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Author M.M. van der Graaff
Faculty Faculty of Medicine
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Summary

This thesis deals with upper motor and extra-motor neuron involvement at an early stage of disease in bulbar-onset amyotrophic lateral sclerosis (ALS-B), limb-onset ALS (ALS-L), and progressive spinal muscular atrophy (PMA). Findings in these cohorts were compared with healthy controls and with patients with primary lateral sclerosis (PLS). In **chapter 1** we gave an introduction on the history of the definition of the various phenotypes along the spectrum of motor neuron diseases (MND). In addition, we summarized what was known about 1) the mechanisms of disease onset and disease progression with a focus on involvement of the upper motor neurons, and 2) extra-motor neuron involvement in MND. We then described the aims of this thesis.

In **chapter 2** we reviewed the evidence for upper motor neuron and extra-motor neuron dysfunction in ALS, PMA and PLS with a focus on what is known about the disease process at an early stage of disease. We concluded that 1) delineation of the clinical entities is still under debate, 2) many study cohorts were heterogeneous with respect to disease duration and clinical phenotype, and thus not informative on mechanisms of disease onset in the various phenotypes, and 3) there is a growing body of evidence that ALS and possibly also the other phenotypes are multisystem disorders rather than pure motor neuron diseases.

In **chapter 3** we described several cases of ALS manifesting with vocal cord abduction paresis and we reviewed the literature. In contrast to what was previously thought, occurrence of vocal cord dysfunction in ALS is far from rare, and may lead to potentially hazardous episodes of stridor and choking due to glottic narrowing. Vocal cord dysfunction may be of infranuclear as well as of supranuclear origin.

Diagnosis of ALS and other motor neuron disease phenotypes depends on the presence of clinical upper and/or lower motor neuron signs in the bulbar, cervical, thoracic and lumbosacral regions. However clinical signs in the bulbar region suggestive of upper motor neuron pathology are either unspecific or not systematically investigated in the MND population. We investigated whether dysarthria type (flaccid, spastic, "mixed flaccid/spastic", cerebellar and hypokinetic, with the flaccid, mixed and spastic type being relevant for the MND population) can be clinically identified and described the results in **chapter 4**. We found that clinical identification of dysarthria type by neurologists is not reliable, with a correct identification of 40% of the samples, residents and speech therapists performing likewise. Kappa for the interrater agreement among neurologists was 0.26, for intrarater agreement 0.46. When provided with clinical information, correct identification improved somewhat for neurologists and residents.

Finger and foot tapping speed (FiTS and FoTS) have been used in ALS studies as a parameter for upper motor neuron dysfunction in the cervical and lumbosacral regions. However, reliability of the measurement of FiTS and FoTS without the use of any device to register the number of taps such as (mouse) buttons, keyboards, or electronic, infrared or magnetic sensors was unknown at the start of our research. In **chapter 5** we presented the results of our reliability study in which we also obtained 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 measured without the use of devices except for a stopwatch. We found a good agreement of the two raters with the gold standard (video recordings) and with each other. 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 the second trial, in which the intraclass correlation coefficient was 0.97 ($p < 0.001$) and 0.95 ($p < 0.001$) for both raters respectively. Similar values were found for agreement between both raters and between the raters and the gold standard with respect to FoTS. FiTS was inversely related to age, FoTS was not. We found no significant differences of FiTS between males and females. However, FoTS was slower in females. We found a strong relation between FiTS and dexterity, and concluded that FiTS being slower in the dominant hand is very rare in healthy individuals and may suggest pyramidal or extrapyramidal pathology, depending on the clinical context.

In **chapter 6** we studied involvement of the upper motor neuron at the level of the motor cortex with MR spectroscopy in 5 cohorts: PLS, ALS-B, ALS-L, PMA and healthy controls ($n=12$ per cohort) at baseline and after 6 months. Disease duration of patients with ALS-B, ALS-L and PMA was < 1 year, thus indicating an early stage of clinical disease. Metabolites measured with MR spectroscopy provide information on the composition of brain tissue in the selected region. A decreased N-acetyl aspartate (NAA) reflects a dysfunction or loss of neurons, an increase of myo-inositol (ml) indicates increased membrane turnover and is considered to represent glial (hyper)activity. At baseline, only in the PLS cohort (per definition disease duration > 3 years) we found a significantly decreased NAA and increased ml compared to the healthy controls. In both ALS cohorts we found a trend towards decreased NAA and increased ml. At follow up, the PMA cohort was the only cohort showing a significant decrease of NAA, which implies that corticomotoneuronal involvement may occur at a slightly later stage of disease in this cohort. At baseline, correlation between metabolite levels and clinical parameters was significant. A change of NAA levels over time was not correlated with a change in clinical parameters. However, we found a strong inverse correlation between increased ml levels

and decreased FiTS over time which is compatible with the hypothesis of glial (hyper) activation being important in disease progression but not in disease onset. Due to the small sample size per cohort we could not confirm this at group level.

We concluded that the properties of MR spectroscopy of the primary cortex to differentiate between the phenotypes or to pick up longitudinal changes were disappointing but that it provides data on the process of degeneration/glial activation in a chosen area of interest and is therefore useful to gain insight into underlying disease mechanisms.

In **chapter 7** we described the results of a diffusion tensor imaging MR study in the same cohorts as mentioned in chapter 6. First, with diffusion tensor fibre tracking we reconstructed the corticospinal tract, and performed a spatiotemporal analysis with fractional anisotropy along the tract as a parameter for its integrity. Compared to the healthy controls, we found the most prominent decrease of fractional anisotropy along the entire course of the corticospinal tract in PLS, a spatial difference between ALS-B (caudal changes) and ALS-L (rostral changes), and subtle rostral changes in PMA. At follow up, 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. We found no further decrease of fractional anisotropy in PMA. The mean fractional anisotropy of the corticospinal tract was strongly correlated with FiTS and the revised ALS functional rating scale, but clinical changes over time were not correlated with the changes in fractional anisotropy.

In a whole brain voxel-based analysis we found, besides involvement of motor related areas, evidence of involvement of structures involved in cognitive tasks in all phenotypes, including PMA. These findings support the idea of ALS and phenotypes being multisystem diseases, and corroborate the findings that (mild) cognitive changes can be found in a fair proportion of all MND phenotypes. At baseline the decrease of fractional anisotropy in these structures was modest, at follow up extensive, especially in ALS-B and PMA. In addition the anterior, middle and posterior part of the corpus callosum were involved to a varying extent in all phenotypes. We concluded that voxel-based analysis was more sensitive to pick up longitudinal changes than a selective analysis of the corticospinal tract.

Chapter 8 consists of a general discussion of our findings in the context of available evidence and suggestions for future research.