

# Validation of hospital register-based diagnosis of Parkinson's disease

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## ABSTRACT

**INTRODUCTION:** Denmark has a long-standing tradition of maintaining one of the world's largest health science specialized register data bases as the National Hospital Register (NHR). To estimate the prevalence and incidence of diseases, the correctness of the diagnoses recorded is critical. Parkinson's disease (PD) is a neurodegenerative disorder and only 75-80% of patients with parkinsonism will have idiopathic PD (iPD). It is necessary to follow patients in order to determine if some of them will develop other neurodegenerative diseases and a one-time-only diagnostic code for iPD reported in the register may be incorrect.

**MATERIAL AND METHODS:** This was a large nationwide population-based study of risk factors for iPD, called Parkinson's disease in Denmark (PASIDA). We evaluated the iPD diagnosis reported in the NHR. Medical records with primary diagnoses of iPD from six neurological departments were collected and abstracted using a standardized system to review the diagnostic accuracy of the ICD codes.

**RESULTS:** Among the 1,040 medical records abstracted, 857 (82.4%) patients met our criteria for iPD. 183 (17.6%) of the patients suffered from other diagnoses such as atypical PD (66 patients), secondary PD (60 patients) and other diagnoses (46 patients).

**CONCLUSION:** Possibly only about 82% of the patients with the primary diagnosis of iPD in the Danish NHR actually suffered from iPD. To improve diagnostic validity, we appeal to update the ICD code and to identify the correct parkinsonian phenotype to reduce biased case sampling in register-based studies and appropriate treatment for these rare diseases.

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Idiopathic Parkinson's disease (iPD) is a neurodegenerative disorder characterized by progressive loss of dopaminergic neurons of the substantia nigra pars compacta (SNPC) and a rising number of Lewy bodies in the surviving neurons [1]. The changes lead to a decrease in the

level of the neurotransmitter dopamine in SNPC, resulting in characteristic motor symptoms: bradykinesia, rigidity, postural instability and resting tremor. According to the Danish Parkinson Society, a total of 6,000-8,000 patients live with this diagnosis in Denmark, and its aetiology is not well understood [2]. A small fraction of cases are due to genetic mutations in familial disease and, additionally, iPD is multifactorial and probably results from undetected gene-environment interactions [3]. The public health relevance of iPD is rising due to its increasing prevalence in the aging populations with entailing burdens such as loss of quality of life and rising health care costs. Denmark has a tradition of maintaining one of the world's largest health science information data banks based on a series of specialized registers. This includes the Danish National Hospital Register (NHR) operated by the Danish National Board of Health [4]. To base estimates of variations in prevalence and incidence of diseases over time on register records, the correctness of the diagnoses recorded in the NHR is critical. In order to ascertain the number of insidious, progressive diseases such as iPD which are suspected when the characteristic motor symptoms appear, it is necessary to follow patients with such symptoms over time as some cases will develop other neurodegenerative diseases, and a one-time only diagnostic code for iPD reported in the NHR may consequently be incorrect [5, 6]. In fact, among patients with parkinsonism (Parkinson-like symptoms), only 75-80% suffer from iPD [7-9]. In the present study, we evaluated how many of the patients registered in the NHR with an International Classification of Diseases code (ICD-code) for iPD (ICD-8 342 and ICD-10 G20) in 1996-2006 suffered from iPD, and how many suffered from other neurodegenerative diseases. The evaluation included a fixed group of cases and was based on medical record review. The present study is a sub-study in what is currently the largest populations-based register and interview study on the aetiology of iPD called Parkinson's disease in Denmark (PASIDA).

## MATERIAL AND METHODS

### Study population

We evaluated the iPD diagnosis reported to the NHR by six Danish neurological hospital departments. The NHR

## ORIGINAL ARTICLE

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TABLE 1

Descriptive characteristics of patients included in the medical abstraction study (n = 1,040). The values are %.

	iPD (n = 857)	MSA (n = 25)	DLB (n = 16)	PSP (n = 10)	Other PD-like syndromes <sup>b</sup> (n = 15)	ET (n = 16)	Second- ary PD (n = 60)	Other diagnoses (n = 30)
<i>Gender</i>								
Male	56.1	56.0	75.0	60.0	66.7	62.5	38.3	56.7
<i>Year of birth</i>								
1920-1929	13.1	16.0	12.5	10.0	–	25.0	31.7	10.0
1930-1939	45.6	36.0	68.8	50.0	33.3	50.0	45.0	40.0
1940-1949	31.0	32.0	18.7	20.0	26.7	18.8	18.3	33.3
1950-1959	8.5	16.0	–	20.0	6.7	6.2	5.0	10.0
1960 and later	1.8	–	–	–	33.3	–	–	6.7
<i>First hospital PD diagnosis calendar year<sup>a</sup></i>								
Before 1996	13.1	4.0	–	10.0	–	–	1.7	3.3
1996-2004	70.1	60.0	37.5	60.0	60.0	37.5	70.0	66.7
After 2004	16.8	36.0	62.5	30.0	40.0	62.5	28.3	30.0

DLB = dementia with Lewy bodies; ET = essential tremor; iPD = idiopathic Parkinson's disease; MSA = multiple systemic atrophy; PD = Parkinson's disease; PSP = progressive supranuclear palsy.

a) A primary or secondary diagnosis could be given at another hospital before 1996.

b) Patients met most of the criteria for atypical Parkinson's disease syndromes, but at the same time suffered from other diagnoses affecting the central nervous system.

was instituted on 1 January 1977 and contains information on all non-psychiatric hospital admissions [4]. Out-patient visits to departments for somatic diseases were included from 1 January 1995. Any contact of a Danish resident with the hospital system generates a record in the NHR including the patient's personal identification number, dates of admission and discharge (inpatient registration), dates of first and last contact (outpatient registrations), treating department, a code for the primary discharge diagnosis, and up to 19 supplementary diagnoses. Diagnoses are coded according to the 8th revision of the ICD in 1977-1993 and thereafter according to the 10th revision (ICD-10). In May 2007, we searched the Hospital Register for all primary and supplementary diagnoses in the period from 1 January 1996 to 31 December 2006 using the diagnostic codes for iPD. We included only patients with a primary discharge diagnosis for iPD as these diagnoses are a priori considered to be more accurate. We required that a primary iPD diagnosis was made at one of the following six selected hospitals: Odense, Aarhus, Bispebjerg, Naestved, Esbjerg or Glostrup. To minimize the risk of survivor bias (i.e. bias due to overrepresentation of long-term survivors in the case group), we established a set of sampling criteria: subjects should be under 70 years of age at the date of diagnosis if the diagnosis was made in 1997-2001, and cases had to be under 80 years of age at diagnosis if the diagnosis was made after 2001. Also, patients had to be alive by May 2007. We identified a total of 1,266 patients registered in the six hospital departments with at least one in- or outpatient hospital contact labelled as iPD. For patients with both a primary and a supplementary iPD

diagnosis at more than one visit, we used the first hospital contact date for iPD – whichever came first – to approximate debut as closely as possible. We asked the departments for permission to retrieve a copy of the patients' records. Again, only records of patients alive at the time when we contacted a centre were requested. Thus, 226 subjects were excluded as they had passed away between request and retrieval of the record.

### Abstraction

To achieve a high standardization, the record review followed structured guidelines. The date the patient was in contact with a neurological department/outpatient clinic was noted as was examination by a specialist in neurology and by a private practitioner specialized in neurology. Contacts to relevant hospital services, e.g. neurosurgeon consultation, were noted. Presence of cardinal symptoms of iPD (resting tremor, bradykinesia, rigidity and asymmetrical onset), atypical symptoms (dementia before cardinal symptoms, early falls, severe symptomatic dysautonomia, rapid progression, sudden symptoms, supranuclear gaze palsy, hallucinations unrelated to medication, freezing phenomena and Babinski sign), self-reported time of onset of disease, and symptoms indicating diseases clearly distinct from iPD (e.g. a cerebrovascular insult or arteriosclerotic dementia) were noted. The date of first appearance of each relevant symptom in the record was also abstracted, as was information on types of and response to treatment. The results of cognitive tests and of computed tomography scan, DaTSCAN, magnetic resonance scan, etc., were abstracted.

### Idiopathic Parkinson's disease

The criteria for iPD used in the study were partly based on those of the United Kingdom Parkinson's Disease Society Brain Bank [5] and those of Gelb et al [10]. We determined whether patients suffered from iPD on the basis of the presence of cardinal motor symptoms, atypical symptoms, response to anti-parkinsonian medication and the treating physician's final diagnosis. In general, patients were not assigned to the iPD category if they had (i) fewer than two cardinal signs, (ii) atypical features, (iii) not been treated with levodopa or dopamine agonists, (iv) no substantial effect of treatment with levodopa or dopamine agonists or (v) clear indications of a non-iPD diagnosis, e.g. a cerebrovascular insult. Cases were excluded if the observation period was too short to ascertain key features from the clinical course or if information about cardinal symptoms were missing. A few cases with incomplete data were retained as later treatment records of these patients clearly indicated an iPD diagnosis, e.g. an STN operation. Reviewers were trained in a course conducted over two months by a physiotherapeutic expert in movement disorder (LH) and by a specialist in movement disorders (LW). Also, 25% of all records were evaluated by LH and among these, 80% were also evaluated by LW to achieve a second opinion. Abstracted data were entered into an electronic database. A quality check of data entry for 50 records selected at random and entered twice showed a high level of agreement for data entry (98%). Furthermore, an independent re-evaluation of diagnoses in a random sample of 50 iPD patients resulted in the same conclusion for 48 patients (96%).

### Atypical Parkinson's disease syndromes

Multiple systemic atrophy (MSA) is characterized by parkinsonism (PS), dysautonomia, cerebellar and corticospinal deficits. The disease frequently begins with bladder dysfunction, and the motor disorder often consists of bradykinesia, rigidity, gait instability and at times tremor, but in more patients, cerebellar ataxia is the initial motor disorder [11]. Progressive supranuclear palsy (PSP) is characterized by bradykinesia and rigidity, often with symmetric onset and vertical supranuclear gaze palsy, with instability and falls occurring already within the first year of diagnosis [12]. In dementia with Lewy bodies (DLB), cognitive impairment comes before or at the same time as motor symptoms, often combined with fluctuating cognition and recurrent visual hallucinations [9].

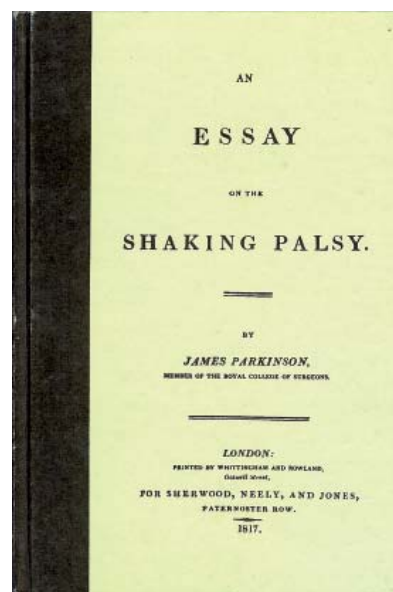
Fifteen medical histories could not be attributed directly to the above referenced groups (iPD, MSA, PSP, DLB) (Table 1, footnote). This group may also include patients with possible corticobasal degeneration [13]. These are termed Parkinson-like syndromes. Secondary

causes of PS include medication-induced PS or vascular PS. Drug-induced PS occurs most often in patients who are treated with dopamine receptor blockers and the symptoms are typically symmetric. Tremor and postural instability are less common. Vascular PS often has an abrupt onset of symptoms, predominant lower body involvement, postural instability, a history of falls, early dementia and it is less likely to respond to levodopa [9]. Neuroimaging may show multiple vascular territories with periventricular and subcortical ischaemic white matter changes, as well as ischaemia of the basal ganglia and brainstem. Essential tremor is a monosymptomatic disorder characterized by intention tremor, often inherited. Other diagnosis could be any other disease, e.g. based on a mistaken ICD code like Chorea Huntington G10.9.

*Trial registration:* Ethical approval: The study protocol was approved by the Danish Data Protection Agency (No 2006-41-7323) and by UCLA-IRB.

### RESULTS

A total of 857 patients (82.4%) met our criteria for iPD. Table 1 shows some descriptive characteristics of the patients included in this study. A total of 25 patients suffered from MSA (2.4%), 16 patients from DLB (1.5%), and ten from PSP (0.9%). Fifteen patients had PD-like syndromes (1.4%). Sixteen patients (1.5%) were diagnosed with essential tremor. Sixty patients (5.8%) suffered from secondary PS, among these 17 attributed to chemical exposures such as alcohol and solvents, 34 due to vascular central nervous system diseases, and in nine patient other unspecific aetiologies for PS were sus-



James Parkinson, a British surgeon and London-based pharmacist, who lived from 1755 to 1822 wrote a remarkable dissertation in 1817 entitled, "An essay on the Shaking Palsy." This dissertation described a common case story seen in six patients; a story later named Parkinson's disease. The features of this disease were described as follows: "Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace: the senses and intellects being uninjured".



TABLE 2

Clinical manifestations from medical record by diagnostic group.

	iPD (n = 857)	MSA (n = 25)	DLB (n = 16)	PSP (n = 10)	Other PD-like syndromes (n = 15)	ET (n = 16)	Sec- ondary PD (n = 60)	Other diagnoses (n = 30)
Disease duration, mean, years <sup>a</sup>	9.8	7.2	5.5	6.1	7.6	6.7	7.6	6.8
Resting tremor, %	88.5	68.0	81.3	70.0	86.7	81.3	75.0	53.3
Bradykinesia, %	94.9	100	93.8	90.0	80.0	37.5	71.6	40.0
Rigidity, %	95.6	96.0	93.7	100	93.3	50.0	80.0	50.0
Asymmetric onset, %	87.6	64.0	68.8	60.0	66.7	62.5	70.0	63.3
Postural dysreflexia, %	45.7	76.0	68.8	90.0	60.0	18.8	51.7	36.7
Severe dysautonomy, %	14.7	84.0	43.8	40.0	33.3	6.3	25.0	6.7
Fast time to progression, %	1.5	36.0	25.0	60.0	13.3	–	18.3	3.3
Sudden symptoms, %	12.0	28.0	12.5	40.0	33.3	18.8	40.0	26.7
Supranuclear gaze palsy, %	0.5	12.0	68.8	70.0	60.0	–	8.3	36.7
Babinsky sign, %	5.0	24.0	6.3	50.0	20.0	12.5	20.0	10.0
Early falls, %	2.8	32.0	18.8		26.7	–	20.0	6.7
Hallucinations unrelated to medication, %	1.1	8.0	37.5	50.0	33.3	–	6.7	3.3
Freezing phenomena, %	11.3	8.0	31.3	30.0	6.7	–	6.7	3.3
Dementia, %	16.6	28.0	93.8	50.0	40.0	12.5	25.0	20.0
Persistent asymmetry, %	78.7	48.0	50.0	40.0	60.0	62.5	48.3	26.7

DLB = dementia with Lewy bodies; ET = essential tremor; iPD = idiopathic Parkinson's disease; MSA = multiple systemic atrophy; PD = Parkinson's disease; PSP = progressive supranuclear palsy.

a) Number of years from first symptom date in medical record to medical record abstraction date.

pected (details not shown). Thirty patients (2.9%) suffered from other non-parkinsonian diseases. Finally, for 11 patients (1.1%) the medical record was incomplete and a diagnosis could not be determined, and multiple diagnoses were recorded for three patients (details not shown).

**Table 2** shows the number of years from first symptom date in medical record to abstraction date, the distribution of clinical signs abstracted from the records according to disease subgroups: iPD, MSA, DLB, PSP, other PD syndromes, secondary PS and essential tremor, and for those with various non-parkinsonian diseases. Specifically, for very few patients with iPD, the records showed fast progression of motor symptoms in the first 2-4 years after diagnosis (1.5%), in contrast to other patients – especially those with PSP. Likewise, sudden symptom onset was seldom found in patients with iPD in contrast to PSP and secondary PD. More patients with iPD showed persistent asymmetry of symptoms (78.7%) than did persons with atypical syndromes and secondary causes of PS. Supranuclear gaze palsy is characteristic of PSP, severe dysautonomia is an important clinical sign in association with MSA and postural dysreflexia is common in both PSP and MSA (90% and 76%, respectively).

## DISCUSSION

Conditions with PS display heterogeneous phenotypes and have different causes, prognoses and responses to treatment [14]. We identified a group of patients diagnosed with ICD-codes for iPD in the NHR and abstracted

their records in order to review the diagnostic accuracy. We found that in 17.6% of the records, the information from six speciality departments did not support our diagnostic criteria for iPD. Among those not meeting the iPD diagnostic criteria, we revised the diagnosis and determined that 66 (36%) of the patients suffered from atypical PD, 60 (33%) from secondary PD and 46 (25%) from other diagnoses. More patients who meet iPD criteria have several or even all of the characteristic motor symptoms, including resting tremor, bradykinesia, rigidity, asymmetric onset and persisting asymmetry. Furthermore, iPD patients have fewer atypical features than the other PS patients. Hughes et al reported that only 76% of clinical iPD diagnoses could be confirmed at autopsy and attempted to draw attention to features that can improve the accuracy of the diagnosis [5, 7]. Other clinico-pathological studies have been conducted, and in 2002 a study reported an improved 90% accuracy for the diagnosis of iPD given by movement disorder specialists [8]. The rate of misdiagnosed iPD at early stages of disease or by non-specialists is probably higher [15]. Findings at autopsy provide the most definite diagnosis; however, as long as the patient is alive and no biological markers are available, the diagnosis will essentially be made clinically and rely on parkinsonian features to identify iPD [10]. A study by Jancovic found that 8.1% of a group of 800 patients initially diagnosed in a tertiary specialty clinic as having iPD were later found to have another diagnosis after 7.6 years of follow-up [6]. The iPD diagnosis can be difficult to make, not least because

there are no pathognomonic features that discriminate between the iPD, MSA, DLB and PSP. The use of certain medications, the rapid rate of disease progression and atypical features like early onset of falling, the presence of certain dysautonomic symptoms, cognitive or behavioural changes, or a history of poor response to dopaminergic therapy can be used to discriminate between iPD and atypical PD [14]. Our record review indicated that 82% of the patients suffered from iPD based on the symptoms, treatments and atypical features recorded. Any study that identifies iPD patients solely on the basis of the Danish Hospital Register should be aware of this problem. In the future, regular update of the information on these neurological patients from the clinical departments to the NHR could reduce biased case sampling in register based studies.

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