Walking ability and daily functioning in Multiple Sclerosis

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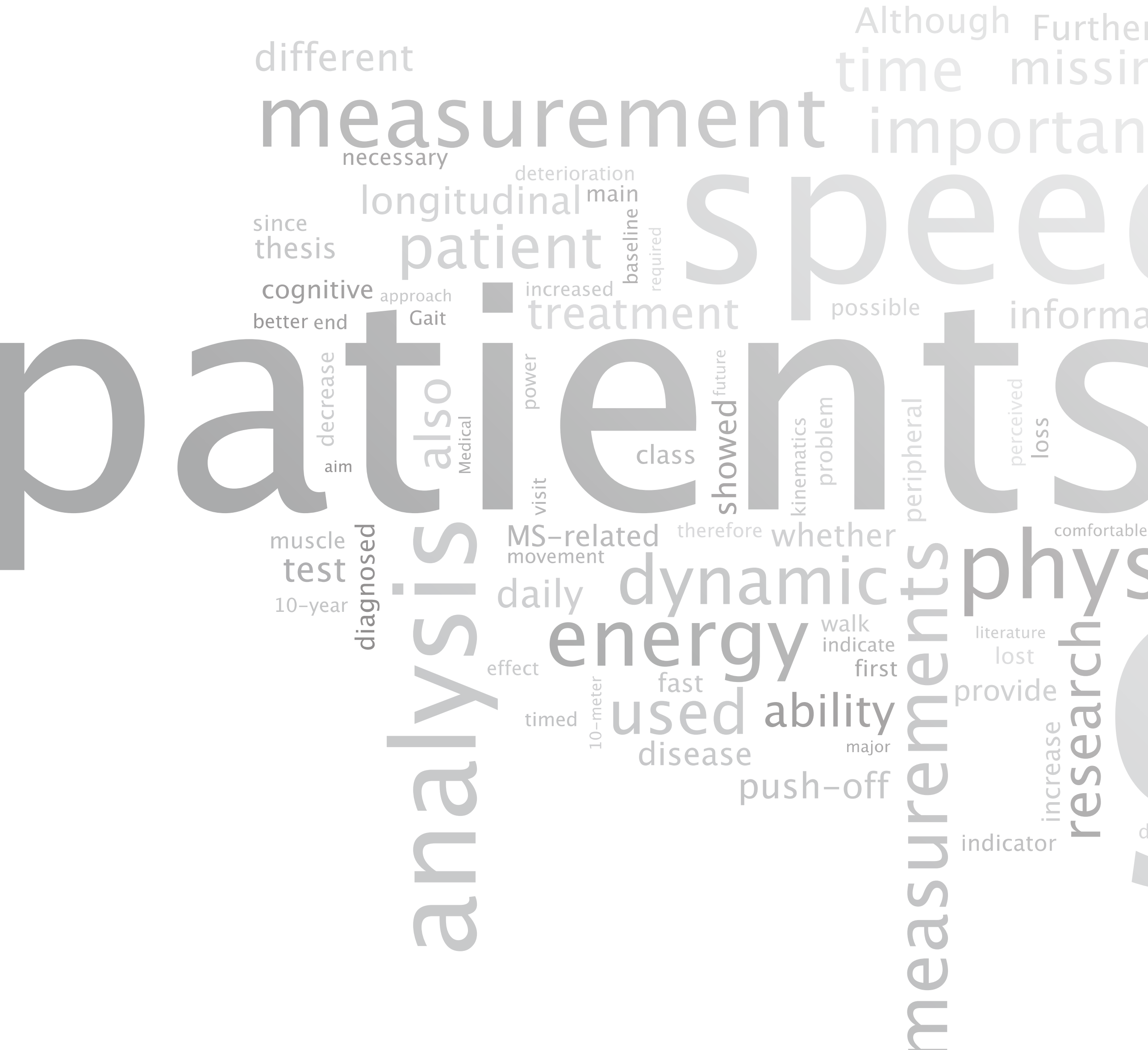
2013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General Discussion

CHAPTER 7

INTRODUCTION

The first aim of this thesis was to gain insight into the 10-year course of daily functioning in patients with MS in order to capture the decline in daily functioning in the domains neurological deficits, physical functioning, mental health, cognitive functioning, social functioning and general health. The second aim was to achieve a better understanding of the relationship between MS-related impairments and walking ability. In this general discussion, we critically reflect on the research described in this thesis. First, we discuss the methodology applied in this thesis and how this methodology may have specifically influenced our findings. We then discuss the main findings, together with their contribution to improving the treatment of walking ability in patients with MS. Finally, we provide recommendations for further research and formulate the clinical implications of our findings.

METHODOLOGICAL CONSIDERATIONS

Study population

The patients in the studies described in this thesis participated in a longitudinal cohort study.[1,2] This inception cohort of 156 recently (< 6 months) diagnosed patients was recruited between 1998 and 2000. All consecutive eligible patients visiting the participating neurology outpatient clinics were invited to participate. A study design of this type is unique in the field of rehabilitation medicine and in MS. For a longitudinal study on the course of daily functioning in patients with MS, an inception cohort is the most robust manner in which to study the functional prognosis. At the inception, the male-female ratio, the type of MS at onset and the mean age at onset were all in accordance with the typical epidemiological characteristics of MS.[3-5]

Missing data

Although it is inevitable that some patients drop out in a longitudinal study of this type, we made strenuous efforts to minimise drop out. These efforts resulted in only 19 patients being lost to follow-up after ten years, while 28 patients decided not to participate in the 7th follow-up measurement, for a variety of reasons. Ultimately, only ten percent of the 1092 possible measurements (156 patients with seven measurements each) were missing. While loss to follow-up is unavoidable, it commonly leads to bias and loss of statistical power.[6] In general, a distinction is made between three types of missing data: (1) missing completely at random, (2) missing at random, and (3) missing not at random. Information on the type of missing data is important for interpretation of the results of longitudinal analyses.[7,8] To estimate the effect of the missing data in the longitudinal analyses described in Chapters 2 and 3, it is first necessary to ascertain the type of missing. This can be done by comparing the patients who were lost to follow-up with those who were present at the 10-year measurement. Since patients dropped out at various time points during the study, a comparison is made at baseline. As physical functioning is the main subject of the studies described in this thesis, three physical outcome measures were used to estimate the type of missing: the Expanded Disability Status Scale (EDSS), gait speed measured with the 10-meter timed walk test (10m TWT) and physical functioning measured with the Medical Outcome Study Short Form (SF36 PF). All three were significantly different at baseline. The differences between the EDSS (-0.5 points, 95%-CI_{diff}: -0.957 to -0.199)), the 10m TWT (-1.94 seconds, 95%-CI_{diff}: -3.03 to -0.84) and, the SF36 PF (-8.85 points, 95%-CI_{diff}: -0.24 to -17.94) were all in favor of the long-term participants. Fatigue (measured with the Fatigue Severity Scale [FSS]) and age did not differ between dropouts and the remaining patients. Furthermore, slightly more data was missing for patients with non-relapsing onset type of MS (NRO) at ten years, with 17.9% (n=28) NRO patients at the inception and 16.5% (n=18) at the 10-year measurement. Based on these results, we have to conclude that the missings were 'not at random', but depended on the baseline level of physical functioning of the patients. Although it appears that physical functioning in the group that remained was better than that in patients lost to follow-up, it is not evident that these differences would still present after ten years, as the disease course is unknown.

Although the baseline scores of the 10-year participants were somewhat better than the patients who were lost to follow-up, we would argue that this difference had no major consequences for the results of the studies described in this thesis. The differences at baseline on the 10m TWT and the SF36 PF were clinically relevant, but none of the patients were immediately lost to follow-up subsequent to the baseline measurement. Moreover, since 21% of the patients only missed one measurement moment and 17% of the patients missed two or more measurement moments, there was not a complete loss of data for patients who were 'lost to follow-up'. The above mentioned, together with the use of longitudinal data-analysis techniques robust to missing data, leads us to conclude that the missing values did not have a major effect on the results relating to the 10-year course of daily functioning described in Chapter 2. In the second part of Chapter 3, we investigated the Minimally Important Difference in absolute gait speed, focusing on the within-patient changes between two consecutive measurements. Since some patients failed to attend all of the measurement moments but did not entirely drop out, missing data fluctuated over time and resulted in effects that were difficult to determine exactly. As the analyses focused on within-patient changes, we assume that the results were not biased by these missing values.

In Chapters 4, 5 and 6, we used data obtained during measurements at the VU University Medical Center. This addition to the measurements at 10 years consisted of physical performance tests concentrating on walking ability. Of the 109 patients who participated in the 10-year measurement, 28 did not participate in this supplementary aspect for reasons including: physically incapable (13), too great a burden (8), fatigue (4), too busy (2) and living abroad (1). Patient characteristics indicate that the more severely impaired dropped out or were excluded. As expected, there were significant differences with regard to the level of physical functioning (SF36 PF and 10M TWT) and the EDSS between the 81 patients participating in the additional physical performance tests and the 28 patients who only filled in the questionnaires and were visited at home. Scores on the FSS, male-female ratio and age were not different between these two groups. Due to this selection of participants, it is important to keep in mind that the results related to fatigue, balance and gait in Chapters 4, 5, and 6 only apply to minimally and moderately impaired patients with MS, and cannot be generalised to severely impaired patients with MS.

Design and measurements

In Chapter 4, we investigated the relationship between experienced fatigue and the energy cost during walking, using data from a questionnaire, a home visit and the visit to the VU University Medical Center. The time between the questionnaire and the home visit was two weeks, but due to logistical reasons the median time between the home visit and the visit to the VU University Medical Center was 14 weeks (range 0 - 54 weeks). First, we checked that a patient had not had a relapse during this period. Second, we used gait speed to verify any deterioration in a patient. Gait speed was determined at both measurement moments and using regression analysis, we investigated whether the time (in days) between the measurement moments had a significant influence on the relationship between gait speeds. As this was not the case, we could therefore conclude that the time interval between the measurements had no influence on performance in these mildly affected patients.

The sequence of measurements at the VU University Medical Center was not randomised, since the protocolised alternation between physically demanding tests and the less demanding tests was deemed necessary to avoid reduced performance due to fatigue. However, we cannot exclude that fatigue had an impact on the measurements by the end of the assessment, since all measurements demanded active patient involvement and the average duration of the total visit was three hours. Fatigue may have affected our results in two different ways. Firstly, fatigue may have negatively influenced the measurements at the end of the assessment compared with those at the start. This may have affected the results described in Chapter 5, since dynamic balance data was derived from the first measurement in the assessment, the six-minute walking test, whereas posturography data were collected at the end. However, as we found a relatively high correlation, $r = 0.864$ ($p < 0.001$), between gait speed measured at the start (during the six-minute walking test) and at the end of the measurement moment (during the clinical gait analysis), this may indicate that physical performance was not affected by fatigue. Similar results were reported in a study by Feijs et al.,[9] which concluded that walking capacity did not change over time in a day. Secondly, patients who experience fatigue may be more prone to affects due to the length of the measurement session. Consequently, the differences between patients with and without fatigue as a symptom of MS could increase towards the end of the measurements. The gait analyses described in Chapter 6 were carried out towards the end of the assessment and therefore may have been affected by fatigue. However, considering the high percentage of gait analyses with no or minimal deviations, we feel that it is safe to conclude that fatigue did not play a major role during the clinical gait analysis. As regards the FSS-score, fatigue was experienced by 60% of the patients in gait class 1 (cut-off point FSS = 4), while the figures were 92% and 94% for gait classes 2 and 3, respectively. However, Crenshaw et al.[10] have demonstrated that fatigue does not influence kinematics during gait, Rietberg et al.[11] found no significant association between physical activity and self-reported fatigue, and Feys et al.[9] showed that an increase in self-reported fatigue during the day did not affect performance on walking tests. Taken together, these results indicate that gait speed remains stable during the day; a beneficial finding for clinical gait analysis, since kinematics, EMG and GRF are sensitive to changes in gait speed.

MAIN FINDINGS

Gait speed

Gait speed has been singled out as being particularly important in a range of pathologies due to the relevance to community walking, predicting the incidence of health events, length of in-patient rehabilitation and discharge destination, and mortality.[12-15] Furthermore, Studenski et al.[16,17] and Fritz et al.[18] even recommended gait speed as a clinical vital sign.

Although we also found that gait speed is highly related to community walking (Chapter 3), and that gait speed was significantly different between the three distinctive gait classes (Chapter 6), it is important to consider how gait speed can be used in the rehabilitation treatment of patients with MS. These considerations should be two-sided: first, the clinimetric properties of each gait speed measurement must be known, and second, which conclusions with regard to rehabilitation can be drawn from gait speed as an indicator of a patients' physical functioning.

In contrast to walking distance or walking time, gait speed is a parameter with less day-to-day variability.[9,19,20] Gait speed can be quickly and easily assessed and is a reliable and valid measurement.[12,21] In stroke and the elderly, research has shown that gait speed is also a responsive measurement.[15,22-25] In MS, the responsiveness of the 10-meter timed walking test is often established as part of the Multiple Sclerosis Functional Composite (MSFC).[26,27] These studies reported only the relative changes and concluded that 20% is a clinically meaningful change. In our study of the minimally important change in gait speed (Chapter 3), none of the patients showed a relative change of 20% between measurement moments. Additional analysis after an earlier study[9] showed that the smallest real change in fast gait speed was equal for patients with different disease levels independent of initial gait speed, this in contrast to the relative changes. More grip and an easier clinical interpretation could be an additional advantage of the use absolute changes in gait speed. It may be worthwhile exploring whether absolute changes in gait speed are a better parameter to define the minimum change on the 10-meter timed walk test.

There is wide variation in the walk tests used to assess gait speed. These variations concern the start protocol (static versus dynamic start), the instructed speed (comfortable versus fast speed), the distance covered or the time frame used[28], and the use of walking aids. Although these various walk tests have revealed all of the above mentioned clinimetric properties, differences in execution may yield different clinically meaningful information regarding walking performance. Longer walks may be preferable when studying endurance, and for research on the effectiveness of rehabilitation management on the walking capacity of patients with MS, a long walking test is believed to be more appropriate. Motor fatigue is also more apparent in long walking tests than in shorter tests.[28,29] For a general description of the walking capacity of an MS patient, a short walking test is sufficient.[28] An advantage of short tests, e.g. 10-meter timed walking test or the 2-minute timed walking test, is that patients with severe walking problems are still able to accomplish such tests. In Chapter 3, we advocated the use of a fast walking speed in relation to community walking, a conclusion also supported by Gijbels et al.[28]

While the discrepancies between short or long walk tests and comfortable or fast gait speed have been extensively discussed,[9,28] research on the use or non-use of a walking aid during walk tests is still lacking. It is possible to argue that gait speed measurements with or without a walking aid provide different information. A walking aid (e.g. cane, walker or orthosis) facilitates an increased walking speed, which could then result in an incorrect conclusion on the level of functioning of a patient. When gait speed is used as an indicator for daily functioning, gait speed measurements can be conducted with a walking aid since the patient will also use the walking aid during the execution of daily activities. In Chapter 3, patients were allowed to use their walking aid and this resulted in well-defined cut-off points to determine the level of community walking. When a deterioration in physical functioning is being determined, e.g. muscle weakness, spasticity or balance impairments, the use of a walking aid can impede results. In Chapter 6, the results of the latent class analysis indeed showed a change when gait speed, measured with a walking aid, was added as a variable in the analysis. Patients with clear gait impairments were also classified in a better gait class, due to the positive effect of their walking aid. When seeking information on the physical functioning of a patient, it is thus better to measure gait speed without the use of walking aids.

Gijbels et al.[28] noted that the difference between usual and fast gait speed decreases as the degree of ambulatory dysfunction increases. A decrease in the gait speed capacity could be an important indicator for the deterioration in walking ability in patients with MS. To the best of our knowledge, the change over time in the absolute difference between fast and comfortable gait speed in patients with MS has not yet been investigated, but could potentially provide clinically important information.

Walking is a complex movement and many variables influence gait speed, e.g. motor control, muscle strength, musculoskeletal condition, sensory and perceptual function, endurance, cognitive functioning and health status.[16,18,30] Gait speed could potentially be used as a simple indicator, or so-called vital sign, to monitor patients and act as a prognostic indicator of poor health.[16,18] Abnormalities in gait speed have numerous potential causes, which means that gait speed can provide a first impression of the patient, but comprehensive rehabilitation treatment still requires that the problem underlying reduced gait speed should always be examined.

In this thesis, two chapters describe the use of gait speed as an indicator of walking ability in patients with MS. We investigated the relationship between gait speed and community walking in Chapter 3, and in Chapter 6 we showed that gait speed was significantly different between the three gait classes. We compared the mean gait speed of the gait classes with the cut-off points for the level of community walking (MFWC) found in Chapter 3 (both measured with the 10-meter timed walking test, fast speed). The patients in class 1, i.e. the good walkers, could be considered as unlimited community walkers (MFWC 6). Patients in class 2, the minimally impaired walkers, are most-limited community walkers (MFWC 4). The mean gait speed is below the cut-off point of the least-limited community walkers (MFWC 5). However, taking the 95% confidence interval into account, some patients in class 2 will be classified as least-limited community walkers. This may indicate the possibility to distinguish another gait class, lying between classes 1 and 2. Patients in class 3, the moderately impaired walkers, are unlimited household walkers (MFWC 3). Thus, we confirmed that there is an agreement between the level of community walking and the gait classes.

Fatigue

Patients with diseases of the central nervous system (e.g. stroke, Parkinson and MS) often complain of fatigue, which is defined as 'a subjective lack of physical and mental energy that interferes with usual daily activities'. Fatigue in neurological disorders is often divided into peripheral and central fatigue.[31-33] Peripheral fatigue is used as a term for muscle fatigue due to disorders of the muscles and neuromuscular junction.[32] Central fatigue is perceived as a subjective sense of fatigue and can be present in disorders of the peripheral, autonomic and central nervous systems. It is often seen in association with lesions in pathways related to arousal and attention, the reticular and limbic systems and the basal ganglia. Furthermore, central fatigue is not only a sense of physical exhaustion, it also contains an important cognitive component.[32]

In Chapter 4, we used structural equation modeling (SEM) to investigate whether patients with MS show the same relationship between perceived fatigue and the energy cost of walking as that seen in patients with cerebral palsy or poliomyelitis.[34,35] Prompted by the absence of this relationship, we suggested that central fatigue is an important component of MS-related fatigue. The contribution of central fatigue is expected, given the nature of MS.[36] Whereas our study focused on the relationship between energy cost and fatigue, Steens et al.[37,38] approached MS-related fatigue from a physiological perspective and therefore used a physiological definition of fatigue. By this definition, fatigue is an exercise-induced reduction in force-generating capacity. A distinction is also made between peripheral and central fatigue. Their physiological definition of central fatigue is the failure of the central nervous system to adequately drive the motor neurons. In this case, central fatigue can be measured with a twitch-interpolated technique during maximal voluntary contraction (MVC).[38] Steens et al.[38] stated that central fatigue is the main cause of MS-related fatigue and they found a significant positive association between the Fatigue Severity Scale (FSS) and central fatigue. In accordance with the conclusion drawn from our model, no association was found between the FSS and peripheral fatigue. These results indicate that the physiological approach could eventually lead to an objective measurement of the perceived fatigue in patients with MS. Furthermore, Steens et al.[38] mentioned that deconditioning in extremities, related to diminished muscle usage and muscle weakness, which is in turn related to peripheral fatigue, may cause an increased perception of fatigue. This explanation clarifies the relationship found in our model between physical functioning and perceived fatigue, and the energy cost during walking. Although diverse research areas are providing greater insights into the origin of MS-related fatigue, the problem of the lack of an appropriate treatment still remains. This is not only a problem in MS, but is also problematic in other neurological diseases, such as stroke and post-poliomyelitis.[39,40] The multifactorial nature of fatigue and the diversity of central and peripheral factors are seen as the major problem in finding an optimal treatment.[36,40]

The results in Chapter 4 showed that a higher energy cost during walking (ECw) was not related to the perceived fatigue in patients with MS, but that an increase in the ECw was related to a decrease in physical functioning. Furthermore, patients with MS often have a higher ECw in comparison to healthy individuals.[41-43] Poorer physical functioning causes a decrease in physical condition, which will in turn increase energy costs. This tends to be a vicious circle and it is therefore imperative to ensure that the ECw is as low as possible. Although an increased ECw could have multiple causes, it is often attributed to an altered, less efficient movement pattern.[44] However, the effort required for balance control can be an important contributory factor in the increase of energy cost.[44-46] Differentiation between the energy cost needed to perform the walking movement and the energy cost related to balance problems is not entirely clear. Adaptations to balance perturbations are often directly related to adaptations in walking movement,[47] an example being an increase in step width. However, this will also result in a less efficient movement pattern and thus a higher energy cost. In order to reduce the Ecw, it is important to consider the causes of the increase. This cannot depend solely on the energy cost of walking test (ECWT). In addition to the ECWT, more detailed tests are required to determine the initial causes of the increased ECw and how it should be treated. For example, the posturography measurements described in Chapter 5 could be used to determine if a patient experiences balance problems, and the 2D gait analysis described in Chapter 6 can be used to establish if altered walking movements are the main problem behind the increased ECw. Ideally, the effect of the intervention should also be evaluated.

Besides reducing the Ecw, breaking the vicious circle of physical inactivity due to fatigue should involve engaging with the decrease in physical functioning.

There is strong evidence for exercise-based rehabilitation in terms of improving muscle power, exercise tolerance, and mobility-related activities.[11] It is important to realize that although reduced energy costs do not effect MS-related fatigue, it could contribute to an increase in physical functioning and to the lowering of peripheral fatigue.

The value of 2D gait analysis

In Chapter 6, we identified a core set of nine gait variables that can be used to classify patients into groups based on their walking ability. Initially, 73 variables (kinematics, EMG and GRF) were chosen, dependent on their known contribution to the specific requirements in the gait cycle and the possibility of objectifying them in a 2D clinical gait analysis.[48] Two-dimensional gait analyses are easy to execute and the necessary equipment is reasonably affordable. This, and a relatively simple analysis, makes 2D gait analysis accessible in numerous clinical settings. A 2D gait analysis provides a good general impression of the gait deviations of a patient, but is less useful when specific information on the kinematics of a single joint is required.[49] Therefore, three-dimensional gait analysis is considered to be the gold standard for assessment of gait abnormalities in patients with movement disorders, since it provides a detailed description of kinematics and kinetics during gait.[48,50,51] However, a number of extrinsic errors, such as inconsistent marker placement, variation in gait speed or data processing, or measurement equipment error, can contribute to data variation and preclude a simple conclusion on the reliability of 3D gait analysis.[52] Furthermore, although 3D gait analysis requires special equipment, is time consuming and is not available in every setting, it is a requirement for model studies of gait deviations,[53] calculations of joint powers,[54] or for measuring small differences in joint angles.[55]

The choice of 2D or 3D gait analysis should depend on the context of proposed use. A 2D gait analysis is preferred when investigating particular gait patterns, due to its wide applicability. This provides the widespread use of gait patterns, which is beneficial for both the communication between physicians and for research purposes.

The push-off was found to be one of the distinguishing variables between the three gait classes described in Chapter 6. Reduced push-off is a common problem in neurological diseases[13,56-60] and should be considered one of the critical features of human gait. However, a general guideline to quantify the push-off in observational clinical gait analysis is lacking. McGinley et al.[61,62] investigated the accuracy and reliability of the clinical judgment of push-off in observational gait analysis. They concluded that physiotherapists were able to make accurate judgments as to whether the push-off was normal or abnormal. Thus, even without clear clinical landmarks for properly assessing the push-off, an accurate and reliable decision is possible. Therefore, observational gait analysis seems to be sufficient to estimate whether the push-off is normal or abnormal. For more detailed information on the push-off, measurement of ankle power by 3D gait analysis is recommended. Changes in ankle power can be used to evaluate treatment, recovery or deterioration.[54,59] In conclusion, both 2D or 3D gait analysis are appropriate when estimating the push-off, but the clinical aim of the rehabilitation physician determines which method is most appropriate.

The safe environment of a clinical gait laboratory is often a topic of discussion.[63-65] Mulder et al.[64] state that, in rehabilitation medicine, assessment of patient skills should be more important than a detailed analysis of forces, joint angles and muscle activation. These patient skills could be the capability to perform activities in daily life, performance of activities under various environmental conditions, the ability of a patient to anticipate disturbances in the environment and/or the ability to carry out several tasks at the same time.[66] Or in other words: what is their level of community walking? From the patient's perspective an outcome parameter on the level of activity is the most relevant, but when supporting clinical decision-making, an evaluation of gait at the level of body functions and structures is important. Harlaar et al.[67] introduced the nested model, integrating the level of body functions and structures, and the activity level. Decision-making and evaluation should include both levels. A clinical gait analysis is pre-eminently suitable when identifying impairments, and gives the rehabilitation physician insight into which structures or body functions should be treated in order to improve walking ability. Measuring community walking (e.g. with gait speed measurement) should provide information on whether the impairments have consequences for activity levels.

Recommendations for future research

The studies described in this thesis generated new research questions that will provide the basis for important investigations in the future and may contribute to the improvement of rehabilitation treatment for patients with MS.-

Continue the longitudinal FuPro MS study

In Chapters 2 and 3, we used longitudinal data from the FuPro MS study. This 10-year follow-up of patients with MS from the moment of definite diagnosis is unique and provides valuable information on the changes that occur over time in these patients. This information is essential when determining appropriate rehabilitation treatments and the long-term prognosis. In future research, it will be interesting to investigate the prognostic value of physical functioning at the moment of definite diagnosis for the long-term course of daily functioning. Furthermore, follow-up measurements focusing on walking ability will provide more detailed information on the deterioration in this specific area.

The maintenance of respondents in a longitudinal study is a well-known issue.[68] Loss to follow-up will cause missing data and loss of statistical power, and selection bias or response bias cannot be excluded. To avoid the loss of power or bias, the sample size can be increased for further follow-up. There are several options available to extend the cohort: a) supplement the cohort with a group of recently diagnosed patients, b) add MS patients with a definite diagnosis dating to 1998-2000, c) add patients with a different disease duration, or d) combine the FuPro cohort with data from other (European) MS cohorts.

A disadvantage of adding newly-diagnosed patients to the cohort is that patients are currently diagnosed according to the McDonald criteria or the recently revised McDonald criteria,[69,70] while the FuPro cohort is composed of patients diagnosed with the Poser criteria.[71] The McDonald criteria allow the demonstration of disease dissemination either clinically or solely using MRI, making it possible to diagnose MS in individuals who have had a single attack.[72,73] These differing diagnosis criteria will cause the "Will Rogers phenomenon", an apparent epidemiological paradox.[74] New diagnostic tests make it possible to detect the presence of a disease at an earlier stage, with the consequence that the classification of patients differs compared to the older and less sensitive tests. With the McDonald criteria, the "Will Rogers phenomenon" is also apparent in MS. There is a possibility that earlier diagnosis of MS may change the subsequent disease prognosis in these patients, due to early treatment with disease modifying drugs. Furthermore, early diagnosis can be expected to lead to patients who are less impaired at the inception of the study than patients from the 1998-2000 cohort.

The second option is to include patients who were diagnosed in 1998-2000, according to the same diagnostic Poser criteria, and so avoid differences between patients diagnosed with the McDonald and Poser criteria. A drawback of this approach is the possible introduction of a selection bias by the inclusion of patients who have had MS for 10 years, as the more severely impaired patients may decide not to join the study, lacking the commitment of similarly impaired patients from the original cohort. This bias could be partly solved by continuing the home measurements.

Using a simulation approach, Kristman et al.[6] found that while up to 20% lost to follow-up is acceptable, a larger percentage can influence results. This means that ensuring the quality of our longitudinal study will require the inclusion of 125 patients in the next follow-up measurement. The existing cohort could nominally provide up to 134 patients, but given the experience from previous measurements this will not allow the inclusion of 125 suitable cases. Despite the above-mentioned disadvantage, we favour complementing the cohort with patients with a longer disease duration and diagnosed according to the Poser criteria. An important consideration in this choice is that our objective is to obtain information on the course in daily functioning in the second decade of MS, and supplementation with newly diagnosed patients will not serve this goal. Nevertheless, modern methods of longitudinal data analysis are sufficiently sophisticated to allow a third option, the inclusion of patients with differing disease durations.

A fourth option is to combine results with other (European) MS cohorts with broadly similar outcome measures. In such a case, ensuring comparable variables would be very important and we would prefer a cohort that included patients with a disease duration of 10 or more years.

The optimal treatment of fatigue in MS

In Chapter 4, we investigated the relationship between self-reported fatigue and energy cost during walking. We did not find a relationship between these two variables, which suggests that treatment to minimise the energy cost during walking would not be effective in reducing the experienced fatigue. The energy cost during walking is more closely related to peripheral fatigue, while our results suggest that central fatigue may be the most important component in fatigue experienced by patients with MS. Learning how to deal with fatigue using approaches such as cognitive behavioural therapy or energy conservation management may be more suitable treatments in reducing MS-related fatigue. The use of cognitive behavioural therapy and energy conservation management have shown promising results in the literature.[75-78] However, high quality randomised clinical trials focused on fatigue in MS are rare.[79,80] In September 2010, the rehabilitation research program 'Treating Fatigue in Multiple Sclerosis' (TREFAMS) was launched in several outpatient clinics in the Netherlands. The effectiveness of three different treatment options (aerobic training, energy conservation management and cognitive behavioural therapy) and the neurobiological mechanisms of MS-related fatigue will be investigated.

Energy cost of walking

It is well-known that healthy subjects chose a comfortable gait speed based on the maximise energy efficiency principle,[65,81,82] indicating that comfortable gait speed is the speed with a minimal energy cost. This principle results in an U-curve with respect to the relation between energy cost and gait speed. Studies in above-knee amputees[81] and children with Cerebral Palsy[83] show a similar U-curve. In research on the energy cost during walking in patients with MS we also assume that patients choose a gait speed according to this energy efficiency principle. Since patients with MS have varying symptoms, it is reasonable to question whether patients are always able to choose the most energetically efficient speed. Other variables, such as balance or cognitive attention, might force the patients to walk at a less energetically efficient speed. Investigating the ability of MS patients to fulfill the maximise efficiency principle would be a worthwhile research goal.

Dynamic balance during gait: a challenge to measure

In Chapter 5, our attempts to define a robust dynamic balance measure for patients with MS showed that the margin of stability may not be a valid dynamic balance variable. Balance is an important issue, both in MS and in other diseases such as stroke[13] and Parkinson[84]; a reliable dynamic balance variable is therefore much needed. There are two challenging topics for future research of dynamic balance.

A major concern is the almost complete lack of consensus in the literature regarding balance measurements. A few studies have highlighted the difficulties and contradictions of static balance measurements.[85,86] Although no reviews of dynamic balance have yet appeared, a literature search shows a wide range of non-validated measurement tools. To generate a clear picture of dynamic balance, a worthwhile starting point would be an overview of all measurements that aim to quantify dynamic balance. A thorough literature review of the reliability and validity of all dynamic balance measurements would be a very useful tool for future research in all pathologies where loss of balance is an important impairment.

Furthermore, one of the main problems in our study was the present lack of a gold standard for dynamic balance. To investigate whether the margin of stability is a valid variable for dynamic balance, we correlated the MoS with variables from the posturography measurement, step width and double support time, which are often used as dynamic balance variables in the elderly.[87,88] Posturography is, despite criticism, still seen as the gold standard for static balance.[85,86] Although it seems plausible that a decrease in static balance may be associated with dynamic balance, regarding posturography as a gold standard for dynamic balance remains questionable.

Modern research of dynamic balance is diverging in two distinct directions, the mathematical and the more clinical direction. Measures derived from the dynamic systems theory, such as Lyapunov exponents,[89] maximum floquet multipliers[90] and long range correlations[91] are examples of the more mathematical approach. The more clinical investigations of dynamic balance focus on double support time, step width, variability in spatiotemporal gait parameters and fall risk. Neither direction has yet reached a satisfying solution. Our preference, in the search for a dynamic balance variable, is for the clinical direction in order to provide measurement tools that are accessible and that support a clear understanding of dynamic balance measurements amongst clinicians. We recommend that the search for a valid assessment procedure for dynamic balance should continue. For example, a sensitivity study of the MoS to perturbations in healthy subjects should be performed in order to investigate if the MoS is affected by the loss of balance. Furthermore, a more heterogeneous patient group (both mildly and severe impaired patients) may result in a larger variability of the MoS. Both approaches could demonstrate the validity of the MoS as a measure of balance.

Gait analysis

We showed in this thesis that a core set of nine gait variables can divide patients with MS into different gait classes. Although this core set defines clinically relevant groups, this is the first time that gait classes based on kinematics and EMG have been described. Further research is necessary to investigate the external validity of our findings.

The score form used in the 2D gait analysis, composed by an expert panel and from the gait literature,[48,92] has never previously been used. Therefore, both the intra-rater and inter-rater reliability of the score form should be studied. Furthermore, the validity of the score form should be investigated, as observations of video analyses are a subjective measurement. One approach would be to compare results with the results from a 3D gait analysis. Moreover, a repeated measure of the 81 patients who performed a 2D gait analysis in this study provides insight into the changes in gait over time.

Many patients indicate that walking worsens as they tire. During our measurements, the gait analysis was performed following 2 hours of physical examination, but as it was not our intention to measure tired patients, enough rest time was allowed before commencing the gait analysis. Feys et al.[9] and Crenshaw et al.[10] have shown that performance on walking tests or gait analyses do not change during the day. However, as it is unknown if and how gait may change when patients are physically stressed just prior to analysis, investigation of the effect of physical stress in MS patients is recommended in order to establish the validity of the gait classes.

Our study population consisted of a large number of minimally impaired patients, resulting in two remaining gait classes with a rather small number of patients. To investigate if the progressive insufficiency of the push off is the main object to estimate the level of walking ability, further clinical gait analyses including greater numbers of moderate to severely impaired patients (EDSS 3.0 or higher) are required. Furthermore, we expected distinctive gait patterns based on clinical items, similar to those found in cerebral palsy and stroke.[93,94] Our results showed that the three classes are based on the degree of deterioration of nine gait variables, rather than each class being formed by 2 or 3 exclusive variables. The classes including patients with impaired walking ability were too small to allow the detection of such distinctive patterns. Larger gait analysis studies, with patients with EDSS 3.0 and higher, are necessary to determine whether such distinctive patterns can be detected.

CLINICAL IMPLICATIONS

The results of our longitudinal study demonstrate that the various domains of daily functioning show a specific time course. In clinical practice this means that the rehabilitation physician should perform regular assessments and monitoring, with the aim of identifying the changes in the various domains.

This would facilitate an early and appropriate rehabilitation treatment in the required domain(s), thus contributing to maintaining the desired level of participation.

The measurement of gait speed provides considerable diagnostic and prognostic information. In order to facilitate a proper understanding of patient functioning we therefore recommend that fast gait speed be measured during periodic patient visits. Fast gait speed (with a walking aid when necessary) is a good indicator of the level of daily functioning and community walking. Although gait speed provides a good first impression, further clinical assessment of the patient is necessary to establish the underlying cause of reduced gait speed. Clearly, a patient's perspective on treatment goals should still be leading the rehabilitation treatment.

This thesis also showed that perceived patient fatigue is not related to the energy cost of walking. However, as physical functioning was worse in patients with a higher level of experienced fatigue, fatigue in patients with MS should be treated on different levels. Energy management and cognitive behavioural therapy appear to be promising treatments for MS-related fatigue, and as fatigue is associated with a decrease in physical functioning, physical training should also be considered.

We concluded from the gait analysis study that a relatively easy observation of nine gait variables allows patients to be divided into three distinct gait classes. In general, reduced push-off seems to be the main problem in MS patients with a relatively mild decrease in walking ability. A 2D video analysis is sufficient to establish whether a patient shows push-off problems.

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