Clinimetrics, clinical profile and prognosis in early Parkinson’s disease
Post, B.

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Chapter 9

General discussion
The main objective of this thesis was to study the clinical profile, progression and prognostic factors of (early) Parkinson's disease (PD). Because the assessment of patient's neurological impairment and physical disability is an essential part of the studies presented, two chapters specifically focus on clinimetric issues. In the current chapter the main findings of this thesis are summarized and discussed with reference to recent scientific insights in PD. Finally, future research will be discussed.

Clinical profile and prognosis

Nowadays PD is described as a heterogeneous disease with various etiologies and with a mixture of motor and non-motor features. Because of the etiological heterogeneity opinion leaders favour the term Parkinson's Diseases.(1,2) This should remind physicians that multiple etiologies are possible to explain patients' symptom patterns and the prognostic heterogeneity. This term 'diseases' is also useful in daily care to help patients understand that they are confronting a syndrome and not a single disease. So it is advisable to distinguish the various Parkinsonian syndromes by their pathological and genetic characteristics. This is what is now called the 'splitter approach' leaving the term idiopathic PD to cases with clinical parkinsonism associated with Lewy body pathology for which we are not sure of the genetic etiology.(2)

The concept of the clinical features of PD is broadening in parallel with the pathological and etiological understanding of the disease. Olfactory, gastrointestinal, sleep, sensory, autonomic, cognitive dysfunction and psychiatric manifestations are thought to be an important part of the disease and many of these may even predate the onset of the classical motor disorder.(3-5) The non-motor symptoms cognitive dysfunction and psychiatric manifestations together with the non-dopaminergic reactive motor symptoms (mainly postural instability and gait difficulty (PIGD)), are the main prognostic factors for future disability, nursing home placement and mortality(Table 1).(6-8)

To describe the clinical profile of this heterogeneous disease we postulate that the course of PD can be divided into three phases (Figure 1). The first phase describes the first five years of the disease in which there is gradual progression of all motor and non-motor symptoms with relatively mild disability. In this phase treatment of PD is relatively easy and the mainstay is symptom reduction using levodopa (chapter 8). Thereafter comes the phase of motor-complications, due to the treatment of disease, and further progression of the motor (especially non-dopaminergic reactive) and non-motor symptoms lasting for about another five years.(9,10) In this period treatment becomes more complex, but there are still a range of opportunities for interventions, such as Catechol-O-methyl-transferrase (COMT) inhibition, mono-amine-oxidase–B inhibition, dopamine agonists, and surgery.
The last phase is defined by the ongoing progression of non-dopaminergic motor symptoms (especially PIGD) and non-motor symptoms leading to severe disability (Table 2). The stage is characterized by difficulties in treating these patients by other means then supportive care, although new treatments are underway.

Cluster analysis

Classification of this heterogeneous disease is an attempt to explore the underlying etiology and may help to predict treatment response and prognosis. Using a statistical approach of cluster analysis we identified three subgroups in patients with newly diagnosed PD. (chapter 6) There was a younger onset group (mean age at onset 57), an intermediate older onset group (mean age at onset 64) with more anxiety and depressive symptoms and an oldest onset group (mean age at onset 73). The older onset-groups had higher rates of disease progression and motor impairment both responsive and non-responsive.
to dopaminergic treatment. These findings are in line with three recent systematic reviews showing higher age at onset as the most important factor for predicting increased motor impairment and rapid accumulation of disability.(6-8)

To date four studies, including ours (chapter 6), have been published using cluster analysis to describe subgroups in PD.(15-18) In the most recent study Schrag described three homogeneous groups (young onset, older onset and older onset group with cognitive impairment and rapid disease progression), which were mainly based on age and age at onset.(16) The research group of Graham also identified three subtypes: patients who were motor impaired only, patients with motor and cognitive impairment, and patients with an older age at disease onset who rapidly progressed.(15) Lewis described four groups; a young age at onset group, a tremor dominant group, a non-tremor dominant group with cognitive and mood disturbances, and a group with rapid disease progression and no cognitive impairment.(17) To summarize age at disease onset, cognitive impairment and motor subtype seem to be important determinants for classification of subgroups in PD.
Figure 1. The progression of Parkinson’s disease I = progression of motor function; showing slowly decreasing motor function during the course of the disease, II = development of disability; showing relatively mild disability in the first years of the disease, and increasing disability when dopamine system complications and non-motor features are more frequent. III = development of non-motor symptoms; showing non-motor features throughout the course of the disease, becoming more important in the later stages of the disease.

Table 2. Predominant problems in Parkinson’s disease among survivors at 15 years and 20 years follow-up in the Sydney multi centre study.

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>15 years of follow-up (n=52)</th>
<th>20 years of follow-up (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuropsychiatric</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognitive decline</td>
<td>84</td>
<td>…</td>
</tr>
<tr>
<td>Dementia</td>
<td>48</td>
<td>83</td>
</tr>
<tr>
<td>Daytime sleepiness</td>
<td>79</td>
<td>…</td>
</tr>
<tr>
<td>Depression</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>21</td>
<td>74</td>
</tr>
<tr>
<td>Axial motor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Falls</td>
<td>81</td>
<td>87</td>
</tr>
<tr>
<td>Fractures</td>
<td>23</td>
<td>35</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>50</td>
<td>48</td>
</tr>
<tr>
<td>Severe dysarthria</td>
<td>27</td>
<td>81</td>
</tr>
<tr>
<td>Autonomic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>41</td>
<td>71</td>
</tr>
<tr>
<td>Symptomatic postural hypotension</td>
<td>35</td>
<td>48</td>
</tr>
</tbody>
</table>

Inception cohort of the Sydney multicentre study included 136 patients. All numbers are % of the group alive patients; ellipses = not reported.(12,13)
The technique of cluster analysis (19) has the advantage that one does not have to make any assumption about the classification in advance. However, it should be stressed that the choice of number and types of variables has an impact on the results and so different results can be obtained using different clinical variables measured with different instruments. In the future, this problem can partly be resolved by using a minimal clinical data set of predefined variables and measures when clinically assessing patients. Such a systematic approach has already been implemented in the evaluation of stereotactic surgery for PD.(20) A first attempt for a minimal dataset is also made in an appendix to the revised version of the UPDRS which provides recommendations about the preferred measures to evaluate the different and broad range of symptoms in PD.(21,22)

**Cognitive disturbances**

The reviews written about prognostic factors in PD suggest that cognitive impairment plays a significant role in predicting future functioning, especially later in the disease. Furthermore it is one of the most important non-motor symptoms in PD(Table 1). To investigate the importance of cognitive impairment in (early) PD, all newly diagnosed patients underwent an extensive neuropsychological assessment at baseline (chapter 5). The results indicate that 24% of the patients in our PD sample showed cognitive dysfunction, compared to 4% of the age-matched and sex-matched subjects in the control group. Additional analysis of individual test performances revealed that deficits in the domains of memory, attention and executive function are the core impairment. The cognitively impaired PD group was older, included more males, had a later onset of disease, greater overall severity of disease, higher depression score, and more severe axial symptoms and speech impediments than the cognitively intact PD group. Multivariable analysis showed that only age at disease onset was an independent predictor of cognitive dysfunction in PD.(23)

When examining our PD sample three years later, we observed a significant decrease in performance on most cognitive measures with an incidence of dementia of 8.5% during follow-up. The most severe decline occurred on measures of psychomotor speed and attention. In the domains of memory, visuospatial skills, and executive function deterioration was smaller in magnitude, but still significantly greater than in controls. Analysis of cognitive change at an individual level revealed that 48% of the patients exhibited cognitive decline not seen in the control group. Cognitive decline appeared to occur in a diffuse rather than a specific manner, but deterioration in psychomotor speed and attention seemed to be more prominent than in other cognitive areas. None of
the baseline demographic and clinical features appeared to be associated with cognitive change in the first few years following the PD diagnosis.

In a population-based cohort of patients with newly diagnosed PD patients, 36% performed poorly on at least one of three cognitive tasks (global cognitive function, predominant frontostriatal cognitive dysfunction, and predominant temporalstriatal cognitive dysfunction).(24) Cognitively intact subjects were younger at diagnosis and had significantly higher premorbid IQ scores compared to patients who were cognitive impaired. Follow-up of this cohort, 3.5 years later, showed dementia in 10% of subjects and a similar overall proportion of patients with cognitive dysfunction. Patients without tremor on baseline and patients performing poorly on the cognitive tasks semantic fluency and pentagon copying had faster progression of cognitive dysfunction.(25) Recently another population-based incidence cohort confirmed cognitive impairment in early PD, with 19% performing poorly on one of the three cognitive domains measured.(26)

To conclude there is evidence of cognitive impairment early in PD, mainly in the domains of memory and executive functioning. Furthermore progression of this cognitive dysfunction is reported, with non-tremor symptoms being the most important clinical predictor of this decline. None of the above studies mentioned the impact of cognitive dysfunction on activities of daily living (ADL), although the reported incidence of dementia (8 and 10%) is consistent with problems in ADL functioning in this particular subgroup.

Progression and prognostic factors

In our review (chapter 4) we conclude that cognitive disturbance is an important factor for predicting future disability later on in PD. However, when analysing the relation between cognitive disturbances and functional outcome using a multivariate model no significant association could be demonstrated (chapter 7 and 8). This finding is in contrast with earlier systematic reviews in which the prognostic meaning of cognitive function on functional outcome has been suggested. A possible explanation of this inconsistency is that the studies reported in these reviews had enrolled patients in a later phase of the disease, and also had included more demented PD patients.

Both the review (chapter 4) and the cohort study (chapter 7 and 8) showed that axial impairment and age at onset were the main prognostic factors for the progression of PD in several domains. In the cross-sectional baseline study (chapter 7) axial impairment (PIGD) was strongly associated with disability in mild to moderate PD, whereas self-reported mood symptoms and axial impairment were the main factors explaining impaired quality of life (QoL). The level of comorbidity had an independent impact on disability and QoL beyond the contribution of demographic and clinical features of PD. In the follow-up
study (chapter 8) the results of the baseline analysis were used to describe the decline and the prognostic factors of motor impairment, disability and QoL over a three year period. Motor impairment progressed with three UPDRS-ME points per year. Disability also showed a small, albeit significant decline during follow-up, whereas the level of QoL slightly deteriorated in the domains Parkinson symptoms and emotional functioning. Older age at onset predicted worse motor impairment, more disability and poorer QoL. Non-dopaminergic reactive symptoms (axial impairment) and comorbidity contributed to more disability and poorer QoL. Affective symptoms were associated with poorer QoL. Female sex was associated with a slower progression of motor impairment and less decline of QoL.

The results of the follow-up study are largely consistent with the three reviews published about the prognosis of PD (Table 1). Sex was described in two of the reviews as a prognostic factor with conflicting evidence. Our results in chapter 8 showed that females progress slower in time as was stated by Suchowersky. Furthermore we identified comorbidity as a new prognostic factor for disability and poorer QoL. Suchowersky already suggested that comorbidity may indeed be a possible factor of clinical importance. The other two reviews, however, found no evidence. (6,7)

There is an increasing number of longitudinal studies focusing on QoL as outcome parameter in PD (27-29), but only one research group described the progression and prognostic factors of QoL in early PD. Marras describes a slight decline in physical and mental component score of the SF-36 over 1.5-2 years time, although she questions the clinical relevance of her findings. In this study baseline depression and self rated cognitive function turned out to be associated with the physical component score, whereas older age and worse ADL at baseline were associated with the mental component score. PIGD was the only features that deteriorated concurrently with QoL. In the only population-based prospective study with prevalent PD there was a significant decline in QoL during eight years of follow-up as measured with the Nothingham Health Profile. Follow-up time, higher HY staging (reflecting PIGD), severity of depressive symptoms, and presence of insomnia were related to overall change in QoL. Both studies are difficult to compare with the results of our follow-up study because of the use of different outcome instruments. Nevertheless, all studies, including ours, identified non-dopaminergic reactive symptoms and mood disturbances as important prognostic factors for decline in QoL.
Clinimetrics

The Unified Parkinson’s Disease Rating (UPDRS) scale is a widely used instrument for the clinical evaluation of PD. The scale is subdivided in four sections (complications of therapy, mentation, activities of daily living, and motor examination). The motor examination (UPDRS-ME) part quantifies type, number, and severity of extra-pyramidal signs in terms of 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. Traditional the UPDRS is scored by experienced neurologists. In search for the most efficient combination of health care professionals to deliver care, nowadays nurses perform tasks that traditionally belonged to the domain of the physician. Regarding the care of PD patients, this trend is reflected by the fact that the administration of the UPDRS is performed increasingly more by nurse practitioners. In chapter 2, we studied whether nurse practitioners, residents in neurology and movement disorders specialists (MDS) are able to score PD-patients on the UPDRS-ME with comparable reliability. We observed systematic differences in UPDRS-ME scores between nurses and residents on the one hand and the MDS on the other. This result stresses the importance of quantifying the agreement of clinical assessors before the start of a longitudinal study or clinical trial. Ideally (but for practical reasons mostly not possible), the same observer should be responsible for the assessment of each patient, since intra-rater agreement is in general better than inter-rater agreement. This applies even more for individual patient management, since the reliability of an instrument for individual patient management should be higher than for use in group comparisons in clinical research. Finally, the evaluation of rater agreement should not be limited to the calculation of kappa and ICC statistics, but should also include the assessment of the extent of inter-rater bias using a Bland-Altman plot.

During our study an important initiative was taken to revise the present UPDRS. The main reasons for this revision were ambiguities in the written text, inadequate instruction for the assessors, some metric flaws and the absence of screening questions on several important non-motor aspects of PD. The concept of this new scale (the MDS-UPDRS) has already been published, showing promising metric qualities. However, more clinimetric research is needed (especially with regard to translations in other than English language and responsiveness to health change over time) before the MDS-UPDRS can be broadly implemented into patient care and clinical research.

Next to motor impairment, disability in activities of daily life (ADL) is another patient-relevant health indicator. Assessment of early signs of disability becomes increasingly important in the context of current research on neuroprotection and symptomatic treatment in PD. Neuroprotection 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 section of the UPDRS is most often used. In chapter 3, we presented a new generic instrument to measure patient’s level of ADL: the AMC linear Disability Score (ALDS). The ALDS has been developed within the flexible framework of 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 a type II error. In our PD cohort the ALDS showed convincing clinimetric properties in terms of internal consistency reliability, construct and clinical validity, and absence of ceiling effects. At that time of the study no data was available to compare the ALDS with the ‘gold standard’ UPDRS-ADL. Recently, we have finished a small sub-study comparing both scales at the three years follow-up of 70 newly diagnosed PD patients. As the two scales intend to measure the same disability concept the correlation between both scales was relatively lower ($r = 0.62$) than one might expect. The moderate correlation can be explained by the item content of the UPDRS-ADL, which is a confusing mix of items reflecting both ALD disability and neurological impairments in terms of tremor and salivation. The ALDS and the UPDRS-ADL were able to detect differences in disease severities. Probably due to the sample size both scales had insufficiently statistical power to discriminate between H&Y grading 1 and 2. In contrast to the UPDRS-ADL, the ALDS turned out to be sufficiently sensitive to discriminate between HY stages 2 and 3.

Nowadays, IRT health measurements are becoming increasingly important in diverse areas of medicine, including neurology, internal medicine, surgery and rehabilitation. A large incentive for the construction of IRT based items banks is the possibility of computer adaptive testing (CAT). With CAT, items are selected from an item bank on the basis of individual patient’s responses to previously administered items. With this approach patients need only a very limited number of items to obtain a measure that accurately estimates, which would have been obtained had the entire set of items been administered. At present we are developing a CAT version of the ALDS.

**Future research**

For the near future our research group has defined the following scope of research: (1) further insight in the long-term course of motor impairment, disability and QoL, including the building of prognostic models to use in individual patient care; (2) the development of non-motor signs and symptoms especially with regard to orthostatic hypotension;
(3) the interplay between genetics and cognitive profiles; and (4) the development of balance and gait disorders.

About half of the patients with PD suffer from orthostatic intolerance, which has a major impact on daily life functioning. Although some underlying mechanisms for orthostatic hypotension (OH) are known, essential insights for the diagnosis and treatment are lacking. Recently, the concept of delayed OH was described. As PD is associated with generalized sympathetic denervation (the system thought to be affected in delayed OH), it is likely that OH in PD is often of this delayed type. The objective of our recently started study is to assess the frequency of early and delayed OH. Additionally, the association between the various characteristics of OH and other symptoms of autonomic nervous system dysfunction, motor symptoms, cognitive profile, sleep disturbances, and medication use will be investigated.

Another important part of the non-motor symptom complex in PD is cognitive dysfunction. Neurochemical changes in PD patients are linked to specific cognitive deficits; for example dopaminergic deficits to the dysexecutive syndrome; cholinergic deficits to memory loss; and noradrenergic deficits to attentional dysfunction. The influence of the dopaminergic system on executive functioning is complex. It is postulated that there maybe an optimal relative level of dopaminergic activity in the prefrontal cortex compared with the striatum that is required for normal cognitive function, with both low and very high levels of prefrontal synaptic dopamine causing impaired cognitive performance. The dopaminergic homeostasis is regulated by several enzymes one of which is COMT. The enzyme activity is influenced by a single nucleotide polymorphism of the human COMT gene named COMT val158met. It is speculated that knowing the genotype of the COMT-val158met polymorphism might influence executive function by regulating dopamine levels in the prefrontal cortex. When this is true the COMT-val158met polymorphism might influence the management of levodopa in clinical practice.

As PD progresses non-motor symptoms and motor symptoms not reactive to dopaminergic therapy become more prominent and contribute substantially to the disablement process. One of the key features of motor symptoms not reactive to dopaminergic therapy is postural instability. The ability to maintain balance deteriorates and patients are predisposed to falls, which lead to more morbidity. There is growing evidence that cognition is related to gait and postural stability. In our cohort study we assess postural stability at the five year follow-up using several standardised tests and we have register the incidence of falls during the last year before the five year follow-up. Furthermore the neuropsychological examination is repeated at five year follow-up. This data gives us the opportunity to identify patients at risk of falling and to study the role of cognitive functioning in relation to postural stability and gait.
The clinical different phenotypes described in literature and this thesis most likely arise from complex combinations of genetics and environmental modifiers. To investigate these complex interactions research in large patient groups is needed. It is time for a large nationwide population-based study on PD to make further progress in understanding the etiology, pathophysiology, pathology and heterogeneity in clinical profiles. Hopefully, this will give rise to new therapies for this disease. (48)
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