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Diagnostic accuracy of parkinsonism syndromes by general neurologists

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ABSTRACT

Introduction: Movement disorder specialists can achieve a high level of accuracy when clinically diagnosing parkinsonism syndromes. However, data about the diagnostic accuracy among general neurologists is limited.
Objectives: This study investigated the recent diagnostic accuracy of parkinsonism syndromes by general neurologists.
Methods: A retrospective examination of 1362 post-mortem cases diagnosed in the years 2000–2012 by neuropathologists was performed. Out of these cases, we identified 111 patients who received a clinical parkinsonism diagnosis during life and 122 patients who received a neuropathological diagnosis of a parkinsonism syndrome post-mortem including 11 incidental cases.
Results: Fifty-eight (75.3%) of the 77 patients who had received clinical Parkinson's disease (PD) diagnoses were confirmed after the neuropathological examination. The sensitivity of the clinical diagnosis for idiopathic Parkinson's disease (PD) was 89.2% and the specificity was 57.8%. The corresponding numbers for progressive supranuclear palsy (PSP) were 52.9% and 100%, and for multiple system atrophy (MSA) were 64.3% and 99.0%, respectively.
Conclusions: Parkinson's disease is heavily overdiagnosed by general neurologists, whereas parkinsonism plus syndromes are underdiagnosed. Despite improvements in the diagnostic methods during recent decades and the development of diagnostic clinical criteria for parkinsonian syndromes, the diagnostic accuracy of Parkinson's disease remains relatively low, and 1/4 of diagnoses are incorrect.

1. Introduction

The clinical diagnostics of parkinsonism is often challenging, and a definite diagnosis can only be reached at autopsy [1]. Although no certain disease progression modifying treatment exists so far, the diagnostic accuracy is essential for optimizing patient care and conducting clinical trials. Even in highly specialized centers, more than one in seven patients with parkinsonism are misdiagnosed during life [2].

The diagnostic accuracy of the most common parkinsonism syndrome, idiopathic Parkinson's Disease (PD), is reported to be very high (99%) in tertiary hospitals by movement disorder specialists [2]. However, the diagnosis of PD by general neurologist or general practitioners (GPs) is likely to be substantially less accurate. For example, in the early 1990s the reported accuracy of the final clinical diagnosis of PD was only 76%, which probably reflects diagnoses made in the 1970s and 1980s [3]. In another study of that time that consecutively examined patient samples from the UK that are in the Parkinson's Disease Society Brain Bank (PDSBB), the clinical accuracy was also reported to be 76% [4]. By applying similar methods a decade later, the authors reported that diagnostic accuracy had improved to 90% [5]. However, most of the patients in the studies by Hughes et al. were clinically evaluated by specialized neurologists at a movement disorder unit, which probably improved the accuracy compared to evaluation by general neurologists. Very recently, Horvath et al. reported a retrospective study investigating the accuracy of making a correct clinical diagnosis of parkinsonian syndromes by various medical field specialists (neurologists, psychiatrists, internists) over the last century [6]. During that period, the accuracy of clinical diagnosis of PD was 71%,

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which improved over the study period to 86% between 2000 and 2010 [6], which is similar to the findings of earlier reports [3–5].

Atypical parkinsonism syndromes are rare compared to PD making the assessment of diagnostic accuracy even more challenging. The accuracy for diagnoses of progressive supranuclear palsy (PSP) and multiple system atrophy (MSA) has been reported to be 78% and 86%, respectively [7,8]. Additionally, a recent European study noted a 71% accuracy of clinical PSP diagnoses [9]. The sensitivity for detecting these disorders has been reported to be good, at least among movement disorder specialists (88% for PSP and 84% for MSA) [2]. The diagnosis of corticobasal degeneration (CBD) is highly accurate, but the sensitivity is poor, and approximately only half of the patients are diagnosed during life [10]. The diagnostic accuracy of atypical parkinsonism syndromes among general neurologists without a specialization in movement disorders has not been investigated. Additionally, most of the studies have been conducted in patients diagnosed before modern neuroimaging methods or published clinical diagnostic criteria were available.

In the present study, we investigated the accuracy of recent clinical diagnoses of parkinsonism by general neurologists in Finland. In Finnish clinical guidelines and clinical practice, the diagnosis of PD is established applying uniform diagnostic criteria [11] by general neurologists – there are no tertiary specialized movement disorder centers or movement disorder subspecialty training programs. Finnish public health care system is organized into two main levels: general (GPs at health care centers) and hospitals (regional, central and university). Neurologists work on the hospital level and also treat outpatients in the private sector. The neuropathological units in Finland are, on the other hand, active and locally centralized providing an opportunity to investigate modern diagnostic accuracy by general neurologists using a sample that is representative of all levels of patient care.

2. Materials and methods

2.1. Patients

We searched through the records of all 1362 individuals who had been examined post-mortem at the neuropathological unit of the Turku University Hospital, Finland, during the years 2000–2012. The hospital is one of five centers that conducts neuropathological examinations in Finland. This patient sample represents all cases that were referred for neuropathological examination during the 12-year period. To identify the cases that had a clinical and/or neuropathological diagnosis of parkinsonism, we first searched the referral texts for a clinical history of PD, PSP, MSA, CBS, Lewy body dementia (LBD), vascular parkinsonism (VaP), or other parkinsonisms. The same diagnoses were searched for in the neurolopathological reports irrespective of the clinical diagnosis. In all, 122 cases that had a clinical and/or neuropathological diagnosis of parkinsonism were found and selected for detailed examination. The study received approval from the local ethical committee and was conducted according to the principles of the Declaration of Helsinki.

2.2. Clinical data

The clinical features of all 122 cases were recorded and abstracted by a consultant neurologist experienced with movement disorder diagnostics and treatment (V.K.), unblinded to the pathological diagnosis. Clinical records from the university hospital and referrals for neuropathological examinations were used as sources of information. The final clinical diagnosis at the time of death was retrieved from available records.

The physician who first established the diagnosis of parkinsonism was not identifiable in many of the cases. However, according to Finnish guidelines, the diagnosis of idiopathic Parkinson's disease and related disorders should be performed by a neurologist, which is also the requirement for social benefits and for eligibility for medication re-imbursement. Currently, the United Kingdom Parkinson Disease Society Brain Bank (UKPDSBB) [11] criteria are used for diagnosing PD. The guidelines also recommend structural brain imaging to be performed, and thus, it is likely that almost all patients had been scanned with CT or MRI during the course of their disease. Unfortunately, we lack more detailed information of the structural imaging performed to the patients in this sample. In addition, 21 of the 122 patients had undergone a functional brain imaging examination (PET or SPECT) during life for diagnostic or scientific purposes. PET/SPECT imaging included [123I]FP-CIT or [123I]β-CIT SPECT in 17 patients of whom one was also scanned with [18F]fluorodeoxyglucose PET and one with [18F]fluorodopa PET. Two patients were scanned with [18F]fluorodopa PET, one with [11C]raclopride PET, and one with [18F]CFT.

Table 1
Patients with clinical parkinsonism ($n = 111$).

Clinical dg	*n*	%	Neuropathological dg
PD	77	69.4	PD (58)
			PSP (5)
			AD (5)[a]
			MSA (4)
			VaP (3)
			IatrP (1)
			WE (1)
MSA	10	9.0	MSA (9)
			CBD (1)
PSP	9	8.1	PSP (9)
CBS	2	1.8	CBD (1)
			PSP (1)
LBD	1	0.9	PD (1)
VaP	1	0.9	VaP (1)
Parkinsonism plus	1	0.9	MSA (1)
Undetermined	10	9.0	PD (7)
			PSP (2)
			CBD (1)

% = percentage of all patients with clinical parkisonism. PD = Parkinson's disease, MSA = multiple system atrophy, PSP = progressive supranuclear palsy, CBS = corticobasal syndrome, CBD = corticobasal degeneration, LBD = Lewy body disease, VaP = vascular parkinsonism, Parkinsonism plus = parkinsonism with atypical features, Undetermined = undetermined parkinsonism, AD = Alzheimer's disease, IatrP = iatrogenic parkinsonism, WE = Wernicke's encephalopathy.

[a] Three of the patients showed also ischemic degeneration in the basal ganglia area.

In comparison to previous studies in tertiary specialized movement disorder centers, the present sample represents a heterogeneous group of individuals who were diagnosed by general neurologists and referred for neuropathological examination mostly by non-neurologist physicians. The most common reason for conducting the autopsy was therefore to investigate the cause of death, not to characterize or confirm neurodegenerative diseases. The general autopsy was often performed in regional hospitals where the patient had also been treated. Neuropathological examinations were performed by the discretion of the general pathologist for patients with suspected or diagnosed neurological disorders, or due to abnormal findings in the macroscopic brain examination in the general autopsy.

2.3. Neuropathological examination

A neuropathologist (M.G.) re-evaluated the neuropathological data that led to the diagnoses of all 122 cases individually. The re-evaluation included immunohistochemical analyses when considered necessary for diagnostic confirmation, if not performed initially. For a definitive neuropathological diagnosis of PD, the criteria proposed by Gelb et al. were used [12]. In short, this meant a loss of pigmented neurons and gliosis in the substantia nigra and at least one Lewy body in the substantia nigra or locus ceruleus. As a modification, in acknowledgment of the relevance of alpha-synuclein pathology, we required characteristic immunohistochemistry positive for alpha-synuclein in intraneural inclusions and neurites [13]. For the neuropathological diagnosis of MSA, CBD and PSP, the following guidelines were used with slight modifications: The diagnostic criteria proposed by the Neuropathology working group on MSA [14], the Office of Rare Diseases neuropathological criteria for CBD [15], and the preliminary NINDS neuropathology criteria for PSP [16]. To meet these criteria, 31 cases that had typical PD or MSA pathology on routine hematoxylin–eosin and Bielschewsky's stains, but had not been investigated with alpha-synuclein stains, were retrospectively stained with anti-alpha-synuclein (clone KM51, Novocastra, Newcastle Upon Tyne, UK). In all retrospectively stained cases, typical PD or MSA alpha-synuclein pathology was found and no changes were made to previous neuropathological diagnoses. Additionally, five cases with a neuropathological diagnosis of PSP or CBD were retrospectively confirmed by anti-tau immunohistochemistry (clone AT8, Innogenetics, Gent, Belgium).

2.4. Clinicopathological comparisons

Final neuropathological diagnoses were considered to be the correct diagnoses. Positive predictive values (PPVs, true positive from all positive diagnoses), negative predictive values (NPVs, true negative from all negative diagnoses), sensitivity (true positive from real positive), and specificity (true negative from real negative) were calculated with their 95% confidence intervals for all patients with clinical parkinsonism, separately by diagnoses. When comparing the clinical to neuropathological

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