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

Motor neuron disease is not a single disease entity but rather a spectrum of diseases with a varying degree of upper motor neuron and lower motor neuron involvement. At the one end of the spectrum progressive muscular atrophy (PMA) is found, a disease with clinically only lower motor neuron signs and symptoms. Primary lateral sclerosis (PLS) is found at the other end of the spectrum, with a clinical picture restricted to symptoms and signs of upper motor neuron degeneration. Bulbar onset amyotrophic lateral sclerosis (ALS-B) and limb onset ALS (ALS-L) are in the middle range of the spectrum, with a characteristic mix of upper and lower motor neuron signs. Epidemiological differences between ALS-L and ALS-B include a predominance of female patients, worse prognosis, older age at onset, better response to riluzole, and a higher frequency of cognitive dysfunction in ALS-B. These differences are not well understood so far.

The cause of PMA, PLS and ALS is unknown, in 5-10% the cause is genetic. An increasing number of studies provided evidence over the past years that both PMA and PLS may evolve into ALS. Furthermore, in recent years there is growing evidence that extra motor neuron signs, such as cognitive decline and behavioural abnormalities, are far more frequent than previously thought.

It is relevant to obtain insight into the disease process in these phenotypes as prognosis is variable. It is as yet unknown whether the various phenotypes of MND can or should be lumped in therapeutic studies. So far, riluzole is the only evidence based therapy for ALS with a very modest effect. If future therapies prove to be more effective than riluzole, it is important to know whether this effect is targeted at lower motor neuron, or upper motor neuron degeneration or at both, or even at extra motor neurons. Therefore the involvement of the UMN in the various phenotypes should be known, as well as the properties of clinical and surrogate markers of upper motor or extra motor neuron involvement.
THE VARIOUS PHENOTYPES ALONG THE MOTOR NEURON DISEASE SPECTRUM: A BRIEF HISTORY

ALS
Charcot was one of the first neurologists to describe the clinical symptoms in ALS and it was his merit to link clinical and pathological findings.\textsuperscript{16, 17} Criteria for the diagnosis of ALS meant to be used in a research setting were defined at a meeting in El Escorial in 1994 and were further refined at the Airlie House meeting in 1998.\textsuperscript{18, 19} Recently, it was stated that with the Awaji algorithm, using electrodiagnostic criteria superimposed on the El Escorial criteria, a greater sensitivity without losing specificity in the diagnosis of ALS may be realized although the exact benefit with regard to sensitivity is subject to further research.\textsuperscript{20-22} Traditionally, ALS is subdivided in bulbar onset ALS (25%), limb onset ALS (70%) and ALS with respiratory onset (5%).\textsuperscript{23}

During the years of our research conceptual thinking about the spread of disease has undergone a change. First there was an ongoing discussion whether ALS was primarily a disease of the upper motor neurons or of the lower motor neurons, Chou and Norris postulated that ALS is primarily a lower motor neuron disease spreading to upper motor neurons ("dying back").\textsuperscript{24} Eisen however proposed an anterograde ("dying forward") transsynaptic degeneration of the anterior horn cells, which is in keeping with Charcot’s opinion on this matter in his days.\textsuperscript{25-27} However, a clinical spatiotemporal analysis of disease progression on 100 patients with early-onset ALS (published in 2007) revealed that, although UMN and LMN signs were both most conspicuous in the region of onset, further progress and extension to other body regions were essentially independent of each other, supporting a simultaneous and independent process of degeneration in upper and lower motor neurons.\textsuperscript{28} Since then, dual focality of onset (cortex and anterior horn) with contiguous spread outwards from these foci in both lower and upper motor neuron pathways is one of the most widely supported views of ALS pathogenesis.\textsuperscript{29, 30} Hypotheses with regard to the concept of contiguous spread have been twofold. Firstly, it has become clear that hyperactivity of glial and microglial cells enhances disease progression at later stages, rather than transsynaptic degeneration in motor neurons.\textsuperscript{31-33} Secondly, a prion-like mechanism has been proposed very recently. A mechanism of protein misfolding, possibly involving also the TDP 43 protein, might lead to propagation of disease from the first affected motor neurons to adjacent neurons.\textsuperscript{30, 34}
Another unsolved issue is to what extent UMN and LMN degeneration contribute to functional status. Imaging studies found contradicting results with respect to correlation of functional status and surrogate markers for UMN degeneration. Results varied from a robust to a weak correlation between surrogate markers for UMN degeneration and the revised ALS functional rating scale (ALSFRS-R). The studies that found no correlation hypothesized that the ALSFRS-R may be determined rather by LMN than by UMN degeneration.

Over the last decade there is accumulating evidence that ALS affects other structures of the central nervous system as well, which is illustrated by the prevalence of cognitive and behavioural impairment in ALS. Therefore, a concept of ALS as a multisystem disease is evolving. Although it was already known in the first half of the 20th century that ALS was sometimes accompanied or preceded by mental symptoms, not much attention was paid to this until quite recently.

**PMA**

PMA was first described by Aran in 1850, who believed it was a myopathy. In the 1994 El Escorial criteria PMA was classified as suspected ALS, and defined by progressive lower motor neuron signs in 1 or more of 4 regions (bulbar, cervical, thoracic, lumbosacral), with the (electromyographic) exclusion of other lower motor neuron syndromes such as multifocal motor neuropathy. However, in the 1998 revised El Escorial criteria, this subgroup was omitted because a pure LMN syndrome was not regarded sufficiently certain for the diagnosis of ALS. The exact relationship between PMA and ALS is unresolved. There is accumulating evidence that the prognosis of PMA resembles that of ALS and that upper motor neuron signs and cognitive decline may occur in the course of the disease. Furthermore, some patients with a superoxide dismutase I mutation do have a purely lower motor neuron phenotype.

**PLS**

PLS is a pure upper motor neuron syndrome which was described by Charcot, more than 100 years ago. Survival is generally longer than that of ALS. PLS remains a clinical diagnosis after excluding an extensive list of other disorders. Gordon et al. defined pure PLS as a syndrome with isolated UMN signs 4 years after symptom onset, and UMN dominant ALS as a syndrome with prominent UMN disease and minor LMN signs. Disability in the latter group is similar to that found in ALS, but with a slower progression. The description of 2 patients with PLS and a positive (SOD1-negative)
family history of ALS provided evidence that PLS can be linked pathophysiological to ALS. PLS sometimes evolves into ALS although the criterion of a disease duration of more than 4 years seems to exclude these cases. This criterion may be useful in a research setting, but does not help diagnosis when a patient first presents with upper motor neuron signs.

**STARTING POINT OF OUR STUDY**

When we designed our study, signs and symptoms of degeneration of the LMN in motor neuron disease were better delineated than those of the UMN signs, as the former can be readily recognised through clinical examination and electrophysiology. Although surrogate markers for UMN degeneration were rapidly developing, many were not well-established. As the concept of ALS being a multisystem disease was evolving, surrogate markers for extramotor involvement were developed as well. However, none of the surrogate markers for UMN or extramotor neuron degeneration were examined at an early stage of disease, nor were they analysed for the several clinical phenotypes (ALS-B, ALS-L, PMA, PLS) separately.

**AIM OF THIS THESIS**

We focused our research on investigating several surrogate markers for UMN and extramotor neuron degeneration (see below) at an early stage of disease, and in a longitudinal setting, including cohorts of well-defined clinical subtypes. This approach would enable us to learn more about:

- the similarities or differences with respect to UMN and extramotor neuron involvement at an early stage of disease between the various subtypes
- the spread of disease
- the correlation between the surrogate markers and clinical measures
- the potential of the various surrogate markers to pick up longitudinal changes, in other words: are they suitable to be applied in intervention studies to monitor disease progression
CHOICES WE MADE

Clinical parameters
Clinical parameters for upper motor neuron involvement in the bulbar region do exist, but reliability studies are sparse. One of the parameters sometimes used in studies is the presence of a pseudobulbar type of dysarthria. However, the reliability of identifying the type of dysarthria without the use of additional validated tools or rating scales in a clinical setting is unknown. We chose to study the reliability of clinical identification of dysarthria type before including this parameter in our study.

Finger- and foot tapping speed can be used as a continuous parameter to measure upper motor neuron dysfunction over time. Deceleration of tapping speed suggests an upper motor neuron lesion. Measurement of finger- and foot tapping speed is very simple and easy to use in daily practice. Decreased foot tapping speed was found to be a more reliable, sensitive and specific indicator of upper motor neuron dysfunction than the extensor plantar response. Reliability of measurement in a research setting, with the use of a device to register the number of taps such as (mouse) buttons, keyboards, or electronic, infrared or magnetic sensors has been studied. However, reliability of the visual measurement of finger and foot tapping speed in a clinical setting, without any devices except for a stopwatch, has not been formally studied in adults. Given the potential of this very simple measure, we chose to study the reliability of measurement of finger and foot tapping speed without devices, and to provide normative data related to age.

Surrogate markers
The search for “surrogate markers” of upper motor and extramotor neuron involvement was performed in several disciplines varying from neuroradiology and electrophysiology (e.g. transcranial magnetic stimulation, blink reflexes) to biochemistry (e.g. markers in cerebral spinal fluid) and yielded data with varying sensitivity and specificity. Electrophysiological studies focussed mainly on cortical hyperexcitability in ALS. Biochemical markers may be of interest as they may shed light on pathomechanisms, but potentially may also be used to support the diagnosis of ALS and to monitor disease progression over time.

For this thesis we chose to use neuroradiological “surrogate markers” as they would enable us to gather information on the involvement of specific anatomic structures in the
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brain in the various phenotypes over time, in other words to perform a spatiotemporal analysis. We used MR spectroscopy and diffusion tensor imaging for this purpose. We applied MR spectroscopy and diffusion tensor imaging as complementary modalities. Diffusion tensor imaging is suitable for the analysis of subcortical white matter, and MR spectroscopy is suitable to analyse cortical areas. Previous studies using MR spectroscopy or diffusion tensor imaging revealed evidence of upper motor neuron degeneration but none of them focussed on patients at an early stage of disease.\(^{36, 64-69}\) In addition, none of those studies included equal cohorts of the various phenotypes of MND, most of them lumped ALS-L and ALS-B, and the definition of PMA that was used varied.

**MR spectroscopy**

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.\(^{70}\) Several cross-sectional MR spectroscopy studies of the motor cortex showed abnormally low levels of NAA in patients with advanced ALS.\(^{71-75}\) Increased levels of myo-inositol (mI) indicate increased membrane turnover and are considered to represent glial (hyper)activity.\(^{76}\) Measurement of mI is of interest given the results of recent studies suggesting that glial hyperactivity is responsible for disease progression.\(^{31-33}\) A cross-sectional MR spectroscopy study among ALS patients demonstrated better sensitivity and specificity of NAAx and mI combined in a NAA/mI index for detecting disease than that of NAAx or mI separately.\(^{77}\) Glutamate is also of great interest given its role in the pathogenesis of ALS but its spectroscopic measurement is hampered by technical shortcomings.\(^{78, 79}\)

**Diffusion tensor imaging and diffusion tensor tractography**

Diffusion tensor imaging is able to characterize the diffusion properties of water molecules in vivo.\(^{80}\) This diffusion is restricted or hindered by the presence of barriers, such as cellular membranes and subcellular structures, which behave as obstacles to the free motion of water. As a result, the water molecules tend to diffuse preferentially in orientations relatively free of obstruction, such as along axons, leading to a directional bias or anisotropic diffusion.\(^{81}\) Therefore, changes in anisotropy, which can be quantified by diffusion tensor imaging by assessing for instance the fractional anisotropy, reflect changes in tissue microstructure and organization of fibres.\(^{82}\) In particular, it has been suggested that a reduction in anisotropy can reflect axonal fiber degeneration.\(^{83}\) With diffusion tensor tractography it is possible to reconstruct specific major white matter...
tracts such as the corticospinal tract.\textsuperscript{54} 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 in a single comparison.\textsuperscript{57, 65, 66} Diffusion tensor imaging and diffusion tensor tractography have been applied to ALS and less frequently to PMA and PLS, finding evidence of corticospinal tract abnormalities and extra-motor neuron involvement.\textsuperscript{68, 86, 87} However, none of these studies was done at an early stage of disease, and only few studies included a systematic follow up.

**OUTLINE OF THE STUDY**

In *chapter 2* we review the evidence for dysfunction of upper motor neurons and extra-motor neurons in ALS, PMA and PLS with a focus on what is known about the disease process at an early stage of disease.

In *chapter 3* we describe several cases of vocal cord abduction paresis in ALS. With these case reports we illustrate how upper motor neuron involvement may affect even one of the smallest muscles of the body.

*Chapter 4* aims to investigate the accuracy of clinical identification of dysarthria types amongst neurologists, residents in neurology and speech therapists.

In *chapter 5* we present the results of a study on interrater and test-retest reliability of tapping speed with the index finger and foot tapping speed measured without any device to register the number of taps such as (mouse) buttons, keyboards, or electronic, infrared or magnetic sensors. We also provide normative values for finger tapping speed of the thumb, index finger and middle finger, and for foot tapping speed, related to age, gender and dexterity.

In *chapter 6* we describe the results of a longitudinal proton MR spectroscopy study of the primary motor cortex in patients with bulbar onset and limb onset ALS, and PMA, all of them with a disease duration of less than 1 year, using healthy individuals, and PLS patients as controls.

In *chapter 7*, we describe the results of diffusion tensor tractography of the corticospinal tract, and of a whole-brain voxel-based analysis study, performed in the same cohorts as described in chapter 6.

In *chapter 8* the general discussion focuses on our main findings and on future prospects.
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