Original Article

Migraine and Tension-type Headache in Parkinson's Disease and Progressive Supranuclear Palsy/Corticobasal Syndrome

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Abstract

Objective: To compare the prevalence and characteristics of migraine and tension-type headache (TTH) among patients with Parkinson's disease (PD), progressive supranuclear palsy/corticobasal syndrome (PSP/CBS), and healthy controls (HCs). **Methods:** This cross-sectional study involved the collection of data from consecutive PD (n = 81) and PSP/CBS (n = 21) patients along with 104 HCs. Migraine and TTH were diagnosed using the International Classification of Headache Disorders 3rd edition criteria. Demographic data, PD or PSP/CBS details, and the presence and characteristics of migraine and TTH were collected. Montreal Cognitive Assessment Scale, Patient Health Questionnaire-9, and Pittsburgh Sleep-Quality Index were used to assess cognition, depression, and sleep quality, respectively. **Results:** A comparable proportion of PD and PSP/CBS patients reported lifetime headache (46.9% vs 23.8%; $P = 0.06$). TTH was more common, observed in 84.3%, 100%, and 93.5% of PD, PSP/CBS, and HCs with lifetime headache, respectively. A comparable proportion of participants in all three groups had bilateral ($P = 0.10$), dull-aching headache ($P = 0.09$), and occurring <5/month ($P > 0.99$). The mean severity score of headache among three groups was comparable ($P = 0.39$). Although the demographic and clinical characteristics of PSP/CBS patients with and without headache were comparable, PD patients with headache had a higher MDS-UPDRS-III score than those without. More than two-third PD and all PSP/CBS patients with lifetime headache reported headache improvement following parkinsonism onset. **Conclusion:** The prevalence and characteristics of migraine and TTH were comparable in PD, PSP/CBS, and HCs. Headache was associated with greater motor severity in PD. Following parkinsonism onset, headache improved in the majority of PD and PSP/CBS patients with lifetime headache.

Keywords: Corticobasal syndrome, headache, migraine, Parkinson's disease, progressive supranuclear palsy, tension-type headache

Introduction

Parkinson's disease (PD), progressive supranuclear palsy (PSP), and corticobasal syndrome (CBS) are neurodegenerative disorders pathologically characterized by abnormal deposition of proteinaceous particles intracellularly as inclusions or extracellularly as plaques.[1,2] While deposits of alpha-synuclein are characteristically seen in PD, both PSP and CBS are grouped as tauopathies.[2] Despite the importance given to motor features, several non-motor features affect patients with PD, PSP, and CBS.[1–3] Pain is one of the common non-motor symptoms reported by these patients, affecting up to 85% patients with PD[4] and up to one-third patients with PSP/CBS.[5,6]

Of all the pain-related disorders, headache is one of the most common and disabling disorder globally. A recent study reports headache in more than half the studied general population, with 26% reporting tension-type headache (TTH) and 14% reporting migraine.[7] A substantial proportion of elderly population suffer with TTH or migraine.[8-10] In addition to sensitization of peri-cranial myofascial pain receptors, possible sensitization of second-order neurons in spinal dorsal horn or trigeminal nucleus along with a reduced descending inhibition from supraspinal structures has been implicated as the major pathophysiological factors in TTH. Moreover, recent evidences favor stimulation of the trigemino-vascular system, rather than the vascular theory as the major contributor in migraine pathophysiology.[10] Due to the progressive degeneration of brainstem nuclei in PD and PSP/CBS, which include the regions regulating pain transmission, e.g., raphe nuclei, the appearance of headache or change in already existing headache disorder appears likely in these patients.[11]

Despite the apparent pathophysiological explanation, literature regarding the assessment of headache in patients with PD and PSP/CBS is scarce. A number of studies have assessed proportion of PD patients having primary headache including migraine and TTH and compared it with healthy controls (HCs)

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and reported primary headache in either equal or lower proportion of PD patients.[12–15] Some studies tried to correlate primary headache with onset of PD. While two studies reported improvement in primary headaches after onset of PD,[16,17] one study reported that 27.9% of PD patients with lifetime headache had onset of headache following PD diagnosis.[18] Despite the conflicting results, a recent metanalysis favored that migraine and TTH may have a possible link with PD.[19]

Thus, literature exploring relation between primary headache disorders and PD is not only sparse but also inconclusive. Several questions are still unanswered. In view of the neurodegenerative nature of PD and PSP/CBS, the characteristics of primary headaches in these disorders may differ with regard to individual symptoms of these headache. The prevalence and characteristics of headache may differ among the subtypes of PD, i.e. tremor-dominant PD (TDPD) and postural instability and gait disorder (PIGD). TTH may accompany depressive features and poor sleep. Similarly, poor sleep quality may precipitate migraine.[20–22] These factors have never been examined in patients with PD or PSP/CBS. To the best of our knowledge, reports regarding the assessment of headache in patients having PSP/CBS are lacking. The present study is an attempt to fill this void and aimed to evaluate the prevalence and characteristics of headaches among PD patients and compare it with those with PSP/CBS and HCs.

Materials and Methods

PD and PSP/CBS patients were recruited from the Movement Disorder Clinic at a University hospital between February 2022 and January 2023, following approval from the Institutional Ethics Review Board (AIIMS/IEC/22/79). Considering the low prevalence of PSP/CBS, purposive sampling was done. Consecutive 102 patients with either PD (n = 81) or PSP/CBS (n = 21) and 104 age- and gender-matched healthy controls (HCs) were recruited in the study [Supplementary Figure 1]. All participants had age ≥18 years, and PD or PSP/CBS patients were on stable dopaminergic therapy for the past 4 weeks. Participants were excluded if they were pregnant; had a history suggestive of secondary headache including those related to intracranial space-occupying lesion, arteriovenous malformation, aneurysm, prior head injury or stroke; or had cognitive impairment (Montreal Cognitive Assessment Score <24).[23] Written informed consent was obtained from all participants before including them in the study. PD was diagnosed using Movement Disorders Society-Parkinson's Disease criteria.[24] PSP and CBS were diagnosed using standard criteria.[25,26] Accompanying age- and gender-matched relatives (not genetically related) and friends of patients who did not have any neurological, psychiatric, or other chronic medical disorders were recruited as HCs. In addition to the clinical assessment of PD and PSP/CBS patients (NK), all participants underwent detailed clinical assessment for cognition and headache (VJ, AT, and MK) and depression, and sleep quality (RG).

Assessment of headache

Demographic data of all participants were collected. Diagnosis of migraine or TTH was based on clinical interview and examination as per International Classification of Headache Disorders 3rd edition (ICHD3) criteria.[27] Secondary causes of headache were ruled out based on clinical history and examination. Neuroimaging was done wherever required. Information was collected for the occurrence of headache during lifetime and included details regarding aura, location, laterality, character, frequency, radiation, referred pain, and associated symptoms, e.g., nausea, vomiting, photophobia (PHT), and/or phonophobia (PHN). Patients were requested to grade the severity of their headaches using a visual analog scale (VAS) from 0 (no headache) to 10 (worst possible headache). In addition, the course of headache in relation to onset of parkinsonian features and the occurrence of headache in past one year was ascertained.

Assessment of PD and PSP/CBS

Information collected regarding PD and PSP/CBS included age of onset of PD or PSP/CBS, disease duration, disease phenotype (tremor dominant, postural instability/gait difficulty or indeterminate type),[28] Movement Disorders Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS)-III (motor) score in "off" state,[29] Hoehn and Yahr (H-Y) stage,[30] duration of dopaminergic therapy and levodopa equivalent daily dose (LEDD),[31] and non-motor symptoms scale (NMSS) score.[32] Associated comorbidities were also recorded. Any reduction in either frequency or severity of headache by >50% was defined as "improvement of headache."[16] Cognition status, depressive symptoms, and sleep quality were assessed using Montreal Cognitive Assessment (MOCA) score, Patient Health Questionnaire-9 (PHQ-9),[33] and Pittsburgh Sleep Quality Index (PSQI),[34] respectively.

Assessment of depressive features

Patient Health Questionnaire (PHQ-9) assesses subjects on nine criteria for depression, each scored on a four-point Likert scale ranging from not at all (score 0) to nearly every day (score 3).[33] It has a score ranging between 0 and 27. PHQ-9 score of 0-4 shows no or minimal depression. Scores among 5-9, 10-14, 15-19, and >20 represent mild, moderate, moderately severe, and severe depression, respectively. PHQ-9 score ≥5 has a sensitivity and specificity of 88% each for major depressive disorder.[33] We used the Hindi version of the PHQ-9 to assess depression and mood.[35,36]

Assessment of sleep quality

Pittsburgh Sleep Quality Index (PSQI) is a 19-item, self-rated questionnaire that evaluated sleep quality over past one month.[34] The items are grouped into seven components, including (1) sleep duration, (2) sleep disturbance, (3) sleep latency, (4) daytime dysfunction due to sleepiness, (5) sleep efficiency, (6) overall sleep quality, and (7) sleep medication use. A score ranging from 0 to 3 is given for each component, with three indicating the greatest disturbance. Summing the scores of all seven components gives the global score, which

ranges from 0 to 21. Higher the global score, worse the sleep quality. A global PSQI score >5 gives a sensitivity of 89.6% and a specificity of 86.5% with an internal consistency of 0.75 to differentiate good sleepers from poor sleepers.[34]

Statistical analysis

The analysis was done using Statistical Package for Social Sciences (SPSS) v 28.0 (IBM Corp. Released 2021. IBM SPSS Statistics for Mac, Version 28.0.1.0 (142) Armonk, NY: IBM Corp.). Categorical variables were expressed as proportions and percentages, while continuous variables were expressed as mean ± standard deviation for normally distributed, or median with interquartile range for skewed data. Normality of data was tested using the Shapiro–Wilk test. The Chi-square test was used to compare categorical variables across groups. To compare continuous variables across groups that were normally distributed, independent *t* test or analysis of variance (ANOVA) was applied, while the Mann–Whitney U test or the Kruskal–Wallis test was used for continuous but skewed variables. A variable with a two-tailed *P* value of less than 0·05 was considered statistically significant.

Results

Demographic and clinical characteristics of patients and healthy controls (HCs)

Of a total of 105 PD or PSP/CBS patients screened, three were excluded due to MOCA < 24. Among the 102 recruited patients, 81 had PD and 21 had PSP/CBS. In the PSP/CBS group, 14 had PSP, and 7 had CBS [Supplementary Figure 1]. We grouped patients with tauopathies (PSP and CBS) together for analysis. Table 1 compares the baseline demographic and clinical characteristics of participants. Although not significant, a higher proportion of PD (46.9%) patients reported lifetime headache than PSP/CBS (23.8%) ($P = 0.06$). The proportion of patients with "headache in the past 1 year" were comparable in the three groups ($P = 0.72$).

Comparison of clinical characteristics of healthy controls, PD, and PSP/CBS with headache

Demographic and clinical characteristics of headache were comparable between the three groups. A higher proportion of PSP/CBS patients with headache were hypertensive. The overall characteristics of headache were similar between the three groups. However, a higher proportion of patients with PD and PSP/CBS reported headache duration of >6 hours compared to HCs (76.3% vs 60% vs 28.3%; $P < 0.01$). Comparison of headache characteristics among patients with PD, PSP/CBS, and HCs is shown in Table 2.

Among the PD and PSP/CBS patients with lifetime headache, improvement in headache was observed in all 5 PSP/CBS and more than two-third (26/38 = 68.4%) PD patients. Headache in past one year was reported by 11 (13.6%) PD and 1 (4.8%) PSP/CBS patients. Among parkinsonian patients with lifetime headache, those with PSP/CBS had a higher median H-Y stage as compared to PD group [Table 2]. While sleep quality was comparable among the three groups, a significantly higher proportion of PD patients reported depressive symptoms as compared to HCs.

The demographic and clinical characteristics of PD patients reporting improvement vs no improvement in

Table 1: Comparison of demographic and clinical characteristics of participants in healthy control, Parkinson's disease, and progressive supranuclear palsy/corticobasal syndrome groups

Characteristics	Healthy Controls (*n*=104) A	PD (*n*=81) B	PSP/CBS (*n*=21) C	*P* (A vs B vs C)	*P* (A vs B)	*P* (A vs C)	*P* (B vs C)
Demographic profile							
Age at presentation (years): median (range)	57 (30–82)	62 (35–81)	64 (38–82)	0.15	0.35	0.04	0.28
Age at onset of Parkinsonism (years): median (range)	-	55 (31–73)	56 (36–79)	<0.01	-	-	0.38
Male gender *n* (%)	70 (67.3)	54 (66.7)	13 (61.9)	0.89	0.93	0.63	0.68
Duration of disease (years): mean (SD)	-	5 (1–17)	5 (1–20)	<0.01	-	-	0.68
Comorbidities							
Diabetes *n* (%)	4 (3.8)	7 (8.6)	5 (23.8)	0.007	0.17	<0.01	0.12
Hypertension *n* (%)	10 (9.6)	14 (17.3)	4 (19.0)	0.24	0.12	0.25	>0.99
Parkinsonism characteristics							
MDS-UPDRS-III score ("off" state): median (range)	-	37 (7–67)	42 (16–69)	0.04	-	-	0.04
Hoehn and Yahr stage: median (range)	-	2.5 (1–4)	3 (1–4)	0.05	-	-	0.05
Levodopa Equivalent Daily Dose (mg): median (range)	-	500 (0–1025)	500 (0–1200)	0.09	-	-	0.09
Non-motor symptoms scale score: median (range)	-	36 (6–194)	35 (0–140)	<0.01	<0.01	<0.01	0.24
Presence of lifetime migraine/TTH *n* (%)	46 (44.2)	38 (46.9)	5 (23.8)	0.16	0.72	0.08	0.06
Depressive symptoms (PHQ9 ≥5) *n* (%)	32 (30.8)	42 (51.9)	11 (52.4)	<0.01	<0.01	0.06	0.97
Poor sleep quality (PSQI >5) *n* (%)	41 (39.4)	53 (65.4)	14 (66.7)	<0.01	<0.01	0.02	0.92
MOCA: median (range)	26 (25–30)	26 (24–30)	24 (24–28)	<0.01	0.23	<0.01	<0.01

MOCA: Montreal Cognitive Assessment; MDS-UPDRS: Movement Disorders Society-Unified Parkinson's Disease Rating Scale; PD: Parkinson's disease; PHQ9: Patient Health Questionnaire-9; PSQI: Pittsburgh Sleep Quality Index; PSP/CBS: Progressive supranuclear palsy/corticobasal syndrome; SD: Standard deviation

Table 2: Comparison of demographic and clinical characteristics among participants having headache in the healthy control, Parkinson's disease, and progressive supranuclear palsy/corticobasal syndrome groups

Characteristics	Healthy Controls with headache (*n*=46) A	PD with headache (*n*=38) B	PSP/ CBS With headache (*n*=5) C	*P* (A vs B vs C)	*P* (A vs B)	*P* (A vs C)	*P* (B vs C)
Demographic profile							
Age at presentation: median (range)	55.5 (30–71)	62 (37–78)	64 (57–72)	0.26	0.52	0.06	0.41
Age at onset of Parkinsonism (years): median (range)	-	58 (31–73)	56 (51–71)	-	-	-	0.78
Male gender: *n* (%)	29 (63.0)	23 (60.5)	2 (40.0)	0.61	0.81	0.37	0.63
Duration of parkinsonism (years): median (range)	-	5 (1–8)	8 (1–10)	-	-	-	0.10
Comorbidities							
Diabetes: *n* (%)	3 (6.5)	4 (10.5)	1 (20.0)	0.30	0.51	0.35	0.48
Hypertension: *n* (%)	4 (8.7)	9 (23.7)	4 (80.0)	<0.01	0.06	<0.01	0.02
Headache characteristics							
Age of onset of headache (years): median (range)	40.5 (20–65)	44.5 (18–70)	45 (30–48)	0.18	0.06	0.89	0.54
Headache prior to onset of parkinsonism: *n* (%)	-	27 (71.1)	5 (100)	-	-	-	0.31
Headache subtypes (lifetime headache)							
TTH *n* (%)	43 (93.5)	32 (84.2)	5 (100)	0.28	0.17	>0.99	>0.99
Migraine *n* (%)	3 (6.5)	6 (15.7)	0 (0)				
Location—bilateral *n* (%)	38 (82.6)	25 (65.8)	5 (100)	0.10	0.08	0.58	0.30
Duration of headache >6 hours *n* (%)	13 (28.3)	29 (76.3)	3 (60)	<0.01	<0.01	0.31	0.59
Moderate-to-severe headache (VAS>5) *n* (%)	15 (32.6)	13 (34.2)	1 (20.0)	0.82	>0.99	>0.99	>0.99
VAS score: mean (SD)	5 (1.2)	4.68 (1.6)	5.2 (1.1)	0.39	0.23	0.68	0.39
Character of headache: dull aching: n (%)	43 (93.5)	30 (78.9)	5 (100)	0.09	0.049	>0.99	0.26
Frequency of headache (per month): median (range)	4 (1–25)	4 (1–25)	5 (1–20)	>0.99	0.97	0.96	>0.99
Associated symptoms (Nausea±vomiting±PHT±PHN): *n* (%)	6 (13)	8 (21)	0 (0)	0.37	0.33	>0.99	0.57
Worsening of headache after disease onset* *n* (%)	-	12 (31.6)	0 (0)	-	-	-	-
Presence of headache in past 1 year *n* (%)	16 (34.8)	11 (28.9)	1 (20)	0.72	0.57	0.51	>0.99
Headache subtypes (in past 1 year)							
TTH *n* (%)	16 (34.8)	8 (21.1)	1 (20)	0.08	0.03	>0.99	0.55
Migraine *n* (%)	0 (0)	3 (7.9)	0 (0)				
Parkinsonism characteristics							
MDS-UPDRS-III score ("off" state): median (range)	-	40 (13–67)	38 (22–62)	0.66		-	0.67
Hoehn and Yahr stage: median (range)	-	2.25 (1–4)	3 (3–4)	0.01		-	0.01
Levodopa Equivalent Daily Dose (mg): median (range)	-	500 (375–1000)	750 (0–1200)	0.19		-	0.27
Non-motor symptoms scale score: median (range)	-	34 (6–194)	37.5 (11–54)				0.98
Depressive symptoms (PHQ9 ≥5) *n* (%)	12 (26.1)	18 (47.4)	3 (60)	0.07	0.04	0.14	0.60
Poor sleep quality (PSQI >5) *n* (%)	24 (52.2)	23 (60.5)	3 (60)	0.73	0.44	>0.99	>0.99
MOCA: median (range)	26 (25–30)	26 (24–30)	24 (24–27)	0.02	0.03	0.02	0.24

*New-onset headache after disease onset and worsening of previous headache after disease onset. MOCA: Montreal Cognitive Assessment; MDS-UPDRS: Movement Disorders Society-Unified Parkinson's Disease Rating Scale; PD: Parkinson's disease; PHQ9: Patient Health Questionnaire-9; PSQI: Pittsburgh Sleep Quality Index; PHT: Photophobia; PHN: Phonophobia; PSP/CBS: Progressive supranuclear palsy/corticobasal syndrome; SD: Standard deviation; TTH: Tension-type headache; VAS: Visual analogue score

headache/appearance of new-onset headache following onset of Parkinson's disease (NOHPD) were comparable. However, the latter group had a significantly older age at headache onset compared to those reporting improvement of headache (56 years vs 44 years, $P = 0.02$) [Supplementary Table 1]. Eleven (11/38 = 28.9%) PD patients with lifetime headache reported NOHPD.

A proportion of participants reporting headache in past one year in the three groups were comparable (HCs: PD: PSP/CBS = 34.8%: 28.9%: 20%; $P = 0.72$). While all the HCs and PSP/CBS patient with headache in past one year reported TTH, three-fourth of those in the PD group had TTH ($P = 0.03$ in HCs vs PD).

Comparison of clinical characteristics among headache patients in tremor-dominant (TDPD) and postural instability and gait disorder (PIGD) subtype of PD

A comparable proportion of TDPD and PIGD patients reported headache (43.5% vs 66.7%; $P = 0.14$). Most of the demographic and clinical features between TDPD and PIGD patients having headache were comparable except a latter age of the onset of parkinsonism and poorer sleep quality in the PIGD group [Table 3].

Table 3: Comparison of demographic and clinical characteristics among headache patients with tremor-dominant and postural instability and gait disorder type of Parkinson's disease

Characteristics	TDPD with headache (*n*=30)	PIGD with headache (*n*=8)	*P*
Demographic profile			
Age of presentation (years): median (range)	60 (37-75)	65 (55–78)	0.08
Age at onset of parkinsonism (years): median (range)	56 (31–70)	61 (47–73)	0.02
Male gender *n* (%)	18 (60.0)	5 (60.5)	>0.99
Duration of illness (years): median (range)	5 (2-8)	4.5 (1–8)	0.79
Comorbidities			
Diabetes *n* (%)	3 (10)	1 (12.5)	>0.99
Hypertension *n* (%)	8 (26.7)	1 (12.5)	0.65
Headache characteristics			
Age of onset of headache (years): median (range)	42.5 (18–70)	48 (44–60)	0.06
Headache prior to onset of parkinsonism *n* (%)	22 (73.3)	5 (62.5)	0.42
Headache within 1 year	9 (30)	2 (25)	>0.99
Headache subtype			
TTH *n* (%)	25 (83.3)	7 (87.5)	>0.99
Migraine *n* (%)	5 (16.7)	1 (12.5)	
Location—bilateral *n* (%)	19 (63.3)	6 (75)	0.69
Duration of headache >6 h *n* (%)	6 (20)	3 (37.5)	0.36
Moderate-severe headache (VAS >5) *n* (%)	9 (30)	4 (50)	0.41
Associated symptoms *n* (%)	6 (20.0)	2 (25.0)	>0.99
(Nausea±vomiting±photophobia and phonophobia			
Dull aching	23 (76.7)	7 (87.5)	0.66
Worsening of headache after disease onset* *n* (%)	9 (30)	3 (37.5)	0.69
Presence of headache in past 1 year *n* (%)	9 (30)	2 (25)	>0.99
Parkinsonism characteristics			
MDS-UPDRS-III score ("off" state): median (range)	35 (7–67)	42 (13–67)	0.38
Hoehn and Yahr stage: median (range)	2.5 (1–4)	2.75 (1–4)	0.41
Levodopa Equivalent Daily Dose (mg): median (range)	500 (0–1025)	500 (500–1000)	0.40
Non-motor symptoms scale score: median (range)	31.5 (6–79)	36.5 (20–194)	0.28
Depression (PHQ9 ≥5) *n* (%)	12 (40)	6 (75.0)	0.08
Poor sleep quality (PSQI >5) *n* (%)	15 (50)	8 (100)	0.01
MOCA: median (range)	26 (24–30)	26 (24–30)	0.59

MOCA: Montreal Cognitive Assessment; MDS-UPDRS: Movement Disorders Society-Unified Parkinson's Disease Rating Scale; PD: Parkinson's disease; PHQ9: Patient Health Questionnaire-9; PSQI: Pittsburgh Sleep Quality Index; PHT: Photophobia; PHN: Phonophobia; PIGD: Postural instability and gait disorder; SD: Standard deviation; TDPD: Tremor-dominant Parkinson's disease; TTH: Tension-type headache; VAS: Visual analogue score

Comparison of demographic and clinical characteristics between parkinsonian patients with and without headache

Supplementary Table 2 and Supplementary Table 3 show the comparison of demographic and clinical characteristics between PD and PSP/CBS patients with and without headache. Both groups had comparable demographic and clinical factors as well as the LEDD. A comparable proportion of patients in both headache and no headache categories reported depressive symptoms and poor sleep quality, both in the PD and PSP/CBS groups.

Discussion

Lifetime headache was reported by a comparable proportion of PD, PSP/CBS, and HCs. TTH was more common than migraine. Bilateral, dull-aching headache with duration >6 hours, mild-to-moderate severity (VAS ≤5), and a frequency <5 per month was reported by a majority of PD and PSP/CBS patients. Demographic and clinical characteristics of patients with and without headache in both PD and PSP/CBS groups were comparable. Among those with lifetime headache, an improvement of headache following the onset of parkinsonism was reported in more than two-third PD patients and all PSP/CBS patients. Headache worsening/NOHPD was reported by 28.9% PD patient with lifetime headache and was associated with a higher age at onset of headache. Prevalence and characteristics of headache were comparable among patients with TDPD and PIGD.

We observed TTH as the predominant headache subtype in all three groups. Although not from India, some studies have assessed headache in PD patients.[12–14,16–18,37] Our data are in line with the previous studies, which reported a prevalence of 38–93% for lifetime headache in PD patients,[14,17,18] with a metanalysis reporting a pooled prevalence of nearly 50% for any headache (including TTH and migraine) in PD patients.[19] While 39.5% of our PD patients had TTH and 7.4% had migraine, Rocha-Filho *et al*.[18] have reported a 67.4% prevalence of TTH

and 26.1% for migraine in PD patients. Although ICHD-3 criteria were used in both studies, Rocha-Filho *et al*.[18] had a smaller sample size of 46 PD patients. The headache location, character, frequency, severity, and associated symptoms were comparable among the three groups in our cohort. A majority of our PD and PSP/CBS patients had bilateral, dull-aching headache with duration >6 hours, mild-to-moderate severity (VAS ≤5), and a frequency <5 per month, similar to those reported in the literature.[38]

A proportion of participants with migraine/TTH in past one year was comparable in the three groups ($P = 0.72$). Previous studies have reported past one-year headache prevalence of 12.2% for TTH[14] and 6.7–28.3% for migraine[14,16–19] in PD patients, which is comparable to 9.8% and 3.7% observed in our cohort, respectively. Among the participants with headache in past one year, a significantly higher percentage of HCs had TTH as compared to PD. The proportion of patients with migraine or TTH in both PD and PSP/CBS groups were lower than the general Indian population in a similar age group, with the latter reporting TTH in 28.7% and migraine in 23.1%.[39] Moreover, following onset of parkinsonian features, improvement of headache was reported by more than two-third of our PD patients and all PSP/CBS patients with lifetime headache. A metanalysis reported headache improvement in 61.5% of PD patients with lifetime migraine.[19] Thus, parkinsonism may have a protective effect on headache, which may be related to the overlap of neuronal structures implicated in both disorders.[16] PD and PSP/CBS disorders, by involving the subcortical and brainstem nuclei including substantia nigra, may have a beneficial impact on migraine pathophysiology.[14,40,41] In addition, aging-related degeneration of pain regulatory systems may also contribute to amelioration of migraine in PD.[15,19] Moreover, long-term levodopa use in PD and PSP/CBS patients may benefit headache disorders.[16]

On the contrary, nearly one-third of our PD patients with lifetime headache reported new-onset headache following the development of parkinsonian features, which is comparable to that (27.9%) reported in another study.[18] It may be possible that a subset of PD patients may be prone to develop NOHPD or worsening of their previous headache including migraine or TTH.

The demographic and clinical characteristics were comparable between patients of TDPD and PIGD subtypes of PD having lifetime headache, except that age of the onset of parkinsonism was lower in the TDPD group, which may be related to the fact that early gait difficulty, as seen in PIGD, is less likely in early-onset PD.[1] Although the difference was not significant, a higher proportion of PIGD patients reported headache as compared to TDPD patients. This may be related to the higher non-motor symptoms (including pain) scores in PIGD than TDPD patients.[42,43]

There are several limitations in the present study. First, this is a single-center study at a tertiary care teaching hospital and may have associated referral bias. Second, information for lifetime headache may have been affected by a recall bias. Moreover, we did not consider primary headache disorders other than migraine and TTH. Third, the sample size of PSP/CBS patients was small. Fourth, the effect of motor fluctuations on the headache characteristics was not assessed. Fifth, we did not evaluate the impact of headache on quality of life in parkinsonian patients. Sixth, since more than three-fourth of NOHPD patients reported TTH, PD-related increased craniofacial muscle rigidity appears a likely factor contributing toward the late-onset headache in these cases. Evaluating a larger cohort may help understand impact of headache on the quality of life in PD. However, this is the first study to assess prevalence and characteristics of migraine and TTH in PSP/CBD patients and compare them with PD patients and HCs. Moreover, this study assessed prevalence and characteristics of migraine and TTH in TDPD and PIGD subtypes. These preliminary results need to be confirmed by a multi-center longitudinal study involving a larger sample size.

Conclusion

Prevalence and characteristics of migraine and TTH in PD and PSP/CBS patients are comparable to HCs, with TTH being the more common primary headache subtype. Following onset of parkinsonian features, no worsening of headache was seen in more than two-third PD patients, and all PSP/CBS patients reporting lifetime headache. Worsening of headache or appearance of new headache following parkinsonism onset in PD was associated with a higher age at onset of headache.

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Conflicts of interest

There are no conflicts of interest.

References

1. Rizek P, Kumar N, Jog MS. An update on the diagnosis and treatment of Parkinson disease. Can Med Assoc J 2016;188:1157-65.
2. Mcfarland NR. diagnostic approach to atypical Parkinsonian syndromes. Contin Lifelong Learn Neurol 2016;22:1117-42.
3. Rowe JB, Holland N, Rittman T. Progressive supranuclear palsy: Diagnosis and management. Pract Neurol 2021;21:376-83.
4. Schapira AHV, Chaudhuri KR, Jenner P. Non-motor features of Parkinson disease. Nat Rev Neurosci 2017;18:435-50.
5. Chaithra SP, Prasad S, Holla VV, Stezin A, Kamble N, Yadav R, *et al*. The non-motor symptom profile of progressive supranuclear palsy. J Mov Disord 2020;13:118-26.
6. Ohtomo R, Tsuji S, Iwata A. Persistent pain as a non-motor symptom in corticobasal syndrome. J Clin Neurosci 2016;29:35-7.
7. Stovner LJ, Hagen K, Linde M, Steiner TJ. The global prevalence of headache: An update, with analysis of the influences of methodological factors on prevalence estimates. J Headache Pain 2022;23:1-17.
8. Sharma TL. Common primary and secondary causes of headache in the elderly. Headache 2018;58:479-84.
9. Togha M, Karimitafti MJ, Ghorbani Z, Farham F, Naderi-Behdani F, Nasergivehchi, *et al*. Characteristics and comorbidities of headache in patients over 50 years of age: A cross-sectional study. BMC Geriatr 2022;22:1-10.
10. Ashina M. Migraine. N Engl J Med 2020;383:1866-76.

11. Shen Y, Wang J, Peng J, Wu X, Chen X, Liu J, *et al*. Abnormal connectivity model of raphe nuclei with sensory-associated cortex in Parkinson's disease with chronic pain. Neurol Sci 2022;43:3175-85.
12. Lorentz IT. A survey of headache in Parkinson's disease. Cephalalgia 1989;9:83-6.
13. Şen HM, Oruç Tunç T, İnan LE. Parkinson Hastalığı ve Baş Ağrısı. Turk J Neuroloji 2014;20:37-40.
14. Nunes JC, Costa Bergamaschi EN, Freitas FC, Diaz AP, Queiroz LP, Debona R, *et al*. Prevalence of headache in patients with Parkinson's disease and its association with the side of motor symptom onset. Neurol Sci 2014;35:595-600.
15. Vilaça C de O, Leite MAA, de Souza JA, Orsini M, Pereira JS, Amaral C. The behavior of migraine in patients with Parkinson's disease. Neurol Int 2015;7:66-9.
16. Barbanti P, Fabbrini G, Vanacore N, Rum A, Lenzi GL, Meco G, *et al*. Dopamine and migraine: Does Parkinson's disease modify migraine course? Cephalalgia 2000;20:720-3.
17. Suzuki K, Okuma Y, Uchiyama T, Miyamoto M, Sakakibara R, Shimo Y, *et al*. The prevalence, course and clinical correlates of migraine in Parkinson's disease: A multicentre case-controlled study. Cephalalgia 2018;38:1535-44.
18. Sampaio Rocha-Filho PA, Leite Souza-Lima CF. Parkinson's disease and headaches: A cross-sectional study. Headache 2020;60:967-73.
19. Angelopoulou E, Papadopoulos AN, Spantideas N, Bougea A. Migraine, tension-type headache and Parkinson ' s Disease : A systematic review and meta-analysis. Medicina 2022;58:1684.
20. Fernández-De-Las-Peñas C, Fernández-Muñoz JJ, Palacios-Ceña M, Parás-Bravo P, Cigarán-Méndez M, Navarro-Pardo E. Sleep disturbances in tension-type headache and migraine. Ther Adv Neurol Disord 2018;11:1-6.
21. Giri S, Tronvik EA, Hagen K. The bidirectional temporal relationship between headache and affective disorders: Longitudinal data from the HUNT studies. J Headache Pain 2022;23:1-10.
22. Duan S, Ren Z, Xia H, Wang Z, Zheng T, Liu Z. Association between sleep quality, migraine and migraine burden. Front Neurol 2022;13:955298.
23. Thomann AE, Berres M, Goettel N, Steiner LA, Monsch AU. Enhanced diagnostic accuracy for neurocognitive disorders: A revised cut-off approach for the Montreal Cognitive Assessment. Alzheimer's Res Ther 2020;12:1-10.
24. Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, *et al*. MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord 2015;30:1591-601.
25. Höglinger GU, Respondek G, Stamelou M, Kurz C, Josephs KA, Lang AE, *et al*. Clinical diagnosis of progressive supranuclear palsy: The movement disorder society criteria. Mov Disord. 2017;32:853-64.
26. Armstrong MJ, Litvan I, Lang AE, Bak TH, Bhatia KP, Borroni B, *et al*. Criteria for the diagnosis of corticobasal degeneration. Neurology 2013;80:496-503.
27. International Headache Society HCC. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia 2018;38:1-211.
28. Stebbins GT, Goetz CG, Burn DJ, Jankovic J, Khoo TK, Tilley BC. How to identify tremor dominant and postural instability/gait difficulty groups with the movement disorder society unified Parkinson's disease rating scale: Comparison with the unified Parkinson's disease rating scale. Mov Disord 2013;28:668-70.
29. Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, *et al*. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Scale presentation and clinimetric testing results. Mov Disord 2008;23:2129-70.
30. Hoehn MM, Yahr MD. Parkinsonism: Onset, progression and mortality. Neurology 1967;17:427-42.
31. Schade S, Mollenhauer B, Trenkwalder C. Levodopa equivalent dose conversion factors: An updated proposal including opicapone and safinamide. Mov Disord Clin Pract 2020;7:343-5.
32. Chaudhuri KR, Martinez-Martin P, Brown RG, Sethi K, Stocchi F, Odin P, *et al*. The metric properties of a novel non-motor symptoms scale for Parkinson's disease: Results from an international pilot study. Mov Disord 2007;22:1901-11.
33. Kroenke K, Spitzer RL, Williams JBW. The PHQ-9: Validity of a brief depression severity measure. J Gen Intern Med 2001;16:606-13.
34. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. Buysse DJ, *et al*. The pittsburgh sleep quality index: A new instrument for psychiatric practice and research. Psychiatry Res 1989;28:193–213.
35. Mehra A, Agarwal A, Bashar M, Grover S. Evaluation of psychometric properties of hindi versions of geriatric depression scale and patient health questionnaire in older adults. Indian J Psychol Med 2021;43:319-24.
36. Avasthi A, Varma SC, Kulhara P, Nehra R, Grover S, Sharma S. Diagnosis of common mental disorders by using PRIME-MD Patient Health Questionnaire. Indian J Med Res 2008;127:159-64.
37. Meco G, Frascarelli M, Pratesi L, Linfante I, Rocchi L, Formisano R. Headache in Parkinson's disease. Headache 1988;28:26-9.
38. Indo T, Naito A, Sobue I. Clinical characteristics of headache in parkinson's disease Headache J Head Face Pain 1983;23:211-3.
39. Kulkarni GB, Rao GN, Gururaj G, Stovner LJ, Steiner TJ. Headache disorders and public ill-health in India: Prevalence estimates in Karnataka State. J Headache Pain 2015;16:67.
40. Akerman S, Goadsby P. Dopamine and migraine: Biology and clinical implications. Cephalalgia 2007;27:1308-14.
41. Akerman S, Holland PR, Goadsby PJ. Diencephalic and brainstem mechanisms in migraine. Nat Rev Neurosci 2011;12:570-84.
42. Wu Y, Guo XY, Wei QQ, Ou RW, Song W, Cao B, *et al*. Non-motor symptoms and quality of life in tremor dominant vs postural instability gait disorder Parkinson's disease patients. Acta Neurol Scand 2016;133:330-7.
43. Ren J, Hua P, Li Y, Pan C, Yan L, Yu C, *et al*. Comparison of three motor subtype classifications in de novo Parkinson's disease patients. Front Neurol 2020;11:601225.

Supplementary Table 1: Comparison of demographic and clinical profile of PD patients with and without improvement of headache

Characteristics	PD with no improvement of headache/ onset of headache after PD onset ($n=12$)	PD with improvement of headache ($n=26$)	*P*
Demographic profile			
Age of presentation (years): median (range)	58.5 (37–75)	63 (39–78)	0.55
Age at onset of parkinsonism (years): median (range)	53 (31–68)	58 (36–73)	0.59
Male gender *n* (%)	7 (58.3)	16 (61.5)	>0.99
Duration of illness (years): median (range)	5 (2–8)	5 (1–8)	0.55
Comorbidities			
DM *n* (%)	2 (16.7)	2 (7.7)	0.58
HTN *n* (%)	3 (25)	6 (23.1)	>0.99
Headache characteristics			
Age of onset of headache (years): median (range)	56 (35–70)	44 (18–56)	0.02
Headache prior to onset of parkinsonism: *n* (%)	1 (8.3)	26 (100)	<0.01
Headache within 1 year	8 (66.7)	3 (11.5)	<0.01
Headache subtype			
TTH *n* (%)	9 (75)	23 (88.5)	0.36
Migraine without aura *n* (%)	3 (25)	3 (11.5)	
Location–bilateral: *n* (%)	7 (58.3)	18 (69.2)	0.51
Duration of headache >6 h *n* (%)	8 (66.7)	21 (80.8)	0.34
Moderate-severe headache (VAS >5) *n* (%)	5 (58.3)	8 (30.8)	0.71
Associated symptoms *n* (%)	2 (16.7)	3 (11.5)	0.64
(Nausea±vomiting±photophobia±phonophobia)	2 (16.7)	1 (3.8)	0.23
Headache frequency	4.5 (1–15)	4 (1–25)	0.72
Parkinsonism characteristics			
MDS-UPDRS-III score (“off” state): median (range)	43.5 (13–67)	38.5 (14–67)	0.28
Hoehn and Yahr stage: median (range)	2.25 (1–4)	2.25 (1–4)	0.89
Levodopa Equivalent Daily Dose (mg): median (range)	500 (500–625)	500 (375–1000)	0.47
Non-motor symptoms scale score: median (range)	34.5 (12–194)	34 (6–79)	0.59
Depressive symptoms (PHQ9 ≥5) *n* (%)	7 (58.3)	11 (42.3)	0.36
Poor sleep quality (PSQI >5) *n* (%)	8 (66.7)	15 (57.7)	0.60
MOCA: median (range)	26.5 (24–30)	26 (24–29)	0.20

MOCA: Montreal Cognitive Assessment; MDS-UPDRS: Movement Disorders Society-Unified Parkinson’s Disease Rating Scale; PD: Parkinson’s disease; PHQ9: Patient Health Questionnaire-9; PSQI: Pittsburgh Sleep Quality Index; PHT: Photophobia; PHN: Phonophobia; PSP/CBD: Progressive supranuclear palsy/corticobasal degeneration; SD: Standard deviation; TTH: Tension-type headache; VAS: Visual Analog Scale

Supplementary Table 2: Comparison of demographic and clinical characteristics among Parkinson's disease patients with and without headache

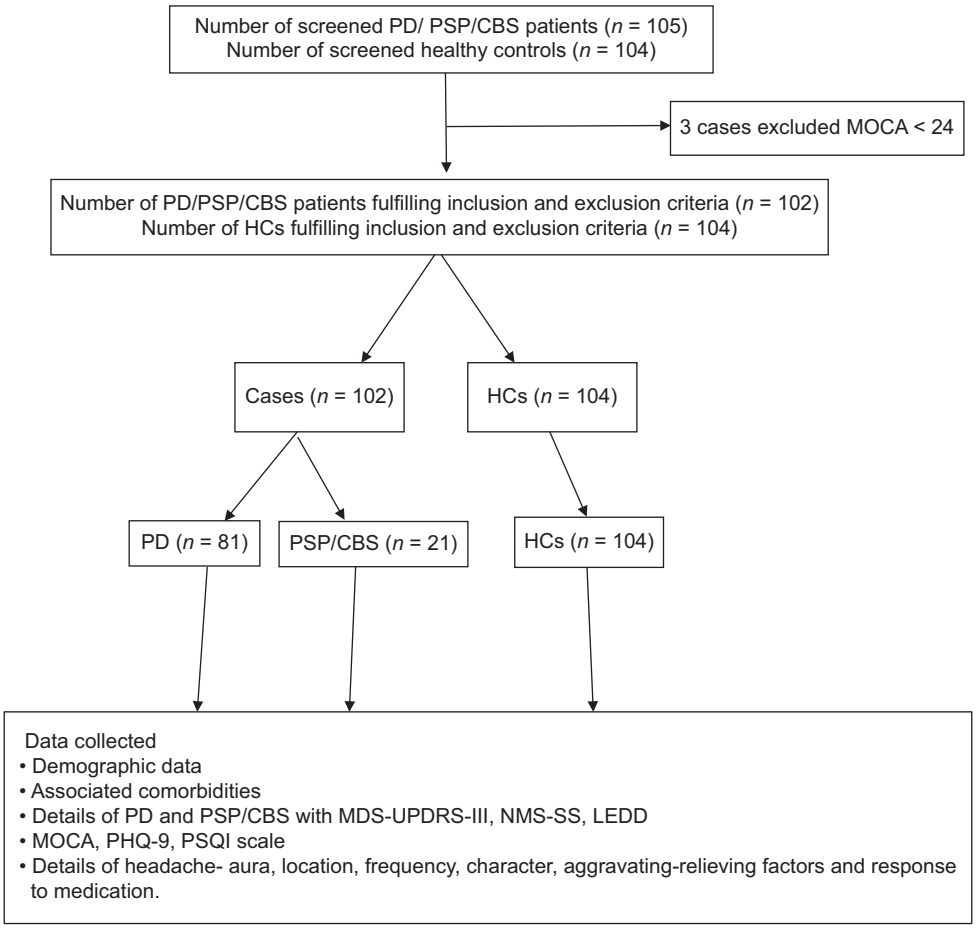
Characteristics	PD with headache (*n*=38)	PD without headache (*n*=43)	*P*
Demographic profile			
Age at onset of PD: median (range)	58 (31–73)	52 (34–72)	0.88
Age at presentation: median (range)	62 (37–78)	62 (35–81)	0.48
Male *n* (%)	23 (60.5)	31 (72.1)	0.27
Duration of disease: median (range)	5 (1–8)	5 (1–17)	0.45
Comorbidities			
Diabetes *n* (%)	4 (10.5)	3 (7.0)	0.70
Hypertension *n* (%)	9 (23.7)	5 (11.6)	0.15
Parkinsonism profile			
MDS-UPDRS III score ("off" state): median (range)	40 (13–67)	34 (7–64)	0.05
Hoehn and Yahr stage: median (range)	2.25 (1–4)	3 (1–4)	0.95
Levodopa Equivalent Daily Dose (mg): median (range)	500 (375–1000)	500 (0–1025)	0.98
Non-motor symptoms scale score: median (range)	34 (6–194)	38 (9–134)	0.36
Depressive symptoms (PHQ9 ≥5) *n* (%)	18 (47.4)	24 (55.8)	0.45
Poor sleep quality (PSQI >5) *n* (%)	23 (60.5)	30 (69.8)	0.38
MOCA : median (range)	26 (24–30)	27 (24–30)	0.06

MOCA: Montreal Cognitive Assessment; MDS-UPDRS: Movement Disorders Society-Unified Parkinson's Disease Rating Scale; PD: Parkinson's disease; PHQ9: Patient Health Questionnaire-9; PSQI: Pittsburgh Sleep Quality Index; SD: Standard deviation; TTH: Tension-type headache; VAS: Visual Analog Scale

Supplementary Table 3: Comparison of clinical characteristics among progressive supranuclear palsy/corticobasal syndrome patients with and without headache

Characteristics	PSP/CBS with headache (*n*=5)	PSP/CBS without headache (*n*=16)	*P*
Demographic profile			
Age at onset of PSP/CBD: median (range)	56 (51–71)	56 (36–79)	0.91
Age at presentation: median (range)	64 (57–72)	62.5 (38-82	0.84
Male *n* (%)	2 (40)	11 (68.8)	0.33
Duration of disease: median (range)	8 (1–10)	4 (2–20)	0.35
Comorbidities			
Diabetes *n* (%)	1 (20.0)	4 (25)	>0.99
Hypertension *n* (%)	4 (80)	0 (0)	-
Parkinsonism profile			
MDS-UPDRS III score ("off" state): median (range)	38 (22–62)	44.5 (16–69)	>0.99
Hoehn and Yahr stage: median (range)	3 (3–4)	3 (1–4)	0.08
Levodopa Equivalent Daily Dose (mg): median (range)	750 (0–1200)	100 (0–750)	0.08
Non-motor symptoms scale score: median (range)	35 (0–54)	30 (0–140)	0.60
Depression (PHQ9 ≥5) *n* (%)	3 (60)	8 (50)	>0.99
Poor sleep quality (PSQI >5) *n* (%)	3 (60)	11 (68.8)	>0.99
MOCA : median (range)	24 (24–27)	24.5 (24–28)	0.72

MOCA: Montreal Cognitive Assessment; MDS-UPDRS: Movement Disorders Society-Unified Parkinson's Disease Rating Scale; PHQ9: Patient Health Questionnaire-9; PSQI: Pittsburgh Sleep Quality Index; PSP/CBS: Progressive supranuclear palsy/corticobasal syndrome; SD: Standard deviation; TTH: Tension-type headache; VAS: Visual Analog Scale



Supplementary Figure 1: CONSORT flowchart for screening, inclusion, and exclusion of cases. HCs: Healthy Controls; LEDD: Levodopa Equivalent Daily Dose; MOCA: Montreal Cognitive Assessment; NMS-SS: Non-motor symptoms scale score; PD: Parkinson's disease; PHQ9: Patient Health Questionnaire-9; PSP/CBS: Progressive supranuclear palsy/corticobasal syndrome; PSQI: Pittsburgh Sleep Quality Index; SD: Standard deviation; MDS-UPDRS: Movement Disorders Society-Unified Parkinson's Disease Rating Scale