PROGNOSTIC FACTORS ASSOCIATED WITH DISEASE PROGRESSION IN PARKINSON'S DISEASE

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ABSTRACT

This thesis examined the factors correlated with rapid and benign progression of disease in a group of 1452 Parkinson's disease (PD) patients. The data were collected in a movement disorders clinic at the Royal University Hospital, University of Saskatchewan run by Dr. Alex Rajput and Dr. Ali Rajput. This data is a clinical dataset of PD patients collected from 1970 through to February, 2005. This was a retrospective cases-only study, with anticipated analytical follow-up if any correlations were detected between progression type of PD and the many independent variables available in the dataset.

Rapid progression was defined as those subjects who reached Hoehn and Yahr stage 3 within three years or H&Y stage 4 or 5 within five years. Subjects who remained in Hoehn and Yahr stage 1 or 2, ten years after onset of disease, were defined as having benign progression. The study analyzed demographic and clinical findings at first visit to this clinic associated with rapid and benign progression of PD.

Analysis revealed that, at first clinic visit, benign progression was positively associated with disease duration (OR=1.41; 95% CI 1.27, 1.57), male sex (OR=3.23; 95% CI 1.70, 6.16), and current smoking habit (OR=2.33; 95% CI 0.67, 8.11). Benign progression was negatively associated with older age of onset (OR=0.36; 95% CI 0.25, 0.50), past history of smoking (OR=0.46; 95% CI 0.24, 0.89), current or past use of levodopa (OR=0.45; 95% CI 0.21, 0.98), and mild to severe rigidity (OR=0.43; 95% CI 0.23, 0.80).

Analysis also revealed that, at first clinic visit, rapid progression was positively associated with older age of onset (OR=2.45; 95% CI 1.80, 3.33) and mild to severe rigidity (OR=1.73; 95% CI 1.02, 2.94). Rapid progression was negatively associated with disease duration (OR=0.52; 95% CI 0.44, 0.62), male sex (OR=0.58; CI 0.35, 0.95), and mild to severe resting tremor (OR=0.47; CI 0.28, 0.77).

The results of this study indicate that age of onset, disease duration, male sex, and rigidity are good potential predictors of disease progression in PD because they have opposite associations with rapid and benign progression. History of levodopa use was negatively associated with benign progression and as such may be good indicator of non-benign progression. Although previous studies found no predictive value for smoking history, the current study reported a unique association between smoking history and benign progression. Past smoking history was negatively associated with benign progression. While there was a positive association with current smoking history, the result was not statistically significant. Resting tremor was negatively associated with rapid progression and as such may be a good indicator of non-rapid progression.

Disease characteristics collected at first clinic visit are useful in predicting the course of progression of PD. With more rapid progression of PD closer and more frequent follow-up of patients may be necessary.

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May all of you find the peace and happiness you so deserve.

DEDICATION

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Table of Contents

PERMISSION TO USE i

ABSTRACT ii

ACKNOWLEDGEMENTS iii

DEDICATION iv

TABLE OF CONTENTS v

LIST OF TABLES vii

LIST OF FIGURES viii

ABBREVIATIONS ix

1 Introduction

1.1 Rationale of the Study 1
1.2 Purpose of the Study 2
1.3 Research Objectives 2

2 Literature Review

2.1 Parkinsonism and Parkinson's Disease 4
2.2 Applicable Neurophysiology 5
2.3 The Pathophysiology of Parkinson's Disease 5
2.4 Epidemiology of Parkinson's Disease 6
2.4.1 Prevalence 6
2.4.2 Incidence 7
2.4.3 Mortality 7
2.5 Risk Factors for Parkinson's Disease 8
2.5.1 Age & Age of Onset 8
2.5.2 Sex Differences 9
2.5.3 Lifestyle Risk Factors 10
2.5.4 Occupational Risk Factors 11
2.5.5 Multi-Factorial Models 12
2.6 Pharmacological Treatment 13
2.7 Progression of Disease 13
2.7.1 Tools to Predict Progression 13
2.7.2 Defining Progression of PD 15
2.7.3 Prognostic Factors that predict progression of PD 16

2.8 Chapter Summary 18

3 Methodology

3.1 Study Location 19
3.2 Collected Data 19
3.2.1 The Clinical Dataset 19
3.2.2 Variable Selection 20
3.2.3 Ethical Approval 22
3.3 Methods of Analysis 24
3.3.1 Data Entry 24
3.3.2 Data Analysis 24

4 Results

4.1 Clinical Characteristics of Sample Population 27
4.2 Distribution by Progression 32
4.3 Benign Progression 36
4.3.1 Univariable Analysis for Benign Progression 36
4.3.2 Multivariable Logistic Regression for Benign Progression . . . 39
4.4 Rapid Progression 40
4.4.1 Univariable Analysis for Rapid Progression 40
4.4.2 Multivariable Logistic Regression for Rapid Progression 43

5 Discussion

5.1 Characteristics of Sample Population 45
5.2 Observations on Univariable Analysis. 48
5.3 Benign Progression 48
5.4 Rapid Progression 51
5.5 Comparison of the Benign and Rapid Models 53
5.6 Strengths of this Study 53
5.7 Potential Limitations of this Study 54

6 Conclusion 56

7 References 58

8 Appendices

A Ethics Application Letter of Approval 67

List of Tables

2.1 Comparison of Original and Modified Hoehn and Yahr Scales 15

3.1 Independent Variables Available in the Database 21

3.2 Independent Variables Used in Data Analysis 23

.

4.1 Demographic and Clinical Characteristics at First Visit 28

4.2 Use of Anti-Parkinson Medications and Reported Motor Fluctuations at First Visit 31

4.3 Motor Function Assessment at First Visit 33

4.4 Other Neurological Findings at First Visit 34

4.5 Univariable Analysis of Significant Independent Variables for Benign Progression 37

4.6 Final model from Multivariable Analysis for Benign Progression 40

4.7 Univariable Analysis of Significant Independent Variables for Rapid Progression 42

4.8 Final model from Multivariable Analysis for Rapid Progression 44

List of Figures

4.1 Age of Onset at First Visit for Study Population 29

4.2 Disease Duration at First Visit for Study Population 30

4.3 Flow Chart of Inclusion Criteria and Distribution by Progression 35

Abbreviations

Study Abbreviations

ADL:	Schwab & England Activities of Daily Living
D2:	Dopamine type 2 Receptors
EPD:	Early Onset Parkinson's Disease
F-Dopa:	Fluorodopa
H&Y:	Hoehn and Yahr Scale of Global Disability
IPD:	Idiopathic Parkinson's disease
MAO-B:	Monoamine Oxidase – B
MSA:	Multiple System Atrophy
OPD:	Older Onset Parkinson's Disease
OR:	Odds Ratio
PET:	Positron Emission Tomography
PD:	Parkinson's disease
PIGD:	Postural Instability, Gait Difficulty type Parkinson's Disease
PS:	Parkinsonism
PSP:	Progressive Supranuclear Palsy
QoL:	Health Related Quality of Life
SMR:	Standardized Mortality Rate(s)
SPECT:	Single Photon Emission Computerized Tomography
TD:	Tremor Dominant Parkinson's disease
UPDRS:	Unified Parkinson's Disease Rating Scale
US:	United States

Chapter 1
Introduction

1.1 Rationale of the Study

Parkinson's disease (PD) exhibits heterogeneity of progression which can influence clinical treatment and follow-up patterns. The detection of clinical features and characteristics correlated with more rapid progression of PD can help identify patients who may benefit from closer and more frequent clinical follow-up. Furthermore, the detection of clinical features and characteristics correlated with benign progression of PD can aid identification of patients who require less frequent clinical follow-up. Taken together these findings can support more specific medical care based on the speed with which PD progresses.

PD is a progressive, neurodegenerative disorder of unknown etiology [1,2] that generates the characteristic symptoms of bradykinesia, resting tremor, rigidity, and postural instability.[1] This loss of nerve cells occurs primarily in the presynaptic dopaminergic cells of the substantia nigra, with concomitant loss of dopamine neurotransmitter in the corpus striatum.[3] Degeneration of this nigrostriatal pathway decreases signal transduction to the motor cortex and thus diminishes fine tuning of motor movement.[3]

PD progresses at different rates in different patients.[4,5] A definitive profile of the characteristics of rapid and benign progression can help specify medical interventions and the frequency of clinical follow-up. There have been many Canadian and Saskatchewan studies concerning various aspects of PD, but minimal focus on progression.

This current Saskatchewan study was unique for several reasons. First, the database included 1648 Parkinsonism (PS) patients who came from all over Saskatchewan for treatment in one Movement Disorders clinic. Second, the database was a longitudinal collection of patient information from 1970 to February 2005. Third, patients were assessed, diagnosed, and treated by only one of two neurologists. The definitive diagnosis

of PD is obtained on post-mortem neuropathologic examination,[6,7] but because so few patients in this database received that definitive diagnosis, a clinical diagnosis of PD was used for this study. The clinical diagnosis of PD rests on the clinical presence of two out of three symptoms of bradykinesia, resting tremor, and rigidity.[8] It is generally accepted that clinical diagnosis be performed by a neurologist with experience in movement disorders and an interest in PD.[9] These criteria were more than adequately met with this database.

1.2 Purpose of the Study

PD is a significant health issue that currently has no cure. The per capita direct economic burden was determined, in one U.S. study, to be $6000.00 USD per year, while the hidden costs borne by families, such as lost wages and informal care, was triple the direct cost.[10] A recent study of costs associated with PD, for the province of Ontario between 1993 and 1999, reported that costs for services in several areas were significantly higher.[11] The study, which compared costs for PD patients with age-matched controls, detailed that average annual cost of physician services were 1.4 times higher, there were 1.45 times more acute hospitalizations and number of patients admitted, the length of hospital stays were 1.19 times greater, and the average annual drug costs were 3.02 times greater.[11] Those with PD experience a significant deterioration in health related quality of life (QoL) with advancing disease predominantly associated with deterioration of mobility, activities of daily living, physical and social function, and self-care.[12] This deterioration in QoL results from disease progression, not the normal aging process.[12] These studies point to the fact that, when progression of PD is more rapid, deterioration in QoL and the burden of disease will be more immediate and more profound.

The primary interest of this study was to ascertain those factors and clinical features, present at the initial visit to a clinician, associated with rate of progression of PD. The identification of how rapidly PD will progress will facilitate the equitable administration of treatment and clinical follow-up.

1.3 Research Objectives

The general research objectives of this study were as follows:

1. To determine the characteristics of the study population at their first visit.
2. To determine the correlates of benign progression in PD.
3. To determine the correlates of rapid progression in PD

CHAPTER 2

Literature Review

2.1 Parkinsonism and Parkinson's Disease

Parkinsonism (PS) is a neurological syndrome caused by many diseases and conditions. PS encompasses Idiopathic Parkinson's Disease (IPD), atypical Parkinsonism such as Multiple System Atrophy (MSA) and Progressive Supranuclear Palsy (PSP), pseudoparkinsonism where Parkinsonian signs are associated with other diseases, symptomatic parkinsonism where Parkinsonian symptoms manifest from insults such as drug abuse, and inherited forms of PD.[13] The task faced by the neurologist is to differentiate IPD from the other less common forms of PS. IPD is the most common form of PS representing 42 to 69 percent of all cases.[14] The reported relative frequency of IPD varies from study to study and depends upon how the various forms of PS are identified and evaluated.[2,14] For the remainder of this paper the use of PD will infer IPD unless otherwise indicated.

There are three commonly used levels of diagnosis: possible, probable and definitive. A diagnosis of possible PD requires the presence of two of the four cardinal features of tremor, bradykinesia, rigidity, and postural instability. These symptoms generally begin unilaterally (on one side of the body) in most PD patients.[14,15] There is also a marked and sustained response to either levodopa or dopamine agonist pharmacology.[13,14] A probable diagnosis of PD requires the presence of three of the four cardinal features, which have been present for at least three years, and a sustained response to Levodopa or dopamine agonist.[14,15] Definitive diagnosis requires postmortem pathologic confirmation of neuronal loss in the substantia nigra along with the presence of Lewy bodies in any surviving nigral neurons.[15] A detailed discussion of the pathophysiology of PD is in section 2.3 below.

2.2 Applicable Neurophysiology

Normal voluntary movement involves several areas of the brain. First, the thought of movement manifests in the frontal lobe from which signals are sent to the pre-motor cortex for sequence planning of the desired movement. Signals then pass to the motor cortex where specific muscle commands are executed. Output signals from the striatum, one of the basal ganglia, connect to the thalamus, which in turn connect to the motor cortex.[16] This feedback is responsible for fine tuning so that the enacted movement is fluid. The striatum receives input from several areas of the brain. Some of this input stimulates the striatal neurons to fire, while input from the substantia nigra, another basal ganglia, inhibits striatal neurons from firing. The neural tract that runs from the substantia nigra to the striatum, called the nigrostriatal pathway, consists of dopaminergic neurons.[16] These neurons have dopamine as a neurotransmitter. When stimulated to fire a signal, the dopaminergic neurons release dopamine in the target area of the striatum. The dopamine binds to specific dopamine receptors which in turn inhibit striatal neurons from firing.

2.3 The Pathophysiology of Parkinson's Disease

PD is a neurodegenerative disorder. Postmortem autopsy of PD reveals a decreased presence of pigmentation in the substantia nigra. This correlates with a loss of dopaminergic neurons. The rate of degeneration is eight to ten times higher than in healthy age-matched controls.[17] Some surviving neurons have eosinophilic cytoplasmic inclusions called Lewy bodies, which are glassy or translucent in appearance. Due to this dopaminergic neuronal loss there is decreased dopamine release in the striatum and subsequent decreased signal transduction to the motor cortex. This leads to diminished fine tuning of voluntary motor movement that manifests the cardinal symptoms of PD. The cardinal symptoms are: tremor while at rest, bradykinesia or slowed voluntary movements, rigidity or stiffness with passive movement of limbs, and postural instability that increases the likelihood of falls.[3] In the early stages of disease the symptoms appear on one side of the body and pathologically there is degeneration of the substantia nigra on the opposite side (contralateral) to the symptoms.

2.4 Epidemiology of Parkinson's Disease

2.4.1 Prevalence

Prevalence studies of PD have been conducted since the 1950's with variation in reported prevalence ranging from as low as 18 to as high as 244 per 100,000 population.[1,2] A recent review reported a variation in age-adjusted prevalence from 104.7 to 258.8 per 100,000 population.[18] These figures vary from study to study, and place to place, and by methodology. Another review of worldwide occurrence of PD revealed a 13 fold difference in prevalence between the highest (Uruguay) and lowest (China) in survey studies, and a three fold difference between the highest (Iceland) and the lowest (Libya) for prevalence studies using clinical or administrative data sources.[19] Although some of this wide variation in prevalence can be attributed to differences in methodology, some of the variation could result from differences in diagnostic criteria and how cases are ascertained.[18] Use of administrative and clinical data sources, while relatively cost effective, underestimate prevalence and incidence rates. On the other hand, door-to-door surveys provide more accurate results, but at a high financial cost.[1,18] Recent Canadian figures show that, during the period from 1991 to 1999, age-adjusted prevalence has increased from 3.54 to 3.73 per 1,000 population for men and increased from 3.18 to 3.49 per 1,000 population for women.[11] The western provinces have the highest prevalence rates in Canada.[19,20,21] Two separate studies reported that Saskatchewan had the highest prevalence rate of PD of any Canadian province.[19,21] One study, that used hospital separation data from 1976 to 1995, found the highest prevalence of PD in Saskatchewan, 23.5 and 16.4 per 100,000 population for men and women respectively.[19] This was about 1.5 times the national average for both sexes.[19] It is evident that PD has a significant and increasing prevalence in Saskatchewan.

The temporal variation, or the change in frequency of PD over time, reveals that over the past 20 years the mean age of death has increased by 5 years, as a direct result of improved pharmacological treatment.[2] Given that the majority of persons affected by PD are in older age groups and that there is an expected six fold increase in the size of this group over the next 50 years,[9] the social and familial burden of PD will become profound.

2.4.2 Incidence

Different systematic reviews have reported considerable variation in the estimated crude incidence rates of PD from as low as 4 to as high as 25 per 100,000 population.[1,2,22] One of these systematic reviews reported that the best incidence studies yielded an approximate incidence rate of 17 per 100,000 per year.[22] Yet another recent review reported an average age-adjusted incidence rate of 14 per 100,000 person-years for several US studies.[18] Most incidence studies ascertain data from treatment settings or administrative data sources. The drawback of these sources is they underestimate incidence by omitting individuals who do not seek medical attention.[23] Studies that used a two study survey method reported higher incidence rates than other methods.[23,24] What these different studies do show is that incidence of PD increases sharply after the age of fifty and generally peaks between 70 and 79 years of age.[22,25] Studies that were able to include the very old reported a doubling of incidence per year between the 70-79 age group and the 80-84 age group.[22,24]

Incidence of PD was reported to be 1.5 to 2.0 times higher among men than women for all age groups.[24,25,26,27,28] The low frequency of PD and the difficulty in establishing a proper diagnosis are the two main challenges that consistently underestimate both incidence and prevalence. One US study used incident cases from the Olmstead County PD study from 1976 to 1990 as the numerator, and US census data from the same period of time to calculate the denominator in terms of person-years, for calculating age adjusted incidence rates.[26] Person-years is defined as the sum of the periods of study time for each of the subjects. This study reported that while the total incidence over the life course for men was 13.03 per 100,000 person-years, the incidence peaked in the 75-79 age group at 182.46 per 100,000 person-years. Incidence rates for women, on the other hand, peaked in the 80-99 age group at 72.91 per 100,000 person-years and had a total rate over the life course of 8.76 per 100,000 person-years.[26] This study demonstrated that men have a higher incidence rate of PD and that their peak level occurs in a younger age group than women.

2.4.3 Mortality

A 1967 Hoehn and Yahr clinical study on PD reported a standardized mortality ratio (SMR) of 2.9,[4] while a population-based study conducted about the same time, reported a SMR of 1.6.[29] After the introduction of levodopa therapy there was an initial significant

decrease in mortality followed by an increase well above the pre-levodopa levels. The SMR has since returned to those levels observed before the introduction of levodopa.[30] Regardless of the type of study, it has been shown that despite improved morbidity with levodopa therapy, those with PD have a shorter life expectancy than the general population.[18,30,31] It has been suggested that this compromised life expectancy stems from two potential causes. First, severe motor dysfunction in the advanced stages of PD may lead to increased likelihood of falls.[30] Second, end-stage immobility could increase the risk of fatal infections.[31]

However, there is considerable variation in the reported SMR's of these studies. Some studies have reported SMR close to pre-levodopa levels between 2.3 and 4.1.[30,32] Yet other studies report a moderately increased SMR between 1.58 and 1.7.[26,31,33,34] SMR increases with age and is higher in males than in females.[19,26,31] A Canadian study revealed an absolute mortality rate of 3.4 per 100,000 and illustrated an increase in this rate over the study period of 1977 to 1996.[19] This study also showed that mortality rate increased with age and did not reach a peak, and also revealed that the mortality rate for males was higher than females.[19] An Ontario study revealed a significantly higher mortality rate of 2.5 for PD patients compared to controls.[35] Methodological differences can account for these reported variations in SMR. Use of death certificates can yield inaccurate results due to inconsistent identification of PD as a cause of death. Use of clinical data can under- or over-estimate SMR depending on the type of study population.[31] A more recent population based study reported a moderately elevated SMR for PD at 1.32. This study purported that its methodology identified only clinically defined PD and as such reflected a more accurate SMR.[31]

2.5 Risk Factors for Parkinson's Disease

2.5.1 Age and Age of Onset

Although there is considerable variation in the absolute prevalence of PD, the incidence and risk of the disease is directly proportional to increasing age.[1,18] Incidence varies with age for both men and women and begins to rise after 50 years of age.[25] A variety of different categorical definitions of age of onset have been used.[36, 37, 38, 39] Onset under the age of 40 characterizes Early Onset Parkinson's Disease (EPD), which represents about 3-

10% of all PD.[39,40] By contrast, the average age of onset of Older Onset Parkinson's Disease (OPD) is above 70 years of age.[36,37]

It has been reported that those with EPD were more likely exposed to rural living environment and to have used well water while growing up.[39,40] At the same disease duration of about 5 years, greater motor impairment was reported in OPD than EPD.[36,37,38] EPD patients experienced a longer duration of disease, were treated with a higher daily dose of levodopa for a longer period of time, and more frequently experienced levodopa induced dyskinesias, but had less frequent occurrence of psychotic symptoms.[37,41] Those with EPD however, experienced a slower initial disease progression as evidenced by the significantly longer period of time before commencing levodopa treatment.[36,41,42] Further evidence of slower initial disease progression in EPD is evident in decreased occurrence of bradykinesia, disability, and mortality.[43] It was also noted that those with EPD had fewer co-morbid conditions.[36] Thus, earlier age of onset is associated with slower progression of disease and less impairment of motor function.

There are several explanations for the different evolutions of PD related to age of onset. First, EPD and OPD could be etiologically different as evidenced by the strong genetic component to EPD compared to OPD.[43] Second, differences in the severity of neuronal damage reflect differential progression in EPD and OPD.[43] Thus, EPD could have a more selective dopamine deficiency due to environmental or occupational exposures that manifest specific neuronal damage.[37,39] OPD, on the other hand, could be the result of non-selective atrophy involving neurotransmitter systems other than the nigrostriatal system.[37] It has been suggested that these age differences could result from an age-related neuronal vulnerability or a time-dependent causal mechanism.[1]

2.5.2 Sex Differences

Although earlier prevalence studies demonstrated no significant male/ female differences,[44,45] a higher percentage of studies now demonstrate that men have a slightly higher age-adjusted prevalence and incidence of PD.[1,18,25,46,47] The higher prevalence of PD in males is persistent across race.[1] These sex differences could be the result of differences in environmental and/or occupational exposures.[18] There could also be a sex-linked

genetic predisposition, or sex hormones could confer differences in susceptibility to risk.[18] The ratio of males to females ranges from 0.8, as seen in Japanese studies, to as high as 3.7 in some areas of China.[1,18] It has been suggested that the Japanese results may be an artifact, or may be related to the longer survival rate of Japanese women.[18]

The age of diagnosis of PD is similar for men and women and they experience similar symptoms at onset. As the disease progresses the number of reported symptoms increases and sex differences in symptom profile emerge.[48] Men develop more severe Parkinsonian motor symptoms despite higher doses of levodopa treatment, while women develop more levodopa-induced dyskinesias.[48,49] It has been suggested that PD progresses more rapidly in men, but the exact reason for this has not been determined.[49] However, some investigators suggest that PD may be more malignant in men and progress more rapidly. Men may also have less than optimal response to levodopa therapy.[50] Other studies have suggested a possible protective role for estrogen.[49]

2.5.3 Lifestyle Risk Factors

Many epidemiological studies have been conducted on cigarette smoking as a risk factor for PD. Two systematic reviews of this literature revealed that never smokers are twice as likely to develop PD as smokers.[51,52] Although the incidence of PD rises sharply with age in both sexes, smoking was associated with a lower incidence in both sexes and in all age groups.[27,53] A recent systematic review of 48 case-control and cohort studies reported that the pooled relative risk versus never smokers was 0.39 for current smokers and 0.80 for past smokers.[54] The protective effect increases in a dose-dependent manner as the number of cigarette-pack-years increases.[18,55] A study by Gorell et al. showed that moderate smokers had an OR of 0.7 while heavy smokers had an OR of 0.43 when both were compared with those who had never smoked.[56] It has been suggested that the observed protective effect may actually result from behavioural and/or environmental factor(s) associated with smoking, such as coffee drinking, while others have suggested that having PD itself leads to reduced smoking behaviour.[57]

Case-control studies [58,59,60] and prospective studies [53,61,62] have found a strong inverse association between both coffee drinking and caffeine intake and the incidence of PD.

Ross et. al. found that this strong inverse association was independent of smoking.[62] The Ascherio et al. study evaluated gender differences in the effect of coffee consumption, caffeine intake, and smoking habit on the incidence of PD.[61] For men there was a strong inverse association between coffee consumption and caffeine intake for both never and ever smokers. For women there was a U-shaped association between coffee consumption and risk of PD with the lowest risk at 1-3 cups of coffee per day. Analysis of total caffeine intake per day revealed similar findings to coffee consumption.[61] These results demonstrate a protective effect for chronic consumption of moderate amounts of caffeine.[61] A systematic review of 13 studies revealed that the pooled relative risk for coffee drinkers was 0.69 when compared to non-coffee drinkers.[54]

Investigations of the association between dietary factors and PD have had inconsistent results. Some studies have found a protective effect for the consumption of antioxidant food and supplements,[63] while others have demonstrated no such association.[64] Conflicting findings have also demonstrated that a diet high in dietary fat can either increase the risk of PD, [64] or have no impact on risk.[58] In a case-control study by Fall et al. several dietary items containing niacin, including coffee, were reported to have a protective effect.[58] Some authors have suggested that the geographic variability of the prevalence of PD is a function of these lifestyle risk factors.[65,66]

2.5.4 Occupational Risk Factors

There have been several studies conducted on the long-term exposure to specific and combinations of transition metals because of their accumulation in the substantia nigra of PD patients and their involvement in oxidative reactions.[67] Lai et. al. reviewed eight studies on the relationship between metal exposure and the development of PD and found that while some studies revealed a positive association between PD and exposure to metals such as mercury, lead, manganese, copper, and iron, other studies showed no such association.[66] Two separate studies, also reviewed by Lai et al. additionally revealed that long-term exposure to combinations of metals was associated with PD.[66] Overall the epidemiological evidence of the association between long-term metal exposure and PD is inconclusive.[66,67]

The majority of studies that investigated the association between pesticide exposure and PD reported a positive association with a variation in OR of 1.02 to 7.0.[66,67] Two of the earlier studies reviewed by Lai et. al. showed no association.[66] A meta-analysis of 19 studies by Priyadarshi et. al. calculated the combined OR at 1.94.[68] Some of these studies, as reviewed by Lai et. al., found a positive correlation between PD and duration of pesticide exposure.[66] Despite these conclusions the high variability between the odds ratios of the different studies suggests the associations are not definitive and more detailed study of pesticide exposure is required.[66,67]

Rural living, farming, and well water drinking are all positively associated with PD.[66] Half of the 22 studies reviewed by Lai et al. reported a statistically significant increased risk of PD associated with these conditions.[66] Rural living, farming, and drinking well water may be surrogates for pesticide exposure by use,[69] or leaching into the soil and ground water.[70] More recent studies report greater occurrence of PD in the rural population with age-adjusted prevalence 1.2 to 1.5 fold higher than in the urban population.[46] Canadian studies have also found a higher prevalence in the rural population.[20,39]

2.5.5 Multi-Factorial Models

Various studies suggest that most cases of PD have multi-factorial etiologies consisting of both genetic and environmental components.[57,71,72,73,74,75] The specific models produced by the respective studies reveal differences in risk factors and protective factors. Some of these differences are related to the specifics of the study, such as the type of metal subjects may have been exposed to during their lives, or the specific amount of cigarette-pack-years that define categories of smoking. The specific geographic location of the study also plays a role in the characteristics of the model proposed. A study in Taiwan is inherently different than a Canadian study. Reducing to a common denominator it can be deduced that smoking remains a protective factor, in the majority of studies.[71,74,75] Risk factors can be generalized. One risk factor appears to be exposure to pesticides, either through direct exposure in specific occupations such as farming, or indirectly as an environmental toxin in well water, for example. Another risk factor appears to be familial history of PD. Some of these studies also investigated other possible risk factors such as medical history and psychiatric history, the results of which were inconsistent.[73,74] Thus, the specific

environmental and genetic factors that interact in determining risk of PD require further and more detailed study.

2.6 Pharmacological Treatment

Levodopa is the treatment of choice for patients with PD. The majority of pharmacological treatments in PD are symptomatic, which reduce the severity of symptoms.[76] Drugs may also be classified by their protective effect where disease progression is slowed, stopped, or reversed.[76] Recent investigations have focused on the potential protective effects of selegiline and rasagiline. Although both of these drugs are selective MAO-B inhibitors, it is believed that their mechanism of neuroprotection is multi-factorial.[77] Other clinical investigations demonstrated that selegiline and rasagiline, in untreated PD patients, delayed the average time before patients must begin levodopa therapy.[77,78,79] Selegiline and rasagiline have also been shown to decrease the rate of progression of PD.[78,79,80,81] A study by Diederich et al reported that less aggressive treatment strategies were used with OPD patients, where levodopa mono-therapies were preferred over combined therapies.[36] Although levodopa is the treatment of choice, other anti-Parkinson medications such as MAO-B inhibitors can be used to potentially delay its inevitable use.

2.7 Progression of Disease

2.7.1 Tools to Predict Progression

There are three tools for predicting progression of PD. First, there are neuro-imaging techniques like Positron Emission Tomography (PET) and Single Photon Emission Computerized Tomography (SPECT) that monitor changes in Fluorodopa (F-Dopa) uptake and Dopamine type 2 (D2) receptor binding respectively.[82] These neuro-imaging techniques measure dopaminergic dysfunction and it has been shown that functional neurological decline correlates well with clinical measures of progression.[82,83,84] Neuro-imaging techniques are not typically used in a clinical setting and clinicians are limited by the frequency of follow-up visits to track changes in functionality.[82] There is also a significant cost associated with the use of neuro-imaging techniques. As such, previous studies used small samples sizes and generally had short-term follow-up periods.[83,84,85] Neuro-imaging information was not available in the database used for the current study.

The second tool for predicting progression is genetic research. About 10-24% of those with PD have a family history of the disease.[86] Both autosomal dominant and autosomal recessive modes of transmission have been identified, some of which have a phenotype similar to PD.[87,88] Since the occurrence of genetic forms of PD is relatively low and since the database used in this study did not have genetic information, the usefulness of genetic research to predict progression of disease for this current study is limited.

The third tool for predicting progression is the use of clinical indicators. There are several clinical rating scales that almost exclusively focus on motor impairment as it relates to deterioration in the cardinal clinical features of PD.[89] Another commonly used scale is the Unified Parkinson's Disease Rating Scale (UPDRS), a multi-modular, four part scale that evaluates mentation, ADL, motor functioning, and complications of therapy.[89] Although this scale provides a more complete assessment of patients, it is time consuming to complete and is usually reserved for specific investigations rather than everyday clinical use.

The Hoehn and Yahr Scale of Global Disability (H&Y) was introduced in 1967 and remains the most ubiquitous rating scale in assessment of PD.[4,90] The H&Y is a five point, non-linear or ordinal scale that estimates the clinical functioning of PD patients using both impairment (objective signs) and disability (functional deficit) of movement, balance, and gait.[4,90] The scale focuses on milestones of disease and as such reflects progression of disease from unilateral to bilateral limb involvement, then to loss of postural reflexes, and finally to loss of independent mobility.[89] Since the vast majority of subjects in the database used in the current study had H&Y scores, this study used this clinical rating scale as a tool for assessing progression of PD. During the 1990's some neurologists began to use a modified H&Y scale that added two 0.5 increments between stages 1 and 2 and stages 2 and 3.[90] The original and modified scales are presented in Table 2.1 below.[90]

The Movement Disorders clinic in Saskatoon began using the modified H&Y scale in the 1990's. For the purposes of this investigation any modified H&Y scores were converted to original scores where 1.5 was counted as a 1 and 2.5 was counted as a 2 on the original H&Y scale. The logic behind this decision was two fold. First, the modified 1.5 is not a 2

on the original scale because there is no bilateral involvement of the disease and the modified 2.5 is not a 3 on the original scale because postural instability is not yet present. Second, far more patients in this database were assessed using the original scale than the modified scale.

Table 2.1 Comparison of Original and Modified Hoehn and Yahr Scales

Hoehn and Yahr Scale	*Modified Hoehn and Yahr Scale*
1: Unilateral involvement only; usually with minimal or no functional disability	1.0: Unilateral involvement only
	1.5: Unilateral and axial involvement
2: Bilateral or midline involvement without impairment of balance	2.0: Bilateral involvement without impairment of balance
	2.5: Mild bilateral disease with recovery on pull test
3: Bilateral disease: mild to moderate disability with impaired postural reflexes; physically independent	3.0: Mild to moderate bilateral disease; some postural instability; physically independent
4: Severely disabling disease; still able to walk or stand unassisted	4.0: Severe disability; still able to walk or stand unassisted
5: Confinement to bed or wheelchair unless aided	5.0: Wheelchair bound or bedridden unless aided

2.7.2 Defining Progression of PD

In their 1967 study, Hoehn and Yahr identified 20 of 183 subjects who were still in either H&Y stage 1 or 2 after having had PD for ten years.[4] This slow progression of disease is now commonly identified as benign progression. Subsequent studies also identified small groups of patients with benign progression. Marttila and Rinne reported that ten percent of their study population had benign progression.[5,91] Hely et al also reported 13 of 136 subjects with benign progression.[34] The most recent publication of their Sydney Multi-center Study revealed that 12 of the 13 patients with benign progression were still alive after 15 years, 4 of which were still at H&Y stage 2, while the remainder had progressed to more severe stages.[92]

On the opposite extreme, rapid progression has been defined as reaching H&Y stage 3 within three years of disease onset, or reaching H&Y stage 4 or 5 within five years of disease onset.[5] Marttila and Rinne reported 20 of 400 subjects with rapid progression.[91] Other studies, such as Goetz et al. have used similar definitions of rapid progression.[93]

2.7.3 Prognostic Factors that predict progression of PD

Progression of PD is heterogeneous across a population.[4,91] It has also been shown that progression of PD is more rapid initially then slows down as the disease advances.[94] Many studies have investigated different prognostic factors that predict progression of PD. Marras et al. conducted a systematic review of 13 articles investigating the predictors of motor decline and disability.[95] Articles were chosen based on an assessment of methodological quality. In this systematic review, most variables assessed in the different articles had inconclusive results for their ability to predict increased disability and motor impairment. However, some variables demonstrated useful predictive value. Five articles demonstrated a positive correlation between older age of onset and more rapid progression of disease. In two separate articles by Hely et al. age of onset per 10 years was found to have a relatively consistent OR of about 3.0 when correlated with two different measures of progression of disease.[34,96] PD is believed to be an active pathological process combined with an age-related neuronal degeneration.[97] This neuronal degeneration increased with age[97] and was reported to be eight to ten times higher in PD than in age matched controls.[17,98] Others have suggested that old onset PD (OPD) has a different natural course with a different extent or rate of degeneration, that OPD manifests reduced compensatory mechanisms, and that the higher motor impairment is the result of co-morbidities.[36]

Five articles in the Marras et al. systematic review demonstrated that the predominance of tremor (TD) was correlated with a more benign progression of disease, while predominance of bradykinesia and rigidity were correlated with more rapid progression of PD.[95] One study, in this systematic review, reported an OR of 0.43 for progression to H&Y stage 3 for patients with tremor dominant symptoms at baseline. Marttila and Rinne also supported a more favorable prognosis for those patients who present at initial visit with TD compared to those with akinetic/rigid PD.[91] Marras et al. also found one study that reported a predictive role for the Schwab and England activities of daily living scale.[95] A baseline ADL score below 70% was predictive of increased motor impairment and thus progression of disease. Marras et al. found two studies that reported an association between the presence of dementia at baseline with more rapid motor decline and higher impairment.[95]

Some studies have reported differences in the duration of disease at baseline between subjects who have benign and rapid progression. In one study the mean duration of disease was reported to be three times (8 years) longer in benign progression.[99] Another study reported that patients with shorter disease duration progressed more rapidly.[100]

Inconclusive results were reported by Marras et al. when investigating the predictive value of sex and depression.[95] This paper also reported that several studies demonstrated no predictive value for rural living, family history of PD, smoking history, and presence of dyskinesias at baseline.

Based on the findings of the Marras et al. systematic review, the prognostic characteristics associated with benign and rapid progression can be identified.[95] Rapid progression was generally associated with older age at disease onset, predominance of bradykinesia and gait disturbances, ADL scores below 70%, and more frequent diagnosis of dementia. Benign progression was characterized by younger age of disease onset, lateralization of Parkinsonian symptoms, predominance of tremor, and generally better prognosis and QoL.

Although Marttila and Rinne completed a direct comparison of rapid and benign progression,[91] more recent studies have tended to focus on comparisons of either rapid or benign progression against a control group.[34,93,101] Another shortcoming of a majority of these studies is that they have short timeframes such as a two-year follow-up in the Goetz study,[93] or a retrospective analysis of progression over one year as in the Hoehn and Yahr study.[4] The shorter timeframes of these studies were a direct result of the study design. Subjects included in the studies were not receiving levodopa treatment.[4,93] The endpoint of progression was often defined by the need for levodopa treatment due to progression to H&Y stage three.[93,102] This limits the applicability of the results to a minority of PD subjects because the vast majority are eventually treated with levodopa.[102]

A more recent study by Goetz et al. investigated some aspects of disease progression in levodopa-treated PD patients.[102] They reported that progression of motor impairment was greater over a four year period for subjects who were in H&Y stage 3 at baseline compared

to subjects in H&Y stage 2 at baseline. Although Goetz et al. are critical of previous studies conducted over a short timeframe, their study was conducted over a relatively short period of four years.[102] Some studies, such as Hely et al. have been conducted over an extended period, but have limited their investigation of progression.[34,92]

2.8 Chapter Summary

The prevalence and incidence of PD in Saskatchewan is the highest in all of Canada and over time has been increasing. As such PD is a significant and growing health concern. In general, studies demonstrated that some prognostic factors had significant associations with progression of PD. Rapid progression was reported to be associated with older age of onset, the predominance of bradykinesia and rigidity, ADL scores below 70%, and the presence of dementia. On the other hand, benign progression was reported to be associated with younger age of onset and the predominance of tremor. Many other factors that were investigated, such as a family history of PD and smoking habit, had inconclusive results.

Previous investigations generally had three limitations. First, they had low numbers of subjects, second, progression was studied over a limited timeframe, and third, the study focused on either rapid or benign progression. This thesis investigated the clinical features associated with benign and rapid progression using a single database and involved data collected over an extended period of time. Another advantage is that this database included both levodopa treated and non-levodopa treated subjects at baseline.

CHAPTER 3

Methodology

3.1 Study Location

This study was conducted at the University of Saskatchewan, Saskatoon, Saskatchewan in the College of Medicine, in (1) the Department of Community Health and Epidemiology; and (2) the Division of Neurology of the Department of Medicine.

3.2 Collected Data

3.2.1 The Clinical Dataset

The dataset used in this study was a sub-set of a larger clinical database of Parkinsonian patients treated at one Movement Disorders Clinic in Saskatoon, Saskatchewan between 1970 and February, 2005. The vast majority of these patients were treated by one neurologist who was joined by another neurologist five years ago. The clinical database contained 1648 subjects diagnosed with one form of Parkinsonism or another. The dataset used for this study was restricted to patients clinically diagnosed with PD, which reduced the number of subjects to 1479. Another 27 subjects were removed from the dataset because they did not have H&Y score, or did not have a recorded date of onset of symptoms. Thus, the dataset analyzed in this study contained 1452 subjects. The dataset was de-identified so that individual identifying numbers such as Saskatchewan Health Services numbers and names had been removed.

The scope, or catchment of this dataset includes patients who had been referred to the Movement Disorders Clinic by their family physician, or by another Neurologist. Some of these patients may have been treated by their family physician for a number of years before referral because their condition had worsened and the family physician was seeking the assistance of a movement disorders specialist. Other patients may have been referred to the clinic after an initial visit to their family physician had indicated a need for treatment by a movement disorders specialist. Regardless of the specific reason for referral, the dataset

was comprised of patients who were at a more advanced stage of disease. The frequency of follow-up varies in that some patients may have been seen only once because they were subsequently well managed by their family physician while other patients may have been seen infrequently, and yet other patients were seen as often as once ever three to nine months over many years.

It is difficult to determine how representative this dataset was compared to the general population. It is likely that a significant proportion of patients with PD in the Saskatoon Health Region have been seen in this movement disorders clinic, however the exact proportion is unknown. A small number of patients have come to this clinic from other health regions in Saskatchewan.

Patients had been asked a series of questions during initial and follow-up visits to the clinic with the intention of collecting clinically useful information that would assist the Neurologists in providing effective long-term medical intervention. The other use of this database was to help the Neurologists identify potential participants in future clinical trials and studies as they became available.

3.2.2 Variable Selection

The variables that were available for analysis are summarized in Table 3.1. Some of these variables were not included in the study analysis for a number of reasons. The variables of sleeping sickness, poisoning of any kind, tranquilizer use, drug abuse, and drug allergies were not included because they lacked analytic value for the study of disease progression. The dose of medication variables were not included in this study because much of this data was not entered into the electronic database. Experimental drug and drug discontinued variables were not included in this analysis as these variables were collected for a specific drug trial conducted over a short period of time. The variables reporting the site of disability were not included in the analysis because each respective disability site is highly correlated with the actual disability. For example, there was no need to include the site of resting tremor variable when the variable of resting tremor was already in the analysis.

Table 3.1 Independent variables available in the database

Variable Category	*Variable*	*Description*
Personal Information	Age of Onset	Age of patient's recollection of first symptom
	Sex	Male or female
	Place of Birth	Urban, rural, unknown
Relevant Past History	Smoking History	Current & past smoking habits
	Stroke	Ever had stroke
	Seizures	Ever had seizures
	Family History of PD	Any family member had PD
	Sleeping Sickness	Problems with getting to sleep and adequate sleep
	Poisoning of any kind	Any poisoning of any kind
	Tranquilizer Use	Any prolonged use of Tranquilizers
	Drug Abuse	Any use if illegal drugs
	Drug Allergy	Any allergies to drugs
Use of Anti-Parkinson Medication	Levodopa	At first visit is patient taking this Medication
	COMT Inhibitor	At first visit is patient taking this Medication
	Amantadine	At first visit is patient taking this Medication
	Anticholinergics	At first visit is patient taking this Medication
	Dopamine Agonist	At first visit is patient taking this Medication
	MAO-B Inhibitor	At first visit is patient taking this Medication
	Experimental Drugs	Is patient enrolled in drug study
	Dose of Medication	Daily dose of any & all medications used
Motor Fluctuations	Response to Medications	Any response to previous medications used
	Adverse Effects	Adverse effects to drug use
	Dyskinesias	Dyskinesias from drug use
	Wearing Off	Any wearing off
	On-Off	Any on-off periods
	Drug Discontinued	Ever ceased medication use
Motor Function Assessment	Tremor at Rest	Any Tremor & Severity
	TAR – Site	Most Pronounced site of TAR
	Action Tremor	Any Action tremor & severity
	AT - Site	Most Pronounced Site of AT
	Postural Tremor	Any postural tremor & severity
	Rigidity	Any rigidity & severity
	Rigidity – Site	Most Pronounced Site of rigidity
	Bradykinesia	Bradykinesia & severity
	Bradykinesia – Site	Most Pronounced Site of Bradykinesia
Other Neurological Findings	Schwab & England	Activities of daily living assessment
	Essential Tremor	Is essential tremor present
	Dementia	Any dementia
	Depression	Any depression
	Abnormal Eye Movement	Any Abnormal Eye Movement
	Cerebellar Dysfunction	Any Known Cerebellar Dysfunction
	Corticospinal Dysfunction	Any Known Corticospinal Dysfunction
	Sensory Abnormalities	Any Sensory Abnormalities
	Autonomic Dysfunction	Any Autonomic Dysfunction
	Peripheral Neuropathy	Any Peripheral Neuropathy

The independent variables used in this analysis are summarized in Table 3.2. Data was collected during the initial visit of each patient to the clinic. All personal information variables were self-reported by the patient during the initial visit. Place of birth was self-reported as urban, rural, or unknown. Date of onset was the year in which the first symptom of PD occurred as recollected by the patient in consultation with the neurologist. Disease duration was calculated by subtracting date of first visit from date of onset and was reported in years. All relevant past history variables were also self-reported. Most of the variables in this category were reported as yes, no, or unknown with the exception of smoking which was reported as current smoker, past smoker, never smoker, or unknown. All variables in the history of anti-Parkinson medication category were reported based on combined information from self-report of the patient during the initial visit and information provided to the neurologist in any consultation documentation that may have been provided. The majority of these variables were recorded as either yes or no. All variables in the motor fluctuation category were based on assessment by the neurologist and were recorded as yes or no.

Most variables in the motor function assessment category were determined from the neurological examination performed at the initial visit. These variables were recorded as an ordinal scale that indicated the severity of functional loss with the exception of ADL score. The ADL score is determined from patient responses to a series of questions concerning the patient's perception of their current level of ability to perform tasks of daily living. This variable is reported as an interval scale from 0 to 100%. This variable was dichotomized to scores above 70% and scores equal to or less than 70 percent. An ADL score ≤70% is clinically significant because the subject is not completely independent. Dementia and depression were self-reported as yes, no, or unknown.

3.2.3 Ethical Approval

A study proposal was submitted to and approved by the Research Ethics Board (Biomedical) at the University of Saskatchewan (March 15, 2005 - Appendix A).

Since this is a retrospective statistical and epidemiological analysis of a de-identified database the following assurances were made to the Research Ethics Board:

Table 3.2 Independent variables Used in Data Analysis

Variable Category	*Variable*	*Description*	*Type*
Personal Information	Age of Onset	Age of patient's recollection of first symptom	Interval & Nominal
	Sex	Male or female	Nominal
	Place of Birth	Urban, rural, unknown	Nominal
	Disease Duration	Disease Duration at First Visit	Interval
Relevant Past History	Smoking History	Current & past smoking habits	Nominal
	Stroke	Ever had stroke	Nominal
	Seizures	Ever had seizures	Nominal
	Family History of PD	Any family member had PD	Nominal
Use of Anti-Parkinson Medication	Levodopa	At first visit is patient taking this Medication	Nominal
	COMT Inhibitor	At first visit is patient taking this Medication	Nominal
	Amantadine	At first visit is patient taking this Medication	Nominal
	Anticholinergics	At first visit is patient taking this Medication	Nominal
	Dopamine Agonist	At first visit is patient taking this Medication	Nominal
	MAO-B Inhibitor	At first visit is patient taking this Medication	Nominal
Motor Fluctuations	Response to Medications	Any response to previous medications used	Nominal
	Adverse Effects	Adverse effects to drug use	Nominal
	Dyskinesias	Dyskinesias from drug use	Nominal
	Wearing Off	Any wearing off occur	Nominal
	On-Off	Any on-off periods	Nominal
Motor Function Assessment	Tremor at Rest	Any Tremor & Severity	Ordinal
	Action Tremor	Any Action tremor & severity	Ordinal
	Postural Tremor	Any postural tremor & severity	Ordinal
	Rigidity	Any rigidity & severity	Ordinal
	Bradykinesia	Bradykinesia & severity	Ordinal
Other Neurological Findings	Schwab & England	Activities of daily living assessment	Nominal
	Essential Tremor	Is essential tremor present	Nominal
	Dementia	Any dementia	Nominal
	Depression	Any depression	Nominal

1. Any use of the data, e.g., publication will be unlinked.
2. No research subject will be contacted in any way to obtain additional information.
3. The research results will be presented in aggregate fashion.

3.3 Methods of Analysis

3.3.1 Data Entry

The data was initially entered in Microsoft "Excel" during the course of its clinical collection. The data were then transferred to Microsoft "Access" before later transfer to Statistical Package for Social Sciences (SPSS ver. 13.0) software at the College of Medicine, Division of Neurology of the Department of Medicine. Data checks were run for out-of-range values and all edits were completed by May 3, 2005.

3.3.2 Data Analysis

This was a retrospective cases-only study of a sample of 1452 PD patients. Analysis was completed using SPSS ver. 13.0. The first phase of this analysis was a descriptive analysis of the sample population at first clinic visit. Frequency tables were produced for the selected independent variables listed in Table 3.2 along with the distribution of the H&Y scale in the sample population.

In the second phase of this analysis subjects were divided into different progression groups. Progression was defined in terms of how rapidly subjects progressed through the H&Y stages. Diagnosis of H&Y stage was determined at initial and all subsequent clinic visits. As such longitudinal use of the dataset was required in order to determine the progression category of each subject. This study used existing definitions of "rapid" and "benign" progression. Marttila and Rinne defined rapid progression as reaching H&Y stage 3 within three years of disease onset, or reaching H&Y stage 4 or 5 within five years of disease onset.[5] Benign progression was characterized as still less than H&Y stage 3 ten years after disease onset.[34,91] Average progression was defined as those who reached H&Y stage 3 between 4 and 10 years after disease onset, or in other words not benign nor rapid. Some subjects could not be allocated to the rapid, benign, or average groups due to insufficient follow-up information. For example, a subject who attended the clinic for an initial visit may not have subsequent visit information because their disease was well

managed by their family physician. As such, there is no follow-up information to categorize progression of this subject. This group of subjects was termed "unknown". A portion of the unknown group were termed "Unknown, but not rapid" and represents subjects who did not meet the criteria for rapid, but lacked information to be definitively categorized as either benign or average. For example, a subject who had an initial visit in 1998 and was diagnosed in H&Y Stage 2 in a 2004 visit and has not had a subsequent visit since, does not have rapid progression, because they are not H&Y Stage 3 after three years nor H&Y Stage 4 or 5 after 5 years. This subject lacks follow-up information to be categorized as benign progression because there is not 10 years of follow-up and the subject is not average because they have not reached H&Y Stage 3 as of yet.

The third phase of the analysis was a series of univariable logistic regressions each containing a single independent variable. This was conducted to identify factors associated with rapid and benign progression based on initial clinical findings. For rapid progression the outcome variable was dichotomized into rapid progression, based on the definition established in phase two above, and "not rapid" progression, a combination of those allocated to the average, benign, and unknown, but not rapid groups. For benign progression the outcome variable was dichotomized into benign progression, based on the definition established in phase two above, and "not benign" progression, those allocated to the average and rapid groups. Univariable logistic regression was performed on each independent variable against the dichotomized outcome variables for both rapid and benign progression to obtain Odds Ratios (OR), 95% Confidence Intervals (CI), and p-values for each independent variable.

In the fourth phase of this analysis independent variables that were identified as statistically significant in the univariable analysis along with other independent variables deemed to be clinically and biologically important were selected for logistic regression modeling. The specific logistic regression analysis used in this study was the stepwise backward elimination approach designed by Hosmer and Lemeshow.[103]

It is important to understand that longitudinal information was used to categorize subjects into progression groups. Those groups were then combined to generate dichotomous

outcome variables for logistic regression of benign and rapid progression. These outcome variables were assessed for associations with independent variables at first clinic visit. In other words, looking back at first clinic visit, what characteristics are associated with future progression of disease.

CHAPTER 4

Results

4.1 Clinical Characteristics of Sample Population

There were 1452 patients in this sample population. The clinical characteristics at first visit to the clinic are provided in Tables 4.1 to 4.4. Table 4.1 summarizes demographic and clinical characteristics at first visit. The mean age of onset was 65±11 years and ranged from 25 to 98 years. The graph of age of onset (Figure 4.1) demonstrates a gradual increase in the number of patients with advancing age of onset which peaks at about 75 years of age before falling off sharply. The graph of disease duration (Figure 4.2) shows a sharp rise in the frequency of duration peaking at two years, and falling off gradually, and showing minimal frequencies after 10 years of disease duration. The mean disease duration was 4.4 years with a SD of 4.8 years and ranged from zero to 45 years. Approximately 59% of the study population was male. Over 63% were born in a rural setting. About 12% of subjects reported being born in an urban setting while 24% did not report a place of birth. While approximately 37% had never smoked during their lives, over 51% had some past or current history of smoking. The vast majority had no history of stroke or seizures. About 22% of subjects reported a family history of PD.

Table 4.2 summarizes the use of anti-Parkinson medications and reported motor fluctuations at first visit. About half the subjects were taking levodopa at their initial visit. Only about one percent of subjects were taking COMT Inhibitors. About 10 to 15% of the study population was taking amantadine, anticholinergics, dopamine agonists, or MAO-B inhibitors. Although 25-35% of subjects experienced previous responses to medication use and adverse effects, 45-55% reported these effects as unknown. Of those taking any medication, a small proportion were experiencing dyskinesias, wearing off, and on-off periods as a result.

Table 4.1 Demographic and Clinical Characteristics at First Visit

Variable	*Frequency (%)*
N	1452 (100)
Age of onset (years)	
Mean (SD)	65.2 (11.0)
Range	25 to 98
Disease Duration	
Mean (SD)	4.4 (4.8)
Range	0 to 45
Sex	
Male	859 (59.2)
Female	593 (40.8)
Place of Birth	
Urban	170 (11.7)
Rural	922 (63.5)
Unknown	360 (24.8)
Smoking History	
Never	543 (37.4)
Past	632 (43.5)
Current	114 (7.9)
Unknown	163 (11.2)
Stroke	
Yes	71 (4.9)
No	1189 (81.9)
Unknown	192 (13.2)
Seizures	
Yes	18 (1.2)
No	1244 (85.7)
Unknown	190 (13.1)
Family History PD	
Yes	316 (21.8)
No	1053 (72.5)
Unknown	83 (5.7)

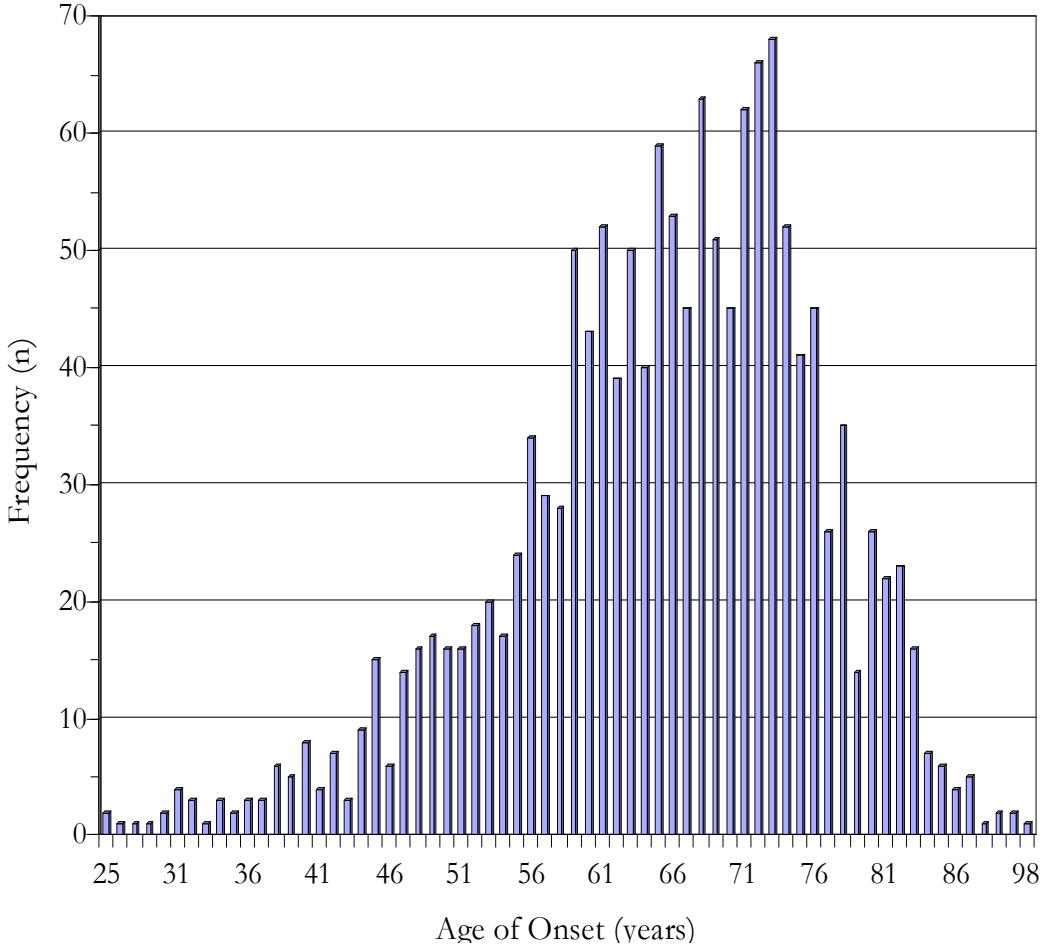

Figure 4.1 Age of Onset at First Visit of Study Population (N=1452)

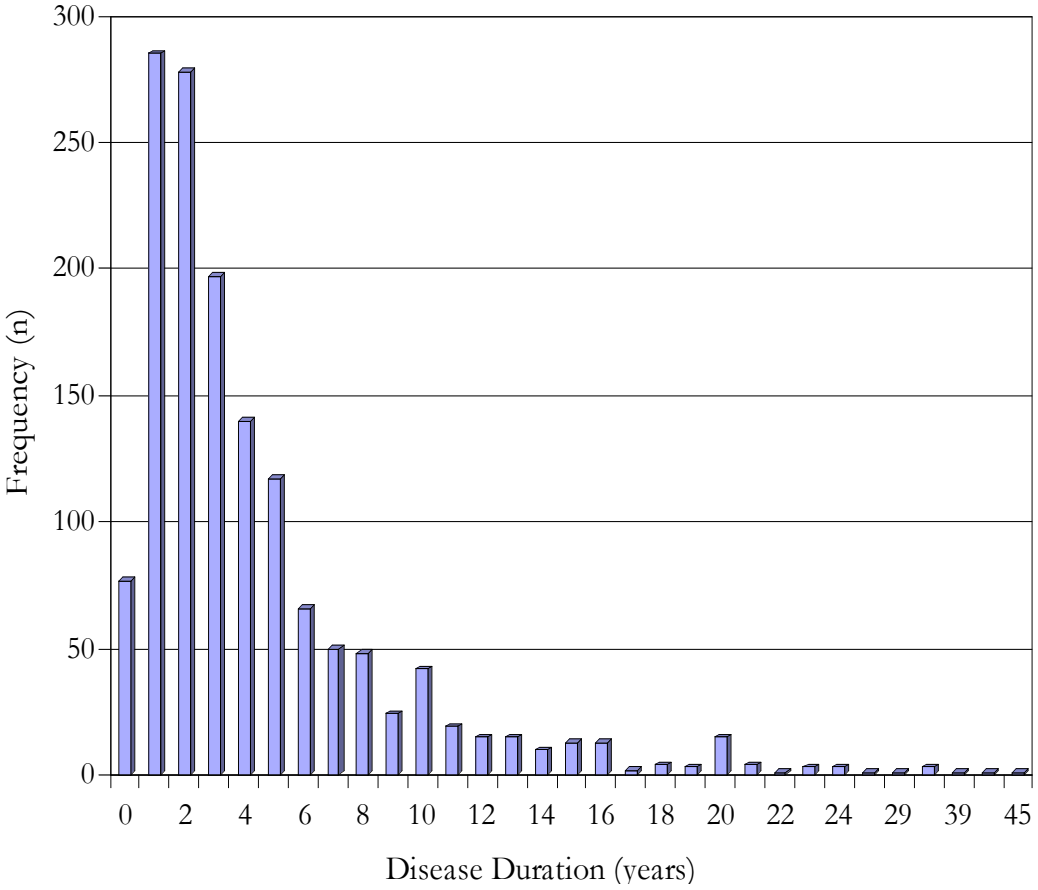

Figure 4.2 Disease Duration at First Visit of Study Population (N=1452)

Table 4.2 Use of Anti-Parkinson Medications and Reported Motor Fluctuations at First Visit

Variable	*Frequency (%)*	*Variable*	*Frequency (%)*
Levodopa		Previous Medication Response	
Yes	728 (50.1)	Yes	516 (35.5)
No	721 (49.7)	No	125 (8.6)
Unknown	3 (0.2)	Unknown	811 (55.9)
COMT Inhibitor		Previous Adverse Effects	
Yes	18 (1.2)	Yes	320 (22.0)
No	1432 (98.6)	No	478 (32.9)
Unknown	2 (0.1)	Unknown	654 (45.0)
Amantidine		Previous Dyskinesias	
Yes	188 (12.9)	Yes	111 (7.6)
No	1261 (86.8)	No	575 (39.6)
Unknown	3 (0.2)	Unknown	766 (52.8)
Anticholinergics		Previous Wearing off	
Yes	153 (10.5)	Yes	59 (4.1)
No	1297 (89.3)	No	575 (39.6)
Unknown	2 (0.1)	Unknown	818 (56.3)
Dopamine Agonists		Previous On-Off Periods	
Yes	163 (11.2)	Yes	10 (0.7)
No	1286 (88.6)	No	605 (41.7)
Unknown	3 (0.2)	Unknown	837 (57.6)
MAO-B Inhibitor			
Yes	228 (15.7)		
No	1220 (84.0)		
Unknown	4 (0.3)		

Table 4.3 summarizes the motor function assessment findings at first visit. Approximately 80% of subjects presented with some form of resting tremor, of which the majority had slight to mild symptom severity. Over 90% of subjects at first visit had symptoms of bradykinesia, noted on exam; in almost half it was of moderate severity. Action tremor was present in about 70% of the study population, however most subjects experienced slight severity. Rigidity was present in over 95% of subjects, most of which was slight to moderate in severity. Approximately 20% of the study population had either the presence or absence of postural tremor noted on initial visit. Nearly twice as many had presence compared to absence of postural tremor.

Table 4.4 summarizes other neurological findings at first visit. About 65% of the study population had a reported ADL score, of which approximately 30% had an ADL score below 70 percent. The mean ADL score was 81.6±19.4%, the median score was 90%, and the range was 10 to 100 percent. The vast majority of subjects did not have essential tremor or dementia at first visit. Only about 20% of the study population had reported the presence or absence of depression, of which about 10% had reported depression at first visit. The H&Y disability was distributed in this population as follows: about 70% mild disability, those in H&Y stages 1 and 2, and approximately 22% moderate disability, those in H&Y stage 3, and about 7% severe disability, those in H&Y stages 4 and 5.

4.2 Distribution by Progression

Figure 4.3 illustrates the flow chart of inclusion criteria for this study and the distribution by progression. The entire database is a collection of subjects who were treated at the Movement Disorders Clinic from 1970 to February 2005. These subjects were all suspected cases of Parkinsonism. For this study subjects who received a follow-up clinical diagnosis of IPD were included. Subjects with other diagnoses such as PSP, drug induced Parkinsonism and so on were excluded as were subjects who did not have a reported year of onset of symptoms, or H&Y score. As a result 196 subjects were excluded from this analysis leaving 1452 subjects in the sample population.

As described earlier in Chapter 3, the sample population was divided into three different progression groups; rapid, benign, and average. The distribution by progression is

Table 4.3 Motor Function Assessment at first visit

Variable	*Frequency (%)*
Resting Tremor	
Absent	284 (19.6)
Slight	421 (29.0)
Mild	613 (42.2)
Moderate	120 (8.3)
Marked	7 (0.5)
Unknown	7 (0.5)
Bradykinesia	
Normal	70 (4.8)
Mild	337 (23.2)
Moderate	665 (45.8)
Severe	346 (23.8)
Barely performs task	22 (1.5)
Unknown	12 (0.8)
Action Tremor	
Absent	478 (32.9)
Slight	703 (48.4)
Moderate	227 (15.6)
Moderate (+)	13 (0.9)
Marked	2 (0.1)
Unknown	29 (2.0)
Rigidity	
Absent	59 (4.1)
Slight	532 (36.6)
Mild to Moderate	713 (49.1)
Marked	136 (9.4)
Severe	4 (0.3)
Unknown	8 (0.6)
Postural Tremor	
Yes	199 (13.7)
No	106 (7.3)
Missing Information	1147 (79.0)

Table 4.4 Other Neurological Findings at first visit

Variable	*Frequency (%)*
Schwab & England ADL Score	
≤ 70%	224 (15.4)
> 70 %	717 (49.4)
Missing Information	511 (35.2)
Essential Tremor	
Yes	76 (5.2)
No	1361 (93.7)
Unknown	1 (0.1)
Missing Information	14 (1.0)
Dementia	
Yes	93 (6.4)
No	1293 (89.0)
Unknown	66 (4.5)
Depression	
Yes	25 (1.7)
No	265 (18.3)
Unknown	4 (0.3)
Missing Information	1158 (79.8)
Hoehn & Yahr Scale	
1	236 (16.3)
2	793 (54.6)
3	330 (22.7)
4	50 (3.4)
5	43 (3.0)

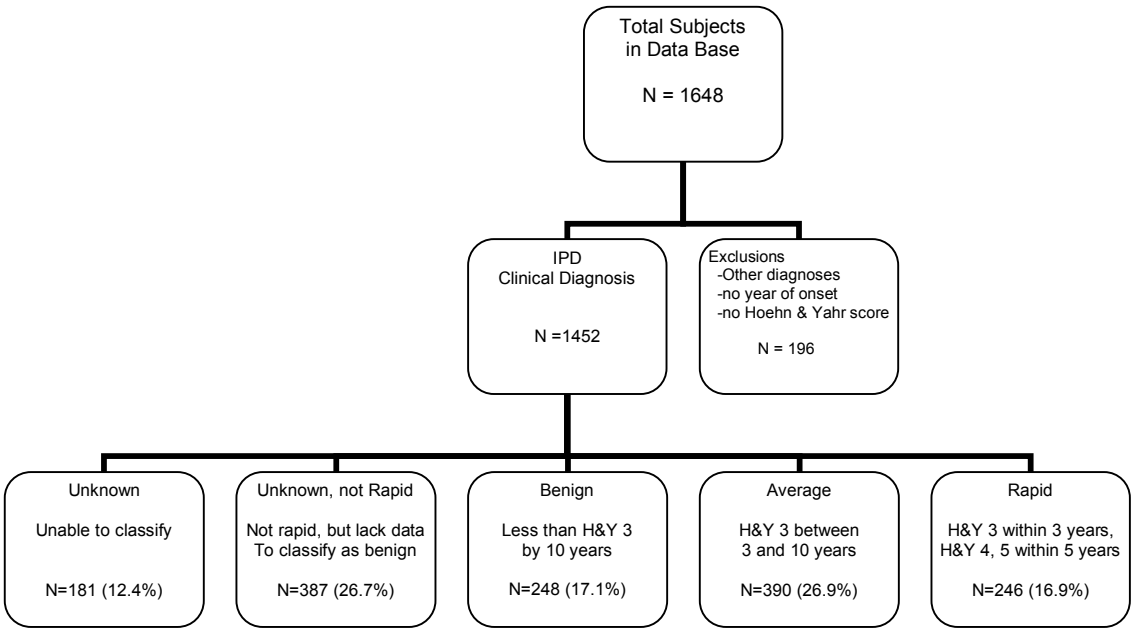

Figure 4.3 Flow Chart of Distribution by Progression Category

illustrated in Figure 4.3. We were unable to classify 181 (12.4%) subjects due to insufficient follow-up information, or the first clinic visit was more than 10 years after onset of symptoms. About 27% (387 subjects) of the sample population could only be classified as "not rapid" in that they did not meet the criteria for rapid progression, but did not have sufficient follow-up information to confirm benign or average progression. The frequency of both benign and rapid progression was virtually the same at about 17 percent. Those subjects classified with average progression represented about 27% of the sample population.

4.3 Benign Progression

4.3.1 Univariable Analysis for Benign Progression

Univariable analysis of the independent variables against benign progression was conducted. Those variables that were determined to be statistically significant by univariable analysis along with those variables determined to be biologically and/or clinically important are presented in Table 4.5. In accordance with the protocol established by Hosmer and Lemeshow those variables that had reported p-values of 0.25 or less were retained for later multivariable analysis.[103]

For every 10 year increase in age of onset subjects were one third as likely to develop benign progression. This result was significant with a reported p-value of <0.001. The narrow CI indicates good precision of this estimate. For every one year increase in disease duration subjects were 1.30 times more likely to have benign progression. The result was significant with a reported p-value of <0.001. The narrow CI indicates good precision of this estimate. Men were 1.86 times more likely to develop benign progression as women. The result is highly significant with a p-value of <0.001 and the narrow CI indicates good precision of this estimate.

Subjects who were current smokers at first visit were 2.36 times more likely to have benign progression. The result was significant with a p-value of 0.004. Subjects with a past history of smoking were slightly less likely to have benign progression. The result was significant with a p-value of 0.034. There was good precision in both of these estimates as

Table 4.5 Univariable Analysis of Significant Independent Variables for Benign Progression

Variable	*N (%) Benign*	*N (%) not Benign* [a]	*Odds Ratio*	*CI*	*p-value*
N	248	636			
Age of Onset ***	56.1 (10.8)	68.8 (9.7)	0.32	0.27, 0.38	0.001
Disease Duration ****	8.0 (7.0)	3.5 (2.5)	1.30	1.24, 1.36	<0.001
Male	164 (66.1)	326 (51.3)	1.86	1.37, 2.52	<0.001
Smoking History					
Past	82 (37.8)	278 (49.6)	0.70	0.50, 0.97	0.034
Current	27 (12.4)	27 (4.8)	2.36	1.32, 4.21	0.004
Stroke *	6 (2.9)	40 (7.4)	0.37	0.15, 0.88	0.025
Family history PD *	67 (28.3)	120 (20.0)	1.58	1.12, 2.23	0.010
Levodopa *	138 (55.6)	336 (53.0)	1.11	0.83, 1.50	0.478
Other Medications *	125 (50.4)	227 (35.7)	1.83	1.36, 2.46	<0.001
Motor Fluctuations *	138 (86.3)	294 (76.6)	1.92	1.16, 3.19	0.012
Resting Tremor **	133 (53.8)	303 (47.9)	0.77	0.58, 1.04	0.088
Rigidity **	42 (27.5)	404 (63.7)	1.46	1.08, 1.96	0.014
Bradykinesia **	154 (63.1)	484 (76.6)	1.91	1.39, 2.63	<0.001
ADL ≤ 70%	14 (11.8)	149 (39.4)	0.21	0.11, 0.37	<0.001
Dementia *	9 (3.7)	49 (8.1)	0.44	0.21, 0.91	0.026

[a] not benign group is combination of the average and rapid groups (refer to Figure 4.3)
* Reported values are for a response of yes.
** Reported values are for mild to severe severity of the symptom.
*** Represents OR for a 10 year increase in age of onset.
**** Represents OR for a 1 year increase in disease duration.

indicated by the narrow CI's. Those subjects with a reported history of stroke were significantly less likely to have benign progression with an OR of 0.37. The result was statistically significant with a p-value of 0.025 and the narrow CI indicates good precision of this estimate. Subjects with a family history of PD were 1.58 times more likely to have benign progression. The result was statistically significant with a p-value of 0.010. There was good precision of this estimate as indicated in the narrow CI. Subjects who were taking levodopa at first visit or had reported prior use of levodopa were slightly more likely to have benign progression. The narrow CI indicates good precision of this estimate.

All anti-Parkinson medications excepting levodopa were combined into a single variable called Other Medications. This variable was binomial and yes to other anti-Parkinson medication use was defined as a yes to use of any one or more of the other anti-Parkinson medications. The motor fluctuation variables were combined into a single variable called Motor Fluctuations. This variable was binomial and a yes to the presence of motor fluctuations was defined as a yes to presence of any one or more motor fluctuations. The results of univariable analysis demonstrated that subjects who were taking or had a history of taking any other medications were 1.83 times more likely to have benign progression. The result was highly significant with a p-value of <0.001. Subjects with motor fluctuations were 1.92 times more likely to have benign progression. The result was highly significant with a p-value of 0.012. Both estimates had good precision as indicated by the narrow CI's.

Each motor function assessment variable, excepting postural tremor, has five levels of severity rated on an ordinal scale from zero to four. The results show that several of these severity levels had very low or absent reported values. As such, the levels of severity for these variables were dichotomized by grouping absent and slight severity, a score of 0 or 1, into one category and grouping mild to severe severity, a score of 2,3, or 4, into another category. Univariable analysis (Table 4.5) showed that subjects with mild to severe resting tremor were less likely to have benign progression with a reported OR of 0.77. The result had borderline significance with a reported p-value of 0.088. Subjects with mild to severe rigidity were 1.46 times more likely to have benign progression. The result was highly significant with a p-value of 0.014. Subjects with mild to severe bradykinesia were nearly

twice as likely to have benign progression. The result was highly significant with a p-value <0.001. All of the CI's for these motor function assessments were narrow indicating good precision of the estimates.

Subjects with self-reported ADL scores of 70% or less were unlikely to have benign progression. The result was statistically significant with a p-value <0.001. Subjects with a reported history of dementia were about half as likely to have benign progression. The result was statistically significant with a p-value of 0.026. Both of these variables had narrow CI's indicating good precision of the estimates.

4.3.2 Multivariable Logistic Regression for Benign Progression

From univariable logistic regression analysis it was determined that age of onset, disease duration, sex, smoking history, family history of PD, other medications, motor fluctuations, stroke, resting tremor, rigidity, bradykinesia, ADL, and dementia all had some association with benign progression and as such would be included in the multivariable logistic regression model based on significant p-values less than 0.25. Levodopa was also included based on its clinical significance. Multivariable logistic regression was conducted on these variables using backward stepwise elimination method using the Likelihood Ratio Test in SPSS ver. 13.0. Interaction tests had no impact on the outcome of the final model. A second multivariable logistic regression analysis was performed with the ADL variable removed from the model. ADL was removed because over 35% of the reported values were missing. The final multivariable model is presented in Table 4.6.

Age of Onset, disease duration, sex, smoking history, levodopa, and rigidity remained significant after multivariable analysis. In the multivariable model for every 10 year increase in age of onset at first visit subjects were one third as likely to have benign progression. For every one year increase in disease duration at first visit subjects were 1.41 times more likely to have benign progression. Males were 3.23 times more likely to have benign progression. Subjects who reported a past history of smoking were less than half as likely to have benign progression as non-smokers, while current smokers were 2.33 times more likely to have benign progression as non-smokers. Subjects who reported past or

Table 4.6 Final Model from Multivariable Analysis for Benign Progression (N=400)

Variables	*Odds Ratio*	*C.I.*	*p-value*
Age of Onset *	0.36	0.25, 0.50	0.000
Disease Duration **	1.41	1.27, 1.57	0.000
Male	3.23	1.70, 6.16	0.000
Smoking Habit			
Past Smoker [a]	0.46	0.24, 0.89	0.021
Current Smoker [a]	2.33	0.67, 8.11	0.184
Levodopa ***	0.45	0.21, 0.98	0.043
Rigidity ****	0.43	0.23, 0.80	0.008

* Represents OR for a 10 year increase in ago of onset
** Represents OR for an increase of 1 year in disease duration
*** Reported values are for a response of yes
**** Reported values are for mild to severe severity of symptom
[a] Reference category is Never Smoking

current use of levodopa were about half as likely to have benign progression. Subjects who had mild to severe rigidity were about half as likely to have benign progression as those subjects with absent or slight rigidity.

Age of Onset, disease duration and male sex had stronger associations while smoking history, levodopa use, and rigidity had weaker associations when controlling for other variables. Male sex was the only variable with a stronger association to demonstrate a meaningful difference between the crude and adjusted OR's where it increased by over 73 percent. Past history of smoking, levodopa use, and rigidity all demonstrated meaningful decreases from crude to adjusted OR's by 34%, 59% and 69% respectively. Both levodopa use and rigidity had their associations with benign progression flip from positive to negative.

4.4 Rapid Progression

4.4.1 Univariable Analysis for Rapid Progression

Univariable analysis of the independent variables against the rapid progression outcome was conducted. Variables determined to be statistically significant by univariable analysis along with variables determined to be biologically and/or clinically important are presented in Table 4.7. In accordance with the protocol established by Hosmer and Lemeshow those variables that had reported p-values of 0.25 or less were retained for later multivariable

analysis.[103] For every 10 year increase in age of onset subjects were over three times as likely to have rapid progression. This result was significant with a reported p-value of <0.001. The narrow CI indicates good precision of this estimate. For every one year increase in disease duration subjects were 0.63 times less likely to have rapid progression. The result was highly significant with a p-value of <0.001. The very narrow CI indicates good precision for this estimate.

Males were less likely to have rapid progression than women, an effect that was statistically significant. The precision of the estimate was good as reflected in the narrow CI. Subjects with a history of past and current smoking habits were less likely to have rapid progression. Since the CI's are narrow the precision of this estimate is good. Subjects with a self-reported family history of PD were half as likely to have rapid progression. This effect was statistically significant with a p-value of 0.001. The narrow CI indicates good precision of the estimate. Subjects taking levodopa were slightly less likely to have rapid progression. There is good precision in this estimate as reflected in the narrow CI.

All anti-Parkinson medications excepting levodopa were combined into a single variable called Other Medications. This variable was binomial and yes to other anti-Parkinson medication use was defined as a yes to use of any one or more of the other anti-Parkinson medications. The motor fluctuation variables were combined into a single variable called Motor Fluctuations. This variable was binomial and a yes to the presence of motor fluctuations was defined as a yes to presence of any one or more motor fluctuations. The results of univariable analysis demonstrated that those subjects who were taking or had a history of taking any other medications were half as likely to have rapid progression. The result was highly significant with a p-value of <0.001. Subjects with motor fluctuations were about half as likely to have rapid progression. The result was slightly above significance level with a p-value of 0.056. Both estimates have good precision as indicated in the narrow CI's.

Each disability assessment variable, excepting postural tremor, has five levels of severity reported on an ordinal scale from zero to four. The results show that several of these

Table 4.7 Univariable Analysis of Significant Independent Variables for Rapid Progression

Variable	*N (%) Rapid*	*N (%) not Rapid* [a]	*Odds Ratio*	*CI*	*p-value*
N	246	1025			
Age of Onset ***	72.8 (9.0)	63.3 (10.7)	3.09	2.54, 3.75	<0.001
Disease Duration ****	2.0 (1.1)	4.8 (4.5)	0.63	0.57, 0.69	<0.001
Male	125 (50.8)	622 (60.7)	0.67	0.51, 0.89	<0.001
Smoking History					
Past	104 (47.7)	443 (48.6)	0.91	0.67, 1.23	0.540
Current	14 (6.4)	82 (9.0)	0.66	0.36, 1.21	0.182
Family history PD *	35 (14.9)	246 (25.5)	0.51	0.35, 0.75	0.001
Levodopa *	113 (46.1)	524 (51.2)	0.82	0.62, 1.08	0.156
Other Medications *	66 (26.8)	426 (41.6)	0.52	0.38, 0.71	<0.001
Motor Fluctuations *	101 (73.2)	501 (80.5)	0.66	0.43, 1.01	0.056
Resting Tremor **	98 (39.8)	558 (54.8)	0.55	0.41, 0.73	<0.001
Rigidity **	166 (67.5)	591 (58.1)	1.50	1.12, 2.01	0.007
Bradykinesia **	196 (79.7)	716 (70.5)	1.64	1.17, 2.30	0.004
Postural Tremor *	35 (76.1)	114 (63.0)	1.87	0.89, 3.93	0.098
ADL ≤ 70%	73 (46.5)	110 (17.3)	4.16	2.86, 6.05	<0.001
Dementia *	24 (10.1)	52 (5.4)	2.00	1.21, 3.32	0.007

[a] not rapid is combination of Average, benign, and unknown, but not rapid groups (refer to Figure 4.3)

* Reported values are for a response of yes.

** Reported values are for mild to severe severity of the symptom.

*** Represents OR for a 10 year increase in age of onset.

**** Represents OR for a 1 year increase in disease duration.

severity levels have very low or absent reported values. As such the levels of severity for these variables were dichotomized by grouping absent and slight severity, a score of 0 or 1, into one category and grouping mild to severe severity, a score of 2, 3, or 4, into another category. Univariable analysis (Table 4.7) showed that those subjects with mild to severe resting tremor were half as likely to have rapid progression with a reported OR of 0.55. Subjects with mild to severe rigidity were 1.50 times more likely to have rapid progression. The result was highly significant with a p-value of 0.007. Subjects with mild to severe bradykinesia were 1.64 times more likely to have rapid progression. The result was highly significant with a p-value of 0.004. All of the CI's for these disability assessments were narrow indicating good precision of the estimates.

Subjects with postural tremor were 1.87 times more likely to have rapid progression. Subjects with ADL scores ≤ 70% were 4.16 times more likely to have rapid progression. The result was highly significant and the narrow CI indicates good precision of the estimate. Subjects who reported having dementia at first visit were twice as likely to have rapid progression. The result was highly significant and had good precision indicated by the narrow CI.

4.4.2 Multivariable Logistic Regression for Rapid Progression

From the univariable logistic regression analysis it was determined that the variables of age of onset, disease duration, sex, smoking history, family history of PD, levodopa, other medications, motor fluctuations, resting tremor, rigidity, bradykinesia, and dementia all had some association with rapid progression and as such would be included in the multivariable logistic regression model based on significant p-values less than 0.25. Although ADL and postural tremor had statistically significant associations with rapid progression in univariable analysis, they were not included in multivariable analysis because 35% and 79% of reported values (respectively) were missing. Multivariable logistic regression was conducted using backward elimination stepwise method in SPSS. Interaction tests had no impact on the outcome of the final model. The final multivariable model is presented in Table 4.8.

Age of onset, disease duration, male sex, resting tremor, and rigidity remained significant after multivariable analysis. In the multivariable model, for every 10 year increase in age of onset at first visit, subjects were 2.45 times more likely to have rapid progression. For every one year increase in disease duration at first visit subjects were half as likely to have rapid progression. Male subjects were about half as likely to have rapid progression. Subjects with mild to severe resting tremor were about half as likely to have rapid progression as subjects with absent or slight severity. Subjects with mild to severe rigidity were nearly twice as likely to have rapid progression as subjects with absent or slight severity.

Table 4.8 Final Model from Multivariable Analysis for Rapid Progression (N=617)

Variables	*Odds Ratio*	*C.I.*	*p-value*
Age of Onset *	2.45	1.80, 3.33	<0.001
Disease Duration **	0.52	0.44, 0.62	<0.001
Male	0.58	0.35, 0.95	0.03
Resting Tremor ***	0.47	0.28, 0.77	0.003
Rigidity ***	1.73	1.02, 2.94	0.044

* Represents OR for a 10 year increase in age of onset
** Represents OR for a 1 year increase in disease duration
*** Reported OR is for mild to severe severity of symptom

Rigidity had a stronger association, while age of onset, disease duration, male sex, and resting tremor had weaker associations when controlling for other variables. Although rigidity had a 15.3% higher adjusted OR compared to crude OR in univariable analysis, the difference was not meaningful. Of those variables with weaker associations only age of onset had a meaningful difference between the crude and adjusted OR with a 20.7% decrease. Disease duration, male sex, and resting tremor had weaker associations with 17.5%, 13.4%, and 14.5% decreases from crude to adjusted OR's respectively.

CHAPTER 5

Discussion

5.1 Characteristics of Sample Population

Compared to previous disease progression studies our study population had some similarities and some differences. The size of this sample population was more than double the Hoehn and Yahr study [4] and was up to five times larger than a majority of previous studies of disease progression.[94,98,100,101,104] Other retrospective studies have utilized data from specialist's clinics [94] and epidemiological surveys.[91] Previous studies investigating disease progression have also used specialist clinical data,[4,98,101] or administrative data,[97,105] or have been community based studies.[100] The mean age of onset of the current study population was 8 to 10 years older than previous studies that used specialist clinical data.[4,94,98] Other investigations using a community based cohort,[100] outpatient clinical data,[105] or an epidemiological survey [91] reported an age of onset similar to our study population. These findings support the assertion that the current study population is a representative community sample.

Disease duration at first visit was shorter than previous retrospective studies by about 2 to 3 years.[91,94] Most of the previous studies were conducted in the US and all reported longer disease duration than this study.[94,98,100] A Canadian study by Lee et al. reported disease duration double what this current study found.[104] The observed longer disease duration at first visit in the Lee et al. study may reflect a selection bias because a portion of their study population was recruited from chronic care facilities.[104] On the other hand, the shorter disease duration at first visit in our study could reflect earlier referral to specialist care.

Most studies reported a predominance of males in their study populations of around 60%, similar to the current study.[4,94,98,100] Although no studies of progression investigated the potential role for rural place of birth, two studies did investigate the potential role of rural living.[93,106] In one of these studies those who had lived in a rural setting for 10 years or

more comprised 60% of the total study population, a figure similar to our study population.[106] It is likely that both our study and the Ferraz et al. study would normally have a preponderance of rural subjects given that both the Canadian prairies and Brazil are predominantly agricultural.[106]

Previous PD studies reported 5-18% of PD patients as current smokers.[60, 101] The reported occurrence of current smokers in our study falls within that range. Studies reported that 15-24% of PD subjects had a pathological diagnosis of stroke.[107, 108] One study reported a cumulative incidence of lifetime ischemic stroke in PD patients of 8 per 100.[109] Our study reported about 5% incidence of stroke at first visit. In general it has been reported that about 10-24% of PD subjects have some form of family history of PD.[86] The results of our study fall within that range.

Earlier studies of progression, such as Hoehn and Yahr [4] and Marttila and Rinne,[91] were conducted on patients who were not taking anti-Parkinson medications. Some of the more recent studies have investigated progression either with levodopa treatment,[99, 102] or prior to levodopa treatment.[110] The Roos et al. study, which did not manipulate pharmacological treatments, reported that 80% of subjects were taking levodopa at baseline.[105] Another progression study reported that 70% of their subjects were taking levodopa at baseline.[100] These results demonstrate a much higher frequency of levodopa use at baseline than our study. The lower preponderance of levodopa use in our study could result from earlier referral to the clinic. On the other hand, the elevated use of levodopa observed in previous studies could reflect longer disease duration and a higher likelihood of medication use at first visit.[100] The potential association of reported motor fluctuations at baseline with progression was not investigated in previous studies.

Similar to previous studies motor function assessment revealed that the majority of patients present with mild or slight severity of the respective sign.[94,105] The only previous study to investigate the potential association of ADL with progression reported mean and median baseline Schwab and England scores of 69.2% and 70.0% respectively, while the subjects in our study had mean and median scores of 81.6% and 90.0% respectively.[100] The Schwab and England is a self-reported ordinal scale indicating the degree to which activities of daily

living are compromised. A score below 70% is clinically significant because patients are not completely independent and spend a large part of their day completing chores. Since subjects in the Louis et al. study had longer disease duration at baseline, it is probable that they had more compromised motor function as reflected in lower ADL scores.[100]

The distribution of H&Y stages in our study population was comparable to previous studies. The majority of subjects were diagnosed with H&Y Stage 1 or 2 at the commencement of various studies.[4,91,96,105] Although our study found a similar frequency of subjects in H&Y Stage 2, there was about 1.5 to 2.5 times as many subjects in H&Y Stage 1 than in previous studies.[91,96] While a similar frequency of subjects was observed in H&Y Stage 3, there were fewer subjects in H&Y Stages 4 and 5 in our study than in previous studies.[91,105] Subjects appear to be referred to this clinic earlier and as such may have less global disability at baseline.

The occurrence of dementia at first visit in our study is much lower than previous studies with reported frequency at baseline of about 15 to 19 percent.[105,111] The smaller sample size of these two studies could have contributed to the higher reported occurrence of dementia. However, neither study clearly indicated how dementia was assessed. A systematic review of 26 studies of depression in PD reported a mean frequency of 40% and a range of 4-70 percent.[112] The authors did comment that the wide range in reported frequency could have resulted from different definitions of depression. The study demonstrates an association between depression and PD. The frequency of depression reported in our study falls below the above reported range. This is probably because we were reporting the occurrence of depression at first visit while the majority of the studies in the systematic review reported lifetime frequency.

In general, the characteristics of our study population are quite similar to those of previous studies as evidenced by similar male to female ratio, similar frequencies of current smoking, stroke, and family history, and similar baseline distribution of H&Y scores. Unlike previous studies we reported higher ADL scores, shorter disease duration, and less frequent levodopa use at baseline. All of these differences though can be attributed to earlier referral to this clinic.

5.2 Observations on Univariable Analysis

In the analysis of benign progression the OR's for levodopa use and rigidity flipped from positive associations in univariable analysis to negative associations in multivariable analysis. Univariable analysis represents the association of a single variable with the measured outcome. In this case levodopa use by itself and the presence of mild to severe rigidity by itself were apparently predictive of benign progression of disease. However, univariable analysis can only provide information on the effect of a single variable. It is only a single piece of a larger more complex picture of the true biological situation. Rarely would levodopa use be the only available piece of information. If it was, then univariable analysis would inform us of its impact on benign progression. Statistically, univariable analysis is conducted to inform us of which available variables are potentially significant. Thus, rather than putting all available variables into a multivariable model, we can select potentially significant variables for inclusion. Multivariable analysis accounts for the interactive effect of many variables that would naturally co-exist. It is a larger, more complex picture of the true biological situation. In this case, levodopa use and rigidity in the presence of each other and the other variables in the final model interact together in informing the prediction of benign progression.

The univariable analyses of rigidity, bradykinesia, and resting tremor all had associations that were in the same direction in both the rapid and benign analysis. Taken alone, these univariable results show that mild to severe rigidity and bradykinesia and absent or slight resting tremor were predictive of both benign and rapid progression. This conclusion is counter-intuitive. As discussed above, univariable analysis only provides information on a single variable. The multivariable models of benign and rapid progression reveal the effect of many variables that combined predict both rapid and benign progression. The differences between the two models is discussed in more detail below (Section 5.5).

5.3 Benign Progression

Subjects with benign progression had longer disease duration at first visit and had younger age of onset of PD compared to the not benign group. This result was consistent with previous studies.[91,94,97,99] The observed age of onset in the benign group of this study was similar to that reported by Birkmayer et al.,[99] but was 16 years older than that reported in

the Marttila and Rinne study.[91] Since the Marttila and Rinne study restricted its benign group to those with unilateral symptoms their benign group did not include those in H&Y Stage 2. This could account for the lower age of onset and would also account for the smaller reported size of their benign group, which was about one third the frequency of our benign group. The observed disease duration in the benign group in this study was shorter than that reported in other studies.[91,99] Birkmayer et al. reported a mean disease duration of 23 years, three times what we observed.[99] The fact that the Birkmayer et al. benign group only included those with unilateral symptoms after 10 years could account for this difference.[99]

This current study found that males were more likely to experience benign progression than females, was different than previous studies that reported no differences in progression for males and females.[96,99,113] Our findings also appear to contradict the finding by Jankovic and Kapadia that males progress at a significantly higher rate than females.[94] However, the Jankovic and Kapadia study followed subjects for only three years and used a different definition of progression than we employed. Other studies have suggested that PD progresses more rapidly initially and then slows down as the disease advances.[85,104] In these studies progression was defined in terms of decline in Fluorodopa uptake, a surrogate for loss of dopamine cells in the substantia nigra. Neither study reported a sex difference in progression of disease. Since our study covers a much longer period of follow-up, we could be reporting a higher likelihood of long-term benign progression in males even though they may initially progress at a more rapid rate.

Subjects with past history of smoking were less likely to have benign progression, while those who were current smokers at first visit were more likely to have benign progression. Other studies found no significant association between smoking and progression of disease.[93,114] Both of these studies however involved a small sample population studied over a short timeframe. The Alves et al. study [114] had a longer period of study than Goetz et al.,[93] but was still less than half the time of our study. Alves et al. reported no differences between smokers and non-smokers regarding changes to UPDRS scores, H&Y scale, and ADL scores over the course of the study.[114] Since they defined smokers as those subjects who were smoking at the time of the initial evaluation, the non-smoking category

represents both past smokers and never smokers. Grouping these two categories underestimates the effect of a history of smoking. Goetz et al. did investigate a possible dose effect of smoking, but their study had only 31 matched pairs that were followed for only three years.[93]

The current study found that patients who had taken or were taking levodopa at first visit were less likely to have benign progression. Other studies that investigated a potential predictive role for levodopa use reported no significant association between levodopa use and progression of disease.[100,105] It is possible that any potential association could have been masked by the fact that 70-80% of the sample populations in those two studies were taking levodopa at baseline. Subjects in the Roos et al. study, who were taking levodopa, could be at more advanced disease stage as evidenced in the higher frequency of H&Y Stages 4 and 5 compared to our study.[105]

Subjects who presented to this clinic with mild to severe rigidity were less likely to have benign progression. Although the potential association between rigidity and slower progression of disease has not been directly investigated, Hoehn and Yahr did report that a more benign progression was associated with minimal disabilities.[4] Another study also found that patients with early onset PD presented more frequently with rigidity.[115] Several studies investigated differences between tremor dominant PD (TD) and postural instability gait difficulty PD (PIGD) or akinetic/rigid PD and found TD to be associated with slower progression.[94,98] Comparison between these studies and our study is problematic because they defined the classification of PD based on a dominant symptom. The data in this study recorded any and all symptoms that were present at baseline, but our analysis did not dichotomize subjects as TD versus PIGD. Louis et al. reported that while the severity of bradykinesia, rigidity, and gait disturbances increased over time, tremor remained stable leading them to conclude that tremor is relatively independent of disease progression.[100] It is possible then, given our results, that TD is a sub-group within our benign progression category.

Although stroke, family history of PD, ADL, dementia, motor fluctuations, and other medications were significant in univariable analysis, they did not remain significant in

multivariable analysis even when potential confounding was investigated. Most of these potential prognostic indicators have not been investigated in terms of their association with benign progression of disease. However, two studies did find that those subjects with younger age of onset were more likely to develop dyskinesias and fluctuations.[38,116]

5.4 Rapid Progression

Subjects with rapid progression had shorter disease duration at first visit and had older age of onset compared to the not rapid group. This result was consistent with previous studies.[91,93,94,99,101,117] The observed age of onset in the rapid group of this study was similar to that reported by Birkmayer et al.,[99] and Marttila and Rinne.[91] Although the reported age of onset in the rapid group in the Graham and Sagar study was 11 years younger than our study, they still reported that the age of onset in the rapid group was significantly older than the two other groups in their study.[117] This difference could reflect the smaller sample population and the shorter follow-up period of two years as compared to our study. The observed disease duration of this study was similar to that reported by Marttila and Rinne.[91] Other studies have reported disease durations ranging from 4 to 7 years.[99, 117] The much shorter disease duration of the present study could also reflect the referral pattern to this clinic in that the more difficult cases and the more rapidly progressive cases are referred sooner.

This current study found that males were less likely to have rapid progression was different than previous studies that reported no male-female differences in progression.[96,99,113] Although Birkmayer et al. found no statistical difference between males and females, they did report more females in the rapid group than males.[99] Our finding also appears to contradict the findings of two previous studies where Jankovic and Kapadia reported that males progressed at a significantly higher rate than females [94] and Lyons et al. reported that males had significantly higher UPDRS motor scores than females.[49] Our study appears similar to one previous study where women visited the doctor when already in a higher H&Y stage than men.[105] This could account for the negative association between rapid progression and male sex in our study in that more women are reporting to the clinic in a later H&Y stage, even though men may be prone to more rapid progression and higher reported motor dysfunction.

Subjects with mild to severe resting tremor were less likely to have rapid progression. Several studies demonstrated a predominance of tremor with slower progression of disease.[91,94,101] Generally these studies investigated TD versus PIGD or akinetic/rigid classifications of PD. The classifications of PIGD and akinetic/rigid refers to the predominance of postural instability and disturbance of gait, or akinesia and rigidity. Tremor may be present in subjects with PIGD or akinetic/rigid forms of PD, but it is not the predominant symptom. A recent investigation of clinical heterogeneity found four subgroups of PD; young onset, tremor dominant, non-tremor dominant, and rapid.[118] The non-tremor dominant subgroup was characterized by a mixed motor presentation that included tremor (which was not the predominant symptom). The non-tremor dominant subgroup had higher UPDRS scores and more rapid progression than the tremor dominant subgroup. The non-tremor dominant subgroup also had similar UPDRS scores and age of onset compare to the rapid group. Our investigation analyzed any and all symptoms present at baseline for associations with rapid progression. As such, our rapid group could reflect a combination of the characteristics of the rapid and non-tremor dominant subgroups of the heterogeneity study.

Subjects who presented to this clinic with mild to severe rigidity were more likely to have rapid progression. It has been reported that rapid progression is associated with the most severe motor impairment.[117] Another study found that rapid progression was associated with the predominance of bradykinesia, rigidity, and gait disturbance.[101] Several studies, that investigated differences between TD and PIGD or Akinetic/Rigid dominant PD, found PIGD to be associated with more rapidly progressive disease.[94,98] The data in our study recorded any and all symptoms that were present at baseline, but analysis did not differentiate subjects as TD versus PIGD or akinetic/rigid. However, our model reported the presence of slight resting tremor and mild to severe rigidity. This mixed motor presentation is similar to that reported in a previous investigation of heterogeneity of progression.[118]

Although smoking history, family history of PD, levodopa and other anti-Parkinson medication use, motor fluctuations, bradykinesia, and dementia were all significant in

univariable analysis they did not remain so during multivariable analysis. Most other studies that investigated these potential prognostic factors did not find any significant association with progression of disease.[93,99,113,114,117] Louis et al., however did find that ADL scores below 70% and the presence of dementia at baseline were predictive of a higher total UPDRS score, which is indicative of higher disability and the potential for more rapid disease progression.[100]

5.5 Comparison of the Benign and Rapid Progression

With respect to age of onset, disease duration, sex and rigidity the benign and rapid models are opposite to one another. For every 10 year increase in the age of onset of disease subjects are less likely to have benign progression and more likely to have rapid progression. The longer a subject has disease before visiting this clinic for the first time the more likely they are to have benign progression and the less likely they are to have rapid progression. Males were more likely to have benign progression and less likely to have rapid progression. At first visit, if a subject presents with mild to severe rigidity the less likely they are to have benign progression and the more likely they are to have rapid progression. Current smokers were more likely to have benign progression. In rapid progression current smokers were less likely to have rapid progression, but the association did not remain significant in the presence of other potential variables. Subjects with mild to severe resting tremor were less likely to have rapid progression. In the analysis of benign progression subjects with mild to severe resting tremor were more likely to have benign progression, but the association did not remain significant in the presence of other potential variables.

5.6 Strengths of this Study

The database used in our study was very large and included patients who came from all over the province of Saskatchewan. We reported similar age at onset to previous community based studies.[91,100,105] Previous studies that used clinic databases reported longer disease durations and higher frequency of levodopa use than we reported.[94,98,100] This supports our assertion that this study population is a representative community sample.

The database contained a large number of subjects who have been followed for a minimum of three years and for as long as 10 years. Previous progression studies had much smaller sample populations, the largest of which was about one third the size of the database used in this study. Many of the previous studies had much shorter follow-up than we had. Some of this variation was due to study design such as a five year prospective study.[101] Previous retrospective studies such as Marttila and Rinne did have longer follow-up data, but had fewer subjects than our study .[91]

All subjects in this database were assessed, diagnosed, and treated by one of two neurologists, both of whom are movement disorders specialists with an interest in PD. It is generally accepted that ante-mortem clinical diagnosis be performed by a neurologist with such experience.[9] This limits potential variability in diagnosis and as such less potential classification error.

5.7 Potential Limitations of this Study

Some of the independent variables such as age of onset and ADL scale are self-reported and as such have inherit bias. Since age of onset is self reported the calculation of disease duration is affected by this self-reported measure. It is likely that the further one is from the first symptom of PD the less accurate the determination of age of onset. This recall bias results in increasing underestimation of disease duration the longer the patient has had PD. This recall bias can then lead to differential misclassification error. Underestimating disease duration would result in underestimated frequency of benign progression; a bias toward the null. The actual OR's are potentially stronger than observed in this investigation.

The use of the H&Y scale could also be problematic in that the key stage for the determination of rapid progression is Stage 3. At this stage the subject has postural instability, thus it can be argued that the use of H&Y biases findings by dichotomizing results to those with postural instability, the rapid group, and those without postural instability, the benign group. This bias then potentially confounds any real associations of the other, potentially significant motor functions. On the other hand, studies have reported that the H&Y is highly correlated with other standardized clinical scales.[90] It has

also been demonstrated that the H&Y score progresses with PET scan decline in dopaminergic function.[90] The H&Y is clinically valuable in that it provides an overall assessment of clinical severity and functional disability. Finally, it is a ubiquitous and practical assessment scale.[90]

Levodopa use was mixed in this population. This has the potential to lead to misclassification error because treatment with levodopa attenuates the signs and symptoms of PD. As such, subjects who should be classified as rapid may end up in the average group. This "waters down" the effect causing bias toward the null and underestimating any associations observed in the rapid group. The actual OR's are potentially stronger than what was observed in this investigation.

There is a limit to the generalizability of disease duration. There is general agreement on the starting point of disease duration as the date of first symptom of PD, but the selection of the end date of disease duration has varied. For this study the end-date of disease duration was the date of first clinic visit. Other studies have chosen various end dates such as date of visit to outpatients,[105] or date of first use of levodopa.[93] Disease duration is a useful prognostic factor associated with differences in progression of PD for this clinic because it still indicates that the longer a subject has had the disease the less likely they are to have rapid progression and the more likely they are to have benign progression.

The limitations of using a clinical, retrospective database center around the fact the data exists before the questions are asked and as such data is often limited or may not exist for specific questions. One such example is the association of ADL with disease progression. Previous studies have demonstrated an association between lower ADL scores and more rapid progression of disease.[100] In the database used for this study 35% of the ADL scores were missing and as such the variable was excluded from analysis. ADL could be a useful clinical tool to aid neurologists in predicting rapid or benign progression in their patients at first visit. Some variables dropped out, while others entered the rapid and benign models when ADL was removed. This indicates that, while ADL may have predictive usefulness, it may be confounding other important variables associated with progression of PD.

CHAPTER 6
Conclusion

Prognostic factors measured at first clinic visit can be useful in predicting progression of PD. With more rapid progression closer and more frequent follow-up of patients may be required. The knowledge that certain prognostic factors may be associated with a more rapid course could influence the direction of consultation with patients. Those patients identified as potentially having a more rapid course would require appropriate consultation that addresses this poorer prognosis.

This study identified potential prognostic factors that can aid clinicians with diagnosis of progression. Further analysis is required to test the hypothesized models for those prognostic factors associated with both benign and rapid progression of PD by external validation. However, the model does not answer why there is a difference in the progression of disease. Future research should focus on determining why the significant variables in both the rapid and benign models lead to differences in the rate of progression. Another focus of future research would be the development of separate male and female models of progression.

Currently there are many definitions of progression that use different clinical and/or pathological measures. Some factors associated with progression remain significant regardless of the definition used, the major one being age of onset. Most other potential factors have been less consistently reported as significant predictors of progression. A standardized, but clinically expedient definition of progression of PD could be adopted. Doing so would likely lend itself to identifying useful clinical and demographic factors associated with progression of PD. On the other hand, the different definitions of progression may appropriately account for natural differences in respective populations,

which may require different methods of identifying prognostic factors associated with rapid and benign progression.

There are challenges with comparing the reported disease durations in previous progression studies. While most agree that disease duration starts from onset of first symptom, the end point varies. In our study the end point for disease duration was the date of the first visit to the clinic. In the Graham and Sagar study, for example the end point of disease duration is the date of outpatient visit during the two-year time frame of the study.[117] As such it is not clear whether this date of outpatient visit reflects the very first visit or a follow-up visit. This would tend to overestimate disease duration. The much shorter disease duration of our study could also be a reflection of the referral pattern to this clinic in that the more difficult cases and the more rapidly progressive cases are referred sooner to the clinic.

This study investigated the prognostic factors associated with progression of PD. A multivariable logistic regression analysis was conducted for benign progression and rapid progression. The final model for benign progression revealed that subjects with longer disease duration, who are males, and are current smokers at first visit were more likely to have benign progress while those subjects who had older age of onset, were past smokers, had a history of levodopa use, and had mild to severe rigidity at first visit were less likely to have benign progression. The final model for rapid progression revealed that those subjects with older age of onset and mild to severe rigidity at first visit were more likely to have rapid progression while those who had a shorter disease duration, were males, and had mild to severe resting tremor at first visit were less likely to have rapid progression. The intention of this study was to identify the clinical factors of patients at first visit to the clinic that would help determine how quickly patients progress. Knowing whether or not a patient will progress rapidly or have benign progression of PD can influence the adoption of progression specific frequency and detail of follow-up visits.

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Appendix A

Ethics Application Letter of Approval

Research Services

Barry D. McLennan, Ph.D., Chair
Research Ethics Board (Biomedical)
University of Saskatchewan
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110 Gymnasium Place
SASKATOON, SK S7N 5J8 CANADA
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MEMORANDUM

Bio-REB #: 05-43

To: Dr. S. Shah (Leslie Ferguson)

From: Barry D. McLennan, Chair
Research Ethics Board (Biomedical)

Date: March 15, 2005

Re: Predictors of the Rate of disease Progression in Parkinson's Disease

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Thank you for submitting the above-referenced protocol for REB review.

This protocol involves the use of secondary de-identified data. As indicated in the Tri-Council Policy Statement, such an analysis is not subject to ethics review provided the Biomedical REB can be given the following assurances:

1. Any use of the data, e.g., publication, will be anonymized (unlinked)
2. No research subject will be contacted in any way to obtain additional information
3. The research results will be presented in aggregate fashion

Please sign your name below to confirm the above assurances, and return this memo to our office.

Sincerely,

Barry D. McLennan, Ph.D., Chair
University of Saskatchewan
Biomedical Research Ethics Board

BDM/bjk

I confirm the assurances requested above:

Syed Shah (Leslie Ferguson).

Principal Investigator