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## Clinical features and outcomes of new daily persistent headache in patients in China and comparison with medication-overuse headache: a double-center retrospective study

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### Declarations

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### Abstract

**Background:** *This study examined the clinical features and outcomes of NDPH patients and comparison with medication-overuse headache (MOH) in Mainland China.*

**Methods:** *This retrospective study observed patients with NDPH and medication-overuse headache (MOH) visiting two outpatient clinics between November 2011 and December 2019. Clinical information was collected and all patients were followed by telephone.*

**Results:** *The study recruited 73 NDPH and 638 MOH patients. The NDPH patients included 39 males (39/73, 53.4%) and 34 females (34/73, 46.6%), with an average age of 37.4 years and average headache duration of 10.6 years. Headache-precipitating factors included infection (11/73, 15.1%) and stress (22/73, 30.1%). Compared to MOH patients, NDPH patients had a male predominance (53.4% vs. 22.6%,  $p < 0.001$ ), younger age of CDH onset ( $26.7 \pm 12.3$  vs.  $41.4 \pm 11.3$  years,  $p < 0.001$ ), and longer duration of CDH ( $10.6 \pm 11.8$  vs.  $6.1 \pm 6.2$  years,  $p = 0.023$ ). In 62 NDPH patients followed up for 31 months, on average, therapeutic responses were more effective in NDPH patients with trigger factors than in those without trigger factors (71.4% vs. 32.4%;  $p = 0.002$ ); the odds ratio (OR) of an effective outcome was 5.25 (1.73–17.84,  $p = 0.005$ ).*

**Conclusions:** NDPH is significantly different from MOH, with a male predominance, younger age of CDH onset, and longer duration of CDH. The presence of trigger factors is an independent predictor of better treatment effect in NDPH patients.

**Key words:** new daily persistent headache, medication overuse headache, clinical features, prognosis.

## Introduction

New daily persistent headache (NDPH) is a relatively rare primary headache characterized by daily onset and a lack of quick remission; NDPH does not have a specific treatment, and patients invariably recall and can accurately describe its onset [1]. NDPH is also a disabling disease that may affect the quality of life of individuals and threaten public health [2]. According to the International Classification of Headache Disorders 3<sup>rd</sup> edition (ICHD-3), the diagnostic criteria for NDPH include the following: A. persistent headache fulfilling criteria B and C; B. distinct and clearly remembered onset, with pain becoming continuous and unremitting within 24 hours; C. present for >3 months; D. not better accounted for by another ICHD-3 diagnosis [1]. As the most refractory headache disorder, NDPH accounts for 1.7–10.8% of cases of chronic daily headache (CDH) in adult patients [3, 4], and data from China represent 3.6% of patients with CDH [5]. Although some countries and regions have summarized the clinical features, trigger factors and prognosis of NDPH, detailed data of NDPH from mainland China are lacking.

Medication-overuse headache (MOH) occurs in patients with preexisting primary headache due to frequent and long-term use of acute or symptomatic headache medication, which leads to aggravated headache or the emergence of new headache types [1]. MOH accounts for 11–70% of the patients with CDH [6] and epidemiology data from China accounts for 60% of patients with CDH [7]. Although there was a previous study comparing chronic migraine (CM) with NDPH [8], the enrolled participants were children and adolescents, and there is a lack of studies in adult patients. NDPH and MOH are two different types of headaches that have significantly different prevalence in CDH. Basically, NDPH is a rare type of CDH, while MOH is the most common type [5]. Comparing NDPH with MOH may provide some novel information about clinical features of NDPH. Therefore, the present study aimed to provide comprehensive data on the clinical features and outcomes of NDPH patients and comparison MOH in mainland China. Additionally, the predictor factors for treatment efficacy are also involved.

## Subjects and methods

### Study design

This was a retrospective analysis of patient medical records and a phone interview was used for follow-up. Patients who were admitted to the neurology outpatient clinics of Chinese PLA General Hospital (Professor Zhao Dong) and Shandong Provincial Hospital (Professor Chunfu Chen) between November 2011 and December 2019 and who diagnosed with NDPH were recruited. MOH patients visiting the two clinics during the same period were also involved. All enrolled patients were reexamined by another headache specialist (Professor Shengyuan Yu). Patients with MOH met the diagnostic criteria of MOH according to ICHD-3 criteria. The inclusion criteria for NDPH were as follows: (1) met the NDPH diagnostic criteria according to ICHD-2,3; and (2) underwent neuroimaging (MRI with gadolinium) and fundoscopy examination. The exclusion criteria for NDPH were as follows: (1) increasing headache frequency prior to persistent headache; (2) possible secondary headache, such as headache after trauma and headache after intracranial diseases; (3) abnormal neuroimaging, which can account for persistent headache; and (4) papilledema. All headache patients have been recommended to keep a headache diary and instructed to how to correctly record.

The patients who were unconnected and treated for less than 3 months were not included in the analysis of treatment responses and prognostic factors. The clinical response to drug-based treatment was assessed by the patients themselves based on reducing the number of headache days and alleviating headache intensity. Treatment outcome was defined subjectively as “effective” when a patient felt >50% improved and “not effective” when improvement was <50% or the patient was unchanged. NDPH patients were divided into two group according to the treatment outcome. To assess the relationship between the treatment outcome and headache duration, the patients were categorized into two groups: NDPH (6–24 months) and NDPH (>24 months). Another demographic and clinical characteristics factors were included in the analysis.

This study was approved by the ethics committee of Chinese PLA General Hospital and Shandong Provincial

Hospital. Due to the retrospective nature of the study, according to the Declaration of Helsinki of the World Medical Association, verbal informed consent was obtained from the all patients before being included in the study.

### Data collection

All of the patients' medical records collected via a unified chart, which included the following information: (1) demographic characteristics (sex, age, age of CDH onset and education level); (2) the clinical features of the headache (main headache site, severity, frequency, associated feature, pain character and aggravation after activity); (3) the type, frequency and duration of pain reliever use; and (4) comorbid diseases, such as anxiety and depression based on the GAD-7 and PHQ-9 scales. Headache severity was assessed based on the visual analog scale (VAS).

### Statistical analysis

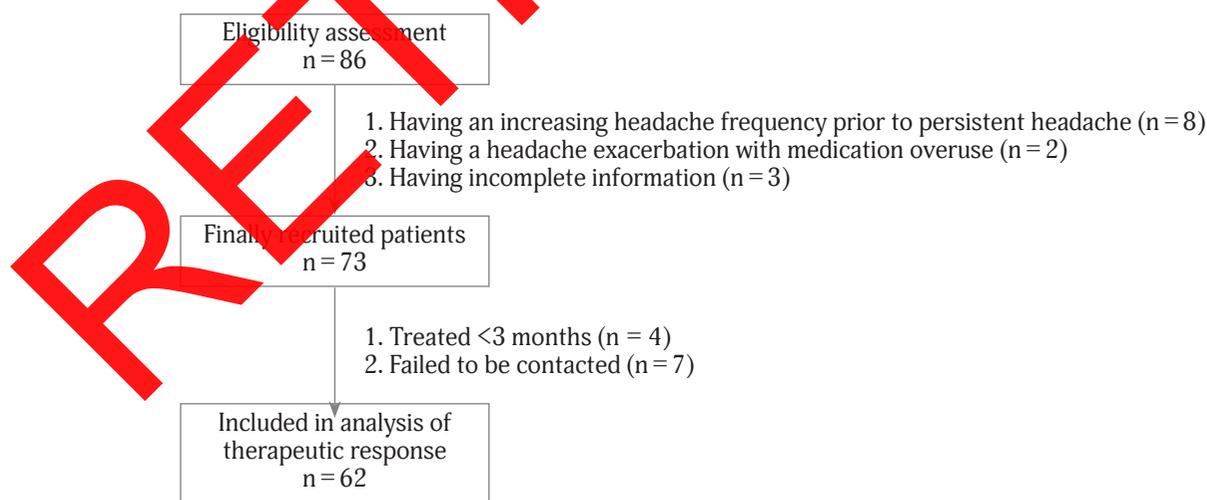
All continuous measurements conforming to a normal distribution are presented as the mean  $\pm$  standard deviation (SD). Nonnormally distributed continuous variables are indicated with medians and quartiles. Categorical variables are presented as rates. The chi-square test or Fisher's exact test was performed for categorical data, and the Wilcoxon test was performed for nonnormally distributed continuous variables. In order to clarify whether a variable is an independent factor, the variable with a  $p < 0.05$  was included in nonconditional logistic regression analysis. The data were analyzed using SPSS for Windows, Version 21.0 (IBM Company, Chicago, Illinois in the United States);  $p < 0.05$  was considered indicative of statistical significance.

## Results

A total of 76 patients with a diagnosis of NDPH initially, including 53 cases from the Chinese PLA General Hospital and 23 cases from Shandong Provincial Hospital, were enrolled. Three patients were excluded because of incomplete information. Finally, a total of 73 patients were recruited in this retrospective study (Fig. 1). A total of 55 (75.3%) patients fulfilled the NDPH diagnostic criteria of ICHD-2. Moreover, we recruited 638 patients with a diagnosis of MOH during the same period, including 518 cases from the Chinese PLA General Hospital and 120 cases from Shandong Provincial Hospital.

### Clinical characteristics of NDPH

All patients distinct and clearly remembered onset day. The headache developed bilaterally in 58 (79.5%) patients and unilaterally in 15 (20.5%), and its nature was throbbing for 7 (9.6%) and non-throbbing for 77 (90.4%). The average pain intensity on VAS was  $5.3 \pm 2.0$ . Among all NDPH patients, 32 (43.8%) patients were aggravated by routine physical activities. Accompanying symptoms included phonophobia in 12 (16.4%) patients, photophobia in 9 (12.3%) patients, nausea in 14 (19.2%) patients and vomiting in 1 (1.4%) patient. Regarding the precipitating factor of the headache, 40 (54.8%) patients had no triggering factors, 11 (15.1%) patients had an infection (respiratory infection), and 22 (30.1%) patients had stressful life events. Only one NDPH patient (1.4%) reported migraine history. Among all NDPH patients, 38 (52.1%) had generalized anxiety disorder (GAD-7 score  $\geq 10$ ), and 27 (36.9%) had depression (PHQ-9  $\geq 13$ ).



**Fig. 1.** Flowchart. Demography of NDPH patients.

The demographic and clinical characteristics of NDPH are summarized in Table 1. Among all NDPH patients, 39 were males (53.4%), and 34 were females (46.6%), with an average age of  $37.4 \pm 14.3$  years (14–66 years). The average age of headache onset was  $26.7 \pm 12.3$  years (13–58 years). The average duration of headache was  $10.6 \pm 11.8$  years (0.5–51 years). The peak age of onset was 11 to 20 years for males and 21 to 30 years for females

**Table 1.** Demographic and clinical characteristics of patients with NDPH (n = 73)

	All n (%)	Male n (%)	Female n (%)	p
No. of patients	73	39 (53.4%)	34 (46.6%)	
Age (years, mean ± SD)	37.4 ± 14.3	38.0 ± 11.8	36.6 ± 16.8	0.41
Age at onset (years, mean ± SD) (years, median(quartiles))	26.7 ± 12.3 (23.0, 16.0)	25.3 ± 12.1 (20.0, 10.0)	28.3 ± 12.5 (25.5, 17.2)	0.14
Duration of headache: (years, mean ± SD) (years, median(quartiles))	10.6 ± 11.8 (5.0, 17.0)	12.7 ± 12.3 (7.0, 17.5)	8.3 ± 10.8 (3.5, 9.3)	0.055
Education level				0.65
Low education level	19 (26.0%)	11 (28.2%)	8 (23.5%)	
High education level	54 (74.0%)	28 (71.8%)	26 (77.5%)	
Location of headache				0.080
Unilateral	15 (20.5%)	5 (12.8%)	10 (29.4%)	
Bilateral	58 (79.5%)	34 (87.2%)	24 (70.6%)	
Pain character				
Non-throbbing	66 (90.4%)	37 (94.9%)	29 (80.6%)	
Throbbing	7 (9.6%)	2 (5.1%)	5 (19.4%)	
Pain intensity (VAS, mean ± SD) (years, median(quartiles))	5.3 ± 2.0 (5.0, 2.0)	5.6 ± 2.0 (5.0, 2.0)	4.9 ± 2.5 (5.0, 1.5)	0.49
Aggravation by routine physical activities	32 (43.8%)	17 (43.6%)	15 (44.1%)	
Associated feature				
Nausea	14 (19.2%)	2 (5.1%)	12 (35.3%)	
Vomiting	1 (1.4%)	1 (2.6%)	0	
Phonophobia	12 (16.4%)	6 (15.4%)	6 (17.6%)	
Photophobia	9 (12.3%)	5 (12.8%)	4 (11.8%)	
Psychiatric co-morbidities				0.66
Anxiety (GAD-7 ≥ 10)	18 (24.7%)	19 (51.4%)	19 (55.9%)	
Depression (PHQ-9 ≥ 10)	27 (36.9%)	15 (44.1%)	12 (35.3%)	
Triggering factors				
Infection	11 (15.1%)	7 (17.9%)	4 (11.8%)	
Stress	22 (30.1%)	11 (28.2%)	11 (32.4%)	
None	40 (54.8%)	21 (53.8%)	19 (55.8%)	

BMI: body mass index; VAS: visual analog scale; CDH: chronic daily headache; MOH: medication overuse headache; NDPH: new daily persistent headache; Low education level: illiteracy, elementary school and middle school; High education level: high school, secondary vocational school, three-year college, a bachelor's degree and above.

### Comparison between NDPH and MOH

The demographic and clinical characteristics of patients with NDPH were compared to those of patients with MOH (Fig. 2, Fig. 3). There were significant differences in sex, age at onset of CDH, duration of CDH, educational level and pain intensity between the NDPH and MOH patients (Table 2). The proportion of males among the NDPH patients (39/73, 53.4%) was significantly higher than that among the MOH patients (144/638, 22.6%). The age of onset of CDH of the NDPH patients ( $26.7 \pm 12.3$ ) was significantly younger than that of the MOH patients ( $41.4 \pm 11.3$ ). However, the duration of CDH of the NDPH patients ( $10.6 \pm 11.8$ ) was significantly longer than that of the MOH patients ( $6.1 \pm 6.2$ ). The average pain intensity on the VAS for the NDPH patients ( $5.3 \pm 2.0$ ) was significantly lower than that for the MOH patients ( $6.9 \pm 1.6$ ). In addition, the educational level of NDPH patients (54/73, 74.0%) was significantly higher than that of MOH patients (293/638, 45.9%).

### Treatment and prognosis

Among 73 NDPH patients, seven patients failed to be contacted, and four patients were treated for less than 3 months. In total, 62 NDPH patients completed more than

3 months of follow-up by telephone (Fig. 1). The average follow-up was 31 months. Of these, 31 demonstrated the effectiveness of treatment, and 31 demonstrated unsatisfactory treatment. We compared the relationship between the therapeutic responses of NDPH patients and their demographic and clinical characteristics (Table 3). The therapeutic responses were more effective in NDPH patients with trigger factors than in those without trigger factors (71.4% vs 32.4%;  $p = 0.002$ ). The NDPH patients with stress-related trigger factors had better therapeutic responses than those with infection-related trigger factors (85.0% vs 37.5%;  $p = 0.002$ ) (Table 4). No significant differences in sex, pain intensity, headache duration, headache characteristics or education level were observed between patients who had effective outcomes and those who had non-effective outcomes (Fig. 4). NDPH with trigger factors was included in the logistic regression analysis, and the odds ratio (OR) for an effective outcome was 5.25 (1.73–15.84,  $p = 0.006$ ) (Fig. 4).

### Discussion

This study assessed the clinical features of NDPH, the effectiveness of drug-based treatment and the risk factors for treatment effects in the largest sample in China mainland to date. We found that there were significant differ-

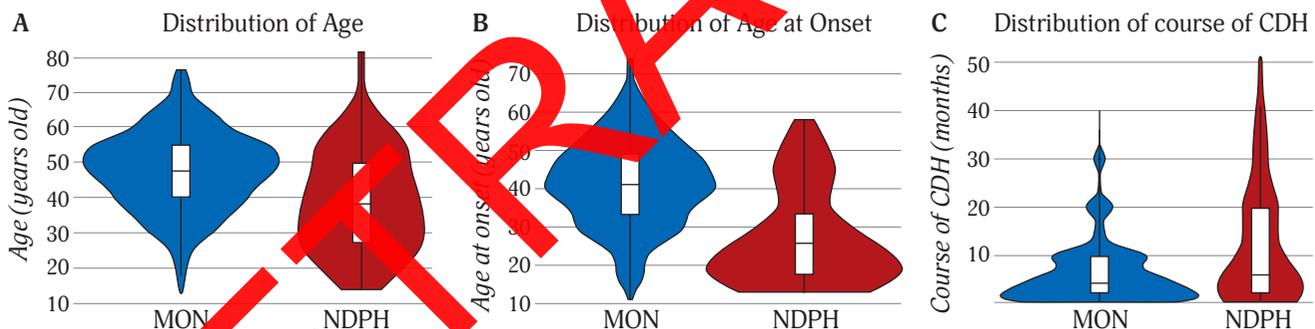


Fig. 2. Demographic and clinical characteristics between MOH and NDPH

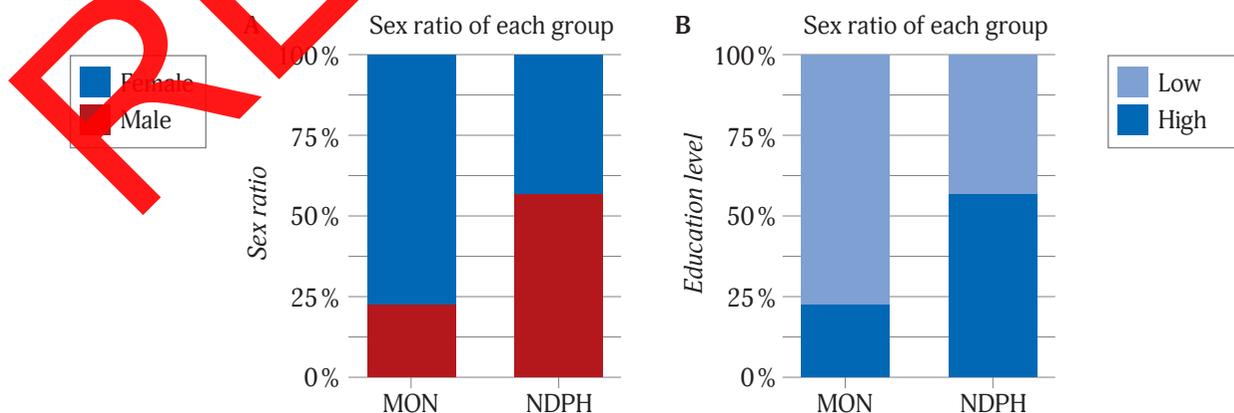


Fig. 3. Sex ratio and education level between MOH and NDPH

**Table 2.** Demographic and clinical characteristics between MOH and NDPH

	MOH (n = 638) (%)	NDPH (n = 73) (%)	p
Sex, n			<0.001
male	144 (22.6%)	39 (53.4%)	
female	494 (77.4%)	34 (46.6%)	
Age (years, mean ± SD) (years, median(quartiles))	47.6 ± 10.9 (48.0, 15.0)	37.4 ± 14.3 (35.0, 23.0)	<0.001
Age at onset of CDH (years, mean ± SD) (years, median(quartiles))	41.4 ± 11.3 (41.0, 16.0)	26.7 ± 12.3 (23.0, 16.0)	<0.001
Duration of CDH (years, mean ± SD) (years, median(quartiles))	6.1 ± 6.2 (4.0, 8.0)	10.6 ± 11.8 (5.0, 17.0)	0.023
Education level, n			0.001
low education level	345 (54.1%)	19 (26.0%)	
high education level	293 (45.9%)	54 (74.0%)	
Pain intensity (VAS, mean ± SD) (years, median(quartiles))	6.9 ± 1.6 (7.0, 2.0)	5.3 ± 2.0 (5.0, 2.0)	0.001

VAS: visual analog scale; CDH: chronic daily headache; MOH: medication overuse headache; NDPH: new daily persistent headache; Low level: illiteracy, elementary school and middle school; High level: high school, secondary vocational school, three-year college, a bachelor's degree and above.

**Table 3.** The relationship between therapeutic responses in patients with NDPH and demographic and clinical characteristics of these patients (n = 62)

	Effective (n = 31)	Noneffective (n = 31)	p
NDPH with trigger factors, n (%)	20 (64.5%)	8 (25.8%)	0.002
NDPH without trigger factors n, (%)	11 (35.5%)	23 (74.2%)	
NDPH (6–24 months), n (%)	11 (68.8%)	5 (31.2%)	0.082
NDPH (>24 months), n (%)	20 (64.5%)	26 (83.5%)	
Sex			0.80
male	17 (44.7%)	18 (55.3%)	
female	14 (51.9%)	13 (48.1%)	
Education level, n (%)			0.78
low education level	8 (47.1%)	9 (52.9%)	
high education level	23 (51.1%)	22 (48.9%)	
Pain intensity (VAS, mean ± SD) (years, median(quartiles))	4.9 ± 1.6 (5.0, 2.0)	4.9 ± 1.8 (5.0, 2.0)	0.78
Headache characteristics, n (%)			0.25
Like migraine	10 (62.5%)	6 (37.5%)	
Like tension type headache	21 (45.7%)	25 (54.3%)	

BMI: body mass index; VAS: visual analog scale; NDPH: new daily persistent headache;

Low level: illiteracy, elementary school and middle school;

High level: high school, secondary vocational school, three-year college, a bachelor's degree and above.

**Table 4.** The relationship between therapeutic responses and different trigger factors of NDPH patients (n = 28)

	Effective (n = 20)	Noneffective (n = 8)	p
NDPH with infection factor n (%)	3 (37.5%)	5 (62.5%)	0.002
NDPH with stress factor n (%)	17 (85.0%)	3 (15.0%)	

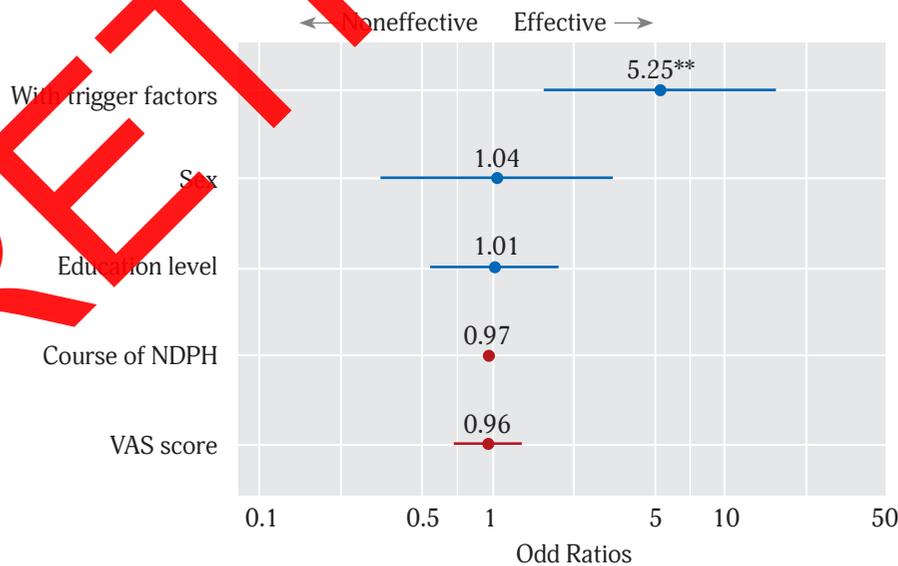
NDPH: new daily persistent headache

ences in demographic and clinical characteristics between NDPH and MOH patients. The presence of trigger factors is an independent factor for the treatment effect of NDPH patients. The patients with stress-related trigger factors had a better outcome than those with infection-related trigger factors.

**Clinical features of NDPH**

Our study revealed a male predominance (female/male = 0.9:1), which is nearly similar to data from India (0.8:1) [9] but contrary to data from the USA (2:1) [10]. The mean age at onset for NDPH is 26.7 years, which is similar to that reported by Uniyal et al. (28.24 years) [9] (Table 5). The clinical characteristics of the NDPH in our study were bilateral localization, non-throbbing nature, and a typical lack of association with nausea and vomiting; these characteristics were similar to those of classic tension type headache in many cases. However, other summarized literature demonstrated the presence of migraine-like features in NDPH patients, with a proportion of 35–64.1% [8, 9, 11–13]. NDPH typically occur in individuals without a prior headache history [1]. In our study, there was one patient (1.4%) had headache histo-

ry. However, other summarized literature demonstrated the presence of prior headache history in NDPH patients, with a proportion of 7–54% [4, 24]. In terms of comorbid mental disorders in NDPH, the majority of our patients had anxiety (38/73, 52.1%) and depressive (27/73, 36.9%) symptoms. Uniyal et al. even reported a more common prevalence of anxiety (92.7%) and depression (89.1%) in their patients [9]. The causal relationship between anxiety, depression and chronic headaches or vice versa is still unclear [9] (Table 6). None of the patients had medication overuse in our study. However, Prakash et al. and Kung et al. reported medication overuse in 13% and 8.7% of their patients, respectively [12, 14]. Moreover, an observational study by Peng et al. also reported that NDPH patients had a higher proportion (34.8%) of medication overuse [13]. We consider the following possible reasons for these findings. First, most of the patients in our cohort showed headache characteristics similar to those of tension-type headaches, which means that the headache is mild to moderate, so analgesics may not be necessary. Reidy et al. also found that youth with NDPH were less likely to have medication overuse compared to youth with CM [8]. Another reason may be that



**Fig. 4.** Forest plot of variables of NDPH that have influence on therapeutic effect. Variable-specific odds ratios (95% CIs) are denoted by dots (lines). Blue dots (lines) represent categorical variables. Red dots (lines) represent continuous variables. \*\*P-value < 0.01

**Table 5.** Demographic, clinical characteristics and triggering factors of patients with NDPH in different study

Study	Li [23] 2002	Takase [4] 2004	Robbins [11] 2010	Peng [13] 2011	Prakash [12] 2012	Rozen [10] 2016	Uniyal [9] 2017	Current study
Diagnostic criteria	S-L	ICHD2	M-ICHD2	M-ICHD2	M-ICHD2	ICHD-3 $\beta$	ICHD-3 $\beta$	ICHD-3
No. of patients	56	30	71	92	63	97	55	73
Female/male	2.5	0.8	2.5	1.4	1.3	2.0	0.8	0.9
Age of onset (years)	Range: 12–78	Mean: 35.0 Range: 13–73	Median: 28 Range: 8–76	Mean: 43.1	Mean: 36.8 Range: 18–68	Mean: F: 32.4 M: 35.8	Mean: 28.2	Mean: 26.7 Range: 13–55
Prior headache history	38%	7%	25.4%	32%	54%	41.2%	38.2%	1.4%
Duration of headache (months)	> 6	Mean: 39.5	–	Mean: 5	Mean: 27.5 Range: 3–72	–	Mean: 24.6	Mean: 16.8 Range: 6–61
Bilateral pain, n (%)	36 (64)	26 (87)	63 (88.7)	43 (46.7)	52 (83)	–	45 (81.8)	58 (79.5)
Throbbing Pain, n (%)	31 (55)	8 (27)	32 (45.1)	38 (41.3)	32 (51)	–	25 (41.8)	7 (9.6)
Pain intensity (VAS)	–	–	–	–	–	–	Mean: 7.5	Mean: 5.3
Mild (1–3)	10 (18)	–	16.9%	–	–	–	–	–
Moderate (4–6)	34 (61)	–	57.7%	–	–	–	–	–
Severe (7–10)	12 (21)	–	23.9%	–	–	–	–	–
Aggravation by physical activities, n (%)	18 (32)	–	33 (46.5)	53 (57.6)	17 (27)	–	9 (16.4)	32 (43.8)
Associated feature	–	–	–	–	–	–	–	–
Nausea, n (%)	38 (68)	10 (33)	31 (43.7)	32 (34.8)	31 (49)	–	31 (56.4)	14 (19.2)
Vomiting, n (%)	13 (23)	–	9 (12.7)	7 (7.6)	3 (5)	–	11 (20)	1 (1.4)
Phonophobia, n (%)	34 (61)	–	29 (40.8)	53 (57.6)	12 (19)	–	–	12 (16.4)
Photophobia, n (%)	37 (66)	1 (3)	32 (45.1)	44 (47.8)	21 (33)	–	25 (45.5)	9 (12.3)
Medication overuse, n (%)	–	–	32 (45.1)	32 (34.8)	8 (13)	–	34 (61.8)	–
Psychiatric comorbidities	–	–	Self-reported	–	Self-reported	–	–	–
Anxiety, n (%)	–	–	24 (33.8)	–	10 (16)	–	51 (92.7)	38 (52.1)
Depression, n (%)	–	–	25 (35.2)	56 (60.9)	12 (19)	–	49 (89.1)	27 (36.9)
Triggering factors	–	–	–	–	–	–	–	–
Infection/flu-like illness, n (%)	17 (30)	a	10 (14.1)	3 (3.3)	18 (29)	21 (22)	10 (18)	11 (15.1)
Stress, n (%)	7 (12)	6 (20)	7 (9.9)	24 (26.1)	5 (8)	9 (9)	5 (9.1)	22 (30.1)
Trauma/surgery, n (%)	7 (12)	a	–	–	10 (16)	9 (9)	5 (9.1)	–

Study	Li [23] 2002	Takase [4] 2004	Robbins [11] 2010	Peng [13] 2011	Prakash [12] 2012	Rozen [10] 2016	Uniyal [9] 2017	Current study
None, n (%)	> 33%	24 (80)	38 (53.5)	65 (70.7)	29 (46)	51 (53)	35 (63.5)	40 (54.8)
Other, n (%)			6 (8)		9 (14)	7 (7)		–

VAS: visual analog scale; NDPH: new daily persistent headache; S-L: Silberstein-Lipton criteria; CHD: International classification of headache disorders; M-ICHD2: Modified ICHD2 (NDPH according to the criteria A and B of the ICHD-2 regardless of the presence of migraine features.). a – Takase et al. excluded persistent headache occurred in relation to an infection or flu-like illness and headache after head and neck injury or surgery

even when analgesics were used, most of them were not effective for NDPH patients.

Infection and stress events are the two main trigger factors of NDPH [10], while the proportion varies among different studies. Most of our patients (22/73, 30.1%) complained that their self-reported triggering events were related to stressful events, which is higher than the corresponding data reported by Uniyal et al. (5/55, 9.1%) [9] and Rosen (9/97, 9%) [10]. Another factor in our study was infection (15.1%). Some authors have found that some NDPH patients who had been infected with viruses before headache, such as Epstein-Barr virus (EBV) [15], herpes simplex virus (HSV) [16], cytomegalovirus (CMV) [16], and dengue virus (DENV) [17], speculated that chronic central nervous system inflammation may be involved in the pathophysiological mechanism of NDPH [2]. However, only a few patients suffered NDPH after infections, which suggests that some unknown mechanism needs to be further explored. Other trigger factors reported by other studies, such as surgery procedures with intubation, withdrawal from SSRIs, human papilloma virus vaccination [2, 10], and Valsalva event [18], were absent in our study.

### Comparison between NDPH and MOH

We found several significant differences in sex predominance, age at onset of CDH, duration of CDH, educational level and pain intensity between NDPH and MOH. First, NDPH occurred more often in males than in females. The most likely reason is that primary headache diseases in general, especially migraine, are more common in women [7], and these are the main risk factors for MOH because pre-existing headache is a necessary prerequisite. Second, our study showed that NDPH patients, compared to MOH patients, had an earlier age at onset of CDH but a longer duration of CDH, which would lead to more severe disability and therefore significantly affect the individual's quality of life. Finally, compared with MOH, NDPH patients are more likely to have a higher educational level, which has not been revealed in a previous study. The main reason may be that MOH patients attained a lower education level [19], which is a risk factor for medication

overuse in headache patients [20]. This difference needs to be confirmed in further clinical studies.

### Treatment and prognosis of NDPH

NDPH has two subtypes: a self-limiting subtype that typically resolves within several months without therapy and a refractory subtype that is resistant to aggressive treatment regimens [1]. Vanast first found that 78% of patients became headache-free by 24 months [21] and considered NDPH a benign headache. In contrast, most subsequent studies considered it to be the most refractory to treatment and can persist for many years [2]. The likely reason for NDPH becoming more refractory was that most studies enrolled NDPH patients who had headache durations of more than 6 months [22]. In our study, the duration of headache was also more than 6 months in all patients, and the mean headache duration was 10.6 years. Our current study did not reveal that any NDPH patients self-resolved during an average follow-up of 31 months. The effective treatment rate of NDPH was 50% in our study, which was close to the effective treatment rate (67%) found by Prakash et al [12]. Although there was no significant difference in headache duration, it seems that the shorter duration has a better outcome (68.8% vs. 43.5%). Our results also supported that treatment in the early stage might improve the effectiveness of NDPH, which is similar to the result from Peng et al [13]. In our study, we found that the patients with trigger factors had a better prognosis than those without trigger factors (71.4% vs 32.4%,  $p = 0.002$ ), which is similar to the data from India [12]. In addition, stress is the main trigger factor of NDPH patients, and patients with stress-related trigger factors had a better outcome than those with infection-related trigger factors. We speculate that the likely reason is that these patients may handle life stress appropriately after consulting a doctor, which is helpful in reducing the frequency and severity of headaches.

### Limitations

There are some limitations in our study. First, because the two hospitals are both tertiary care centers, the study

may include selection bias. Second, because this study is a retrospective study, there could be recall bias, and the results need to be further confirmed in prospective studies.

## Conclusions

Our study revealed that NDPH is predominant in males. NDPH patients rarely have medication overuse in China. Tension-type headache features were very common in patients with NDPH. Moreover, NDPH is significantly different from MOH in demographic and clinical characteristics, demonstrating a younger age of CDH onset, a longer duration of CDH, and a higher educational level. Additionally, the presence of trigger factors is an independent factor for the treatment effect of NDPH patients. NDPH patients with trigger factors had a better treatment outcome.

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### Клінічні особливості й наслідки первинного щоденного стійкого головного болю у пацієнтів Китаю та порівняння з головним болем від надмірного вживання ліків: двоцентрове ретроспективне дослідження

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#### Анотація

**Передумови.** У цьому дослідженні вивчалися клінічні особливості та результати пацієнтів з NDPH та порівняння з головним болем від надмірного вживання ліків (МОН) у материковому Китаї.

**Методи.** Це ретроспективне дослідження спостерігало за пацієнтами з NDPH та головним болем від надмірного вживання ліків (МОН), які відвідували дві амбулаторії в період з листопада 2011 р. по грудень 2019 р. Клінічну інформацію збирали, а всіх пацієнтів спостерігали телефоном.

**Результати.** У дослідження було залучено 73 пацієнти з NDPH та 638 МОН. Серед пацієнтів з NDPH були 39 чоловіків (39/73, 53,4%) та 34 жінки (34/73, 46,6%), із середнім віком 37,4 року та середньою тривалістю головного болю 10,6 років. Фактори, що викликають головний біль, включали інфекцію (11/73, 15,1%) та стрес (22/73, 30,1%). Порівняно з пацієнтами із МОН, у пацієнтів з NDPH переважали чоловіки (53,4% проти 22,6%,  $p < 0,001$ ), молодший вік початку CDH ( $26,7 \pm 12,3$  проти  $41,4 \pm 11,3$  року,  $p < 0,001$ ) та більша тривалість CDH ( $10,6 \pm 11,8$  проти  $6,1 \pm 6,2$  років,  $p = 0,023$ ). Із 62 пацієнтів з NDPH, які спостерігались протягом 31 місяця, терапевтичні відповіді були ефективнішими у пацієнтів з NDPH із тригерними факторами, ніж у пацієнтів без тригерних факторів (71,4% проти 32,4%;  $p = 0,002$ ); коефіцієнт шансів (OR) ефективного результату становив 5,25 ( $95\% \text{ CI } 1,73-17,84$ ,  $p = 0,005$ ).

**Висновки.** NDPH суттєво відрізняється від МОН з переважанням чоловіків, молодшим віком початку CDH та більшою тривалістю CDH. Наявність тригерних факторів є незалежним предиктором кращого ефекту лікування у пацієнтів з NDPH.

**Ключові слова:** первинний щоденний стійкий головний біль, головний біль від надмірного вживання ліків, клінічні особливості, прогноз.

### Клинические особенности и последствия первичной ежедневной устойчивой головной боли у пациентов Китая и сравнение с головной болью от чрезмерного употребления лекарств: двухцентровое ретроспективное исследование

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#### Резюме

**Предпосылки.** В этом исследовании изучались клинические особенности и исходы у пациентов с NDPH и сравнивались с головной болью от чрезмерного употребления лекарств (МОН) в материковом Китае.

**Методы.** В этом ретроспективном исследовании наблюдались пациенты с NDPH и головной болью при чрезмерном употреблении лекарств (МОН) посещавшие две амбулаторные клиники в период с ноября 2011 г. по декабрь 2019 г. Была собрана клиническая информация, и все пациенты наблюдались по телефону.

**Результаты.** В исследование были включены 73 пациента NDPH и 638 МОН. Пациенты NDPH включали 39 мужчин (39/73, 53,4%) и 34 женщины (34/73, 46,6%) со средним возрастом 37,4 года и средней продолжительностью головной боли 10,6 года. Факторы, провоцирующие головную боль, включали инфекцию (11/73, 15,1%) и стресс (22/73, 30,1%). По сравнению с пациентами МОН, пациенты NDPH имели преобладание мужчин (53,4% против 22,6%,  $p < 0,001$ ), более молодой возраст начала CDH ( $26,7 \pm 12,3$  против  $41,4 \pm 11,3$  года,  $p < 0,001$ ) и более длительную продолжительность CDH ( $10,6 \pm 11,8$  против  $6,1 \pm 6,2$  года,  $p = 0,023$ ). Из 62 пациентов с NDPH, наблюдавшихся в течение 31 месяца, в среднем терапевтические ответы были более эффективными у пациентов с NDPH с триггерными факторами, чем у пациентов без триггерных факторов (71,4% против 32,4%;  $p = 0,002$ ); отношение шансов (OR) эффективного результата составило 5,25 ( $95\% \text{ CI } 1,73-17,84$ ,  $p = 0,005$ ).

**Выводы:** NDPH значительно отличается от МОН, с преобладанием мужчин, более молодым возрастом начала CDH и большей продолжительностью CDH. Наличие триггерных факторов является независимым предиктором лучшего эффекта лечения у пациентов с NDPH.

**Ключевые слова:** первичная ежедневная постоянная головная боль; головная боль, вызванная чрезмерным употреблением лекарств, клинические особенности, прогноз.