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NEUROLOGY AND PRECLINICAL NEUROLOGICAL STUDIES - ORIGINAL ARTICLE

Levodopa responsiveness in Parkinson's disease: harnessing real-life experience with machine-learning analysis

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Abstract

Responsiveness to levodopa varies greatly among patients with Parkinson's disease (PD). The factors that affect it are ill defined. The aim of the study was to identify factors predictive of long-term response to levodopa. The medical records of 296 patients with PD (mean age of onset, 62.2 ± 9.7 years) were screened for demographics, previous treatments, and clinical phenotypes. All patients were assessed with the Unified PD Rating Scale (UPDRS)-III before and 3 months after levodopa initiation. Regression and machine-learning analyses were used to determine factors that are associated with levodopa responsiveness and might identify patients who will benefit from treatment. The UPDRS-III score improved by ≥ 30% (good response) in 128 patients (43%). On regression analysis, female gender, young age at onset, and early use of dopamine agonists predicted a good response. Time to initiation of levodopa treatment had no effect on responsiveness except in patients older than 72 years, who were less responsive. Machine-learning analysis validated these factors and added several others: symptoms of rigidity and bradykinesia, disease onset in the legs and on the left side, and fewer white vascular ischemic changes, comorbidities, and pre-non-motor symptoms. The main determinants of variations in levodopa responsiveness are gender, age, and clinical phenotype. Early use of dopamine agonists does not hamper levodopa responsiveness. In addition to validating the regression analysis results, machine-learning methods helped to determine the specific clinical phenotype of patients who may benefit from levodopa in terms of comorbidities and pre-motor and non-motor symptoms.

Keywords Parkinson's disease · Levodopa responsiveness · Machine learning · Comorbidities · Rigidity · Pre-motor symptoms

Introduction

It is well recognized that the most effective treatment for motor symptoms of Parkinson's disease (PD) is levodopa, to the extent that an excellent response is a supportive feature for diagnosis of the disease. In clinical studies, the rate of response to levodopa is usually determined by a short-term levodopa challenge test. A decrease of 30% on the Unified PD Rating Scale (UPDRS) is considered a good response to levodopa. This cut-off value was validated in studies showing that a positive initial acute levodopa challenge predicts chronic levodopa responsiveness (Merello et al. 2002, 2011; Schade et al. 2017; Verschuur et al. 2019). However, unresponsiveness to acute levodopa challenge does not exclude the diagnosis of idiopathic PD (Martin et al. 2021). An estimated 10–30% of patients with idiopathic PD do not seem to respond well to levodopa preparations (Hauser et al. 2009; Pitz et al. 2020). Only a few studies have evaluated the clinical features that might predict patient response to levodopa and which patients will benefit from the drug (Malek et al. 2019; Merello et al. 2002; Saranza and Lang 2021), and most of them had only a short-term follow-up. Therefore, whether the acute response can be sustained on long-term treatment remains unclear.

In a recent prospective study of newly diagnosed patients with PD, levodopa challenge test was performed at year 2 of enrollment. A positive response was defined as a more than 24.5% improvement in the Movement Disorders Society

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(MDS)-UPDRS score (Cilia et al. 2020). The results showed that patients with a positive response were younger, had a lower score at baseline, and progressed more slowly than non-responders. Patients with a definite response were prescribed monoamine oxidase inhibitors more often than poorer responders. In recent decades, there has been a shift towards initiation of dopamine agonists as first-line treatment of PD. However, there are no data on whether the early prescription of dopamine agonist is associated with or has a ceiling effect on levodopa responsiveness.

The aim of the present real-life follow-up study was to identify factors predictive of long-term levodopa responsiveness in patients with PD.

Patients and methods

Setting and design

Consecutive patients with PD attending the outpatient Movement Disorders Unit of Rabin Medical Center from 2000 to 2020 were retrospectively identified by file review. Those for whom long-term follow-up data were available, including clinical assessment before and after initiation of levodopa therapy, were included in the study. The study was approved by the local ethics committee.

PD was defined according to the criteria of the United Kingdom PD Society Brain Bank (Hughes et al. 1992). Patients with drug-induced parkinsonism, vascular parkinsonism, and normal pressure hydrocephalus were excluded, as were patients with red flags for the diagnosis of idiopathic PD (prominent gaze palsy, cerebellar signs, severe orthostatic hypotension, pyramidal signs, amyotrophy, or limb apraxia). Patients in whom the diagnosis of PD was altered during the follow-up period were excluded as well.

Procedure

The medical records were screened for demographic data, occupation, presence of early non-motor symptoms, first clinical signs, time to levodopa initiation, and initial treatment with dopamine agonists. Age of onset was self-reported and defined as the age at which the affected individual could first recall noticing one of the primary signs of PD. Disease severity was assessed with the UPDRS and the Hoehn and Yahr (H&Y) scale. Patients were examined twice annually. If they felt they needed a change in treatment, they were invited for an interim appointment for evaluation with the motor UPDRS. The decision to administer dopaminergic treatment was based on the patient's lifestyle, occupation, functional disability, and preference. Once started on treatment, patients were scheduled for a visit after 3–6 months to assess their response, both subjectively and by repeating the motor UPDRS. Post-treatment scoring was performed without knowledge of the pretreatment scores and conducted in all cases by the same study examiner (R.D.) after taking the first morning dose, i.e., in the "on" period. For the final analysis, patients were included if they had been assessed with the motor UPDRS before starting treatment (baseline), and again 3–6 months after starting treatment (by which time the treatment should have had an effect), and if they were receiving adequate treatment of at least 300 mg levodopa. Patients treated with an anticholinergic agent, monoamine oxidase B inhibitor, or dopamine agonist were included if they had been receiving stable doses at least 3 months before initiation of levodopa to achieve the net effect of levodopa treatment.

Brain magnetic resonance imaging (1.5 T or 3 T scanners) was performed within 1 year of diagnosis. The degree of white-matter burden was rated as normal, mild, or severe periventricular white matter ischemic changes and/or basal ganglia lacunar infarct.

The response to levodopa therapy was assessed with the UPDRS-III. If the patient was examined several times during the first 6 months, the best UPDRS score was chosen. Patients with a reduction of 30% or more in the UPDRS score were categorized as responders. After the first 6 months, all patients were routinely assessed semiannually for motor function, H&Y score, and late disease complications (falls, dementia) or death.

Statistical and machine-learning analyses

Regression analysis. Two-way relationships between two continuous variables were statistically analyzed with Pearson's correlation test; between a categorical variable and a continuous variable, with the F test; and between two categorical variables, with chi-squared test. Linear regression was used to predict responsiveness, and the adjusted R^2 measure was used to compare regression models. To assess which variables most affect responsiveness to levodopa, the data were fitted to a univariate linear regression model to statistically test the correlation with each variable separately. Only variables with a p value lower than 0.05 were included.

Stratification by response to levodopa. Patients were categorized into three groups according to their response to levodopa, as per medical convention: non-responders, i.e., no change or increase in UPDRS score or worsening of symptoms; mild responders, i.e., $<30\%$ increase in UPDRS score; and good responders, i.e., $\geq 30\%$ increase in UPDRS score. Analyses were conducted to identify patient- and treatment-related variables that distinguished the three groups. In addition, logistic regression was fitted to the data to distinguish good from mild responders.

Stratification by clinical characteristics. Patients were categorized automatically on the basis of their clinical

characteristics using machine learning. Machine learning has been applied previously for the prediction of PD (Bind et al. 2015; Tahir and Manap 2012; Tsanas et al. 2012) and other neurodegenerative diseases (Gordon and Lerner 2019), prediction of PD severity (Armananzas et al. 2013; Avisar et al. 2021; Sriram et al. 2013), and identification of lipid profiles that characterize PD (Avisar et al. 2021, 2022). Agglomerative hierarchical clustering with complete linkage (Duda et al. 2001) and Gower's distance (Gower 1971) yielded two patient groups according to the silhouette coefficient (Rousseeuw 1987): non-to-mild responders and good responders.

Results

UPDRS data before and after initiation of levodopa treatment were available for 296 patients. Forty percent were women. Mean age at disease onset was 62.2 ± 9.7 years, mean disease duration was 9.2 ± 4.5 years, and time from disease onset to levodopa initiation was 3.7 ± 2.8 years.

Treatment with dopamine agonist was administered before initiation of levodopa therapy in 32% of patients ($n = 94$); mean time from dopamine agonist to levodopa treatment was 2.3 ± 1.8 years. UPDRS scores were available before and after dopamine agonist administration in 44/94 patients of whom 22 showed an improvement of ≥ 30% following dopamine agonist use. There was a positive correlation between the response to dopamine agonist and the response to levodopa, i.e., patients who responded to dopamine agonist were more likely to respond to levodopa as well (Pearson's $r = 0.27$, $p < 0.07$), regardless of age at disease onset.

A good response to levodopa (≥ 30% improvement in UPDRS score) was documented in 128 patients (43%). Table 1 compares the demographic and clinical characteristics of the responders and non-responders. The responders had a nonsignificantly higher mean UPDRS score before levodopa initiation (27.4 ± 10.4 vs. 25.7 ± 10.0) and a significantly lower mean score after treatment (14.3 ± 6.6 vs. 23.6 ± 9.6). There was a significant difference between the groups in sex distribution and age at disease onset. Female patients responded significantly better to levodopa than male

Table 1 Demographic and clinical characteristics of responders and non-responders to levodopa

Characteristics	Responders ($n = 128$)	Non-responders ($n = 168$)	p value
UPDRS pre-levodopa, mean ± SD	27.4 ± 10.4	25.7 ± 10.0	0.17
UPDRS post-levodopa, mean ± SD	14.3 ± 6.6	23.6 ± 9.6	~0
Gender (% females)	48	34	0.0033
Age at disease onset (yrs), mean ± SD	60.6 ± 10	63.5 ± 9.0	0.0001
Early use of dopamine agonist (%)	35	29	0.32
Time to levodopa (yrs), mean ± SD	3.9 ± 3.2	3.6 ± 2.6	0.23
Origin (%)			0.54
Ashkenazi	63.6	57.1	
Sephardic	26.5	35.4	
Yemenite	7.6	5.5	
Arabic	2.3	1.8	
Smoker (%)	26	35	0.13
First symptom (%)			0.21
Tremor	45	53	
Rigidity	18	16	
Bradykinesia	10	7	
Tremor + bradykinesia	19	12	
Tremor + rigidity	5	9	
Tremor + rigidity + bradykinesia	2	3	
Pre-motor symptoms (%)			
Loss of smell	37	37	0.89
Constipation	33	41	0.20
RBD	27	26	0.98
Orthostatic hypotension	12	17	0.48
Pain	41	48	0.37

RBD rapid eye movement sleep behavior disorder

patients (30 ± 28% vs. 20 ± 29%, $p = 0.0033$). Most of the patients with a young age of onset started treatment with dopamine agonists, so the time from disease onset to initiation of levodopa treatment was longer in this subgroup than in patients who were not treated first with a dopamine agonist.

Regression analysis

On linear regression analysis, age at disease onset and age at initiation of levodopa treatment were the variables most highly correlated with levodopa responsiveness. Younger age at disease onset and younger age at levodopa initiation were associated with a better response (Supplementary Fig. 1). However, as these two variables were significantly correlated with each other ($r = 0.95$), to determine if the relationship was consistent for different age groups, we tested the effect of their interaction on levodopa responsiveness by comparing three linear models: (A) main effect of age at disease onset, (B) main effect of time to levodopa initiation, and (C) the two main effects and their interaction. Model C had the highest adjusted R^2 of 0.052, followed by model A ($R^2 = 0.0453$) and model B ($R^2 = 0.007$). In model C, the interaction coefficient was significant ($p = 0.012$). To determine whether the impact of time to levodopa treatment on response to levodopa was related to age at disease onset, each group was divided into subgroups by several age cutoffs, and the p-value of the difference in slopes (response vs. time to levodopa) was measured between the groups for each cutoff. The results showed that the p-value was lowest for disease onset at age 72 years. Supplementary Fig. 2 demonstrates that for patients aged 72 years or more, responsiveness was better when levodopa was initiated early after symptom onset, whereas for younger patients, delaying treatment was less critical in terms of levodopa responsiveness.

Regarding white matter hyperintensities, there was a significant difference in levodopa responsiveness between patients with a high overload of ischemic changes (value of 2 or 3) and those with normal or minimal changes (value of 0 or 1) (17.5% vs 26.0%, respectively, $p = 0.03$). First symptoms were unrelated to responsiveness, although tremor showed a nearly significant effect, with a responsiveness rate of 22% for patients in whom tremor was the first symptom compared to 28% for patients in whom it was not ($p = 0.057$).

Stratification by response to levodopa

Stratification by clinical response to levodopa yielded three groups: non-responders ($n = 45$), mild responders ($n = 123$), and good responders ($n = 128$). The radar plots in Fig. 1a–c show the differences among the groups in demographic and clinical characteristics. Compared to the other two groups, non-responders were older at disease onset, at agonist

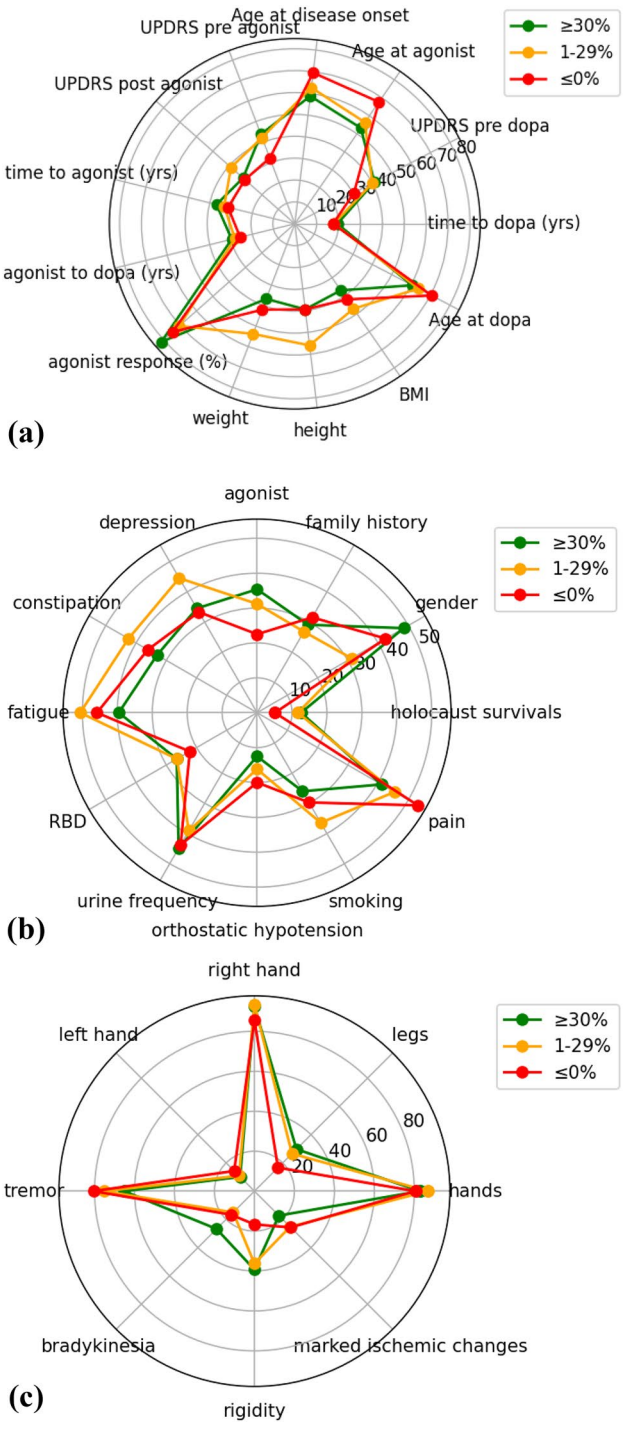

Fig. 1 Stratification by response to levodopa. Three radar plots, each using a different subset of variables for better visibility, demonstrating differences among patient groups by response to levodopa: non-responders (≤0%) ($n = 45$), mild responders (1–29%) ($n = 123$), and good responders (≥ 30%) ($n = 128$). **a** Plot of continuous variables normalized to values between 0 and 100. **b** Plot of categorical variables converted to binary variables (where a variable value between 0 and 100 for a group indicates the mean value over the group patients as a percent of the maximal variable value). **c** Same as **b** for other distinctive categorical variables, e.g., first motor symptoms

initiation, and at levodopa initiation and showed the least improvement following agonist treatment (Fig. 1a). Good responders were younger at disease onset, at agonist initiation, and at levodopa initiation, and had a good response also to dopamine agonist (Fig. 1a). Mild responders were mainly male (gender not shown in the figure), which explains their higher values of height, weight, and body mass index (Fig. 1b). Good responders were mostly female and nonsmokers, and had lower rates of pre-motor symptoms: pain, orthostatic hypotension, fatigue, constipation, and depression (Fig. 1b). In good responders, rigidity and bradykinesia were the first symptoms (as opposed to tremor in non-responders), the disease tended to start in the legs, and ischemic changes were less marked (Fig. 1c). In the logistic regression model fitted to the variables in Fig. 1 to predict good or mild responders, only gender was significant, and age at disease onset was nearly significant (0.545).

Figure 2 depicts the differences among the three groups in medical history. Fifty-three patients had no comorbidities at disease onset. Among the remainder, the most frequent comorbidities were hyperlipidemia (100 patients), hypertension (116 patients), cancer (34 patients), ischemic heart disease (36 patients), diabetes (53 patients), and other diseases (45 patients); some patients had more than one comorbidity. The radar plot in Fig. 2a shows that good responders had fewer comorbidities overall than the other groups, except for the rate of cancer which fell between the non-responders and mild responders. Vascular risk factors were the main comorbidities associated with response to levodopa. The histograms in Fig. 2b detail the distribution of these comorbidities among the three groups. Recall the differences in sample size among the groups.

Stratification by clinical characteristics

Stratification by hierarchical clustering and the silhouette score (see section *Statistical and Machine-Learning analyses*) yielded two groups: non-to-mild response ($n=227$) and good response ($n=69$). Like in the analysis of patient stratification by response to levodopa, the difference in mean rate of response to levodopa between these two groups was statistically significant ($22\pm27\%$ vs $34\pm23\%$; $p<0.0009$). Figure 3 shows that the patients with no-to-mild response were older at disease onset, had more pre-motor symptoms of constipation, fatigue, and rapid eye movement-sleep behavior disorder, and presented with tremor as the first symptom, with onset mostly on the right side and in the hands. Most did not receive dopamine agonists before levodopa treatment. The patients with a good response were younger at disease onset, had fewer pre-motor symptoms and marked ischemic changes, and presented with rigidity as the first symptom, more on the left side and in the legs. Most were treated initially with dopamine agonists. These findings were similar to those derived by stratifying the patients on the basis of medical convention (Fig. 1).

Discussion

To the best of our knowledge, this is the first study that investigates the response to levodopa in a real-life context while offering new perspectives on risk factors. Demographic and clinical factors of response to levodopa were evaluated together with those gained using statistical and machine learning methods. The results showed that young age at disease onset, female gender, and early use of dopamine agonist are associated with a good response. The predictive value of age and gender in levodopa responsiveness has been reported by others as well (Lyons et al. 1998; Malek et al. 2019; Wickremaratchi et al. 2009).

In addition, we found that in patients younger than 72 years, time to initiation of levodopa treatment had no effect on responsiveness. This result is important as it may provide some relief to the many patients who seek to delay treatment because of concerns of levodopa-induced late motor complications. However, in patients older than 72 years, who may have a less robust response, it is crucial to initiate levodopa at diagnosis so they may benefit from the drug.

The machine-learning models revealed that the presence of white matter hyperintensities was a significant factor in levodopa response. Reports in the literature are inconsistent (Arena et al. 2016; Pitz et al. 2020). The multicenter Tracking Parkinson study concluded that although vascular comorbidity was associated with a lower levodopa response, it was not considered an independent factor because age was the driving force (Malek et al. 2019). Another study showed that 24% of patients with vascular abnormalities and abnormal DaTScan did not respond to levodopa (Antonini et al., 2012).

Machine-learning analysis also added other factors. Good response was shown to be related to fewer comorbidities (especially vascular-related), fewer pre-motor signs, rigidity as the first symptom, and disease onset in the legs and on the left side. Heterogeneity of the clinical symptoms was very likely to influence levodopa responsiveness. Our patients with tremor did not respond well to levodopa treatment, although the data in the literature regarding tremor-dominant patients are conflicting (Imbach et al. 2014; Malek et al. 2019; Sung et al. 2008; Zach et al. 2020). The finding might be explained by the possible involvement of several neurotransmitters in the physiology of tremor (Doder et al. 2003; Helmich et al. 2011; Isaias et al. 2012; Qamhawi et al. 2015).

Almost all studies used the levodopa challenge test with high doses of levodopa as the gold standard for response assessment. Our findings were based on a different concept

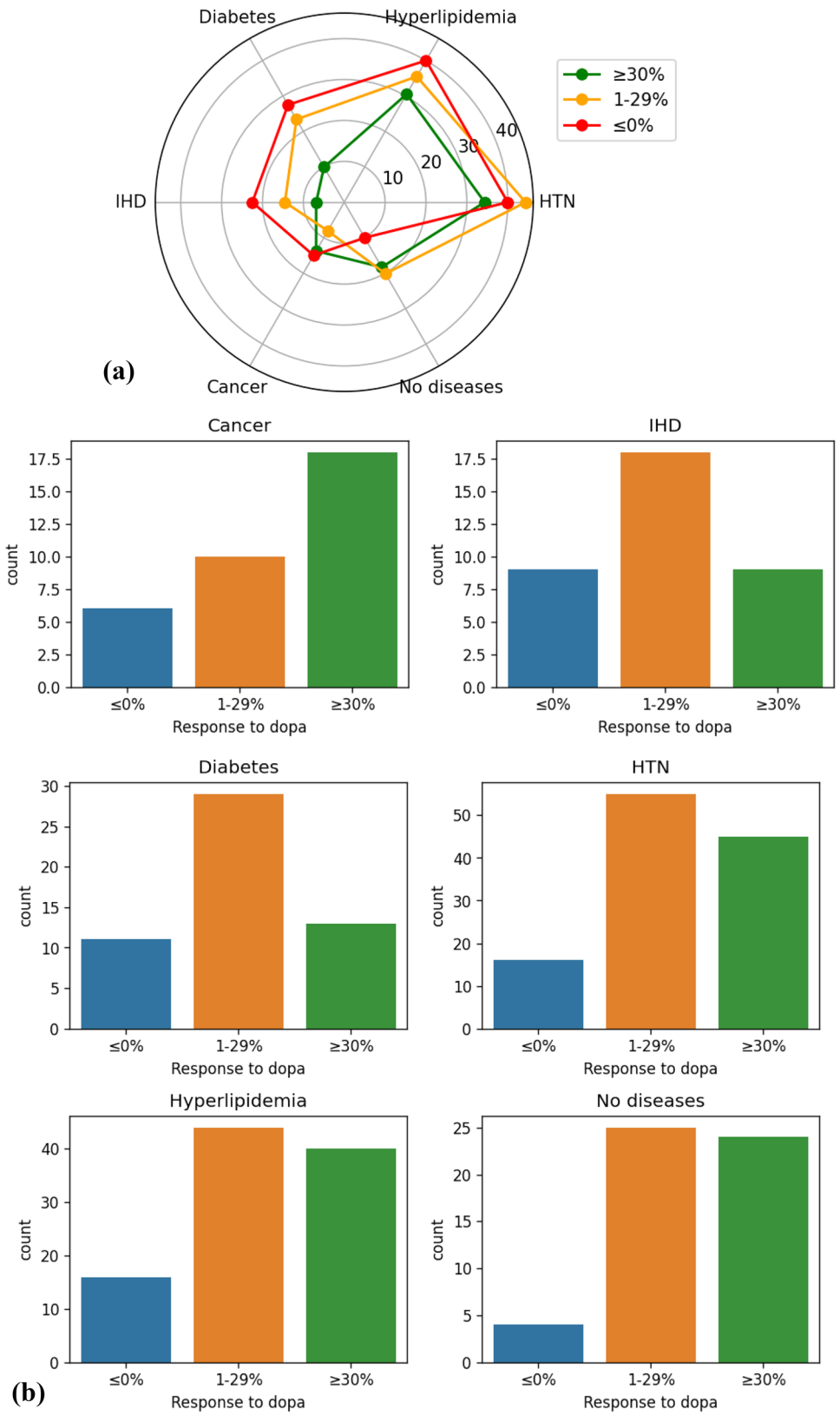

Fig. 2 Medical history. **a** Radar plot for the three patient groups demonstrating differences in patient comorbidities (cancer; IHD; diabetes; hyperlipidemia; HTN; and no diseases) by response to levodopa: non-responders (≤0%) ($n=45$), mild responders (1–29%) ($n=123$), and good responders (≥ 30%) ($n=128$). **b** Patient distributions over the three responder groups for the six comorbidities. Note the different sample sizes of the groups: non-responders, mild responders, and good responders, and patients with each disease (as above). *IHD* ischemic heart disease, *HTN* hypertension

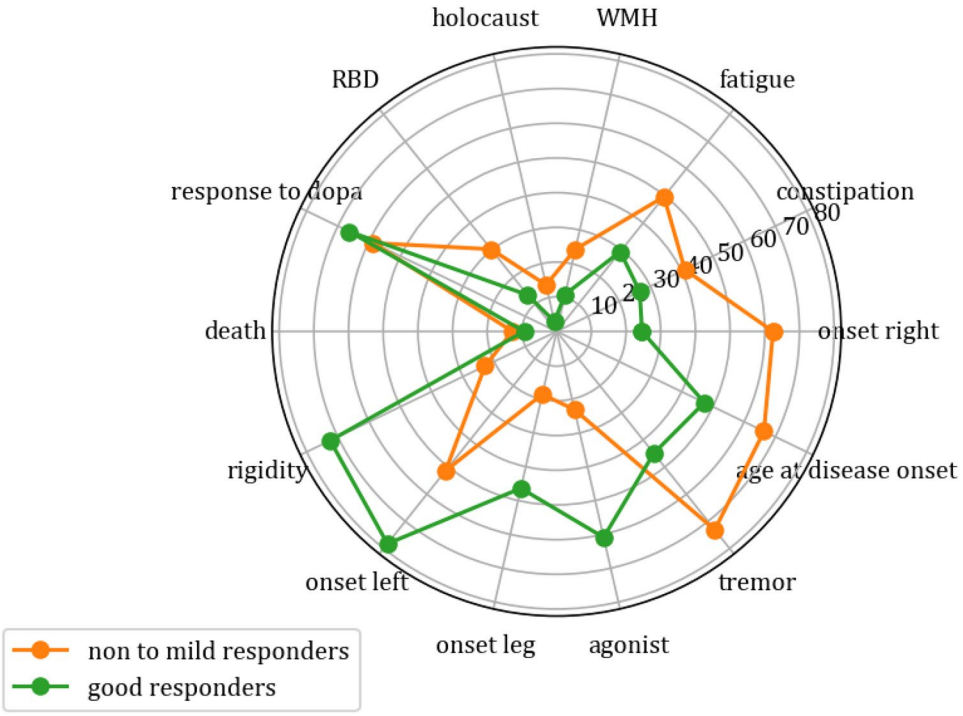

Fig. 3 Stratification by clinical characteristics. Patient stratification based on hierarchical clustering and clinical characteristics yielded two groups: non-to-mild responders ($n=227$) and good responders ($n=69$). Significant between-group differences were found for all variables. *RBD* rapid eye movement sleep behavior disorder, *WMH* white matter hyperintensities

of long-term response to levodopa. Indeed, it has been shown that patients with an initial poor response can become positive responders with long-term treatment (Zappia et al. 1997). This implies that our real-life assessment may be more accurate than the acute challenge test. We used the patients' standard doses as long as the minimal expected dose for response was achieved. Although it may be argued that higher doses might have yielded a better response, a study in which patients' standard dose was used in the challenge test reported no significant difference in levodopa doses between definite and limited responders (Malek et al. 2019). Other researchers rated the long-term response of patients who started treatment with either levodopa or dopamine agonists and found that 37% had no or less than 25% improvement (Davidson et al. 2012) and others had a reduction of up to 14% in the UPDRS score after 80 weeks (Verschuur et al. 2019).

Responsiveness to levodopa was not hampered by prior treatment with dopamine agonists. This finding contrasts with our expectation that early treatment with dopamine agonist would create a ceiling effect, so that patients would achieve near maximal improvement with no further beneficial response to levodopa. Rather, a 30% improvement in UPDRS score was documented in 49% of patients who were treated with a dopamine agonist compared to 42% of patients who were not.

A higher UPDRS score at baseline predicted better response to levodopa. By contrast, an earlier study reported higher baseline motor scores in patients who were less responsive to levodopa (Malek et al. 2019). It is possible that patient age may be related to disease severity such that the benefit of levodopa in patients with a high UPDRS score is actually influenced by age, as observed previously (Velseboer et al. 2013).

The response to levodopa was variable, ranging from an exacerbation of motor symptoms despite treatment to dramatic improvement. Clearly, between 30 and 46% of patients have a poor response (Merello et al. 2002; Zappia et al. 1997). The retrospective evaluation of response to levodopa in the ELLDOPA study yielded an average improvement in UPDRS-III score of 27.4% at 9 weeks and 26.2% at 24 weeks (Hauser et al. 2009).

There are clues that genetic background and molecular pharmacologically related genes play a role in levodopa responsiveness (Guin et al. 2017; Reilly et al. 1980; Sampaio et al. 2018). The relationship between mutations in *LRRK2* and *GBA* as well as other PD-related genes should be explored further.

Our study has several limitations. We used a retrospective chart review design which depends on clinical information reported by patients, not confirmed by objective measures. The diagnosis of PD was based on clinical grounds without corroboration of nuclear imaging. However, a movement disorder specialist was responsible for recording symptoms and clinical assessments, with special emphasis on the presence of pre-motor symptoms. The long-term follow up made diagnosis more reliable as patients who developed symptoms of other neurodegenerative diseases were excluded. The lack of standardized timing for follow-up could have affected the results. This limitation was inevitable as the time of response

assessment was based on the highest dose of levodopa that achieved a good response. Although there were variations in levodopa dosage, we included only patients who reached a minimal dose of 300 mg, which is sufficient to yield a clinical response. Levodopa equivalent dose (LED) was not calculated; yet, as not all patients reached maximal doses due to adverse effects or unwillingness to increase the dose, LED might not have been a reliable factor in this cohort. The lower percentage of responders than in other studies may be explained by a lower robustness of the long-term daily effect compared to the acute challenge test, as noted as well in the retrospective ELLDOPA study (Hauser et al. 2009). Finally, the analysis of the MRI findings was qualitative and not based on scales grading the degree of ischemic changes. The strengths of the present study are the absence of selection bias and the long-term follow-up which assured diagnostic accuracy even in patients who did not respond to levodopa, as they did not develop symptoms compatible with any other neurodegenerative disease. Also, all patients were examined by the same rater to ensure the validity of the results.

In conclusion, our application of several statistical and machine-learning methods to real-life data revealed that levodopa responsiveness in patients with PD was associated with gender, age at disease onset, and number of comorbidities, and that delaying treatment with levodopa and early use of dopamine agonists do not hamper a good response. More studies are needed to determine whether symptom onset and genetic background also affect the response to levodopa treatment.

Data availability statement

The datasets generated and/or analyzed during the present study are available from the corresponding author on reasonable request.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00702-022-02540-2.

Author contributions (1) Research project: A. Conception, B. Organization, C. Execution; (2) Experimental procedures and statistical analysis: A. Design, B. Execution, C. Review and critique; (3) Manuscript: A. Writing of the first draft, B. Review and critique. RD: 1A, 1B, 1C, 2C, 3A, and 3B. BH: 2A, 2B, 2C, 3A, and 3B. JR: 1B, 1C, and 3B. BAK: 1B, 1C, and 3B. BL: 1A, 1C, 2A, 2B, 2C, 3A, and 3B.

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Declarations

Conflict of interest None.

Ethics approval The authors confirm that all procedures involving experiments on human subjects were done in accord with the ethical standards of the Committee on Human Experimentation of the institution in which the experiments were done or in accord with the Helsinki Declaration of 1975.

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