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Cervical dystonia in Parkinson's disease: Retrospective study of later-stage clinical features

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Abstract

Objective: Cervical dystonia (CD) is a clinically under-recognized symptom occurring at the later- to end-stages of Parkinson's disease (PD). The frequency of CD and its influence on prognosis have not been well studied. Here, we conducted an in-depth examination of CD incidence and impact on disease progression in later-stage PD. *Methods:* We retrospectively reviewed the clinical features of 22 deceased patients with sporadic PD treated at a hospital in Japan from 1983 to 2008. *Results:* The most common cause of death in PD was pneumonia. CD, in particular retrocollis, was frequent in the later stages of the disease in elderly patients (9/22, 40.9%). Pneumonia incidence increased sharply in the later period with CD. There was a positive trend between CD duration and duration of pergolide use. *Conclusion:* Analysis revealed that CD increases markedly in late- to end-stage PD, which may be associated with aspiration pneumonia due to dysphagia. Pathological mechanisms underlying CD might be influenced by treatments including dopamine agonists. Prevention of CD may increase quality of life and prolong survival of PD patients.

Keywords: Parkinson's disease, cervical dystonia, retrocollis, dopamine agonist, pneumonia

INTRODUCTION

Cervical dystonia (CD) is occasionally observed in Parkinson's disease (PD) and, at its later stages, is associated with reduced quality of life and poor prognosis due to dysphagia. However, there has been little research on the frequency and form of CD in PD patients[1–3], nor have there been any reports on the influence of CD on disease prognosis or cause of death in patients with PD. To address this research gap, we evaluated the clinical features of later-stage PD to clarify CD incidence, risk factors, and role in PD progression.

METHODS

Consecutively deceased PD patients hospitalized at the Kida Hospital, a private neurological institution in Japan, from January 1983 to December 2008 were enrolled retrospectively. All patients who fulfilled the UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria[4] received a neurological examination by one of the authors. Patients with PD who died at home or were transferred to a different hospital were excluded. Twenty-two PD cases were recruited. Clinical records were reviewed for patient background (sex, age at onset, disease duration, age at death, cause of death, and Hoehn and Yahr [H&Y] Staging just before death) and treatment (maximum dose of levodopa, maximum dose of levodopa equivalent dose [LED][5], dopamine agonist type, duration of administration of dopamine agonist, and stereoencephalotomy [functional neurosurgical procedure]). We divided patients into two groups based on presence/absence of CD (termed CD(+) and CD(–) groups). CD was defined as neck extension/flexion accompanied by enhanced muscle tone or spasm. There were

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nine and 13 cases of presence and absence of CD, respectively. Both groups were compared for background and surgical treatment variables. Furthermore, the frequency of pneumonia was compared between the period with CD of nine cases and the period without CD of all 22 cases.

To evaluate groups' differences, Fisher's exact test was used for sex ratio and proportion of patients receiving stereoencephalotomy; Welch's two-sample *t*-test for age at onset, age at death, disease duration, maximum dose of levodopa, maximum dose of LED, cause of death, and difference in frequency of pneumonia episode; and Wilcoxon rank-sum test (Mann–Whitney *U* test) for H&Y Staging at death. The correlation between duration of drug exposure of each dopamine agonist and CD duration of all 22 cases was examined by Spearman's rank correlation test.

We represented each patient by a multivariate profile (a high-dimensional feature vector), in which each element corresponds to a feature of the patient, and constructed a multivariate dataset. The profiles are based on 11 features: disease duration, CD(+) duration, death by pneumonia, maximum dose of levodopa, maximum dose of LED, bromocriptine, pergolide, cabergoline, pramipexole, stereoencephalotomy, and H&Y Staging at death. Each feature was normalized scaled such that the average is zero and the standard deviation is one. To analyze the relationships among these features, we performed principal component analysis (PCA). The goal of PCA is to reduce the dimensionality of multivariate data for easier interpretation by identifying a few meaningful latent components. All statistical analyses in this study were conducted using the free R statistical software package (http://www.r-project.org).

RESULTS

We recruited 22 PD cases (Table 1) and summarized their background and treatment information (Table 2). There were no differences in sex ratio, age at onset, age at death, or H&Y stage at death between the CD(+) and CD(–) groups. Of the nine cases with CD (40.9%), eight showed retrocollis (RC), one showed antecollis, and no cases showed laterocollis. Age at onset was younger in CD(+) patients, although the difference did not reach statistical significance. PD duration was significantly longer for CD(+) patients (15.0 ± 2.2 years vs. 9.4 ± 1.1 years, p = 0.039). Regarding treatment, maximum dose of levodopa was significantly higher for CD(+) patients (433 ± 163 mg/day vs. 236 ± 126 mg/day, p = 0.009), and the maximum dose of LED tended to be higher for CD(+) patients. There was a correlation between CD duration and duration of exposure to dopamine agonists (p = 0.001, r = 0.628), especially pergolide (p = 0.009, r = 0.539). The average CD duration of all 22 cases was 1.2 ± 0.4 years. The cases that underwent longer treatment by dopamine agonists had a longer CD duration. Four cases received stereoencephalotomy, including one CD(–) case. One case (Case No. 18) that received deep brain stimulation in the bilateral globus pallidus internus showed increased cervical rigidity within one month and RC by the third postoperative month.

Pneumonia was the most common cause of death (13 cases, 59%) (Figure 1A). Other causes of death were malignant tumor (four cases), acute heart failure (two cases), malignant syndrome (two cases), and asphyxiation (one case). The cause of death differed between groups, with a higher proportion of CD(+) patients succumbing to pneumonia (77.8% vs. 46.2%, p = 0.069), although the difference did not reach statistical significance. In nine cases, CD occurred at 13.0 ± 2.1 years from PD onset and remained at death (Figure 1B). The frequency of pneumonia episodes was significantly higher during the period with CD than the period without CD (0.314 ± 0.211 times/year vs. 0.070 ± 0.067 times/year, p = 0.004) (Figure 1C). The scatter-plot of scores for the first and second principal components representing the relations among the nine features of all 22 patients reveals possible positive relationships between CD duration and lengths of pergolide and cabergoline use (Figure 1D, E).

DISCUSSION

The average age at death in our study population was consistent with the average lifespan of the general Japanese population (Ministry of Health, Labour and Welfare, http://www.mhlw.go.jp /english/database/db-hss/shw-index.html). However, the causes of death were quite different, with pneumonia accounting for about 60% of PD deaths compared to just 9.40% for the general Japanese population (Ministry of Health, Labour and Welfare, http://www.mhlw.go.jp/english/database/db-hh/index.html). As many of the late-stage patients in this study were bedridden during hospitalization, we speculate that they were more susceptible to aspiration pneumonia[6], as reported by previous studies.[7]

Table 1: Summary of cases

Case No.	Sex	Onset age (y.o)	Death age (y.o)	Disease duration (y)	H&Y staging at death	Cause of death	Treatment					Feature of CD			Frequency of pneumonia	
							L-dopa/DCI (Max dose (mg) ; Age of use (y.o))	Dopamine agonist (Max dose (mg) ; Age of use (y.o))	Other Drugs (Max dose (mg) ; Age of use (y.o))	Maximum dose of LED (mg/day)	Stereoencephalotomy Age of operation (y.o)	CD	CD (−) duration (y)	CD (+) duration (y)	CD (−) period (times)	CD (+) period (times)
1	F	77	78	2	5	Malignant melanoma	L/C (200; 77–78)	-	Amantadine (150; 77)	350	-	-	2	0	1	-
2	F	71	74	4	3	Heart failure	L/C (200; 72–73)	Bromocriptine (7.5; 73)	Amantadine (300; 72–73)	575	-	-	4	0	1	-
3	F	76	81	6	5	Appendiceal cancer	-	-	-	-	-	-	6	0	0	-
4	M	73	79	7	5	Pneumonia	L/C (400; 73–79)	Bromocriptine (10; 74−78)	-	500	-	-	7	0	1	-
5	F	81	88	8	5	Heart failure	L/C (200; 80–89)	-	-	200	-	-	8	0	2	-
6	M	77	84	8	4	Pneumonia, DIC	L/C (300; 78–81, 82–84)	Bromocriptine (7.5; 81−82)	-	375	-	-	8	0	3	-
7	F	68	77	10	5	Pneumonia	L/C (250; 74–77)	-	-	250	-	-	10	0	2	-
8	F	84	93	10	5	Metastatic cancer	L/B (200; 89–93)	-	-	200	-	-	10	0	0	-
9	F	63	74	12	5	Pneumonia	L/C (300; 66–74) L/B (300; 73–74)	Bromocriptine (22.5; 70−74)	-	825	-	-	12	0	1	-
10	M	64	75	12	4	Lung cancer	L/B (300; 68–75)	Bromocriptine (5; 67−68, 69, 70−72) Cabergoline (2; 68−69) Pramipexole (1.25; 72−74)	Selegiline (2.5; 74)	458.3	-	-	12	0	0	-
11	F	60	73	14	5	Pneumonia	-	-	Amantadine (150; 60–73)	150	-	-	14	0	1	-
12	F	54	67	14	5	Pneumonia	L/C (300; 73–77)	-	Amantadine (150; 63–67)	450	Rt. stereoencephalotomy (54)	-	14	0	2	-
13	M	73	87	15	5	Malignant syndrome, DIC	L/C (300; 78–87)	Bromocriptine (7.5; 78−83) Pergolide (1; 83−85)	Amantadine (150; 79–82, 84–85)	550	-	-	15	0	0	-

Case No.	Sex	Onset age (y.o)	Death age (y.o)	Disease duration (y)	H&Y staging at death	Cause of death	Treatment					Feature of CD			Frequency of pneumonia	
							L-dopa/DCI (Max dose (mg) ; Age of use (y.o))	Dopamine agonist (Max dose (mg) ; Age of use (y.o))	Other Drugs (Max dose (mg) ; Age of use (y.o))	Maximum dose of LED (mg/day)	Stereoencephalotomy Age of operation (y.o)	CD	CD (−) duration (y)	CD (+) duration (y)	CD (−) period (times)	CD (+) period (times)
14	M	83	88	6	5	Pneumonia	L/C (200; 85–88)	Pergolide (0.75; 83–88)	-	275	-	RC	4	2	0	1
15	M	68	77	10	5	Pneumonia	L/C (400; 69–77)	Bromocriptine (7.5; 71–74) Pergolide (0.75; 74–77)	Amantadine (150; 77)	625	-	RC	8	2	2	3
16	F	74	83	10	5	Pneumonia	L/C (250; 79–83)	Bromocriptine (5; 77–79, 80–82)	Amantadine (100; 75–79)	450	-	RC	7	3	0	1
17	F	61	73	13	5	Pneumonia, DIC	L/B (450; 67–72) L/C (500; 72–73)	Bromocriptine (11.25; 67–72)	-	562.5	-	RC	11	2	1	2
18	F	64	77	14	5	Malignant syndrome, DIC	L/C (600; 64–70) L/B (300; 70–77)	Cabergoline (5; 70–75) Pergolide (1.5; 72–75)	Amantadine (150; 70, 72–75) Selegiline (5; 70, 72, 74–75)	1083.3	Bil. Gpi-DBS (75)	RC	11	3	1	2
19	M	66	81	16	5	Pneumonia	L/C (500; 66–79) L/B (400; 79–81)	Pergolide (0.75; 79–80)	Selegiline (5; 79–81)	625	-	RC	13	3	0	1
20	M	46	70	25	5	Pneumonia	L/C (600; 46–69)	Pergolide (0.25; 67) Bromocriptine (15; 67–69)	Amantadine (300; 46)	1050	Lt. stereoencephalotomy (46)	RC	23	2	1	1
21	M	50	74	25	5	Asphyxiation	L/B (600; 66–73)	Bromocriptine (5; 66–72) Pergolide (0.5; 72–74)	-	650	Lt. thalamotomy (52)	RC	21	4	3	7
22	M	80	95	16	5	Pneumonia	L/B (400; 85–95)	Cabergoline (5; 86–95)	Amantadine (100; 85–95)	833.3	-	AC	10	6	0	4

CD, Cervical Dystonia; DIC, disseminated intravascular coagulation; RC, Retrocollis; AC, Antecollis; DCI, dopa-decarboxylase inhibitor; L/B, Levodopa/Benserazide; L/C, Levodopa/Carbidopa; H&Y Staging on death; Hoehn & Yahr Staging just before clinical event of death; LED, levodopa equivalent dose

Table 2: Analysis of background and treatment based on presence of CD

Background				
	Total (n = 22)	CD (−) (n = 13)	CD (+) (n = 9) (RC: AC = 8:1)	P value CD (−) vs. CD (+)
Sex (M:F)	10:12	4:9	6:3	p = 1 (Fisher's exact test)
Age at onset (y.o)	68.2 ± 2.2	70.8 ± 2.4	65.8 ± 4.1	p = 0.309 (Welch's two-sample *t*-test)
Age at death (y.o)	79.5 ± 1.6	79.2 ± 2.0	79.8 ± 2.6	p = 0.870 (Welch's two-sample *t*-test)
Disease duration (y)	11.7 ± 1.2	9.4 ± 1.1	15.0 ± 2.2	p = 0.039 (Welch's two-sample *t*-test)
H & Y Staging on death	4.8 ± 0.1	4.7 ± 0.2	5.0 ± 0.0	p = 0.145 (Wilcoxon rank-sum test)
Internal treatment				
<L-Dopa/DCI>				
	Total (n = 22)	CD (−) (n = 13)	CD (+) (n = 9) (RC: AC = 8:1)	P value CD (−) vs. CD (+)
Maximum dose of levodopa (mg L-dopa/day)	318 ± 170	238 ± 126	433 ± 163	p = 0.009 (Welch's two-sample *t*-test)
Maximum dose of LED (mg/day)	501 ± 279	404 ± 224	641 ± 302	p = 0.064 (Welch's two-sample *t*-test)
<Dopamine agonist>				
	Duration of medication with dopamine agonists (n = 22)		CD duration (n = 22)	P value, correlation coefficient (Spearman's rank correlation test)
Total Dopamine agonist (y)	4.3 ± 0.9			p = 0.001, *r* = 0.628
Breakdown of dopamine agonists: Bromocriptine (y)	2.3 ± 0.6			p = 0.541, *r* = 0.137
Breakdown of dopamine agonists: Pergolide (y)	1.0 ± 0.4		1.2 ± 0.4	p = 0.009, *r* = 0.539
Breakdown of dopamine agonists: Cabergoline (y)	0.8 ± 0.5			p = 0.111, *r* = 0.348
Breakdown of dopamine agonists: Pramipexol (y)	0.1 ± 0.1			p = 0.437, *r* = −0.174
Surgical treatment				
	Total (n = 22)	CD (−) (n = 13)	CD (+) (n = 9) (RC: AC = 8:1)	P value CD (−) vs. CD (+)
Stereoencephalotomy (cases)	4	1	3 (3:0)	p = 0.2643 (Fisher's exact test for Count Data)

CD, cervical dystonia; RC, Retrocollis; AC, Antecollis; DCI, dopa-decarboxylase inhibitor; H&Y, Hoehn & Yahr; LED, levodopa equivalent dose

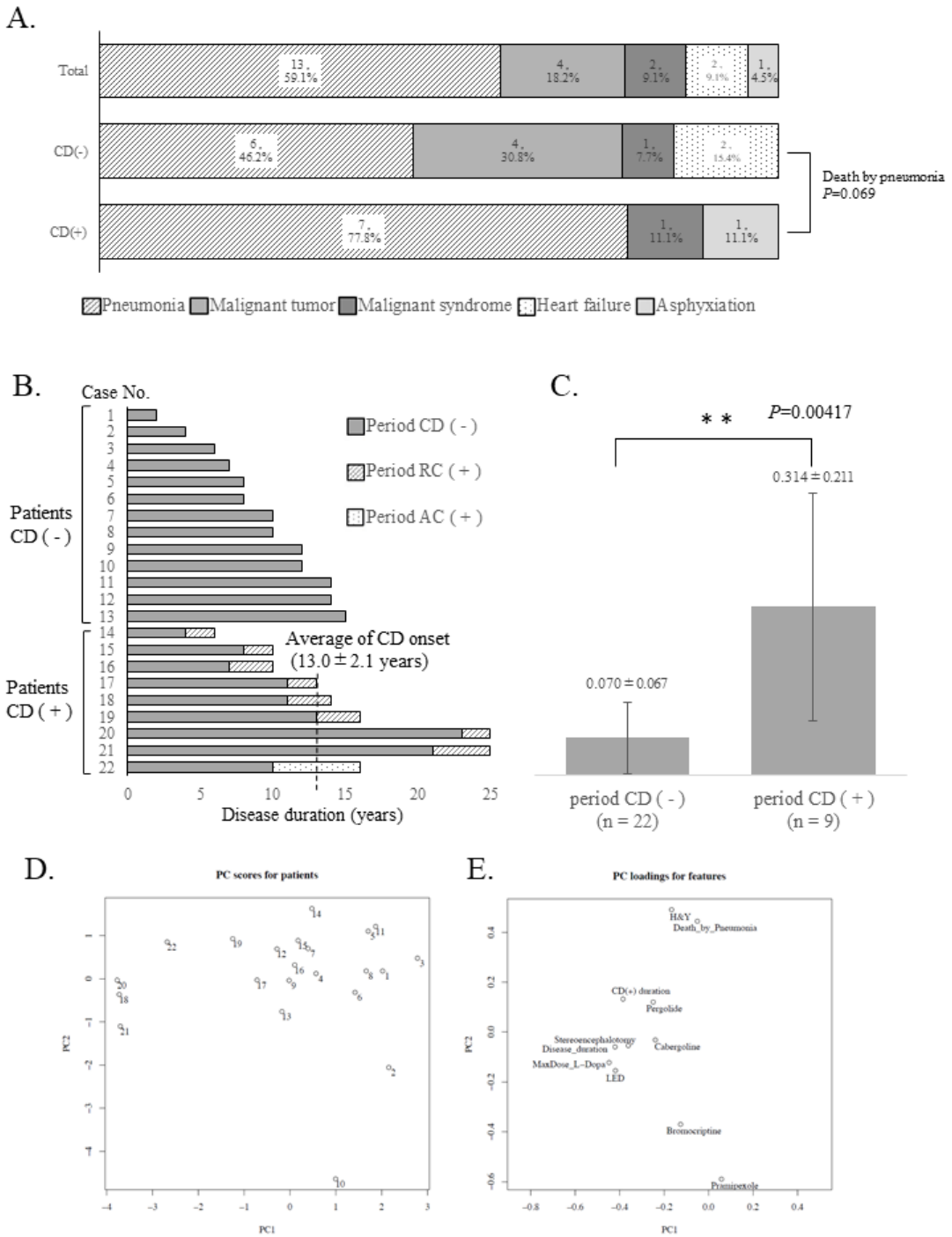

Figure 1. Clinical manifestation of PD. (A) Comparison of cause of death between patients with and without CD (cases, %). (B) Clinical course of all patients. (C) Frequency of pneumonia episodes in patients with CD (mean ± SD/years). (D) Scatter-plot of the first and second principal component scores derived from PCA for the multivariate data of 22 patients. Each number corresponds to the index number of one patient. (E) Scatter-plot of the first and second principal component weights derived from PCA for the multivariate data of 22 patients. Correlated features are located in proximity (CD(+) duration, duration of pergolide use, and duration of cabergoline use).
H&Y, Hoehn & Yahr; LED, levodopa equivalent dose

A contributory factor of death by pneumonia might be CD in later periods. A higher death rate due to pneumonia was observed in patients with CD despite no difference in age or PD severity at death between patients with and without CD. Indeed, frequency of non-lethal pneumonia episodes increased sharply in later-stage CD. Cervical hyperextension causes mechanical changes and affects aspiration even in healthy subjects.[8] Thus, these pneumonia cases may be due to swallowing difficulties secondary to abnormal cervical position, which can favor inhalation.

Of the few studies on CD in PD patients, most have reported incidence of antecollis.[1,2] Only one study found that advanced PD patients with long disease duration had more frequently RC[3], consistent with our results. In this study, the average disease duration was significantly longer and the age at onset tended to be younger in PD patients with CD. Whereas patients without CD died around 10 years after PD onset, CD generally developed after 10 years, suggesting that the risk of CD increases progressively with longer PD duration. Although the reason for the high incidence of CD is unknown, it is speculated that dystonia may arise from dysfunction of the striosomal pathway[9], i.e., the circuit between substantia nigra and striosomes in the striatum. In their study of X-linked recessive dystonia-parkinsonism (XDP), Goto et al. (2005) proposed that a hyperkinetic state resulting from predominant impairment of the striosomal pathway compared to the direct pathway in early-stage PD causes dystonia and, as basal ganglia dysfunction gradually extends to other pathways, dystonia is replaced by Parkinsonism.[10] In contrast to XDP, we speculate that progression from direct pathway dysfunction in the early stage of PD to dysfunction in the indirect and striosomal pathways occurs in the transition from hypokinetic symptoms to dystonia, particularly in neck muscles, during the later period.

Several PD treatments have been reported to exacerbate or mitigate CD.[11,12] In this study, the maximum dose of levodopa differed significantly between CD(–) and CD(+) patients. Moreover, associations between CD duration and length of pergolide and cabergoline use were suggested by PCA. Perhaps these treatments are involved in CD development by differential influences on direct, indirect, and striosome circuits.

In conclusion, aging PD patients appear predisposed to CD, in particular RC. CD may interfere with swallowing function, leading to aspiration pneumonia, a common cause of death in PD. Pathological mechanisms underlying CD might be influenced by levodopa and dopamine agonists. Prevention of CD may increase quality of life and extend survival of PD patients.

DISCLOSURE

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Conflict of interest: None

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