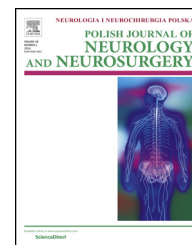


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Original research article

Comparison of dystonia between Parkinson's disease and atypical parkinsonism: The clinical usefulness of dystonia distribution and characteristics in the differential diagnosis of parkinsonism



Won Tae Yoon*

Department of Neurology, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Republic of Korea

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ABSTRACT

Objective: Dystonia is occasionally found in patients with Parkinson's disease (PD) and atypical parkinsonisms. However, systematic comparative analysis of the association between dystonia and parkinsonism have seldom been reported. The goals of this study are to compare the clinical characteristics and distributions of dystonia between PD, multiple system atrophy (MSA), progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD).

Methods: We prospectively enrolled 176 patients who presented with dystonia and parkinsonism out of 1278 patients with parkinsonism. We analyzed the clinical features of dystonia and parkinsonism.

Results: The frequencies of dystonia were 11.0% in PD, 20.9% in MSA, 40.7% in PSP and 66.7% in CBD. Dystonia symptoms were most frequent in CBD and relatively more frequent in PSP and MSA ($p < 0.001$). Moreover, multiple types of dystonia occurred most frequently in MSA ($p = 0.034$). According to the distribution of dystonia, cranio-facial dystonia (CFD) and cervical dystonia (CD) were more frequently observed in atypical parkinsonism ($p = 0.001$). In contrast, limb dystonia (LD) was more frequently observed in both PD and CBD, and truncal dystonia (TD) was more frequently detected in PD ($p < 0.001$). Levodopa medication related dystonia was markedly more frequent in PD than in atypical parkinsonism ($p = 0.030$).

Conclusions: In this long-term, observational, prospective study, we concluded that levodopa medication related LD and TD were more frequently observed in PD than in atypical parkinsonism. Conversely, levodopa medication non-related CFD and CD were more frequently observed in atypical parkinsonism, and coexisting of some types of multiple dystonia may be unique features of atypical parkinsonism. TD or multiple types of LD, might be representative of PD rather than atypical parkinsonism.

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* Correspondence to: Department of Neurology, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, #29 Saemunan-ro, Jongno-gu, Seoul 03181, Republic of Korea.

E-mail addresses: wtyoon@skku.edu, wtyoon@gmail.com<https://doi.org/10.1016/j.pjnns.2017.11.004>

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1. Introduction

Dystonia is a syndrome that is characterized by sustained muscle contraction associated with twisting, repetitive, and patterned movements, abnormal posture, or both [1]. Dystonia may coexist with parkinsonism in a number of neurodegenerative, genetic, toxic, and metabolic disorders of which Parkinson's disease (PD) and atypical parkinsonisms are the most common [2,3]. Clinical associations between dystonia and various parkinsonisms have been reported in some studies [4–7]. Although rare, one such study also reported the overall frequency and clinical features of dystonia in atypical parkinsonism [8].

However, the clinical relationships remain unclear; for example, one study commented that the true frequency and range of dystonia manifestations remain unknown in autopsy-proven cases of parkinsonism, including multiple system atrophy (MSA), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD) and PD [9], and systematic prospective, comparative analysis of the clinical features of dystonia associated with parkinsonism have seldom been reported.

The aims of the present study were to investigate the clinical characteristics of dystonia associated with parkinsonism in a larger patient sample than that in previous reports and compare these characteristics among the various types of parkinsonism to identify the clinical usefulness of the distributive pattern of dystonia in the differential diagnosis of parkinsonism.

2. Materials and methods

Between January 2002 to December 2004, we investigated 185 consecutive patients who presented with dystonia combined with parkinsonism. Among these patients, we prospectively enrolled 176 patients who presented with dystonia combined with parkinsonism out of 1278 patients with parkinsonism registered at the Movement Disorder Clinic of the Samsung Medical Center during the same period, from January 2002 to December 2004. We included patients with long-term follow-up data over five years (to December 2009), full evaluations for parkinsonism and clinical diagnoses confirmed by at least two specialist neurologists from movement disorder clinics. Under the established diagnostic criteria [10–15], 1278 patients with parkinsonism were divided into 1045 patients with PD, 191 patients with MSA, 27 patients with PSP and 15 patients with CBD. Moreover, we excluded 9 patients with uncertain diagnosis of parkinsonism ($n = 2$), those lost to follow-up ($n = 2$) and those with combined dystonia due to medical or neurological reasons other than parkinsonism with the following other diagnosis: dementia with Lewy bodies (DLB) ($n = 2$), normal pressure hydrocephalus (NPH) ($n = 1$), metabolic encephalopathy ($n = 1$), and post-stroke parkinsonism with dystonia ($n = 1$).

We clinically diagnosed dystonia using the established definition [2,16] and analyzed the clinical features of dystonia and parkinsonism, including demographics, the temporal profiles of the symptoms, the distribution and characteristics

of dystonia, the clinical diagnosis of parkinsonism and the relationship with levodopa treatment. Dystonia was subclassified as cranio-facial dystonia (CFD), cervical dystonia (CD), truncal dystonia (TD) and limb dystonia (LD) according to the distribution of dystonia among the enrolled parkinsonism patients, and we also clinically examined cases of unusual dystonia phenotypes, such as dystonia preceding parkinsonism (Pre-Dystonia) and clinically dominant dystonia if there were multiple coincidentally emerging variant types of dystonia (Multi-Dystonia), as occurred in one parkinsonism patient.

All data are presented as the mean \pm standard error of the mean (SEM). The PASW (Version 22.0; IBM SPSS Inc., Chicago, IL) program for Windows was used for statistical analysis. The baseline demographic and clinical data were analyzed by Student's t-test, and data regarding sex differences and the number of subjects with the presence of dystonia between each group were analyzed using the chi-square test. Data related to age of onset, the interval from onset to parkinsonism, and the number of characteristics regarding dystonic symptoms were analyzed using one-way analysis of variance (one-way ANOVA). Fisher's exact test was used to evaluate the difference in the number of dystonias between each group, and the statistical significance level was set at $p < 0.05$.

3. Results

Among 176 dystonic patients with parkinsonism, 115 patients were clinically diagnosed with PD, 40 were probable MSA, 11 were probable PSP, and 10 were probable CBD. Fig. 1 shows the patient flow, including information about 9 excluded patients. Demographic and clinical profiles of the dystonic patients in each parkinsonism group are presented in Table 1. Among the total 1278 parkinsonism patients (1045 PD, 191 MSA, 27 PSP and 15 CBD), the frequencies of dystonia among each parkinsonism type were 11.0% (115/1045) in PD, 20.9% (40/191) in MSA, 40.7% (11/27) in PSP and 66.7% (10/15) in CBD. Overall, dystonia symptoms were more frequent in CBD and PSP than in PD ($p < 0.001$), and in terms of sex differences, dystonia was more frequent in men than in women among PSP patients ($p = 0.019$). The onset age of initial dystonic symptoms was older in CBD and younger in PD ($p < 0.001$).

In CBD patients, only limb dystonic symptoms without other types of dystonia were observed, with no unusual Pre-Dystonia phenotypes. Despite the small number of patients, Multi-Dystonia was relatively more frequent in MSA than in PD or PSP ($p = 0.034$). Aside from these findings, no other significant clinical demographic differences were observed among the various types of parkinsonism (Table 1).

According to the distribution of dystonia, CFD and CD were more frequently observed in atypical parkinsonism (39/61, 63.9% and 7/61, 11.5%, respectively) than in PD (16/115, 13.9% and 1/115, 0.9%, respectively) ($p < 0.001$). In contrast, TD and LD were more frequently observed in PD (32/115, 27.8% and 66/115, 57.4%, respectively) than in atypical parkinsonism (2/61, 3.3% and 13/61, 21.3%, respectively) ($p = 0.001$). TD, including camptocormia, was detected only in PD and levodopa medication non-related MSA ($p < 0.001$). In terms of the relationship with levodopa treatment, levodopa medication related dystonia was markedly more frequent in PD than in

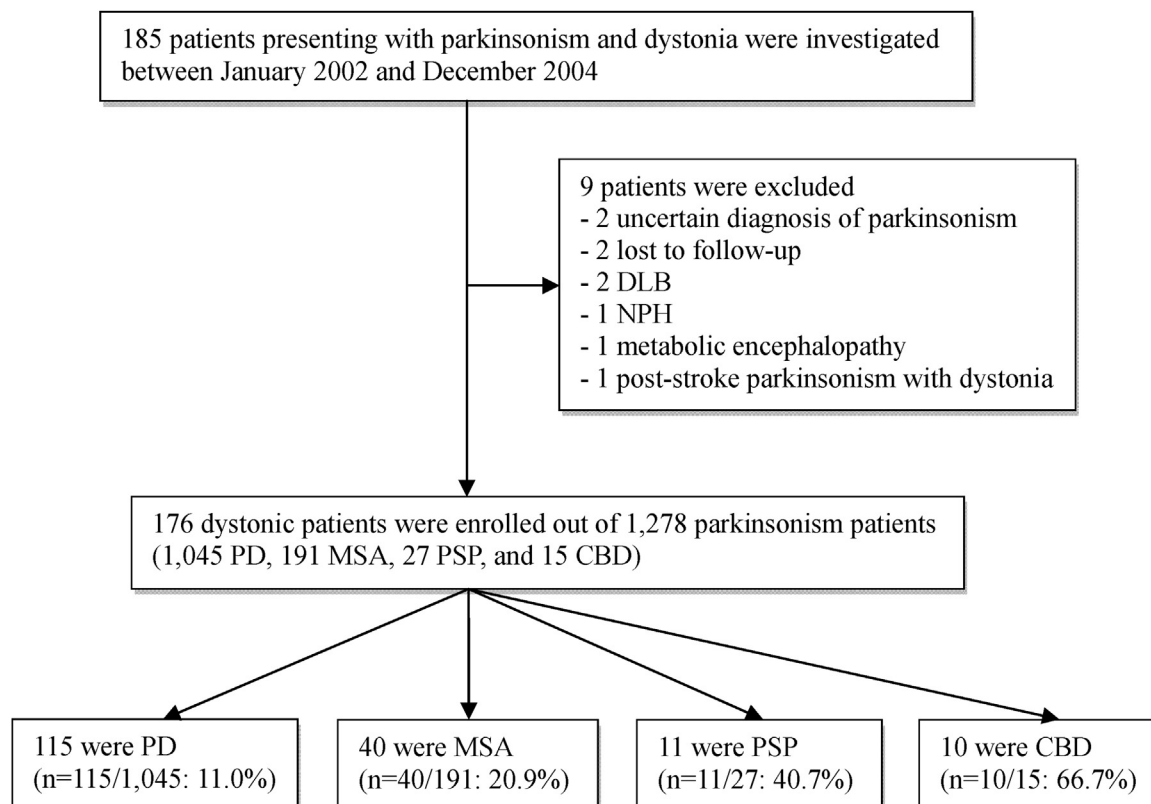


Fig. 1 – Patient flow. DLB, dementia with Lewy bodies; NPH, normal pressure hydrocephalus; PD, Parkinson's disease; MSA, multiple system atrophy; PSP, progressive supranuclear palsy; CBD, corticobasal degeneration.

Table 1 – Demographic and clinical profiles of dystonic patients in each type of parkinsonism.

Patients	PD ^a	MSA ^b	PSP ^c	CBD ^d	p Value
Dystonia/total patients (N)	115/1045	40/191	11/27	10/15	<0.001
(Prevalence of dystonia, %)	(11.0%)	(20.9%)	(40.7%)	(66.7%)	
Sex (M/F)	41/74	19/21	9/2	5/5	0.019
Onset age (y): initial symptom	54.6 ± 10.8	60.8 ± 9.0	59.8 ± 4.1	67.1 ± 7.7	<0.001
Onset interval (m): to dystonia	54.9 ± 45.6	41.9 ± 35.6	47.5 ± 43.5	69.0 ± 28.7	0.217
Multiple types of dystonia (N)	12	18	5	0	0.034
Preceding dystonia to parkinsonism (N)	8	5	2	0	NA ^e

^a Parkinson's disease (PD).

^b Multiple system atrophy (MSA).

^c Progressive supranuclear palsy (PSP).

^d Corticobasal degeneration (CBD).

^e Not available (NA).

atypical parkinsonism ($p = 0.034$). Although TD was more frequent in PD regardless of the relationship with levodopa medication, CFD and CD were more frequent in levodopa medication non-related atypical parkinsonism ($p < 0.001$), and LD was more frequent in levodopa medication related PD, as shown in Table 2 ($p = 0.030$).

Among the 35 patients with multiple types of dystonia, twenty-three were diagnosed with atypical parkinsonism, and twelve were diagnosed with PD. According to the subclasses of the combinations of multiple types of dystonia, combination

groups with two-variable CFD or CFD with CD were observed only in atypical parkinsonism, and other combination groups of CD with LD, TD with LD and two-variable LD were observed only in PD (Table 3). Excluding some small groups of patients, the two major multiple-type dystonias were two-variable CFD (19/35, 54.3%) and two-variable LD (7/35, 20%), with all patients in the former group being diagnosed as atypical parkinsonism (15 MSA and 4 PSP) and all patients in the latter group being diagnosed as PD with significant clinical and demographic differences ($p < 0.001$).

Table 2 – Distribution of dominant dystonia in each parkinsonism patient according to the relationship with levodopa medication.

Parkinsonism	PD ^a	Atypical parkinsonism (AP)	MSA ^b	PSP ^c	CBD ^d	p-Value
						PD vs. AP/All groups
Total number of dystonic patients (N)	115	61	40	11	10	<0.001/0.001
CFD ^e (N)	16	39	31	8	0	
CD ^f (N)	1	7	5	2	0	
TD ^g (N)	32	2	2	0	0	
LD ^h (N)	66	13	2	1	10	
Levodopa medication non-related	58	55	35	11	9	<0.001/<0.001
CFD ^e (N)	6	36	28	8	0	
CD ^f (N)	0	6	4	2	0	
TD ^g (N)	24	2	2	0	0	
LD ^h (N)	28	11	1	1	9	
Levodopa medication related	57	6	5	0	1	0.034/0.030
CFD ^e (N)	10	3	3	0	0	
CD ^f (N)f	1	1	1	0	0	
TD ^g (N)	8	0	0	0	0	
LD ^h (N)	38	2	1	0	1	

^a Parkinson's disease (PD).
^b Multiple system atrophy (MSA).
^c Progressive supranuclear palsy (PSP).
^d Corticobasal degeneration (CBD).
^e Cranio-facial dystonia (CFD).
^f Cervical dystonia (CD).
^g Truncal dystonia (TD).
^h Limb dystonia (CBD).

Table 3 – Distribution of multiple types of dystonia in each type of parkinsonism.

Parkinsonism	PD ^a	Atypical parkinsonism (AP)	MSA ^b	PSP ^c	CBD ^d	p-Value
						PD vs. AP/All groups
Total number of patients with multiple dystonias (N)	12	23	18	5	0	<0.001/<0.001
Multiple types of dystonia						
CFD ^e + CFD ^e (N)	0	19	15	4	0	
CFD ^e + CD ^f (N)	0	2	1	1	0	
CFD ^e + TD ^g (N)	1	1	1	0	0	
CFD ^e + LD ^h (N)	1	1	1	0	0	
CD ^f + TD ^g (N)	0	0	0	0	0	
CD ^f + LD ^h (N)	1	0	0	0	0	
TD ^g + LD ^h (N)	2	0	0	0	0	
LD ^h + LD ^h (N)	7	0	0	0	0	

^a Parkinson's disease (PD).
^b Multiple system atrophy (MSA).
^c Progressive supranuclear palsy (PSP).
^d Corticobasal degeneration (CBD).
^e Cranio-facial dystonia (CFD).
^f Cervical dystonia (CD).
^g Truncal dystonia (TD).
^h Limb dystonia (CBD).

4. Discussions

In this long-term, observational study, we prospectively surveyed dystonia in patients with parkinsonism. In cases with coexisting dystonia and parkinsonism, we retrospectively analyzed the distribution and characteristics of dystonia

and prospectively investigated the clinical pattern of dystonia, the relationship between dystonia and levodopa treatment, and the long-term prognosis to confirm the clinical diagnosis.

Parkinsonism and dystonia may coexist not only in neurodegenerative disorders such as PD, MSA, PSP and CBD but also in a number of genetic, toxic and metabolic disorders and as a result of structural lesions in the basal ganglia [2]. Some reports have described the characteristics of the

dystonias of each single disease entity, groups of atypical parkinsonism or PD [4,6-8,17,18]. In most of these previous studies, the overall frequency of dystonia was found to be relatively high in atypical parkinsonism. However, few studies have compared PD and each atypical parkinsonism. Furthermore, no descriptions regarding the presence of multiple other types of dystonia and preceding dystonia parkinsonism are available, except in some cases reports [19,20].

In terms of the symptoms of each dystonic, previous clinical studies have reported the clinical subtypes of dystonia in parkinsonism. For example, blepharospasm, a type of CFD, is common and more prevalent in atypical parkinsonism than in PD [21,22]. Although these studies are rare, one recent study reported the clinical subtypes of anterocollis in parkinsonian syndromes, finding no other significant clinical differences between the clinical subtypes of anterocollis or primary diagnosis, with the exception that patients with atypical parkinsonian syndromes had more advanced motor symptoms [23]. Another study reported on reversible Pisa syndrome in PD patients on dopaminergic therapy. Similar to the results of our study, a clinically important association between Pisa syndrome as a TD in patients with PD and dopaminergic therapy was found [24].

In general, PD is associated with the loss of midbrain dopamine neurons [25], and parkinsonism and dystonia have been reported to occur subsequent to strokes in various sites in the basal ganglia, including the striatum and globus pallidus [26-29]. However, some other studies have revealed that dystonia and parkinsonism might be associated with other focal brain lesions or brainstem lesions [30,31]. For these reasons, the co-existence of dystonia and parkinsonism usually results from multiple lesions or the involvement of more than one pathway [2], and one recent animal study reported that parkinsonism and dystonia are differentially induced by the modulation of different territories of the basal ganglia [32]. The pathophysiology and mechanism underlying the co-existence of parkinsonism and dystonia remain unknown, but clinical presentations of dystonia in PD and atypical parkinsonism are relatively common, and dystonia among the clinical set of symptoms and signs associated with parkinsonism may have diagnostic value in the differential diagnosis of parkinsonism [2,22].

In terms of the relationship between dystonia and levodopa treatment, we also found that dystonia may have occurred as an 'off' symptom or as a 'peak-dose' effect of levodopa treatment. Dystonia that is improved by levodopa treatment is more strongly related to PD, while some dystonic symptoms that are aggravated by levodopa treatment are more strongly related to atypical parkinsonism. Moreover, in terms of the relationship between dystonia preceding and following parkinsonism, we also found that some preceding dystonia may occur as a prodromal symptom of parkinsonism, and preceding dystonia is more strongly related to atypical parkinsonism. However, these two suggestions were not statistically confirmed because the number of patients was small. Additionally, we could not assess the history of other medications, mainly including dopamine agonists and anticholinergics, which would have potential effects on dystonia in parkinsonism patients. This point is more likely to be encountered in the clinic, and this issue will be a good subject for clinical studies of

differential diagnoses in parkinsonism if prospective observations are performed in the future.

According to our experience during the progression of this study, most cases of CFD and CD were treated with botulinum toxin injection, and most cases of TD and LD were treated with symptomatic medications, including muscle relaxants or anticholinergics and changes in levodopa medication dose. Even though these treatment results regarding dystonic symptoms in all groups were not statistically evaluated because of too many variable factors, many CFD patients treated with botulinum toxin injection might have a good prognosis. Additionally, compared with CD and TD patients, many LD patients treated with medications might have a relatively good prognosis regardless of the methods of treatment.

This study had several limitations. First, even though patient enrollment was conducted in a prospective study design, after enrollment, the clinical data of some patients regarding dystonia and parkinsonism were retrospectively corrected using the patients' direct explanations and subjective history taking. However, the clinical features of the presence of a single type or multiple types of dystonia and the comparative prevalence of dystonia among all study subjects were systemically evaluated. Second, we conducted this study based on only clinical diagnosis of parkinsonism. Clinico-pathologic evaluations of the correlation between dystonia and parkinsonism and confirmation of neuropathological diagnosis would be needed to disclose the relationship between dystonic manifestations and pathological substrates of each type of parkinsonism. Third, the pattern and distribution of dystonia and dystonia's co-existence with parkinsonism were assessed for this study. The severity and frequency of dystonia measured by a clinical scale regarding dystonia and the frequency and average of levodopa medication dose were not assessed in detail, which should be considered in future comprehensive studies. Fourth, in addition to levodopa medications, other medications, including dopamine agonists, antipsychotic medications, antidepressants, and symptomatic medications for the treatment of dystonia, were not assessed in detail. However, in this study, relationships between levodopa medication and dystonia were critically observed in all study subjects during the long-term follow-up period regardless of other medications. Fifth, we could not evaluate the previous history of other neurological disorders and medical problems, which could possibly affect the dystonic symptoms or could be hidden causative factors. Future studies with well-designed, detailed evaluations of all factors and long-term comparison between dystonia and parkinsonism are needed to solve these fundamental issues.

5. Conclusions

In summary, this study demonstrated that the symptoms of dystonia were most frequent in CBD and more frequent in atypical parkinsonism (e.g., CBD, PSP and MSA, in descending order of frequency) than in PD. Moreover, levodopa medication non-related CFD including blepharospasm or CD, were more frequently observed in atypical parkinsonism (MSA and PSP),

and some types of multiple combined dystonias (multiple types of CFD or CFD with CD) may be a unique feature of atypical parkinsonism. Conversely, all TD and LD groups were more frequently observed in PD than in atypical parkinsonism, regardless of levodopa medication. TD, including camptocormia or multiple types of LD, might therefore be representative of PD rather than atypical parkinsonism. Moreover, levodopa medication related LD and TD presenting as 'off' symptoms, 'peak-dose' effects or levodopa responsiveness might be representative of PD and not atypical parkinsonism.

Conflict of interest

The authors have no financial or personal relations that could pose a conflict of interest.

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This manuscript is dedicated to the loving memory of Won Yong Lee (1961–2011), who designed and conducted this study.

Ethics

The work described in this article was performed in accordance with the Code of Ethics of the World Medical Association (the Declaration of Helsinki) for experiments involving humans and the Uniform Requirements for Manuscripts Submitted to Biomedical journals.

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