Chapter 120

Headache Attributed to a Disorder of Homeostasis

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INTRODUCTION

The headache disorders within this category were previously referred to as headache associated with metabolic or systemic disease. However, headache attributed to disorder of homoeostasis was felt to more fully encompass disorders of homeostatic mechanisms affecting a variety of organ systems, including altered arterial blood gases, systemic arterial pressure, volume disturbances that occur as a result of dialysis, and disorders of endocrine function. Headache attributed to fasting and cardiac ischemia are also included in this category.

HEADACHE ATTRIBUTED TO HYPOXIA AND/OR HYPERCAPNIA

Headache as a result of disturbances in arterial blood gas concentrations is well established, although it is often difficult to distinguish between the effects of hypoxia and hypercapnia.

HIGH ALTITUDE HEADACHE

International Headache Society (IHS) International Classification of Headache Disorders (ICHD) II code and diagnosis:
10.1.1 High altitude headache
World Health Organization (WHO) code and diagnosis:
G44.882 High altitude headache
Short description: the headache occurs within 24 hours after acute onset of hypoxia with PaO_2 less than 70 mm Hg or in chronically hypoxic patients with PaO_2 persistently at or below this level.

Clinical Features

The ICHD-II diagnostic criteria for HAH are as follows:

A. Headache with at least two of the following characteristics and fulfilling criteria C and D:
  1. Bilateral
  2. Frontal or frontotemporal
  3. Dull or pressing quality
  4. Mild or moderate intensity
  5. Aggravated by exertion, movement, straining, coughing, or bending
B. Ascent to altitude above 2500 m.
C. Headache develops within 24 hours after ascent.
D. Headache resolves within 8 hours after descent.

Headache is the most common neurologic symptom and complication arising from ascent to altitudes greater than 2500 ms (30,62). Until recently, there were few systematic attempts to define the clinical features of HAH and only a small number of therapeutic trials, which at times yielded conflicting results (8,16). Most descriptions of HAH were originated with clinicians with extensive personal experience at altitude (4).

A recent study prospectively analyzed the incidence, risk factors, and clinical characteristics of HAH in members of an expeditionary unit to the Kanchenjunga base camp in Nepal (5100 m) (65). Participants were interviewed prior to the trip and while trekking, they recorded headaches experienced at greater than 3000 m using a structured questionnaire incorporating original diagnostic criteria for HAH and acute mountain sickness (AMS) from the ICHD-I. In addition, clinical features of headaches in 19 trekkers from other groups above 3000 m were recorded using the same questionnaire. This study demonstrated that 83% (50/60) reported at least one HAH (median 2, range 0 to 10) at a mean altitude of 4723 m. Those who developed HAH were significantly younger, suggesting that age-related cerebral atrophy might allow a greater capacity to accommodate mild cerebral edema. Women and people with headaches in daily life were also more likely to report severe headaches at altitude. In this study, 95% of the

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women reported headaches compared to 82% of the men, and headaches were reported more frequently and were described to be of greater severity compared with the men. At normal altitudes, women have a higher rate of migraine and most other headache disorders than men, raising the possibility that they may be more susceptible to headache at altitude. HAH often awakened participants from sleep or occurred upon awakening and was exacerbated by bending, coughing, or sneezing, suggesting the possibility of intracranial hypertension as a contributing factor.

The typical features of HAH are an onset within 24 hours of reaching a particular height, duration of less than a day, and in most cases a bilateral, generalized, dull pressure sensation. HAH is usually not accompanied by hypoxic symptoms such as a desire to overbreathe or exertional dyspnea, perhaps because subjects may consider these to be normal features at altitude.

Persons rapidly ascending to high altitudes are also at risk of developing AMS, the principal symptom of which is moderate or severe headache, combined with one or more other symptoms including nausea, anorexia, fatigue, dizziness, and sleep disturbances (31). In extreme cases, AMS may progress to an acute encephalopathy characterized by ataxia and a depressed level of consciousness termed high-altitude cerebral edema (HACE). Magnetic resonance imaging (MRI) studies of individuals with HACE have shown vasogenic cerebral edema (32). This suggests that a proportion of headaches at altitude, and certainly AMS, may be part of a similar pathogenic process with HACE at the extreme of the continuum.

MANAGEMENT

The management of HAH is empiric in the absence of controlled trials. Preventative strategies include allowing 2 days of acclimatization prior to engaging in strenuous exercise at high altitudes, avoiding alcohol, and liberalizing fluid intake. Acetazolamide (125 mg, two or three times daily) may reduce susceptibility to AMS. Most high-altitude headaches respond to simple analgesics such as acetaminophen (paracetamol) or ibuprofen (65). Triptans have also been shown to be effective for migraine headaches experienced at altitude (8).

DIVING HEADACHE

IHS ICHD-II code and diagnosis: 10.1.2 Diving Headache
WHO code and diagnosis: G44.882 Diving headache

CLINICAL FEATURES

The ICHD-II diagnostic criteria for diving headache are as follows:

A. Headache, no typical characteristics known, fulfilling criteria C and D.
B. Diving to depth below 10 m.
C. Headache develops during diving and is accompanied by at least one of the following symptoms of CO_2 intoxication in the absence of decompression illness:
  1. Lightheadedness
  2. Mental confusion
  3. Dyspnea
  4. Flushed feeling in the face
  5. Motor incoordination
D. Headache resolves within 1 hour after treatment with 100% O_2.

The cause of headache in divers is diverse. Primary headache disorders may occur while diving, including migraine, tension-type headache, primary exertional headache, cervicogenic headache, and headache or facial pain attributed to temporomandibular joint (TMJ) disorder. Divers may also experience headache or facial pain as a result of decompression sickness, arterial gas embolism, paranasal sinus, or otic barotrauma, and due to compression from the mask ("mask squeeze") or goggles ("goggle headache"). Germane to this discussion, however, are the headaches in divers that can occur as a result of hypercapnia and carbon monoxide toxicity.

Hypercapnia (arterial $PCO_2 > 50$mm Hg) is known to cause relaxation of cerebrovascular smooth muscle and lead to vasodilation and increased intracranial pressure (66). Hypercapnia is a common cause of headache in divers, as well as a provocative trigger for migraine and cluster headache in susceptible divers (17,33,35). Carbon dioxide may accumulate in a diver who intentionally holds his or her breath intermittently (skip breathing) in a mistaken attempt to conserve air, or takes shallow breaths to minimize buoyancy variations in the narrow passages of a wreck or cave (18). Divers may also hypoventilate unintentionally when a tight wetsuit or buoyancy compensator jacket restricts chest wall expansion, or when ventilation is inadequate in response to physical exertion. Strenuous exercise increases the rate of CO_2 production more than 10-fold, resulting in a transient elevation of PCO_2 to more than 60 mm Hg (18). Diving headache usually intensifies during the decompression phase of the dive or upon resurfacing. A mechanism analogous to AMS has also been hypothesized to explain headaches affecting professional divers.

In a prospective study of Norwegian saturation divers, 4% reported headache during the first day of decompression, 23% on the last day of decompression, and 34% on the first day after reaching the surface (25). The pain was located over the frontal or vertex regions, recorded as mild in severity with a median of 2.5 on a 10-point visual analog scale (range 0.1 to 7.8), and lasted a median duration of 6 hours (range 1 to 84 hours).

Additional symptoms of CO_2 intoxication can include lightheadedness, mental confusion, dyspnea, a flushed

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feeling in the face, and motor incoordination, progressing, as CO_2 tension rises, to central respiratory and cardiac depression followed by unconsciousness and convulsions. Because the exotic underwater milieu can mask these symptoms, and some divers will not develop headache, the affected diver may have little or no warning preceding apnea and loss of consciousness. Some individuals will have a markedly reduced ventilatory response to elevated $PaCO_2$ and are at greater risk of developing toxicity. Retention of CO_2 also potentiates O_2 toxicity or inert gas narcosis and may render the diver more susceptible to decompression illness (18).

Headache also is an early symptom of poisoning from carbon monoxide (CO), an odorless gas that rarely has contaminated a diver's compressed air supply when, during tank preparation, the air intake system is inadvertently positioned toward street traffic and exposed to the combustion engine exhaust of an idling vehicle (20). Binding to hemoglobin with 250-fold greater affinity than oxygen, CO impairs the oxygen-carrying capacity of hemoglobin. The resulting tissue hypoxia and CO-mediated release of nitric oxide dilates cerebral vessels. Frontal headache, dizziness, exertional dyspnea, and nausea result once blood carboxyhemoglobin levels exceed 10 to 15% (20). Treatment of CO poisoning consists of inhaling 100% oxygen or hyperbaric oxygen to hasten carboxyhemoglobin dissociation and should be administered without delay (20).

MANAGEMENT

Prevention is the best treatment. The diver should take slow, deep breaths and avoid skip breathing or prolonged physical exertion underwater. The regulator should be maintained to a satisfactory performance level to minimize breathing resistance. Treatment of hypercapnia consists of ensuring a patent airway, physical rest, and comfortable deep breathing. Nonsteroidal anti-inflammatory drugs (NSIADs) and ergotamine preparations have been reported to be ineffective (17).

Sedating medications, such as opioids, butalbital, or phenothiazines, should be avoided when diving because they can impair alertness and judgment, especially at depths beyond 20 to 30 m where inert gas narcosis may compound the diver's cognitive impairment. Opioids carry the additional risk of respiratory depression, which can worsen CO_2 retention. β-Blockers for migraine prophylaxis in the diver should be prescribed cautiously because of their potential to unmask latent asthma and because they can reduce exercise capacity.

SLEEP APNEA HEADACHE

IHS ICHD-II code: 10.1.3 Sleep apnea headache
WHO code and diagnosis: G44.882 Sleep apnea headache
Short description: although morning headache is significantly more common in patients with sleep apnea than in the general population, headache present upon awakening is a nonspecific symptom that occurs in a variety of primary and secondary headache disorders, in sleep-related respiratory disorders other than sleep apnea (e.g., pickwickian syndrome, chronic obstructive pulmonary disorder), and in other primary sleep disorders such as periodic leg movements of sleep. A definitive diagnosis of 10.1.3 Sleep apnea headache requires overnight polysomnography.

It is unclear whether the mechanism of 10.1.3 Sleep apnea headache is related to hypoxia, hypercapnia, or disturbance in sleep.

CLINICAL FEATURES

The ICHD-II diagnostic criteria for sleep apnea headache are as follows:

A. Recurrent headache with at least one of the following characteristics and fulfilling criteria C and D:
  1. Occurs >15 days per month
  2. Bilateral, pressing quality and not accompanied by nausea, photophobia, or phonophobia
  3. Each headache resolves within 30 minutes.
B. Sleep apnea (respiratory disturbance index ≥5) demonstrated by overnight polysomnography.
C. Headache is present upon awakening.
D. Headache ceases within 72 hours and does not recur after effective treatment of sleep apnea.

The prevalence of obstructive sleep apnea syndrome (OSA) in an adult population is estimated to be 2% in women and 4% in men, applying the minimum diagnostic criteria of the nocturnal apnea/hypopnea index (AHI) of more than five per hour and daytime sleepiness (74). Sleep-associated disturbances of breathing without daytime sleepiness were even more frequent, demonstrating the importance of applying standardized diagnostic criteria (74). Equally if not more frequent in Western societies is the prevalence of chronic daily headache with a prevalence of about 4 to 5% (60). Due to the high prevalence of both disorders, the association between headache and OSA has generated considerable controversy on the basis of conflicting data.

Several studies have addressed the relationship between OSA and headache. Paiva et al. found that about half of the patients with nocturnal or early morning headache suffered from a sleep disorder including OSA (53). When the sleep disorder was treated with success, the headache generally disappeared, supporting a causal role of the sleep disorder for headache. Previous studies have suggested that headaches, particularly morning headaches, are more common in patients with sleep apnea than in normal subjects (53,68). Furthermore, the prevalence of headache is

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reported to be higher in patients with OSA than in a control group (68). Headaches claimed to be associated with OSA are brief, and the occurrence and severity correlated with OSA severity in one study (45). Others have reported that while morning headache is common in OSA, it occurred just as frequently in other sleep-related disorders, and the headache characteristics are quite nonspecific (2,50,55). Furthermore, in a study involving tertiary care headache patients who reported heavy snoring and episodes of interrupted nocturnal breathing, only 1.5% who were examined with polysomnography (PSG) had an apnea/hypopnea index of 5 or higher (38).

MANAGEMENT

Obstructive sleep apnea–hypopnea syndrome (OSAHS) is a chronic disease that requires consultation and ongoing follow-up with a sleep medicine specialist, patient education, and alleviation of upper airway obstruction. Because many patients with OSAHS are overweight or have comorbid cardiovascular risk factors or diseases, they must be informed of the interaction of OSA and overall health. Prospective data on the cardiovascular and perioperative benefits of OSAHS treatment are emerging, but the current, most widely accepted patient and physician treatment target is hypersomnolence (24,52).

In many patients, lifestyle modifications including weight loss, alcohol/sedative avoidance, smoking cessation, avoidance of sleep deprivation, and, if appropriate, sleep position restriction will decrease both the symptoms of OSA and the comorbid conditions.

Continuous positive airway pressure (CPAP) is the standard treatment for OSA. CPAP involves the use of a device that pneumatically splints the upper airway during inspiration and expiration. A placebo-controlled, randomized trial showed that CPAP decreases sleepiness and increases quality of life (24). During polysomnography, CPAP is titrated to a level that eliminates snoring and apneas/hypopneas and is then most often prescribed at a "fixed" pressure level that will maintain airway patency during conditions of greatest vulnerability (rapid eye movement [REM] sleep while supine). For most patients, the prescribed pressure is in the 7- to 11-cm H_2O range.

Compliance with CPAP continues to be a major issue limiting its use. Usage patterns and problems with CPAP vary among patients, and patient characteristics that consistently predict CPAP compliance have not been identified. Only a few comprehensive, long-term compliance studies have been published, and they indicate that continuing CPAP use generally correlates with AHI severity, average nightly use of fewer than 2 hours at 3 months predicts failure, and ongoing use at 5 years is 65 to 90% (39,47).

Alternative treatment options, including oral appliances, have been developed for mechanically enlarging or stabilizing the upper airway by advancing the mandible or tongue. Subjective improvements in snoring are reported in most case series with oral appliances. Approximately 50% of patients achieve an AHI lower than 10 with the use of oral appliances, and long-term compliance rates are 50 to 100% (61). Randomized crossover comparisons reveal that CPAP devices are more effective at lowering the AHI than oral appliances, which are most appropriate for patients with mild to moderate OSA (73).

Uvulopalatopharyngoplasty, an operation that modifies the retropalatal airway by excision of the uvula, a portion of the soft palate, and tonsils (if present), produces mixed results. Although snoring is usually subjectively improved, objective improvements have not been well documented. Furthermore, less than 50% of patients achieve an apnea index lower than 10 and at least a 50% reduction in apneas (64). Laser-assisted uvulopalatoplasty is not currently recommended for the treatment of OSAHS (44). Radiofrequency ablation techniques can be applied focally to reduce the size of the palate and base of tongue, but efficacy data are limited. Other surgical options include tracheostomy (used rarely) and oral maxillofacial procedures.

DIALYSIS HEADACHE

IHS ICHD-II code and diagnosis: 10.2 Dialysis headache
WHO code and diagnosis: G44.882
Short description: Headache that commonly occurs in association with hypotension and dialysis disequilibrium syndrome. The disequilibrium syndrome may begin as headache and then progress to obtundation and finally coma, with or without seizures. This syndrome is relatively rare and may be prevented by changing dialysis parameters.

As caffeine is rapidly removed by dialysis, 8.4.1 Caffeine-withdrawal headache should be considered in patients who consume large quantities of caffeine.

CLINICAL FEATURES

The ICHD-II diagnostic criteria for dialysis headache are as follows:

A. At least three attacks of acute headache fulfilling criteria C and D.
B. Patient is on hemodialysis.
C. Headache develops during at least half of hemodialysis sessions.
D. Headache resolves within 72 hours after each hemodialysis session and/or ceases altogether after successful transplantation.

Approximately 70% of patients receiving dialysis complain of headaches (3,7). Until recently, headaches in this

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population of patients were not systematically evaluated. A recent prospective study of 123 patients with chronic renal failure from three Brazilian hemodialysis services reported headache in 87 of 123 patients (70.7%) (3). Before dialysis, 48% had migraine, 19% had episodic tension-type headache, and 8% had both. Headache related to arterial hypertension was the second most frequent headache diagnosis in these patients (25.4%). Fifty patients (57.5%) experienced headache during the session of hemodialysis. Thirty-four were classified as dialysis headache, seven were classified as migraine, seven as episodic tension-type headache, and two were unclassified. Twenty-four patients (27.6%) reported dramatic improvement of their headaches after the beginning of the dialysis program.

Similar to other studies, there was a male preponderance in this study, and when headache occurred during hemodialysis, a higher incidence was observed between the third and fourth hour. Similarly, another recent study showed that the prevalence of headaches during hemodialysis was directly proportional to the number of hours in session (15). The headaches that occurred during hemodialysis sessions resembled migraine without aura in 19 patients, tension-type headache in 13, migrainous disorder in 1, and tension-type headache disorder not fulfilling all criteria in 1 patient. They also observed a relative increase in the prevalence of tension-type headache after the beginning of the dialysis program.

While it is clear that hemodialysis can be a trigger for antecedent headache disorders (migraine, tension-type headache), it is equally clear that headaches can occur de novo during hemodialysis. However, the clinical features and their pathogenesis remain to be elucidated. A number of mechanisms may be involved including hypoxemia that occurs at the beginning of the sessions, hyponatremia, changes in serotonin levels, alterations in levels of urea, aldosterone, and dialysis disequilibrium syndrome. Because these metabolic derangements do not resolve immediately, the resolution of dialysis headaches has been lengthened in ICHD-II from 24 hours to 72 hours after a hemodialysis session.

HEADACHE ATTRIBUTED TO ARTERIAL HYPERTENSION

IHS ICHD-II code and diagnosis: 10.3 Headache attributed to arterial hypertension
WHO code and diagnosis: G44.813 Headache attributed to arterial hypertension
Short description: Mild (140 to 159/90 to 99 mm Hg) or moderate (160 to 179/100 to 109 mm Hg) chronic arterial hypertension does not appear to *cause* headache. Whether moderate hypertension *predisposes* to headache at all remains controversial, but there is little evidence that it does. Ambulatory blood pressure monitoring in patients with mild and moderate hypertension has shown no convincing relationship between blood pressure fluctuations over a 24-hour period and presence or absence of headache. However, headache related to various disorders that lead to abrupt, severe, and paroxysmal elevations in blood pressure are associated with headache.

HEADACHE ATTRIBUTED TO PHEOCHROMOCYTOMA

IHS ICHD-II code and diagnosis: 10.3.1 Headache attributed to pheochromocytoma
WHO code and diagnosis: G44.813 Headache attributed to pheochromocytoma

CLINICAL FEATURES

The ICHD-II diagnostic criteria for headache attributed to pheochromocytoma are as follows:

A. Intermittent discrete attacks of headache accompanied by at least one of the following and fulfilling criteria C and D:
  1. Sweating
  2. Palpitations
  3. Anxiety
  4. Pallor
B. Pheochromocytoma demonstrated by biochemical investigations, imaging, and/or surgery.
C. Headache develops concomitantly with abrupt rise in blood pressure.
D. Headache resolves or markedly improves within 1 hour of normalization of blood pressure.

Pheochromocytomas are catecholamine-producing tumors that arise from chromaffin cells. Although rare, pheochromocytomas must be considered in patients with hypertension, autonomic disturbances, panic attacks, adrenal incidentalomas, or predisposing familial diseases (multiple endocrine neoplasia type II [MEN II], von Hippel–Lindau disease, neurofibromatosis type 1, familial carotid body tumors). These tumors are mostly situated within the adrenal medulla, although in about 9 to 23% of cases, tumors develop from extra-adrenal chromaffin tissue (adjacent to sympathetic ganglia of the neck, mediastinum, abdomen, and pelvis) and are often referred to as paragangliomas (40). Sudden-onset headache is the most common symptom of pheochromocytoma, occurring in up to 80% of patients. The headache is often severe, frontal or occipital, and generally described as either pulsating or steady in quality. An important feature of the headache is its short duration: less than 15 minutes in 50% and less than 1 hour in 70% of patients. Hypertension is present

in 80% of patients and is paroxysmal in 50% of patients (41). However, 13% have normal blood pressure, and 8% are completely asymptomatic. For these reasons, the definitive diagnosis of pheochromocytoma rests primarily on the demonstration of excessive and inappropriate catecholamine production. When paroxysms do occur, they may last 15 to 60 minutes and can occur several times per day or once or twice per year. They can occur spontaneously or may be provoked by physical exertion, emotional stress, pressor medications, changes in posture, or increases in intra-abdominal pressure. Symptoms and signs of adrenergic stimulation such as sweating, palpitations, facial pallor or flushing, and tachycardia are each present in about 70% of patients, while other features such as anxiety, sense of impending doom, tremor, visual disturbances, abdominal or chest pain, nausea, vomiting, and occasionally paraesthesia may occur as well.

DIAGNOSIS

The diagnosis is established by the demonstration of increased 24-hour urinary excretion of metanephrine and normetanephrine (98%), vanillylmandelic acid (60%), and total catecholamines (60 to 80%) (37). Computed tomography (CT) and MRI of the neck, chest, abdomen and pelvis have a sensitivity, respectively, of 86 to 95% and 93 to 100% for detecting adrenal pheochromocytoma. CT is the imaging modality of first choice at most institutions, but if the CT is negative, in a patient with biochemically proven pheochromocytoma, MRI should be performed. MRI should be substituted for CT in children, pregnant women, and situations where radiation exposure must be minimized (37).

Adrenal masses are present in about 5 to 9% of the general population. Although most adrenal masses are benign, nonfunctional incidentalomas, about 6.5% of incidentally discovered adrenal masses are indeed pheochromocytoma (37,67). Thus, most adrenal abnormalities are not pheochromocytoma, highlighting the need for specific diagnostic imaging after anatomic studies are performed in patients with suspicion of pheochromocytoma. Additionally, there is no consensus on the existence of absolute clinical, imaging, or laboratory criteria to predict malignancy and multiplicity of pheochromocytoma (56,69). Thus, in patients diagnosed with pheochromocytoma, the need to exclude metastatic disease or multiple tumors is important. This need might be fulfilled with functional imaging modalities using various radiopharmaceuticals that provide physicians with whole body, pheochromocytoma-specific scans. Pheochromocytoma cells usually abundantly express specific catecholamine plasma membrane and vesicular transporter systems, enabling imaging with [^{131}I]- and [^{123}I]MIBG (metaiodobenzylguanidine), as well as with several positron emission tomography (PET) ligands. [^{123}I]MIBG scintigraphy has a sensitivity ranging from 83 to 100% and a high specificity (95 to 100%) for pheochromocytoma (51,70). [^{18}F]DOPA PET imaging may have a higher sensitivity and specificity than [^{123}I]MIBG scintigraphy, but further studies are needed to compare the two modalities (37).

TREATMENT

The management of pheochromocytoma has been dominated by efforts to prevent hypertensive episodes and associated complications and to diminish the magnitude of postoperative hypotension. For control of blood pressure, selective postsynaptic α-1 adrenergic receptor antagonists (prazosin, terazosin, doxazosin) have been used to circumvent some of the disadvantages of phenoxybenzamine (a nonspecific, α-blocking agent). Phenoxybenzamine produces significant orthostatic hypotension and reflex tachycardia and may prolong and contribute to the hypotension that follows removal of the tumor.

Labetalol, an α- and β-adrenergic blocker, was reported effective in the control of blood pressure and clinical manifestations associated with pheochromocytoma. Its safety has been questioned, however, because it has precipitated hypertensive crises in some patients (37).

Calcium channel blockers have also been successful in controlling blood pressure in pheochromocytoma. These agents do not produce hypotension or orthostatic hypotension and therefore may be used safely in patients who are normotensive but have occasional episodes of paroxysmal hypertension. Calcium channel blockers are useful agents in managing cardiovascular complications because they may also prevent catecholamine-induced coronary vasospasm and myocarditis. It is likely that they reduce arterial pressure by inhibiting norepinephrine-mediated increase in intracellular calcium in vascular smooth muscle, not by decreasing catecholamine synthesis in tumors.

HEADACHE ATTRIBUTED TO HYPERTENSIVE CRISIS WITHOUT HYPERTENSIVE ENCEPHALOPATHY

IHS ICHD-II code and diagnosis: 10.3.2 Headache attributed to hypertensive crisis without hypertensive encephalopathy

WHO code and diagnosis: G44.813 Headache attributed to hypertensive crisis without hypertensive encephalopathy

CLINICAL FEATURES

The ICHD-II diagnostic criteria for headache attributed to hypertensive crisis without hypertensive encephalopathy are as follows:

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A. Headache with at least one of the following characteristics and fulfilling criteria C and D:
  1. Bilateral
  2. Pulsating quality
  3. Precipitated by physical activity
B. Hypertensive crisis defined as a paroxysmal rise in systolic (to >160 mm Hg) and/or diastolic (to >120 mm Hg) blood pressure but no clinical features of hypertensive encephalopathy.
C. Headache develops during hypertensive crisis.
D. Headache resolves within 1 hour after normalization of blood pressure.
E. Appropriate investigations have ruled out vasopressor toxins or medications as causative factors.

Paroxysmal hypertension may occur in association with failure of baroreceptor reflexes. The arterial baroreceptors play a critical role in the control of arterial pressure in humans by buffering moment-to-moment changes so that acute and excessive fluctuations do not occur. Baroreceptors in each carotid sinus relay information regarding vessel distension via the glossopharyngeal nerves to the nucleus of the tractus solitarius, which in turn activates cardiac parasympathetic outflow and inhibits sympathetic vasomotor outflow. Other mechanoreceptors in the aortic arch and great vessels of the thorax transmit similar information via the vagus nerves to the nucleus tractus solitarius and generate similar depressor responses. Because of this functional redundancy, bilateral lesions involving the carotid sinus are frequently required to produce baroreflex failure, although a central lesion in the region of the nucleus of the solitary tract can produce the same effect.

Baroreceptor reflex failure has been described in patients with bilateral lesions of the nucleus of the solitary tract or familial paraganglioma syndrome and after surgical resection of the glossopharyngeal nerves (23). Idiopathic cases, referred to as Page syndrome, have been described (58). The syndrome has also been well described as a delayed consequence in patients who have undergone radiation therapy to the neck for head and neck malignancies, as well as after carotid endarterectomy (1,10). This may reflect the relative importance of carotid baroreceptor input over the cardiopulmonary afferents.

In patients with chronic baroreflex failure, the pressor episodes are associated with transient increases in plasma norepinephrine concentration (9). This correlation suggests that the episodes are caused by unrestrained activation of the sympathetic nervous system. A spectrum of symptoms may accompany these pressor episodes, including headache, palpitation, a hot sensation, diaphoresis, cutaneous flushing, and emotional lability (58). The clinical presentation of baroreflex failure bears a striking resemblance to pheochromocytoma. However, although patients with baroreceptor failure may have elevated circulating levels of norepinephrine, urinary catecholamine and metanephrine levels and negative imaging studies for pheochromocytoma are usually sufficient to distinguish between the two entities. Furthermore, patients with baroreceptor failure have been reported to have a dramatic response to clonidine, a centrally acting sympathoinhibitor (23). Clonidine acts at the level of the rostral ventrolateral medulla to produce sympathoinhibition and, perhaps, at the level of the nucleus of the solitary tract to sensitize baroreflex responses (9). Clonidine produces a significant decrease of arterial pressure in patients with baroreflex failure and autonomic dysreflexia, another centrally mediated hypertensive syndrome, but not in patients with pheochromocytoma.

HEADACHE ATTRIBUTED TO HYPERTENSIVE ENCEPHALOPATHY

IHS ICHD-II code and diagnosis: 10.3.3 Headache attributed to hypertensive encephalopathy
WHO code and diagnosis: G44.813 Headache attributed to hypertensive encephalopathy

The ICHD-II diagnostic criteria for headache attributed to hypertensive encephalopathy are as follows:

A. Headache with at least one of the following characteristics and fulfilling criteria C and D:
  1. Diffuse pain
  2. Pulsating quality
  3. Aggravated by physical activity
B. Persistent blood pressure elevation to >160/100 mm Hg with at least two of the following:
  1. Confusion
  2. Reduced level of consciousness
  3. Visual disturbances (other than those of typical migraine aura) including blindness
  4. Seizures
C. Headache develops in close temporal relation to blood pressure elevation.
D. Headache resolves within 3 months after effective treatment and control of hypertension.
E. Other causes of the neurologic symptoms have been excluded.

Hypertensive encephalopathy is an acute cerebral syndrome caused by sudden severe hypertension. The rate and extent of rise in blood pressure are the most important factors in the development of this syndrome. Encephalopathy may develop in previously normotensive persons at a level of 160/100 mm Hg with no evidence of retinopathy at the time of clinical presentation. However, in patients with chronic hypertension, hypertensive encephalopathy is usually not until significant elevations in systolic (>250) and diastolic (>120) blood pressures occur. These patients often have grade 3 or 4 hypertensive retinopathy (Keith-Wagner classification) at the time of presentation.

Hypertensive encephalopathy has become part of an emerging clinical–neuroradiologic entity referred to as

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posterior leuko- (reversible) encephalopathy syndrome (PLES). PLES is a rapidly evolving neurologic condition characterized by headache, nausea and vomiting, visual disturbances, altered mental status, decreased alertness, seizures, focal neurologic signs, and a diagnostic MRI picture (34,36). PLES is associated with an abrupt and severe increase in blood pressure in most cases, including patients with pre-eclampsia, eclampsia, or renal disease with hypertension. Although hypertensive encephalopathy is the most common cause of PLES, a number of cases without hypertension have been described. The syndrome is also seen in patients treated with immunosuppressive drugs such as intravenous immunoglobulin, cyclosporin A, tacrolimus, and interferon-α (34). The main finding on neuroimaging or autopsy studies is posterior white matter edema, particularly involving the parietal and occipital lobes, which may spread to the basal ganglia, brainstem, and cerebellum (19,36,63). Complete clinical and radiologic recovery often occurs with prompt antihypertensive treatment or withdrawal of the immunosuppressive drug. Occasionally, the clinical features and CT or standard MRI findings may be indistinguishable from a bilateral posterior cerebral artery stroke syndrome. Thus, early recognition of PLES is essential.

The pathogenesis of hypertensive encephalopathy is unclear, but a failure of cerebral autoregulation that may be facilitated in posterior brain regions due to a sparse sympathetic innervation of the vertebrobasilar vascular system has been proposed (36). In these cases, compensatory cerebrovascular vasoconstriction can no longer prevent cerebral hyperperfusion as blood pressure rises. As normal cerebral autoregulation of blood flow is overwhelmed, endothelial permeability increases and cerebral edema occurs.

HEADACHE ATTRIBUTED TO PRE-ECLAMPSIA

IHS ICHD-II code and diagnosis: 10.3.4 Headache attributed to pre-eclampsia
WHO code and diagnosis: G44.813 Headache attributed to pre-eclampsia

CLINICAL FEATURES

The ICHD-II diagnostic criteria for headache attributed to pre-eclampsia are as follows:

A. Headache with at least one of the following characteristics and fulfilling criteria C and D:
  1. Bilateral
  2. Pulsating quality
  3. Aggravated by physical activity
B. Pregnancy or puerperium (up to 4 weeks postpartum), and pre-eclampsia defined by both of the following:
  1. Hypertension (>140/90 mm Hg) documented on two blood pressure readings at least 4 hours apart
  2. Urinary protein excretion >0.3 g per 24 hours
C. Headache develops during periods of high blood pressure.
D. Headache resolves within 7 days after effective treatment of hypertension.
E. Appropriate investigations have ruled out vasopressor toxins, medications, or pheochromocytoma as causative factors.

HEADACHE ATTRIBUTED TO ECLAMPSIA

IHS ICHD-II code and diagnosis: 10.3.5 Headache attributed to eclampsia
WHO ICD-10NA code: G44.813

The ICHD-II diagnostic criteria for headache attributed to eclampsia are as follows:

A. Headache with at least one of the following characteristics and fulfilling criteria C and D:
  1. Bilateral
  2. Pulsating quality
  3. Aggravated by physical activity
B. Pregnancy or puerperium (up to 4 weeks postpartum), and eclampsia defined by all of the following:
  1. Hypertension (>140/90 mm Hg) documented on two blood pressure readings at least 4 hours apart
  2. Urinary protein excretion >0.3 g per 24 hours
  3. A seizure has occurred
C. Headache develops during periods of high blood pressure.
D. Headache resolves within 7 days after effective treatment of hypertension.
E. Appropriate investigations have ruled out vasopressor toxins, medications, or pheochromocytoma as causative factors.
F. Stroke has been excluded.

Pre-eclampsia is a multisystem disorder that usually occurs after 20 weeks gestation. It was classically defined as a triad of hypertension, edema, and proteinuria, but a more modern definition of pre-eclampsia concentrates on a gestational elevation of blood pressure in combination with a greater than 0.3-g proteinuria per 24 hours. Edema is no longer included because of the lack of specificity (14,57). Eclampsia is defined as the occurrence of a generalized seizure in association with preeclampsia, although it may be the first presentation of the condition. Approximately 6.5% of patients have other neurologic problems, including aphasia, paralysis, blindness, strokes, psychosis, or coma (57). The headache associated with pre-eclampsia and eclampsia is often bilateral, pulsating, and aggravated by activity. Thunderclap headache has been described, and reversible cerebral vasospasm in association with

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posterior leukoencephalopathy syndrome may also occur (5,71).

Pre-eclampsia and eclampsia complicate, respectively, 5 to 6% and 1 to 2% of pregnancies. The incidence is significantly influenced by the presence of existing hypertension, although other risk factors are recognized, including nulliparity, multiple pregnancies, previous history or family history of preeclampsia, and chronic hypertension (13). An estimated 50,000 women die annually from preeclampsia worldwide and morbidity includes placental abruption, intra-abdominal hemorrhage, cardiac failure, intracerebral hemorrhage, and multiorgan failure (13,59). The risks to the fetus from pre-eclampsia include growth restriction secondary to placental insufficiency, and premature delivery.

PATHOGENESIS

Pre-eclampsia involves uteroplacental maladaption with failure of the normal cardiovascular changes of pregnancy resulting in hypertension, reduction in plasma volume, and impaired perfusion to virtually every organ of the body. There is vasospasm and activation of platelets and the coagulation system, resulting in microthrombi formation. The link between the placenta and the systemic disorder appears to involve endothelial dysfunction and oxidative stress. The management of pre-eclampsia involves recognition of the syndrome and delivery of the placenta, which is curative. Since pre-eclampsia may arise with few symptoms, all women are screened during pregnancy through regular antenatal care. Those women who are recognized to be at increased risk have additional screening and more intensive monitoring. Because of the circulating plasma volume contraction, women may be very sensitive to relatively small doses of antihypertensive agents (and diuretics), risking abrupt reductions in blood pressure. Good control of hypertension in severe pre-eclampsia can reduce the incidence of complications such as cerebral hemorrhage until delivery of the placenta. Management of severe hypertension involves adequate blood pressure control using parenteral hydralazine or labetalol. Hydralazine should be given after a colloid challenge to reduce the reflex tachycardia and after abrupt hypotension, precipitated by vasodilation of a volume contracted circulation. Both angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are fetotoxic, and the greatest risk to the fetus appears to be associated with exposure in the third trimester (57). These drugs should therefore be avoided in the third trimester. These women are high risk and should be managed in a high-dependency unit setting because of the risk of noncardiac pulmonary edema through capillary leak, respiratory failure, or the development of a severe systemic inflammatory response syndrome (SIRS). Seizure prophylaxis, with intravenous magnesium sulfate, may be required in these cases (57).

HEADACHE ATTRIBUTED TO ACUTE PRESSOR RESPONSE TO EXOGENOUS AGENT

IHS ICHD-II code and diagnosis: 10.3.6 Headache attributed to acute pressor response to exogenous agent
Coded elsewhere: 8.1.6 Cocaine-induced headache
WHO code and diagnosis: G44.813 Headache attributed to acute pressor response to exogenous agent

The ICHD-II diagnostic criteria for headache attributed to acute pressor response to exogenous agent are as follows:

A. Headache, no typical characteristics known, fulfilling criteria C and D.
B. An appropriate agent or toxin has been administered or ingested and an acute rise in blood pressure has occurred.
C. Headache develops in close temporal relation to the acute rise in blood pressure.
D. Headache resolves within 24 hours after normalization of blood pressure.
E. No other mechanism for the headache is apparent.

Apart from cocaine, agents that can produce acute elevations of blood pressure include sympathomimetics and amphetamines, as well as monoamine oxidase inhibitors when interactions with tyramine-containing foods or other drugs such as opioids occur. There is insufficient evidence to set criteria for how large an elevation in blood pressure is required to produce headache, and this may vary from person to person. Criterion D is arbitrary, but included to increase the specificity of the diagnostic criteria.

HEADACHE ATTRIBUTED TO HYPOTHYROIDISM

IHS ICHD-II code and diagnosis: 10.4 Headache attributed to hypothyroidism
WHO code and diagnosis: G44.882 Headache attributed to hypothyroidism

CLINICAL FEATURES

The ICHD-II diagnostic criteria for headache attributed to hypothyroidism are as follows:

A. Headache with at least one of the following characteristics and fulfilling criteria C and D:
  1. Bilateral
  2. Nonpulsatile
  3. Continuous
B. Hypothyroidism is demonstrated by appropriate investigations.

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C. Headache develops within 2 months after other symptoms of hypothyroidism become evident.
D. Headache resolves within 2 months after effective treatment of hypothyroidism.

Although headache has been associated with hypothyroidism since the 1940s (26), the only prospective study evaluating patients with de novo hypothyroidism employing ICHD-I criteria was conducted in 1988 (48). In this study, 31 of 102 (30.2%) newly identified cases of hypothyroidism were noted to have a recent history of headache. The major characteristics of the headache were female predominance; bilateral localization (80%); nonpulsating quality (90%); continuous pain with no paroxysmal attacks (95%); mild intensity (95%); nausea, vomiting, or phonophobia; good response to salicylate therapy; and a duration of greater than 72 hours (82%). The headache decreased in intensity and duration near the 15th day after hormonal therapy in 18 patients, while in the remaining 13 patients, the headache disappeared during a 12-month follow-up. Personal and family histories of migraine were present in 39.8% and 12.6% of patients, respectively. The rate of migraine in hypothyroid patients who did not present with headache was 15.4%, whereas both headache and nonheadache patients had equal rates of migraine in the family. The female predominance and the high rate of migraine in the hypothyroid patients with headache suggest that migraineurs are more susceptible to developing headache in the setting of hypothyroidism. The mechanism of headaches in hypothyroidism is not known.

HEADACHE ATTRIBUTED TO FASTING

IHS ICHD-II code and diagnosis: 10.5 Headache attributed to fasting
WHO code and diagnosis: G44.882 Headache attributed to fasting
Coded elsewhere: Hypoglycemia-induced migraine is coded according to subtype under 1. Migraine, with hypoglycemia considered as a precipitating factor.

CLINICAL FEATURES

The ICHD-II diagnostic criteria for headache attributed to fasting are as follows:

A. Headache with at least one of the following characteristics and fulfilling criteria C and D:
  1. Frontal location
  2. Diffuse pain
  3. Nonpulsating quality
  4. Mild or moderate intensity
B. The patient has fasted for >16 hours.
C. Headache develops during fasting.
D. Headache resolves within 72 hours after resumption of food intake.

Fasting is frequently reported by patients and noted in textbooks as a trigger for headache. Two systematic studies have investigated the relationship between fasting and headache (6,49). Mosek and Korczyn reported headache in 370 hospital employees (60% female) before and immediately after a 25-hour fast for the 1993 Day of Atonement (Yom Kippur). A history of recurrent headache was reported by 101 (29%) of those screened; 52 (15%) were migraineurs, 45 (13%) suffered from tension-type headache, and 4 (1%) had other types of headache. Of the 211 participants, 39% of those who fasted developed headache, compared with only 7% of nonfasters, a result that was highly significant. Headache was usually of a nonpulsating quality, mild to moderate in intensity, and bilateral and frontal in location. Subjects with a history of headache were more likely to develop fasting-induced headache than were those without such history (66% vs. 29%; $p < 0.000002$). Moreover, photophobia, phonophobia, nausea, and vomiting accompanied the headache significantly more often among previous headache sufferers than among those not reporting a history of previous headache (39% vs. 18%; $p < 0.05$). The number of headache sufferers increased in direct relation to the duration of the fast. Headaches first appeared after about 16 hours of fasting (in the morning hours of the holiday), and additional headaches developed in other fasters at later time points after the fast began. However, 15 subjects developed their headache 30 to 60 minutes after the meal that concluded the fast. Caffeine and nicotine withdrawal and oversleeping did not appear to have an influence on the development of headache. The authors concluded that fasting is a strong trigger for headache, especially but not exclusively in those with a prior headache history (49).

The headache associated with fasting does not appear to be associated with hypoglycemia, although this relationship has not been systematically examined (21,22,46). Fasting headache can occur in the absence of hypoglycemia, insulin-induced hypoglycemia does not precipitate headache in migraine sufferers, and headache is not a complaint of patients presenting to the emergency department with symptomatic hypoglycemia (21,22,46,54).

CARDIAC CEPHALGIA

IHS ICHD-II code and diagnosis: 10.6 Cardiac cephalgia
WHO code and diagnosis: G44.882 Cardiac cephalgia

CLINICAL FEATURES

The ICHD-II diagnostic criteria for cardiac cephalgia are as follows:

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A. Headache, which may be severe, aggravated by exertion and accompanied by nausea and fulfilling criteria C and D
B. Acute myocardial ischemia has occurred.
C. Headache develops concomitantly with acute myocardial ischemia.
D. Headache resolves and does not recur after effective medical therapy for myocardial ischemia or coronary revascularization.

Short description: Diagnosis must include careful documentation of headache and simultaneous cardiac ischemia during treadmill or nuclear cardiac stress testing. Failure to recognize and correctly diagnose 10.6 Cardiac cephalalgia can have grave consequences. Therefore, distinguishing this disorder from migraine without aura is crucial, particularly since vasoconstrictor medications (e.g., triptans, ergots) are indicated in the treatment of migraine but contraindicated in patients with ischemic heart disease. Both disorders can produce severe head pain accompanied by nausea, and headaches in both disorders can be triggered by exertion. Migrainelike headache may be triggered by angina treatment such as nitroglycerin.

Headache occurring during acute myocardial ischemia (cardiac cephalgia) has now been carefully documented in several cases (11,12,27,28,42,43,72). Cardiac cephalgia can often be distinguished from other forms of exertional headache by the temporal profile of the pain. The headache typically begins in close proximity to the onset of vigorous exercise and subsides with rest or with antianginal treatment. However, just as symptomatic myocardial ischemia can occur at rest, cardiac cephalgia occurring at rest has been described (29). The headache is often unilateral but may be located at the vertex and is usually moderate or severe. Nausea is a frequent accompanying symptom, but other migrainous symptoms such as vomiting, photophobia, and phonophobia are absent. Valsalva maneuvers such as coughing, sneezing, and bending do not precipitate cardiac cephalgia. The diagnosis should be suspected in patients with headache onset after age 50 years and in patients with risk factors for cardiac disease. In such patients, a prompt cardiac evaluation is essential before a diagnosis of primary exertional headache, primary sexual headache, or migraine is diagnosed. Headache onset must be demonstrated to occur with evidence of acute myocardial ischemia, and the headache should resolve after effective medical or endovascular therapy or surgical revascularization.

The mechanism of cardiac cephalgia is speculative, but likely involves convergence of sympathetic or vagal input at the level of the trigeminal nucleus caudalis (28). However, other possibilities, such as increased intracranial pressure as a result of impaired cardiac venous return due to raised right heart pressures or as a result of an as yet unidentified mediator released secondary to cardiac ischemia that might act on intracranial pain-sensitive structures, should be considered. Serotonin, bradykinin, histamine, and substance P have been proposed as mediators of ischemic pain and might also have distant intracranial effects (43).

HEADACHE ATTRIBUTED TO OTHER DISORDERS OF HOMEOSTASIS

IHS ICHD-II code and diagnosis: 10.7 Headache attributed to other disorders of homeostasis
WHO code and diagnosis: G44.882 Headache attributed to other disorders of homeostasis

The ICHD-II diagnostic criteria for headache attributed to other disorders of homeostasis are as follows:

A. Headache fulfilling criteria C and D
B. Evidence of a disorder of homoeostasis other than those described above.
C. Headache develops within 2 months after onset of the disorder, and other evidence exists that the disorder can cause headache.
D. Headache resolves within 3 months after relief from the disorder of homoeostasis.

Although the relationship between headache and a variety of other systemic and metabolic disease has been proposed, systematic evaluation of these relationships has not been performed and there is insufficient evidence to allow for operational diagnostic criteria. This is clearly an area with tremendous potential for future clinical and nosologic research. The disorders for which there is insufficient evidence have been outlined in the appendix of the ICHD-II (A10.7.1). Headaches attributed to the following disorders are not sufficiently validated: anemia, hypercapnia, adrenocortical insufficiency, mineralocorticoid deficiency, hyperaldosteronism, polycythemia, hyperviscosity syndrome, thrombotic thrombocytopenic purpura, plasmapheresis-induced headache, anticardiolipin antibody syndrome, Cushing disease, hyponatremia, hyperthyroidism, hyperglycemia, hypercalcemia, systemic lupus erythematosus, chronic fatigue syndrome, and fibromyalgia. Well-controlled, prospective studies are needed to define more clearly the incidence and characteristics of headaches that occur in association with these disorders. In each case, only those patients who meet well-established diagnostic criteria for the disorders themselves should be evaluated. In addition, there is insufficient evidence to validate the persistence of headache as a result of a disorder of homeostasis. Consequently, the ICHD-II also includes a category in the appendix—A10.8 Chronic posthomeostasis disorder headache. Operational criteria have been proposed to facilitate future nosologic research in this area.

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CHRONIC POSTHOMEOSTASIS DISORDER HEADACHE

IHS ICHD-II code and diagnosis: 10.8 Chronic posthomeostasis disorder headache

The ICHD-II diagnostic criteria for chronic posthomeostasis disorder headache are as follows:

A. Headache, no typical characteristics known, fulfilling criteria C and D.
B. A disorder of homeostasis has been present but has been effectively treated or has remitted spontaneously.
C. Headache has been attributed to the disorder of homeostasis.
D. Headache persists for >3 months after treatment or remission of the disorder of homeostasis.

Short description: Some patients may suffer from persistent headache after resolution of a disorder of homeostasis. Such headache has never been the subject of systematic study.

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