Is Nocturnal Panic a Distinct Disease Category? Comparison of Clinical Characteristics among Patients with Primary Nocturnal Panic, Daytime Panic, and Coexistence of Nocturnal and Daytime Panic

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Objective: Many patients with panic disorder (PD) experience nocturnal panic attacks. We investigated the differences in demographic variables and symptom characteristics as well as response to treatment among patients with primary day panic (DP), primary nocturnal panic (NP), and the coexistence of DP and NP (DP/NP), and discuss whether NP is a distinct disease category.

Method: One hundred one consecutive untreated patients with PD were enrolled and subsequently divided into the NP, DP, and DP/NP groups. The presence of 13 panic attack symptom items as well as scores on the Panic Disorder Severity Scale (PDSS) and the Pittsburgh Sleep Quality Index (PSQI) were compared among the groups. After 3 months of regular treatment, PDSS scores were assessed again to evaluate treatment response.

Results: Nocturnal panic attacks of the participants were mostly reported to occur in the first tertile of nocturnal sleep. The number of males, onset age, and presence of choking sensation were significantly higher, and the PDSS score was

significantly lower in the NP group compared with the other groups. The DP/NP group showed the highest PDSS score, and participants in this group were prescribed the highest doses of medication among all groups. Only diagnostic subcategory was significantly associated with treatment response. The total score for PDSS and PSQI correlated significantly only in the NP group.

Conclusions: DP/NP could be a severe form of PD, while primary NP could be a relatively mild subcategory that may partially share common pathophysiology with adult type night terror.

Keywords: Panic disorder, nocturnal panic, the Panic Disorder Severity Scale (PDSS), the Pittsburgh Sleep Quality Index (PSQI)

Citation: Nakamura M; Sugiura T; Nishida S; Komada Y; Inoue Y. Is nocturnal panic a distinct disease category? Comparison of clinical characteristics among patients with primary nocturnal panic, daytime panic, and coexistence of nocturnal and daytime panic. *J Clin Sleep Med* 2013;9(5):461-467.

Panic disorder (PD) is an anxiety disorder characterized by recurrent daytime panic (DP) attacks (primary DP).¹ However, some patients who fulfill the clinical criteria for PD experience panic attacks mainly during the nocturnal sleep period.²⁻⁴ These nighttime attacks occur without any obvious triggers during periods of sleep-wake transition and are referred to as nocturnal panic (NP) attacks.⁵ In general, 18% to 45% of PD patients experience both DP and NP attacks (DP/NP).^{6,7} Meanwhile, there are a considerable number of patients who have panic attacks only during the nocturnal sleep period (primary NP). However, most previous reports have not mentioned the clinical characteristics of primary NP, except for one report in which the response to pharmaceutical treatment in such patients was discussed.⁷ Mainly due to the lack of this information, the Diagnostic and Statistical Manual of Mental Disorders-IV-Text Revision (DSM-IV-TR)⁸ has not clarified whether NP alone should be included within the PD category. Similarly, the description of PD in the International Classification of Sleep Disorders, 2nd edition,⁹ does not address this issue.

Previous studies have suggested that individuals with NP have more frequent panic attacks, more severe anxiety symptomatology,^{6,10} and higher rates of comorbid depression, which may lead

BRIEF SUMMARY

Current Knowledge/Study Rationale: Many patients with panic disorder experience nocturnal panic attack during sleep time (coexistence of day panic and nocturnal panic attacks: DP/NP), and some patients have panic attacks mainly during the nocturnal sleep period (primary nocturnal panic: NP). The aim of this study was to discuss whether NP is a distinct disease category from DP/NP.

Study Impact: NP was differ from DP/NP in demographic and clinical characteristics. Our findings suggest that DP/NP could be a severe form of panic disorder, while NP could be a relatively mild subcategory partially sharing common pathophysiology with adult type night terror.

to an increased risk of suicide compared with those without NP.¹¹ However, these comparisons were mainly made on patients with DP/NP and those with primary DP. Meanwhile, one study that included both primary NP and DP/NP demonstrated no differences between NP and primary DP in terms of frequency of comorbid depression.¹² Thus, the clinical significance of primary NP as well as that of DP/NP remains unclear, although it is possible that the latter is a severe subcategory of PD.

This study set out to compare clinical characteristics including demographic variables, panic symptom items, severity of

PD, subjective sleep disturbances, and response to treatment for PD among patients with primary NP, primary DP, and DP/NP. Based on the results, we discuss whether primary NP is a subcategory of PD distinct from DP or DP/NP.

METHODS

Participants

This retrospective study was approved by the ethics committee of the Neuropsychiatric Research Institute, and all patients gave written informed consent to participate.

The study comprised 101 consecutive untreated individuals seeking treatment for panic-anxiety symptoms (56 males, 45 females; mean age 36.9 ± 9.9 years) who visited the outpatient clinic of Japan Somnology Center and Seiwa Hospital, both of which are affiliated with the Neuropsychiatric Research Institute (Tokyo, Japan) from May 2003 to January 2008. Some of the patients (most with primary NP) were referred to our clinic with suspicion of obstructive sleep apnea syndrome (OSAS). However, results of clinical interviews and screening with a portable device as described below indicated that they had neither habitual snoring nor pathological apnea. Based on this, attending physicians judged that the core symptoms of these patients were panic-anxiety rather than OSAS. Eighty-nine of the patients met the diagnostic criteria of PD with and without agoraphobia by the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Forth Edition). The remaining 12 patients (all of them in the NP group) had limited panic attacks with ≤ 3 panic attack symptom items, and none of the NP patients reported experiencing nightmares with the episodes of panic anxiety during sleep.

After diagnosis of PD, all patients received regular pharmacological treatment over 3 months with fixed doses of medication for at least 1 month before the investigation. The treatment drug was determined individually based on the decision of the attending physician. No patients had abnormal findings on physical or laboratory examinations at their first visit, or had a current or previous diagnosis of other psychiatric disorders, psychoactive substance abuse, respiratory disease, cardiovascular disease, thyroid disease, or OSAS.

With regard to OSAS, all patients were screened with a portable device (Stardust, Respironics; Murrysville, PA, USA) including 4 channels (airflow monitoring with pressure sensor, respiratory movements, oxyhemoglobin saturation, and heart rate) for 1 night.¹³ All patients had a respiratory disturbance index $< 5/h$, and only a few had episodes of airflow limitation.

The disease course of PD was evaluated by psychiatrists with expertise in sleep disorders who performed detailed interviews with patients and their bed partners, if necessary. NP attacks were determined when a patient experienced an abrupt and uncomfortable sensation and fear immediately upon waking from nocturnal sleep, when symptoms were not attributable to frightening dreams, external interruptions, or other sleep disorders such as nightmares, night terrors, sleep paralysis, hypnopompic hallucinations, or choking associated with sleep apnea.¹⁴

We divided the patients into 3 groups with the main purpose of differentiating NP and NP/DP. Patients with primary DP in whom the rate of frequency of NP attacks to total panic attacks

was less than 25% during the 3 months before the first visit, as noted by themselves and/or their bed partners, were placed in the DP group ($n = 41$). Patients with primary NP in whom the rate of the frequency of NP attacks to total panic attacks was $\geq 75\%$ were placed in the NP group ($n = 40$), and patients with coexistence of DP and NP (rate of frequency of NP attacks was from 25% to 50% of all panic attacks) were placed in the DP/NP group ($n = 20$). No patient had a rate of frequency of NP attacks to total panic attacks of 50% to 75%.

Measurements

Before starting treatment, patients were interviewed regarding the occurrence of 13 panic attack symptoms listed by the DSM-IV-TR. The items were (1) palpitations, pounding heart, or accelerated heart rate; (2) sweating; (3) trembling or shaking; (4) sensations of shortness of breath or smothering; (5) feeling of choking; (6) chest pain or discomfort; (7) nausea or abdominal distress; (8) feeling dizzy, unsteady, lightheaded, or faint; (9) derealization or depersonalization; (10) fear of losing control or going crazy; (11) fear of dying; (12) paresthesia; and (13) chills or hot flashes. The Panic Disorder Severity Scale (PDSS), a self-rating scale, was used by patients to assess the severity of PD with 7 items scored on a scale of 0 to 4 and total score ranging from 0 to 28.¹⁵ This scale has sufficiently high reliability, with a Cronbach α of 0.86; a total score > 16 corresponds to severe panic disorder in the Japanese version.¹⁶ Subjective sleep conditions were assessed using the self-rating Pittsburgh Sleep Quality Index (PSQI).¹⁷ The PSQI is an effective instrument to evaluate subjective sleep disturbance by measuring 7 domains. Scoring is based on a 0 to 3 scale for each domain. A global sum score (ranging 0 to 21) ≥ 5.5 indicates a poor sleep quality in Japanese (Cronbach $\alpha = 0.77$) individuals.¹⁸

Patients with NP were asked about the distribution of NP attacks in the first, second, and third tertiles of their nocturnal sleep. As with DP attacks, the frequency of NP attacks were assessed and expressed using the score on item 1 (frequency of panic attacks) on the PDSS (e.g., 0: no panic attacks, 1: < 1 attack per week and ≤ 1 attack per day, 2: 1-2 attacks per week and/or many attacks per day, 3: ≥ 2 attacks per week and ≤ 1 attack per day, 4: ≥ 1 attack per day, more days than not).

After 3 months of treatment for PD, PDSS was evaluated again in all patients to determine their therapeutic response. As an indicator of treatment response, we calculated the reduction rate of PDSS with treatment ($[\text{pre-treatment PDSS total score}] - [\text{post-treatment PDSS total score}] / [\text{pre-treatment PDSS total score}]$).

Medication

All patients were treated pharmacologically. No types of psychotherapies such as cognitive behavioral therapy were used during the study. The following drugs were used: selective serotonin reuptake inhibitors, including paroxetine (10 to 40 mg/day), fluvoxamine (25 to 100 mg/day), and sertraline (25 to 50 mg/day); tricyclic antidepressants (25 to 75 mg/day of imipramine or amitriptyline); benzodiazepine anxiolytics including alprazolam (0.4 to 1.6 mg/day), ethyl loflazepate (1 to 2 mg/day), lorazepam (0.5 to 3 mg/day), clonazepam (5 to 30 mg/day), and etizolam (0.5 to 3 mg/day); and benzodiazepine or benzodiazepine agonist hypnotics including triazolam (0.125 to 0.25 mg/day), flunitrazepam (1 to 2 mg/day), brotizolam

Table 1—Descriptive variables by group

Characteristic	DP (n = 41)			DP/NP (n = 20)			NP (n = 40)		
	M	SD	%	M	SD	%	M	SD	%
Female			56.1			55.0			27.5 [†]
Onset age (year)	30.6 ^{a,**}	6.8		26.5 ^{a,**}	7.5		40.4	9.5	
Duration of PD morbidity	2.0 ^{a,*}	1.1		3.8	6.2		4.3	2.5	

DP, day panic group; DP/NP, the coexistence of day panic and nocturnal panic; NP, primary nocturnal panic. [†]Post hoc cell contribution test showed a significantly lower rate of female ($p < 0.05$). ^avs NP, * $p < 0.05$, ** $p < 0.01$.

(0.25 mg/day), zopiclone (7.5 to 10 mg/day), and zolpidem (5 to 10 mg/day). The daily doses of antidepressants were calculated according to the imipramine-equivalent dose, and those of anxiolytics and hypnotics were calculated on the basis of diazepam-equivalent dose.¹⁹

Data Analysis

Continuous variables including demographics were compared among groups using analysis of variance (ANOVA) followed by post hoc Bonferroni corrections. Statistical analyses of categorical variables (gender, distribution of NP in each tertile of nocturnal sleep period, and presence of each panic attack symptom) among groups were made using the χ^2 test with cell contribution rate test as the post hoc rest error test. The post hoc cell contribution rate test is a form of standardized rest-error test that provides significance information among groups when the absolute value exceeds 1.96. Backwards stepwise multiple regression analysis was used to investigate factors associated with the reduction rate in PDSS score after treatment. Diagnostic subcategories which were dummy coded with d1 (pure NP or not; 0: DP and DP/NP, 1: NP) and d2 (pure DP or not; 0: NP and DP/NP, 1: DP), self-reported onset age of the disorder, gender, pretreatment total scores of PDSS and PSQI, and daily dosage of medication (antidepressants, anxiolytics, and hypnotics) were included as independent variables. The correlation between PDSS and PSQI scores in the 3 groups was estimated using Spearman rank correlation coefficient. A p value < 0.05 was considered statistically significant. Data analyses were made using SPSS version 10 (SPSS Inc., Chicago, IL, USA).

RESULTS

Descriptive Variables

Based on detailed clinical interviews, it was confirmed that the first attacks occurred during the nocturnal sleep period in all NP patients, and during the daytime in DP and DP/NP patients. The NP group included a significantly larger number of male patients than DP and DP/NP groups (**Table 1**). The self-reported age of onset of PD was significantly different among groups (df: 2, F -value: 33.3, $p < 0.01$), and post hoc test revealed that the onset age in the NP group was significantly higher than that in the other 2 groups. Duration of PD morbidity was also significantly different among groups (df: 2, F -value: 5.07, $p < 0.05$), and the duration in NP group was significantly longer than in the DP group. In the DP/NP group, the duration did not differ significantly from the other 2 groups.

Distribution of NP Attacks during Sleep

NP attacks were reported to occur predominantly in the first tertile of nocturnal sleep in both the NP group (32/40, 80%) and the DP/NP group (14/20, 70%). The distribution of tertiles in which attacks mainly occurred did not differ significantly between these 2 groups (first/second/third tertile: NP = 32/6/2, DP/NP = 14/5/1, $p = 0.64$).

Presence of Panic Attack Symptoms before Treatment

Chi-square test revealed that the presence of all PD symptoms except palpitations, sweating, sensation of shortness of breath or smothering, and paresthesias significantly differed among the groups before treatment. Rest error test revealed that the NP group had the highest rate of feelings of choking (DP: 23/41, DP/NP: 15/20, NP: 35/40; $p < 0.01$; $\chi^2(2) = 10.06$, $p < 0.01$). However, in this group, symptoms of trembling or shaking, chest pain or discomfort, nausea or abdominal distress, feeling dizzy, derealization or depersonalization, fear of losing control or going crazy, fear of dying, and chills or hot flashes were lowest. On the other hand, the DP group had a significantly higher rate for symptoms of trembling or shaking (DP: 18/41, DP/NP: 8/20, NP: 6/40), chest pain or discomfort (DP: 24/41, DP/NP: 12/20, NP: 9/40), nausea or abdominal distress (DP: 12/41, DP/NP: 5/20, NP: 2/40), feeling dizzy (DP: 20/41, DP/NP: 8/20, NP: 6/40), fear of losing control or going crazy (DP: 24/40, DP/NP: 12/20, NP: 9/40), fear of dying (DP: 27/41, DP/NP: 14/20, NP: 11/40), and chills or hot flashes (DP: 18/41, DP/NP: 6/20, NP: 7/40) compared with the other groups. In the DP/NP group, the rate of derealization or depersonalization was significantly higher than in the other groups (DP: 17/41, DP/NP: 12/20, NP: 7/40). In terms of the total number of symptoms, the NP group showed a significantly lower number than the other 2 groups (DP: 6.7 ± 1.8 , DP/NP: 7.1 ± 2.2 , NP: 4.3 ± 2.2 ; df: 2, F -value: 25.55, $p < 0.01$, $p < 0.01$ vs DP, $p < 0.01$ vs DP/NP, respectively).

PDSS and PSQI Scores before Treatment

The total PDSS score and all sub-item scores of the PDSS were significantly different among the groups (**Table 2**). Post hoc tests revealed that all the sub-item scores as well as the total score in the DP/NP group were significantly higher than in the NP group. Scores for frequency of panic attacks, anticipatory anxiety, agoraphobic fear and avoidance, and total score were also significantly higher in the DP/NP group than in the DP group. The NP group showed significantly lower scores than the DP group in terms of agoraphobic fear and avoidance, interoceptive fear and avoidance, impairment of

Table 2—PDSS scores before treatment

	DP		DP/NP		NP	
	M	SD	M	SD	M	SD
1:Frequency of panic attacks	2.4	0.7	3.0 ^{a,*b,*}	0.7	2.4	0.7
2:Distress during panic attacks	2.1	0.7	2.5 ^{b,*}	1.0	1.8	0.7
3:Anticipatory anxiety	2.0	0.7	2.5 ^{a,*b,**}	0.8	1.8	0.7
4:Agoraphobic fear and avoidance	1.7	0.9	2.4 ^{a,*b,**}	0.6	1.2 ^{a,**}	0.7
5:Interceptive fear and avoidance	2.2	0.8	2.2 ^{b,**}	0.8	0.4 ^{a,**}	0.5
6:Impairment of work functioning	1.1	0.8	1.2 ^{b,**}	0.9	0.1 ^{a,**}	0.3
7:Impairment of social functioning	0.9	0.8	1.3 ^{b,**}	0.8	0.1 ^{a,**}	0.2
Total Score	12.4	2.4	15.0 ^{a,**b,**}	2.8	7.7 ^{a,**}	2.3

DP, day panic group; DP/NP, day panic and nocturnal panic group; NP, nocturnal panic group. ^avs DP, ^bvs NP, *p < 0.05, **p < 0.01.

Table 3—PSQI scores (pre-treatment scores)

	DP		DP/NP		NP	
	M	SD	M	SD	M	SD
C1:Subjective sleep quality	1.3	0.7	1.7 ^{a,**}	0.7	1.0	0.9
C2:Sleep latency	0.7	0.6	1.2	0.9	1.0	0.8
C3:Sleep duration	1.0	0.9	1.5	0.8	1.1	0.8
C4:Habitual sleep efficiency	0.7	0.8	0.9	0.7	0.4	0.6
C5:Sleep disturbances	0.9 ^{a,**}	0.9	0.7 ^{a,**}	0.7	1.5	0.8
C6:Use of sleeping medicine	0.6	1.0	0.9	1.3	0.6	1.0
C7:Daytime dysfunction	0.7	0.8	0.8	0.9	0.7	0.9
Total Score	5.9	3.0	7.6	2.5	6.2	3.1

DP, day panic group; DP/NP, day panic and nocturnal panic group; NP, nocturnal panic group. ^avs NP, *p < 0.05, **p < 0.01.

Table 4—Daily doses of medication

	DP		DP/NP		NP	
	M	SD	M	SD	M	SD
Doses of antidepressants (mg)	85.6	19.4	116.1 ^{a,**b,**}	27.0	41.4 ^{a,**}	16.3
Doses of anxiolytics (mg)	10.7	9.1	14.8 ^{b,**}	10.5	1.9 ^{a,**}	3.0
Doses of hypnotics (mg)	1.5	2.5	4.6 ^{a,**b,**}	3.8	0.1 ^{a,*}	0.6

DP, day panic group; DP/NP, day panic and nocturnal panic group; NP, nocturnal panic group. The dose equivalents of psychotropic drugs were calculated according to the report by Inagaki A et al.¹⁶ The doses of antidepressants are presented in mg basis of imipramine, and those of anxiolytics and hypnotics are presented in mg basis of diazepam. ^avs DP, ^bvs NP, *p < 0.05, **p < 0.01.

work functioning, impairment of social functioning, and total score. On the comparison result of PDSS (after excluding the 12 patients with limited panic attacks), the total PDSS score of NP (7.7 ± 2.3) was also lower than DP and DP/NP (p < 0.01, p < 0.01, respectively).

The total PSQI score did not differ significantly among the groups (**Table 3**). However, the scores of subjective sleep quality (C1), habitual sleep efficiency (C4) and sleep disturbance (C5) differed significantly among the 3 groups. Post hoc Bonferroni testing showed that the score of C5 was higher in NP group than in DP group and DP/NP group, and that DP/NP group showed higher score of subjective sleep quality (C1) than that of NP group (**Table 3**). As with the PDSS score, the total score of PSQI did not differ among these 3 groups (excluding the 12 patients with limited panic attacks). The total scores for PDSS and PSQI correlated significantly in the NP group (r = 0.59, p < 0.001), but not in the other

groups (DP group, r = 0.30, p = 0.06; DP/NP group, r = 0.14, p = 0.59).

Medications and Treatment Response

As shown in **Table 4**, the final daily doses of antidepressants, anxiolytics, and hypnotics differed significantly among the groups. Multiple comparisons by the Bonferroni test indicated that the DP/NP group received significantly higher daily doses of antidepressants and hypnotics than the other 2 groups. As for anxiolytics, the daily dose was not significantly different between the DP/NP group and DP group (p = 0.16), but was significantly lower in the NP group compared with the other 2 groups (p < 0.01 vs DP/NP, p < 0.01 vs DP).

After 3 months of treatment, all groups showed significant improvements in PDSS total score (p < 0.01 DP, p < 0.01 DP/NP, p < 0.01 NP) (**Table 5**). ANOVA revealed significant differences among groups for the reduction rate in PDSS score

Table 5—Change in PDSS score with treatment

	Pre-treatment PDSS score		Post-treatment PDSS score		Reduction rate (%) [†]	
	M	SD	M	SD	M	SD
DP	12.4	2.4	6.8	2.5	43.8 ^{a,*}	20.7
DP/NP	15.0	2.8	8.1	2.6	45.6 ^{a,*}	14.7
NP	7.7	2.2	1.7	1.7	76.6	25.9

DP, day panic group; DP/NP, day panic and nocturnal panic group; NP, nocturnal panic group. [†]Reduction rate = [(pre-treatment score) – [post-treatment score)] / [pre-treatment score]. ^avs NP, *p < 0.01.

(df: 2, F-value: 25.92, p < 0.01), with the NP group showing a significantly greater reduction in score than the other 2 groups (p < 0.01). No significant difference in the reduction rate was found between the DP/NP group and DP group.

Stepwise multiple regression analysis showed that only the diagnostic subcategory (pure NP was dummy coded as d1) was significantly associated with the reduction rate in PDSS score (p < 0.01, B-hat = -0.32, with intercept B-hat = 0.76, p < 0.01)

DISCUSSION

This study investigated differences in clinical features among three panic disorder subcategories stratified based on presence/absence of nocturnal or daytime panic attack. The results revealed significant differences in demographics, severity of the disorder, and response to pharmacological treatment among the groups.

Several epidemiological studies have shown that the prevalence of PD is higher in females than in males, and that the mean age of onset of PD is in the 20s and 30s.^{20,21} These demographic characteristics were recognized in the DP group and DP/NP group in our study. However, of note, the NP group showed a clear male predominance and significantly later age of onset than the other two groups. The patients with OSAS, which develops most frequently in middle-aged males, occasionally wake up with choking sensation during nocturnal sleep. However, OSAS was completely ruled out in the participants of the present study by examination with a portable device together with thorough clinical interviews. In addition, we excluded the possibility of upper airway resistance syndrome based on a lack of flow limitation on the air flow pressure sensor of the portable device.²² Moreover, the NP group had a significantly longer self-reported duration of the disorder than previously reported by Levitan,²³ but had a milder severity of the disorder evaluated with the PDSS score at their first visit compared with the other two groups, even after excluding 12 patients with limited panic attacks, suggesting that a majority of NP patients remain stable in mild severity and symptoms do not become progressively more severe. Taking these findings together, primary NP can be considered a mild subcategory of PD with slow progression that is likely to occur among a middle-aged male population.

Many previous studies have indicated that PD patients with NP attacks experience significantly more frequent and severe panic symptoms^{6,11,24} and more depressive and other psychiatric symptoms.²⁵ However, in contrast to the findings in this

study, sociodemographic characteristics did not differ between patients with and without NP attacks in these studies.^{4,6,11,24,25} The reason for this discrepancy is unknown. However, in most previous studies, the definition of NP was primarily made based on the answer to a one-item screening questionnaire such as “Have you ever been woken from your sleep by a panic attack?”¹⁴ Thus, it is possible that NP reported in previous studies included many patients with DP/NP who actually may have had a younger age of onset and a female predominance with higher PD severity, as seen in the present study.

Nocturnal panic attacks have been reported to occur during NREM sleep, especially during delta sleep.² However, no study has ascertained the distribution of panic attacks among tertiles of nocturnal sleep. Interestingly, most patients with NP or DP/NP in the present study reported that their NP attacks occurred mainly in the first tertile. Although we did not perform polysomnographic evaluations of sleep structure among the patients, in general, delta sleep occurs mainly in the early part of sleep.²⁶ Thus, our results could be consistent with the previous report showing that NP attacks are likely to occur during delta sleep.² With regard to the nocturnal distribution of events, NP in our patients seemed to share common characteristics with sleep terrors, which occur during the transition period of arousal from slow wave sleep, mainly in the early part of the night. These two disorders also share common symptoms, such as autonomic symptoms including tachycardia, acute respiratory distress, sweating, and intense fear.²⁷ It has been reported that a considerable number of patients with sleep panic have a history of sleep terrors in their early childhood,²⁸ and that respiratory symptoms frequently appear during episodes of night terrors in adults.²⁹ Given these findings, it is possible that the pathophysiological mechanism of sleep panic attacks is related to that of adult type sleep terrors, although there is a clear difference in that patients are fully aroused and conscious during sleep panic episodes, while night terror occurs under the condition of clouded consciousness. Further research comparing polysomnographic variables and subjective symptoms between NP and adult type sleep terror is needed to clarify this issue.

In the present study, primary NP patients had fewer panic attack symptom items than patients in other groups. However, feelings of choking occurred in a significantly larger number of patients in the NP group than in the other groups. This finding is compatible with previous reports, suggesting that respiratory symptoms such as choking or shortness of breath are specifically common in NP.^{30,31} Thus, a respiratory symptom during sleep may be a primary symptom in the NP group.

The milder form of PD in the NP group compared with the other groups was thought to be attributable to the lower score for agoraphobic or interoceptive fear and avoidance and lower scores for both impairment of work functioning and social functioning in this group. The reasons for these findings are unclear.

Overall, primary NP patients did not have a tendency toward disturbance in initiation and/or maintenance of sleep (insomnia), although they experienced attacks mainly during sleep. However, the severity of panic symptoms during sleep time in the NP group as manifested on the PDSS was significantly correlated with sleep disturbance measured with the PSQI. Considering that there was no significant correlation between PDSS and PSQI in either DP or DP/NP patients, the PD severity-dependent aggravation of sleep disturbance may be a specific clinical characteristic of primary NP.

In the present study, all three groups showed an improvement of PD symptoms with standard treatment including antidepressants, anxiolytics, and hypnotics. However, the dosages of antidepressants and benzodiazepine anxiolytics as well as hypnotics used for the treatment were significantly lower in the NP group than in the DP and DP/NP groups. Moreover, the reduction rate of PDSS with the treatment in this group was significantly higher than that of the other groups. In addition, among the descriptive variables, only the diagnosis of primary NP *per se* was significantly associated with a higher reduction rate of PDSS, possibly suggesting a better treatment response in this group. These findings could indicate that primary NP is most responsive to treatment among the three groups.

On the other hand, similar to the findings of a study by Agargun and Kara,¹¹ the DP/NP group in our study showed the highest values in terms of number of panic attack symptoms and total PDSS score. Moreover, among the three groups, the DP/NP group received the highest doses of both antidepressants and hypnotics as treatment. These findings strongly impress that DP/NP is the most severe and treatment-resistant subcategory of PD.

This study has several limitations. First, since the Japan Somnology Center mainly treats patients with sleep-related disorders, referral bias could exist. Thus, the sample of NP in our study might not be a representative of the general NP population. Second, there might be recall bias, especially regarding subjective distribution of panic attacks in subjects. Third, the assessment of depressive symptoms may be necessary because depression is frequently comorbid with panic attacks and would affect the severity of panic symptoms. Fourth, this study was an observation-based study, and we need further study with simultaneous measurement of autonomic system markers and polysomnographic recordings to investigate of the nature of the physiological change that occurs during episodes of NP.

In conclusion, NP attacks are likely to occur in the first tertile of the nocturnal sleep period both in NP and DP/NP. However, primary NP is thought to be a mild and treatment-responsive subgroup of PD, while DP/NP patients showed severe PD symptoms and the worse treatment response. Identification of these two NP categories would be helpful for making better treatment plans.

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ACKNOWLEDGMENTS

The authors thank their colleagues at the Japan Somnology Center for their helpful comments on this manuscript. This work was supported by JSPS KAKENHI Grant Number 23791374 (Grant-in-Aid for Young Scientists [BJ]). Preliminary results were presented at the 29th Congress of the Japanese Society for Psychiatric Diagnosis on October 17th, 2009, in Tokyo.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication May, 2012

Submitted in final revised September, 2012

Accepted for publication October, 2012

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DISCLOSURE STATEMENT

This was not an industry supported study. The authors have indicated no financial conflicts of interest.