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Epidemiology and Neuropsychiatric Manifestations of Young Onset Parkinson's Disease in the United States

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Abstract

Background—To determine the demographic distribution of Young Onset Parkinson's Disease (YOPD) in the United States and to quantify the burden of neuropsychiatric disease manifestations.

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Contributorship

1. Research project:
 - A. Conception. Dr. Allison Willis conceived this study.
 - B. Organization. Dr. Allison Willis organized the design of this study.
 - C. Execution. Dr. Allison Willis is responsible for the execution of this study.
2. Statistical Analysis:
 - A. Design. Dr. Allison Willis, Dr. Mario Schootman, and Dr. Brad Racette collaborated in the design of this study.
 - B. Execution. Dr. Allison Willis, Dr. Mario Schootman, Dr. Nathan Kung. Dr. Allison Willis had full access to and takes full responsibility for the accuracy of the data.
 - C. Review and Critique. Dr. Allison Willis, Dr. Mario Schootman, Dr. Nathan Kung, contributed to reviewing and critiquing the statistical analyses.
3. Manuscript Preparation:
 - A. Writing of the first draft. Dr. Allison Willis and Dr. Kung wrote the first draft of this manuscript.
 - B. Review and Critique. Dr. Allison Willis, Dr. Mario Schootman, Dr. Nathan Kung, and Dr. Brad Racette each contributed to reviewing and critiquing the manuscript.

Competing Interests

Dr. Willis: none

Dr. Schootman: none.

Dr. Racette: none.

Dr. Kung: none.

Methods—Cross sectional study of 3,459,986 disabled Americans, aged 30 to 54, who were receiving Medicare benefits in the year 2005. We calculated race and sex distributions of YOPD and used logistic regression to compare the likelihood of common and uncommon psychiatric disorders between beneficiaries with YOPD and the general disability beneficiary population, adjusting for race, age, and sex.

Results—We identified 14,354 Medicare beneficiaries with YOPD (prevalence = 414.9 per 100,000 disabled Americans). White men comprised the majority of cases (48.9%), followed by White women (34.7%), Black men (6.8%), Black women (5.0%), Hispanic men (2.4%), and Hispanic women (1.2%). Asian men (0.6%) and Asian women (0.4%) were the least common race sex pairs with a YOPD diagnosis in this population (chi square, $p < 0.001$). Compared to the general population of medically disabled Americans, those with YOPD were more likely to receive medical care for depression (OR: 1.89, 1.83-1.95), dementia (OR: 7.73, 7.38-8.09), substance abuse/dependence (OR: 3.00, 2.99-3.01), and were more likely to be hospitalized for psychosis (OR: 3.36, 3.19-3.53), personality/impulse control disorders (OR: 4.56, 3.28-6.34), and psychosocial dysfunction (OR: 3.85, 2.89-5.14).

Conclusions—Young Onset Parkinson's Disease is most common among white males in our study population. Psychiatric illness, addiction, and cognitive impairment are more common in YOPD than in the general population of disabled Medicare beneficiaries. These may be key disabling factors in YOPD.

Keywords

Young Onset Parkinson's Disease; Psychiatry; Addiction; Dementia; Medicare

1. Introduction

Parkinson's disease (PD) is a common neurodegenerative disease, affecting nearly 2% of the elderly in the United States [1]. Young Onset Parkinson's disease (YOPD), commonly defined as PD occurring in those aged 21-49 [2-4] is clinically similar to Older Onset PD (OOPD) [5], although some data suggest that YOPD patients are more likely to have earlier onset of motor fluctuations [6]. There are clear differences in race and sex distributions of older onset PD with white men having the highest risk. However, the epidemiological data on YOPD are limited; with most studies including patients aged 21-49 drawing conclusions based on fewer than 50 cases [7;8]. The prevalence of YOPD among those living in Europe is estimated to be 12-20 per 100,000, [8;9], and up to 45 per 100,000 among those living in Asian countries [10]. However, population based epidemiological data, and data on non-whites with YOPD are limited.

YOPD presents unique challenges and stressors to patients and their families. The disease strikes at a time in life that for many is the most productive, rewarding, and demanding. YOPD may be associated more frequently with psychiatric disorders such as depression, anxiety, and psychosis, due to both disease process and treatment side effects [2;11;12]; however, none of these studies was population-based, so biases inherent in clinic-based studies cannot be excluded. PD patients may be at higher risk of addictive behaviors [13] and addictive behavior has been described as a side effect of all classes of dopaminergic medications used to treat the motor symptoms of PD [14]. Although people with OOPD have an increased risk of dementia compared to those without PD, the risk of dementia in Young Onset PD is less clear. A recent study suggested that dementia in PD is more strongly associated with older age at onset than duration of illness, [15;16] in which case those with YOPD could be expected to be relatively free of cognitive impairment.

There is no population-based disease registry for Young Onset PD in the US; however, YOPD cases frequently receive disability benefits prior to reaching the age 65 Medicare eligibility. As such, Medicare records obtained from the Center for Medicare Services (CMS) serve as a population-based registry of disabled YOPD for the US. The aim of this study was to investigate the epidemiology of disabling PD by studying clinical diagnostic and health service utilization data from YOPD cases receiving Medicare benefits with a focus on psychiatric manifestations. Understanding the cognitive and behavioral comorbidities encountered by those with YOPD may facilitate treatment guidelines to prolong the independent function of those with YOPD.

2. Methods

This study was approved by the Human Studies Committee at Washington University School of Medicine.

2.1. Study Population and Clinical Data

PD cases were identified from Medicare research-identifiable files, which contain individual-level data on Medicare benefit recipients, including ICD-9 codes, date of birth, race, sex, and zip code of residence. Medicare is a government mandated insurance and prescription program that provides benefits to elderly and disabled Americans. The study population consisted of Medicare beneficiaries between the ages of 30 and 54, who were living in the United States in the year 2005 and who had qualified for Medicare insurance by virtue of being awarded medical disability status. From that population, we further identified Parkinson's disease cases using ICD-9 codes 332 (Parkinson's disease) or 332.0 (paralysis agitans). Beneficiaries who also had diagnoses of secondary parkinsonism (332.1) or other degenerative diseases of the basal ganglia (333.0) were excluded from analysis. Gender and ethnicity were identified using standard Medicare sex and race codes. Age was determined using the date of birth. We excluded patients aged < 30 years with a diagnosis of PD to exclude juvenile onset parkinsonism, which is not likely due to PD [17], and patients aged 55 years or older, as these cases could be considered the lower limit of older onset PD. We included cases aged 50 to 54 because of the length of time typically required to apply for and be declared legally disabled, then start receiving Medicare benefits.

We extracted individual level data from the Medicare Beneficiary Annual Summary File, which contains data on common medical conditions, health service utilization. These data use ICD-9 based algorithms to indicate whether each beneficiary has had a claim submitted for diagnosis or treatment of common medical conditions, including depression and dementia/cognitive impairment [18]. These data also contain indicator variables that identify all beneficiaries who had Medicare claims for substance abuse or dependence treatment, and Diagnosis Related Group (DRG) codes for each of the first ten inpatient admissions in a given year. DRG codes indicate the primary clinical reason for a hospitalization and are used nationwide by Medicare providers to justify claims for inpatient care. We used these data to detect all beneficiaries who 1) received medical care for depression, dementia/cognitive impairment or substance abuse/dependence, or 2) were hospitalized with a primary diagnosis of: acute adjustment reaction, neuroses, impulse control/personality disorder, or psychosis.

2.2. Statistical Analysis

Descriptive analyses were performed to evaluate the race, gender, and age distributions of YOPD in our study population. We calculated the crude prevalence of disabled YOPD by race, sex, and age strata, using all disabled Medicare beneficiaries as the denominator population. One year diagnosis/treatment rates for dementia/cognitive impairment,

depression, and substance abuse/dependence were calculated for YOPD cases; the proportion of YOPD patients with dementia/cognitive impairment was compared by 5 year age strata. Logistic regression models were fitted with the following outcome variables: depression, dementia/cognitive impairment, and substance abuse/dependence to determine if disabled beneficiaries with YOPD were more or less likely to be diagnosed with or treated for these conditions than the general disabled Medicare population. In a second set of analyses, the risk of hospitalization for the following psychiatric conditions was compared between disabled beneficiaries with YOPD and those without YOPD: Acute adjustment reaction/psychosocial dysfunction, personality/impulse control disorder, psychosis, neuroses (non-depressive), depressive neuroses, and alcohol/substance abuse or dependence. All models included diagnosis with YOPD as the main predictor variable; age, sex, and race were covariates. Continuous variables were compared using a t-test or ANOVA; categorical variables were compared using chi-square tests. All statistical analyses were performed using PASW v. 16, 17, 18 or SAS version 9.2 software.

3. Results

3.1. Demographics of YOPD in the U.S

We identified 14,354 disabled Medicare beneficiaries aged 30-54 with PD in the year 2005, equaling a prevalence of 414.9 per 100,000 disabled Americans. The number of persons with YOPD increased steadily with age: 316 were 30-34 years, 994 were 35-39 years, 2,225 were 40-44 years, 4,200 were 45-49 years, and 6,619 were 50-54 years of age. The race and gender distribution of YOPD in this population mirrored that seen in population based studies of elderly onset PD [1]. White men comprised the majority of cases (48.9%, 95%CI: 48.1-49.7), followed by White women (34.7%, 95%CI: 34.0-35.4), Black men (6.8%, 95%CI: 6.4-7.2), Black women (5.0%, 95%CI: 4.7-5.3), Hispanic men (2.4%, 95%CI: 2.2-2.6), and Hispanic women (1.2%, 95%CI: 1.0-1.4). Asian men (0.6%, 95%CI: 0.50-0.73) and Asian women (0.4%, 95%CI: 0.31-0.50) had the lowest rates of YOPD diagnosis in this population (chi square, $p < 0.001$). Prevalence ratios, calculated with Whites and men as the reference groups, were also very similar to those found with identical techniques applied to our previous population based studies of OOPD [1] (Table 1).

3.2. Neuropsychiatric Manifestations of Disabling YOPD

Mood disturbance in YOPD was common, with 40.7% of persons with YOPD identified as receiving care for depression (in either the outpatient or inpatient setting) in the year 2005. In fact, 8,278 (57.7 %) YOPD cases were evaluated or treated for a psychiatric illness of any kind during the year. Compared to the non-YOPD disabled Medicare population, disabled Medicare beneficiaries with YOPD were almost twice as likely to receive medical care (either outpatient or inpatient) for depression (unadjusted OR 1.89, 1.83-1.95; adjusted OR 1.83, 1.78-1.90). Finally, 17% of cases in our YOPD cohort received a diagnosis of or treatment for substance abuse/dependence in the year 2005, corresponding to a three-fold increase in the likelihood of these illnesses compared to the general disabled population (unadjusted OR: 3.00, 2.99-3.01; adjusted OR: 3.14, 3.03-3.24) (Table 2).

3.3. Hospitalization for Psychiatric Illness

In addition to having a significant overall burden of psychiatric illness, our examination of hospitalization data investigated whether YOPD patients are likely to have severe manifestations (defined as those requiring hospitalization) of both common (e.g., neuroses, mood disorders) and uncommon psychiatric (e.g. impulse control disorders) illnesses. Medicare Beneficiaries with YOPD underwent 12,322 hospitalizations in the year 2005. Thirty-two percent ($n=4028$) of these hospitalizations were for psychiatric illnesses. Compared to the general disabled population, YOPD patients had a greater likelihood of

hospitalization for specific psychiatric illnesses. Psychosis was the most frequently documented reason for hospitalization in YOPD, accounting for 82.6 % of psychiatric hospitalizations, and 11.6% of all YOPD patient hospitalizations (Table 3). Less common psychiatric conditions seemed to have a greater impact on disabled Americans with YOPD compared to those without the diagnosis. As shown in Table 3, the greatest increase in odds of hospitalization associated with a diagnosis of YOPD was found for “impulse control disorders” (unadjusted OR 4.56, 95% CI 3.28-6.34; adjusted OR 5.60, 95% CI 4.02-7.80). YOPD patients had a two to four-fold increase in the risk of hospitalization for psychosis (OR 3.36, 95% CI 3.19-3.53), acute adjustment disorder/psychosocial dysfunction (OR 3.85, 95% CI 2.89-5.14), and alcohol/substance abuse (OR 2.18, 95% CI 1.75-2.71). This increase in risk did not change significantly when variables for patient race, age, and sex were included in regression models. There was a relatively lower increase in the odds of hospitalization for common psychiatric illnesses-depressive neuroses (unadjusted OR 1.39, 95% CI 1.19-1.63; adjusted OR 1.47, 95% CI 1.26-1.72) and non-depressive neuroses (unadjusted OR 1.39, 95% CI 1.19-1.63; adjusted OR 1.47, 95% CI 1.26-1.72).

3.4 Cognitive impairment/Dementia in YOPD

Nineteen percent (n=2745) of YOPD cases carried a diagnosis of dementia or cognitive impairment according to chronic condition warehouse diagnosis algorithms [19] (Table 2). The frequency of dementia/cognitive impairment increased steadily with age group category: 12.0 % (aged 30-34), 12.3% (aged 35-39), 13.8% (aged 40-44), 24.4% (aged 50-54) (chi square, $p < 0.05$, p for trend < 0.05). Unlike what has been reported in a large OOPD Medicare beneficiary cohort [20] (in which cognitive impairment/dementia diagnosis occur most often in non-whites and women), we found that disabled whites (81.2%, non-whites 18.8%) and men (62.2%, women 37.8%) with YOPD were more often had a cognitive impairment/dementia diagnosis (chi square for each < 0.05). Even after adjusting for patient race, age, and sex, Medicare disability beneficiaries had substantially greater odds of having a cognitive impairment/dementia diagnosis compared to the general disabled beneficiary population (unadjusted OR 7.73, 7.38-8.09; adjusted OR 7.12, 6.80-7.46).

4. Discussion

In this nationwide epidemiological study, we report the demographic distribution and psychiatric disease burdens of Young Onset Parkinson's using a population-based cohort of disabled Medicare recipients. Our data demonstrate that YOPD, like OOPD, is most common among Whites and men. Moreover, we found that the race and gender distributions of YOPD were nearly identical to that found in a population-based study of OOPD (which used 98% of the U.S. population over the age of 65 as the denominator) [1], despite the fact that our YOPD prevalence estimates were calculated using disabled Medicare beneficiaries as the denominator. Our data also indicate that depression, cognitive impairment, and addictive behaviors are common in YOPD, more so than in the disabled Medicare population. Finally, our data suggest that YOPD patients are at greatly increased risk being hospitalized for relatively uncommon psychiatric illnesses.

There are several strengths to our study design. Our study included over 14,000 cases of YOPD whereas previous studies included fewer than 300. This sample size provides greater power and precision to detect clinically important differences in psychiatric disease rates by various demographic features, such as age, and provides important data on the burden of YOPD among women and non-whites. The similarity in prevalence rates between our OOPD and this YOPD study suggests that identification of disabled YOPD cases may provide meaningful, population-based, and generalizable data on the race and gender epidemiology of YOPD.

In addition to finding that the demographic distribution of YOPD among Medicare beneficiaries mirrors that of OOPD, our data suggest that neuropsychiatric diagnoses—dementia/cognitive impairment and disorders of mood or impulse control—are very common among disabled YOPD patients. Our finding of an age-related increase in the prevalence of dementia/cognitive impairment is in agreement with previous studies that dementia risk in PD increases with age [21;22]. Moreover, this finding has important pathophysiological and clinical study design implications. Dementia in OOPD is more commonly diagnosed in women and blacks [23]. Our YOPD data here do not follow that pattern. Rather, in our population of disabled Americans with YOPD, cognitive impairment was most commonly diagnosed amongst whites and males. Possible explanations include an increased susceptibility to cognitive impairment, greater recognition or reporting of cognitive symptoms. Cognitive impairment in men with YOPD may be associated with greater perceived or actual social/professional dysfunction, and result in a greater need for disability benefits. Alternatively, these data may reflect in part a disparity in the awarding of disability status and benefits that favors men and whites with YOPD. Because studies of cognitive change in this population are less likely to be confounded by manifestations of co-existing Alzheimer or vascular pathology, YOPD patients may be an ideal population for future clinical studies that seek to characterize patterns of cognitive dysfunction that are unique to PD. Additionally, the study of non-familial younger onset cases may be better suited for long term studies of measures to improve and maintain executive function.

In addition to providing comparative demographic data on YOPD vs. OOPD, and describing age and race-sex trends in cognitive impairment in YOPD, our data allowed us appreciate the burden of common psychiatric comorbidities in YOPD. Psychiatric illness in OOPD is well described [24], with data suggesting that involvement of the mesolimbic, frontocortical, amygdalal, and nigral circuits contribute to altered mood and behaviors [25]. Depression and anxiety may precede PD motor manifestations by several years [26;27], evident pathologically as neurodegenerative change or dysfunction of dopaminergic or noradrenergic innervation in the limbic system and lateral ventral striatum [28;29]. Our data support the findings that psychiatric illnesses are common comorbidities in YOPD, requiring a significant use of health services. In addition to having a greater likelihood of common psychiatric conditions, our YOPD population had more severe manifestations of both common (depression) and uncommon (impulse control, substance abuse) mental disorders than other young disabled Medicare beneficiaries, as shown by our comparative psychiatric hospitalization analysis. The greatest increase in odds of hospitalization was for disorders of impulse control, a potentially important finding that merits cautious interpretation. Previous studies have found an increased risk of gambling, shopping, and sexual addiction in those being treated with dopaminergic medications—a nearly three-fold increase in those taking dopamine agonists (the preferred class in YOPD) and a 50% increase associated with levodopa treatment [30]. However, PD clearly affects dopamine reward pathways, and it is possible that PD patients would exhibit increased risk taking behavior in the absence of treatment. It is unclear from this study the extent to which pathophysiological, treatment, and health service utilization variables contribute to the relative increases we found in treatment for impulse control disorders, alcohol/substance abuse among those with YOPD. Psychiatric illness in YOPD has been shown to correlate with poorer perceived quality of life, and greater disability [31;32]. If these behaviors contribute significantly to the need for or practice of applying for disability, changes in common treatment paradigms may be necessary. Future longitudinal studies using detailed clinical data and prescription records may clarify the role of dopaminergic medications in the development and relative functional impact of these behaviors in YOPD.

There are several limitations to this study. We do not have complete case ascertainment, as not all YOPD patients receive Medicare benefits. Therefore, our data do not reflect the total

number, groupings or health behavior of YOPD patients in the entire U.S population, although the similarity of race-sex groupings to our OOPD Medicare study suggests that our findings may approach generalizability to the U.S. YOPD population. Undoubtedly, there are personal, physician, socioeconomic, and local political factors that influence when in the course of the illness a patient will seek disability status. Similarly, there could be differences in the ease, interest, or ability of women, non-whites, those with mild symptoms or those without psychiatric manifestations to obtain Medicare benefits in this age group. As a result, our findings could be biased to finding a higher prevalence of psychiatric illness or addiction than may be seen in a working population of YOPD patients. Finally, our case finding method relied on physician diagnostic coding; therefore, we cannot exclude misdiagnosis of essential tremor, under-diagnosis of psychiatric comorbidities between physicians. Despite these caveats, our study provides valuable data regarding the current epidemiology of disabled Young Onset Parkinson's Disease in the United States, and the psychiatric burdens experienced by this large group of patients.

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Table 1
Parkinson Disease prevalence among young Medicare Beneficiaries, year=2005

Characteristic	Disabled YOPD N (%) Total= 14,354	Disabled Beneficiaries N (%) Total =3,459,986	Crude YOPD prevalence* (95%CI)	Prevalence ratio (95% CI)
Race				
White	12043 (83.9)	2586434 (74.8)	465.6 (457.4-474.0)	Ref.
Black	1659 (11.6)	675113 (19.5)	245.7 (234.1-257.8)	0.53 (0.50-0.53)
Hispanic	509 (3.5)	134928 (3.9)	377.2 (345.5-411.1)	0.81 (0.74-0.81)
Asian	125 (0.9)	35374 (1.0)	353.4 (295.4-419.6)	0.76 (0.64-0.76)
Native American	18 (0.1)	28137 (0.8)	63.9 (39.1-99.1)	0.14 (0.09-0.14)
Sex				
Male	8452 (58.9)	1865291 (53.9)	453.1 (443.5-462.9)	Ref.
Female	5902 (41.1)	1594695 (46.1)	370.1 (360.7- 379.6)	0.82 (0.79-0.82)
Age strata				
30-34	316 (2.2)	276782 (8.0)	114.2 (102.0-127.1)	0.19 (0.17-0.19)
35-39	994 (6.9)	433856 (12.5)	229.1 (214.7-243.1)	0.38 (0.35-0.38)
40-44	2225 (15.5)	700486 (20.2)	317.6 (303.7 -330.0)	0.53 (0.51-0.53)
45-49	4200 (29.3)	940708 (27.2)	446.5 (431.2-458.1)	0.75 (0.72-0.75)
50-54	6619 (46.1)	1108154 (32.0)	593.8 (579.6-608.2)	Ref.

*
per 100,000 disabled Medicare beneficiaries

Table 2
Odds of treatment for Psychiatric Illness Among Young Medicare beneficiaries with Parkinson Disease (year=2005)

Diagnosis	Disabled YOPD N=14, 354		Likelihood of Condition Compared to the Young Disabled Medicare Population	
	%	n	Unadjusted odds ratio (95% CI)	Adjusted odds ratio* (95% CI)
Dementia/Cognitive impairment	19.1	2732	7.73 (7.38-8.09)	7.12 (6.80-7.46)
Depression	40.7	5847	1.89 (1.83-1.95)	1.83 (1.78-1.90)
Substance Abuse/Dependence	17.4	2491	3.00 (2.99-3.01)	3.14 (3.03-3.24)

* Adjusted for age, race, and sex.

Table 3
Odds of Psychiatric Hospitalization in YOPD (year=2005)

Primary Diagnosis *	Hospitalizations of Disabled YOPD N=12, 322		Likelihood of Hospitalization for Psychiatric Diagnosis **	
	%	n	Unadjusted odds ratio (95% CI)	Adjusted odds ratio [†] (95% CI)
Acute Adjustment reaction/Psychosocial dysfunction	0.3	47	3.85 (2.89-5.14)	4.05 (3.03-5.40)
Personality and Impulse control disorder	0.2	36	4.56 (3.28-6.34)	5.60 (4.02-7.80)
Psychosis	11.6	1661	3.36 (3.19-3.53)	3.80 (3.60-4.00)
Neuroses, not depressive	0.2	29	1.95 (1.36-2.82)	2.24 (1.55-3.23)
Depressive neuroses	0.6	81	1.39 (1.19-1.63)	1.47 (1.26-1.72)
Alcohol/substance abuse	1.1	156	2.18 (1.75-2.71)	2.41 (1.93-3.00)

* Based on the Diagnosis Related Group (DRG) Code for hospitalization submitted by physician or hospital to the Centers for Medicare Services.

** Compared to the general disabled Medicare population

[†] Adjusted for age, race, and sex.