Clinimetrics, clinical profile and prognosis in early Parkinson’s disease
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Chapter 1

Part 2

Aims and outline of this thesis
In this thesis the results of a prospective three year follow-up cohort study of patients with Parkinson Disease (PD) are described. Our cohort study is part of the CARPA (Comorbidity and Aging in Rehabilitation patients; the influence on Activities) research program, which investigates the functional course, determinants and prognosis of three different chronic disorders; postpoliomyelitis syndrome, osteoarthritis and PD. Ultimately the results of CARPA must lead to an improvement of care for these patients.

The main focus of the studies is to investigate the clinical profile, progression and prognostic factors of (early) PD. As a sound assessment of patient’s neurological impairment and physical disability forms an essential part of the studies presented, the first two chapters of the thesis specifically concentrates around some clinimetric issues.

The Unified Parkinson’s Disease Rating (UPDRS) scale is a widely used instrument for the clinical evaluation of PD. This scale is subdivided in four separate parts (mentation, activities of daily living, motor examination and complications of therapy). The motor examination (UPDRS-ME) part quantifies type, number, and severity of extra-pyramidal signs. The UPDRS-ME scores facial expression, speech, tremor (at rest and in action), rigidity, bradykinesia (arms, legs and whole body), arising from a chair, posture, gait, and postural stability. In general, the scale scores are assigned by experienced neurologists.

In search of the most effective and efficient combination of health care professionals to deliver care for chronic patients, nowadays nurse practitioners perform tasks that traditionally belonged to the domain of the physician. Regarding care of PD patients, this trend is reflected by the fact that the administration of the UPDRS is performed more and more by nurses. In chapter 2 we assessed whether nurse practitioners, residents in neurology and movement disorders specialists can score PD-patients on the UPDRS-ME with comparable reliability. Next to assessing motor impairment disability is another important and patient-relevant health domain. Assessment of early signs of disability becomes increasingly important in the context of current research on neuroprotection and symptomatic treatment in PD. Neuroprotection in the context of PD refers to slowing the degeneration of neurons relative to the rate of degeneration in the absence of the intervention early in the disease course. If effective this would translate into slowing the progression of physical disability. In symptomatic treatment early in the disease the ADL part of the UPDRS is most often used, but this part of UPDRS is confounded by items that examine patients perceptions of primary disease manifestations (e.g. tremor and salivation). Therefore, in chapter 3, we present a new generic instrument to measure level of activities of daily living (ADL) in PD patients: the AMC linear Disability Score (ALDS). The ALDS is validated as being one of the first disability measures for the PD population developed within the flexible framework offered by item response theory (IRT). Using IRT based outcome measures will lead to a more accurate and sensitive way in measuring functional outcome. This is especially important in early
PD, because the current outcome measures have considerably floor effects which make neuroprotective trials prone to type II error.

The clinical profile, progression and prognostic factors of (early) PD form the main components of the further chapters of this thesis. Although the clinical signs of PD have been described extensively, there is still debate about the way the disease progresses and how to use this type of clinical information in daily patient care. In *chapter 4* a systematic review is presented summarizing and analyzing almost forty years of literature on prognostic factors for the progression of PD. One of the conclusions of this study and also of two other reviews on this subject is that cognitive impairment plays an important prognostic role in future motor impairment.(6,7) To investigate the importance of cognitive impairment in (early) PD, all newly diagnosed PD patients included in the CARPA research program underwent an extensive neuropsychological assessment. The results of these neuropsychological tests are reported in *chapter 5*. Despite the identification of several prognostic factors for the progression of PD it is still difficult to predict the mid- and longterm outcome for the individual patients. One of the possible reasons for this is the marked clinical heterogeneity in the PD population, suggesting the existence of subgroups of patients with different clinical phenotypes in terms of motor impairments, disabilities, and progression of the disease.(8) Identification of these subgroups is important because these different subgroups are most likely to arise from different combinations of genetics and (environmental) modifiers and so gives new insights for studying the neuropathological background, etiology, (neuroprotective) therapies and prognosis of PD. For this reason the heterogeneity of newly diagnosed PD is analyzed using the statistical technique of cluster analysis. The results of this study are presented in *chapter 6*. Another way to analyze this heterogeneity is to describe prognostic factors and the course of the disease and use this information to try to identify subgroups with a similar course of the disease. Insight in this variability can help us guide clinical decision making, improve understanding of the disease process, improve the design and analysis of clinical trials, and to define risk groups with more rapid progression.(9) *Chapter 7* identifies the determinants of patient’s level of disability and quality of life in mild to moderate PD. The knowledge of the preceding chapters is then used to describe, in *chapter 8*, the magnitude of progression of impairments and functional health and their predictors using the longitudinal data of the three year follow-up in our PD cohort. *Chapter 9* presents a general discussion in which we first elaborate on what is known about prognostic variables in PD. Then we describe the progression in early PD in the context of three different stages in clinical PD. Next we comment on the use of non-neurologist for assessing and scoring patients and new IRT-based techniques for rating scales. Finally, we describe our future research project in which we will further explore the motor and disability progression of PD, the progression of cognitive functioning, the
problem of orthostatic hypotension, and the influence of genetic variability on the clinical features of PD. A Summary in English and Dutch concludes the thesis.
Reference List


