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Analysis of Motor Complications in Parkinson's Disease Phenotypes

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Author's contribution

This work was carried out in collaboration between both authors. Author NM designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Author QKD managed the analyses of the study and managed the literature searches. Both authors read and approved the final manuscript.

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Original Research Article

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ABSTRACT

Patients with PD were enrolled in the research study and underwent examination on movement disorder and drug-induced motor complication by UPDRS III and IV. Hoehn and Yahr scale was used to describe the intermediate course of disease. All antiparkinsonian drugs were calculated on theoretical equivalence to L-dopa. 208 patients were divided into three subgroups: tremor-dominant 50,4%, akinetic-rigid 41,9% and mix type 7,7%. All patients were treated with L-dopa, and about three quarters were in combination with a dopamine agonist.Regarding disease duration and developing of wearing off, there was significant difference according to clinical phenotype. AR and mix subtype of PD develop wearing off earlier within 3 years compare to TD. 72,4% TD type develop wearing off after 6 years and further while AR and Mix type develop earlier. It should be also noted that when gender was included in the analysis, we didn't found a positive association

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with wearing off as well as LID. Peak dose is the most found dyskinesia type in patients. The same no association with average LED with LID. Our findings support the hypothesis that tremor dominant type manifests with a bit benign clinic and complication.

Keywords: Motor fluctuation; levodopa-induced dyskinesia; advanced Parkinson's disease.

1. INTRODUCTION

Parkinson's disease is a progressive neurodegenerative disorder characterised by a combination of motor symptoms and a wide spectrum of non-motor symptoms. The incidence rate was estimated to be 16,9 per 100 000 person-years in one Japanese study [1]. Levodopa, a dopamine precursor, is an effective and well-tolerated dopamine replacement agent used to treat Parkinson's disease (PD). Despite the development of several new medications for controlling PD symptoms, levodopa remains the most efficacious treatment. However, its long-term might induce motor complications (MC), namely, motor fluctuations and dyskinesia. The appearance of levodopa-induced dyskinesia is closely related to plasma levels of levodopa. Most levodopa-induced dyskinesia occurs when antiparkinsonian effects of levodopa are maximal, hence the term peak-dose dyskinesia. There are extensive individual variations in the nature, severity, and topographical pattern of levodopa-induced dyskinesia(LID). It has been estimated that the annual incidence of levodopa-induced dyskinesia is approximately 10% in treated patients. However, at least 10% to 20% of patients with levodopa-responsive PD never develop dyskinesia. Once LID has developed, its severity increases but the topographical pattern tends to remain. It has been consistently observed that levodopa-induced dyskinesia occurs more frequently in patients with a younger age of onset [2,3]. However, more than 80% of PD patients present after age 60, and in this age group, dyskinesia and fluctuation risks are markedly less. For those between ages 60-70, the dyskinesia risk after 5 years of levodopa is 26%; it drops to 16% after age 70 [4,5]. The term dyskinesia is applied to any involuntary movement, such as chorea, ballism, dystonia, tic, or myoclonus [6]. During early levodopa treatment, peak dose dyskinesia may be apparent only during the maximum antiparkinsonian effect of levodopa. With a longer duration of treatment, the dyskinetic phase expands to the whole "on" period, with the severity varying little throughout. Even during the "off" state, a brief episode of dyskinesia may be provoked by stress. This square wave response usually accompanies the development of sudden "on-off" responses [7].

Peak-dose dyskinaesias occur at the peak of benefit following the administration of levodopa, when patients are hypotonic and show only minimal signs of parkinsonism, and plasma levodopa levels are above a certain critical individual concentration [8]. They most commonly affect the upper part of the body, especially the face, the neck and the trunk, but they tend to be generalized, the upper limbs being more severely involved than the lower limbs [9]. Studying the risk of developing LID in PD patients according to its subtype might predict the timing or course of disease in term of motor complication.

Thus, not many data given on whether patients with different clinical phenotypes of Parkinson's disease (PD) differ in their risk of developing levodopa-induced dyskinesia. Therefore, the present study was designed to investigate a possible association between the specific phenotype of PD and development of LID, along with an analysis of its targeted distribution and pattern.

Purpose: To evaluate the possible association between levodopa-induced dyskinesia and PD subtype.

2. METHODS

This analytic study was conducted in 208 patients diagnosed with idiopathic PD who were consecutively recruited from the inpatient clinic of the movement disorders unit at Hospital University of Juntendo, Tokyo, Japan from 2006 to 2017 by using the medical records evaluated for deep brain stimulation (DBS). Diagnostic procedures at baseline included a full medical history, comprehensive clinical, neuropsychological and neuropsychiatric assessments, laboratory tests, cerebral MRI, and, if indicated clinically, dopamine transporter imaging and MIBG. Indication in patients with advanced PD include motor symptoms that have not responded to multiple treatments intended to control them, significant freezing episodes that

limit daily activities, and non-motor complication, including 'off-time' anxiety attacks that negatively impact both the patient and family members.

2.1 Subject Recruitments

Eligible subjects were 29–81 years old and were diagnosed with advanced stage of Parkinson's disease as well as wearing off and dyskinesias of the limbs or trunk. Patients with multiple system atrophy, supranuclear palsy, vascular parkinsonism, drug-induced parkinsonism, and patients who had undergone deep brain stimulation surgery were excluded. Patients were subtyped into one of three clinical groups following the method proposed by Schiess and coworkers; The three subtypes were (1) akinetic–rigid (which includes postural instability, gait difficulty); (2) tremor-dominant; and (3) mixed (features of akinetic –rigid and tremor. Dyskinesias were recorded as choreic, atheoid, ballistic, dystonic or myoclonic character. Chorea was defined as random and chaotic flexion and extensions of the limbs. Chorea was often superimposed upon more repetitive, stereotypic dyskinesias. Dystonia was characterized by brief or sustained repetitive abnormal posturing associated with flexion or extension of the limbs.

2.2 Standardized Instruments

A motor examination was carried out, including the Unified Parkinson's Disease Rating Scale (UPDRS) part III examination. The total UPDRS part III score was used as a measure of disease severity (total score = 108, a higher score is worse). Motor complications were assessed using items of the UPDRS part IV. Only scores during the "on" medication state were included in the analysis. We used the modified Hoehn and Yahr Scale (five-point scale) to assess PD-related disabilities. Calculation of daily L-dopa equivalent daily dose (LEDD) was based on theoretical equivalence to L-dopa as follows: same anti-parkinsonian effect as 100 levodopa calculated for Ropinirole x 9, Amantadine x1, pamipexole x1, Rotigotine x 4, (all doses in mg).

2.3 Statistical Analysis

Statistical analysis was performed using GraphPad Prism 7 software for Mac. To gather all the information, a database was created using Microsoft Excel for Mac. Descriptive data are presented as means, standard deviations (SDs) and percentages. The statistical significance among mean values in different groups and subgroups was determined by one and two way analysis of variance(ANOVA) followed by *post hoc* tests (Tukey's test). Between-group differences were compared using t-tests and χ^2 -tests as appropriate. Statistical threshold of $*p < 0.05$, $**p < 0.01$ and $***p < 0.001$ were considered statistically significant.

3. RESULT

Finally 208 PD cases (105 men (50,4%); mean age 65±8,51 years) were included in the analysis. According to the symptom at onset of the 208 patients 105 (50,4%) were classified as TD, 87 (41,9%) as AR and 16 (7,7%) as MT. Concerning the age at onset, out of the 208 PD patients 103 (49,5%) had the onset of disease before the age 50 years. PD occurred before the age of 40 in 20% patients predominantly in male that have used the term "young onset". Patients in the tremor-dominant subtype were somewhat older (p=0.027). TD phenotype was significantly more common among the late onset, while AR was more frequent among the early onset (p<0,0001). There were no statistically significant differences in baseline HY stage, UPDRS, LEDD, disease duration in the comparison of PD subtypes. Baseline characteristics according to the clinical phenotype are shown in Table 1.

Regarding disease duration and developing of wearing off, there was significant difference according to clinical phenotype. AR and mix subtype of PD develop wearing off earlier within 3 years compare to TD (p<0,05). 72,4% TD type develop wearing off after 6 years and further while AR and Mix type develop earlier. (OR was 0.43; 95% CI 0.24–0.89, RR was 0,69). It should be also noted that when gender was included in the analysis we didn't found a positive association with wearing off as well as LID (wearing off= OR was 0,78; 95% CI 0,43-1.41; p value 0,45; LID= OR was 0.73; 95% CI 0.42–1.26; RR=0,85, p value 0.27). Dyskinesias were predominantly peak dose in 64%. The same no association with average LED with LID (p=0,26). (Table 2). 75% patients, dyskinesias started on the side of the most affected one of the onset of disease. Chorea was more severe in the legs than in the arms, characterised by chaotic alternating flexion and extensions of the limbs, with adduction and abduction of the shoulder and hip and circling and twisting movements of the hands and feet. The time of

Table 1. Baseline characteristics of PD patients according to the clinical phenotype

	AR	TD	MT	p value
	N %	N %	N %	
Gender				
Men	57 (27,4%)	40 (19,2%)	8 (3,8%)	
Women	48 (23,1%)	47 (22,6%)	8 (3,8%)	NS
Age	63,6±9,59	67,2±8,91	65,3±7,03	<0,027
Duration	15,9±5,22	17,6±6,22	15,3±5,30	NS
Age at onset	47,6±8,64	49,5±9,36	50,1±7,22	NS
Hoehn and Yahr stage	2,6±063	2,7±0,52	2,4±0,68	NS
UPDRS III	20.9±8,08	21,9±8,43	20,6±7,19	NS
Average LED	1065,9±371,82	1007,6±304,67	986,4±355,76	NS
TR duration	13,9±5,29	15,3±6,63	13,7±6,07	NS

Quantitative variable are expressed as mean ±SD.AR= akinetic-rigid PD, TD= tremor dominant PD, MT= mix type PD, UPDRS = Unified Parkinson's Disease Rating Scale; MMSE = Mini-Mental State Examination; LED= Levodopa equivalent dose. NS=not significant p>0.05

Table 2. LID and wearing-off prevalence according to PD subtypes and duration

	After 0-3 years		After 3-6 years		After 6 years	
	WO	LID	WO	LID	WO	LID
TD (n=87)	4 (4,6%)	3 (3,4%)	27 (31,4%)	20 (23,2%)	55 (63,2%)	63 (72,4%)
AR (n=105)	15 (14,4%)	7 (6,7%)	44 (42,3%)	31 (29,8%)	45 (43,2%)	66 (63,4%)
Mix (n-16)	4 (26,6%)	4 (26,6%)	6 (37,5)	2 (12,5%)	6 (40%)	10 (66,6%)

WO=wearing off, LID= levodopa induced dyskinesia

peak effect was between 60 and 140 min after treatment, coinciding with the time of peak locomotor activity. There is a developmental sequence of dyskinesia that usually began in the lower limbs and later involved the upper limbs and orofacial musculature.

Unlike chorea, dystonias were observed at the time of peak-dose dystonia and as drug-effects were diminishing end-of-dystonia. Young-onset parkinsonian patients also develop dyskinesias restricted to the extremities, unlike older patients whose dyskinesias are more widespread, including the head and oral parts.

4. DISCUSSION

With continued levodopa therapy readily dyskinesia develops and it became more severe, more continues, and of longer duration. In patients with idiopathic Parkinson's disease of young onset, complications of therapy as a dyskinesia have been registered to emerge at an early stage in treatment. In three fourth patients, dyskinesias particularly affected those limbs which had initial parkinsonian symptoms, suggesting that the severity and location of the lesion are predisposing factors for dyskinesia. Peak-dose dyskinesia most commonly affect the upper part of the body, especially the face, the neck and the trunk, but they tend to be generalised, the upper limbs being more severely involved than the lower limbs. They are predominantly choreic in nature but may also show dystonic features. Several studies have confirmed that patients with tremor at onset have a slower progression of disease than those with a AR subtype[10-12]. Even if different risk factors have been suggested to be associated with the occurrence of dyskinesia in PD patients [13,14], it is unclear whether patients with different clinical subtypes of PD differ in their risk of developing LID.

We evaluated the risk of od dyskinesia among TD and AR phenotypes and we have also found a decreased risk of developing dyskinesia among the TD subtype respect to the AR one, supporting the observation of a more benign course of PD in TD forms. In agreement with literature data and also in our sample, presence of LID was related to other well-recognized risk factors such as disease duration, duration of dopaminergic drugs intake and average LED [15,16].

Tremor-dominant patients show different morphologic lesion patterns compared to bradykinesia and rigidity dominant patients. The tremor-dominant type shows more severe cell loss in the medial substantia nigra (SN), which projects to the dorsolateral striatum and ventromedial thalamus, causing hyperactivity of thalamo motor and cerebellar projection. For the akinetic-rigid type, a more severe cell loss occurs in the ventro lateral part of SN and posterior putament, which causes inhibition of the glutamatergic thalamo-cortical pathway and reduced cortical activation. Different patterns of dopamine loss may reflect a variety of neuropathological features [17]. Tremor-dominant patients compared to akinetic-rigid patients showed a higher iodine-123 fluoropropyl-carbomethoxy (FP-CIT) uptake, which meant increased dopamine transportor (DAT) [18]. These data were confirmed by Eggers and colleagues during the clinical course and quantitative analyses of iodine-123 FP-CIT SPECT [19]. More recently, research on cerebrospinal fluid (CSF) revealed that PD patients who have postural instability and gait difficulties phenotype have reduced alfa-synucleinopathy amyloid-B markers levels compared to tremor-dominant patients [20]. Also, evidence suggested that low CSF amyloid-B might contribute to motor and cognitive decline in PD [21]. In this respect, tremor-dominant symptoms are related to a slower progress of PD.

The mechanism underlying the different types of dyskinesias remain largely unknown. Striatal cholinergic hyperfunction and a functional dopaminergic deficit, possibly involving only one subclass of dopamine receptors, have been proposed as the underlying mechanisms of foot dystonia in parkinsonism [22].

We noted that the age at the onset of PD was a strong determinant of LID: the occurrence of dyskinesia decreased with increased age of onset. One explanation is that younger PD patients have strong plasticity mechanisms, which leaves them at an extremely high risk of developing LID even with low doses of levodopa and mild dopamine depletion [23]. As a previous study [24] suggested, chronic drug treatment and the severity of dopamine depletion associated with a long history of PD were major factors for LID. Our study demonstrated that the daily dose of levodopa, duration of disease and levodopa treatment^ Hoehn-Yahr stage and UPDRS III score were related to the occurrence of LID. Our results support these findings. Overall, the significant risk factors for LID in multivariate logistic regression analysis were younger age at the onset of PD and the longer duration of levodopa therapy.

Dyskinesias usually appear first on the most affected side in asymmetrical parkinsonism, indicating that they are related to the severity of dopaminergic denervation. Dyskinesias are more frequent in patients with severe central dopaminergic depletion and with a good levodopa response [25-27].

5. CONCLUSION

Our findings support the hypothesis that aside from the known clinical predictors of LID, occurrence of resting tremor as an initial manifestation of PD may predict not only slower progression of the disease, but also lower probability of developing LID and onset of developing site of LID. In – depth knowledge about these subtypes may lead to further insights into mechanism of disease and pathogenesis-targeted and symptomatic treatments. The clinical information provided by the present study might help to improve strategic planning of future studies.

CONSENT

As per international standard or university standard written patient consent has been collected and preserved by the author.

ETHICAL APPROVAL

As per international standard or university standard written ethical permission has been collected and preserved by the author.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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