The modern pre-levodopa era of Parkinson's disease: insights into motor complications from sub-Saharan Africa

Roberto Cilia,[1] Albert Akpalu,[2] Fred Stephen Sarfo,[3] Momodou Cham,[4] Marianna Amboni,[5,6] Emanuele Cereda,[7] Margherita Fabbri,[8] Patrick Adjei,[2] John Akassi,[3] Alba Bonetti[1] and Gianni Pezzoli[1]

1 Parkinson Institute, Istituti Clinici di Perfezionamento, Milan, Italy
2 Korle Bu Teaching Hospital, Accra, Greater Accra region, Ghana
3 Komfo Anokye Teaching Hospital, Kumasi, Ashanti region, Ghana
4 Comboni Hospital, Sogakope, Volta region, Ghana
5 Department of Medicine and Surgery, University of Salerno, Salerno, Italy
6 IDC Hermitage-Capodimonte, Naples, Italy
7 Nutrition and Dietetics Service, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy
8 IRCCS Institute of Neurological Sciences, Bologna, Italy

Correspondence to: Roberto Cilia, M.D.,
Parkinson Institute, Istituti Clinici di Perfezionamento,
via Bignami 1, 20126 Milano, Italy
E-mail: roberto.cilia@gmail.com

See Lang (doi:10.1093/brain/awu212) for a scientific commentary on this article.

During the past decade, a number of large drug trials suggested that the initiation of levodopa therapy should be delayed to reduce the risk of motor complications in patients with Parkinson's disease. However, the relative contribution of the cumulative exposure to levodopa and of disease progression to the pathophysiology of motor fluctuations and dyskinesias is still poorly understood. In this 4-year multicentre study, we investigated a large cohort of patients with Parkinson's disease in a sub-Saharan African country (Ghana), where access to medication is limited and the initiation of levodopa therapy often occurs many years after onset. The primary objective was to investigate whether the occurrence of motor complications is primarily related to the duration of levodopa therapy or to disease-related factors. Study design included a cross-sectional case-control analysis of data collected between December 2008 and November 2012, and a prospective study of patients followed-up for at least 6 months after the initiation of levodopa therapy. Ninety-one patients fulfilled criteria for clinical diagnosis of idiopathic Parkinson's disease (58 males, mean age at onset 60.6 ± 11.3 years). Demographic data were compared to those of 2282 consecutive Italian patients recruited during the same period, whereas nested matched subgroups were used to compare clinical variables. Demographic features, frequency and severity of motor and non-motor symptoms were comparable between the two populations, with the only exception of more frequent tremor-dominant presentation in Ghana. At baseline, the proportion of Ghanaian patients with motor fluctuations and dyskinesias was 56% and 14%, respectively. Although levodopa therapy was introduced later in Ghana (mean disease duration 4.2 ± 2.8 versus 2.4 ± 2.1 years, $P < 0.001$), disease duration at the occurrence of motor fluctuations and dyskinesias was similar in the two populations. In multivariate analysis, disease duration and levodopa daily dose (mg/kg of body weight) were associated with motor complications, while the disease duration at the initiation of levodopa was not. Prospective follow-up for a mean of 2.6 ± 1.3 years of a subgroup of 21 patients who were drug-naïve at baseline [median disease duration 4.5 (interquartile range, 2.3–5) years] revealed that the median time to development

of motor fluctuations and dyskinesias after initiation of levodopa therapy was 6 months. We conclude that motor fluctuations and dyskinesias are not associated with the duration of levodopa therapy, but rather with longer disease duration and higher levodopa daily dose. Hence, the practice to withhold levodopa therapy with the objective of delaying the occurrence of motor complications is not justified.

Introduction

More than 50 years after its introduction by George C. Cotzias (Cotzias *et al.*, 1967), levodopa still is the most effective treatment for the motor symptoms of Parkinson's disease. In studies including patients in the pre-levodopa era, early treatment with levodopa proved to increase life expectancy (Diamond *et al.*, 1987). However, long-term management of patients on chronic levodopa is hampered by the occurrence of motor fluctuations and dyskinesias which, as the disease progresses, usually become major causes of disability and reduced quality of life (Chapuis *et al.*, 2005). To date, the pathophysiological mechanisms underlying the occurrence of levodopa-induced complications are still poorly understood.

In animal studies, the occurrence of motor fluctuations and dyskinesias has been associated with the extent of nigral neuronal loss and with the duration and dose of levodopa therapy, as independent factors (Boyce *et al.*, 1990; Guigoni *et al.*, 2005; Jenner, 2008). Motor complications have been described to occur very early after the initiation of levodopa therapy in monkeys and humans with MPTP-induced parkinsonism, who display rapid and severe depletion of dopaminergic neurons (Williams, 1984; Ballard *et al.*, 1985). However, current experimental models of levodopa-induced motor complications cannot replicate the pathophysiological changes that occur during the progressive neurodegenerative process of idiopathic Parkinson's disease, mainly due to the rapid and extensive nigral denervation. Thus, the issue of the relationship between levodopa and motor complications should be addressed by clinical studies in patients with Parkinson's disease. A number of large drug trials reported that the initial treatment with a dopamine agonist was associated with a lower incidence of motor complications than initial treatment with levodopa (Parkinson Study Group, 2000; Rascol *et al.*, 2000; Fahn *et al.*, 2004; reviewed in Stowe *et al.*, 2008). Likewise, higher rates of dyskinesias were reported in association with higher cumulative doses of levodopa (Hauser *et al.*, 2006; Olanow *et al.*, 2013) and longer duration of levodopa treatment (Miyawaki *et al.*, 1997; Grandas *et al.*, 1999; Schrag and Quinn, 2000). Overall, these observations led clinicians to consider levodopa therapy as an additional source of disability within the natural history of Parkinson's disease (Poewe and Mahlknecht, 2009) and supported the clinical practice of delaying the initiation of levodopa therapy as long as possible to reduce the risk of motor complications (Fahn, 1999, 2006; Kieburtz, 2008). The ELLDOPA study was specifically designed to provide conclusive evidence as to whether levodopa could be safely initiated early or should be delayed in

newly diagnosed patients with Parkinson's disease (Fahn, 1999). The ELLDOPA study was specifically designed to provide conclusive evidence as to whether levodopa could be safely initiated early or should be delayed in newly diagnosed patients with Parkinson's disease (Fahn, 1999). Unfortunately, although the ELLDOPA study did not find any clinical or imaging evidence indicating that early use of levodopa could negatively impact the course of the disease (Fahn *et al.*, 2004), it failed to change the patterns of treatment of Parkinson's disease (as neurologists remained concerned about levodopa's likelihood to induce motor complications) (Fahn, 2006). Therefore, the question as to whether the risk of levodopa-induced motor complications is primarily associated with levodopa therapy or disease progression itself remained unanswered.

Theoretically, the differences between the effects of treatment-related variables (i.e. levodopa therapy duration versus daily dose) and the effects of disease progression (i.e. disease duration versus severity) in promoting motor complications without confounders (such as concomitant dopamine agonist therapy) could be conclusively demonstrated only by a trial including patients with Parkinson's disease left untreated for several years after onset of disease and then followed-up after the initiation of levodopa. Obviously, such a study design is not ethically acceptable. Early motor complications have been described in series including patients from the pre-levodopa era, who had longer disease duration at the initiation of levodopa therapy (Ahlskog and Muenter, 2011). However, the exact relationship between disease-related variables and levodopa dose could not be established, because of the tendency towards more aggressive levodopa dosing (due to the initial lack of DOPA decarboxylase inhibitors), and the lack of systematic assessment of motor fluctuation rates (Ahlskog and Muenter, 2011) and of motor symptom severity using validated rating tools [e.g. the Unified Parkinson's Disease Rating Scale (UPDRS); Fahn *et al.*, 2004; Poewe and Mahlknecht, 2009]. In sub-Saharan African countries, the access to medication is limited and the initiation of levodopa therapy often occurs several years after the onset of motor symptoms (Cilia *et al.*, 2011; Dotchin *et al.*, 2011), closely resembling what is described in series containing patients with Parkinson's disease from the pre-levodopa era (Ahlskog and Muenter, 2011). In this scenario, we conducted a 4-year naturalistic study investigating a large cohort of patients with Parkinson's disease from a sub-Saharan African country (Ghana), whose primary objective was to disentangle the relative role played by treatment-related variables and disease progression *per se* in the pathophysiology of motor complications.

Materials and methods

Participants

All subjects consecutively attending three out-patient clinics in different regions of Ghana between December 2008 and November 2012 were examined and screened for any movement disorder by local neurologists (A.A., F.S.S.) or by a medical officer (M.C.). Parkinsonism was suspected by the local clinician on the basis of the presence of at least three of the four cardinal features (i.e. resting tremor, rigidity, bradykinesia, and postural or gait abnormality). Patients were then assessed in consecutive order by a neurologist specialized in movement disorders (R.C.) and by another movement disorder specialist (M.A., M.F., G.P.), who made the diagnosis according to current criteria (Hughes *et al.*, 1992; Litvan *et al.*, 2003). In case of any doubt or disagreement between the investigators, the patient was admitted to hospital for in-depth clinical evaluation and additional investigation (e.g. neuroimaging). Onset of the disease was defined at the first appearance of any motor symptom, as reported by the patient, a family member or a clinician. In case of any doubt or uncertainty, we adopted a recall technique tailored to major events in the patient's life. Considering the relatively high average number of offspring and grandchildren, we used information on offspring to investigate the relationship between the year of onset and either major preschool milestones of development of grandchildren (e.g. birth, first unassisted steps) or other meaningful events in the family (e.g. wedding of offspring). Early onset was defined as age at onset $\leqslant 50$ years. Family history for Parkinson's disease was limited to first-degree relatives.

Clinical work-up included the UPDRS from part I to part IV (Fahn and Elton, 1987) and Hoehn and Yahr (HY) staging (Hoehn and Yahr, 1967). Major milestones of disease progression were assessed using the UPDRS items of part I (psychosis, item 2 score $\geqslant 2$; depression or apathy, sum of items $3 + 4 \geqslant 4$), part II (dysphagia, item 7 score $\geqslant 2$; falls, item 13 score $\geqslant 2$) and part III (postural instability, item 30 score $\geqslant 2$) (as described in Merola *et al.*, 2011). Dementia was diagnosed according to the Diagnostic and Statistical Manual, Fourth Edition, Text Revision (DSM-IV-TR) criteria (American Psychiatric Association, 2000). Motor phenotype at disease presentation was assessed in the 'OFF' state (Jankovic *et al.*, 1990). Acute levodopa challenge was performed using dispersible levodopa/benserazide 100 mg + 50 mg, giving either a 150-mg or 200-mg levodopa dose, according to body weight ($\leqslant$ or >70 kg, respectively); all patients were assessed after 12-h medication withdrawal (OFF state) and 90 min after levodopa intake (ON state). In drug-naïve patients, levodopa therapy was initiated immediately, starting from 50 mg once daily and slowly titrating up to 100 mg three times daily, 20–30 min before meals. If further treatment was required, an additional 50 or 100 mg of levodopa could be added to each of the doses, as appropriate, to achieve adequate control of motor symptoms. At each visit, the presence of motor fluctuations and dyskinesias was assessed by recall and prolonged direct observation, and time of their first occurrence was recorded. Patients were observed for a minimum of 4 h after the administration of dispersible levodopa/benserazide to monitor motor response. In case of uncertainty about either the response to levodopa therapy or the presence of motor fluctuations or dyskinesias, patients were admitted to hospital. Motor fluctuations were defined as predictable wearing-off, unpredictable ON–OFF fluctuations and sudden OFF periods according to UPDRS part IV (Fahn and Elton, 1987). Dyskinesias were defined as abnormal involuntary movements, including chorea and dystonia, that could be peak dose or diphasic; OFF-related dystonia was not included. In-between the follow-up visits by the principal investigator, local doctors visited all patients every 2 months to review therapy tolerability, onset of motor complications, and to provide levodopa supplies free of charge (Cilia *et al.*, 2011). Follow-up visits were performed by the principal investigator every 6 months during the study period.

A large cohort of consecutive patients with Parkinson's disease ($n = 2282$) assessed for the first time at the Parkinson Institute in Milan during the same 4-year period was considered as control group for demographic and general clinical features. During this period, a total of nine neurologists examined on average three new patients every work week (of whom 42–48% were diagnosed as probable idiopathic Parkinson's disease) for a total of 46 weeks in a year. Nested matched subgroups were then used to investigate the frequency and severity of major motor and non-motor symptoms, including the relationship between levodopa therapy and the onset of motor complications.

Ethics

The study was performed in agreement with the principles of the Declaration of Helsinki and the protocol was approved by the local Ethics Committee. We obtained written informed consent from every patient; an additional consent was requested for video recording. Informed consent was translated into local Ghanaian dialect whenever required and/or it was provided by a first-degree relative in cases with clinical dementia.

Statistical analysis

Data were analysed using the software program SPSS (Windows Release 17.0; SPSS Inc.). We conducted a cross-sectional data analysis and a prospective cohort study. A two-sided P-value of <0.05 was set as significant. A flow diagram of study analyses is provided as Fig. 1.

Cross-sectional data analysis

Demographic features were initially compared with those of the whole control Italian Parkinson's disease population consecutively recruited during the same 4-year period. In the second instance, we used a subgroup of Parkinson's disease control subjects matched 1:2 for gender, age and disease duration at the first assessment. Finally, to minimize the obvious bias associated with the difference in drug availability between the two countries, we performed an additional analysis after matching also for therapy regimen. Descriptive statistics were provided for continuous [mean and standard deviation (SD) or median and interquartile range (IQR, 25th–75th percentile)] and categorical (count and percentage) variables. Two-group comparisons were performed using Fisher's exact test (categorical variables) and Student's *t*-test or Mann-Whitney U-test (continuous variables), as appropriate. When the analyses included multiple groups and *post hoc* comparisons, differences in clinical features were analysed with ANOVA or the χ^2 test as appropriate. *Post hoc* comparison of means was performed using Scheffe's test.

Finally, the risk of developing wearing-off and dyskinesias was computed as odd ratio (OR) and 95% confidence interval (95% CI) using multivariable logistic regression analysis including non-collinear variables (identified from the literature and based on consensus among the authors) showing an association at univariate analysis.

Prospective data analysis

All patients examined by the principle investigator at least twice $\geqslant 6$ months apart at any of the three clinics were included in the longitudinal analysis. Time-course comparisons of paired datasets were performed by using Wilcoxon's (continuous variables) or McNemar's (categorical variables) test.

Results

Whole cohort of patients with any parkinsonian syndrome

During the period between December 2008 and November 2012, a total of 101 patients presenting with any Parkinsonism were identified at the three Ghanaian clinics (males, $n = 64$; age at onset, 60.8 ± 11.7 years; OFF-state UPDRS III, 35.1 ± 14.7) and subsequently underwent neurological examination by the Italian team of movement disorders specialists. Among those with a probable degenerative aetiology, 91 fulfilled diagnostic criteria for idiopathic Parkinson's disease and two for progressive supranuclear palsy. Neuroimaging was available for 26 of 101 cases (CT, $n = 22$; MRI, $n = 4$); of these, 21 were diagnosed as having Parkinson's disease, three had vascular parkinsonism, one had extensive calcinosis of basal ganglia and cerebellar nuclei, and another had young-onset rapid-progressing parkinsonism of unknown aetiology. Brain imaging of patients with Parkinson's disease was either normal ($n = 14/21$) or showed mild-to-moderate cortical atrophy ($n = 7/21$) with concomitant mild chronic small-vessel disease in three cases.

Idiopathic Parkinson's disease

Cross-sectional analysis

Ghanaian patients with Parkinson's disease and Italian consecutive control patients had similar demographic features, including age at onset (Table 1). Nineteen of 91 patients with Parkinson's disease (20.9%) had early onset. Positive family history was reported in eight patients with early-onset and 11 with late-onset Parkinson's disease.

In case-control analysis, Ghanaian patients with Parkinson's disease presented more frequently with a tremor-dominant phenotype and had longer disease duration at diagnosis and, subsequently, at the initiation of levodopa therapy (Table 2). OFF state disability and severity of motor symptoms at assessment was, overall, comparable between the two groups, with the only exception of higher resting tremor scores in Ghanaians. Likewise, there was no difference in the frequency of major non-motor symptoms and non-levodopa-responsive motor symptoms (Table 2).

The mean disease duration at the baseline assessment was 5 years and ~35% of Ghanaian patients with Parkinson's disease were drug-naïve, a frequency 4-fold higher than in the control population (Table 1). Although levodopa daily dose was slightly
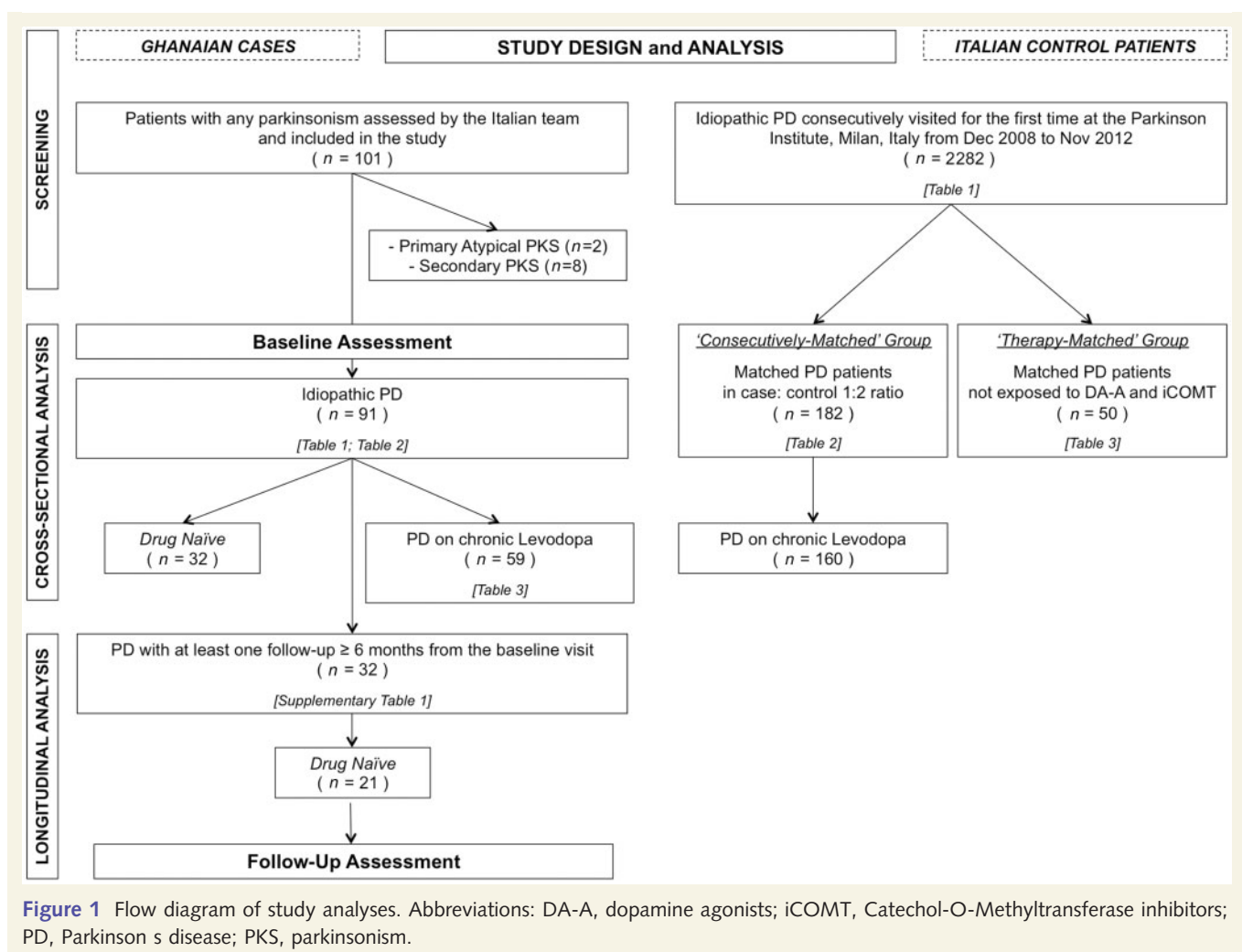

Figure 1 Flow diagram of study analyses. Abbreviations: DA-A, dopamine agonists; iCOMT, Catechol-O-Methyltransferase inhibitors; PD, Parkinson s disease; PKS, parkinsonism.

Table 1 Cross-sectional analysis of demographic and general clinical features of Ghanaian patients with Parkinson's disease at the baseline visit compared to all consecutive Italian patients with Parkinson's disease examined for the first time during the same 4-year study period

Features	Ghanaian Parkinson's disease (n = 91)	Italian Parkinson's disease (n = 2282)	P-value
Males n (%)	58 (63.7)	1291 (56.6)	0.196
Age at onset, mean (SD) [range], y	60.6 (11.3) [27–91]	62.0 (10.7) [20–89]	0.217
Early onset n (%)	19 (20.9)	344 (15.1)	0.137
Positive family history for Parkinson's disease n (%)	19 (20.9)[a]	356 (15.6)	0.140
Right body side of Parkinson's disease onset n (%)	47 (51.7)	1,355 (59.4)	0.176
Never treated n (%)	32 (35.2)	143 (6.3)	**<0.001**
Education, mean (SD), y	9.0 (6.3)	10.3 (4.5)	**0.016**
Cigarette smoking n (%)	6 (6.6)	361 (15.8)	**<0.001**

[a]Family history of Parkinson's disease in Ghana could not be directly documented by a neurologist in the majority of cases.

higher in the Italian group, this difference was no longer significant after adjusting for body weight (Table 2). Disease duration at the initiation of levodopa therapy was significantly longer in Ghanaian patients with Parkinson's disease, so that the two cohorts differed according to the duration of levodopa therapy (Table 2). Mean levodopa daily dose adjusted for body weight was similar in the two groups at the time of the baseline assessment. Accordingly, it was reasonable to argue that cumulative exposure to levodopa substantially relied on the duration of treatment. The frequency of motor complications were calculated using the number of patients on chronic levodopa therapy as denominator (n = 59 for the study population; n = 160 for the control population, Table 2). After a median time of 1 year since the initiation of levodopa, the frequency of prevalent motor fluctuations and dyskinesias in Ghanaian patients was 56% and 14%, respectively. Motor fluctuations were recorded as wearing-off phenomenon in the majority of patients (n = 30/33, 90.9%). Median disease duration at the first appearance of motor fluctuations and dyskinesias was comparable between Ghanaians and Italian patients [6.0 (IQR 5–8) versus 5.5 years (IQR 4–7), P = 0.149 for motor fluctuations; 7.0 (IQR 6–10.25) versus 6.5 years (IQR 5–8), P = 0.567 for dyskinesias], despite significantly shorter median duration of levodopa therapy at their onset in Ghanaians [0.5 (IQR 0–1) versus 2.0 years (IQR 1–4), P = 0.001 for motor fluctuations; 1.0 (IQR 0.25–2) versus 3.0 years (IQR 2–5.25), P = 0.004 for dyskinesias; Fig. 2A].

However, a large disparity in medication availability and affordability was responsible for the large differences between the two countries in terms of prescription schedule and introduced a bias in the estimation of the frequency of motor complications. In particular, Ghanaians could not benefit from dopamine-agonists and COMT-inhibitors (Table 2), because these drugs are not commonly available in most sub-Saharan African countries due to their high cost. Likewise, they were less exposed to MAO-B inhibitors, whereas anticholinergics and amantadine were more commonly prescribed as first-line therapy because they are cheaper than levodopa (Table 2). Therefore, to minimize confounders of our estimate of motor complications, we used a control group of patients with Parkinson's disease who had never been

exposed to any dopamine agonist or COMT inhibitor (defined as 'therapy-matched', Fig. 1 and Table 3). The motor fluctuation rate was similar in the two patient populations, with a slightly lower prevalence of dyskinesias in Ghanaians. Levodopa daily dose was higher in Italians, but this difference was no longer significant after adjusting for body weight. Severity of motor symptoms was similar in terms of UPDRS scores and Hoehn and Yahr stage (Table 3). Again, this analysis confirmed that the disease duration was similar at the onset of motor complications, despite significant differences in the duration of exposure to levodopa (Fig. 2B).

According to ANOVA, age at Parkinson's disease onset was lower in Italian control patients with motor fluctuations than in those without, whereas Hoehn and Yahr stage and median levodopa dose (including weight-adjusted) were higher. These features did not differ in Ghanaians. OFF-state UPDRS III scores were higher in patients with Parkinson's disease with motor fluctuations (defined as 'fluctuators') than in those without (defined as 'non-fluctuators') in both groups (Table 3). The subgroups of 'fluctuators' included all patients who developed dyskinesias. Ghanaian patients who developed dyskinesias were younger at onset than those who did not [median 55.6 (IQR 51.5–58) versus 63.1 (IQR 58–68.5), P = 0.011]. In Ghana, neither males nor females showed any significant difference relating to the severity of motor symptoms, the time from onset to the initiation of levodopa, and the frequency of motor fluctuations and dyskinesias controlled for weight-adjusted levodopa dose (data not shown).

Finally, logistic regression analysis confirmed that wearing-off and dyskinesias were associated with disease duration and levodopa daily dose, but not with the duration of levodopa therapy (Table 4). A correct classification of motor fluctuations and dyskinesias was possible in 77% and 79% of patients, respectively, as quantified by the area under the receiver operating characteristic curve (AUC). This set of variables predicted motor fluctuations and dyskinesias better than the model including disease severity.

As paradigmatic case, we describe a 61-year-old female with a 6-year Parkinson's disease duration and relatively mild motor symptoms (UPDRS III 19/108), who had peak-dose dyskinesias 60 min after her first-ever levodopa dose (150 mg, 2.2 mg/kg; Supplamantary Video Segment 1).

Table 2 Clinical features of Ghanaian patients with Parkinson's disease compared to Italian matched Parkinson's disease controls at the baseline visit

Features	Ghana (n = 91)	Controls (n = 182)	P-value*
Males n (%)	58 (63.7)	110 (60.4)	0.692[a]
Age at onset, y	60.6 (11.3)	60.4 (10.9)	0.862[a]
Disease duration at diagnosis, mean (SD) [range], y	3.9 (2.4) [1–12]	1.1 (1.4) [0–8]	**<0.001**
Disease duration at levodopa initiation, mean (SD) [range], y[b]	4.2 (2.8) [1–12]	2.4 (2.1) [0–11]	**<0.001**
Disease duration at assessment, y	5.0 (3.0)	5.1 (2.9)	0.830[a]
Tremor-dominant presenting phenotype n (%)	68 (74.7)	94 (52.2)	**<0.001**
UPDRS part I	2.2 (2.2)	2.0 (1.9)	0.616
With dementia n (%)	9 (9.9)	12 (6.6)	0.455
With psychosis n (%)	5 (5.5)	7 (3.8)	0.527
With depression/apathy n (%)	13 (14.3)	30 (16.5)	0.878
UPDRS part II – ON	7.0 (4.9)	9.5 (5.5)	0.110
UPDRS part II – OFF	12.4 (7.8)	11.4 (6.4)	0.256
With dysphagia n (%)	7 (8.4)	30 (16.5)	0.09
With falls n (%)	12 (13.1)	31 (17.0)	0.484
With freezing of gait n (%)	12 (13.2)	16 (8.8)	0.192
UPDRS part III – ON	23.5 (11.2)	20.4 (10.9)	0.115
UPDRS part III – OFF	34.9 (15.1)	24.9 (10.8)	**<0.001**
Tremor at rest[c]	4.6 (3.6)	1.7 (2.1)	**0.001**
Axial symptoms[c]	5.4 (4.0)	3.9 (2.7)	0.268
With postural instability n (%)	27 (29.7)	62 (34.1)	0.892
Response to acute levodopa challenge, %	45.0 (13.1)	41.0 (11.6)	0.328
Hoehn and Yahr stage – OFF			
On Stage I n (%)	9 (10)	29 (16)	0.164
On Stage II n (%)	52 (57)	104 (57)	
On Stage III n (%)	21 (23)	38(21)	
On Stage IV-V n (%)	9 (10)	11 (6)	
Therapy			
On chronic levodopa n (%)	59 (64.8)	160 (87.9)	**<0.001**
Levodopa duration at assessment, median [IQR], y	1.0 [0–2]	2.5 [1–5]	**<0.001**
Levodopa dose, mg/day[b]	365 (154)	426 (182)	**0.012**
Levodopa dose, mg/kg/day[b]	6.5 (3.2)	6.0 (2.2)	0.589
On dopamine agonists n (%)	0 (0)	131 (72)	**<0.001**
On anticholinergics n (%)	28 (30.8)	20 (11)	**<0.001**
On amantadine n (%)	7 (7.7)	2 (1.1)	**0.007**
On COMT inhibitors n (%)	0 (0)	35 (19.2)	**<0.001**
On MAO-B inhibitor n (%)	4 (4.4)	52 (28.6)	**<0.001**

[a]Matching criteria.
[b]Calculated on the subgroup of patients on levodopa therapy.
[c]Tremor at rest is defined as the sum of UPDRS III items 20, wheras axial symptoms as the sum of items 27 + 28 + 29 + 30.
*By Student's *t*-test or Fischer's exact test as appropriate. Data are reported as mean (SD), unless otherwise specified.
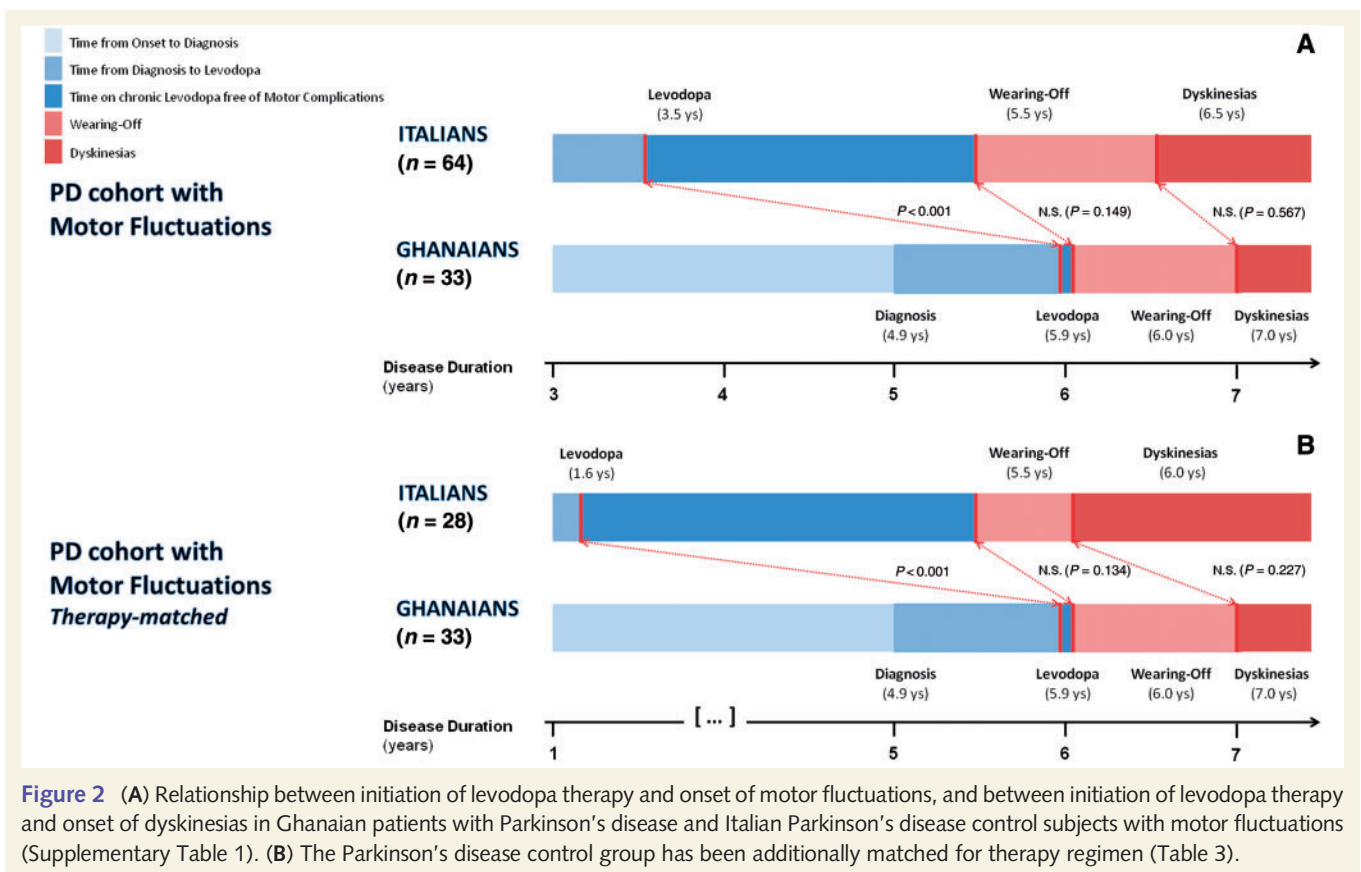
Longitudinal analysis

Thirty-two patients with Parkinson's disease were included in the longitudinal analysis (Supplementary Table 1). Of these, 21 were drug-naïve at baseline (65.6%), whereas the remaining 11 patients had started levodopa therapy before our first examination. During the follow-up, medical therapy was optimized, leading to an overall improvement in motor disability and activities of daily living. Wearing-off and dyskinesias were effectively managed by adjusting the levodopa dosing regimen in the majority of patients. At the last follow-up all patients were on levodopa, and motor fluctuations and dyskinesias had occurred in 56% and 22% of cases, respectively.

After a mean follow-up of 2.6 years, starting from the initiation of levodopa therapy, 10 of 21 (48%) patients who were drug-naïve at baseline had incident wearing-off and 3/21 (14%) developed dyskinesias. Median disease duration at the time of initiation of levodopa was slightly >4 years. In agreement with cross-sectional findings, wearing-off and dyskinesias appeared very early, after a median levodopa duration of 6 months and at a median disease duration of 7 years (IQR, 4.3–9).

As paradigmatic case, we describe a 69-year-old patient with Parkinson's disease with a 12-year history of untreated disease and severe motor disability, who developed wearing-off phenomena 24 h after the introduction of levodopa (each levodopa dose lasted <3 h), whereas peak-dose dyskinesias took 4–5 weeks to appear; levodopa dose was 150 mg four times/day (6.5 mg/kg/day) (Supplementary Video Segment 2).

Figure 2 (**A**) Relationship between initiation of levodopa therapy and onset of motor fluctuations, and between initiation of levodopa therapy and onset of dyskinesias in Ghanaian patients with Parkinson's disease and Italian Parkinson's disease control subjects with motor fluctuations (Supplementary Table 1). (**B**) The Parkinson's disease control group has been additionally matched for therapy regimen (Table 3).

Discussion

In the present 4-year naturalistic study, we had the unique opportunity to observe the effects of chronic levodopa therapy on a large sample of patients with Parkinson's disease untreated for years and produced compelling evidence that the duration of levodopa therapy itself is not a risk factor for the occurrence of 'levodopa-induced' motor complications. The results were consistently provided by a cross-sectional analysis of data collected at the baseline assessment and further supported by the subsequent prospective follow-up of a subgroup of newly diagnosed, untreated patients with Parkinson's disease. In the first part of the study, we showed that the onset of motor complications occurred at comparable disease duration in the two populations, despite the large difference in the duration of exposure to levodopa. In line with data from community-based studies (Schrag and Quinn, 2000; Evans et al., 2011), motor fluctuations and dyskinesias occurred after a mean of 6 to 7 years from onset regardless of the timing of initiation of adequate levodopa therapy. Since the 1980s, there has been much debate about whether levodopa could be safely started early or late in the course of the disease (Fahn, 1999, 2006). A number of studies suggested that dyskinesias could be best predicted by high daily levodopa dose (Fahn et al., 2004) and longer duration of levodopa treatment (Miyawaki et al., 1997; Schrag and Quinn, 2000) and that delaying the initiation of levodopa was the best therapeutic strategy to prevent motor fluctuations and dyskinesias (Fahn and Calne, 1978; Melamed, 1986; Fahn, 1999; Montastruc et al., 1999; Rascol et al., 2000; Fahn et al., 2004).

This induced neurologists to withhold the introduction of adequate levodopa therapy as long as possible (especially in younger patients) and patients to avoid it, generating a sort of widespread 'levodopa phobia' (Kurlan, 2005). However, whether the delay of onset of motor complications in patients initially treated with a dopamine agonist was primarily due to delaying levodopa or rather to the lower levodopa dose needed to compensate motor symptoms remained unclear. The putative protective role of delayed levodopa was challenged by post hoc analyses of the CALM-PD trial (Parkinson Study Group, 2000), which revealed that the incidence of dyskinesias after initiating levodopa was independent of the initial treatment, after adjusting for disease duration and levodopa daily dose (Constantinescu et al., 2007). Cumulative levodopa dose has been suggested to be an independent predictor of dyskinesias in patients with Parkinson's disease (Hauser et al., 2006). However, whether this is primarily related to the duration of treatment or to the daily dose remained unclear. In an experimental study in 6-hydroxydopamine-lesioned rats, animals treated with higher levodopa doses for a short period developed dyskinesias earlier than rats treated chronically with lower doses and exposed to higher cumulative doses (Tsironis et al., 2008). Taken as a whole, these findings are in line with our data and further support the hypothesis that the timing of initiation of levodopa therapy does not modulate the risk of motor complications. Accordingly, the main variables we need to focus on are individual daily levodopa dose and disease progression itself.

After a mean of 6 years from onset of motor symptoms, the rates of motor fluctuations and dyskinesias in Ghanaian patients on chronic levodopa therapy were 56% and 14%, respectively.

Table 3 The relationship between motor complications and therapy features in Ghanaian patients with Parkinson's disease on chronic levodopa compared to a group of Italian Parkinson's disease controls never treated with any dopamine agonist or COMT inhibitor (defined as 'therapy-matched')

General features and therapy	Ghana (n = 59)	Therapy–matched controls (n = 50)	P-value[†]
Males n (%)	37 (62.7)	26 (52)	0.450[a]
Age at onset, y	60.8 (9.7) [35–78]	60.8 (8.4) [29–73]	0.966[a]
Disease duration at levodopa initiation, y	4.2 (2.8) [1–12]	1.8 (1.6) [0.3–7]	**<0.001**
Disease duration at assessment, y	5.8 (3.3) [1–20]	5.7 (2.9) [1–12]	0.663[a]
UPDRS part III – OFF	36.8 (15.4) [7–74]	34.4 (17.9) [13–69]	0.615
UPDRS part III – ON	23.5 (11.2)	21.8 (9.4)	0.726
Hoehn and Yahr stage – OFF	2.6 (0.9) [1–5]	2.4 (0.7) [1–5]	0.151
Hoehn and Yahr stage – ON	1.9 (0.6) [1–4]	1.8 (0.6) [1–4]	0.311
Levodopa duration at assessment, median [IQR], y	1.0 [0–2]	4.0 [2–6]	**<0.001**
Levodopa dose, mg/day	365 (154) [100–750]	496 (227) [150–1050]	**0.002**
Levodopa dose, mg/kg/day	6.5 (3.2) [2–17]	7.0 (3.2) [1.9–17.2]	0.473
Body weight, kg	62.9 (13.7) [37–93]	71.5 (14.1) [48–102]	**0.006**
Body mass index, kg/m^2	22.4 (3.9) [15.8–30.5]	26.3 (4.1) [16.6–36]	**0.003**
Motor complications			
Motor fluctuations n (%)	33 (55.9)	28 (56)	0.931
Disease duration at onset of motor fluctuations, median [IQR], y	6.0 [5–8]	5.5 [4–6]	0.134
Levodopa duration at onset of motor fluctuations, median [IQR], y	0.5 [0–1]	4.5 [3–5]	**<0.001**
Dyskinesias n (%)	8 (13.6)	17 (34)	**0.013**
Disease duration at onset of dyskinesias, median [IQR], y	7.0 [6–10.25]	6.0 [4–7]	0.227
Levodopa duration at onset of dyskinesias, median [IQR], y	1.0 [0.25–2]	5.0 [4–6]	**0.003**

	Non–Fluctuators (n = 26)	Fluctuators (n = 33)	Non-Fluctuators (n = 22)	Fluctuators (n = 28)	P-value[‡]
Age at onset, y	61.6 (8.8)	59.4 (9.7)	630.5 (50.3)[§]	58.6 (9.7)	**0.044**
Disease duration at levodopa initiation, y	3.4 (2.0)[§§]	5.9 (2.6)[##]	10.9 (10.8)	1.6 (1.4)	**0.002**
Disease duration at Assessment, y	4.5 (2.0)	6.3 (3.0)	40.2 (20.9)	6.8 (2.4)	0.098
UPDRS part III - OFF	32.6 (12.0)[§]	41.3 (16.2)[##]	220.0 (90.7)[§§]	30.8 (11.8)	**<0.001**
Hoehn and Yahr stage - OFF	2.3 (0.9)	2.7 (0.9)	20.0 (00.3)[§§]	2.6 (0.7)	**0.004**
Levodopa Ddose, median [IQR], mg/day	300 [300–400]	300 [300–450][##]	300 [300–4310.25][§]	600 [400–775]	**0.008**
Levodopa dose weight-adjusted, median [IQR], mg/kg/day	5.0 [4.4–5.6]	6.0 [4.8–8][#]	40.7 [40.1–60.35][§§]	7.8 [6.2–10.25]	**0.004**

Data are reported as mean (SD) [range], unless otherwise specified.

[a] Matching criteria.

P-values were computed using Student's *t*-test or Fischer's exact test as appropriate (†) or one-way ANOVA (‡; *post hoc* comparison of means were performed using Sheffe's test: [§]P < 0.05 and [§§]P < 0.01 for comparisons between 'Non-Fluctuators' versus 'Fluctuators'; [#]P < 0.05 and [##]P < 0.01 for comparisons between Ghanaian 'Fluctuators' versus Italian 'Fluctuators'). Significant values (P<0.05) are in bold.

Considerable variability in motor complication rates has been reported in literature so far, due to important differences in the population assessed, in levodopa dosage, in time from onset to the initiation of levodopa, and in disease duration and severity at assessment (Schrag and Quinn, 2000; Hauser *et al*., 2006; Stowe *et al*., 2008). The motor complication rates in series containing patients from the pre-levodopa era are similar to those found in Ghana after a comparable interval from onset to the initiation of levodopa (58% versus 56% of the present study; Ahsklog and Muenter, 2001). On the other hand, series containing pre-levodopa era patients reported a considerably higher frequency of early dyskinesias compared to the modern era series and to our 'modern pre-levodopa era' study, as ~50% of patients developed dyskinesias after a median time of 6 months since the initiation of chronic levodopa therapy (Ahsklog and Muenter, 2001). Cotzias *et al*. (1969) were the first who reported the early appearance of involuntary movements after the initiation of levodopa therapy in 50% of patients with Parkinsonism, describing them as 'dose dependent in each case'. However, in contrast to the present study, patients from the pre-levodopa era had considerably longer median disease duration at introduction of levodopa (6–10 years versus 4 years of the present study) and there was the bias of more aggressive levodopa dosing (reviewed in Ahsklog and Muenter, 2001; Fahn, 2006). Therefore, it was not possible to

Table 4 Logistic regression analysis for predictors of motor complications

Set of variables[b,c]	Model prediction (AUC)[a]	
	Motor fluctuations	Dyskinesias
A + B + C	0.77[d]	0.79[e]
B + C + D	0.71	0.75
Model for motor fluctuations[d]	**OR (95%CI)**	**P-value**
Levodopa dose (mg/kg)	1.33 (1.05–1.68)	**0.019**
Duration of levodopa at occurrence (years)	1.09 (0.80–1.48)	0.606
Disease duration at onset of motor fluctuations (years)	1.36 (1.01–1.83)	**0.040**
Model for dyskinesias[e]		
Levodopa dose (mg/kg)	1.19 (1.00–1.42)	**0.045**
Duration of levodopa at occurrence (years)	0.93 (0.73–1.18)	0.550
Disease duration at onset of motor fluctuations (years)	1.42 (1.07–1.87)	**0.014**

[a]Capacity to correctly classify positive cases as quantified by the area under the receiver operating characteristic curve (AUC): the closer to 1, the better the model performance.
[b]A, levodopa daily dose (mg/kg); B, duration of levodopa at occurrence of complications (years); C, disease duration at occurrence of complications (years); D, disease severity (OFF-state UPDRS part III score).
[c]The model including the set of variables A + B + C + D could not be performed due to high collinearity (Pearson's r > 0.5) between disease severity and levodopa daily dose.
[d,e]Best predictive models for motor complications were those including Levodopa dose, duration of levodopa and duration of disease at their onset. Significant values (p < 0.05) are in bold.

disentangle the long duration of the disease from the very high levodopa daily dose and establish which was the most relevant factor for the early development of dyskinesias. Similarly, early motor complications in patients with longstanding and untreated Parkinson's disease have been described even in the modern era in association with high individual levodopa daily doses (Onofrj et al., 1998).

In agreement with the modern-era literature, our multivariate analysis confirmed that the individual levodopa dosing regimen is a major risk factor for motor fluctuations and dyskinesias (Sharma et al., 2008; Olanow et al., 2013). Despite the collinearity between levodopa daily dose and disease severity, the early appearance of motor complications was not associated with levodopa overdosing in the Ghanaian cohort, as levodopa was slowly titrated up and kept at a relatively low dose. In particular, mean levodopa daily dose was slightly lower than the recommended initial target dose considered to be the threshold for dyskinesias in the post hoc analysis of the STRIDE-PD study (365 mg daily of the present study versus 400 mg daily in Olanow et al., 2013). This is even more evident when we consider that Ghanaian patients had longer disease duration at the initiation of levodopa (4 versus 2 years, respectively) and that none of them had concomitant dopamine agonist therapy compared to the majority of patients from the drug trial (~60% in Olanow et al., 2013), thus unbalancing individual levodopa-equivalent daily dose even further. Overall, we believe that the primary cause for the early appearance of motor

complications in the Ghanaian Parkinson's disease population was disease progression rather than the relatively high levodopa daily dose. This hypothesis is further supported by a recent imaging study showing that identical doses of levodopa induced increasingly larger changes in striatal dopamine levels as the duration of motor symptoms increased, due to a compensatory mechanism secondary to the reduction in buffering capacity and presynaptic reuptake of dopamine that occurs as Parkinson's disease progresses (de la Fuente-Fernández et al., 2004). In line with our clinical data, the authors concluded that the primary cause of peak-dose dyskinesias was disease progression and not levodopa per se (de la Fuente-Fernández et al., 2004).

Hence, it seems that we should emphasize the role of substantia nigra pars compacta neuronal loss and the subsequent synaptic dopamine depletion rather than levodopa therapy per se to shed light on the pathophysiology of 'levodopa-induced' motor complications. According to presynaptic models of levodopa-induced dyskinesias, the extent of dopamine denervation and striatal dopamine reduction increases the sensitivity of post synaptic receptors and the downstream signalling pathway (Carta and Bezard, 2011), and regulates the level and duration of exposure to levodopa that is required to induce dyskinesias (Jenner, 2008). From a clinical perspective, it is generally assumed that the severity of motor symptoms reflects the extent of nigrostriatal neuronal loss. In contrast with experimental studies, however, we did not observe a strong association between the severity of parkinsonism and the latency to the onset of dyskinesias, at both multivariate analysis of cross sectional data and during the prospective follow-up of patients. The post hoc analyses of the STRIDE-PD trial are consistent with our observations, as the severity of motor symptoms had no predictive role for dyskinesias (Olanow et al., 2013). Interestingly, Cotzias et al. (1969) similarly reported in their pivotal study on levodopa that 'the most severe involuntary movements were induced among the patients whose disease had the longest duration, not necessarily among those with the most severe disease'. This discrepancy might be explained considering that patients with different degrees of neuronal loss may present with comparable severity of motor symptoms, as compensatory mechanisms may modulate the length of the pre-motor stage of Parkinson's disease considerably (de la Fuente-Fernández et al., 2011). In particular, younger age at onset is associated with better presynaptic and postsynaptic compensatory mechanisms aimed at keeping normal striatal dopamine. Thus, early-onset patients may tolerate greater severity of substantia nigra pars compacta neuronal loss before dopamine levels decrease below the estimated threshold for the first motor symptoms to appear (de la Fuente-Fernández et al., 2011). Therefore, it could be argued that the higher risk of dyskinesias associated with younger age at Parkinson's disease onset, consistently described so far (Kempster et al., 2007; Olanow et al., 2013) and confirmed in the present study, might be due to a greater extent of neuronal loss in patients with similar severity of motor symptoms. Overall, these data support the idea that it is the duration of Parkinson's disease rather than the severity of motor symptoms that is closely associated with the extent of neuronal loss. In turn, it is the extent of substantia nigra pars compacta neuronal loss that causes the decrease in striatal dopamine levels that predisposes to the development of motor complications once

a patient with Parkinson's disease is exposed to levodopa. Nevertheless, preclinical (Guigoni *et al.*, 2005) and clinical (Linazasoro *et al.*, 2009) studies show that similar extension of neuronal loss may lead to involuntary movements in some individuals and not in others after exposure to similar levodopa doses, suggesting that individual predisposition is likely to play a role in addition to disease-related variables, including genetic factors (reviewed in Manson *et al.*, 2012). Further evidence is provided by the Ghanaian patient who developed peak-dose dyskinesias after the first-ever levodopa intake despite her mild disease severity, which is in contrast to the relatively delayed appearance of dykinesias in patients with more severe motor symptoms. This paradigmatic case supports the hypothesis that the induction of levodopa-induced dyskinesias (defined as 'priming' process) does not require chronic dopaminergic treatment and brain sensitization (Cotzias, 1971; Huot *et al.*, 2013), but may occur even after the first-ever dose of levodopa in a dopamine-depleted brain (Nadjar *et al.*, 2009). Nigrostriatal degeneration has generally been considered to be mandatory in the pathogenesis of dyskinesias in view of the absence of dyskinesias in animals or humans with intact dopamine system despite long-term exposure to levodopa (Boyce *et al.*, 1990; Jenner, 2008), including patients with DOPA-responsive dystonia due to *GCH1* mutations (Nutt *et al.*, 2001; Trender-Gerhard *et al.*, 2009). However, levodopa-induced dyskinesias may be generated under extreme conditions even when basal ganglia are normal, as shown in animals and humans with preserved substantia nigra pars compacta neuronal density that received very high doses of levodopa (Hwang *et al.*, 2001; Togasaki *et al.*, 2005; Jenner, 2008). On the other hand, dyskinesias may develop in the absence of substantia nigra pars compacta neuronal loss even after exposure to low levodopa doses in the dopamine-depleted brain of patients with tyrosine hydroxylase deficiency, most likely via postsynaptic dopamine receptor supersensitivity (Carta and Bezard, 2011; Bézard *et al.*, 2013; Pons *et al.*, 2013). Taken as a whole, these data suggest that striatal dopamine levels and levodopa dose are inversely related in the equation predicting dyskinesias, in a continuum that does not include the duration of levodopa therapy. Age at onset and individual genetically-inherited predisposing factors have a modulatory effect (Manson *et al.*, 2012).

This study has some limitations that should be acknowledged. First, we used a control Parkinson's disease population with a different genetic and environmental background (Cilia *et al.*, 2011, 2012). Therefore, we cannot definitely exclude the possibility that Parkinson's disease in black Africans may have a different phenotype and response to levodopa and further studies are needed to confirm the present findings without the bias related to the assessment of different populations. Nevertheless, we found that major demographic and clinical characteristics 5 years after onset were overall comparable, suggesting that potential differences related to the geographical setting did not play a substantial role in the current findings. In particular, our extensive analysis did not reveal any significant difference in terms of mean age at onset, frequency of major non-motor features, and severity of motor symptoms, including response to acute levodopa challenge, non-levodopa-responsive motor symptoms, activities of daily living and

progression to advanced disease stages. As the awareness of the disease and the skills of local doctors are progressively increasing in several sub-Saharan African countries, the disease is diagnosed at earlier stages and levodopa therapy started accordingly. Therefore, it is conceivable that in the near future it will be possible to perform a direct comparison between patients with an early-start compared to those with a delayed-start of levodopa. Second, the different access to medications between the two populations forced us to add a control subgroup of patients with Parkinson's disease who had never been exposed to dopamine agonists or COMT inhibitors and thus complicated the design of study analyses. Finally, this study was not designed as a community-based trial and inclusion bias might have occurred. In the attempt to make the study cohort as representative as possible of the general Parkinson's disease population in the sub-Saharan African region, we conducted a long-term naturalistic study observing outpatients consecutively referred not only to two neurology clinics in large cities of densely populated regions, but also to a small clinic in a rural area of the country. Nonetheless, the higher frequency of patients presenting with a tremor-dominant phenotype reasonably reflects the low awareness of Parkinson's disease that still induces most doctors and patients to place stronger emphasis on resting tremor as the 'cardinal symptom' leading to suspect Parkinson's disease (as gait and balance disturbances are generally attributed to normal ageing) so that non-tremor-dominant subtypes are likely to be under-represented. This observation underlines further the need to promote educational initiatives in developing countries (The Movement Disorders Society, 2013). The different phenotype at presentation might have had a confounding effect on clinical variables, including the risk of motor complications. It has been recently suggested that the tremor-dominant presenting phenotype may be a negative predictor of dyskinesias (Kipfer *et al.*, 2011; Zhang *et al.*, 2013). In a clinicopathological study, the onset of dyskinesias was delayed by ~2 years in patients presenting with a tremor-dominant motor phenotype compared to those with a non-tremor phenotype (although this difference was not statistically significant, Selikhova *et al.*, 2009). Accordingly, we might assume that, if the Ghanaian cohort had had a similar proportion of patients with non-tremor-dominant phenotype to the Italian control population, the main finding of the present study would have been strengthened even further, as the rate of motor complications would have been expected to be higher and their appearance even earlier than what we found. Overall, we believe that our naturalistic case-control study including a matched control population from a Western country was the only possible way to provide conclusive answers about the relationship between levodopa therapy and disease progression in the pathophysiology of motor complications, overcoming the limitations of previous studies.

Conclusion

The present study provides evidence that motor fluctuations and dyskinesias are not associated with the duration of exposure to levodopa therapy, but rather to disease progression itself.

Therefore, there is no reason to delay the initiation of adequate levodopa therapy in patients with Parkinson's disease. In contrast with past drug trials, recent experimental studies suggest that the best therapeutic option to delay the molecular changes in gene expression, synaptic morphology and abnormal corticostriatal connectivity associated with dyskinesias may be early initiation of levodopa treatment (Marin *et al.*, 2009). We emphasize the importance of considering the pharmacokinetic properties of levodopa and recommend (i) to adjust the individual levodopa dose regimen per kilogram of body weight to reduce the risk of dyskinesias (Zappia *et al.*, 2002; Sharma *et al.*, 2008; Olanow *et al.*, 2013); and (ii) to consider the potential benefits of dietary protein redistribution during the daytime to minimize levodopa requirement and improve the control of motor fluctuations (Mena and Cotzias, 1975; Cereda *et al.*, 2010). Further studies are needed to better understand the natural course of Parkinson's disease without the confounding effect of medications, and the pathophysiology of motor and non-motor symptoms. Whether the answers will come from Africa, time will tell.

Acknowledgements

Funding

Supplementary material

Supplementary material is available at *Brain* online.

References

Ahlskog JE, Muenter MD. Frequency of levodopa-related dyskinesias and motor fluctuations as estimated from the cumulative literature. Mov Disord 2001; 16: 448–58.

American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th edn. Washington, DC: American Psychiatric Association; 2000.

Ballard PA, Tetrud JW, Langston JW. Permanent human parkinsonism due to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP): seven cases. Neurology 1985; 35: 949–56.

Bézard E, Olanow CW, Obeso JA. Levodopa-induced dyskinesias in the absence of nigrostriatal degeneration. Mov Disord 2013; 28: 1023–4.

Boyce S, Rupniak NM, Steventon MJ, Iversen SD. Nigrostriatal damage is required for induction of dyskinesias by L-DOPA in squirrel monkeys. Clin Neuropharmacol 1990; 13: 448–58.

Carta M, Bezard E. Contribution of pre-synaptic mechanisms to L-DOPA-induced dyskinesia. Neuroscience 2011; 198: 245–51.

Cereda E, Barichella M, Pedrolli C, Pezzoli G. Low-protein and protein-redistribution diets for Parkinson's disease patients with motor fluctuations: a systematic review. Mov Disord 2010; 25: 2021–34.

Chapuis S, Ouchchane L, Metz O, Gerbaud L, Durif F. Impact of the motor complications of Parkinson's disease on the quality of life. Mov Disord 2005; 20: 224–30.

Cilia R, Akpalu A, Cham M, Bonetti A, Amboni M, Faceli E, et al. Parkinson's disease in sub Saharan Africa: step-by-step into the challenge. Neurodegen Dis Manage 2011; 1: 193–202.

Cilia R, Sironi F, Akpalu A, Cham M, Sarfo FS, Brambilla T, et al. Screening LRRK2 gene mutations in patients with Parkinson's disease in Ghana. J Neurol 2012; 259: 569–70.

Cotzias GC, Van Woert MH, Schiffer LM. Aromatic amino acids and modification of parkinsonism. N Engl J Med 1967; 276: 374–9.

Cotzias GC, Papavasiliou PS, Gellene R. Modification of Parkinsonism-chronic treatment with L-DOPA. N Engl J Med 1969; 280: 337–45.

Cotzias GC. Levodopa in the treatment of Parkinsonism. JAMA 1971; 218: 1903–8.

Constantinescu R, Romer M, McDermott MP, Kamp C, Kieburtz K. CALM-PD Investigators of the Parkinson Study GroupImpact of pramipexole on the onset of levodopa-related dyskinesias. Mov Disord 2007; 22: 1317–9.

de la Fuente-Fernández R, Sossi V, Huang Z, Furtado S, Lu JQ, Calne DB, et al. Levodopa-induced changes in synaptic dopamine levels increase with progression of Parkinson's disease: implications for dyskinesias. Brain 2004; 127: 2747–54.

de la Fuente-Fernández R, Schulzer M, Kuramoto L, Cragg J, Ramachandiran N, Au WL, et al. Age-specific progression of nigrostriatal dysfunction in Parkinson's disease. Ann Neurol 2011; 69: 803–10.

Diamond SG, Markham CH, Hoehn MM, McDowell FH, Muenter MD. Multi-center study of Parkinson mortality with early versus later dopa treatment. Ann Neurol 1987; 22: 8–12.

Dotchin C, Jusabani A, Walker R. Three year follow up of levodopa plus carbidopa treatment in a prevalent cohort of patients with Parkinson's disease in Hai, Tanzania. J Neurol 2011; 258: 1649–56.

Evans JR, Mason SL, Williams-Gray CH, Foltynie T, Brayne C, Robbins TW, et al. The natural history of treated Parkinson's disease in an incident, community based cohort. J Neurol Neurosurg Psychiatry 2011; 82: 1112–8.

Fahn S, Calne DB. Considerations in the management of parkinsonism. Neurology 1978; 28: 5–7.

Fahn S, Elton RL. UPDRS Program Members. Unified Parkinson's disease rating scale. In: Fahn S, Marsden CD, Goldstein M, Calne DB, editors. Recent developments in Parkinson's disease. Vol. 2. Florham Park, NJ: Macmillan Healthcare Information; 1987. p. 153–63, 293–304.

Fahn S. Parkinson disease, the effect of levodopa, and the ELLDOPA trial. Arch Neurol 1999; 56: 529–35.

Fahn S, Oakes D, Shoulson I, Kieburtz K, Rudolph A, Lang A, et al. Levodopa and the progression of Parkinson's disease. N Engl J Med 2004; 351: 2498–508.

Fahn S. A new look at levodopa based on the ELLDOPA study. J Neural Transm 2006; 70 (Suppl): 419–26.

Grandas F, Galiano ML, Tabernero C. Risk factors for levodopa-induced dyskinesias in Parkinson's disease. J Neurol 1999; 246: 1127–33.

Guigoni C, Dovero S, Aubert I, Li Q, Bioulac BH, Bloch B, et al. Levodopa-induced dyskinesia in MPTP-treated macaques is not dependent on the extent and pattern of nigrostrial lesioning. Eur J Neurosci 2005; 22: 283–87.

Hauser RA, McDermott MP, Messing S. Factors associated with the development of motor fluctuations and dyskinesias in Parkinson disease. Arch Neurol 2006; 63: 1756–60.

Hoehn M, Yahr M. Parkinsonism: onset, progression and mortality. Neurology 1967; 17: 427–42.

Huot P, Johnston TH, Koprich JB, Fox SH, Brotchie JM. The Pharmacology of L-DOPA-induced dyskinesia in Parkinson's disease. Pharmacol Rev 2013; 65: 171–222.

Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 1992; 55: 181–4.

Hwang WJ, Calne DB, Tsui JK, de la Fuente-Fernández R. The long-term response to levodopa in dopa-responsive dystonia. Parkinsonism Relat Disord 2001; 8: 1–5.

Jankovic J, McDermott M, Carter J, Gauthier S, Goetz C, Golbe L, et al. Variable expression of Parkinson's disease: a base-line analysis of the DATATOP cohort. The Parkinson Study Group. Neurology 1990; 40: 1529–34.

Jenner P. Molecular mechanisms of L-DOPA-induced dyskinesia. Nat Rev Neurosci 2008; 9: 665–77.

Kempster PA, Williams DR, Selikhova M, Holton J, Revesz T, Lees AJ. Patterns of levodopa response in Parkinson's disease: a clinico-pathological study. Brain 2007; 130: 2123–8.

Kieburtz K. Therapeutic strategies to prevent motor complications in Parkinson's disease. J Neurol 2008; 255 (Suppl 4): 42–5.

Kipfer S, Stephan MA, Schüpbach WM, Ballinari P, Kaelin-Lang A. Resting tremor in Parkinson disease: a negative predictor of levodopa-induced dyskinesia. Arch Neurol 2011; 68: 1037–9.

Kurlan R. "Levodopa phobia": a new iatrogenic cause of disability in Parkinson disease. Neurology 2005; 64: 923–4.

Linazasoro G, Van Blercom N, Bergaretxe A, Inaki FM, Laborda E, Ruiz Ortega JA. Levodopa-induced dyskinesias in Parkinson disease are independent of the extent of striatal dopaminergic denervation: a pharmacological and SPECT study. Clin Neuropharmacol 2009; 32: 326–9.

Litvan I, Bhatia KP, Burn DJ, Goetz CG, Lang AE, McKeith I, et al. Movement Disorders Society Scientific Issues Committee report: SIC Task Force appraisal of clinical diagnostic criteria for Parkinsonian disorders. Mov Disord 2003; 18: 467–86.

Manson A, Stirpe P, Schrag A. Levodopa-induced-dyskinesias clinical features, incidence, risk factors, management and impact on quality of life. J Parkinsons Dis 2012; 2: 189–98.

Marin C, Aguilar E, Mengod G, Cortés R, Obeso JA. Effects of early vs. late initiation of levodopa treatment in hemiparkinsonian rats. Eur J Neurosci 2009; 30: 823–32.

Melamed E. Initiation of levodopa therapy in parkinsonian patients should be delayed until the advanced stages of the disease. Arch Neurol 1986; 43: 402–5.

Mena I, Cotzias GC. Protein intake and treatment of Parkinson's disease with levodopa. N Engl J Med 1975; 292: 181–4.

Merola A, Zibetti M, Angrisano S, Rizzi L, Ricchi V, Artusi CA, et al. Parkinson's disease progression at 30 years: a study of subthalamic deep brain-stimulated patients. Brain 2011; 134: 2074–84.

Miyawaki E, Lyons K, Pahwa R, Tröster AI, Hubble J, Smith D, et al. Motor complications of chronic levodopa therapy in Parkinson's disease. Clin Neuropharmacol 1997; 20: 523–30.

Montastruc JL, Rascol O, Senard JM. Treatment of Parkinson's disease should begin with a dopamine agonist. Mov Disord 1999; 14: 725–30.

Movement Disorders Society. Regional sections, Task Force on Africa. [updated 2013 December 19]. http://www.movementdisorders.org/regional_sections/sub-saharan/courses/accra-ghana.php. (10 March 2014, date last accessed).

Nadjar A, Gerfen CR, Bezard E. Priming for l-dopa-induced dyskinesia in Parkinson's disease: a feature inherent to the treatment or the disease? Prog Neurobiol 2009; 87: 1–9.

Nutt JG, Nygaard TG. Response to levodopa treatment in dopa-responsive dystonia. Arch Neurol 2001; 58: 905–10.

Olanow WC, Kieburtz K, Rascol O, Poewe W, Schapira AH, Emre M, et al. Stalevo Reduction in Dyskinesia Evaluation in Parkinson's Disease (STRIDE-PD) Investigators. Factors predictive of the development of Levodopa-induced dyskinesia and wearing-off in Parkinson's disease. Mov Disord 2013; 28: 1064–71.

Onofrj M, Paci C, Thomas A. Sudden appearance of invalidating dyskinesia-dystonia and off fluctuations after the introduction of levodopa in two dopaminomimetic drug naive patients with stage IV Parkinson's disease. J Neurol Neurosurg Psychiatry 1998; 65: 605–6.

Parkinson Study Group. Pramipexole vs levodopa as initial treatment for Parkinson disease: a randomized controlled trial. Parkinson Study Group. JAMA 2000; 284: 1931–8.

Poewe W, Mahlknecht P. The clinical progression of Parkinson's disease. Parkinsonism Relat Dis 2009; 15 (Suppl 4): S28–S32.

Pons R, Syrengelas D, Youroukos S, Orfanou I, Dinopoulos A, Cormand B, et al. Levodopa-induced dyskinesias in tyrosine hydroxylase deficiency. Mov Disord 2013; 28: 1058–63.

Rascol O, Brooks DJ, Korczyn AD, DePeyn PP, Clarke CE, Lang AE. A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa. N Engl J Med 2000; 342: 1484–91.

Schrag A, Quinn N. Dyskinesias and motor fluctuations in Parkinson's disease. A community-based study. Brain 2000; 123: 2297–305.

Selikhova M, Williams DR, Kempster PA, Holton JL, Revesz T, Lees AJ. A clinico-pathological study of subtypes in Parkinson's disease. Brain 2009; 132: 2947–57.

Sharma JC, Ross IN, Rascol O, Brooks D. Relationship between weight, levodopa and dyskinesia: the significance of levodopa dose per kilogram body weight. Eur J Neurol 2008; 15: 493–6.

Stowe RL, Ives NJ, Clarke C, van Hilten J, Ferreira J, Hawker RJ, et al. Dopamine agonist therapy in early Parkinson's disease. Cochrane Database Syst Rev 2008; CD006564.

Togasaki DM, Tan L, Protell P, Di Monte DA, Quik M, Langston JW. Levodopa induces dyskinesias in normal squirrel monkeys. Ann Neurol 2001; 50: 254–7.

Trender-Gerhard I, Sweeney MG, Schwingenschuh P, Mir P, Edwards MJ, Gerhard A, et al. Autosomal-dominant GTPCH1-deficient DRD: clinical characteristics and long-term outcome of 34 patients. J Neurol Neurosurg Psychiatry 2009; 80: 839–45.

Tsironis C, Marselos M, Evangelou A, Konitsiotis S. The course of dyskinesia induction by different treatment schedules of levodopa in Parkinsonian rats: is continuous dopaminergic stimulation necessary? Mov Disord 2008; 23: 950–7.

Williams A. MPTP parkinsonism. Br Med J (Clin Res Ed) 1984; 289: 1401–2.

Zappia M, Crescibene L, Arabia G, Nicoletti G, Bagalà A, Bastone L, et al. Body weight influences pharmacokinetics of levodopa in Parkinson's disease. Clin Neuropharmacol 2002; 25: 79–82.

Zhang YH, Tang BS, Song CY, Xu Q, Lou MX, Liu ZH, et al. The relationship between the phenotype of Parkinson's disease and levodopa-induced dyskinesia. Neurosci Lett 2013; 556: 109–12.