Outcome Measurement and Functional Prognosis in early Multiple Sclerosis

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Summary

This thesis describes the results of the FuPro MS study (Functional Prognosis in Multiple Sclerosis) that was financially supported by the Netherlands Organization for Scientific Research (NWO 940-33-009), and that was carried out in close cooperation with the Functional Prognostication and disability (FuPro) study group. In the period 1998-2000 all consecutive potentially eligible patients visiting the outpatient clinics of neurology departments of the VU University Medical Center, the Academic Medical Center Amsterdam, the Sint Lucas Andreas Hospital Amsterdam, the OLVG Hospital Amsterdam, and the Erasmus Medical Center Rotterdam were invited to participate. We recruited a cohort of 156 recently (less than six months previously) diagnosed patients, aged 16 to 55 years. The cohort was prospectively monitored for five measurements in three years. Diagnosis was determined according to the Poser-criteria for definite Multiple Sclerosis (MS). Patients with other neurological disorders, systemic diseased or malignant neoplastic diseases were excluded. The patients were visited at home in order to minimise drop-out, and four well-trained raters were responsible for the scoring. The aims of this thesis were to study the disease course of MS and its determinants, and the clinimetric properties of the outcome measures that can be used to study this disease course.

CHAPTER 2 describes a systematic review of available methods to measure comorbidity and to assess their validity and reliability. We searched Medline and Embase, with the keywords comorbidity and multi-morbidity, to identify articles in which a method to

measure comorbidity was described. We also checked the references of these articles for other relevant articles. With a standardized checklist we extracted the relevant data from these articles. Subsequently, we assessed the content, concurrent, predictive and construct validity, and the reliability of the methods to measure comorbidity.

We identified thirteen different methods to measure comorbidity: one disease-count and 12 indexes. Data on content and predictive validity were available for all measures, while data on construct validity were available for nine methods, data on concurrent validity and inter-rater reliability for eight methods, and data on intra-rater reliability for three methods.

It was concluded that the Charlson Index, the Cumulative Ilness Rating Scale (CIRS), the Index of Coexisting Disease (ICED) and the Kaplan Index were valid and reliable methods to measure comorbidity that can be used in clinical research. The Charlson Index is the most extensively studied comorbidity index for predicting mortality. The CIRS addresses all relevant body systems without using specific diagnoses. The ICED has a two-dimensional structure, measuring disease severity and disability, which can be useful when mortality and disability are the outcomes of interest. The Kaplan Index was specifically developed for use in diabetes research. For the other indexes, insufficient data on the clinimetric properties were available.

In CHAPTER 3 we aimed to select the most useful evaluative outcome measures for early multiple sclerosis (MS). All 156 recently diagnosed MS patients were included in a three-year follow-up study, and assessed on 23 outcome measures in the domains of disease-specific outcomes, physical functioning, mental health, social functioning, and general health. A Global Rating Scale (GRS) and the Expanded Disability Status Scale (EDSS) were used as external criteria to determine the Minimally Important Change (MIC) for each outcome measure. Subsequently, we determined whether the outcome measures could detect their MIC reliably.

From these, per domain the outcome measure that was found to be most sensitive to changes (responsive) was identified.

We found that at group level, eleven outcomes of the domains of physical functioning, mental health, social functioning and general health could reliably detect the MIC. Of these eleven, the most responsive measures per domain were the Medical Outcome Study 36 Short Form sub-scale physical functioning (SF36pf), the Disability and Impact Profile (DIP) sub-scale psychological, the Rehabilitation Activities Profile sub-scale occupation (RAPocc), and the DIP sub-scale mental health, respectively. Overall, the most responsive measures were the SF36pf and the RAPocc. However, in individual patients, none of the measures could reliably detect the MIC.

We concluded that in the early stages of MS the most useful evaluative outcome measures for research are the SF36pf (physical functioning) and the RAPocc (social functioning).

In CHAPTER 4 we studied the initial course of daily functioning in multiple sclerosis. All longitudinally gathered data of the whole cohort of 156 recently diagnosed patients in the domains neurological deficits, physical functioning, mental health, social functioning and general health were used in the analysis. We made an a priori distinction between a relapse onset group (n=128) and a non-relapse onset group (n=28).

We showed that at baseline, neurological deficits are relatively minor for most patients, 26.3% have aberrant physical functioning scores, 38.5% have aberrant social functioning scores, 9.0% have aberrant mental health scores and 25.0% have aberrant general health scores. In the subsequent three years the neurological deficits and physical functioning deteriorated significantly. This deterioration was more pronounced and clinically relevant in the non-relapse onset group. Mental health showed a significant, but not clinically relevant deterioration in this period. Social functioning and general health showed non-significant changes in this period of three years.

We concluded that in the initial stage of multiple sclerosis, when neurological deficits are relatively minor and mental health is relatively unaffected, patients in both groups experience limitations in daily functioning. Patients in the non-relapse onset group have progressive neurological symptoms that are accompanied by progressive limitations in physical functioning, but not by progressive limitations in the other domains.

CHAPTER 5 shows the results of a detailed analysis of the determinants of social functioning. The aim was to identify the strongest determinants of social functioning in the first three years after the diagnosis multiple sclerosis (MS) has been made. We used all longitudinally collected data in the cohort of 156 recently diagnosed MS patients. Social functioning was measured using the three social subscales of the Medical Outcome Study Short Form 36 (SF36) and a composite outcome based on these subscales. Forty-three, longitudinally collected, determinants were divided into the following clusters: 12 patient and disease characteristics, ten psychosocial characteristics, 18 basic functions, and three basic activities. The results were analyzed with generalized estimating equations (GEE), using the following steps: 1) a stepwise backwards selection procedure for all clusters per outcome, 2) an overall stepwise backwards selection procedure for each outcome using the significant variables identified in step one, 3) examine whether the associations are based on within subject changes, *i.e.* is a change in the determinant for a patient associated with a change in the outcome for that same patient, and 4) a sensitivity analysis.

In the first step of the analysis 17 determinants were selected in any of the four models. In step 2 we showed that vitality, the number of self-reported exacerbations and the perceived amount of social support were associated with social functioning in three or four of the models. In the next step we showed that almost all associations are based on within subject changes. In the final step the T2-weighted supratentorial lesion load was additionally selected.

Summarizing, vitality, the perceived amount of social support, and disease activity, *i.e.* the number of self-reported exacerbations and the T2-weighted supratentorial lesion load, are determinants of social functioning. These results suggest that, in the early stages of MS, it might be beneficial to improve vitality, *e.g.* by promoting an active life-style, to optimize the perceived amount of social support, *e.g.* by counselling, and to suppress disease activity, *e.g.* by prescribing interferon.

CHAPTER 6 investigated whether it is possible to accurately predict functioning after three years in patients with recently diagnosed MS. For this study we used the data of 146 recently diagnosed MS patients. For the other ten patients data of the outcome measurement at three years were missing. At baseline, predictors were obtained from history-taking, neurological examination and Magnetic Resonance Imaging. The outcomes of interest after three years were: inability to walk at least 500 metres, impaired dexterity, cognitive impairments, incontinence, inability to drive a car or use public transportation, social dysfunction, and reliance on a disability pension. We constructed clinical prediction rules for the models that were well calibrated, *i.e.* that showed sufficient agreement between predicted and observed outcomes, based on visual inspection of calibration curves, and that showed sufficient discrimination, *i.e.* the Area Under the receiver operation characteristic Curve (AUC) > 0.70, after internal bootstrap validation.

The results indicated that the models for inability to walk at least 500 metres, impaired dexterity and cognitive impairments were well calibrated. Discrimination was sufficient for all seven models, except for the one predicting social dysfunction (AUC = 0.67).

So we have shown that inability to walk at least 500 metres, impaired dexterity and cognitive impairments can be predicted with predictors that are obtained shortly after the definite diagnosis has been made. The ability to predict physical and cognitive functioning might facilitate the counselling of patients with MS and the planning of their (rehabilitation) treatment.