



# Chronic Daily Headache and Medication Overuse Headache in First-Visit Headache Patients in Korea: A Multicenter Clinic-Based Study

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**Background and Purpose** Chronic daily headache (CDH) is defined as a headache disorder in which headaches occur on a daily or near-daily basis (at least 15 days/month) for more than 3 months. Chronic migraine (CM) and medication overuse headache (MOH) are very disabling headaches that remain underdiagnosed. The aim of this study was to establish the frequency of CDH and its various subtypes, and examine the associations with MOH among first-visit headache patients presenting at neurology outpatient clinics in Korea.

**Methods** Eleven neurologists enrolled first-visit patients with complaints of headaches into outpatient clinics for further assessment. Headache disorders were classified according to the International Classification of Headache Disorder (third edition beta version) by each investigator.

**Results** Primary CDH was present in 248 (15.2%) of the 1,627 included patients, comprising CM (143, 8.8%), chronic tension-type headache (CTTH) (98, 6%), and definite new daily persistent headache (NDPH) (7, 0.4%). MOH was associated with headache in 81 patients (5%). The association with MOH was stronger among CM patients (34.5%) than patients with CTTH (13.3%) or NDPH (14.3%) ( $p=0.001$ ). The frequency of CDH did not differ between secondary and tertiary referral hospitals.

**Conclusions** The frequencies of CDH and MOH diagnoses were 15.2% and 5%, respectively in first-visit headache patients presented at secondary or tertiary referral hospitals in Korea. CM was the most common subtype of CDH and was most frequently associated with MOH.

**Key Words** chronic daily headache, epidemiology, medication overuse headache, migraine, tension-type headache, headache.

## INTRODUCTION

Chronic daily headache (CDH) is an umbrella term used to describe headache disorders that are present on more than 15 days per month and persist for longer than 3 months.<sup>1</sup> CDH encompasses a broad range of headache disorders that includes primary headache disorders such as chronic migraine (CM), chronic tension-type headache (CTTH), new daily persistent headache (NDPH), and hemicrania continua (HC).<sup>1</sup> The prevalence of CDH reportedly ranges from 1% to 5% among the general adult population, and affects 27–39% of headache patients visiting special headache clinics.<sup>2–4</sup> Medication overuse headache (MOH) is defined as the development or marked worsening of a pre-existing headache disorder in association with medication overuse. MOH are usually refractory to treatment, and patients with CDH experience a remarkable degree of disability.<sup>5–8</sup>

Recent advances in medicine may provide an opportunity for the successful treatment of CM and MOH, but most CM and MOH patients do not receive the correct diagnosis at

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their initial visit.<sup>9,10</sup> The failure of patients to accurately report headaches often results in the misdiagnosis of CDH as episodic headaches, which may lead to incorrect and delayed treatment of CDH.<sup>11</sup> Therefore, diagnosing headache disorders based on a detailed patient history and standardized diagnostic criteria is crucial. New diagnostic criteria for CM and MOH were recently published in the third edition beta version of the International Classification of Headache Disorder (ICHD-3 $\beta$ ).<sup>12</sup> Most previous studies of MOH or CDH have applied the previous version or ICHD-3 $\beta$  retrospectively,<sup>10,12,13</sup> and so the frequency of CDH and MOH still needs to be evaluated in a clinic-based setting according to ICHD-3 $\beta$ . The early detection and accurate diagnosis of CM and MOH in CDH patients in neurology clinics is important because only 20–36% of them are reportedly correctly diagnosed by a physician or specialist.<sup>9,14</sup>

The aim of this multicenter study was to estimate the frequency of CDH, its subtypes, and MOH using ICHD-3 $\beta$  in Korea.

## METHODS

This investigation was based on the Headache Registry using ICHD-3 $\beta$  for First-Visit Patients (HEREIN) study, which is a cross-sectional multicenter registry study that uses data collected from first-visit headache outpatients presenting at neurology clinics in Korea between August 2014 and February 2015.<sup>15–17</sup>

Briefly, the inclusion criteria for the patients were as follows: 1) aged 19–100 years and have a primary complaint of headaches at the outpatient visit, 2) having no communication disability that might interfere with the collection of medical history, and 3) being willing to participate in the study. We excluded patients who: 1) had a chief complaint other than headaches, 2) had any significant communication problems in hearing, speaking, or cognition, or 3) had any other serious medical or psychiatric problems that might impede continuation of the study according to the physician's judgment.

### Collection of data

This study was conducted in six tertiary referral university hospitals, three secondary referral university hospitals, and two secondary referral general hospitals in accordance with the guidelines of the Declaration of Helsinki and Good Clinical Practice. The study protocol and the informed consent and information use agreement forms were reviewed and approved by the institutional review board of each center (Dongtan Sacred Heart Hospital Institutional Review Board/Ethic Committee IRB approval number: 2014-018). Each patient

provided written informed consent prior to their participation in the study or waived the informed consent process according to the decision of the institutional review board of each center.

### Assessment for CDH

The classification of a headache disorder was established by each investigator using the current headache phenotypes described in ICHD-3 $\beta$ . This was determined according to the initial evaluation of the patients using a structured questionnaire, a clinical evaluation, and laboratory or neuroimaging studies, as necessary. The history of headache were obtained at the initial visit, which included the routes of access to the hospitals, onset times of the first and the current headaches, presence of aura, severity as assessed on a visual analog scale (VAS), and duration of headache attacks. The investigators selected the most appropriate headache subtype for each patient, and MOHs were assessed separately. Before enrolling patients, all investigators were informed about ICHD-3 $\beta$  principles during an educational meeting and a further session was convened to confirm any uncertain cases. CM, CTTH, NDPH, and HC were defined by ICHD-3 $\beta$  as CDH when patients experienced headaches at least 15 days per month for at least 3 months and for longer than 4 hours per day.<sup>1,18</sup> Any probable diagnoses were excluded from enrollment of CDH. Migraine with aura, migraine without aura, and probable migraine with headache on fewer than 15 days per month were classified as episodic migraine (EM). Infrequent episodic tension-type headache (ETTH), frequent ETTH, and probable ETTH were together classified as ETTH.<sup>19</sup> MOH was diagnosed according to ICHD-3 $\beta$  criteria.

### Statistical analysis

All analyses were performed using SPSS (Windows version 21.0, IBM, Armonk, NY, USA), and a *p* value of <0.05 was considered to indicate statistical significance. Demographic characteristics were compared using an independent-samples *t*-test or a chi-square test for categorical variables. Methods of analysis such as the *t*-test, chi-square test, and ANOVA were used for comparisons between patients with CM, CTTH, EM, and ETTH. ANOVA was used to assess MOH in CDH patients. The data are presented as mean $\pm$ SD values.

## RESULTS

### Demographic characteristics and frequency of CDH and its subtypes

Of 1,627 patients, CDH was diagnosed in 248 patients (15.2%) and MOH was diagnosed in 81 patients (5%), which included CM ( $n=143$ , 8.8%), CTTH ( $n=98$ , 6.0%), and NDPH ( $n=7$ ,

0.4%). No patient fulfilled the criteria for HC. The age at the diagnosis of CDH was  $50.1 \pm 15.2$  years, and the age at onset of CDH was  $41.88 \pm 16.82$  years. Most of those diagnosed with CDH were aged 50–59 years, whilst headache onset occurred mainly in those aged 40–49 years (Fig. 1).

An additional diagnosis of MOH was made in 49 CM, 13 CTTH, 1 NDPH, 9 episodic headache (7 migraine without aura, 1 frequent ETTH, and 1 probable tension-type headache), and 9 secondary headache patients. Three MOH patients received an additional diagnosis of a secondary headache disorder, including headache attributed to traumatic head injury (ICHD-3 $\beta$  code 5.2,  $n=1$ ), alcohol-induced headache (ICHD-3 $\beta$  code 8.1.4,  $n=1$ ), and cervicogenic headache (ICHD-3 $\beta$  code 11.2.1,  $n=1$ ). The remaining six patients were diagnosed with MOH without an additional diagnosis because there were no symptoms that were better accounted for by another ICHD-3 $\beta$  diagnosis. The frequency of MOH was 25.4% among CDH patients. An additional diagnosis of MOH was more common in CM patients (34.5%) than in CTTH patients (13.3%) or NDPH patients (14.3%) ( $p=0.001$ ) (Fig. 2).

The overused medications involved in MOH were mainly combination analgesics ( $n=34$ , 42%) and nonsteroidal anti-inflammatory drugs ( $n=23$ , 28.4%), followed by other drugs ( $n=15$ , 18.5%), triptans ( $n=5$ , 6.2%), ergot derivatives ( $n=2$ , 2.5%), and opioid analgesics ( $n=2$ , 2.5%).

The frequency of CDH did not differ according to the hospital setting [secondary vs. tertiary referral hospitals,  $n=123$  (15%) vs.  $n=125$  (15.5%),  $p=0.816$ ]. The frequency of MOH also did not differ according to the hospital setting (secondary vs. tertiary referral hospitals, 4.4% vs. 5.6%,  $p=0.282$ ).

### Clinical characteristics of CDH according to its subtypes

The CM patients were significantly younger than the CTTH patients ( $45.6 \pm 14.6$  years vs.  $56.6 \pm 13.8$  years,  $p<0.001$ ). CM was more common in women ( $p<0.001$ ), with a higher incidence of MOH than CTTH (34.3% vs. 13.3%,  $p<0.001$ ). The VAS score was higher in CM than in CTTH ( $7.3 \pm 1.5$  vs.  $5.2 \pm 1.9$ ,  $p<0.001$ ). The headache onset occurred significantly earlier in CM patients than in CTTH patients ( $34.9 \pm 14.7$  years vs.  $51.5 \pm 14.7$  years,  $p<0.001$ ) (Table 1).

### Comparisons between CDH and episodic primary headache or CDH with MOH

CDH was more common in women ( $p<0.001$ ) and occurred in older patients relative to episodic primary headache (EPH) ( $50.12 \pm 15.21$  years vs.  $46.55 \pm 14.26$  years,  $p<0.001$ ). Headache duration was longer in CDH than in EPH ( $64.22 \pm 11.01$  years vs.  $35.56 \pm 77.83$  years,  $p<0.001$ ), and the frequency of

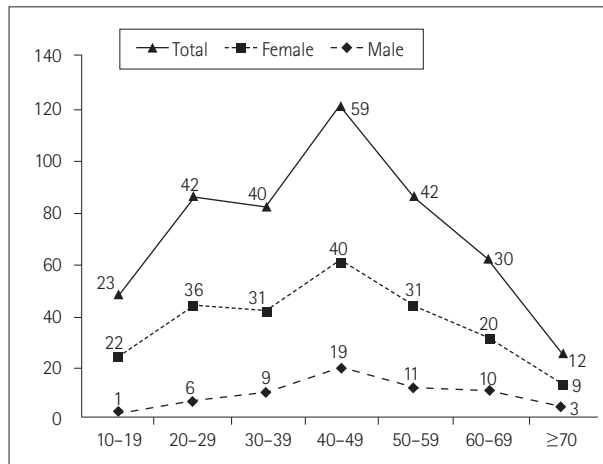


Fig. 1. Frequency of chronic daily headache by age at onset and sex.

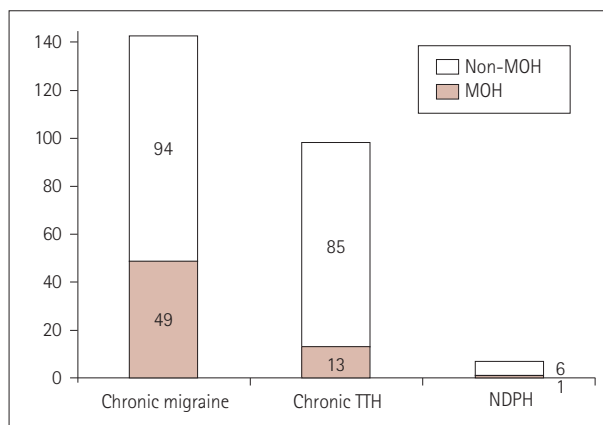


Fig. 2. Proportion of medication overuse headache (MOH) among patients with CDH and other headache disorders. CDH: chronic daily headache, NDPH: new daily persistent headache, TTH: tension-type headache.

MOH was higher in CDH than in EPH (25.4% vs. 12.5%,  $p<0.001$ ). VAS score and age at headache onset did not differ significantly between CDH and EPH (Table 2).

The proportion of women was higher in CDH patients with MOH than in those without MOH ( $p=0.006$ ). The severity and duration of headache were significantly greater and longer, respectively, in CDH with MOH than in CDH alone ( $p=0.003$  vs.  $p<0.001$ ) (Table 3).

### Comparisons between EM or ETTH and CM or CTTH

Compared to EM, CM was more common in women ( $p=0.004$ ) and had a higher incidence of MOH (34.3% vs. 1.3%,  $p<0.001$ ). The VAS score ( $7.3 \pm 1.5$  vs.  $7.0 \pm 1.9$ ,  $p=0.156$ ) and headache onset age ( $32.7 \pm 12.9$  years vs.  $34.9 \pm 14.7$  years,  $p=0.116$ ) did not differ significantly between CM and EM.

Compared to ETTH, CTTH was detected more commonly in women ( $p=0.018$ ) and was more frequently accompa-

nied by MOH (13.3% vs. 0.6%,  $p < 0.001$ ). The age at headache onset did not differ between CTTH and ETTH ( $51.5 \pm 14.7$  years vs.  $49.6 \pm 14.2$  years,  $p = 0.244$ ). The VAS score tended to be higher in CTTH than ETTH ( $5.2 \pm 1.9$  vs.  $4.6 \pm 1.6$ ,  $p = 0.050$ ), but with marginal significance (Table 4).

## DISCUSSION

Our study is the first to investigate the frequencies of CDH

and MOH, as diagnosed using ICHD-3 $\beta$  in first-visit headache patients presenting at neurology clinics in Korea. The frequency of CDH was 15.2%, of which two-thirds were patients with CM (57.7%) and the frequency of MOH was 5%. About 60% of MOH patients had a primary diagnosis of CM, and one-third of CM patients received an additional diagnosis of MOH.

According to ICHD-3 $\beta$ , patients meeting criteria for CM and MOH should be given both diagnoses.<sup>12</sup> About two-

**Table 1.** Comparison between demographic characteristics in chronic migraine (CM), chronic tension-type headache (CTTH), and new daily persistent headache (NDPH)

	CM (n=143)	CTTH (n=98)	NDPH (n=7)	p
Age, years	45.62±14.56	56.61±13.84	50.12±15.21	<0.001
Sex, female	124 (86.7)	59 (60.2)	6 (85.7)	0.001
MOH	49 (34.3)	13 (13.3)	1 (14.3)	<0.001
VAS	7.27±1.52	5.16±1.88	7.43±2.14	<0.001
Headache onset age, years	34.85±14.70	51.53±14.69	50.43±16.15	<0.001

Data are mean±SD or n (%) values.

MOH: medication overuse headache, VAS: visual analog scale.

**Table 2.** Comparison between demographic characteristics in chronic daily headache (CDH) and episodic primary headache (EPH)

	CDH (n=248)	EPH (n=1181)	p
Age, years	50.12±15.21	46.55±14.26	<0.001
Sex, female	189 (76.2)	733 (62.1)	<0.001
VAS	6.44±1.97	6.29±2.14	0.306
MOH	63 (25.4)	9 (12.5)	<0.001
Headache onset age, years	41.88±16.82	41.41±15.96	0.677
Headache duration, months	64.22±111.01	35.56±77.83	<0.001

Data are mean±SD or n (%) values.

MOH: medication overuse headache, VAS: visual analog scale.

**Table 3.** Comparison between demographic characteristics in CDH alone and CDH with MOH

	CDH alone (n=185)	CDH with MOH (n=63)	p
Age, years	49.52±15.49	51.87±14.35	0.291
Sex, female	133 (71.9)	56 (88.9)	0.006
VAS	6.22±1.97	7.08±1.87	0.003
Headache onset age, years	43.09±16.98	38.33±15.94	0.052
Headache duration, months	44.80±86.98	121.27±149.02	<0.001

Data are mean±SD or n (%) values.

CDH: chronic daily headache, MOH: medication overuse headache, VAS: visual analog scale.

**Table 4.** Comparisons between demographic characteristics in CM and episodic migraine (EM), and in chronic tension-type headache (CTTH) and episodic tension-type headache (ETTH)

	Migraine		p	Tension-type headache		p
	CM (n=143)	EM (n=554)		CTTH (n=98)	ETTH (n=347)	
Age, years	45.62±14.56	40.88±12.46	<0.001	56.61±13.84	52.87±13.37	0.016
Sex, female	124 (86.7)	419 (75.5)	0.004	59 (60.2)	162 (46.7)	0.018
MOH	49 (34.3)	7 (1.3)	<0.001	13 (13.3)	2 (0.6)	<0.001
VAS	7.27±1.52	7.03±1.85	0.156	5.16±1.88	4.62±1.64	0.050
Headache onset age, years	34.85±14.70	32.73±12.87	0.116	51.53±14.69	49.58±14.18	0.244

Data are mean±SD or n (%) values.

CM: chronic migraine, MOH: medication overuse headache, VAS: visual analog scale.

thirds of CM patients met MOH criteria in the PREEMPT (Phase III Research Evaluating Migraine Prophylaxis Therapy) study, and medication overuse is a criterion of the ID-CM tool used to screen CM.<sup>11,20</sup> A previous study found that 44.6% of MOH patients retrospectively received a diagnosis of CM using ICHD-3 $\beta$ , and this association can vary according to the applied diagnostic criteria.<sup>10</sup> The association between CM and MOH is clinically very important, and the present study supports the usefulness of ICHD-3 $\beta$  in the diagnosis and management of CDH.<sup>21</sup>

The frequency of CDH in this study was higher than the frequency of approximately 10% reported when using Second edition of the International Classification of Headache Disorder in neurology clinics.<sup>4</sup> This difference may be related to the change in diagnostic criteria for CM that allowed the inclusion of MOH and migraine with aura.<sup>16</sup> This conclusion might be supported by the higher proportion of CM patients in the CDH category. The frequency of CDH found in the present study might differ considerably from that for the general population. Population-based studies have found the frequency of CDH to be 2.0–7.6% in Western countries,<sup>2,22–24</sup> and 1.0–3.9% in Asian countries, including Korea.<sup>25–27</sup> Comparatively, the frequency of CDH was approximately 40% in specialized headache clinics in the USA<sup>28,29</sup> and 23–79% in Asia.<sup>30–33</sup>

The frequency of MOH in neurology clinics was 5% in this study. According to ICHD-3 $\beta$ , MOH can be diagnosed in patients presenting with headache on more than 15 days per month and with a history of regular medication overuse for more than 3 months. Therefore, some patients with MOH did not meet the “3 months” criterion of CDH, and those MOH patients with primary headache disorders were not diagnosed with CDH in this study. The prevalence of MOH was previously found to be 1–5% in the general population and 10–15.9% in patients presenting at headache clinics.<sup>34–38</sup> The proportion of patients with triptan overuse in the present study was 6%, and the proportions of patients with overuse of other medications were similar to those found in previous studies.<sup>13,39</sup>

One-quarter (25.4%) of CDH patients received an additional diagnosis of MOH. The estimated prevalence of MOH among CDH has ranged from 11% to 41% in several population-based studies, and was 15–31% in outpatient-clinic-based studies.<sup>26,27,40–44</sup> These variations in the prevalence of MOH might be related to the application of different diagnostic criteria and the inclusion of different study populations. In our study, the headache severity was greater in CDH patients with MOH than in those without MOH.

Approximately two-thirds of our CDH and MOH patients were diagnosed with CM (57.7% and 60.5%, respectively).

The presenting symptoms were more severe in CM patients than in CTTH patients. A secondary diagnosis of MOH was more likely in CM patients than in EM patients. Patients with CM reported having a greater degree of disability than those with EM.<sup>45,46</sup> The finding that CM is the predominant CDH phenotype is encouraging because CM treatments have progressed markedly in recent years.<sup>47–49</sup>

More than one-third of patients (39.5%) with CDH were CTTH sufferers, and the likelihood of an MOH diagnosis was higher in CTTH patients than in ETTH patients. With regard to the onset of headache and VAS score, there were no significant differences between CTTH and ETTH, in contrast to the case for migraine.

This study was subject to several limitations. Headache-related disability, the impact of headache, and the various comorbidities of CDH and MOH were not evaluated.<sup>46,50</sup> Secondly, CDH and MOH were diagnosed by each investigator based on ICHD-3 $\beta$  criteria. We did not collect information regarding the number of headache days each month, and so secondary headache patients presenting with daily or near-daily headache over a 3-month period were not evaluated.<sup>51,52</sup> The severity or impact of headache could be associated with the number of headache days or days on medication, and hence these variables and the frequency of secondary CDH should be evaluated in future studies.

In summary, the frequency of CDH among first-visit headache patients was 15.2%, with MOH occurring in 5% of the patients when using ICHD-3 $\beta$  in a multicenter study in Korea. The most common subtype of CDH and MOH was CM, which indicates that advanced strategies for CM treatment would be beneficial in improving CDH and MOH.

#### Conflicts of Interest

The authors have no financial conflicts of interest.

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