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# Comprehensive Application of the International Classification of Headache Disorders Third Edition, Beta Version

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The purpose of this study was to test the feasibility and usefulness of the International Classification of Headache Disorders, third edition, beta version (ICHD-38), and compare the differences with the International Classification of Headache Disorders, second edition (ICHD-2). Consecutive first-visit patients were recruited from 11 headache clinics in Korea. Headache classification was performed in accordance with ICHD-3β. The characteristics of headaches were analyzed and the feasibility and usefulness of this version was assessed by the proportion of unclassified headache disorders compared with ICHD-2. A total of 1.627 patients were enrolled (mean age, 47.4 ± 14.7 yr; 62.8% female). Classification by ICHD-3\beta was achieved in 97.8\% of headache patients, whereas 90.0\% could be classified by ICHD-2. Primary headaches (n = 1,429, 87.8%) were classified as follows: 697 migraines, 445 tension-type headaches, 22 cluster headaches, and 265 other primary headache disorders. Secondary headache or painful cranial neuropathies/other facial pains were diagnosed in 163 patients (10.0%). Only 2.2% were not classified by ICHD-3β. The main reasons for missing classifications were insufficient information (1.6%) or absence of suitable classification (0.6%). The diagnoses differed from those using ICHD-2 in 243 patients (14.9%). Among them, 165 patients were newly classified from unclassified with ICHD-2 because of the relaxation of the previous strict criteria or the introduction of a new diagnostic category. ICHD-3β would yield a higher classification rate than its previous version, ICHD-2. ICHD-3β is applicable in clinical practice for first-visit headache patients of a referral hospital.

Keywords: Headache; Diagnosis; Migraine Disorders; Outpatients

# **INTRODUCTION**

Headache is one of the most common diseases. Tension-type headaches (TTH) and migraine are reported as the second and third most common diseases in the world, respectively (1,2). The international classification of headache disorder (ICHD) was first published in 1988, with a second edition in 2004 and a third edition beta in 2013 (3-5). A Korean version of the International Classification of Headache Disorders, third edition, beta version (ICHD-3 $\beta$ ) was also published (6,7). The ICHD-3 $\beta$  expanded the probable categories and no longer requires remission of the underlying causative disorder before the headache diagnosis, so ICHD-3 $\beta$  offers advantages in headache diagnosis for first-visit patients (8). Field-testing of the ICHD-3 $\beta$  is internationally recommended before publishing the final version (8).

According to the International Classification of Headache Disorders, second edition (ICHD-2) based studies, primary headaches corresponded to 50.1%-78.4% of headaches and 2.5%-23% of the cases were unclassified (2,9-11). Correct classification of the headache disorder is a prerequisite for targeted treatment for both headache specialists and clinicians (12,13). Just a minority of people with headache disorders worldwide are properly diagnosed by headache experts. The reported diagnostic rates for migraine and tension-type headaches are as low as 40%, which may be attributed to under-application of ICHD criteria (14). While there have been some papers about field-testing in each category of headache disorders after publication of the ICHD-3β,

the systematic application of the entire ICHD-3 $\beta$  has not been assessed yet (12,15-21).

The purpose of this study was to test the feasibility and usefulness of the ICHD-3 $\beta$  and to evaluate differences in classification between ICHD-3 $\beta$  and ICHD-2 in neurological outpatient clinics in Korea.

#### MATERIALS AND METHODS

# Standard protocol approvals, registrations, and patient consents

This study, the headache registry using ICHD-3 $\beta$  for first-visit patients (HEREIN) study, is a cross-sectional, multicenter headache registry study using prospectively collected data obtained from consecutive first-visit headache outpatients in the headache clinics of 11 hospitals (9 university hospitals and 2 regional hospitals) in Korea between August 2014 and February 2015. Patients with declined cognitive functions or language problems were excluded as well as those who visited the hospitals for other major symptoms than headaches.

# Headache assessment and diagnosis

Each patient completed a self-administered questionnaire and was interviewed by a headache specialist. In cases where secondary headaches might be suggested, blood tests and neuro-imaging or lumbar puncture tests were conducted. The questionnaire comprised questions regarding the routes of access to the hospitals, duration of headache history, aura, frequency, severity using a visual analog scale (VAS), pain characteristics, location, attack duration, presence or absence of aggravation by routine physical activity, accompanying symptoms, and autonomic features.

A final diagnosis was made by applying the criteria in ICHD- $3\beta$  after compiling the results of the questionnaire analysis, medical records, neurological examination, appropriate testing, and response to treatment. The criteria in ICHD-2 were also applied in order to analyze any differences between ICHD-2 and ICHD- $3\beta$ . We only considered current headaches as their chief complaints at the first visit. As an exceptive clause, patients meeting the criteria for both primary headaches and medication-overuse headaches (MOH) were given both diagnoses. However, such cases were classified as only primary headaches. Only headaches caused purely by substances were classified into the headache attributed to a substance or its withdrawal. MOH incidences were measured separately.

For classification details, primary headaches were classified down to the second-digit diagnoses and secondary headaches, painful cranial neuropathies/other facial pains, and other headaches were classified down to the first digit. Headaches that did not satisfy appropriately any of the criteria were classified into "other headache disorders (ICHD-3 $\beta$  code 14.)" as in the ICHD.

Before the study began, changes in classification with reference to ICHD-2 and ICHD-3 $\beta$  were discussed among the researchers. Several meetings were held to achieve diagnostic consensus in the application of ICHD in real cases. The controversial cases were reviewed by researchers through consensus meetings for case analysis.

Using R (Version 3.1.1, The R Foundation for Statistical Computing, Platform: 64-bit/), we randomly assigned 31 patients to estimate the inter-rater concordance of diagnosis. Clinical summaries of the cases were presented by the corresponding investigator at two regular consensus meetings. Each investigator independently reviewed the structured clinical summaries and subsequently reported the diagnosis by e-mail. Kappa values of 0.41-0.60, 0.61-0.80, and  $\geq$  0.81 were considered to indicate moderate, substantial, and almost perfect agreement, respectively (22). Statistical significance was defined as a P value of < 0.05. The mean kappa values among the researchers were 0.62 with ICHD-2 and 0.61 with ICHD-3 $\beta$ , which suggests substantial agreement. Diagnoses with disagreements were probable TTH, probable migraine, and headaches attributed to infection.

# Statistical analysis

Statistical analysis was conducted using IBM SPSS for Windows (Version 18.0) software. The distributions of headache disorders and comparisons between diagnoses based on ICHD-2 and ICHD-3 $\beta$  were presented as descriptive statistics. For continuous data, statistical differences were evaluated using the Student's *t*-test. Categorical variables were analyzed using the chi-square test. The level of concordance of diagnosis among the researchers was calculated as Fleiss' kappa coefficients.

## **Ethics statement**

The study protocol was reviewed and approved by the institutional review board of Seoul Eulji Hospital (IRB No. EMCS 2014-11-014). All patients gave their informed consent to participate in this study or the informed consent process was waived in accordance with the decision of the ethics committee of each hospital.

## **RESULTS**

# Demographic features and distribution of headache disorders

The number of patients included in our study was 1,627 (1,022 women and 605 men; F/M ratio: 1.7:1; mean age:  $47.3 \pm 14.6$  yr; range: 19-96 yr; and VAS score:  $6.4 \pm 2.1$ ). The demographic characteristics are shown in Table 1. Regarding the referral route, 281 (17.3%) patients were referred by primary care physicians, 350 (21.5%) patients by doctors of other departments in the same hospital, and 988 (60.7%) were self-referrals. The group of pa-

tients referred by doctors from other departments in the same hospital experienced a significantly higher percentage of secondary headaches (14.3% vs. 7.1%, P = 0.001).

In this study, 1,592 (97.8%) of the headaches in the first-visit patients were diagnosed using ICHD-3\(\beta\). With ICHD-2, 1,465 patients (90.0%) were classified. Among the patients, 1,429 (87.8%) were diagnosed with primary headaches (ICHD-3β code 1, to 4.), 135 (8.3%) with secondary headaches (ICHD-3B code 5. to 12.), 28 (1.7%) with cranial neuralgias (ICHD-3β code 13.), and 35 (2.2%) with other headache disorders (ICHD-3\beta code 14.) (Fig. 1).

Regarding the primary headaches, migraine (n = 697, 42.8%)

Table 1. Baseline demographic characteristics of the study population

Characteristics (n = 1,627)	No. of patients (%)
Gender (Female)	1,022 (62.8)
Durations of headache history*	
≤ 7 days	464 (28.5)
8 days-1 month	343 (21.1)
1 month-1 yr	371 (22.8)
> 1 yr	445 (27.4)
Age of headache onset (yr)	
≤ 20	100 (6.1)
21-30	285 (17.5)
31-40	339 (20.8)
41-50	340 (20.9)
51-60	313 (19.2)
61-70	167 (10.3)
≥ 71	83 (5.1)

<sup>\*</sup>Data of headache duration were not available for 4 cases.

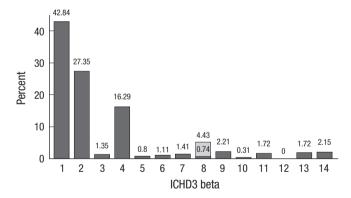


Fig. 1. Distribution of headaches diagnosed according to ICHD-3β. Headache attributed to a substance or its withdrawal (ICHD-3 $\beta$  code 8., 5.2%) consisted of headache attributed to the use of or exposure to a substance (ICHD-3ß code 8.1, 0.74%) and medication overuse headaches accompanied by primary headaches (ICHD-3B) code 8.2, 4.43%). ICHD-3ß indicates International Classification of Headache Disorders third edition, beta version: 1, Migraine; 2, Tension-type headache; 3, Trigeminal autonomic cephalalgias; 4, Other primary headache disorders; 5, Headache attributed to trauma or injury to the head and/or neck; 6, Headache attributed to cranial or cervical vascular disorder; 7, Headache attributed to non-vascular intracranial disorder; 8, Headache attributed to a substance or its withdrawal; 9, Headache attributed to infection; 10, Headache attributed to disorder of homoeostasis; 11, Headache or facial pain attributed to disorder of the cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial or cervical structure; 12, Headache attributed to psychiatric disorder; 13, Painful cranial neuropathies and other facial pains; 14, Other headache disorders.

was the most common followed by TTH (n = 445, 27.4%), trigeminal autonomic cephalalgia (TAC, n = 22, 1.4%), and other primary headaches (n = 265, 16.3%). When the primary headache cases were classified down to the second digit, migraine without aura (ICHD-3 $\beta$  code 1.1, n = 400, 24.6%) was the most common followed by primary stabbing headaches (PSH, ICHD- $3\beta$  code 4.7, n = 179, 11.0%) and probable TTH (ICHD- $3\beta$  code 2.4, n = 147, 9.0%) (Table 2).

Two hundred forty-eight (15.2%) patients reported chronic headaches that had a frequency of  $\geq 15$  days/month over a period lasting  $\geq 3$  months, of which chronic migraine (CM, n = 143, 8.8%) was the most common followed by chronic TTH (n = 98, 6.0%) and new daily persistent headache (NDPH, n = 7, 0.4%). None of these patients had chronic cluster headache or hemicrania continua.

The incidence of secondary headaches was low. Headache attributed to infection (ICHD-3 $\beta$  code 9, n = 36, 2.2%) was the most common of the secondary headaches. It was followed by headache attributed to disorder of the cranium, neck, eyes, ears, nose, sinuses, teeth, mouth, or other facial or cervical structure (ICHD-3 $\beta$  code 11., n = 28, 1.7%) and headache attributed to non-vascular intracranial disorders (ICHD-3 $\beta$  code 7., n = 23, 1.4%). No patient experienced headache attributed to psychiatric disorder (ICHD-3β code 12.).

Brain imaging was conducted with CT (n = 489, 30.1%) or MRI (n = 591, 36.3%). In 50 cases, the headaches were related to brain lesions. The most frequent cause was sinusitis (n = 6)followed by spontaneous intracranial hypotension (n = 4), nontraumatic intracranial hemorrhage (n = 4), reversible cerebral vasoconstriction syndrome (RCVS, n = 3), carotid or vertebral artery dissection (n = 3), and intracranial neoplasm (n = 2).

Seventy-two patients were diagnosed with MOH simultaneously with existing primary headaches. Of these, CM was the most common (n = 49), followed by chronic TTH (n = 13), migraine without aura (n = 7), frequent episodic TTH (n = 1), probable TTH (n = 1), and NDPH (n = 1). With regard to the acute treatment drug, 49.3% of MOH patients used combination analgesics and 33.3% used non-steroid anti-inflammatory drugs.

Table 2. Distribution of 10 common primary headache subtypes diagnosed at firstvisit headache clinics by frequencies

ICHD-3β code	Classification of primary headache disorders	No. (%)
1.1	Migraine without aura	400 (12.2)
4.7	Primary stabbing headache	179 (11.0)
2.4	Probable tension-type	147 (9.0)
1.3	Chronic migraine	143 (9.0)
2.2	Frequent episodic tension-type headache	128 (7.9)
1.5	Probable migraine	112 (6.9)
2.3	Chronic tension-type headache	98 (6.0)
2.1	Infrequent episodic tension-type headache	72 (4.4)
1.2	Migraine with aura	42 (2.6)
4.10	New daily persistent headache	26 (1.6)

**Table 3.** Cases with different diagnosis by ICHD-3β and explanations

ICHD-3β code	Subtypes of headache according by ICHD-3β	Cause of change in diagnosis	No. of patients
1.3	Chronic migraine	Headache ≥ 15 days/M, with ≥ 8 of those days meeting criteria for migraine	17
		Permission of diagnosis with medication overuse headache Permission of migraine with aura	30 2
4.2	Primary exercise headache	Relaxation of the criteria for headache characteristics or duration	5
4.7	Primary stabbing headache	Deletion of the criteria about the first division of the trigeminal nerve	114
4.8	Nummular headache	New diagnostic criteria	1
4.	Probable other primary headache, cough/exercise/external pressure headache/PSH/NPDH	Addition of probable diagnostic criteria	37
6.7.3.1	Headache probably attributed to RCVS	Addition of the probable diagnostic criteria	7
7.3.2	Headache attributed to aseptic meningitis	Addition of a criterion, "viral meningitis or encephalitis has been diagnosed" in 9.1	6
11.5.2	Headache attributed to chronic or recurring rhinosinusitis	New diagnostic criteria	4

PSH, primary stabbing headache; NPDH, new daily persistent headache; RCVS, reversible cerebral vasoconstriction syndrome.

Other headache disorders (ICHD-3 $\beta$  code 14.) were reported in 35 patients (2.2%). The reasons for other headache disorders (ICHD-3 $\beta$  code 14.) were "Headache not elsewhere classified" (ICHD-3 $\beta$  code 14.1, 9 patients), which means headaches that cannot be classified as any of the existing headache disorders, and "Headache unspecified" (ICHD-3 $\beta$  code 14.2, n = 26), which means headaches for which enough information was not available for classification.

# Differences of classification between ICHD-2 and ICHD-3 $\beta$

Of all the patients, 243 (14.9%) showed differences in classification between ICHD-2 and ICHD-3β. The reasons for differences in classification were changes in the diagnostic criteria (n = 193) and the availability of new diagnostic criteria in ICHD-3 $\beta$  (n = 50) (Table 3). Among these patients, 165 were newly classified as those showing relevant headache disorders with ICHD-3β compared to being classified as showing other headache disorders (ICHD-2 14.) with ICHD-2. With ICHD-3β, diagnosis changed from different headache diagnoses under ICHD-2 (n = 79). PSH (n = 114) was the most common diagnosis that was newly classified with ICHD-3ß but was classified as "other headache disorders (ICHD-2 14.)" with ICHD-2. CM (n = 49) was the most common diagnosis that changed upon classification with ICHD-3β. Using ICHD-2, 30 patients were diagnosed with MOH, 2 patients were diagnosed with migraine with aura, and 17 patients were diagnosed with migraine without aura instead of CM under ICHD-3\beta. Headaches that were diagnosed after the establishment of the new criteria for diagnosis were probable other primary headache (n = 37), probable RCVS (n = 7), headache attributed to chronic rhinosinusitis (n = 4), and nummular headache (n = 1).

# **DISCUSSION**

In this study, 97.8% of the headaches in the first-visit patients were diagnosed using ICHD-3 $\beta$ , with kappa values indicating

substantial agreement. ICHD-3 $\beta$  yielded a higher classification rate than that achieved with ICHD-2, with similar kappa values. To our knowledge, this is the first study to apply ICHD-2 and ICHD-3 $\beta$  simultaneously to determine differences in diagnoses between headaches classified with ICHD-2 and with ICHD-3 $\beta$ .

Primary headaches were diagnosed in 87.8% of the patients and secondary headaches and painful cranial neuropathies/ other facial pains were diagnosed in 8.3% and 1.7% of patients. This distribution of headaches was similar to the results of previous studies conducted in specialized headache clinics and had a higher ratio of primary headaches than that in studies conducted in general neurology or emergency departments (2,9,11,23,24).

ICHD-3β is better than ICHD-2 in the area of other primary headaches and CM (5,25,26). According to other ICHD-2-based studies, other primary headaches accounted for 1.5-5.9% of all headaches (2,9,11,23). In this study, other primary headaches were very commonly diagnosed with ICHD-3β, with the percentage being 16.3%. In particular, PSH was the most common type of headache in other primary headaches because the criterion that limited the pain distribution to the first division of the trigeminal nerve has been deleted in ICHD-3 $\beta$  (5,27). In this study, the number of patients who were diagnosed with PSH increased from 65 patients (4.0%) under ICHD-2 to 179 patients (11.0%) under ICHD-3β. One hundred fourteen patients (7.0%) who were diagnosed with "other headache disorders (ICHD-2 14.)" under ICHD-2 were newly diagnosed with PSH under ICHD-3β. There are some relaxed changes like PSH in the other primary headache section. For thunderclap headaches, the criterion of irregular recurrence during subsequent weeks or months has been discarded. Hypnic headaches are no longer defined as headaches with an age of onset of 50 yr. A number of pain characteristics under the NDPH have been eliminated (5). In ICHD-3β, probable diagnoses were added in all other primary headache disorders except primary thunderclap headache. Thus, the addition of probable diagnoses and the relaxation of diagnostic criteria on headache duration or regions of headaches in other primary headaches could lead to a noticeable increase in other primary headaches.

In this study, CM accounted for 20.5% of all migraines under ICHD-3 $\beta$  as opposed to 13.5% under ICHD-2. The revised criteria of ICHD-2 for CM in 2006 were formulated to reduce migraine periods to 8 days/month (26,28). The ICHD-3 $\beta$  criteria for CM also constitute an advancement over the previous version because they allow acute medication overuse and allow both migraines with and without aura (5,29). The ICHD-3 $\beta$  appears more appropriate for the diagnosis of CM than the previous version because classification could be appropriately performed in patients with MOH (29).

Another characteristic of ICHD-3 $\beta$  is the relaxation of criteria of secondary headaches. The ICHD-3 $\beta$  enables diagnosis of secondary headaches before reduction or resolution of headaches is achieved after successful treatment or spontaneous remission of the causative disorders. In previous studies based on ICHD-2, headache attributed to substances or substance withdrawal was the most common among secondary headaches with percentages in a range of 7.4%-9.9% (9-11). In this study, among 72 patients (4.43%) with MOH accompanied by primary headache, headache attributed to substances or substance withdrawal (5.2%) was the most common secondary headache followed by headache attributed to infection (2.2%) (Fig. 1).

With regard to problems in the application of ICHD-3β in first-visit patients, probable TTH accounted for a large number (n = 147, 9%). Low diagnostic stability is expected for probable TTH that has occurred within the previous 3 months. These headaches require follow-up studies because the diagnosis might change after three months. Second, there was no headache attributed to psychiatric disorder in this study; this finding is similar to those in other studies where such headaches accounted for only 0%-0.3% of all headaches (9-11). Headaches are commonly associated with various psychiatric disorders, but evidence of a causal relationship is lacking for most cases. The cases with occurrence of headache during periods of some common psychiatric disorders such as depression, panic attack, anxiety, or trauma/stress-related disorders can be diagnosed with only the appendix diagnostic criteria of ICHD-3β because of uncertainties concerning the causal relationships (5). Additional systematic studies on headaches related to psychiatric diseases are necessary. Third, in the case of lymphocytic meningitis for which the causative viruses had not been identified, diagnoses by the researchers were divided into two categories: 7.3.2 headache attributed to aseptic noninfectious meningitis and 9.1.2 headache attributed to viral meningitis. This caused many discrepancies in inter-rater reliability among researchers during Kappa-value assessment. ICHD-3β requires substantiation of causative viruses as it includes a criterion "Viral meningitis or encephalitis has been diagnosed" in the 9.1.2 diagnostic criteria. Since causative viruses are difficult to detect in a clinical setting, we suggest elimination the criterion "viral meningitis or encephalitis has been diagnosed" in the 9.1.2 diagnostic criteria.

The strengths of the present study are as follows. First, the present study strictly applied both ICHD-3β and ICHD-2 to clarify the differences and to determine the strengths and limitations of ICHD-3 before the release of the final version in 2016. Second, headaches were strictly classified by headache specialists in multiple centers (9 university hospitals and 2 regional hospitals), which is in contrast with what happened in previous studies conducted in a single headache center or a general neurological clinic. Third, the accuracy of diagnoses increased because of the good quality of data such as high imaging rates up to 65% and regular meetings for the conformity of diagnoses in difficult cases or cases of "other headache disorders." Fourth, obscurities in actual interpretations and field applications at clinics could be found through verification of the inter-rater reliability of diagnoses among researchers. Fifth, the short interval between headache onset and diagnosis provided increased accuracy in history taking and classification of headaches. Headache periods in this study were shorter than those in other studies conducted in general neurology clinics. In this study, 72.6% of patients had a headache period of  $\leq 1$  yr, whereas in other studies, the number of patients with a headache period of  $\leq 1$ yr was limited to 20% (2). The National Health Insurance Service system and the easy accessibility to second or tertiary hospital in Korea influenced the shorter duration of headaches and this study population may include initial phenotypes of headache disorders.

This study also has some limitations. First, the data cannot be used to represent the general population because of sample bias due to the hospital setting. Second, there may not have been a sufficient reflection of seasonal variations because this study was carried out for five months from autumn to winter. Third, this study was a cross-sectional study with first-visit patients, and there could be a change in headache diagnosis from baseline to that at follow-up. Finally, primary headache disorders were classified down to the second digit and secondary headache disorders to the first digit in this study. The classification of headache disorders was not in sufficiently detailed to enable simultaneous classification with the World Health Organization's International Classification of Disease (WHO ICD)-11.

In summary, we found that classification using ICHD-3 $\beta$  was possible in 97.8% of first-visit patients with headaches, and ICHD-3 $\beta$  proved to have a higher classification rate than its previous version. This study is also important in that it revealed the problems in the application of ICHD-3 $\beta$  before the final version of ICHD-3 becomes available. After publication of the final version of ICHD-3, further studies that will classify diagnoses in more detail down to the third or fourth digit and include longi-

tudinal follow-up to determine the accuracy and stability of diagnoses, should be conducted.

### **DISCLOSURE**

The authors declared no conflict of interest in this work.

#### **AUTHOR CONTRIBUTION**

Conception and coordination of the study: Moon HS, CHO SJ. Design of ethical issue: Park KY. Acquisition of data: Kim BK. Analysis and interpretation of data: Kim BK, Cho SJ, Kim BS, Sohn JH, Kim SK, Cha MJ, Song TJ, Kim JM, Park JW, Chu MK. Data review and statistical analysis: Park KY. Manuscript preparation: Kim BK, Moon HS. Critical revision of the manuscript: Cho SJ, Sohn JH, Cha MJ, Kim SK, Moon HS. Manuscript approval: all authors.

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# Appendix

ICHD-3 code: Diagnosis

- 1. Migraine
- 2. Tension-type headache
- 3. Trigeminal autonomic cephalalgias
- 4. Other primary headache disorders
- 5. Headache attributed to trauma or injury to the head and/or neck
- 6. Headache attributed to cranial or cervical vascular disorder
- 7. Headache attributed to non-vascular intracranial disorder
- 8. Headache attributed to a substance or its withdrawal
- 9. Headache attributed to infection
- 10. Headache attributed to disorder of homoeostasis
- 11. Headache or facial pain attributed to disorder of the cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial or cervical structure
- 12. Headache attributed to psychiatric disorder
- 13. Painful cranial neuropathies and other facial pains
- 14. Other headache disorders