough to discriminate PLS from other phenotypes of MND. However, compared to controls, the increased levels of mI do suggest the presence of activated glial cells in PLS.

Our findings in both ALS groups do not support the idea that at the corticomotoneuron level there is any difference between the two phenotypes. Two studies found lower NAA levels in patients with ALS-B when compared with those with ALS-L.76,77 The first study positioned the voxel of interest in the brainstem area in patients with advanced disease, in the second study, patients with ALS-B had clinically more prominent UMN involvement than those with ALS-L, which may explain their results.76,77 This was not the case in our study where patients were investigated at an early stage of the disease.

Baseline findings in PMA were not suggestive of corticomotoneuron involvement or activation of glial cells.

**MR spectroscopy study of the primary motor cortex: findings at follow up**

At follow up, the PMA cohort was the only cohort showing a significant decrease of NAA. This may imply that corticomotoneuronal involvement may occur but at a slightly later stage of disease than in both ALS groups. Comparison with other studies is very difficult as inclusion criteria and disease duration vary widely, and sample sizes in those studies are small.37, 64-67, 78

Overall, the fact that we lost 5/12 patients with ALS-L, 3/12 patients with ALS-B and 2/12 patients with PMA to follow up (death, inability to come to the hospital, inability to lie in supine position) may have influenced our follow up data because of the small numbers per cohort, especially the ALS-L cohort.

**MR spectroscopy study of the primary motor cortex: correlation with clinical findings**

At baseline, correlation between metabolite levels and clinical parameters was significant. However, at follow up, the change in NAA levels did not correlate significantly with the change in clinical parameters. In contrast, we found a strong inverse correlation between an increase of mI levels and a decrease of finger tapping speed over time. This may imply that once corticomotoneuron degeneration has been initiated, glial hyperactivity prevails in disease progression, although we could not confirm this at group level probably due to the small sample size per group.71
**Implications of our MR spectroscopy study**

Our MR spectroscopy data suggest that corticomotoneuron degeneration does occur, also in PMA, though somewhat later than in ALS. The profile of metabolite levels along the spectrum of the various phenotypes (healthy individuals - PMA - ALS-L/ALS-B - PLS) shows a tendency towards a gradual decrease of NAA and a gradual increase of ml. However, these findings could not convincingly discriminate between the various patient groups, probably due to relatively small cohorts.

The properties of MR spectroscopy of the primary motor cortex to differentiate between the various phenotypes or pick up longitudinal changes were disappointing. Therefore, we are of the opinion that MR spectroscopy is not the optimal tool for monitoring UMN degeneration in trials. However, MR spectroscopy provides information on the process of degeneration/glial activation in a chosen area of interest and is therefore useful to gain more insight into underlying disease mechanisms.

Future studies including larger numbers of patients with the various phenotypes might be more powerful in providing information for example on the process of glial activation per phenotype. Also, if ameliorated MR spectroscopy techniques enable us to discern glutamate peaks from the metabolite spectrum, this would add to our understanding of underlying mechanisms of disease.

**Diffusion Tensor Imaging**

*Background*

Diffusion tensor imaging is able to characterize the diffusion properties of water molecules in vivo. Water molecules tend to diffuse preferentially in orientations relatively free of obstruction, such as along axons, leading to a directional bias or anisotropic diffusion. It has been suggested that a reduction in (fractional) anisotropy reflects axonal fiber degeneration. Diffusion tensor tractography allows for reconstruction of specific major white matter tracts such as the corticospinal tract. When extending the focus beyond a specific white matter tract, whole-brain voxel-based analysis can be applied to assess the whole-brain white matter.

Most diffusion tensor imaging and diffusion tensor tractography studies included ‘classical’ patients with ALS, with few studies investigating different motor neuron disease phenotypes concomitantly or longitudinally. Also, most studies included patients with heterogeneous disease duration, and none of these studies were
aimed specifically at investigating patients shortly after diagnosis. We performed a fibre tracking study of the corticospinal tract and a whole-brain voxel-based analysis in the same cohorts that were included in the MR spectroscopy study in order to obtain a spatiotemporal profile of corticospinal tract degeneration and to obtain information on extra-motor degeneration in the various phenotypes at an early stage of disease.

The fibre tracking study: baseline findings
Our diffusion tensor tractography study of the corticospinal tract showed a most prominent fractional anisotropy decrease along the entire course in PLS, a spatial difference between ALS-B (caudal target) and ALS-L (rostral target), and subtle changes in the rostral corticospinal tract in PMA. A limited number of previous studies performed spatial profiling along the corticospinal tract, none of which included separate groups of patients with ALS-B and ALS-L or PMA. These studies mainly found decreased fractional anisotropy in the middle and rostral section of the corticospinal tract in cohorts of patients with ALS with heterogeneous disease duration.\textsuperscript{85, 86, 91-93} However, three of these studies only analyzed the middle- and rostral section of the corticospinal tract, thus lacking information on the brainstem trajectory of the corticospinal tract.\textsuperscript{86, 92, 93} Recent voxel-based analysis studies of the corticospinal tract also showed involvement predominantly in the rostral corticospinal tract.\textsuperscript{94-96} This rostral emphasis was interpreted as supportive of an active cortical degenerative process, as opposed to solely a transsynaptic dying back phenomenon with the LMN being the main target of disease.\textsuperscript{94} However, our study showed significant changes predominantly in the caudal section of the corticospinal tract in patients with ALS-B at an early stage of disease. This demonstrates that interpretation of data obtained in a heterogeneous patient population is difficult.

Previous diffusion tensor imaging studies in PMA were based on region-of-interest analysis and yielded contradicting findings. Some studies found no fractional anisotropy changes\textsuperscript{25, 37}, another study demonstrated decreased fractional anisotropy in the rostral section of the corticospinal tract in patients with a LMN phenotype.\textsuperscript{26} However, all patients in this study developed UMN signs in a later course of their disease, whereas none of our patients had clinical evidence of UMN involvement at any time point.

The fibre tracking study: findings at follow up
In our study, fractional anisotropy decreased in both ALS groups along the corticospinal tract beyond the initial target, thus extending more rostrally in ALS-B and more caudally in ALS-L over time. Longitudinal spatial profiling studies of the corticospinal tract are
lacking, but some studies used the mean fractional anisotropy of the corticospinal tract for follow up.37, 90, 91 None of these studies were able to show a decrease of mean fractional anisotropy over time. In contrast, we found a decrease of mean fractional anisotropy over time in ALS-L and a decreased fractional anisotropy along the corticospinal tract both in ALS-L and ALS-B, as described above. Therefore, spatiotemporal profiling of the corticospinal tract may be of use in monitoring disease at the UMN level, for example in intervention studies.

The fibre tracking study: correlation with clinical findings
We found a strong correlation of the mean fractional anisotropy of the CST with finger tapping speed (spearman's correlation coefficient: 0.554 \( p < 0.001 \)) and the revised ALS functional rating scale (ALSFRS-R) (spearman's correlation coefficient: 0.491 \( p < 0.001 \)) at baseline, but no correlation between the change of these clinical parameters and the change of mean fractional anisotropy over time (results not published). In fact, this was in line with the findings in our MR spectroscopy study, showing a good correlation with clinical findings at baseline, but not during follow up. Correlation between fractional anisotropy parameters and clinical UMN parameters such as the UMN “burden” score or finger tapping speed yielded conflicting results in the past.28, 37, 91, 93-98 The studies that found no correlation between fractional anisotropy parameters and the ALSFRS-R hypothesized that the ALSFRS-R may be determined rather by LMN degeneration than by UMN degeneration, however this explanation does not hold true for specific clinical UMN measures such as the UMN “burden” score or finger tapping speed.

The diffusion tensor whole-brain voxel-based analysis study
Voxel-based analysis: baseline findings
Besides involvement of motor-related structures we found evidence of involvement of structures involved in cognitive tasks in all phenotypes, including PMA.

An extensive pattern of extra-motor fractional anisotropy reduction was demonstrated in PLS when compared with controls in the voxel-based analysis, including the genu of the internal capsule, the body and splenium of the corpus callosum, thalamus and the body of the fornix. The fornix is a major output white matter tract between the hippocampal formation and other limbic structures, thus being involved in emotional processing and memory.99, 100 We did not include neuropsychological tests in our study, so we cannot relate these findings to clinical cognitive deficits, but mild cognitive impairment has been found in PLS, especially regarding frontal lobe function and memory.101 Our findings are in line with two previous study in patients with PLS,87, 102
At baseline fractional anisotropy reduction was mainly, but not entirely, limited to structures involved in motor tasks in ALS-B, ALS-L and PMA. However, the body of the fornix, was also involved in ALS-L and PMA. Cognitive decline and behavioural disturbance have been described in ALS\textsuperscript{103-105}, and a recent study found impaired category fluency and working memory in PMA.\textsuperscript{13} Therefore, reduced fractional anisotropy within the structures for executive functioning and memory may provide anatomical substrates for cognitive dysfunction in patients with PMA. An interesting finding is the fact that fractional anisotropy was decreased in the genu of the internal capsule in ALS-B and PMA, similar to PLS, which points towards corticobulbar involvement.

**Voxel-based analysis: findings at follow up**

In ALS-B, an extensive pattern of fractional anisotropy reduction was found over time, in the corticospinal tract as well as in the hippocampus and other structures related to cognition and behaviour. To a lesser extent the same held true for PMA. In ALS-L, a further reduction was found mainly in the corticospinal tract, white matter of the anterior temporal pole, thalamus, optic radiation and cingulum. Both in ALS-B and PMA the genu and the body of the corpus callosum became involved, which is in line with previous studies in patients with ALS.\textsuperscript{107, 108} In ALS-L only the body of the corpus callosum became involved. Recently, attention was drawn to the fact that callosal involvement is a consistent feature of ALS, independent of clinical UMN involvement, and may reflect either independent bilateral cortical involvement or hemispheric spread of pathology.\textsuperscript{94, 95} The genu of the corpus callosum connects orbitofrontal and (pre)frontal cortices that subserve cognitive processes. Reduced fractional anisotropy in the body of the corpus callosum may reflect pronounced degeneration of collaterals of the corticospinal tract that connect the motor cortices.\textsuperscript{97, 108, 110} The splenium (involved in PLS, see above) is related to parietal projections.\textsuperscript{111, 112}

**Implications of our fibre tracking and voxel-based analysis study**

We found upper motor and extra-motor neuron involvement in all phenotypes of MND including PMA, shortly after diagnosis suggesting that ALS, PLS and PMA are all part of the same spectrum of multisystem neurodegenerative disease. Voxel-based analysis was more sensitive to detect longitudinal changes than diffusion tensor imaging of the corticospinal tract. Therefore, in future studies, voxel-based analysis may be a useful tool to monitor progression of white matter involvement.

Our diffusion tensor imaging study did not support a specific dying back or dying forward mechanism of degeneration contributing to the hypothesis that progression of disease seems to be multifocal rather than unidirectional.\textsuperscript{113}
Correlation of involvement of the various structures involved in cognition with the presence of clinical cognitive deficits still needs further exploration.

**General comments on our imaging studies**

The strength of this study is that we carefully defined subtypes of motor neuron disease at an early stage of disease and included equal numbers per group with a systematic follow-up after 6 months. Unfortunately, we lost almost a third of our patients to follow-up because of rapid disease progression. This may be related to the fact that our inclusion criteria introduced a selection bias towards patients with a rapidly progressive disease course. It is well known that a shorter delay until diagnosis is associated with a more aggressive disease course.\textsuperscript{114} Delay until diagnosis in our study was 6.6 months on average, while the diagnostic delay in epidemiological surveys is 12 months on average.\textsuperscript{115}

**FUTURE PROSPECTS**

Our study demonstrated that the concept of PMA being a separate entity cannot be supported. Firstly, the development of better and more reliable clinical UMN measures will in itself cause a shift from PMA towards ALS. Secondly, shortly after diagnosis there is evidence of UMN and extra-motor involvement in the brain. Therefore patients with PMA deserve to be included in ALS intervention trials.

Diffusion tensor imaging, especially voxel-based analysis, has the potential to monitor UMN and extra-motor involvement in future intervention trials. Further understanding of the spread of disease, be it through neuronal or “non-neuronal neighbours” (glial activation) can also be brought a step further through MR spectroscopy and diffusion tensor imaging. Diffusion tensor imaging may be used to explore specifically the role of the corpus callosum in the spread of disease.

Although especially diffusion tensor imaging proved to be sensitive in localizing areas of neurodegeneration compared to healthy controls, a lot of work needs to be done to know the specificity of these findings. Therefore, the inclusion of controls with myopathies or peripheral neuropathies, and controls with neurodegenerative diseases such as hereditary spastic paraplegia or dementia in future studies is essential.
REFERENCES


