Walking ability and daily functioning in Multiple Sclerosis

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role
walk
cut-off
force
decline
relationship
significant
treatment
better
problems
eyes
results
limitations
conditions
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parameters
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support
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10-meter
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assessment
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gait
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analysis
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course
type
research
walkers
findings
cohort
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essential
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mild
neurological
diagnosis
variables
long-term
peripheral
related
level
cost
daily
speed
category
often
discussed
MFWC
impaired
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SF36
social
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Multiple Sclerosis (MS) is a chronic progressive neurological disease, occurs most commonly in young adults and has a high prevalence in Western society. MS is characterised by the occurrence of lesions in diverse locations in the central nervous system and can thus cause a wide variety of neurological symptoms. These symptoms result in limitations in physical, social and cognitive functioning, and affect the activities of daily living. Long-term follow-up studies on the daily functioning of patients are therefore essential for effective healthcare and rehabilitation medicine. The first section of this thesis focused on a 10-year long-term follow-up study of an incident cohort of 156 patients with MS. The second section focused on reduced walking ability in MS patients. Among the many impairments due to neurological loss, one of the most frequently experienced is reduced walking ability. In order to gain a better understanding of the factors contributing to a reduced walking ability, the range of impairments that occur and that may affect gait must be correctly identified.

From a clinical perspective, the aim was to unravel the various effects of neurological impairment on walking ability, in order to improve treatment opportunities.

Chapter 2 describes the results of a long-term follow-up study that measured the course of daily functioning in patients with MS in different domains. Knowledge of the functional prognosis in the areas of physical and cognitive functioning is essential to establishing an appropriate level of care and for the allocation of health care resources for the patients. In 1998, a long-term prospective follow-up study was initiated to investigate the functional prognosis in an inception cohort of 156 patients with a definite diagnosis of MS (FuPro MS study). The domains of interest were physical functioning, cognitive functioning and mental health, social functioning and general health. Although the neurological deficits were relatively minor immediately after diagnosis, between 9% - 39% of the patients had an aberrant score on one or more of these domains. After 3 years it could be concluded that while the neurological deficits and physical functioning deteriorated over time, the other domains showed no significant effects. Deterioration was more prominent in patients with non-relapsing onset (NRO) type, as compared to patients with the relapse onset (R0) type. Since

a 3-year follow-up of a cohort with a slowly progressive disease is relatively short, it was decided to extend the follow-up time. The participants were thus examined at baseline, 6 months, 1, 2, 3, 6 and 10 years after diagnosis. They underwent a neurological assessment, the Expanded Disability Status Scale (EDSS), and filled in the Functional Independence Measure (FIM) and sub-scales from the Medical Outcome Study Short Form (SF36). Furthermore, several potential determinants of the course of functioning were taken into account: age at start of the study, gender, type of MS and the use of disease modifying drugs (DMDs). The within-patient changes over 10 years were analysed using a linear mixed model. The EDSS and physical functioning changed significantly over time and the rate of change was faster in the NRO group. Furthermore, age and DMDs contributed to the course of neurological deficits and physical functioning. The FIM cognitive functioning and SF36 social functioning worsened significantly over time, but at the same rate in both types of MS. The SF36 mental health, SF36 role physical and the SF36 general health showed no time-related decline in the first 10 years following definite diagnosis. We concluded that while a large percentage of patients show functional limitations at diagnosis, ten years later MS patients show relatively mild changes in daily activities.

In **Chapter 3**, the aim of the study was to determine which specific gait speed corresponds to each category of the Modified Functional Walking Categories (MFWC) and to determine the minimally important change (MIC) in absolute gait speed using the changes in the MFWC. The MFWC is a valid scale to measure the level of community walking, and focuses on the functional abilities a patient needs at home or in the community. The advantage of using community walking scales is the possibility to immediately generalise limitations in mobility to the problems faced by patients in daily life. The gait speed measurement, the MFWC and the EDSS from the 156 patients, at six measurement moments, were included in this study. A gait speed cut-off point for every MFWC category was determined with a Receiver Operating Characteristic (ROC) curve. An unlimited community walker has a minimal gait speed of 1.63 ms^{-1}. The least-limited community walkers should walk with a speed of at least 1.35 ms^{-1}, and the most-limited community walkers show a minimal gait speed of 1.04 ms^{-1}. Finally, patients who were considered to

be unlimited household walkers were characterised by a minimal gait speed of 0.48 ms^{-1}. The sensitivity is higher than > 0.8 for each cut-off point, which means that more than 80% of the patients will be classified in the correct MFWC category using these cut-offs. To determine the MIC in gait speed, we divided the patients into three groups. One group included patients who remained stable between two consecutive measurements, a second group included patients who deteriorated by one category on the MFWC and the third group was composed of patients who improved by one category. The mean gait speed over the six years for the stable group and the improved group hardly differed, whereas the mean gait speed of the deteriorated group was clearly slower. However, we could not define a minimal important change in mean gait speed using a change of one category on the MFWC as an anchor. We concluded that a specific gait speed could be assigned to each level of community walking, and that determining the change in community walking requires the actual measurement of the level of community walking, as this could not be derived from a minimal important change in gait speed.

In **Chapter 4**, we investigated the relationship between self-reported fatigue and energy cost during walking (ECw), and how self-reported fatigue and energy expenditure during walking relate to physical functioning. Fatigue is one of the most disabling symptoms in patients with multiple sclerosis, but its aetiology remains unclear. In current MS research, the severity of MS-related fatigue symptoms and their impact on daily functioning are mainly assessed using self-reported questionnaires. Energy expenditure is a more objective outcome measure and it can be used to investigate the role of physical inefficiency in fatigue. The ECw was measured in 75 patients who participated in the 10-year follow-up measurement, and fatigue (Fatigue Severity Scale, Visual Analogue Scale and the Medical Outcomes Study Short Form (SF36) subscale vitality) and physical functioning (SF36, subscale physical functioning) were assessed. Using the three fatigue measurements, the latent variable *fatigue* was formed and structural equation modelling was used to measure underlying hypothetical constructs and their interrelationships. The results showed that the ECw was not a determinant of fatigue, although fatigue, ECw and disease severity were able to explain 75% of the variance in physical functioning. We concluded that the experienced fatigue in MS

patients with mild to moderate walking problems is not related to the ECw. A possible explanation could be that there is a difference between peripheral fatigue (i.e. muscle fatigue) and central fatigue (more subjective sense of fatigue, with a cognitive component), with the ECw effectively a measure of peripheral fatigue, while the latent variable *fatigue* may be an indicator of central fatigue.

In **Chapter 5**, we explored the relationship between dynamic and static balance, with dynamic balance expressed as the margin of stability (MoS). Furthermore, we evaluated whether the MoS was related to the severity of MS. Balance impairments have a potentially major impact on daily living. Current clinical assessment tools, such as the Berg Balance Scale and the Tinetti Performance Oriented Mobility Assessment, appear to be insufficiently sensitive for the detection of balance impairments in minimally impaired MS patients. Posturography is a more quantitative balance measurement and may be a more appropriate measure of subtle balance impairments. However, this assessment measures static balance, whereas balance in dynamic situations is a greater challenge for MS patients. Quantitative values for dynamic balance during walking can be derived from the margin of stability (MoS), but this measure has not yet been investigated in patients with MS. In addition to the MoS, double support and step width were used to study dynamic balance, as people facing balance problems often adopt a more conservative gait. We hypothesised that (1) more challenging conditions during posturography would show a better correlation with dynamic balance, (2) patients with larger static sway parameters would also have a larger MoS, and (3) the MoS can be used to distinguish between levels of disease severity (EDSS), even in minimally impaired patients. Both static and dynamic balance were measured in 81 patients participating in the 10-year follow-up measurements. Static balance was measured under five different posturography conditions (eyes open or eyes closed on a firm surface, eyes open or eyes closed on a foam surface, and a cognitive task). The MoS was derived from the center of pressure trajectory, measured during overground walking, and double support time and step width were measured at the same time. The correlation coefficients between the dynamic balance measures (MoS, double support time and step width) and posturography were significant but low. Moreover, the correlation

coefficients did not increase with the more challenging posturography conditions. Regression analysis was used to investigate the significance of the relationship between the MoS and disease severity; this analysis demonstrated that only 12% of the variance in MoS could be explained with the EDSS. We thus concluded that the MoS and other dynamic balance measurements were, at best, only marginally related to posturography measurements in MS patients walking without an assistive device. Moreover, the usefulness of the MoS as a measure of dynamic balance in patients with MS is questionable, and the simplicity of the double support time and step width makes these variables preferable to the more complex MoS.

In **Chapter 6**, we explored the possibility of identifying different gait patterns in patients with MS by combining kinematics, functional parameters of walking and muscle coordination during walking. Limitations in walking ability are a substantial problem in patients with MS and a better understanding of the functional changes in gait is obligatory when attempting to develop more targeted interventions and early clinical treatment. Categorisation of gait patterns could make a significant contribution to achieving these goals. Gait analysis is a common method in other patient groups and the widespread use of this type of classification is an indication of its utility. In MS, most investigations of walking ability have focused on spatiotemporal parameters, but a disadvantage of global parameters is that they do not reflect potential changes in the lower extremity joints or describe the quality of performance. Advocates for kinematics maintain that they may provide a more complete gait assessment. MS often affects several neurological systems, so there could be several identifiable impairments in gait. We performed a 2-dimensional gait analysis in 81 MS patients with a disease duration of 10 years. The patients were recorded in both the sagittal and frontal planes, and electromyography signals from five muscles of each leg were recorded. A built-in force plate measured the ground reaction force on a 10-meter walkway and in total, 73 kinematic, EMG and force plate variables were scored for each patient. Latent class analysis was used as the statistical method to find subtypes of related cases. Gait patterns were defined by variables based on homogeneity within a latent class and heterogeneity between the latent classes. Using the Bayes theorem, patients were assigned to one of the latent classes by calculating the

posterior probability of a patients' membership in each class. We concluded that three gait classes could be defined in our population of MS patients, the classes based on a set of nine kinematic variables including heel-rise terminal-stance, the push off, clearance initial swing, plantar flexion ankle mid-swing, pelvic rotation, arm-trunk movements, activity gastrocnemius pre-swing, the M-wave and the mean propulsive force. The three classes were based on a gradual deterioration in a few variables related to the push-off during gait.

In **Chapter 7**, we discussed methodological issues arising from our study, emphasised the main findings, elaborated on topics for further research and discussed clinical implications. We reflected on the consequences of our methodological choices with regard to missing data and the study design. We concluded that it should be born in mind that the results discussed in chapters 3 to 6 were based on minimally and moderately impaired patients and therefore cannot be generalised to severely impaired patients.

The main findings of this thesis were:

1) In the first 10 years of MS, physical functioning showed the largest decline when compared to other parameters including cognitive functioning, mental health and social functioning.

2) Fast gait speed, measured with the 10-meter timed walk test, is related to the level of community walking, thus making it possible to use gait speed as an indicator for the walking ability of MS patients.

3) The perceived fatigue of MS patients is not related to the energy cost of walking. The energy cost of walking is an indicator of peripheral fatigue and was shown to relate adversely to physical functioning. MS-related fatigue seems to have a major central component.

4) Based on a core set of nine gait variables observed in a 2D gait analysis, MS patients can be classified in three different gait classes. The nine gait variables were mainly related to the gait features push-off and clearance. The gait classes coincided with the neurodegenerative pattern of MS.

The main findings of this thesis provide directions for further research. We suggest extension of the longitudinal part of this study, to gain further insight into progressive decline and daily functioning. We would also advocate that supplementing the cohort is required to maintain sufficient statistical power. Furthermore, a high-quality randomised clinical trial is needed to determine the most effective treatment aimed at reducing MS-related fatigue. Regarding dynamic balance, more clinimetric research aimed at developing a valid outcome measure is recommended. To be able to apply the gait classes in a clinical setting, further research should establish the validity and reliability of the score form and the gait classes.

With regard to clinical implications, we advocate the use of gait speed as an important indicator for the level of community walking and physical functioning. Furthermore, as central fatigue seems to be the main explanation for MS-related fatigue, energy management and cognitive behavioural therapy may be promising treatments. Finally, MS patients can be classified in one of three different gait classes, following a relatively easy observation of nine gait variables. Reduced push-off seems to be the main problem in MS patients with a relatively mild decrease in walking ability.