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HEADACHE AND MIGRAINE IN PARKINSON'S DISEASE



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COI Disclosure

Presenter : Keisuke Suzuki

There are no companies, etc. in a relation of conflict of interest requiring disclosure in relation to the presentation

Learning objectives



Upon completion, participants will be able to

- ✓ Understand the possible role of dopamine in migraine
- ✓ Describe migraine prevalence in Parkinson's disease
- ✓ Describe changes in migraine severity after the onset of Parkinson's disease
- ✓ Know the rate of depression and insomnia in Parkinson's disease patients with migraine

Dopamine and migraine

Peroutka. Neurology 1997;49:650-656

- "Dopaminergic hypersensitivity"

- A placebo-controlled study: apomorphine (dopamine agonist) induced a higher number of yawns in migraine patients than in a control group. Del Bene et al, Headache 1994;34:536-8

- Central site of action proposed

- Induced yawning was not blocked by peripheral D2 antagonist, domperidone, but blocked by central D1 or D2 antagonists.

Serra et al, Psychopharmacol 1987;91:330-3; Eur J Pharmacol 1986;120:187-92

- Peripheral dopamine receptors involved

- Bromocriptine administration induced an intense hypotensive reaction in migraine patients but not in controls Fanciullacci et al, Headache 1980;20:99-102

- Peripheral dopamine antagonist, domperidone, abolished syncopal effect of bromocriptine.

Sicuteri et al, Adv Neurol 1982;33:199-208

Dopamine in migraine

- When TCC (trigemincervical complex) is activated,
 - **Hypothalamic A11 nucleus** provides inhibitory dopamine to D2-like receptors at neurons in the TCC
 - and inhibits the rostral transmission of nociceptive signals
- Lesioning of neurons in the rat A11 nucleus led to facilitation of evoked nociceptive signaling from the TCC

Charbit et al, J Neurosci 2009; 29:12532–41

Dopamine in premonitory phase of migraine

- Hypothalamic involvement

Yawning, sleepiness, appetite/mood changes Charles, Headache, 2003;53:413-9

- Changes in dopaminergic systems

Administration of dopamine receptor agonists cause premonitory symptoms (yawning and nausea)
Cerbo et al, Clin Neuropharmacol, 1997;20:36-41.

- ✓ Dopamine R antagonists -> suppress premonitory symptoms/ migraine headaches

- ✓ Dopamine R agonist does not usually induce migraine

- **Domperidone** (double-blind, randomized, placebo-controlled study) is effective in preventing an migraine attack when given during the premonitory phase

Becker WJ. Cephalalgia 2012;33:1117-21

PET study of premonitory phase of migraine

Brain activations in the early premonitory phase in patients with nitroglycerine-triggered migraine headaches

- Increased regional cerebral blood flows in
 - ✓ Hypothalamus
 - ✓ Periaqueductal grey
 - ✓ Dorsal pons

Maniyar et al, Brain 2014;137;232-41

Dopamine agonist improved migraine headache and restlessness in 50% of migraine patients with restless legs syndrome

No	Age (y)/sex	IRLS	Age of RLS onset (y)	Age of migraine onset (y)	Migraine characteristics	Morning headache	Headache frequency before / after pramipexole treatment (m)	Pramipexole daily dose (mg)/ treatment duration (m)
1	22F	26	6	6	Pulsating/pressing	+	>15 />15	0.375 / 10
2	27F	31	25	15	Pulsating	-	12-14/12-14	0.5 / 16
3	27F	20	27	17	Pulsating	+	15/15	0.125 / 9
4	53F	21	27	16	Pulsating / pressing	-	>15/>15	0.375 / 30
5	37F	29	36	10	Pressing	-	10-14/10-14	0.125 / 29
6	23F	8	23	17	Pulsating	-	4/1	0.125 / 2
7	57F	22	56	30	Tightening	+	3-4/1	0.125 / 23
8	52F	19	57	30	Pulsating	+	15> /2-3	0.125 / 14
9	20F	29	20	13	Pulsating /tightening	+	15>/3-4	0.125 / 2
10	35F	34	7	20	Pulsating	+	6/1-2	0.125 / 5

- 10 migraine patients with RLS who received pramipexole treatment
- 5/10 (50%) reported improvement in both RLS and migraine headaches

Dopamine and migraine: does Parkinson's disease modify migraine course?

Table 2 Migraine course after Parkinson's disease onset

	M/F	(%)
No modification	5/18	(34.8)
Worsening	0/1	(1.5)
Improvement	11/17	(42.4)
Remission	4/10	(21.3)

- 66 PD with migraine and 66 controls with migraine
- Frequency of current migraines was lower in PD patients with migraines than in control subjects with migraines
- **Two-thirds** of PD patients with migraines reported improvement or remission of migraines after PD onset

Involvement of brainstem and hypothalamic regions in Parkinson's disease

- Serotonergic system
 - Raphe nuclei; 20-40% loss
- Cholinergic system
 - Pedunculo pontine nucleus; 60% loss
 - Basal forebrain; 30-90% loss
- Noradrenergic system
 - Locus coeruleus; 40-50% loss
- Orexinergic system
 - Lateral hypothalamus; 20-60% loss

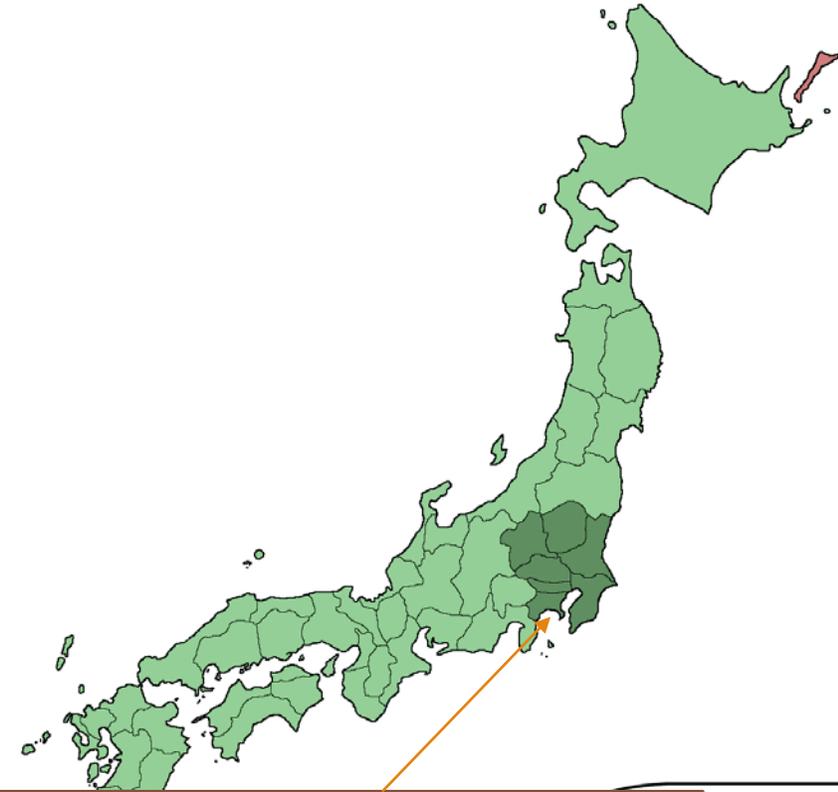
- These brain structures participate in pain and sleep-wake controls

Objective

- Previous studies have reported a lower migraine prevalence in Parkinson's disease (PD) patients and improvements in migraine headaches after PD onset (Barbanti et al, Cephalalgia, 2000), but the clinical association of migraines with PD is unclear.
- There has been reported a shared involvement among neurotransmitters (serotonin, noradrenalin and dopamine), the brainstem and hypothalamic regions in both migraines and PD.
- We sought to investigate the prevalence of headaches and migraines in PD patients, the temporal relations between headache severity and PD disease progression and the clinical characteristics of comorbid migraines in PD patients.

Methods

- A cross-sectional case controlled, multicenter study
- Facilities: 8 Medical University Hospitals in Kanto region
- Period: between September, 2014 and April, 2016



Kanto region
consists of 7 prefectures including the capital Tokyo, referred to as the Greater Tokyo Area, which has an approximate population of 42.6 million

Patient selection

Initial sample

490 patients with PD (age 69.4 ± 8.0 y; 225M)



Final sample

436 patients with PD (age 69.3 ± 7.8 y; 197M; disease duration 7.4 ± 5.3 years; HY stage 2.3 ± 0.7)

Age-matched 401 controls
(age 69.2 ± 8.6 y; 187M)

Exclusion criteria

- ✓ Dementia, defined as MMSE score < 24
- ✓ Those who did not agree to participate in the study

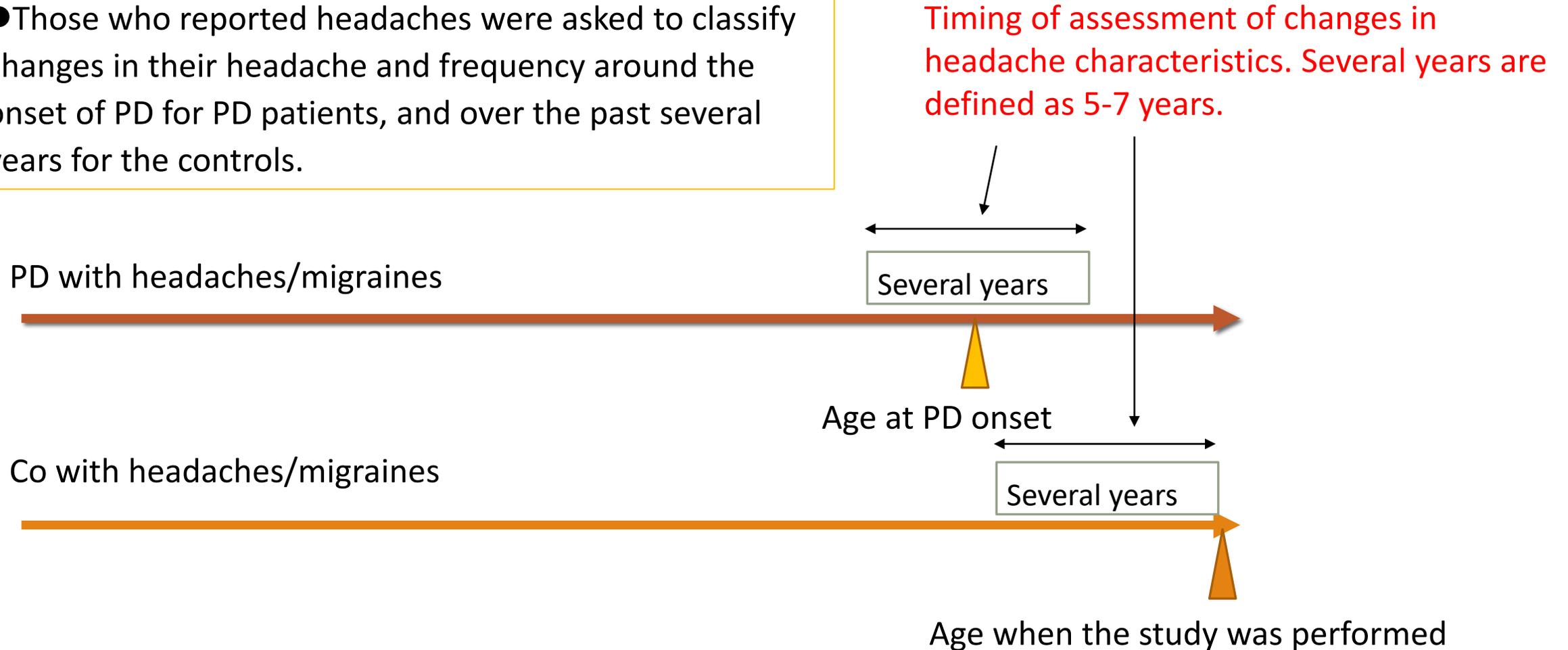
Incomplete data
(n=54) excluded

Clinical evaluation

- Hoehn and Yahr stage: disease severity
- MDS-UPDRS part II
 - Motor experiences of daily living
- MDS-UPDRS part III
 - Motor examination
- MDS-UPDRS part IV
 - Motor complications
- Excessive daytime sleepiness – Epworth Sleepiness Scale (ESS)
- PD-related sleep problems – PD Sleep Scale-2 (PDSS-2)
- Insomnia – Pittsburgh Sleep Quality Index (PSQI)
- Depression- semi-structured MINI psychiatric interview
- **Migraine** - questionnaire based on ICHD-2 and headache screener

Assessment of changes in headache characteristics (intensity, frequency and overall severity) in PD and controls

- Those who reported headaches were asked to classify changes in their headache and frequency around the onset of PD for PD patients, and over the past several years for the controls.



Statistical analysis

- To analyse changes in overall severity, frequency and intensity of lifetime headaches and migraines,
 - ✓ multinomial logistic regression analyses were performed, adjusting for gender and timing at the evaluation of headache changes were assessed.
- To address a difference in a recall period between PD patients and controls,
 - ✓ we have compared changes in headache/migraine characteristics between the PD patients with a disease duration of ≤ 7 years and the total controls.

Demographic characteristics among PD patients without headaches, with non-migraine headaches and with migraines

	No headaches	Non-migraine headaches	Migraines	p-value
n (M/F)	268 (138/130) ¶	139 (49/90)	29 (10/19)	0.0037
Age (y)	69.6±7.5	68.4±8.6	70.0±7.7	0.29
Disease duration (y)	7.4±5.4	7.5±5.0	6.3±5.7	0.53
HY stage, n (%)				0.13
Stage 1	17 (6.3)	22 (15.8)	2 (6.9)	
Stage 2	161 (60.1)	76 (54.7)	17 (58.6)	
Stage 3	76 (28.4)	35 (25.2)	9 (31.0)	
Stage 4	14 (5.2)	5 (3.6)	1 (3.4)	
Stage 5	0 (0.0)	1 (0.7)	0 (0.0)	
MDS-UPDRS part II	12.4±9.0	12.3±8.3	16.1±10.8	0.088
MDS-UPDRS part III	30.2±13.3 ¶	24.9±12.5	30.4±13.3	0.00047
MDS-UPDRS part IV	2.1±3.5	1.8±2.9	2.0±3.3	0.72

*p<0.05 compared to migraines; ¶ p<0.05 compared to non-migraine headaches

Demographic characteristics among PD patients without headaches, with non-migraine headaches and with migraines

	No headaches	Non-migraine headaches	Migraines	p-value
MMSE	28.1±2.0	27.7±2.0	28.0±2.2	0.11
De novo, n (%)	24 (9.0)	8 (5.8)	2 (6.9)	0.51
LED (mg/day)	477.8±343.3	510.1±389.9	480.8±369.9	0.69
Dopamine agonist, n (%)	145 (54.1)	69 (49.6)	13 (44.8)	0.50
Levodopa, n (%)	224 (83.6)	118 (84.9)	23 (79.3)	0.76
EDS, n (%)	102 (38.1)	51 (36.7)	12 (41.1)	0.89
pRBD, n (%)	98 (36.6)	44 (31.7)	11 (37.9)	0.58
Poor sleeper, n (%)	112 (41.8) *	72 (51.8) *	23 (79.3)	0.00029
RLS, n (%)	10 (3.7)	4 (2.9)	1 (3.4)	0.90
PD-related sleep problems, n (%)	94 (35.1) *	41 (29.5) *	18 (62.1)	0.0037
Depression, n (%)	29 (10.8) *	18 (12.9) *	13 (44.8)	<0.0001

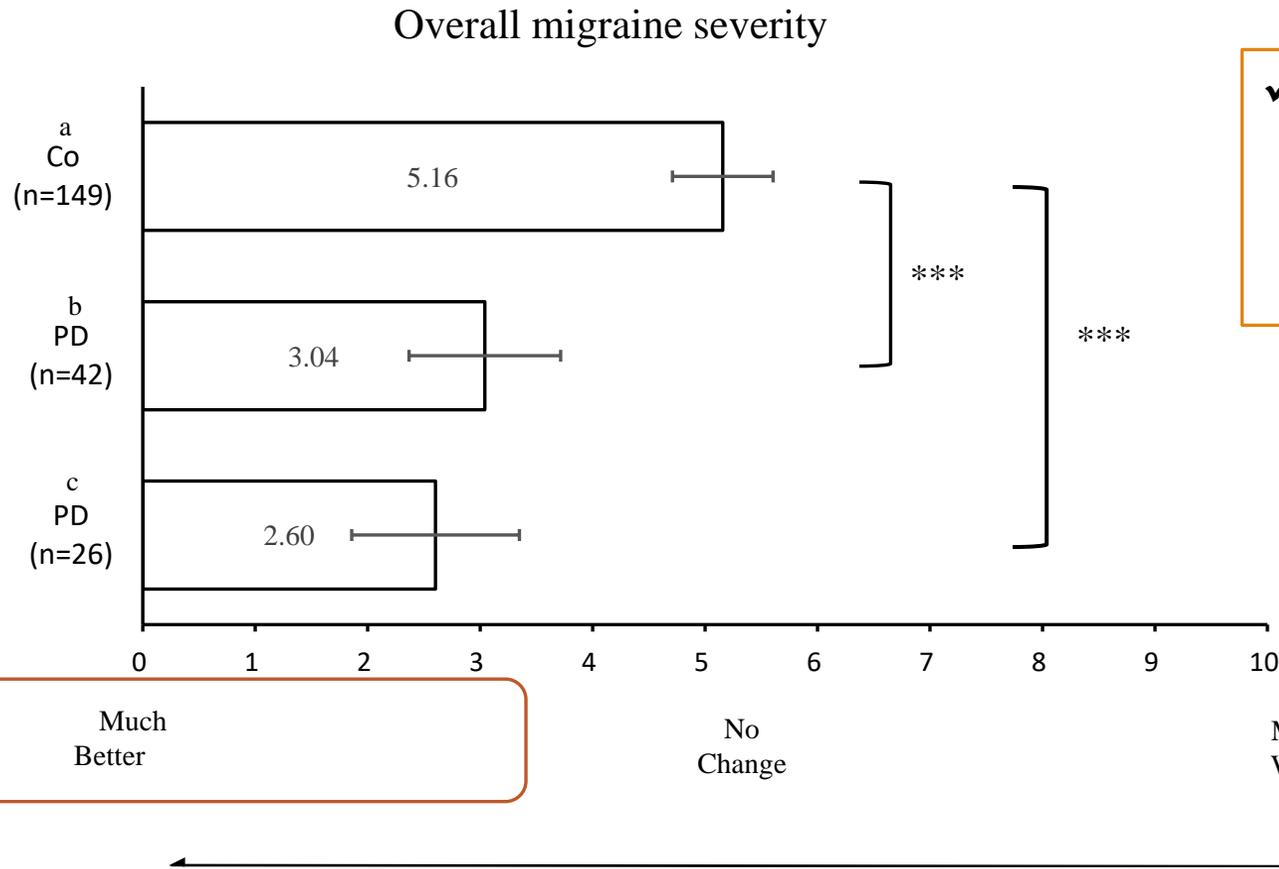
*p<0.05 compared to migraines

¶ p<0.05 compared to non-migraine headaches

Changes in lifetime headache/migraine frequency and intensity in PD patients and controls

- Among PD patients with lifetime headaches or migraines, **62.2% and 73.8%** reported decreased frequency, and **44.0% and 57.1%** reported reduced intensity of headaches and migraines, respectively, after PD onset.
- In contrast, among controls with lifetime headaches or migraines, **36.3% and 25.0%** reported decreased frequency, and **20.1% and 13.9%** reported reduced intensity of headaches and migraines, respectively, over several years.
- After adjusting for gender and timing of the evaluation of headache changes, PD patients had significantly decreased frequency and intensity of lifetime headaches and migraines compared with controls.

Changes in overall lifetime migraine severity in PD patients and controls



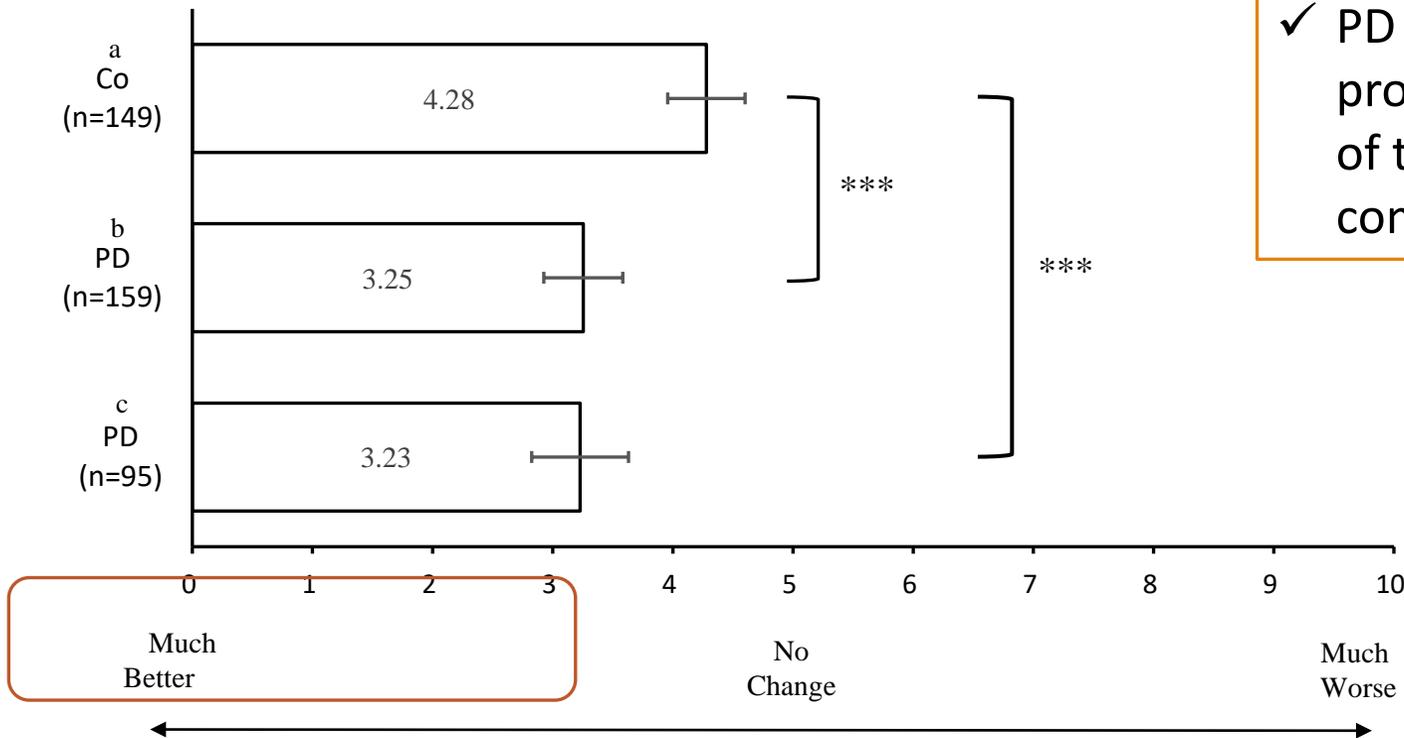
✓ PD patients with migraines showed a pronounced reduction in the overall severity of their and migraines after the onset of PD compared with controls with migraines

a: Co=controls; b: PD=PD in all; c: PD=PD patients who had onset during the last several years (≤ 7 years); ***: $p < 0.001$

The bars show the estimated marginal means and 95% CI based on ANCOVA after adjusting for gender and timing at the evaluation of headache changes.

Changes in overall lifetime headache severity in PD patients and controls

Overall headache severity



✓ PD patients with headaches showed a pronounced reduction in the overall severity of their and headaches after the onset of PD compared with controls with migraines

a: Co=controls; b: PD=PD in all; c: PD=PD patients who had onset during the last several years (≤ 7 years); ***: $p < 0.001$

The bars show the estimated marginal means and 95% CI based on ANCOVA after adjusting for gender and timing at the evaluation of headache changes.

Discussion

- This multicentre, case-controlled study showed that the lifetime (38.5% vs. 38.9%) and 1-year prevalence (26.1% vs. 26.2%) of headaches did not differ between PD patients and control subjects
- However, lower lifetime (9.6% vs. 18.0%) and 1-year (6.7% vs. 11.0%) migraine prevalence was lower in PD patients than in controls.
- PD patients with headaches or migraines reported a more pronounced reduction in overall severity of their lifetime headaches and migraines over a few years after onset of disease, after adjusting for confounding factors.

Discussion

- Our findings suggest that the disease course of PD could modify migraine severity via progressive degeneration of the brainstem including pain regulatory systems.
- The pathology of PD involves not only the substantia nigra, which has abundant 5-HT_{1B} receptors (Castro et al, Neuropharmacology, 1997), but also serotonergic raphe and noradrenergic locus coeruleus nuclei, all of which play crucial roles in pain transmission (Holland, Cephalalgia, 2014).
- Another possibility by which headache severity could be improved during the disease course of PD is that chronic dopaminergic therapy reduces pain in PD patients.
- However, in our study, there was no difference in levodopa-equivalent dose irrespective of headache comorbidities.

Conclusion

- ✓ PD patients had lower lifetime and 1-year prevalence of **migraines** than controls.
- ✓ The lifetime and 1-year prevalence of non-migraine headaches did not differ between PD patients and control subjects.
- ✓ PD patients with migraines showed a higher rate of depression and insomnia than those without headaches.
- ✓ PD patients with headaches or migraines reported a pronounced reduction in the intensity, frequency, and overall severity of their headaches and migraines over a few years after the onset of PD.