PARKINSON'S DISEASE: COGNITION, PULMONARY FUNCTION AND MUSCLE STRENGTH

PARKINSON'S DISEASE: COGNITION, PULMONARY FUNCTION AND MUSCLE STRENGTH

(De ziekte van Parkinson: cognitie, longfunctie en spierkracht)

Proefschrift ter verkrijging van de graad van doctor
aan de ERASMUS UNIVERSITEIT ROTTERDAM
op gezag van de rector magnificus
Prof.Dr. C.J. Rijnvos
en volgens besluit van het college van dekanen.
De openbare verdediging zal plaatsvinden op
woensdag 19 december 1990 om 15.45 uur

door

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geboren te Hooge en Lage Zwaluwe

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Homines enim sumus et occupati officiis, subsicivisque temporibus ista curamus, id est nocturnis, ne quis vestrum putet his cessatum horis.

Plinius, Naturalis Historia, Prefatio

Voor Anneke en mijn vader,

ter nagedachtenis aan mijn moeder

PREFACE

This thesis is the result of studies done at the department of neurology of the Dijkzigt Hospital, Rotterdam, between 1986 and 1990. Some studies have already been published, albeit in a somewhat different form, in several journals of neurology.

Two studies have been made possible by a special grant from the Dutch Parkinson Patiënten Vereniging. I am very grateful for their support. Hoffmann-La Roche Nederland B.V., among others, offered financially support for the printing of this thesis. Several people have helped me in a substantial way. Their names are listed in the acknowledgements.

Rotterdam, september 1990

CONTENTS

ABBREVIATIONS

BDI	Beck's Depression Inventory
BHS	Beck's Hopelessness Scale
DSM	Diagnostic and Statistic Manual
FEV1	Forced Expiratory Volume in 1 second
FIV1	Forced Inspiratory Volume in 1 second
FVC	Forced Vital Capacity
GIT	Groninger Intelligentie Test
HRS	Hamilton Ratings Scale
HY	Hoehn & Yahr scale
LOT	Line Orientation Test
LST	Levodopa Substitution Therapy
MÅ	Montgomery-Åsberg Depression Scale
MEF50, MEF25	Maximal Expiratory Flow after expiration of 50 and 75% of FVC
MEFV	Maximal Expiratory Flow Volume
MIF50	Maximal Inspiratory Flow after expiration of 50% of FVC
MIFV	Maximal Inspiratory Flow Volume
NUDS	Northwestern University Disability Scale
PD	Parkinson's disease
PEF	Peak Expiratory Flow
PIF	Peak Inspiratory Flow
PMRV	Maximal static mouth pressure at residual volume
PMTLC	Maximal static mouth pressure at total lung capacity
ROT	Rod Orientation Test
SD	Standard Deviation
SPMSQ	Short Portable Mental Status Questionnaire
UAO	Upper Airway Obstruction
VC	Vital Capacity
WAIS	Wechsler Adult Intelligence Scale
WCST	Wisconsin Card Sorting Test

INTRODUCTION

James Parkinson defined the "Shaking palsy" by involuntary tremulous motion, lessened muscular power and disturbance of gait. He added: the senses and intellects being uninjured. Six cases were described in detail but no references what so ever were made to cognitive and emotional disturbances. He does refer to a patient described by Maty (page 38) who developed what now may be called posttraumatic parkinsonism. This patient used to be of a cheerful disposition, but appeared now dejected.

At the end of the 19th century reports were published in which "insanity" in connection with Parkinson's disease was discussed [4, 5]. Since then an exponentially growing number of studies have appeared, concluding that the senses and intellects do appear to be "injured". Aside from the more or less primordial symptoms like tremor, weakness, gait disorder and rigidity, other motor phenomena have also been studied, usually involving aspects of motor co-ordination and initiation. In addition many non-motor functions have been investigated. The following list - surely not complete - demonstrates the spectrum of Parkinson's disease (PD):

Related to motor function, co-ordination etc.:

Respiratory dysfunction [117, 119, 163, 165], sensorimotor function [148], swallowing and speech production [26, 33, 141], stridor [137], movement preparation [61, 72, 133, 153], akathisia [86], facial expression [81], reaction time [13, 52].

Global and isolated cognitive deficits:

Dementia, visuospatial impairment, memory [19, 56, 67, 79, 138, 144, 145, 167, 172], learning [28, 49, 57], frontal lobe dysfunction [159], bradyphrenia [103], shifting aptitude [32], concept formation [18, 27], attention [24], language [7].

Mood disturbances:

Depression

Premorbid personality [162].

Autonomic dysfunction [60]

Other:

Sleep disturbances [2, 3, 48, 58, 66, 171], olfactory disturbances [44, 84], contrast sensitivity [25].

The general opinion at present is that cognitive disturbances are an inherent part of PD [23, 99]. Studying patients with PD, and especially the examination of cognitive function is not without its problems. These problems can be summed up as follows:

1. Parkinson's disease is a progressive disease. The rate of progression varies. The duration of the disease and the severity at the time of examination have to be taken into account. Longitudinal studies are to be preferred, but are time-consuming. Changing medication can then be a serious problem.

2. The diagnosis of Parkinson's disease is always a clinical one. Short of pathological verification, one has to rely on the main motor symptoms like bradykinesia, rigidity, tremor and postural instability. A negative CT-scan may rule out several other disorders like hydrocephalus, infarcts and subdural haematoma that may mimic PD, but this does not exclude progressive supranuclear palsy.

3. During the progressive course of the disease, the treatment scheme is often adapted. The range of available antiparkinsonian drugs is continually expanding. Except for selegiline, none of the available drugs is free of side effects with regard to the central nervous system [121]. Cognitive decline, psychosis and confusional states may all occur.

4. Ideally patients with Parkinson's disease should always be compared with healthy age-matched controls. Such controls can be rather scarce depending on the function one is examining. These controls are not always suitable. For instance: in studying depression one might object to the use of the patient's partner. Can one assume that the partner's mood is unaffected when the patient suffers from Parkinson's disease?

5. Motor symptoms are pre-eminent in Parkinson's disease. Many non-motor functions find their expression by means of motor activity of some kind. Cognitive function tests which can be very suitable for people with presumed cognitive decline and without any impairment of motor functions, may be totally unsuitable in Parkinson's disease. An example of this is the performal part of the Wechsler Adult Intelligence Scale (WAIS).

Dementia

The diagnosis of dementia is a clinical one. Dementia can be defined as a slowly progressive deterioration of global cognitive functioning. Psychiatrists use DSM-III-R criteria [42] (see table 0.1).

Table 0.1: DSM-III-R Criteria for dementia [42]

A. Demonstrable evidence of impairment in short- and long-term memory. Impairment in short-term memory (inability to learn new information) may be indicated by ability to remember three objects after five minutes. Long-term memory impairment (inability to remember information that was known in the past) may be indicated by inability to remember past personal information (e.g., what happened yesterday, birthplace, occupation) or facts of common knowledge (e.g., past Presidents, well-known dates).

B. At least one of the following:
   (1) impairment in abstract thinking, as indicated by inability to find similarities and differences between related words, difficulties in defining words and concepts, and other similar tasks
   (2) impaired judgment, as indicated by inability to make reasonable plans to deal with interpersonal, family, and job-related problems and issues
   (3) other disturbances of higher cortical function, such as aphasia (disorder of language), apraxia (inability to carry out motor activities despite intact comprehension and motor function), agnosia (failure to recognize or identify objects despite intact sensory function), and "constructional difficulty" (e.g., inability to copy three- dimensional figures, assemble blocks, or arrange sticks in specific designs)
   (4) personality change, i.e., alteration or accentuation of premorbid traits

C. The disturbance in A and B significantly interferes with work or usual social activities or relationships with others.

D. Not occurring exclusively during the course of delirium.

E. Either (1) or (2):
   (1) there is evidence from the history, physical examination, or laboratory tests of a specific organic factor (or factors) judged to be etiologically related to the disturbance
   (2) in the absence of such evidence, an etiologic organic factor can be presumed if the disturbance cannot be accounted for by any nonorganic mental disorder, e.g., Major Depression accounting for cognitive impairment

The use of these criteria for diagnosing dementia in PD is not without its pitfalls, since one has to take into account any disability which is directly due to motor impairment. Even then, DSM-III-R criteria only allow for a crude, subjective quantification of dementia.

For quantification in one way or another, one has to rely on a range of cognitive function tests. Many authors have done this (table 0.2). Depending on the selection of patients and controls, the percentage of Parkinson patients with dementia varies from 0% to 81%. Usually the effect of medication is not taken into account. Although most authors do agree that dementia occurs more often in PD, it seems artificial to distinguish a separate entity like

Parkinsonian dementia in patients with idiopathic parkinsonism. There appears to be a continuum ranging from PD without any trace of dementia to PD with severe concomitant dementia.

Table 0.2: Studies on dementia in Parkinson's disease

Author	Year of publication	Number of patients	Percentage demented patients
Rajput [136]	1987	118	21
Elizan [50]	1986	203	29
Huber [77]	1986	31	35
Rajput [135]	1984	138	9.4
Portin [131]	1984	79	42
DeSmet [41]	1982	75	36
Mindham [112]	1982	40	40
Sroka [152]	1981	71	15
Mathews [98]	1979	42	0
Lieberman [89]	1979	520	32
Martilla [96]	1976	421	29
Sweet [154]	1976	100	56
Mindham [111]	1976	56	28
Rajput [134]	1975	125	36
Martin [97]	1973	100	81
Sacks [142]	1973	72	19
Celesia [31]	1972	153	40
Loranger [91]	1972	63	37
Mindham [110]	1970	89	35
Hoehn [69]	1967	672	14

The last decade has witnessed the emerging of a concept called subcortical dementia. Cumming and Benson [34] consider changes in mood, personality (i.e. apathy) and mental slowing important features of subcortical dementia. Additionally the presence of motor abnormalities are paramount. Alzheimer's disease is an example of cortical dementia and Parkinson's and Huntington's disease are examples of subcortical dementia. The use of the term subcortical dementia does not improve our understanding of dementia in Parkinson's disease very much. Several questions remain to be answered:

1. is the inclusion of motor abnormalities valid for the distinction of cognitive disorders?
2. are changes of mood indicative of cognitive disorders?
3. are changes like apathy and mental slowing "subcortical"?

Anticholinergic drugs have often been implicated in causing cognitive dysfunction in PD [121]. Since very few studies have addressed this issue, we have decided to evaluate the effect of anticholinergics on cognitive function in PD as compared to amantadine. This topic is discussed in chapter 1.

Another problem with regard to cognitive deterioration in PD is the effect of disease duration. If cognitive dysfunction is an integral part of the disease, one might perhaps expect that this cognitive dysfunction worsens along with the progressive impairment of motor functions. Chapter 2 presents the results of a study in which is examined whether cognitive functions change after a follow-up of one year in a group of patients were an effort was made to keep medication constant.

Visuospatial disturbances

Visuospatial function in PD has been the subject of many studies (table 0.3). Results are conflicting. Several reasons can be suggested:

1. Selection of patients.
2. Effect of medication.
3. Selection of tests used to measure visuospatial disturbances.
4. Motor load of visuospatial tests.

A large variety of tests has been used to examine visuospatial function in PD. They range from route-walking and highly sophisticated computerised tests to the relatively simple and perhaps most popular test of visuospatial function: the line orientation test of Benton [11].

In this test the subject has to tell which of two lines out of eleven, match with regard to orientation in a horizontal plane, two other lines (see figure 0.1). There are some drawbacks:

1. It is two-dimensional.
2. The minimal difference detectable is an angle of 18 degrees.
3. Results can only be scored as right or wrong, since quantification of differences is hardly possible.

Table 0.3: Studies on visuospatial impairment in Parkinson's disease

Author	Date	Test used	Impairment in PD
DellaSalla [38]	1986	Estimation of the point at which two lines will intersect	No
Brown [22]	1986	Right-left discrimination	No
Flowers [56]	1984	Visual recognition memory	No
Boller [15]	1984	Benton visual retention test	Yes
Villardita [164]	1982	Geometric drawing task	Yes
Pirozollo [128]	1982	Spatial orientation test	Yes
Albert [1]	1978	Hooper Visual organisation task	Yes
Danta [35]	1975	Judgment of the visual vertical and horizontal	Yes
Bowen [17]	1972	Route-walking test	Yes
Teuber [161]	1964	Judgment of the visual vertical	Yes
Talland [157]	1962	Geometric drawing task	No

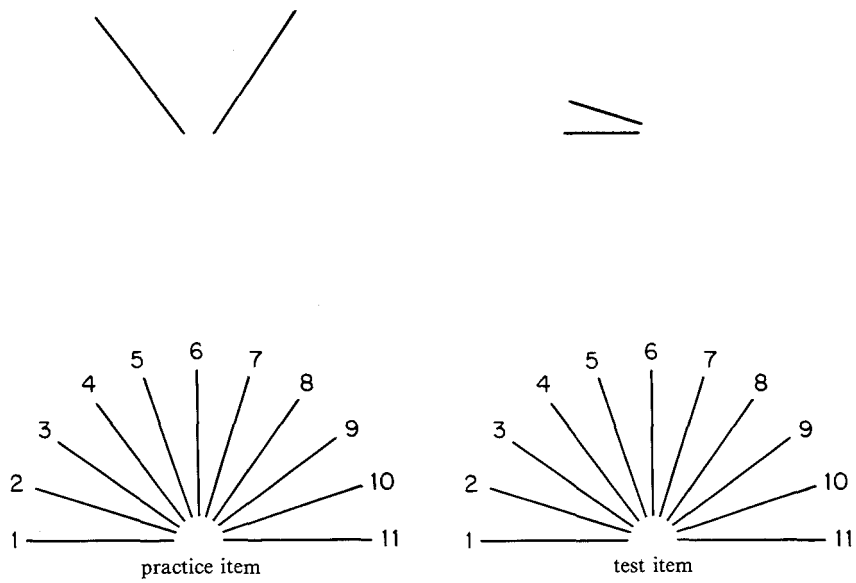

Figure 0.1 Line orientation test.

The advantage is its relatively ease of administration and the fact that no motor component is involved.

De Renzi et al. [37] have developed the rod orientation test (ROT) (for details and description see page 26). This test is three-dimensional and allows

also for differences of less than 18 degrees, in fact any angle can be examined and tested. In addition this test can be performed with eyes closed. Thus also tactile spatial orientation can be examined. Its only drawback is the fact that the subject has to perform a motor act, albeit a relatively simple one.

The rod orientation test (ROT) has been used extensively by Meerwaldt [105, 106]. His studies can be summarised as follows:

- if time is not a limiting factor, results in adults are independent of age.
- in patients with brain infarcts, abnormal ROT-results appear only when brain infarcts are located in the right parietal lobe.

Since the ROT proved to be reliable and easy to administer in these studies [105, 106], it was decided to use this test in the evaluation of spatial orientation in PD. In chapter 3 spatial orientation is explored in patients with relatively mild PD and without levodopa. Chapter 4 examines the effect of levodopa on spatial orientation.

Depression

The presence of depression in PD has been the subject of a number of studies during the last two decades. The percentage of depressed patients with PD seems to range from 28% to 90% (see table 0.4).

Table 0.4: Studies on depression in Parkinson's disease

Author	Year of publication	Number of patients	Percentage depressed patients
Gotham [62]	1986	189	69
Santamaria [147]	1986	34	32
Mayeux [101]	1984	29	28
Mayeux [104]	1981	59	47
Robins [140]	1976	45	*
Mindhamn [111]	1976	56	48
Horn [71]	1974	24	*
Marsh [95]	1973	27	*
Celesia [31]	1972	153	37
Brown [20]	1972	111	52
Mindham [110]	1970	89	90
Warburton [168]	1967	140	56

* No percentage stated: PD were more depressed than controls

Some authors consider depression in PD reactive [62], while others regard it as endogenous [101]. Low levels of dopamine have been implicated [54], while also an altered serotonin metabolism has been considered important [102]. Reviewing the literature, it is clear, that there is no consensus.

Prior to any discussion regarding depression in PD, one should pay attention to the way in which depression is diagnosed and quantified. In individual cases a psychiatric interview is most suitable. As in dementia, DSM-III-R criteria [42] are often used (table 0.5).

Table 0.5: DSM-III-R Criteria for major depressive episode [42]

A. At least five of the following symptoms have been present during the same two-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood, or (2) loss of interest or pleasure. (Do not include symptoms that are clearly due to a physical condition, mood-incongruent delusions or hallucinations, incoherence, or marked loosening of associations.)
   (1) depressed mood (or can be irritable mood in children and adolescents) most of the day, nearly every day, as indicated either by subjective account or observation by others
   (2) markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by subjective account or observation by others of apathy most of the time)
   (3) significant weight loss or weight gain when not dieting (e.g., more than 5% of body weight in a month), or decrease in appetite nearly everyday (in children, consider failure to make expected weight gains)
   (4) insomnia or hypersomnia nearly every day
   (5) psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)
   (6) fatigue or loss of energy nearly every day
   (7) feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
   (8) diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)
   (9) recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

B. (1) It cannot be established that an organic factor initiated and maintained the disturbance
   (2) The disturbance is not a normal reaction to the death of a loved one (uncomplicated bereavement)

   Note: Morbid preoccupation with worthlessness, suicidal ideation, marked functional impairment or psychomotor retardation, or prolonged duration suggest bereavement complicated by Major depression.

C. At no time during the disturbance have there been delusions or hallucinations for as long as two weeks in the absence of prominent mood symptoms (i.e., before the mood symptoms developed or after they have remitted).

D. Not superimposed on schizophrenia, schizophreniform disorder, delusional disorder, or psychotic disorder NOS.

Again, as in dementia, use of DSM-III-R criteria might lead to over-diagnosing depression if one does not adjust for typical motor signs and symptoms of PD.

DSM-III-R criteria are not very suitable for quantification of depression. For this purpose several scales have been developed: The Beck Depression Inventory [8] (BDI), Hamilton Rating Scale [65] (HRS) and Montgomery-Åsberg Depression Scale [113] (MÅ), to name the most popular. All these scales have one major draw-back: the were especially designed for use in a psychiatric population, i.e. for a population without any specific motor disorder. The inclusion of somatic items (for instance referring to sleep, appetite, body image, sex) may then be justified, but these same criteria might detract from the usefulness of these scales in diseases like PD. The use of scales like the BDI and HRS might thus lead to over-diagnosing depression in PD.

To evaluate the validity of two often used depression scales in PD - BDI and MÅ - these scales were compared in three groups of patients: PD, arthritic patients and depressed patients. This study is the subject of chapter 5.

Pulmonary function

Hoehn and Yahr [69] listed bronchopneumonia as the second most important cause of death in Parkinsonism. Bronchopneumonia in PD might be due to aspiration pneumonia, caused by difficulties in swallowing [26, 33, 141], or due to altered respiratory function [117, 119, 165].

Several studies have evaluated respiratory function in PD, using different techniques. Most studies [90, 117, 118] were performed in the 1960's and usually did not make a clear distinction between Parkinson's disease and parkinsonism. In 1984 Vincken et al. [165] published their findings on pulmonary function in a variety of extrapyramidal disorders, including Parkinson's disease. They concluded that upper airway obstruction was the most prominent pulmonary abnormality. To evaluate if upper airway obstruction was prominent and related to clinical disability in relatively homogenous groups of patients with Parkinson's disease we examined patients with the use of the maximal expiratory and maximal inspiratory flow-volume curve. In addition measurement of maximal static mouth pressures was used. Results are discussed in chapter 6.

Muscle strength

Our results on pulmonary function in Parkinson's disease seemed to indicate that loss of muscle strength was a major factor. Although the common name

"shaking palsy" for Parkinson's disease readily acknowledges loss of muscle strength in Parkinson's disease, surprisingly, quantitative data are hardly available. Chapter 7 describes our findings on muscle strength in PD as compared to normal controls.

CHAPTER 1

THE EFFECT OF ANTICHOLINERGICS AND AMANTADINE ON COGNITIVE FUNCTION IN PARKINSON'S DISEASE

Introduction

Until the advent of levodopa in the 1970's, anticholinergic therapy of Parkinson's disease (PD) has been the most effective treatment available [43]. Since the diminishing availability of dopamine leads to a relative overactivity of the cholinergic neurons in the basal ganglia, the administration of anticholinergic drugs was rational. The clearly superior results of levodopa have lead to a decline in the popularity of anticholinergics.

Initial reports [43] did not mention any specific side effects of anticholinergics with regard to mental function, aside from a low incidence of global confusion, usually reversible after the stopping of the medication. The growing body of evidence linking impairment of cholinergic systems to the major signs and symptoms of Alzheimer's disease [123, 124], has lead to a reconsideration of the role of anticholinergic treatment of PD. With the accumulating evidence that cognitive impairment is an integral part of PD [21, 23, 99, 115], several authors have cautioned against the prescription of anticholinergics in PD [41, 109, 121, 143].

Amantadine is relatively safe with regard to cognitive side effects and only global, reversible mental confusion occurs occasionally [120]. More potent drugs like bromocriptine [121] and levodopa [6, 64, 121] both carry their share of cognitive side effects. In addition - although not all authors agree [36, 47, 53, 63, 92, 93, 108] - since early administration of levodopa might be related to disabling side effects as response fluctuations, it might be argued then, that any drug which leads to a postponement of levodopa therapy, is of advantage. Provided anticholinergics are indeed save with regard to cognitive function in PD, these drugs can still be of use in the treatment of PD.

The present investigation was undertaken to examine the effect of anticholinergics as compared to amantadine on cognitive function in patients with PD.

Patients and methods

A total of 52 patients were examined. All patients were treated at the out-patient department for PD. Excluded were those patients who were treated with levodopa-substitution therapy or who showed signs and symptoms of severe dementia, as diagnosed by clinical criteria, when first seen for their PD. Also excluded were patients with PD, who were treated with tricyclic anti-depressants. Selegeline in standard doses and small doses of benzodiazepines were permitted. The 52 patients tested represent all patients fitting the out-lined criteria and were recruited from the out-patient departments of three general hospitals. In each hospital the same treatment scheme is used for PD.

Table 1.1: Patient characteristics. Group 1: Patients without medication or with selegiline, 2: with amantadine, 3: with anti-cholinergics, 4: with amantadine and anti-cholinergics

Group	1.	2.	3.	4.
No. of patients	12	16	16	8
women/men	3/9	8/8	12/4	3/5
Mean age (years)	60.6 (9.5)	64.4 (8.3)	58.4 (8.7)	57.8 (9.8)
range	46 to 73	46 to 75	41 to 69	38 to 70
Mean length of illness (months)	30.1 (28.9)	43.9 (22.1)	38.4 (22.8)	70.5 (58.9)
Bradykinesia / tremor*	7/5	13/3	3/13	4/4
Main affected side (left, right, bilateral)	5/4/3	4/5/7	5/7/4	2/3/3
Hoehn & I	3	3	8	3
Yahr II	8	10	7	4
stage III	1	3	1	1
Webster-score	6.7 (3.7)	9.0 (3.3)	9.3(3.7)	10.0 (6.3)
95%-confidence interval	4.5 to 8.9	7.4 to 10.6	7.5 to 11.1	5.7 to 14.3
NUDS	45.5 (3.7)	43.7 (3.5)	42.0 (3.4)	42.1 (5.8)
95%-confidence interval	43.3 to 47.7	41.9 to 45.5	40.2 to 43.8	38.0 to 46.2
Montgomery-Åsberg-score	3.9 (4.4)	9.9 (6.0)	6.8 (4.0)	4.5 (4.0)
95%-confidence interval	1.4 to 6.4	7.0 to 12.8	4.8 to 8.8	1.8 to 7.2

* scored as bradykinesia, if bradykinesia and tremor were equally severe.
Standard deviations between parentheses

The following items were scored: sex, age, severity of disease, length of illness, initial side of the disease and main symptom (bradykinesia and tremor). The severity of the disease was scored with the Hoehn and Yahr [69] and Webster [170] scales and the Northwestern University Disability Scales [29] (NUDS).

To evaluate the role of any possible disturbances in mood, the Montgomery-Åsberg Depression scale [113] was included. Patient characteristics are tabulated in table 1.1. The 52 patients with PD can be divided in 4 groups.

1. patients (n = 12) without any treatment for PD (n = 8) or on selegiline, 10 mg total daily dose (n = 4).
2. patients (n = 16) treated with amantadine, 100 - 200 mg total daily dose.
3. patients (n = 16) treated with anticholinergics, i.e. orphenadrine (150 - 300 mg) or trihexyfenidyl (6 mg).
4. patients (n = 8) treated both with anticholinergics and amantadine, with the same dose regimens as patients in groups 2 and 3).

The following tests were administered to all patients.

1. Short Portable Mental Status Questionnaire [125] (SPMSQ).
   This test is a global assessment of memory functions and orientation in time and space. It consists of 11 items and the total score ranges from 0 to 30 (= normal).
2. 15-words-test. A total of 15 monosyllable nouns are read aloud to the subject. This is repeated four times and after each time the subject is asked to repeat as many nouns as possible. The total score ranges from 0 to 75 (= maximal). This score is compared with the expected score, adjusted for age, educational level and sex, and transformed to a decile score. This is called the immediate recall score. 30 minutes later the subject is asked how many of the 15 nouns are still remembered. This score is also transformed to a decile score, taking into account the immediate recall score. This is called the delayed recall score. Immediately following this a list of 30 monosyllable nouns is read aloud, containing the original 15 nouns. The subject has to identify the correct fifteen nouns. Scores range from 0 to 30 (= normal). This is called the recognition score.
3. "Groninger Intelligentie Test" (GIT), subtests for wordfluency and calculating. For the wordfluency subtest the patient is asked to name as many animal names as possible in one minute. This same procedure is repeated for names specifying jobs. For the calculating subtest, the subject is asked to make as many additions as possible in one minute, using pen and paper. All GIT-Scores are corrected for age and sex.

4. Line orientation test [11] (LOT). This measures visual spatial orientation. Scores, corrected for age and sex, range from 0 to 34 (=normal).
5. Tapping. The subject is asked to tap as fast as possible, first with the right index finger and then with the left. This is repeated two times. The maximal number of taps for right and left side, in 15 seconds, is registered.
6. Verbal part of the Wechsler Adult Intelligence Scale (WAIS).
7. Rivermead behaviourial memory test (Thames Valley Test Company, Reading, England). This test consists of several subtests and focuses on aspects of memory as encountered in daily life. Items include: remembering a name, remembering hidden objects, remembering an appointment, picture recognition, story recall, face recognition, route recall, orientation. Scores are not adjusted for age or sex. Minimal score is 0, maximal score is 93.
8. Modified Wisconsin Card Sorting test [87, 116] (WCST). This test is considered to assess frontal lobe function. Overall proficiency is assessed by the total number of categories (maximum 6) and the total number of errors. In addition the total number of perseverative errors were counted, both using Milner's [87] and Nelson's [116] method. Using Milner's classification an error is scored as perseverative if it followed the category concept which had previously been correct. Nelson's modification consists of an error being regarded as perseverative if it followed the same category concept as the immediately preceding response [87].

All patients were tested at the out-patient department. A complete session lasted for about 90 minutes. No time limits were imposed, except for tapping and the subtests of the GIT.

For statistical analysis use was made of means, standard deviations, 95%-confidence-intervals and Pearson or Spearman correlation analysis where appropriate.

Results

Patient characteristics are listed in table 1.1. In most aspects groups are comparable. Differences with regard to the mean length of illness and the main presenting symptom are largely due to treatment strategies. As a rule amantadine is first started in those with bradykinesia and anticholinergics in those with tremor as the most prominent symptom. With the progression of symptoms either amantadine or anticholinergics are added, before levodopa is started. This explains the longer mean length of illness in those receiving anticholinergics and amantadine. The relatively high score on the Montgomery-Åsberg-scale in group 2 is surprising, and this score is signi-

ficantly different from the score in group 1. Correlation analysis did not demonstrate any significant effect of the depression scores on the cognition scores.

Results on the cognitive function tests are listed in tables 1.2 - 1.9. As can be seen, mean scores for nearly all tests do not differ for all four groups, differences are small and not significant. There are two exceptions and they regard the results on the tapping test, left and right. Scores for patients using anti-cholinergics are significantly worse when compared with the scores of patients without any medication or only selegiline. Perhaps this is due to the high proportion of patients with tremor in the group using anticholinergics.

Table 1.2: Results on the Short Portable Mental Status Questionnaire. For group definition, see table 1.1.

Group	mean	SD	95%-confidence-interval
1.	29.9	0.3	29.7 to 30.0
2.	29.6	0.9	29.2 to 30.0
3.	29.8	0.5	29.6 to 29.8
4.	29.6	0.7	24.7 to 34.5

Table 1.3: Results on the three subtests of the "Groninger Intelligentie Test". For group definition, see table 1.1

Group	mean	SD	95%-confidence-interval
immediate recall			
1.	3.8	2.7	2.2 to 5.4
2.	5.6	3.1	4.0 to 7.2
3.	3.5	3.0	2.1 to 4.9
4.	3.8	3.1	1.6 to 6.0
delayed recall			
1.	3.9	2.2	2.7 to 5.1
2.	4.7	2.7	3.3 to 6.1
3.	4.4	3.0	2.8 to 6.0
4.	5.4	2.9	3.4 to 7.4
recognition			
1.	26.9	2.1	25.7 to 28.1
2.	26.9	2.7	25.5 to 28.3
3.	25.3	7.4	21.8 to 28.8
4.	26.1	4.2	23.2 to 29.0

Table 1.4: Results on the 15-words-test. For group definition, see table 1.1

	Group	mean	SD	95%-confidence interval
Animals				
	1.	27.3	6.3	23.8 to 30.8
	2.	28.5	5.2	26.0 to 31.0
	3.	24.1	5.5	21.4 to 26.8
	4.	26.0	5.8	21.9 to 30.1
Jobs				
	1.	26.1	7.0	22.2 to 30.0
	2.	25.7	4.8	23.3 to 28.1
	3.	23.3	4.1	21.3 to 25.3
	4.	27.0	5.5	23.3 to 30.7
Calculating				
	1.	26.6	6.2	23.1 to 30.1
	2.	27.3	3.8	25.5 to 29.1
	3.	26.3	4.7	23.9 to 28.7
	4.	26.3	7.6	21.0 to 31.6

Table 1.5: Results on the Line Orientation Test. For group definition, see table 1.1

Group	mean	SD	95%-confidence-interval
1.	25.8	4.6	23.3 to 28.3
2.	22.8	4.9	20.4 to 25.2
3.	23.5	4.4	21.3 to 25.7
4.	23.8	5.7	19.9 to 27.7

Table 1.6: Tapping results. For group definition, see table 1.1

	Group	mean	SD	95%-confidence interval
left side				
	1.	56.6	9.7	51.1 to 62.1
	2.	44.4	17.5	35.8 to 53.0
	3.	44.3	13.8	37.6 to 51.0
	4.	51.9	7.6	46.6 to 57.2
right side				
	1.	59.3	7.6	55.0 to 63.6
	2.	49.6	16.9	41.4 to 57.8
	3.	40.4	16.2	32.6 to 48.2
	4.	60.3	5.5	56.4 to 64.2

Table 1.7: Results on the verbal part of the WAIS. For group definition, see table 1.1

Group	mean	SD	95%-confidence interval
1.	113.2	14.1	105.2 to 121.2
2.	110.8	11.3	105.3 to 116.3
3.	99.4	18.5	90.4 to 108.4
4.	110.4	14.5	100.4 to 120.4

Table 1.8: Results on the Rivermead Behaviourial Memory Test. For group definition, see table 1.1

Group	mean	SD	95%-confidence interval
1.	64.2	9.0	59.1 to 69.3
2.	61.1	8.3	57.0 to 65.2
3.	60.1	13.0	53.8 to 66.4
4.	63.3	9.5	56.6 to 70.0

Table 1.9: Results on the Wisconsin Card Sorting Test. For group definition, see table 1.1

	Group	mean	SD	95%-confidence-interval
total errors				
	1.	7.9	6.9	4.0 to 11.8
	2.	10.2	4.2	8.2 to 12.2
	3.	11.1	6.3	8.0 to 14.2
	4.	11.5	4.7	8.4 to 14.6
Nelson - score				
	1.	2.5	4.5	0.0 to 5.0
	2.	3.0	2.2	1.8 to 4.2
	3.	3.9	4.2	1.7 to 6.1
	4.	1.9	2.2	0.3 to 3.2
Milner - score				
	1.	2.6	3.1	0.8 to 4.4
	2.	4.0	2.6	2.8 to 5.2
	3.	5.4	5.9	2.5 to 8.3
	4.	5.0	5.5	1.1 to 8.9

The results on the verbal part of the WAIS (table 1.7) are somewhat surprising. Differences between groups were not significant, but the scores for three groups are rather high, while the scores for the anticholinergic patient group is just average. This pattern is not replicated in the other tests and an explanation except one involving chance is not at hand.

Discussion

Our results lead us to conclude that the reputed negative effect of anticholinergics in patients with PD is, if any, slight. With a wide range of cognitive function tests no differences can be demonstrated between patients using amantadine and anticholinergics. Although patient-numbers were small, neither any significant differences could be demonstrated between these two group of patients and patients using a combination of amantadine and anticholinergics and patients without those medications.

Aside from acute confusional states, amantadine does not seem to demonstrate any side effects with regard to cognitive function. Parkes et al. [120] evaluated the efficacy of amantadine in a cross-over-trial and did not find any cognitive dysfunction.

Cognitive dysfunction in PD can range from impairment of isolated functions to global dementia [23, 100, 115]. The causative role of dopamine deficiency is probably not great. Some authors found a correlation between the severity of dementia and neuronal loss in the medial part of the substantia nigra [139]. Others concluded that cognitive impairment is strongly correlated to those motor symptoms that usually do not respond to levodopa therapy like postural instability and dysarthria, while there is no correlation with tremor or bradykinesia [126]. Accordingly levodopa therapy does not lead to an overall improvement of general [126] or isolated cognitive deficits [75].

When demented and non-demented patients are compared, demented PD-patients appear to have low concentrations of choline acetyl transferase and acetyl choline transferase [123, 124]. These concentrations are comparable to those in patients with Alzheimer disease. There is a positive correlation with the number of neurons in Meynert nucleus in patients with PD-dementia, but not in patients with Alzheimer disease [123, 124].

Probably there exits a neuronal compensation mechanism for the decreased transferase levels. Dubois et al. [46] administered subcutaneously scopolamine, an anticholinergic drug, both to normal controls and patients with PD. Two of five normal memory tests deteriorated significantly in patients with PD, but not in normal controls.

As demonstrated by DeSmet et al. [41], anticholinergics may be hazardous in PD-patients with dementia. In 13 of 14 demented patients anti-

cholinergics lead to an acute and reversible confusional state, while no confusion occurred in 7 non-demented patients.

Several authors have prospectively studied the effect of anticholinergics in PD. Martin et al. [97] investigated 100 patients who were all treated with anticholinergics. 81 patients were considered demented. On retesting 1 week - perhaps somewhat short - after treatment was discontinued, test-results did not change significantly. Sadeh et al. [143] examined patients using anti-cholinergics in combination with amantadine or levodopa. Four tests were used: digit span, reversed digit span, recall of named objects after five minutes and digit span recall. 19 patients were tested with and without anti-cholinergics and only the results on the digit-span-recall improved significantly when patients were without anticholinergics.

Miller et al. [109] examined two groups of patients with PD, 54 patients were evaluated with a free recall technique and 24 with a signal detection memory test. Patients were taking either levodopa, a dopamine-agonist, benzhexol or a combination of these drugs. Using correlation-analysis they found a significant correlation between impairment on these tests and benzhexol. They concluded: "it would be wise to restrict the prescription of benzhexol ...".The correlation co-efficients were indeed significant but the absolute values were low (-0.44 and -.40) which indicate that only a rather low 19% of the variance of the cognitive impairment is explained by the use of benzhexol [107].

Koller [82] examined recent memory function in 12 patients with PD before and after administration of trihexyfenidyl. Although the digit span task did not show any change, the free recall memory, associated learning task and the supra-digit-span test deteriorated significantly after trihexyfenidyl.

Aside from one case-report [85], general dementia-like deterioration due to anticholinergics have not been reported. From our results, it can be concluded that anticholinergics are relatively safe when compared with amantadine and patients without medication or low dose selegiline. Global confusion is a potential hazard, although it did not occur in our series. Provided no obvious dementia is present, treatment with anticholinergic drugs is justified before starting with more potent drugs like bromocriptine and levodopa.

CHAPTER 2

SHORT-TERM FOLLOW-UP OF COGNITIVE FUNCTION IN PARKINSON'S DISEASE

Introduction

Cognitive function in Parkinson's disease has been investigated in many ways [23, 99]. Usually normal controls were compared with patients with Parkinson's disease, without paying much attention to length of illness and length of treatment. Thus mean values for cognitive function tests in Parkinson's disease (PD) might obscure any possible differences between early and late PD. In addition any possible distinction between subgroups with mild but stable cognitive impairment and subgroups with mild but progressive impairment, perhaps finally resulting in dementia, cannot be made.

Reports on either short-term or long-term follow-up of cognitive function in PD are scarce [16]. In this chapter the results on cognitive function tests are presented in a group of patients with early and mild PD, retested after one year.

Patients and methods

A total of 18 consecutive patients were examined. All patients were referred to the out-patient department for treatment of PD. Excluded were those patients who were treated with levodopa-substitution therapy or who showed signs and symptoms of severe dementia, as diagnosed by clinical criteria, when first seen for their PD.

The following items were scored: sex, age, severity of disease, length of illness, main symptom (bradykinesia or tremor) and initial side of the disease. The severity of the disease was scored with the Hoehn and Yahr [69] and Webster [170] scales and the Northwestern University Disability Scales [29] (NUDS). Mood was assessed with the Montgomery-Åsberg Depression scale [113]. Patient characteristics are tabulated in table 2.1, including the severity of their disability after one year.

Table 2.1: Patient characteristics

No. of patients		18 (11 women, 7 men)	
Mean age (years)		54.9 (8.2)	
range		38 to 66	
Mean length of illness (months)		46 (45)	
Main symptom		9 bradykinesia, 9 tremor	
Main affected side		6 left, 8 right, 4 bilateral	
Hoehn and Yahr stage		at first test	at second test
	I	10	5
	II	7	10
	III	1	3
Webster-score (95% conf. interval)		7.2 to 3.6	9.8 to 4.3
95%-confidence-interval of difference		- 4.2 to - 1.1	
NUDS (95% conf. interval)		44.3 to 3.8	42.2 to 4.4
95%-confidence-interval of difference		- 4.2 to - 0.2	
Montgomery-Åsberg Score (95% conf. interval)		6.1 to 3.9	6.9 to 5.8
95%-confidence-interval of difference		- 4.0 to 2.5	

All patients were retested after 12 to 14 months. Although all deteriorated with regard to their overall clinical disability, an effort was made to keep medication constant. This was not possible for all patients: one needed levodopa and in six others anticholinergic medication was instituted.

The following tests were administered to all patients. Both at testing and retesting the same procedure was followed.

1. Short Portable Mental Status Questionnaire [125] (SPMSQ).
   This test is a global assessment of memory functions and orientation in time and space. It consists of 11 items and the total score ranges from 0 to 30 (= normal).
2. 15-words-test. A total of 15 monosyllable nouns are read aloud to the subject. This is repeated four times and after each time the subject is asked to repeat as many nouns as possible. The total score ranges from 0 to 75 (= maximal). This score is compared with the expected score, adjusted for age, educational level and sex, and transformed to a decile score. This is called the immediate recall score. 30 minutes later the subject is asked how many of the 15 nouns are still remembered. This score is also transformed to a decile score, taking into account the immediate recall score. This is called the delayed recall score. Immediately following this a list of 30 monosyllable nouns is read aloud, containing the original 15 nouns. The subject has to identify the correct fifteen nouns. Scores range from 0 to 30 (= normal). This is called the recognition score.

3. "Groninger Intelligentie Test" (GIT), subtests for wordfluency and calculating. For the wordfluency subtest the patient is asked to name as many animal names as possible in one minute. This same procedure is repeated for names specifying jobs. For the calculating subtest, the subject is asked to make as many additions as possible in one minute, using pen and paper. All GIT-Scores are corrected for age and sex.
4. Line orientation test [11] (LOT). This measures visual spatial orientation. Scores, corrected for age and sex, range from 0 to 34 (=normal).
5. Tapping. The subject is asked to tap as fast as possible, first with the right index finger and then with the left. This is repeated two times. The maximal number of taps for right and left side, in 15 seconds, is registered.
6. Verbal part of the Wechsler Adult Intelligence Scale (WAIS).
7. Rivermead behaviourial memory test (Thames Valley Test Company, Reading, England). This test consists of several subtests and focuses on aspects of memory as encountered in daily life. Items include: remembering a name, remembering hidden objects, remembering an appointment, picture recognition, story recall, face recognition, route recall, orientation. Scores are not adjusted for age or sex. Minimal score is 0, maximal score is 93.
8. Modified Wisconsin Card Sorting test [87, 116] (WCST). This test is considered to assess frontal lobe function. Overall proficiency is assessed by the total number of categories (maximum 6) and the total number of errors. In addition the total number of perseverative errors were counted, both using Milner's and Nelson's method. Using Milner's classification an error is scored as perseverative if it followed the category concept which had previously been correct. Nelson's modification consists of an error being regarded as perseverative if it followed the same category concept as the immediately preceding response [87].

All patients were tested at the out-patient department. A complete session lasted for about 90 minutes. No time limits were imposed, except for tapping and the subtests of the GIT.

Results

Results on the cognitive function tests are listed in table 2.2. Mean scores on all tests were more or less constant. Changes, when present, were usually for the better, but any differences were far from significant. Results in individual patients were fully compatible with this overall pattern. None of the patients demonstrated any overall decline in cognitive function.

Table 2.2: Results on the cognitive function tests

Test	FIRST TEST Mean	SD	SECOND TEST Mean	SD	95%-confidence-interval of the difference
SPMSQ	29.8	0.7	29.7	0.8	- 0.7 to 0.5
15-words-test					
immediate recall	5.0	3.2	5.7	3.6	- 0.9 to 2.1
delayed recall	4.4	2.6	5.7	3.0	- 0.1 to 2.7
recognition	28.4	1.7	27.3	2.4	- 2.1 to 0.1
"Groninger Intelligentie Test"					
animals	27.0	4.8	29.1	2.7	- 0.4 to 4.5
jobs	26.8	4.4	27.4	3.8	- 1.2 to 2.3
calculating	26.8	4.9	25.9	4.4	- 3.5 to 1.7
Line orientation	24.4	4.0	25.8	4.1	- 0.8 to 3.6
Tapping					
right side	49.6	16.7	54.7	15.8	- 1.2 to 11.3
left side	48.8	12.5	48.9	14.3	- 3.5 to 3.8
Verbal WAIS-IQ	111.7	12.4	113.0	10.0	- 3.2 to 5.9
Rivermead	67.3	8.5	67.6	5.8	- 3.3 to 3.9
Wisconsin Card Sorting Test					
total errors	10.9	5.5	6.8	5.0	2.0 to 6.1
Nelson-score	3.2	3.9	5.0	1.9	- 0.0 to 2.6
Milner-score	3.7	3.6	1.9	3.7	- 0.7 to 3.7

Scores on the SPMSQ, the 15-words-test, the GIT-subtests, verbal WAIS and Rivermead behaviourial memory test can be regarded as normal. Scores on the Line orientation test are borderline and slightly better than in our previous studies [74, 75]. Scores on the Wisconsin Card sorting test should be considered normal, although no normal values are available. They are more or less equal to the results obtained by Lees et al. [87] in normal controls but rather better than those obtained in patients with PD by the same investigators.

Discussion

There are two reports on long-term mental changes in patients with PD. Botez and Barbeau [16] compared normal controls with patients with PD who were

treated with anticholinergic or antihistaminic drugs or amantadine and patients treated with levodopa. Retesting after one year demonstrated for patients with PD a slight but significant deterioration on some tests (Kohs block design test) but no change on others (K-T attention test, Porteus maze test), irrespective of treatment. In contrast motor performance improved somewhat. Preliminary results of retesting after two to five years - no details were given - lead these authors to conclude that intellectual functioning deteriorated, both in patients with and without levodopa treatment.

Portin and Rinne [130] followed-up a group of 79 patients with PD for 8-10 years. All patients were treated with levodopa. Compared with the pre-treatment situation most patients demonstrated an improvement in cognitive skill during the first 2-3 months of levodopa treatment. After 2-3 years of levodopa treatment the cognitive functions started to drop to their initial values. After 8-10 years a highly significant deterioration in visuospatial, verbal and memory functions could be demonstrated, along with a decline in motor function. In addition patients became emotionally more disturbed.

Other investigators have tried to analyse possible contributing or causal factors of cognitive decline in PD, usually by way of correlation analysis of large cross-sectional groups. This has lead to conflicting results. Thus age has been reported to have both a positive [100] and a negative [91] correlation with cognitive decline. Factors that correlated negatively with cognitive decline were: length of illness [89], response to levodopa [89] and length of levodopa treatment [50]. Factors that correlated positively were: severity of disease [31, 50, 91, 96, 97, 100], arteriosclerosis [96], depression [100], and the presence of atrophy on the CT-scan [131, 152] and abnormalities on the EEG [134].

With the advance and wide-spread use of antiparkinsonian drugs it has become impossible to study the natural history of cognitive function in patients with PD. Only the natural history of patients treated with anticholinergics, amantadine, levodopa and dopamine-agonists and all possible combinations of these drugs can be studied. Ideally medication should be kept constant for as long as possible to exclude any possible effect of medication change.

In 11 of our 18 patients medication was kept constant for about a year. In most (n = 6) patients where additional medication was needed, anticholinergics in standard doses were added. It is highly unlikely, that this change of therapy in a subgroup of our patients counterbalanced any possible decline in cognitive function, given their reputation to induce drug-related dementia [121]. At most they could have accentuated any cognitive decline (table 1.7). As demonstrated in chapter 1, this seems highly unlikely. Thus it seems that cognitive function - as tested by a wide range of neuropsychological tests - is stable in patients with PD, when retested after one year.

CHAPTER 3

SPATIAL DISORIENTATION AS AN EARLY SYMPTOM OF PARKINSON'S DISEASE

Introduction

Boller et al. [15] have investigated the role of perceptual and motor factors in visual spatial impairment in Parkinson's disease (PD), concluding that there is impairment in performance of visual-spatial tests. They found no correlation between test results and severity of disease, depression, intellectual impairment, or anti-cholinergic medication. Simple visual-spatial tests were more sensitive than complex tests in identifying the disorder. The lack of correlation between the disturbances in spatial perception and severity of PD might be explained by the fact that the conventional classification of Hoehn and Yahr [69] is necessarily crude. In addition, levodopa therapy may change a patient's score without affecting spatial perception. Boller et al. [15] noted the similarity of this disorder to that in patients with right hemisphere lesions.

We have investigated the influence of severity of PD on visual-spatial impairment by scoring the patients with the Hoehn and Yahr [69] and Webster [170] scales and the Northwestern University Disability Scales [29] (NUDS). Only patients without levodopa substitution therapy were included, to determine whether visual-spatial impairment is a symptom of the disease or a result of levodopa therapy.

Patients and methods

We have tested 55 outpatients with idiopathic PD. Exclusion criteria included neurologic diseases other than PD, use of levodopa at present or in the past, use of neuroleptics, dementia, and impaired vision.

The following items were scored: sex, age, severity of disease, length of illness, main symptom (bradykinesia or tremor), and initial side of the disease (table 3.1).

Table 3.1: Patient characteristics

No. of patients	55 (24 men, 31 women)
Mean age	64.8 yrs (SD 9.0 yrs; range, 36-84)
Mean length of illness	61.3 mos (range, 3-480 mos)
Main symptom	30 bradykinesia, 25 tremor
Main affected side	12 left, 17 right, 26 bilateral
WAIS score	103.75 (SD, 12.8; range 78-140)
Hoehn and Yahr stage	I - 6
	II - 23
	III - 21
	IV - 4
	V - 1
Webster-score	Range, 4-23 (0 = normal)
NUDS	Range, 50-11 (50 = normal)

All patients performed the following tests:

1. Rod orientation test (ROT) [37].
   The ROT consists of two pairs of rods (figure 3.1). Each pair is made up of a vertical rod that can rotate 360° around its axis, and a second rod that is fixed to the first by a hinged joint in such a way that it can pivot up and down in the sagittal plane.

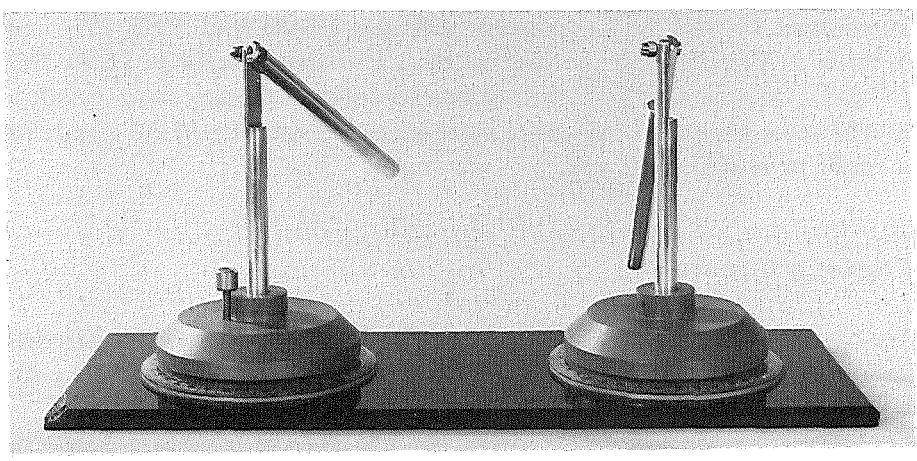

Figure 3.1 Rod orientation test.

The patient is seated in front of the apparatus and is permitted to move the head and eyes but not the trunk, One pair of rods represents the model, and the patient is asked to set the rods of the other pair in the same position as accurately as possible. Two versions of the test are given, by inspection and by palpation. In the visual part of the test, the patient is not allowed to touch the rods of the model. In the tactile part, the patient has to estimate the spatial position of the rods by palpation with eyes closed. No time limit is imposed. During the test, the patient is allowed only to use the preferred hand, and never both hands. Normal data were provided by Meerwaldt and Van Harskamp [105], who studied 40 healthy volunteers and demonstrated that test results on the ROT are independent of sex or age.

2. Line orientation test [11].
3. Facial recognition test [10].
4. Verbal WAIS score.

Results and analysis of data

The scores on the ROT (table 3.2) were significantly higher in patients than in controls (Student's t test, $p < 0.00001$). Only one patient with PD had a normal score, on both the visual and the tactile part of the test (that is, smaller than the mean plus twice the standard deviation of the controls).

Table 3.2: Results on the Rod orientation test

		Mean	SD	95% confidence limits
Visual vertical	NC	2.2	0.8	2.0 - 2.5
	PD	4.4	2.3	3.8 - 5.0
Visual horizontal	NC	2.2	1.1	1.9 - 2.6
	PD	6.2	3.5	5.3 - 7.1
Tactile vertical	NC	3.5	1.1	3.1 - 3.9
	PD	9.9	5.0	8.6 - 11.2
Tactile horizontal	NC	3.5	1.3	3.1 - 3.9
	PD	16.8	13.5	13.2 - 20.4

NC = Normal controls, data provided by Meerwaldt and Van Harskamp [105]
PD = Parkinson's disease

No correlation was found between the scores on the ROT and age, length of illness, scores on the verbal WAIS, and severity of disease as measured with the Hoehn and Yahr and Webster scales and the NUDS (Spearman rank correlation, significance level $p = 0.05$).

Also, subgroup analysis comparing the scores on the ROT of patients with a different initial side or with tremor or bradykinesia as a main symptom showed no significant difference (two-sided Mann-Whitney U, $p > 0.2$).

The test results of the line orientation test and the facial recognition test are shown in table 3.3. No correlation was found with the ROT scores.

Table 3.3: Results on the Line orientation test (normal $\geq$ 19) and the Facial recognition test (normal $\geq$ 40)

	Mean	SD	Pass	Fail
Line orientation test	21.3	6.8	41	14
Facial recognition test	39.5	5.1	32	23

Discussion

We found that PD patients have impaired spatial perception in early stages of the disease. Impaired motor function might affect spatial perception, because a motor act, simple as it may be, is necessary to perform the ROT. However, there was no significant difference between ROT performance in patients with bradykinesia as the main symptom and those with tremor (two-sided Mann-Whitney U, $p > 0.2$). Furthermore, there was no correlation between the impairment of spatial perception and severity of PD as measured by Hoehn and Yahr and Webster scales and NUDS.
Finally, patients with unilateral symptoms had as much difficulty with the unaffected hand as patients with bilateral symptoms.

The line orientation test [11], designed to measure visual spatial disturbances, is advocated for clinical practice because of its brevity and the ease of administration. This may be true, but we did not find a correlation between the scores on the ROT and the line orientation test. Also, only 14 of our patients had an abnormal score on the line orientation test, indicating that this test might be specific but less sensitive. The same is true of the facial recognition test [10], which only 23 of our patients failed.

If we compare our results with those of Boller et al. [15], it can be concluded that, although the patient groups are not strictly comparable (28

patients in their group with levodopa substitution therapy versus non in our group), and although different visual spatial tests were used, our findings confirm their conclusions. Even when using a more extended scoring system for the severity of the disease, we did not find a correlation with the extent of visual spatial impairment. A possible negative role of levodopa substitution therapy could be ruled out as our patients did not receive such therapy. So disturbances of spatial perception are part of the disease.

Concerning the correlation between the key symptoms of PD as tremor, rigidity, and bradykinesia, Mortimer et al. [114] found in a patient group not comparable with ours (60 patients, mostly men, of whom 52 were on levodopa substitution therapy) a significant correlation between bradykinesia and the degree of neuropsychological impairment, especially visual spatial perception and memory. Although their partial correlation coefficients were significant, the correlation itself is rather weak ($r = -0.34$), which means that only 11.6% ($= r \times r$) can be explained on the basis of the correlation between the test results and bradykinesia, leaving 88.4% unexplained. A similar objection can be made to the results of Danta and Hilton [35].

Bowen et al. [17] found that, using a route-walking test, parkinsonian patients with predominantly left-sided symptoms (right basal ganglia levodopa deficiency) scored significantly worse than did patients with right-sided symptoms. This result is in contrast with our findings. In our opinion, however, and also according to others [37], the route-walking test is too complex and therefore does not tap the basic mechanisms underlying spatial perception.

Botez and Barbeau [16] stated that the slope of intellectual deterioration (including impairment in perceptual organization) continues unabated at the same rate in patients with or without levodopa substitution therapy. The effect of such therapy on spatial orientation will be discussed in the next chapter.

Recently two other studies have addressed the problem of visuo-spatial impairment in Parkinson's disease [22, 38]. Brown and Marsden [22] tested 15 Parkinsonians (14 taking levodopa) on a Spatial Choice Reaction Time Task. This task tested visuospatial function, in our opinion, on two levels: on an elementary level by discrimination between left and right, and on a complex level by involving mental rotation. As the authors stated themselves, there is no direct proof that no verbal strategy was used, implying the possibility that something different from visuo-spatial function was tested [73]. Admitting that spatial function is not a unitary entity, it seems fit to quote De Renzi et al. [37]:"... space perception has been studied at a rather complex level, one at which it is difficult to disentangle the influence on performance of spatial as compared with praxic, intelligence and memory factors. It seems reasonable to expect that a more definite answer might be obtained by employing elementary tasks, which tap the basic mechanisms underlying spatial perception".

Della Sala et al. [38] employed such an elementary task, by asking the patient to forecast where a slanted line would intersect a horizontal line. Their test could be considered a sophisticated version of Benton's line orientation test [11]. An advantage is that results can be more readily quantified and that subjects have to indicate exactly where the line intersects instead of choosing from a fixed number of possibilities. The authors did not find any impairment of visuospatial function. They suggested that this might be due to the fact that their sample of patients is highly selected. We should like to stress this point: all patients were younger than 70 years; all were on levodopa substitution therapy; all were in-patients and, most importantly: patients were excluded with "any signs of everyday impairment of their ability to cope socially". Thus patients with a possible visuo-spatial impairment were effectively excluded from their study [73].

Since our patients had disturbances in spatial orientation independent of the modality tested (that is, visual or tactile), the impairment can be defined as supramodal.

Meerwaldt and Van Harskamp [105] studied spatial disorientation in patients with cerebral infarction and demonstrated a significant correlation between the presence of spatial disorientation and an infarct in the right postrolandic region. The area in common on CT was the area of the genu posterior of the splenium.

It is still unknown if spatial impairment in PD can be traced back in part to a dopamine deficiency at cortical levels. It might be argued that spatial disorientation is not caused by malfunction of the right inferior parietal lobule, but by malfunction of thalamic relay nuclei (VPL, MG, LG) or the thalamic reticular nucleus (in which case, one should call it "multimodal" instead of "supramodal"), as seen in infarction of the right thalamus [68, 169]. It seems unlikely that malfunction of the basal ganglia proper is responsible, as no correlation has been found so far between the severity of motor symptoms and the extent of spatial impairment.

An alternative explanation of the abnormalities on the ROT has been offered by Taylor et al. [160]. They commented on the fact that patients with PD had mean scores 5 to 6 times higher than normal on the tactile part, as opposed to 2 to 3 times higher on the visual part [160]. This might point to a failure to integrate sensory input during the organization and planning of movement. This impairment is considered to arise from disturbed activity within the frontostriate motor loop [40]. The discrepancy between the visual and tactile part might indeed point to an additional mechanism and a possible deficit in the frontostriate loop is an attractive explanation. However, such a deficit does not explain the results on the visual part of the ROT and is not even necessary to produce such a discrepancy, as has been demonstrated in patients with brain infarcts [105, 106]. Patients with pre- or postrolandic

infarcts of the left hemisphere had normal results on the ROT. Patients with prerolandic infarcts of the right hemisphere had also normal results, but those with postrolandic infarcts had very abnormal results. The postrolandic infarct patients demonstrated the same discrepancy between the visual and the tactile part of the ROT as did the PD patients, although absolute scores were somewhat better in PD patients.

In conclusion, we demonstrated that a supramodal impairment of spatial orientation, as tested with the ROT, exists in early stages of PD in patients without levodopa substitution therapy, with no significant correlation with length of illness, age of patient, severity of disease, or the verbal WAIS score. We disagree with Marsden [94], who regards PD as a predominantly motor disease without impairment of perceptive functions. Contrary to Marsden's statement [94] that non-motor impairment is largely the result of a decline in motor function, we would like to argue that often this decline in motor function prevents the spatial disorientation from becoming clinically evident. As one of our patients said: "I used to walk alone in the wood, fog or no fog, but when the symptoms of Parkinson's disease appeared, I noticed I could not orient myself any more, and in case of fog, I got lost. Now I am too disabled to get lost any more."

CHAPTER 4

SPATIAL DISORIENTATION IN PARKINSON'S DISEASE: NO EFFECT OF LEVODOPA SUBSTITUTION THERAPY

Introduction

In the previous chapter, findings on spatial orientation in 55 patients with Parkinson's disease (PD) were reported. In 22 of 55 patients, the clinical signs and symptoms deteriorated such, that levodopa substitution therapy (LST) was necessary. These 22 patients were tested again. This chapter reports the results on retesting as compared to the results before the institution of LST.

Patients and methods

Of the 55 consecutive outpatients, 22 were given LST because of progression of disease. We routinely start LST on an outpatient basis and hospitalization has not been necessary. All were tested before (0 - 20) and after (2 - 15 months) LST was started. The interval between the two test sessions varied from 3 to 26 months. The following tests were used: rod orientation test (ROT) [37], line orientation test, facial recognition test and verbal WAIS. We scored severity of PD with the Hoehn and Yahr [69] and Webster [170] scales and Northwestern University Disability Scales [29] (NUDS). We also scored the following items: sex, age, length of illness, main symptom (tremor or bradykinesia) and initial side of the disease. Table 4.1 gives a summary of the patient-characteristics. Details about the ROT-procedure were given earlier [74] (chapter 3). Meerwaldt and Van Harskamp provided normal data for the ROT [105], collected from patients visiting the outpatient clinic for complaints not related to the central nervous system.

Table 4.1: Patient characteristics. Standard deviations between parentheses

Group	PD -	PD +
Number	22	22
Mean age (years)	67.0 (6.8)	68.1 (6.8)
Mean length of illness (months)	85.8	99.3
Main symptom		
Tremor	9	10
Bradykinesia	13	12
Mean WAIS score	104.3 (13.6)	104.5 (15.3)
Hoehn & Yahr		
I	2	0
II	8	9
III	10	10
IV	1	3
V	1	0
Webster score range	4 to 23	6 to 23
Mean	12.1 (5.1)	13.7 (4.4)
NUDS range	11 to 49	24 to 45
Mean	38.9 (8.3)	36.9 (5.4)

PD - = Patients before treatment with levodopa
PD + = Patients treated with levodopa

Results and analysis of data

In all patients with or without LST the scores on the ROT (table 4.2) were significantly higher than in normal controls (Student's t test, p two-sided < 0.00001). LST did not affect total scores, but subscores were affected in different ways. The visual horizontal part improved significantly (Tpair, $p=0.0007$) but in the tactile vertical part the scores showed a trend to worsen ($p=0.06$); the visual vertical and tactile horizontal parts, however, remained virtually unchanged.

No correlations were found between scores on the ROT and age, length of illness, scores on the verbal WAIS and severity of disease as measured with Hoehn and Yahr and Webster scales and the NUDS. Subgroup analysis comparing the score on the ROT of patients with a different initial side of the disease or with tremor or bradykinesia as a main symptom, showed no significant differences. Subgroups were small, however.

Table 4.3 gives the results of the line orientation test and the facial recognition test. Mean results do not differ significantly before and after institution of LST.

Table 4.2: Results on the rod orientation test

	Group	Mean	SD	95%-confidence-interval
Visual vertical				
	NC	2.2	0.8	2.0 to 2.5
	PD -	5.1	2.3	4.1 to 6.9
	PD +	5.7	2.9	4.5 to 6.9
Visual horizontal				
	NC	2.2	1.1	1.9 to 2.6
	PD -	7.4	3.7	5.8 to 5.7
	PD +	4.4	3.1	3.1 to 5.7
Tactile vertical				
	NC	3.5	1.1	3.1 to 3.9
	PD -	11.8	6.6	9.0 to 14.6
	PD +	15.5	7.8	12.2 to 18.9
Tactile horizontal				
	NC	3.5	1.3	3.1 to 3.9
	PD -	18.3	15.6	11.6 to 25.0
	PD +	14.9	13.8	9.1 to 20.8

PD - = Patients before treatment with levodopa
PD + = Patients treated with levodopa
NC = Normal controls [105]

Table 4.3: Results on the Line orientation test and the Facial recognition test

	Group	Mean	SD	Pass	Fail
Line orientation test					
	PD -	20.7	5.6	17	5
	PD +	20.4	5.6	13	9
Facial recognition test					
	PD -	39.2	5.7	12	10
	PD +	38.6	5.6	11	11

PD - = Patients before treatment with levodopa
PD + = Patients treated with levodopa

Discussion

Spatial orientation in PD has been investigated before, but the effect of levodopa has not been taken into account. In the previous chapter we concluded that spatial disorientation is an early symptom of PD. In this follow-up study we found that LST does not effect this symptom and thus seems not to be directly related to the degree of levodopa-deficiency. As the time between the two ROT tests is relatively short it seems improbable that progression of the disease cancels any positive effect of LST on the results on the ROT.

Both before and after institution of LST WAIS-scores for the total group and individual patients were normal. Thus, the disturbances in spatial orientation found with the ROT probably are not caused by concomitant Alzheimer's disease (in which spatial disorientation can be a prominent symptom).

Assuming that the rod orientation test does indeed test spatial orientation, at a rather elementary level, the conclusion is inevitable that spatial orientation is impaired in PD. The differences on the ROT between PD and controls are highly significant; they cannot be explained by sample bias as all patients belonged to a consecutive series of outpatients with a relatively mild form of PD, initially not warranting LST. Although a longterm longitudinally structured investigation might be preferred (as Spinnler and Della Sala [151] have suggested) it is very unlikely that this will lead to different results.

CHAPTER 5

MEASURING DEPRESSION IN PARKINSON'S DISEASE

Introduction

James Parkinson did not describe any signs or symptoms suggestive of depression with regard to his own patients. The discussion however, whether "mental" symptoms are a part of Parkinson's disease (PD) is an old one [99]. A review of the literature is confounded by the fact that many different definitions have been used to describe "mental" changes. The last decades have seen a more systematic approach in the analysis of these "mental" changes. One of these changes is depression. Many studies have tried to estimate the prevalence of depression and to evaluate whether depression is reactive or belongs to PD. The percentage of PD-patients suffering from depression has been found to range from 27.5% up to 90% [20, 31, 62, 71, 78, 95, 101, 104, 110, 111, 127, 140, 147, 158, 168]. If control groups have been used, patients suffering from PD were significantly more depressed than controls. Sometimes a significant correlation with the severity is reported and sometimes not. A correlation, if present, might be interpreted in two ways: patients react with increasing depression to an increasingly severe and invalidating disease and is consequently reactive. Or an increasing depression is an expression of more severely disturbed neurotransmitter levels and is thus part of the disease.

Measuring depression in PD is not easy. Most depression scales in common use, have been designed to quantify depression in psychiatric patients. Both the Beck Depression Inventory [8] (BDI) and the Hamilton Rating Scale [65] - often used to evaluate mood in PD - were designed to measure change and effect of anti-depressive treatment in those patients in whom the diagnosis of depression had already been made by way of a psychiatric interview. Both scales have items pertaining to somatic features. It may be questioned whether the use of such scales in conditions where somatic features are prominent - as in PD - is valid.

Firstly, somatic symptoms can be assumed to be caused by other processes than any possible concomitant depression, although this might

contribute. Secondly patients with a physically disabling condition can not be considered to be a representative sample of the normal population. Any test valid for a normal population, will not be automatically valid for a strongly deviating group without further adaptation.

Only once the BDI has been evaluated for its somatic features with regard to PD [88], but no comparisons were made with other, possibly less somatically orientated scales, like the Montgomery - Åsberg - scale [113] (MÅ). The purpose of this study was to evaluate the validity of the BDI in PD as compared to the MÅ. Two other patient-groups, one with arthritis, one with endogenous depression, were used for comparison.

Patients and methods

Three separate groups were tested. Group 1 consisted of 24 randomly selected outpatients with idiopathic PD. Exclusion criterium was the presence of neurologic disease other than PD. Group 2 consisted of 22 depressed in-patients of the psychiatric department. Depression was diagnosed using DSM-III criteria [42]. These patients were hospitalised because of the severity of their depression and were tested either before the start or during treatment. Patients were selected to match regarding age and sex-distribution of group 1. Exclusion criterium for group 2 was the presence of neurologic disease, among others dementia. Group 3 consisted of 24 out-patients suffering from rheumatoid arthritis as defined by ARA-criteria. These patients too were selected to match regarding age and sex-distribution, group 1. Exclusion criterium was again the presence of neurologic disease, among others dementia.

The following variables were scored for all patients: sex, age, length of illness, educational level, occupation or former occupation if retired, marital status, living conditions and medication. Impairment of activities of daily living (ADL - functions) were scored using a 11 - item standardized questionnaire covering a broad spectrum of daily activities. Items included are communication (listening, reading, writing and speaking), feeding, visiting the toilet, bathing, dressing, getting in and out of bed, and mobility inside and outside the house. Each item was scored from 0 (no impairment) to 3 (maximal impairment). Patients with PD were additionally assessed by the Hoehn & Yahr [69], Webster [170] and North Western University Disability [29] (NUDS) scales.

Mood was assessed by three scales.

1. Beck's Depression Inventory [8] (BDI). This is a self-rating scale consisting of 21 items. Each item is scored from 0 (normal) to 3 (maximal). These items pertain to the following aspects: 1. mood, 2. pessimism, 3. sense of

failure, 4. lack of satisfaction, 5. guilty feeling, 6. sense of punishment, 7. self hate, 8. self accusation 9. self-punitive wishes, 10. crying spells, 11. irritability, 12. social withdrawal, 13. indecisiveness, 14. body image, 15. work inhibition, 16. sleep disturbance, 17. fatigability, 18. loss of appetite, 19. weight loss, 20. somatic preoccupation, 21. loss of libido. Following Levin [88] the last 7 items are considered to be somatic items. The sumscore of the last seven items (BDI 15-21) is considered to be the somatic subscore of the BDI and the sumscore of the first fourteen items (BDI 1-14) the non-somatic subscore. A BDI-score of 10 or more indicates depression. Depending on the total score (see table 5.3) patients can be classified as mildly, moderately or severely depressed.

2. Montgomery - Åsberg -scale [113] (MÅ) (20). This is a scale scored by the observer and consists of 10 items. Each item ranges from 0 (normal) to 6 (maximal). The 10 items pertain to the following aspects: 1. apparent sadness, 2. reported sadness, 3. inner tension, 4. reduced sleep, 5. reduced appetite, 6. concentration difficulties, 7. lassitude, 8. inability to feel, 9. pessimistic thoughts, 10. suicidal thoughts.

3. Beck's Hopelessness Scale [9] (BHS). This is a scale consisting of 20 statements and the subject has to state whether they do or do not agree with each statement. All statements refer to either an optimistic or pessimistic outlook. An answer indicating an optimistic mood is scored 0 and 1 when pessimistic. A high total score implies a pessimistic mood and a low total score an optimistic one.

Since several patients, especially those with arthritis, suffered from impairment of writing, all questionnaires were read aloud and the answers filled in by the examiner. A carry-over effect was possible from the BDI to the MÅ or vice-versa. To prevent this, each examination was started by either the BDI or the MÅ and ended with the MÅ or BDI, the exact order being determined by randomisation.

Statistics

For statistical analysis, means and 95%-confidence intervals were calculated. Spearman-rank-correlation, including significance levels, was applied.

For both the BDI and the MÅ odds ratio's and 95%-confidence-limits of the odds ratio's were calculated [55]. This statistical method was chosen because the main purpose of this investigation was to evaluate if and how each separate item of both depression questionnaires discriminated between the

different patients groups. Scores on each BDI-item were discretised as normal (scores of 0 and 1) or abnormal (scores of 2 or 3). For the MÅ-items scores were discretised as normal (scores of 0,1 or 2) or abnormal (scores of 3,4,5, or 6). In case of zero patients in any of the four cells 0.5 was added to each cell [173].

Factor analysis was deemed less suitable because a linear or symmetrical relationship and a parametric distribution could not be assumed.

In testing significance, Fisher exact test was utilised. All tests were two-tailed ($p < 0.05$).

Results and analysis of data

Group characteristics are listed in table 5.1. The three groups did not differ in mean age, educational level, past or present professional status and distribution of sex, largely due to deliberate matching. Length of illness differed significantly ($p < 0.05$) between all groups. ADL - scores differed but did reach only significance ($p < 0.05$) between depressed patients and patients with PD.

There were no significant differences between scores on all tests for female and male patients.

Table 5.1: Patient characteristics. Standard deviations between parentheses.

	Parkinson patients	Depressed patients	Arthritis patients
Number	24	22	24
Age (years)	68.5 (9.2)	67.5 (9.6)	65.2 (10.6)
Education	3.5 (1.6)	3.3 (1.5)	3.8 (1.9)
Female/male	15/9	14/8	16/8
Length of illness (months)	100 (67)	19 (20)	233 (127)
Activities of daily living	7.8 (5.0)	3.2 (4.0)	4.7 (4.7)
Hoehn & Yahr I	1		
II	8		
III	8		
IV	5		
V	2		
Webster-score	13.9 (5.6)		
NUDS	31.3 (11.3)		

Table 5.2 lists the mean scores for each group on the separate BDI - items, the total sumscores (BDI) and the sumscores for the first fourteen BDI - items (BDI 1-14) and the sumscores for the last 7 items (BDI 15-21). Mean scores on each separate BDI-item did not differ significantly between patients with PD and arthritis, except for item 9. Nor were there any significant differences between BDI - sumscores, BDI 1-14 and BDI 15-21 sumscores for these two groups.

Table 5.2: Scores on the BDI, expressed as means and standard deviations

BDI-item	Parkinson patients	Depressed patients	Arthritis patients
1	0.17 (0.48)	1.59 (1.10)	0.13 (0.33)
2	0.33 (0.70)	1.64 (1.09)	0.08 (0.28)
3	0.08 (0.28)	0.91 (1.19)	0.08 (0.28)
4	0.38 (0.58)	1.73 (0.83)	0.21 (0.41)
5	0.00 (0.00)	1.18 (1.18)	0.04 (0.20)
6	0.13 (0.61)	1.14 (1.46)	0.13 (0.61)
7	0.21 (0.41)	1.36 (0.85)	0.08 (0.28)
8	0.04 (0.20)	1.77 (1.02)	0.25 (0.60)
9	0.17 (0.38)	0.82 (1.05)	0.00 (0.00)
10	0.29 (0.55)	1.95 (1.17)	0.58 (1.06)
11	0.25 (0.44)	1.27 (1.03)	0.42 (0.58)
12	0.17 (0.48)	1.00 (1.15)	0.00 (0.00)
13	0.75 (1.11)	1.73 (0.98)	0.21 (0.51)
14	0.33 (0.76)	1.00 (1.23)	0.17 (0.56)
15	0.79 (0.88)	1.55 (0.74)	0.58 (0.58)
16	0.75 (0.68)	1.95 (1.17)	0.63 (0.86)
17	1.58 (0.72)	1.73 (0.88)	1.41 (0.58)
18	0.67 (1.05)	1.18 (1.05)	0.21 (0.51)
19	0.63 (1.17)	0.86 (1.17)	0.25 (0.68)
20	0.50 (0.59)	1.36 (1.00)	0.33 (0.56)
21	1.67 (1.46)	2.77 (0.75)	1.54 (1.35)
BDI - sumscore	10.04 (5.62)	30.54 (11.32)	7.29 (5.15)
Sumscore of items 1-14	3.45 (3.24)	19.13 (9.37)	2.33 (2.90)
Sumscore of items 15-21	6.58 (3.66)	11.41 (3.85)	4.95 (2.90)

Table 5.3 tabulates the number of patients per group for the usual BDI-ranges. As can be seen most patients with PD or arthritis are not or only

mildly depressive, although there is a skewed distribution when both groups are compared. This is partly due to the fact that the cut-off points are more or less arbitrary.

Table 5.3: Scores on the BDI, by subgroups

BDI - range	Parkinson patients	Depressed patients	Arthritis patients	Interpretation
0 - 9	10	0	18	none
10 - 17	11	3	5	mild
18 - 24	3	5	1	moderate
> 24	0	14	0	severe

Table 5.4 lists the mean scores for each group on the MÅ and the separate meanscores for each MÅ - item. When patients with PD and arthritis are compared with regard to the scores on each MÅ-item, patients with PD score significantly higher only on item 1. Total MÅ-score is significantly higher ($p < 0.05$) for PD-patients when compared with arthritis-patients.

Table 5.4: Montgomery - Åsberg sumscores and scores per item, means and standard deviations (between parentheses) for each group.

Montgomery- Åsberg items	Parkinson patients	Depressed patients	Arthritis patients
1	2.50 (1.44)	3.18 (1.47)	0.67 (0.76)
2	0.67 (1.05)	4.05 (1.70)	0.38 (0.71)
3	1.20 (1.14)	3.41 (1.40)	0.83 (1.05)
4	1.38 (1.41)	3.45 (1.94)	1.17 (1.52)
5	1.00 (1.59)	2.36 (1.84)	0.38 (0.88)
6	1.58 (1.28)	3.27 (1.35)	1.04 (1.43)
7	1.50 (1.84)	3.14 (1.58)	1.33 (1.13)
8	0.25 (0.74)	3.00 (2.18)	0.00 (0.00)
9	0.33 (0.76)	2.45 (1.77)	0.38 (0.77)
10	0.29 (0.55)	2.00 (1.57)	0.04 (0.20)
Sumscore	10.92 (6.09)	30.05 (10.74)	6.21 (4.87)

Table 5.5 lists the mean scores for each group on the BHS, per item and the total score. PD-patients do not differ significantly from depressed patients or patients with arthritis, but these last two patient-groups do differ at the $p < 0.01$ level.

Table 5.5: Scores on the Beck Hopelessness Score, per item and total, for each group. Means and standard deviations.

Item	Parkinson patients	Depressed patients	Arthritis patients
1	0.57 (0.50)	0.77 (0.42)	0.25 (0.43)
2	0.13 (0.34)	0.36 (0.48)	0.04 (0.20)
3	0.22 (0.41)	0.41 (0.49)	0.17 (0.37)
4	0.78 (0.41)	0.95 (0.21)	0.75 (0.43)
5	0.22 (0.41)	0.27 (0.45)	0.13 (0.33)
6	0.78 (0.41)	0.64 (0.48)	0.33 (0.47)
7	0.39 (0.49)	0.78 (0.45)	0.21 (0.41)
8	0.65 (0.48)	1.00 (0.00)	0.50 (0.50)
9	0.43 (0.50)	0.45 (0.50)	0.25 (0.43)
10	0.43 (0.50)	0.55 (0.50)	0.67 (0.47)
11	0.13 (0.34)	0.73 (0.45)	0.04 (0.20)
12	0.70 (0.46)	0.82 (0.39)	0.54 (0.50)
13	0.91 (0.28)	0.59 (0.49)	0.83 (0.37)
14	0.70 (0.46)	0.77 (0.42)	0.63 (0.48)
15	0.65 (0.48)	0.90 (0.29)	0.42 (0.49)
16	0.30 (0.46)	0.41 (0.49)	0.17 (0.37)
17	0.43 (0.50)	0.55 (0.50)	0.21 (0.41)
18	0.65 (0.48)	0.91 (0.29)	0.25 (0.43)
19	0.65 (0.48)	0.91 (0.29)	0.29 (0.45)
20	0.38 (0.48)	0.27 (0.45)	0.08 (0.28)
Sumscore	10.1 (4.6)	13.0 (4.4)	6.7 (3.8)

Correlation analysis

Spearman-rank-correlation analyses was done for MÅ, BHS, BDI, BDI-7, BDI-14 versus the following group parameters: age, length of illness, ADL, Hoehn & Yahr, Webster, NUDS and age of onset. Most correlations were weak and did not reach significance.

Odds ratios

Table 5.6 (and fig. 5.1) lists the odds ratio's for all BDI-items and the 95%-confidence limits for patients with PD as compared with depressive patients. Items 14, 17, 18 and 19 do not show a significant odds ratio, while all other items do. When PD-patients are compared with arthritic patients only items 13, 15 and 18 have a significant ($p < 0.05$) odds ratio.

Table 5.7 (and fig. 5.2) lists the odds ratio's for all MÅ-items and the 95%-confidence limits for patients with PD as compared with depressive patients. Only item 5 does not show a significant odds ratio. When PD-patients are compared with arthritic patients all odds ratio's are not significant, except for items 1 and 5 ($p < 0.05$).

Both from tables 5.6 and 5.7 and from figures 5.1 and 5.2 can be seen that the odds ratio's differ widely from item to item both for the BDI and the MÅ.

Table 5.6: Odds ratios and 95% confidence-limits. Depressive patients vs PD: 0,1 vs 2,3 (* adjusted according to Woolf [173])

Item	Odds ratios	95% confidence limits
1	0.03	0.00 to 0.26
2	0.04	0.00 to 0.32
3*	0.05	0.00 to 0.95
4	0.03	0.00 to 0.26
5*	0.03	0.00 to 0.57
6	0.08	0.00 to 0.67
7*	0.04	0.00 to 0.76
8*	0.01	0.00 to 0.19
9*	0.08	0.00 to 1.57
10	0.03	0.00 to 0.26
11*	0.06	0.00 to 1.16
12	0.05	0.00 to 0.46
13	0.13	0.03 to 0.47
14	0.53	0.13 to 2.22
15	0.19	0.05 to 0.67
16	0.10	0.02 to 0.43
17	0.95	0.29 to 3.16
18	0.58	0.16 to 2.07
19	0.56	0.15 to 2.14
20	0.05	0.00 to 0.46
21	0.14	0.03 to 0.74

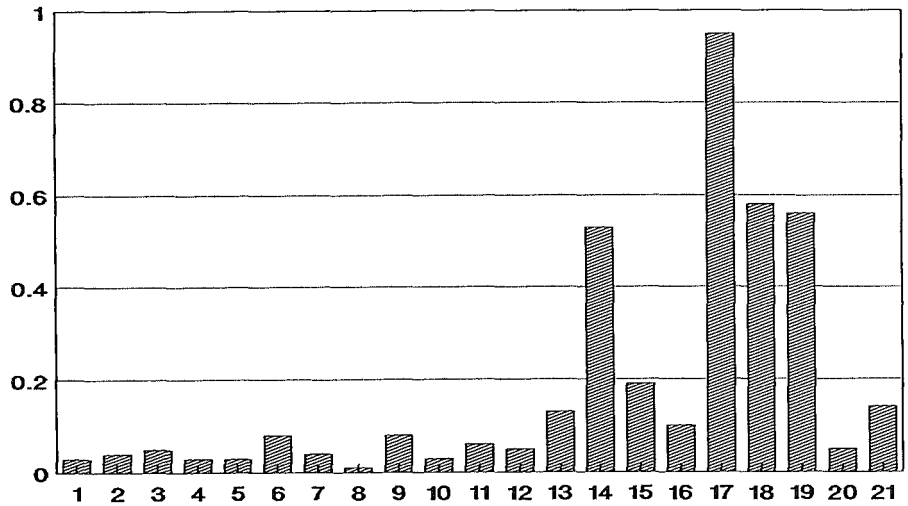

Figure 5.1: Odds ratios and 95% confidence-limits. Depressive patients vs PD: 0,1 vs 2,3 (* adjusted according to Woolf [173])

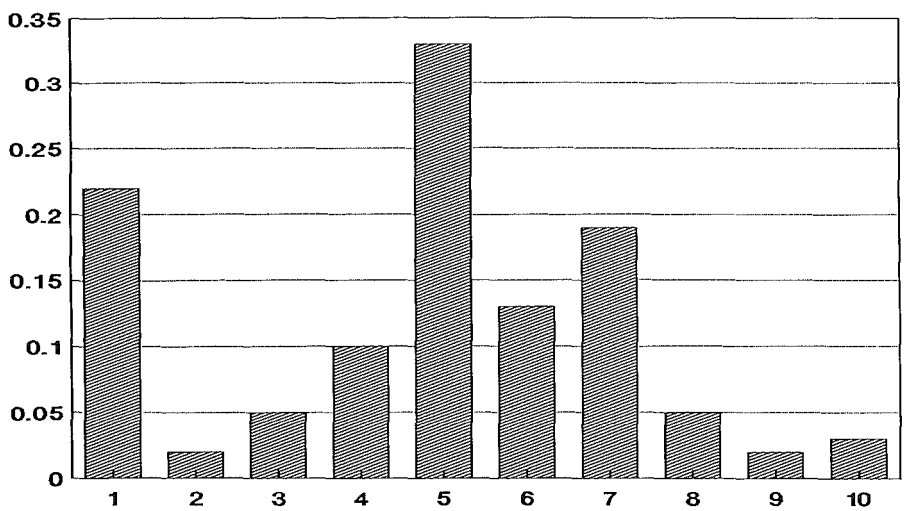

Figure 5.2: Odds - ratios and 95% confidence limits, Montgomery-Åsberg scale, patients with PD vs depressive patients, scores of 0, 1, 2 vs scores of 3, 4, 5, 6 (* adjusted according to Woolf [173]).

Table 5.7: Odds ratios and 95% confidence limits, Montgomery-Åsberg scale, patients with PD vs depressive patients, scores of 0, 1, 2 vs scores of 3, 4, 5, 6 (* adjusted according to Woolf [173]).

Item	Odds ratios	95% confidence limits
1	0.22	0.06 to 0.86
2	0.02	0.00 to 0.12
3	0.05	0.00 to 0.27
4	0.10	0.03 to 0.39
5	0.33	0.29 to 1.16
6	0.13	0.03 to 0.48
7	0.19	0.05 to 0.67
8	0.05	0.00 to 0.44
9*	0.02	0.00 to 0.37
10*	0.03	0.00 to 0.56

Discussion

Our group of patients with Parkinson's disease is at large comparable with the patients investigated by others [62, 101, 104, 147, 88]. In these groups the average scores on the BDI varies from 11.1 to 14.1. When a score of 10 is considered a cut-off point separating depressed from non-depressed patients the published percentage of depressed patients ranges from 44 to 69, well in line with the percentage of 58 in this study. Until now the MÅ has been used in one study [127] only and in this study the MÅ-score was 12.8, more or less comparable with our average of 10.9. From these comparisons, it may be concluded that our results with regard to the global scores on the BDI and MÅ match quite well those published, with regard to patients with PD.

Neither in our study nor in most published reports a significant correlation was found between scores on the BDI and severity of disease, regardless the disability-scales used. Gotham et al. [62], who examined patients with PD and arthritis, did found a significant correlation between scores on the BDI and ADL but commented that the functional disability accounted for only a modest proportion of the variability in the testscores. They too did not find any significant differences on the BDI -scores between arthritis and PD - patients. Details on the scores of separate BDI - items were not reported.

Only one study [88] so far reports the scores on the items composing the BDI. Although factor-analysis demonstrated that including somatic items in the BDI is justified, it should be noted that the somatic items accounts for about 44 % of the total score. In our patients, both with PD and arthritis, a remarkable pattern emerged, when the sumscores of somatic items versus the sumscores of the non-somatic items are compared. The somatic items

comprising one third of all items, were responsible for 60-70% of the total BDI - score. The odds ratio's for patients with PD versus depressed patients (table 5.6, fig. 5.1) confirm this.

Ideally one would expect a more or less evenly distributed pattern if all items contribute equally to the sumscore. This does suggest that the so-called somatic items of the BDI measure features prominent in physically disabled patients, features which do not stand out in patients who are not physically disabled. The results on the odds ratio's support this. This preponderance of somatic items does seem to disqualify the BDI for use in patients having diseases like PD and arthritis. The principal cause for this discrepancy between scores on somatic and non-somatic items of the BDI seems to be the fact that the BDI was specifically designed to measure depression in psychiatric patients. The original group of patients used to validate the BDI consisted of patients without any specific physical disability. To include, for such a group, somatic items in a depression inventory seems justified. Subsequent use of such scales in a quite different group of patients leads to marked discrepancies, as shown above. The MÅ has at first appearance considerably less somatic items. Only the high scores of the first item (regarding facial expression) stands out. Scores on this item correlate significantly with measures of parkinsonian disability (ADL, HY, NUDS) as opposed to the other MÅ-items. This item contributes for about 25% of the total MÅ-score. If one adjusts the MÅ for this item the patient-group with PD can be regarded as not depressed, although with still significantly higher scores than patients with arthritis. When one compares the overall results on the BDI with the MÅ, the latter scale seems preferable, in spite of the high mean score on item 1 of the Montgomery-Åsberg-scale. Comparison of fig 5.2 with figure 5.1 also favours the MÅ.

Use of the BHS does not add much to our understanding of mood in PD. No significant correlations were found with any of the disease-parameters, but there were significant, although modest, correlations with MÅ and BDI. As has been remarked before [62] scores on the BHS perhaps more reflect individual differences in coping style than depressed mood per se.

Measuring depression in physically disabled patients is difficult. Several patients with PD and arthritis actually commented on this. For example, when asked about sleep disturbances, they said that sleep itself was no problem, but that stiffness often caused them to wake up: so how should they score this item (item 16 of the BDI)? Somatic items in questionnaires, usually specifically designed for depressed patients in a psychiatric setting, do distort the total score. In the MÅ 25% and in the BDI 66% of the total score is caused by these items as opposed to resp. 10% and 33% in patients with depression. Perhaps it is time to design depression-scales specific for physically disabled patients.

CHAPTER 6

PULMONARY FUNCTION IN PARKINSON'S DISEASE

Introduction

Pulmonary function has been studied in parkinsonism, including idiopathic Parkinson's disease (PD) [90, 117, 119]. Most studies were performed in the 1960's and were hampered by the fact that Parkinson's disease was not clearly separated from (post)-encephalitic parkinsonism. Although parkinsonism resembles Parkinson's disease in its main clinical features, there are also important differences, viz. absence of tremor and different course of progression. It was postulated then, that there was in parkinsonian patients concomitant chronic obstructive pulmonary disease [119] or obstruction due to increased bronchial muscle tone caused by increased parasympathetic activity [117].

In 1984 Vincken et al. [165] published their findings on pulmonary function in a variety of extrapyramidal disorders, including PD. They used the technique of maximal expiratory and maximal inspiratory flow-volume (MEFV and MIFV)-curve analysis and were able to distinguish two abnormal types of flow-volume-curves. From this they concluded that upper airway obstruction (UAO) was the most prominent pulmonary abnormality.

Our study was aimed at the investigation of a possible relationship between UAO, as detected by flow-volume-curves, and clinical disability in a homogeneous group of patients with relatively severe idiopathic PD. In addition measurement of maximal static mouth pressures was incorporated in the study in order to detect possible influences of impaired respiratory muscle function.

Patients and methods

31 consecutive PD-patients were included in the investigation. The main inclusion criterion was the severity of the disease: according to the Hoehn and Yahr-scale [69] patients had to be at least in stage III. All patients were

physically examined and had to complete a questionnaire about present and past health. Any history of lung disease that might have led to structural or functional pulmonary dysfunction or signs or symptoms suggestive of this led to exclusion. Other exclusion criteria were: use of medication which might result in pulmonary dysfunction, known structural abnormalities of the upper airways including oral cavity and dementia severe enough to interfere with pulmonary testing.

All patients were scored using Hoehn and Yahr [69], Webster [170] and Northwestern University Disability Scale [29] (NUDS) (see table 6.1). In addition age, age of onset of disease, principle symptom (tremor or rigidity) and medication were recorded.

Table 6.1: Patient characteristics. Standard deviations between parentheses

	Hoehn & Yahr scale			
	III	IV	V	Total
men	6	6	4	16
women	6	5	4	15
all	12	11	8	31
mean age men	60.5 (8.5)	65.5 (9.9)	64.6 (5.0)	64.6 (9.1)
mean age women	61.3 (11.8)	69.6 (4.5)	65.7 (4.0)	65.7 (8.9)
mean age all	60.9 (10.3)	67.4 (8.2)	65.1 (4.6)	65.1 (9.1)
Webster-score	15.1 (2.9)	18.9 (1.8)	24.9 (2.2)	19.0 (4.5)
NUDS	37.5 (2.8)	28.4 (6.5)	14.3 (5.1)	28.3 (10.4)
Mean length of illness (months)	82.5 (49.7)	88.4 (67.2)	101.3 (81.0)	89.4 (65.6)

All patients were on levodopa-substitution-therapy. Furthermore all patients used anti-cholinergic drugs and some amantadine as well. Medication was not changed during at least one month prior to testing. The neurological parameters of all patients, including those who suffered from response fluctuations, were scored immediately before testing.

Pulmonary function testing

All patients were subjected to spirography (Lode D 53/R, the Netherlands) which resulted in a measure of vital capacity (VC) and forced expiratory volume in 1 sec (FEV1). Always at least three attempts were made and the

best result was used. A maximal expiratory and maximal inspiratory flow-volume curve (MEFV and MIFV) could be obtained in 28 patients. Of the remaining 3, one patient could only produce a MEFV-curve, while the results in the two other patients were not reliable. The flow-volume-curve relates maximal expiratory and inspiratory flows to displaced volume at the mouth from total lung capacity and residual volume during expiration and inspiration respectively. A normal example is given in fig. 6.1. The following variables were derived:

PEF: peak expiratory flow
PIF: peak inspiratory flow
FVC: forced vital capacity
FIV_1: forced inspiratory volume in 1 sec
MEF50 and MEF25: maximal expiratory flow after expiration of 50 and 75% of FVC and, for the inspiratory phase: MIF50.

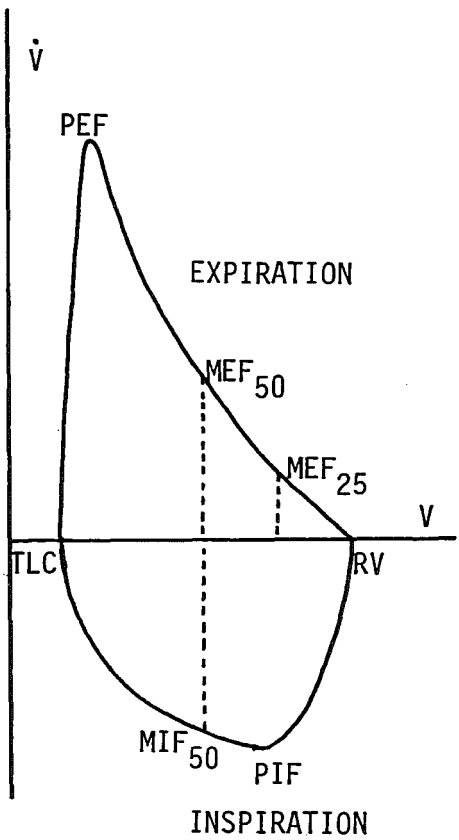

Figure 6.1 Normal MEFV-MIFV-curve. For abbreviations see text

From these parameters the ratios FEV1/PEF and MEF50/MIF50 were calculated.

In 22 of 31 patients (10 Hoehn & Yahr stage III, 8 stage IV, 4 stage V) maximum static mouth pressure at residual volume (PMRV) and total lung capacity (PMTLC) could be measured accurately, according to the protocol of Black and Hyatt [12]. Since a scuba-type mouth-piece was used, reference values were calculated following the guidelines of Vincken et al. [166].

For statistical analysis, besides Student's t test either Spearman or Pearson correlates were used, depending on the parameters examined. All p-values are two-sided [155].

Results

All pulmonary function parameters are expressed as percentages of normal values and are corrected for length, sex and age [12, 132]. For the peak inspiratory flow actual values are given as no reliable reference-values are available. Since our group consisted of almost equal numbers of male and female patients and subgroup analysis showed no significant differences, only combined results will be given. They are tabulated in table 6.2.

Table 6.2: Results on the pulmonary function tests. Standard deviations between parentheses. For abbreviations see text

	Hoehn & Yahr Scale							
	III		IV		V		All	
VC	99.4	(13.0)	95.7	(16.9)	88.8	(23.1)	95.4	(18.0)
FEV1	98.3	(14.7)	98.4	(17.7)	79.5*	(25.8)	93.5	(20.8)
FEV1/VC	99.8	(7.1)	104.7	(13.8)	90.6	(13.7)	99.0	(12.9)
FIV1	110.6*	(17.3)	106.7	(20.3)	95.3	(21.8)	105.1	(19.9)
FVC	102.4	(13.4)	104.2	(14.1)	91.1	(35.0)	100.3	(20.6)
MEF25	89.8	(34.0)	97.2	(40.1)	95.4	(62.2)	93.7	(42.6)
MEF50	89.3	(27.0)	90.9	(28.1)	74.3	(41.3)	86.2*	(30.9)
PEF	98.3	(23.4)	83.4	(29.8)	61.3**	(24.2)	84.2**	(29.0)
PIF	5.1	(2.0)	3.9	(2.1)	2.9*	(1.0)	4.1**	(2.0)
PMTLC	41.9**	(17.0)	24.1**	(9.8)	29.5**	(15.8)	33.2**	(15.4)
PMRV	54.0**	(24.0)	34.2**	(12.4)	35.3**	(24.4)	43.4**	(22.1)
MEF50/MIF50	93.2	(41.6)	123.9	(70.1)	118.0	(49.2)	110.4	(54.9)

* significance difference with normal controls $p < 0.05$, and ** $p < 0.01$

Significant differences with normal controls are indicated where they could be demonstrated. Maximum static mouth pressure at residual volume and total lung capacity (PMRV, PMTLC) and peak expiratory flow (PEF) ($p < 0.01$) and maximal expiratory flow at 50% (MEF50) ($p < 0.05$) were significantly below normal values. Numbers are too small to allow subgroup analysis, but there is a trend for most parameters to decrease from group III to V. Vital capacity, forced inspiratory volume in 1 sec. and the ratio of forced expiratory volume in 1 sec and vital capacity are relatively normal.

28 patients could produce a flow-volume-curve. 4 patients had a type A-curve and 16 had type B, according to the classification of Vincken et al. [165] (see discussion and fig. 6.2). Three pulmonary function parameters can be regarded as indicators of upper airway obstruction (see also discussion): peak inspiratory flow, the ratio of forced expiratory volume in 1 sec. and peak expiratory flow and the ratio of the maximal expiratory and inspiratory flow at 50%. 9 Patients had an abnormal value for one of these parameters, 8 patients for two and only one for all three parameters.

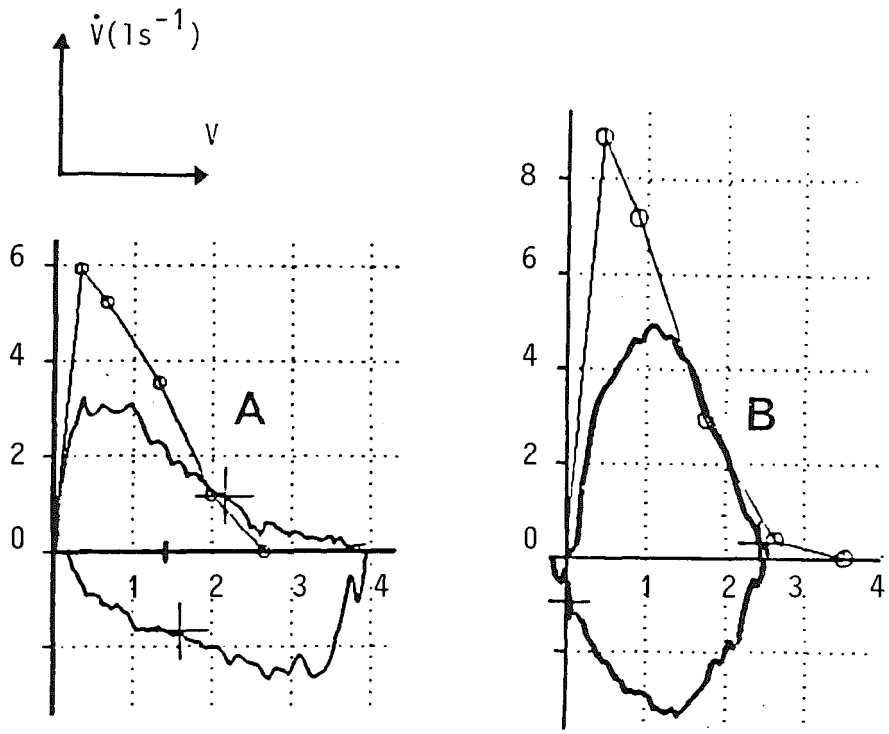

Figure 6.2 A: type A flow-volume-curve and B: type B. See text for details

Several significant correlations (r) could be demonstrated between the neurological disability scores (Webster and NUDS) or the length of illness and the results of the pulmonary function test. They will be not given here as all r-values are rather small. They all remained well below the arbitrary value of 0.7. $r^2 \times 100$ is the percentage of the variation of one parameter caused by the other, and a r of 0.7 would result in 49%, a level indicating clinical relevance [155].

Discussion

Respiratory problems are a major cause of death in patients with PD [69]. Most patients do not, however, report respiratory problems, perhaps because their physical disability does not lead to activities where such problems can manifest themselves. Using modern techniques of pulmonary function testing it is possible to detect subclinical abnormalities and to localize them within the respiratory system. Several investigators have reported on respiratory abnormalities in patients with parkinsonism and several mechanisms were suggested: increased parasympathetic activity [90, 119], coexisting chronic obstructive lung disease [117] and recently upper airway obstruction (UAO) [165].

In our group of patients, all with relatively severe PD and all without clinical signs or symptoms suggesting respiratory problems, two different kind of abnormalities were found. Peak expiratory and inspiratory flows and maximal static mouth pressures at residual volume and total lung capacity were all significantly below normal values. The low mean pressure values can be explained by "muscle weakness" and hypokinesia, two symptoms intrinsic to PD. Peak expiratory and inspiratory flow are effort dependent variables from flow-volume-curves, but are moreover sensitive indicators of UAO [80]. In the upper airways the turbulence of the flow limits predominantly the largest flows produced, i.e. peak expiratory and inspiratory flow, which explains their sensitivity to upper airway narrowing.

Another kind of abnormality is the significant low value of maximal expiratory flow at 50%. This parameter is relatively independent of muscle strength [80] and can be attributed to UAO. Vincken et al. [165] mainly used the following criteria for UAO: ratio of forced expiratory volume in 1 sec and peak expiratory flow (FEV1/PEF) > 8.5 ml per litre per minute, ratio of maximal expiratory and inspiratory flow at 50% (MEF50/MIF50) > 1 and peak inspiratory flow (PIF) < 3 litres per second. These three criteria represent different aspects of an extrathoracal upper airway obstruction.

In the presence of such an obstruction, flow remains relatively small during the first part of the forced expiration. This results in a low peak

expiratory flow (PEF). The integrated flow during the first second of forced expiration is much less sensitive to changes in PEF, which leads to a nearly normal forced expiratory volume in 1 sec (FEV1) [14]. The net result is an increased FEV1/PEF ratio.

Inspiration leads to a lowering of the intraluminal pressure at the site of an obstruction. Since the obstruction is not anatomically fixed, this leads to an increase of the obstruction: maximal inspiratory flow at 50% (MIF50) decreases. The reverse process during expiration leads to an increased maximal expiratory flow at 50% (MEF50). The MEF50/MIF50 ratio is therefore increased in UAO. The same mechanism leads to a relatively low peak inspiratory flow during forced inspiration.

Because of the complex interactions of the mechanisms leading to these disturbances and the interindividual variation which is already present in normal controls, the definition of UAO is in a certain way arbitrary. When one ignores one abnormal score, 9 of our patients have two or more abnormal scores and can thus be considered to have signs of UAO.

The mentioned criteria can be considered as quantitative indices of UAO. The pattern of the flow-volume-curves can give a qualitative indication whether or not an UAO is present.
Vincken et al. [165] have classified for this purpose the curves into three types (see fig. 6.2):

1. Normal type
2. Type A. This consists basically of a normal pattern with superimposed de- and accelerations of the flow, either regular or irregular, which can be traced to tremor. Although the overall pattern is normal, often also lowered maximal flows are found.
3. Type B, which consists basically of a rounding off of the expiratory phase and a delayed appearance of the peak. In addition irregular flow changes occur frequently in the inspiratory phase.

In our group 82% of those with an abnormal curve had type B (n=16), while only 22% of Vincken et al.'s patients had this type and 78% type A. This discrepancy is probably caused by patient selection because a large proportion of their patients had tremor as a prominent symptom and also patients with only essential tremor were included.

The rounding of and the delayed appearance of the peak of type B can be explained by a decrease of the maximal effort, necessary for the flow-volume-curve, and by UAO. The values for the effort dependent peak expiratory and inspiratory flow, as discussed above, are significantly below normal. Although this decrease can also be explained by UAO, the occurrence of this pattern also in cases with only a slightly lowered peak expiratory and

inspiratory flow and the absence of a marked plateau in the curves points to "muscle weakness" as the basic mechanism. The markedly lowered maximal static mouth pressures at residual volume and total lung capacity provide additional evidence. Also hypokinesia will play a role in that it will lead to a less explosive effort and so cause a shift of the peak appearance to lower volume levels.

In our group 4 patients had a type A-curve and all four had two abnormal parameters of the three discussed above (PIF, FEV1/PEF, MEF50/MIF50). This supports the concept of Schiffmann [149] and Vincken et al. [165], that a type A-curve in indicative of UAO. The very presence of deceleration of airflow indicates a narrowing. The flattened slope of the expiratory phase is additional evidence of UAO.

Since de- and accelerations of airflow are regular, it can be assumed that they are caused by tremor of the muscles of the upper airway. Aside from the tremor, obstruction can also be caused by the poor co-ordination of the muscles of the ventilatory system. Muscles of the upper airways have to be in phase with the muscles of the thoracic cage. It can be assumed that the extrapyramidal system plays a role in this co-ordination. Electromyography of the laryngeal muscles [51] and videorecorded fiberoptic endoscopy of the upper airways [165] lend some support to this hypothesis.

In patients with a type B-curve the additive effects of UAO and "muscle weakness" are more difficult to separate due to the intrinsic qualitative nature of the derived parameters. We believe however that "muscle weakness" is the main determinant.

In our group we did not find any signs of increased parasympathetic activity or of chronic obstructive pulmonary disease. If the latter were the case, the ratio of the maximal expiratory and inspiratory flow at 50% would have been considerably smaller than 1 and the tail of the expiratory part of the flow-volume-curve depressed.

We conclude that there exist in relatively severe PD abnormalities of pulmonary function. They consist of a decreased effective strength of the respiratory muscles and of upper airway obstruction. This can lead to retention of secretion and possible subsequent infection. Due to patient selection none of our patients had any pulmonary complaints. That the pulmonary abnormalities remain subclinical can be explained by the fact that these patients are too disabled to perform any activities in which such abnormalities can manifest themselves. Since pulmonary function testing is relatively easy, non-invasive and sensitive it can be a valuable tool to detect these abnormalities.

CHAPTER 7

MUSCLE STRENGTH IN PARKINSON'S DISEASE

Introduction

James Parkinson named the syndrome he described the Shaking palsy, thereby emphasising two of the main symptoms: tremor and loss of muscle strength [122]. In the two centuries following this description many aspects of Parkinson's disease (PD) have been studied, but muscle strength has, somewhat surprisingly, received scant attention. To date two studies have been published, one reporting significant loss of muscle strength [83] and the other reporting normal muscle strength [146]. In our study on respiratory function in PD (chapter 6), loss of muscle strength seemed to explain part of the abnormalities found. To evaluate if loss of strength in muscles of the neck and the limbs was a significant feature, in addition to the already found decrease of strength in respiratory muscles, the present study was undertaken.

Patients and methods

Patients with Parkinson's disease were selected randomly from the out-patient clinic. All patients were optimally treated with amantadine, anti-cholinergics, levodopa, bromocriptine or a combination of these drugs. Exclusion criteria were dementia, severe enough to interfere with understanding of the examination or the presence of any concomitant disease which might influence muscle strength. All patients were scored using the Hoehn & Yahr scale [69], Webster scale [170] and the Northwestern University disability scale [29] (NUDS). All patients with PD with disease severity Hoehn & Yahr scale I (unilateral disease) were suffering from left-sided PD. Patients characteristics are listed in table 7.1. No effort was made to separate patients on the basis of the most severe symptoms, since especially in the more severely disabled patients both tremor and bradykinesia/rigidity were prominent.

Controls were selected to match patients with PD, with regard to age and length. No controls were suffering from disease of the central nervous system nor of any disease which might influence muscle strength. Characteristics of controls are also included in table 7.1.

Table 7.1: Patient characteristics, standard deviations between parentheses

	Controls	Patients with Parkinson's disease				
		All	Hoehn & Yahr groups			
			I	II	III	IV
Number	8	44	7	12	15	10
Women/men	5/3	29/15	6/1	10/2	10/5	3/7
Mean age	61.3	65.5	59.3	68.2	64.0	69.1
	(8.1)	(8.3)	(9.8)	(6.9)	(6.9)	(7.2)
range	41 to 68	44 to 79	44 to 72	51 to 76	50 to 74	56 to 79
Mean length (cm)	169 (12)	163 (9)	160 (10)	161 (8)	166 (10)	163 (8)
main affected side						
left	–	11	7	3	1	0
right	–	5	0	2	2	1
both	–	28	0	7	12	9
Webster score	–	12.0	6.3	8.5	12.9	19.0
		(5.7)	(3.1)	(3.0)	(3.8)	(4.2)
NUDS	–	39.4	46.1	43.8	40.1	28.5
		(8.4)	(3.2)	(4.9)	(5.0)	(8.3)

All patients with PD and controls were right handed. Both groups were tested for each item at least three times, and sometimes four or five times, if it appeared that the patient did not perform adequately or possibly had misunderstood the test. Each time the subject was exhorted by the examiner to perform maximally. For analysis only the maximal score on each item was used. The following tests were performed both left and right, except item 5:

1. Quadriceps muscle. Isometrically with the knee in an angle of 90 degrees and isokinetically with a constant angular velocity of 60 degrees per second. Use was made of the dynamometer developed by Pronk and Niesing [129].
2. Grip strength for each hand. Four different grip distances were used: 3, 4, 5 and 6 centimeters.
3. Pinch grip, i.e.: strength for the thumb in opposition to the forefinger, middle finger, ring finger and little finger respectively.
4. Lateral pinch grip, i.e with the thumb in opposition to the other fingers simultaneously.
5. Isometric flexion of the neck. The trunk was fixed in a upright position, while the head was pressed against a horizontal bar.

The strength of the isokinetic quadriceps exercise was recorded in Newtonmeter. All other measurements are in kilogram-force.

Statistics

For statistical analysis, use was made of means, standard deviations and 95%-confidence-interval determination of means and differences of means. For correlation analysis, Pearson and Spearman rank correlation were applied.

Results

For all controls and patients examined, results with regard to grip strength are independent of the grip-distance used. Therefore, only the results for 1 distance (= 5 cm) will be discussed. The same applies for the pinch grip with the thumb opposed to forefinger, middle finger, ring finger and little finger. Only the results of the thumb vs forefinger will be discussed.

Comparison of controls with all patients with PD (table 7.2): controls performed better than patients with PD on all tests ($p < 0.05$). The 95%-confidence-interval of the difference of the means between controls and patients is always positive.

Table 7.2: Comparison of controls with all patients combined

	Side	PD	Controls	95%-confidence-interval of the difference between means
Quadriceps isometrically	r	82.0 (38.8)	148.5 (44.8)	35.8 to 97.2
	l	71.3 (37.0)	144.4 (50.8)	42.8 to 103.4
Quadriceps isokinetically	r	65.0 (41.7)	129.4 (46.3)	31.7 to 97.1
	l	59.1 (38.2)	115.6 (40.2)	26.9 to 86.3
neck flexion		6.1 (3.1)	12.3 (2.6)	3.9 to 8.5
grip strength, dist. 5 cm	r	23.6 (9.8)	34.1 (10.1)	2.9 to 18.1
	l	19.8 (9.5)	31.2 (10.9)	3.9 to 18.9
pinch grip thumb vs dig 2	r	4.9 (1.4)	6.5 (0.9)	0.6 to 2.6
	l	4.0 (1.4)	6.3 (1.0)	1.3 to 3.3
lateral pinch grip	r	7.3 (2.3)	9.2 (2.1)	0.1 to 3.7
	l	6.8 (2.2)	8.8 (1.9)	0.3 to 3.7

Correlation analysis for patients with PD (table 7.3): Significant correlations were found between scores on the Webster and NUDS scales and the score for the quadriceps, isometrically and isokinetically, and for flexion of the neck. However, correlations were rather weak, maximum 0.47. For all other muscles no meaningful correlations were found.

Correlation-co-efficient for all muscle strength items with regard to age were significant, but weak, and ranged from -0.23 to -0.42.

Table 7.3: Correlation-coefficients for patients between age, NUDS, Webster-score and muscle strength. * significant correlation $p < 0.05$

	Side	Webster	NUDS	Age
Quadriceps/isometrically	r	-0.32*	0.34*	-0.42*
	l	-0.32*	0.35*	-0.35*
Quadriceps/isokinetically	r	-0.47*	0.46*	-0.42*
	l	-0.38*	0.38*	-0.37*
Flexion of the neck		-0.25	0.27	-0.23
grip strength, distance 5 cm	r	-0.07	0.14	-0.35*
	l	-0.04	0.13	-0.23
pinch grip, thumb vs dig 2	r	0.02	0.12	-0.38*
	l	0.03	0.00	-0.33*
lateral pinch grip	r	-0.00	0.09	-0.40*
	l	0.11	-0.09	-0.30*

Comparison of patients with PD with disease stage Hoehn & Yahr I, II, III and IV. (tables 7.4 to 7.8): In general no significant differences were found on all items between the different Hoehn & Yahr groups. In fact performances on most items were remarkably constant, especially for the muscles of the hand and the forearm. For both quadriceps muscles there is a non-significant, downward trend, across the different Hoehn & Yahr groups.

Comparison of left and right side in patients with PD with Hoehn & Yahr stage I: (tables 7.4 to 7.8): In general better scores on all items for the right side when compared with the left, but differences did not reach significance.

Comparison of controls with PD-patients with Hoehn & Yahr stage I. (tables 7.4 to 7.8): In general controls performed better than PD-patients on all items, but differences were significant ($p < 0.05$) only for quadriceps/isometrically (both sides), for flexion of the neck, and for some items of grip strength and pinch grip.

Table 7.4: Isometric and isokinetic quadriceps strength for controls and patients per Hoehn & Yahr group

Group	Side	Mean	SD	95%-confidence-interval
Quadriceps / isometric				
Controls	R	148.5	44.8	117.5 to 179.5
	L	144.4	50.8	109.1 to 179.7
HY I	R	93.5	30.4	71.0 to 116.0
	L	71.6	27.1	51.6 to 91.6
HY II	R	87.4	41.1	64.1 to 110.7
	L	81.6	36.7	60.8 to 102.4
HY III	R	78.8	37.6	54.8 to 97.8
	L	71.1	35.0	53.5 to 88.7
HY IV	R	72.6	45.4	44.4 to 100.8
	L	59.2	46.9	30.2 to 88.2
Quadriceps / isokinetic				
Controls	R	129.4	46.3	97.3 to 161.5
	L	115.6	40.2	87.8 to 143.4
HY I	R	89.1	37.8	56.1 to 112.1
	L	65.4	32.6	41.3 to 89.5
HY II	R	77.2	37.9	55.8 to 98.6
	L	74.1	32.5	55.7 to 92.5
HY III	R	53.4	39.4	33.4 to 73.4
	L	50.3	37.6	31.3 to 69.3
HY IV	R	54.3	48.6	24.1 to 84.5
	L	49.9	46.9	20.9 to 78.9

Table 7.5: Neck flexion strength for controls and patients per Hoehn & Yahr group

Group	Mean	SD	95%-confidence-interval
Controls	12.3	2.6	10.5 to 14.1
HY I	6.2	2.5	4.4 to 8.0
HY II	6.3	3.2	4.7 to 8.3
HY III	6.4	3.4	4.6 to 8.2
HY IV	4.8	2.8	3.0 to 6.6

Table 7.6: Grip strength (distance 5 cm) for controls and patients per Hoehn & Yahr group

Group	Side	Mean	SD	95%-confidence interval
Controls	R	34.1	10.1	27.0 to 41.2
	L	31.2	10.9	23.6 to 38.8
HY I	R	24.1	8.5	17.8 to 30.4
	L	17.5	6.4	12.8 to 22.2
HY II	R	23.4	8.6	8.5 to 28.3
	L	21.3	9.4	16.0 to 26.6
HY III	R	25.0	11.2	19.3 to 30.7
	L	20.8	11.5	14.9 to 26.7
HY IV	R	21.5	10.8	14.8 to 28.2
	L	18.1	9.0	12.6 to 23.6

Table 7.7: Pinch grip, for thumb opposed to forefinger, for controls and patients per Hoehn & Yahr group

Group	Side	Mean	SD	95%-confidence-interval
Controls	R	6.5	0.9	5.9 to 7.1
	L	6.3	1.0	5.5 to 7.1
HY I	R	5.0	1.3	4.0 to 6.0
	L	4.0	1.3	3.0 to 5.0
HY II	R	4.8	1.4	4.0 to 5.6
	L	4.0	1.0	3.4 to 4.6
HY III	R	4.8	1.5	4.0 to 5.6
	L	4.1	1.7	3.3 to 4.9
HY IV	R	5.0	1.3	4.2 to 5.8
	L	3.9	1.4	3.1 to 4.7

Table 7.8: Lateral pinch grip for controls and patients per Hoehn & Yahr

Group	Side	Mean	SD	95%-confidence-interval
Controls	R	9.2	2.1	7.6 to 10.8
	L	8.8	1.9	7.4 to 10.1
HY I	R	7.0	1.7	5.6 to 8.4
	L	6.1	2.0	4.5 to 7.7
HY II	R	7.4	2.0	6.2 to 8.6
	L	7.0	1.7	6.0 to 8.0
HY III	R	7.5	2.9	6.1 to 8.9
	L	6.5	2.5	5.3 to 7.7
HY IV	R	7.2	2.5	5.6 to 8.8
	L	7.3	2.5	5.7 to 8.9

Discussion

Our results lead us to conclude that James Parkinson choose the name "shaking palsy" appropriately [122]: in all muscles examined patients with PD performed significantly worse when compared with controls. Even in patients with unilateral, left-sided PD, the supposedly normal right side performed less then the right side in normal controls, although not always significantly.

Surprisingly there were no significant differences between scores for the severity of the disease and the several muscle strength items, except for the quadriceps muscles, but even then, correlations were weak. When the overall pattern is examined, the decrease of strength in the quadriceps and neck flexion muscles seems to be greater, than the decrease of the muscles of the hand and forearm.

Two reports on muscle strength in PD have been published. Saltin et al. [146] compared an ill-defined group of 6 PD-patients with normal age-matched controls. They did not find any differences in measurements of maximal voluntary contraction of knee and ankle muscle for isometric strength.

Koller and Kase [83] examined 21 PD-patients and 21 normal controls. Investigated were handgrip strength and isometric strength of the wrist, arm and knee bilaterally. They did not find differences with regard to hand grip strength, but maximum isotonic muscle strength was significantly decreased bilaterally for both flexion and extension of the wrist, upper extremity and the knee in PD. In patients with unilateral tremor handgrip strength was decreased when compared to patients with unilateral rigidity. They concluded

that patients with PD have no difficulties with isometric muscle strength testing as opposed to isotonic muscle strength testing. In our study both isometric and isokinetic muscle strength was tested and in both respects patients with PD were worse than controls. The differences between our study and the study of Koller and Kase [83] are probably due to patients selection, since in our study a larger number of patients with more severe PD were included.

Our results can be considered a confirmation of our findings with regard to pulmonary function (chapter 6). As explained earlier, part of the pulmonary function disturbances were probably caused by muscle weakness.

Exactly why there should be a decrease of muscle strength in Parkinson's disease is unclear. Perhaps some explanation can be derived from electrophysiological studies [39]. These have demonstrated that cells in the pars compacta of the substantia nigra, in animals, show no clear phasic modulation of discharge during discrete movements of individual parts. This indicates a "tonic" role of this structure in modulating the striatum. Presumably this loss of tonic activity, leads to a down-regulating of the final motor pathway and thereby to a decrease of muscle strength. A similar situation is encountered in cerebellar syndromes [70].

SUMMARY

Parkinson's disease is a slowly progressive disease: the cause is still unknown. The symptoms can range from tremor, rigidity, bradykinesia, postural instability and autonomic dysfunction to cognitive disturbances. The pathophysiological mechanism for most of these symptoms is the degeneration of the nigrostriatal tract, leading to a shortage of dopamine in the striatum. Levodopa given orally, can be an effective drug for most of these symptoms, but not all symptoms respond equally. In addition, the progression of the disease continues in spite of levodopa treatment. Longterm levodopa treatment can lead to considerable side-effects.

In the early phases of the disease amantadine and anti-cholinergics are to be preferred above levodopa. However, anticholinergics do have a reputation of side-effects with regard to cognitive function, since acetylcholine is an important neurotransmitter for systems involved in memory functions.

Chapter 1 describes the results of an investigation into the effect of anticholinergics, as compared to amantadine, on cognitive function. Scores on a battery of neuropsychological tests were the same for both groups and were not different from those of a group without any antiparkinsonian drugs or with selegiline only.

Depending on the criteria used, 10 to 15% of the patients with Parkinson's disease have dementia. The results come from cross-sectional studies. Longitudinal studies have hardly been performed. Chapter 2 presents the results of an one year follow-up study of 18 patients with regard to cognitive function. An effort was made to keep medication constant. Non of the patients deteriorated in cognition.

Chapter 3 presents the results of a study of spatial orientation. To test spatial orientation the Rod Orientation Test of De Renzi was used, because this is a relatively simple test and because it tests orientation in three dimensions. The popular Line Orientation Test of Benton explores only two dimensions, besides: this test is specific but not very sensitive for detection of disorders of spatial orientation. 55 patients were examined, all without levodopa. Only 1 patient had normal results.

In chapter 4 the effect of levodopa on spatial disorientation is evaluated. 22 of 55 patients were treated for three or more months with levodopa, but

this did not result in improvement of spatial disorientation. As discussed in chapters 3 and 4 it is not likely that disturbances in spatial orientation in Parkinson's disease is the result of dysfunction of the striatum or the fronto-striatal loop.

One striking symptom of Parkinson's disease is the lack of emotional expression, sometimes interpreted by the uninitiated as an indication of depression. In fact: a lot of studies indicate that depression is a frequently occurring disorder in Parkinson's disease. The diagnosis and quantification of depression in cross-sectional surveys usually relies on the use of scales like the Beck's Depression Inventory and the Montgomery-Åsberg scale. These scales were originally developed for purely psychiatric disorders. In chapter 5 these scales are evaluated for three groups of patients, two with a somatic disorder - i.e. Parkinson's disease and rheumatoid arthritis - and one with only depression as diagnosed with DSM-III-R criteria. Somatic items in depression scales lead to a distortion of sumscores and in fact to an overdiagnosis of depression in somatically ill patients. Depression does occur in patients with Parkinson's disease, but both the Beck's Depression Inventory and the Montgomery-Åsberg-scale are not suitable for quantification of this depression.

Disturbances of motor function are prominent in Parkinson's disease. Breathing and ventilation are also motor functions and in chapter 6 the nature of disturbances in ventilatory function is examined in a group of 31 patients without any respiratory complaint. Flow-volume-curves, spirometry and maximal static mouth pressures were analysed. In 9 patients signs of upper airway obstruction were found, while abnormalities in 16 patients were caused by weakness of the respiratory muscles. It is perhaps surprising that non of the patients complained of respiratory problems. An explanation might be, that most patients were to invalidated to perform activities which might result in breathlessness. Our findings do offer an explanation for the relatively high risk of pulmonary stasis and subsequent bronchopneumonia, an important cause of death in Parkinson's disease.

Muscle weakness was an important finding in our studies on ventilatory function. Surprisingly, quantitative data on muscle strength in Parkinson's disease - also known as shaking palsy! - are hardly available. Chapter 7 presents the results with regard to 44 patients and 8 controls. Both axial muscles (neck flexion) and muscles of arms and legs (grip strength and quadriceps) were examined. In all muscles examined a clear weakness was found.

Even in patients with unilateral Parkinson's disease, the supposedly normal side performed badly. No significant correlation was found with the severity of the disease, except for quadriceps strength.

SAMENVATTING

De ziekte van Parkinson is een langzaam progressieve aandoening zonder duidelijke oorzaak. De symptomatologie omvat tremor, rigiditeit, bradykinesie, houdingsinstabiliteit, autonome verschijnselen, en daarnaast ook cognitieve functie-stoornissen.

Het ontstaan van deze symptomen wordt voor een belangrijk deel verklaard door degeneratie van de nigrostriatale banen en het daardoor optredend tekort aan dopamine in het striatum. Door middel van levodopa substitutie therapie is het mogelijk dit tekort aan dopamine voor een belangrijk deel te compenseren. De progressie van de aandoening wordt er evenwel niet door geremd en bovendien blijken niet alle symptomen evengoed behandelbaar te zijn met levodopa. Daarnaast is gebleken dat deze therapie op langere termijn ook tot specifieke bijwerkingen kan leiden die voor de patiënt zeer invaliderend kunnen zijn.

Dit is een belangrijk argument om in de beginfase niet direct te starten met levodopa, maar eerst middelen als amantadine en anticholinergica te geven. Anticholinergica, in tegenstelling tot amantadine, hebben evenwel de reputatie nadelig te werken op het cognitieve functioneren van de patiënt, daar acetylcholine een belangrijke rol speelt bij systemen die betrokken zijn bij het geheugen. In hoofdstuk 1 worden de resultaten besproken van een onderzoek naar het effect van anticholinergica en amantadine op het cognitief functioneren bij Parkinson patiënten. Beide patiënten-groepen behaalden op een breed scala van testen vergelijkbare scores en bovendien waren de resultaten niet verschillend ten opzichte van een groep patiënten die geen medicijnen kreeg. Anticholinergica blijken derhalve bij de onderzochte patiënten geen nadelig effect op het cognitief functioneren te hebben.

Afhankelijk van de gebruikte criteria, blijkt bij 10 tot 15% van de patiënten met de ziekte van Parkinson dementie voor te komen. Deze getallen zijn afkomstig uit onderzoek waarbij patiënten eenmalig onderzocht werden. Over het beloop in de tijd is weinig bekend. In hoofdstuk 2 wordt nagegaan of cognitie, zoals gemeten met een breed scala van neuropsychologische testen, verandert, c.q. verslechtert. 18 patiënten werden na een jaar voor een tweede maal onderzocht. In dat jaar werd getracht de medicatie zoveel mogelijk constant te houden. Zowel de resultaten per patiënt als de resultaten voor de

gehele groep, bleken na 1 jaar niet significant veranderd te zijn. Dit maakt het onwaarschijnlijk dat langdurig gebruik van medicatie of de progressie van de aandoening leiden tot een verslechtering van het cognitief functioneren bij de ziekte van Parkinson.

In hoofdstuk 3 worden de resultaten besproken van een onderzoek naar ruimtelijke oriëntatie stoornissen. Voor het meten van ruimtelijke oriëntatie werd de Rod Orientation Test van De Renzi gebruikt, omdat dit een betrekkelijk eenvoudige test is waarbij de drie-dimensionale ruimtelijke oriëntatie getest wordt. De veelgebruikte Line Orientation Test is slechts twee-dimensionaal en bovendien zijn de resultaten moeilijk te quantificeren. 55 patiënten werden onderzocht, allen zonder levodopa substitutie therapie. Slechts 1 patiënt bleek geen ruimtelijke oriëntatie stoornissen te hebben.

In hoofdstuk 4 wordt het effect van levodopa op de ruimtelijke oriëntatie stoornissen besproken. Het blijkt dat deze stoornissen bij de 22 onderzochte patiënten niet verbeteren na gebruik van minimaal 3 maanden levodopa. Op grond van de resultaten, zoals besproken in hoofdstuk 3 en 4, is het aannemelijk dat de stoornissen niet direct zijn terug te voeren op stoornissen in het striatum of de fronto-striatale loop.

Eén van de opvallende verschijnselen van de ziekte van Parkinson is het maskergelaat. Dat leidt er nogal eens toe dat patiënten somber over komen. In de literatuur wordt depressie vaak genoemd als een veel voorkomende aandoening bij de ziekte van Parkinson. Deze depressie wordt dan vastgesteld en gequantificeerd d.m.v. depressie-schalen, schalen die wel gevalideerd zijn voor patiënten zonder somatische aandoeningen, maar niet voor patiënten waarbij somatische stoornissen, zoals de ziekte van Parkinson, een zeer grote rol spelen. In hoofdstuk 5 wordt aangetoond, dat twee veel gebruikte depressie-schalen - de Beck's Depression Inventory en de Montgomery-Åsberg-schaal - niet zonder meer toepasbaar zijn bij twee vergelijkbare "somatische" aandoeningen, te weten de ziekte van Parkinson en rheumatoide arthritis. De scores per vraag worden onderling vergeleken en afgezet tegen scores bij patiënten met een depressie in engere zin. Somatische vragen leiden tot een misleidend hoge score, waardoor de depressieschaal meer een indruk geeft van de somatische stoornissen en minder van de feitelijke stemming. Hoewel niet ontkend kan worden dat depressie voorkomt bij Parkinson patiënten, leidt het gebruik van genoemde depressie-schalen wel tot een sterk vertekenend beeld.

Stoornissen in de motoriek zijn overheersend in het klinisch beeld bij Parkinson-patiënten. Of deze ook leiden tot stoornissen in de ademhaling c.q. ventilatie, is het onderwerp van hoofdstuk 6. 31 patiënten met een betrekkelijk

ernstige vorm van Parkinson, allen zonder klachten van kortademigheid, werden onderzocht m.b.v. spirometrie, bepaling van de flow-volume-curve en de maximale statische druk bij de mond. Bij 9 patiënten werden er aanwijzingen gevonden voor een bovenste luchtweg obstructie, terwijl er bij 16 hoofdzakelijk sprake bleek te zijn van een verminderde kracht. Geen van de onderzochte patiënten klaagden over kortademigheid. Dat de gevonden afwijkingen subklinisch bleven is vermoedelijk voor een groot deel toe te schrijven aan het feit dat de patiënten motorisch dermate gehandicapt zijn, dat die activiteiten waarbij de kortademigheid manifest zou kunnen worden, eenvoudigweg niet meer ontplooid kunnen worden. Het geeft wel een verklaring voor het verhoogd risico op pulmonaire stase en vervolgens bronchopeumonieën, een belangrijke doodsoorzaak bij de ziekte van Parkinson.

Verminderde kracht bleek een belangrijke bevinding bij het ademhaling onderzoek. Quantitatieve gegevens over de spierkracht bij de ziekte van Parkinson - ook wel bekend als paralysis agitans ! - zijn evenwel nauwelijks voorhanden. In hoofdstuk 7 worden de resultaten besproken van een onderzoek naar de spierkracht bij 44 patiënten en 8 controle personen. De spierkracht van zowel axiale musculatuur (nekflexie) als extremiteitsmusculatuur (knijpkracht en quadriceps) blijkt bij patiënten duidelijk verminderd. Ook bij patiënten met een halfzijdige Parkinson blijkt de "goede" kant duidelijk aangedaan te zijn. Verrassend genoeg werd er geen duidelijke correlatie met de ernst van de aandoening gevonden, behalve voor de kracht in de quadriceps spier.

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ACKNOWLEDGEMENTS

I would like to thank several people, without whose help this thesis would have remained but a draft and an incoherent lot of files.

Jan Meerwaldt guided me in my first efforts to understand Parkinson's disease and made me understand what science is all about. It is sad, that he could not witness the completion of this thesis.

Arthur Staal, my teacher in neurology, always asked the right questions and demanded an answer in plain clear-cut language. His debunking of neurology has proved very valuable for me.

Frans van der Meché, Jan Bogaard, Frans van Harskamp, Hugo van Dongen and Han Nieuwenhuis were pleasant and stimulating in the joint investigation of several topics.

Wim van der Putten receives my thanks for giving simple and understandable answers to fuzzy phrased statistical questions and Hugo Duivenvoorden for explaining to me the statistics of testing.

Jeannette van der Kooij turned a depressive subject in a happy one, and without her untiring efforts an important chapter of this thesis would not have been completed.

Gert-Jan de Jong lent a friendly ear to my several early hypotheses and co-authored some publications. Cees van Donselaar receives thanks for all his critical comments on how to manage results.

All the residents, past and present, should realise, that this thesis is ultimately their result, since they talked all the patients into the studies which together form this thesis. Fortunately this proved to be not so difficult, since all patients were very motivated.

Finally: Anneke Geertman, co-author of an important part of my curriculum, demonstrated rather effectively, that writing a thesis does not necessarily leads to a chaotic home life. Thanks.

LIST OF PUBLICATIONS

1. A. Hovestadt, T.C.A.M. van Woerkom, R.E.M. Hekster
   Het gebruik van de CT-scan in de psychiatrie: een retrospectief onderzoek bij 226 psychiatrische patiënten
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Respiratory parameters in Parkinson's disease
Geriatric Medicine To Day - In press

CURRICULUM VITAE

De schrijver van dit proefschrift werd op 9 mei 1954 te Hooge en Lage Zwaluwe geboren. Hij bezocht de Openbare Scholengemeenschap Nieuwediep te Den Helder, alwaar hij in 1973 het gymnasium β diploma behaalde. Aansluitend begon hij aan de studie geneeskunde, aan de Rijksuniversiteit te Groningen. In 1980 werd hij tot arts bevorderd. Daarna was hij twee jaar werkzaam als assistent op de afdeling neurologie van het St. Elisabeth Hospitaal te Curaçao. Op 1 januari 1983 begon hij aan de specialisatie tot neuroloog, met een stage in het Psychiatrisch Centrum Rosenburg, te Loosduinen (opleider Drs. P.J. Stolk). Vanaf 1 april 1984 was hij werkzaam op de afdeling neurologie van het Academisch Ziekenhuis Dijkzigt te Rotterdam (opleider: Prof. Dr. A. Staal). Op 1 april 1987 werd hij ingeschreven in het specialistenregister als neuroloog. Kort daarna volgde hij de opleiding voor de aantekening klinische neurofysiologie, welke 1 augustus 1988 behaald werd. Van 1 augustus 1988 tot 1 mei 1990 was hij als neuroloog verbonden aan de Daniel den Hoed Kliniek te Rotterdam en tevens als staflid, vanwege de Parkinson Patiënten Vereniging, aan het Academisch Ziekenhuis Dijkzigt. Sedert 1 mei 1990 is hij als staflid verbonden aan het ziekenhuis de Lichtenberg en als buitengewoon staflid aan het St. Elisabeth ziekenhuis, beiden te Amersfoort. Tevens is hij sedert die datum werkzaam als consulent-neuroloog op Psychiatrisch Centrum Zon en Schild, Amersfoort, en het huis voor geestelijk gehandicapten Sterrenberg, Huis ter Heide.

Production: Eburon Publisher Delft
Word processing and lay-out: Book Factor Delft
Cover design: W. Smetek