



## The Role of Drug Efficacy Should be Downgraded in ICHD Diagnostic Criteria

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**Received date:** April 24, 2017; **Accepted date:** May 13, 2017; **Published date:** May 19, 2017

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### Abstract

Headache is a highly complex condition and cannot be explained by a single mechanism. There are no biomarkers for headache, and no effective diagnostic tests which are universally applicable. For instance, the International Classification of Headache Disorders (ICHD) criteria for conditions such as chronic migraine, hemicrania continua and Tolosa-Hunt syndrome require diagnosis to include a detailed medical history and notification of potential sensitivity to treatment drugs.

However, diagnosis is flawed in some of these patients using the normal treatment criteria and can lead to incorrect diagnoses and treatment responses. This paper reviews relevant studies pertaining to treatment response to headache and suggests that the ICHD should remove treatment response as a criterion. The accurate diagnosis of headache must precede treatment, and consideration of drug efficacy should not be required as a diagnostic criterion for headache. We suggest that treatment response could help to confirm the final diagnosis of headache in cases where diagnosis is undefined, and it is entirely reasonable to downgrade the role of treatment response in the ICHD diagnostic criteria for headache.

**Keywords:** Treatment response; International classification of headache disorders; Chronic migraine; Hemicranias continua; Tolosa-Hunt syndrome

### Mini Review

Headache disorders represent a common and disabling condition throughout the world [1]. Almost everyone will experience a headache of some type during their lifetime. A previous study reported that the worldwide prevalence of headaches for lifetime exceeded 90% [1]. Primary headache disorders, particularly migraine and tension-type headache (TTH), are also prevalent on a global scale [2,3] in China, the one-year prevalence of primary headache disorders was estimated to be 23.8% [2]. Headache is a complex disease and headache experts have been carrying out research on this complex condition for many years. However, despite such effort, the pathological mechanisms underlying headache still remains unclear.

Previous studies have shown that multiple mechanisms are involved in the onset of headache. Both peripheral and central sensitization has been recognized as fundamental factors in the symptoms of many headache disorders [4] this can manifest as allodynia during episodes of migraine. This opinion has formed a basis for the current basic studies of central sensitization in the maintenance of chronic migraine (CM). Administering treatment before the onset of allodynia is known to be associated with improved responsiveness to triptans, a common

class of drug used to treat migraines [5]. In our headache clinic, patients with tension-type headache (TTH) occasionally also experience allodynia; this may arise from heightened activity of supra-spinal and spinal nociceptors [4]. In addition, studies have identified potential molecular mechanisms, such as 5-hydroxytryptamine, Nitric oxide and Calcitonin gene-related peptide, which might be involved in the pathogenesis of headache [4,6].

CM is a disabling disorder which is under-diagnosed and under-treated [7]. The International Classification of Headache Disorders-3 $\beta$  criteria (ICHD-3 $\beta$ ) define CM criteria as follows: A: Headache on  $\geq$  15 days per month for at least 3 months; B: Occurring in a patients who has had at least 5 attacks fulfilling criteria for 1.1 migraine without aura and/or 1.2 migraine with aura; C: On  $\geq$  8 days per month for at least 3 months one or more of the following criteria were fulfilled: (1) Criteria C and D for 1.1 migraine without aura, (2) Criteria B and C for 1.2 migraine with aura, (3) Headache considered by patient to be onset migraine and relieved by a triptan or an ergotamine derivative; D: Not better accounted for by another ICHD-3 $\beta$  diagnosis [8]. The ICHD-3 $\beta$  requires migraine-specific medication as one of its criteria, as a previous study showed that patients in some countries were taking triptans prescribed by their headache clinics; this could, of course, increase the sensitivity of the criteria [9].

Table 1 summarizes the usage of migraine-specific medication in different countries.

Reference	Country	Diagnosis	Patients (n)	Triptan	Ergot
Qingqing Huang et al., [10]	China	CDH	304	0	0
Yunfeng Wang et al., [11]	China	MOH	45	0	0

Huahua Jiang et al., [12]	China	CM	261	1 (0.5%)	0
Zhao Dong et al., [13]	China	MOH	217	2 (0.9%)	2 (0.9%)
Beatriz Shand et al., [14]	Argentina and Chile	MOH	240	13 (5.4%)	168 (70%)
N Imai et al., [15]	Japan	MOH	47	1 (2.1%)	1 (2.1%)
Z. Katsarava et al., [16]	Germany	MOH	95	29 (30.5%)	16 (16.8%)
S Cevoli et al., [17]	Italy	Migraine	256	119 (46.5%)	0
Ninett Louise Find et al., [18]	Europe	MOH	669	206 (30.8%)	25 (3.7%)
	Latin America			37 (5.6%)	483 (72.2%)
Pernilla Jonsson et al., [19]	Sweden	MOH	799	66 (8.3%)	72 (0.9%)
Giuliano Relja et al., [20]	Italy	CM	114	13 (11.4%)	12 (10.5%)

**Table 1:** Summary of application of migraine-specific medication in different regions.

It is highly apparent that migraine-specific medications are still not available on a global scale from these data. This may be because other types of analgesics are not only effective and cheaper than triptans. Moreover, migraine-specific medications can also be effective against other primary headaches, such as cluster headaches and some secondary headaches. Consequently, it is very evident that the ICHD-3 $\beta$  criteria for CM are difficult to apply in clinical practice on a worldwide basis. In an attempt to address this significant problem, we conducted a study which involved field-testing the ICHD-3 $\beta$  and expert opinion (EO) criteria for CM; this research showed that EO criteria were more applicable [12,21]. This additional criterion added probable migraine to C1 and C2, and removed criterion C3, based on the treatment and relief of headache by triptan or ergot drugs [21]. We therefore suggest that the EO criteria should be adopted in standard management practice for CM.

Hemicrania continua (HC) is an uncommon type of primary headache characterized by persistent, strictly unilateral headache, associated with ipsilateral conjunctival injection, lacrimation, nasal congestion, rhinorrhoea, forehead and facial sweating, miosis, ptosis and/or eyelid oedema, and occurs with or without restlessness or agitation [8]. Absolute sensitivity to indomethacin is required as one of the diagnostic criteria for HC [8]. However, an earlier report showed that cases with a short history of trigeminal autonomic cephalalgia-like headaches and abnormal neurological examinations upon follow-up, even with an absolute response to indomethacin, should still prompt additional evaluations for secondary causes [22]. Nasopharyngeal carcinoma is also known to mimic HC [22]. Another study reported numerous cases of secondary HC [23]. Moreover, another type of primary headache, known as ‘paroxysmal hemicrania’ (PH) also shows extreme sensitivity to indomethacin. Research showed that indomethacin may also take effect upon various other types of headache, such as jabs and jolts syndrome, benign exertional headache and some cases of cluster headache [24]. If based upon the criterion of an absolute indomethacin response, diagnosis can be controversial. Consequently, we suggest that ICHD remove criterion D items, which state “Responds absolutely to therapeutic doses of indomethacin”.

Tolosa-Hunt syndrome (THS) is an important cause of painful ophthalmoplegia (PO), and is described by the ICHD-2 as episodic orbital pain associated with paralysis of one or more of the third, fourth and/or sixth cranial nerves, which usually resolves

spontaneously but tends to relapse and remit [25]. Some reported cases of THS have been associated with additional involvement of the trigeminal nerve (commonly the first division) or optic, facial or acoustic nerves. Sympathetic innervation of the pupil is occasionally affected [25]. The diagnosis of THS should exclude other causes of PO such as tumours, vasculitis, basal meningitis, neurosarcooidosis and diabetes. The ICHD-2 requires that pain and paresis resolve within 72 hours when treated adequately with corticosteroids, which is used as one of the diagnostic criteria [25]. However, the ICHD-3 $\beta$  criteria published in 2013 for THS removed item D, stating “pain and paresis resolve within 72 hours when treated adequately with corticosteroid”, and instead, commented that pain and paresis of THS resolve when treated adequately with corticosteroids [8]. An Italian study evaluated the ICHD-3 $\beta$  diagnostic criteria for THS and concluded that it was reasonable to delete criterion D but still retain the specific mention of corticosteroid treatments [26]. This revision indicated that corticosteroid response remained meaningful for THS and that corticosteroid treatment could confirm the final diagnosis of THS, rather than diagnose THS. Consequently, downgrading the role of corticosteroid treatment is deemed to be reasonable.

## Conclusion

Based upon criteria regarding responsiveness to treatment drugs, the precise diagnosis of headache remains controversial, and thus implying potential risk for inappropriate diagnosis and poor management. The diagnosis of headache should precede the remedy; drug efficacy should not be required as a diagnostic criterion. Treatment response, however, could help to confirm the final diagnosis of headache in cases where the original diagnosis was undefined. Consequently, we propose that it is entirely reasonable to downgrade the role of treatment response in the ICHD diagnostic criteria for headache.

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