Author Information Page

Vanessa Pitz, MRes[1], Naveed Malek, MD[2], Edward S Tobias, PhD[3,4], Katherine A Grosset, MD[1,5], Steve Gentleman, PhD[6], Donald G Grosset, MD[1,5]

[1]Institute of Neuroscience and Psychology, University of Glasgow, Glasgow, United Kingdom

[2]Department of Neurology, Ipswich Hospital NHS Trust, Ipswich, United Kingdom

[3]School of Medicine, Dentistry and Nursing, University of Glasgow, Glasgow, United Kingdom

[4]Department of Clinical Genetics, Queen Elizabeth University Hospital, Glasgow, United Kingdom

[5]Department of Neurology, Institute of Neurological Sciences, Queen Elizabeth University Hospital, Glasgow, United Kingdom

[6]Department of Medicine, Imperial College London, London, United Kingdom

Title page

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Corresponding Author: Vanessa Pitz, PhD student, Institute of Neuroscience and Psychology, University of Glasgow, UK, v.pitz.1@research.gla.ac.uk

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Abstract

Background:

A good response to L-dopa is a key feature of Parkinson's disease (PD), and a poor response suggests an alternative diagnosis, but the extent of variation in the L-dopa response in definite PD is not well defined.

Literature Review:

A systematic review of papers reporting pathologically confirmed PD and L-dopa responsiveness, from 1971 to 2018, was performed using the medical subheadings 'post-mortem', 'Parkinson's disease', and 'L-dopa', in PubMed, Embase, and LILACS databases.

Cases:

12 papers described 445 PD cases: 61.7% male, age at disease onset 64.0 years (SD 9.6), age at death 77.1 years (SD 7.2). L-dopa responsiveness was reported in 399 (89.7%), either as a graded or a binary response. In the 280 cases (70.2%) describing a graded response, it was excellent in 37.5%, good in 45.7%, moderate in 12.1%, and poor in 4.6%. In the 119 cases describing a binary response (29.8%), 73.1% were L-dopa responsive, and 26.9% were non-responsive. Comorbid brain pathology was present in 137 of 235 cases assessed, being cerebrovascular in 46.0% and Alzheimer's in 37.2% of these, but its contribution to L-dopa responsiveness was unclear.

Conclusions:

The L-dopa motor response varies in definite PD. Explanations other than diagnostic inaccuracy should be explored.

Introduction

Clinical diagnostic criteria for idiopathic Parkinson's disease (PD) require the presence of core motor features, supported by an 'excellent' or 'clear and dramatic' L-dopa response [1, 2]. These criteria help to reduce clinical diagnostic error rates of between 5 and 25%, where idiopathic PD is not confirmed at autopsy [3, 4]. These observations might suggest that a less-than-excellent response to L-dopa is incompatible with a diagnosis of PD, and that variation in the L-dopa response in clinical trials is due to diagnostic error [5]. Clinically, benign disorders can be excluded by functional neuroimaging [5], but this does not exclude other neurodegenerative parkinsonian conditions. Assessing pathologically confirmed PD cases should give a clearer indication of the degree of variation in L-dopa response, and was the objective of the present study.

Case Series

Features of the L-dopa response

445 pathologically confirmed PD patients (61.7% male) were identified, age at onset was 64.0 (SD 9.6) years, L-dopa treatment was started 3.1 (SD 3.6) years after diagnosis, and disease duration at death was 13.0 (SD 6.5) years. Age at death was 77.1 (SD 7.2) years (Tables 1 and 2).

The L-dopa response was reported in 399 of 445 PD cases (89.7%) [1, 4, 6-15]. It was graded in 280 cases: excellent in 105 (37.5%), good in 128 (45.7%), moderate in 34 (12.1%), and none-to-poor in 13 (4.6%). In the remaining 119 cases, a binary response to L-dopa was reported: 87 (73.1%) of these were L-dopa responsive, and 32 (26.9%) were unresponsive. L-dopa doses were reported in 5 of 12 papers, but were largely declared as 'adequate' (often defined as 1000mg per day), rather than quantified. Where quantified, the mean daily L-dopa dose was 917mg (SD 446) in 23 cases [6].

Motor complications (motor fluctuations and dyskinesia)

Motor complications were reported in 148 patients in 4 papers [4, 10, 14, 15], being motor fluctuations in 63 cases (42.6%), and dyskinesia in 79 cases (53.4%).

Comorbid brain pathology

235 patients were assessed for the L-dopa motor response and comorbid brain pathology. 137 of these (58.3%) had additional brain pathology, most commonly cerebrovascular disease (46.0%) and Alzheimer's disease (37.2%) (Table 1). Data about the L-dopa response, motor complications, and comorbid pathology were only available in 25 cases, but did not readily explain the degree of L-dopa responsiveness.

Literature Review

Search strategy

Following PRISMA guidelines, PubMed, Embase and LILACS (and references in identified papers) were searched from 1971 to March 2018, using the combined medical subheadings ‘levodopa’, ‘Parkinson’s disease’, and ‘post-mortem’. The search was limited to humans, research articles, and English language. Studies had to include more than 5 pathologically confirmed PD cases, demographic details, and detail about the motor response to chronic L-dopa treatment. One researcher (VP) screened potentially eligible studies; a second researcher (DG) reviewed these; disagreements were resolved by consensus.

Results

893 studies were found, 757 full text articles were assessed, and 12 studies reporting 445 pathologically confirmed PD cases met inclusion criteria. The pathological diagnosis was made (in all 12 papers) by microscopic confirmation of severe depletion of pigmented neurons and Lewy body formation in the substantia nigra pars compacta. In addition, immunohistochemistry was reported in 7 of 12 papers, including alpha-synuclein staining in 5 of 12. Pathological rating scales were reported in 3 papers. Two papers [1, 10] recorded prospective clinical data; the remainder extracted data retrospectively from patient files. 3 studies also used standardised forms [4, 10, 12]. All studies reported the chronic out-patient L-dopa response.

Clinical assessments

Disease severity was graded by Hoehn and Yahr (H&Y) in 6 of 12 papers, and/or scored by the Unified PD Rating Scale (UPDRS) in 1 of 12 papers. 12 papers assessed the motor improvement on L-dopa [1, 4, 6-15], 4 the occurrence of motor complications, and 6 investigated comorbid pathologies. The degree of motor improvement with L-dopa was defined in 5 of 12 papers following UK Brain Bank descriptors [1, 10]. In the remaining 7 papers, the L-dopa motor response was categorised as either responsive or non-responsive [7, 9, 11-15].

Discussion

There is significant variation in the motor response to L-dopa treatment in pathologically confirmed cases; therefore, errors in the clinical diagnosis of PD do not fully explain this variability. A substantial proportion of pathologically confirmed PD cases have a response to L-dopa that is less than excellent. The definitions of what is 'excellent' regarding the motor response to L-dopa clearly influence this categorisation of patients, and such definitions have evolved. Prior to the MDS criteria for PD [2], the UK Queen Square Brain Bank criteria described an excellent response as '70-100%' but this was subjective, by interpretation of case records [1]. This definition, and the similarly defined lesser degrees of response, was predominant in the papers in the current review, being applied in 70.2% of the 399 cases. In clinical trials, around half of PD cases have an excellent L-dopa response [5]. Around three-quarters of PD cases fulfilling MDS clinical diagnostic criteria (73.4% of 434) have an excellent L-dopa response [16]. Future pathological reports would benefit from inclusion of the more objective definition of an excellent response, being >30% improvement in UPDRS Part 3 [2] or ≥24.5% improvement in the MDS UPDRS 3 [17].

There are several potential explanations for these findings. A worse motor score in men than women despite higher L-dopa doses [18] may indicate a gender difference. Also, the postural instability gait difficulty phenotype is less therapy responsive than tremor dominant Parkinson's [5]. However, an exception to this is benign tremulous PD: in pathologically confirmed cases, the L-dopa response during the first 8 years of treatment was definite in only 6 of 16 cases (37.5%), and 3 of 16 (18.8%) had no L-dopa response [19]. Slower progression in younger patients [20] may be partly due to better L-dopa responsiveness. Some of the variation in drug responsiveness may be due to genetic variations, such as in the dopamine metabolizing enzymes [21]. However, the pathological studies did not include demographic or genetic data to allow these factors to be examined in more detail.

The studies in the current review largely predate developments in testing for genetic mutation and variation related to PD, so that data relating this to the L-dopa response was very limited. Larger studies of L-dopa responses in pathologically confirmed genetic cases are warranted.

Other important variables in assessing the L-dopa response are the dose [5] and duration [1, 2] of treatment. A few cases in the pathological studies had low tolerability of L-dopa which was dose limiting, and detail regarding L-dopa doses was lacking in some studies, but the average treatment duration of 11 years before death was clearly adequate to assess treatment responses.

The development of motor complications (motor fluctuations or dyskinesia) is a key feature in later stages of PD. Dyskinesia was present in around half of the post-mortem confirmed PD cases in this review, which is somewhat lower than the prevalence in clinical trials, and likely indicates under-reporting in clinical notes [22].

Our study had certain limitations. Although tissue diagnosis is the gold standard pathological definition

of PD, just over half of the studies that we included relied on dopaminergic cell loss and Lewy body formation in the substantia nigra, as they predated alpha-synuclein staining. Extraction of clinical information retrospectively may affect the interpretation of the L-dopa response, and be subject of bias. All of the studies reported the chronic L-dopa response, rather than the results from acute challenge tests. Two studies with a total of 176 cases had a partial overlap of up to 69 cases, which could not be unbundled accurately, and affected our results [1, 10]. One study in 23 patients had an older age at onset of 82.7 (SD 2.2) years, and a disease duration of 8.5 (SD 2.7) years at time of death, which was therefore an outlier [14].

Conclusions

Variation in the L-dopa response in pathologically confirmed PD indicates that diagnostic error alone does not explain this observation. Around 10% of pathologically confirmed PD are unresponsive to L-dopa treatment, and an additional 12% have a modest response. Analysis of other modifying factors is required, to further understand the reasons for these observations.

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Author Roles

1) Research project: A. Conception, B. Organization, C. Execution
   VP: 1B, 1C
   KAG: 1A, 1B, 1C
   DGG: 1A, 1B, 1C

2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique
   VP: 2A, 2B, 3A
   NM: 2C
   KAG: 2A, 2B
   DGG: 2B, 2C

3) Manuscript: A. Writing of the first draft, B. Review and Critique
   VP: 3A
   NM: 3B
   EST: 3B
   KAG: 3B
   SG: 3B
   DGG: 3B

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Table 1: Clinical and pathological features in 445 pathologically confirmed Parkinson's disease patients

	PD cases (n=445)	Publications (n=12)
Age at onset (years)	64.0 (9.6)	12
Disease duration at death (years)	13.0 (6.5)	12
Age at death (years)	77.1 (7.2)	12
Symptom onset to starting L-dopa treatment (years)	3.1 (3.6)	2
L-dopa motor response reported	399/445 (89.7%)	12
Graded	280/399 (70.2%)	5
Excellent (>70%)	105 (37.5%)	
Good (50-70%)	128 (45.7%)	
Moderate (30-50%)	34 (12.1%)	
None-to-poor (<30%)	13 (4.6%)	
Binary	119/399 (29.8%)	7
Responsive	87 (73.1%)	
Unresponsive	32 (26.9%)	
Treatment duration (years)	10.9 (0.7)	4
Dementia	51/445 (11.5%)	5
Assessed for comorbid pathology	235/399 (58.9%)	6
Comorbid pathology present	137/235 (58.3%)	
Cerebrovascular	63 (46.0%)	
Alzheimer-type	51 (37.2%)	
Amyloid angiopathy	17 (12.4%)	
Diffuse Lewy body disease	5 (3.7%)	
Progressive supranuclear palsy	1 (0.7%)	

Data are mean (SD) or n (%)

Table 2: Demographics in pathologically confirmed PD patients reporting the motor response to L-dopa.

Study	PD patients total, n	Male, n (%)	PD patients with reported L-dopa response, n (%)	Type of L-dopa response grading	Clinical rating scales used	Mean age at PD onset, years (SD)	Mean age at death, years (SD)	Disease duration years (SD)	Onset to starting L-dopa, years (SD)
TOTAL	**445 (100%)**	**221 (61.7%)**	**399 (89.7%)**			**64.0 (9.6)**	**77.1 (7.2)**	**13.0 (6.5)**	**3.1 (3.6)**
Hughes et al. 1992 [1]	76	Not stated	69	Graded	H&Y	63.6 (13.3)	76.4 (10.25)	12.8 (7.0)	Not stated
Hughes et al. 1993 [10]	100	65	95	Graded	H&Y, MMSE, DSM 3	62.5 (9.2)	75.6 (6.7)	13.1 (6.3)	3.2 (3.7)
Rajput et al. 1993 [15]	26	18	20	Binary	H&Y, Webster	58.8 (8.8)	70.8 (8.5)	11.7 (9.3)	Not stated
De Vos et al. 1995 [7]	18	9	18	Binary	H&Y, MMSE, DSM 3, HAM-D	66.2 (NS)	76.3 (NS)	10.1 (NS)	Not stated
Halliday et al. 1996 [9]	11	8	6	Binary	CDR	67.4 (8.7)	77.6 (5.4)	10.3 (5.7)	Not stated
Louis et al. 1997 [12]	34	22	14	Binary	None	62.0 (NS)	76.0 (NS)	14.5 (NS)	Not stated
Litvan et al. 1998 [4]	11	Not stated	11	Graded	None	54.4 (4.0)	Not stated	15.6 (1.6)	Not stated
Joyce et al. 2002 [11]	23	15	23	Binary	None	65.0 (10.9)	78.1 (6.1)	13.2 (7.9)	Not stated
Halliday et al. 2008 [8]	7	2	7	Graded	H&Y, CDR	59.4 (8.6)	73.4 (9.3)	14.0 (3.4)	1.7 (0.6)
Matsumoto et al. 2014 [13]	16	12	16	Binary	None	63.6 (10.9)	72.8 (8.4)	10.2 (6.1)	Not stated
De Pablo-Fernandez et al. 2017 [6]	100	60	98	Graded	None	63.9 (10.3)	78.5 (6.9)	14.6 (7.7)	Not stated
Rajput et al. 2017 [14]	22	9	22	Binary	H&Y, Webster/UPDRS, MMSE	82.7 (2.3)	91.2 (3.1)	8.5 (2.7)	Not stated

ADL, Activity of Daily Living Scale; CDR, Clinical Dementia Rating; DSM, Diagnostic and Statistical Manual of Mental Disorders; HAM-D, Hamilton Depression Rating Scales; H&Y, Hoehn and Yahr; MMSE, Mini Mental State Examination; PD, Parkinson's disease; UPDRS, Unified Parkinson's Disease Rating Scale