Headache: Physiology and Mechanisms Underlying Differential Diagnosis

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ABSTRACT

Headaches can be a common feature of the clinical presentation of patients who present to physical therapy with neck pain. Occasionally, patients with headaches as the primary/sole symptom may also seek physical therapy. Many physical therapists are comfortable with managing cervicogenic headache but less comfortable with management of migraine or other types of headaches, which can present concurrently with or independently of neck pain. Physical therapists who treat patients with headache, with or without neck pain, must have a thorough understanding of the various headache types and presentations. Knowing a patient's headache type will help guide both the evaluation and treatment plan. As part of the evaluation, investigation of the headache type will assist in determining if a patient is appropriate for physical therapy treatment. Because some secondary headache types may respond better to alternate forms of interventions and other types of headaches can be life threatening, redirection to other clinical specialists must be kept in mind when treating this population. To conclude this monograph, 4 case studies demonstrate the use of red flag screening and the differential diagnostic process for common types of headaches.

Key Words: classification, headache, pathophysiology, red flags

LEARNING OBJECTIVES

Upon completion of this monograph, the course participant will be able to:

1. List common headache diagnoses that would be classified as primary headaches, secondary headaches, or neuropathies/neuralgias.
2. Understand the common signs and symptoms associated with vascular pathologies of the neck.
3. Use clinical reasoning to streamline the identification of red flag signs and symptoms that would warrant referral.
4. Describe the diagnostic criteria for various types of headaches including migraine, tension-type headache, cervicogenic headache, occipital neuralgia, and post-traumatic headache.
5. Understand the proposed pathoanatomical mechanisms behind migraine, tension-type headache, cervicogenic headache, occipital neuralgia, and headache attributed to trauma to the head and/or neck.

INTRODUCTION

Headaches are a common condition. Globally, up to 46% of adults have an active headache disorder.[1] The prevalence of tension-type headache (TTH) in various populations can range from 22% to 40% and the prevalence of migraine headache (MH) can be as high as 15%.[2-6] In the United States, MH occurs in approximately 12% to 16% of the population, 18% of women, and 6% of men.[7] Chronic MH has a global prevalence ranging from 1.4% to 2.2% of the population.[8]

In addition to a high prevalence, headache disorders are one of the leading causes of years lived with disability.[2] Headaches negatively impact quality of life and diminish both paid and household work productivity.[2] In 2016, the Global Burden of Disease Study[9] reviewed published population-based studies from all over the world and reported MH as one of the most disabling conditions, second only to low back pain.[8,9] Compared to other headache types, the societal burden of MH is highest in the second to fifth decades of life, with estimates of up to a total of 20.3 million years lived with disability by those affected.[8,9] The estimated direct cost (ie, medical expenses) and indirect cost (ie, loss of productivity time) for people with MH is nearly $9000 higher per year than for similar people without MH.[8] Given the substantial societal impact of headaches, it is important for clinicians and researchers to identify and use effective management strategies for headache conditions, inclusive of primary headache disorders such as MH.

Currently, the physical therapy literature and research is focused on cervicogenic headache (CGH) and post-traumatic disorders, but arguably is lacking in the management of post-traumatic headache (PTH) specifically, as well as primary headache disorders. Although the physical therapy literature provides limited guidance on the role of physical therapy in the management of other common headache disorders such as MH, physical therapy can be a useful component in the management of numerous types of headaches. This monograph series will help physical therapists develop the knowledge necessary for the diagnosis, evaluation, and treatment of common headache disorders that they encounter in the clinical setting.

This monograph, the first of a 3-part series, will focus on the proposed physiologic mechanisms for the most common headache disorders. The reader will be introduced to the International Classification of Headache Disorders (ICHD) and how to use the system to help with the process of differential diagnosis of headaches. We will then provide detailed information and offer a mnemonic acronym to help screen for red flag diagnoses in determining appropriateness of physical therapy evaluation and treatment. We will present the diagnostic criteria and features specific to MH, TTH, CGH,

occipital neuralgia (ON), and headache attributed to trauma to the head and/or neck. While these are not inclusive of all headache types recognized in the International Headache Classification, these specific diagnoses were selected as the focus for this monograph because these are diagnoses for which the patient will often present with neck pain as well as headaches,[10] and therefore might be evaluated in a physical therapy clinic. Note that these diagnoses are commonly treated using a multidisciplinary approach,[11] so understanding resources available to the patient is key. Finally, this monograph will conclude with case discussions highlighting red flag screening and a differential diagnostic process. The second monograph in this series will help guide the clinician through the physical examination and the third monograph will outline treatment approaches for these headache types.

DIFFERENTIAL DIAGNOSIS

As stated previously, we will focus primarily on headaches that commonly present with corresponding neck pain, thereby creating a differential diagnostic dilemma for physical therapists. Caution should be taken not to proceed with the assumption that this pain is musculoskeletal in nature, as vascular and neurological contributions are possible causative factors as well.

International Classification of Headache Disorders

The first edition of the ICHD (ICHD-I) was published in 1988 and was based largely on expert opinion. The ICHD-II, published in 2004, included many changes based on new evidence. The current ICHD-3, published in 2018, is based largely on scientific evidence and the content is derived entirely from research.[10] The classification is hierarchical. Accordingly, the clinician's first objective is to determine which group of headaches the patient belongs to (eg, MH or TTH), and then determine if there is a more detailed diagnosis (subtype or subform) under that group that fits the patient's clinical presentation (eg, MH with aura). Most patients should be diagnosed according to the classification system based on the headache phenotype that they have been experiencing during the past year. When a headache occurs for the first time in close temporal relationship to a known causative factor of headache, it should be coded as a secondary headache even if it fits the diagnostic criteria for a primary headache disorder. This is of particular importance because the phenotype of PTH is often consistent with migraine.[12] If a known primary headache disorder is made worse or becomes chronic in close temporal relationship to a known causative factor, both a primary and secondary headache are diagnosed.

The classification is divided into 3 parts. The first part is titled "the primary headaches," the second part is "the secondary headaches," and the third part is based on the presence or absence of neuropathies and facial pains, and other headaches (**Table 1**). Primary headaches are headaches that are not caused by other disorders, causes, or diseases. Common examples of primary headache disorders are MH, TTH, and trigeminal autonomic cephalalgias such as cluster headache.

Secondary headaches are headaches that are caused by other disorders that are known to cause headache. Examples of secondary headaches are CGH or headache attributed to head trauma (ie, concussive event). More serious examples of secondary headache disorders are those due to a cranial or cervical vascular disorder, such as vertebrobasilar artery dissection (VAD).

Neuropathies, facial pains, and other headaches describe pain in the head and neck from afferent fibers in the trigeminal,

Table 1. International Headache Classification System Subgroups[10]

Part of the Classification	Type of Headache	Definition	Common Diagnoses
Part 1	Primary headaches	Headaches that have their own pathomechanical processes not caused by other disorders or diseases	Migraine, tension-type headache, cluster headache
Part 2	Secondary headaches	Headaches caused by other disorders	Cervicogenic headache, post traumatic headache, headache due to cranial or cervical vascular disorder (eg, vertebrobasilar insufficiency)
Part 3	Neuropathies, facial pains, and other headaches	Pain in the head, neck, and/or face that arises from the afferent fibers in the trigeminal, intermedius, glossopharyngeal, vagus, and upper cervical nerves	Occipital neuralgia, trigeminal neuralgia

intermedius, glossopharyngeal, vagus, and upper cervical spine nerves. The pain can manifest in a distinct form that helps the clinician diagnose in which group the patient best fits. This is then followed by further diagnostic investigation as to the etiology behind this neuropathic pain. The following are the axes of classification: syndromology (neuralgia or neuropathy), location (central or peripheral neuropathic pain), or etiology (classic, idiopathic, or secondary). In the cases of trigeminal, glossopharyngeal, and intermedius neuralgias; "classic" describes cases with evidence of vascular compression of the specific nerve. In this monograph, we will discuss only ON because individuals with this diagnosis will present with both headache and neck pain.

Red Flag Screening

As mentioned in the examples above, although secondary headaches are not as common as primary headaches, some secondary headache disorders can be life threatening. As physical therapists, we might have patients with a history of trauma, presenting with complaints of neck pain and headaches. Commonly, therapists might proceed in their evaluation and treatment of suspected CGH, but it is important to also consider the potential for vascular pathologies of the neck, which include a tear or hematoma in the wall of the internal carotid or vertebral arteries.[13-16]

The most common early features of vascular pathologies of the neck are unilateral, posterior headache and neck pain, which is similar to the distribution of CGH.[15-17] If CGH is assumed to be the most likely diagnosis it could lead the therapist to use assessment and treatment techniques for the cervical spine, such as cervical manipulation, which have been associated with vascular pathologies of the neck as an adverse event.[16] While cervical manipulation has been a reported risk factor for vascular pathologies of the neck (although the incidence is rare), it is important to realize that a patient could present to the clinic with a vascular pathology already in progress. Understanding the potential signs, symptoms, and risk factors associated with a vascular pathology in the neck region is critical to be able to provide appropriate medical intervention, because ischemic stroke or transient ischemic attack occurs in 67% to 77% of these cases.[16,17] Physical therapists must be comfortable with screening patients for possible vascular pathologies of the neck being in progress, to determine appropriateness for physical therapy evaluation and treatment.

Unfortunately, sustained craniocervical spine positioning, previously thought to screen for vascular pathologies of the neck, may not alter blood flow and therefore may not be a valid clinical test for this purpose.[14] This means there is a need for more useful information to help therapists screen patients presenting with potential vascular pathologies of the neck that cause their head/neck pain. Pathophysiology of vascular pathologies of the neck is multifactorial and understanding the mechanisms involved can help the clinician ask specific questions to help with screening for the condition.[16]

Both intrinsic and extrinsic factors can place the arterial structures at risk for injury. Some clinicians might suggest that screening a patient for general vascular risk factors, such as the presence of cardiovascular disease, hypertension, or hypercholesterolemia is helpful in determining the risk of vascular pathologies of the neck; however, vascular pathologies of the neck are most common between 35 and 55 years of age, which is younger than the typical onset of the above stated vascular diseases.[16,17] Furthermore, many studies assessing risk factors in patients with vascular pathologies of the neck compared to controls, failed to find consistent correlations between cardiovascular risk factors and vascular pathologies of the neck.[15-17] In a prospective case-control study by Thomas and colleagues,[17] 42% of patients with vascular pathologies of the neck had a history of diagnosed MH, which was significantly more likely than in the comparison group. Vascular anomalies or anatomical variants are more likely in individuals with vascular pathologies of the neck, present in up to 39% of patients, but of course, this can only be identified by radiologic imaging and might not be helpful for the purpose of screening.[15,17]

Extrinsic risk factors identified in patients with vascular pathologies of the neck include a history of mechanical trauma to the neck in the previous 3-4 weeks.[15,17] A history of trauma or strain to the neck has been reported in 64% to 71% of individuals with vascular pathologies of the neck.[15,17] Mechanisms of trauma reported have been classified as jerky or abrupt head movements (such as in sporting events involving extension or lateral deviation of the neck, or cervical spine manipulation), intense or unusual physical effort (such as lifting heavy objects on one shoulder, forced Valsalva maneuver, or weight lifting), or activities that involve sustained extreme positions of the neck (such as a prolonged dental procedure).[17] In addition to the above mechanisms of neck trauma, there also seems to be an association between recent respiratory or gastroenterological infection and vascular pathologies of the neck.[15-17] Patients with vascular pathologies of the neck were 2.5 times more likely to have had a recent infection compared to control groups; this is thought to be due to extreme coughing or retching with vomiting, both of which could be classified as mechanical trauma or strain to the neck.[16,17]

The presence of neurologic or ischemic signs and symptoms should raise a clinician's suspicion that something more sinister could be present, making the patient inappropriate for physical therapy. Therefore, while a thorough neurological exam should be performed, including cranial nerve function, it is important to realize that neurologic signs and symptoms are often subtle, transient, and might not be noticed by the patient in the early stages of vascular pathologies of the neck.[16] In fact, the most common clinical symptoms of vascular pathologies of the neck are headache and/or neck pain. Headache has been reported as a symptom in up to 85% of patients with vascular pathologies of the neck.[15-17] Patients with VAD commonly reported headache in the occipital region and neck pain on the ipsilateral side of the

dissection, while patients with internal carotid artery dissection (ICAD) commonly report frontal or retro-orbital pain.[16,17] Particularly in the case of occipital headache and unilateral neck pain, this would mimic a musculoskeletal disorder and lead a patient to potentially seek physical therapy treatment.[14-16] In the case of retro-orbital or frontal pain, this could mimic a migraine, which, as previously stated, is more prevalent in patients with vascular pathologies of the neck.

Generally speaking, for vascular pathologies of the neck, the most common ischemic clinical features are hemiparesis (67%), speech disturbance (63%), balance disturbance (42%), and ptsosis (42%).[17] In cases where neurologic and ischemic signs and symptoms are present, a knowledge of anatomy is helpful in understanding different signs and symptoms and how they might help to infer VAD or ICAD. The vertebral arteries provide circulation to the brainstem, cerebellum, and posterior cerebral cortex and, accordingly, the most common ischemic feature of VAD is a balance deficit.[16,17] Patients with VAD can also present with ataxia, syncope, drop attacks, and speech disturbances, with dysarthria being more common than dysphasia.[16,17] For patients with ICAD, the most common ischemic features are partial Horner's syndrome, including ptosis, facial palsy, and limb weakness.[16,17] Thomas and colleagues[17] reported that these symptoms were transient and occurred in the 5 weeks preceding hospital admission.

Early recognition of the risk factors and signs and symptoms of vascular pathologies of the neck, particularly for the patient seeking physical therapy treatment for head and neck pain after trauma, is key to being able to safely proceed with assessment and intervention related to the cervical spine. More details on vascular pathologies of the neck are provided in the 2020 IFOMPT vascular pathologies of the neck framework document (https://www.ifompt.org/Research+and+Resources/OMPT+Frameworks+and+Clinical+Resources.html).

In the case of vascular pathologies of the neck as well as other potentially dangerous secondary headache disorders, the mnemonic SNNOOP10 (**Table 2**) can be used.[18] This can be helpful in identifying red flags that indicate the headache disorder could be due to a secondary etiology, warranting referral to another healthcare provider before continuing with physical therapy. The SNNOOP10 mnemonic includes 2 Ns and the number 10 indicates that there are 10 Ps within the screening process. **Table 2** outlines the meaning of the mnemonic and the potential clinical relevance of a positive response.

Migraine Headache

To better appreciate the clinical presentation, evaluation, diagnosis, and treatment of MH, it is important to understand its clinical phases and the corresponding pathophysiology. Migraine headache starts with stimulation of peripheral afferents that are a part of the trigeminocervical complex.[19] These afferents include all branches of the trigeminal nerve (V1-3), the posterior dura, and the first 2 cervical dermatomes (C1 and C2),[20] which explains the common pain referral into the trigeminal nerve distribution and why up to 70% of individuals with migraines also report neck pain (**Figure 1**).[21]

In all individuals with MH, the migraine cycle is thought to be initiated due to genetic abnormalities in the central nervous system (CNS) that make the neurovascular system hyperexcitable.[20,22] It has been shown that individuals with migraines have more than 20 gene mutations compared to normal. These mutations affect all 3 branches of the trigeminal nerve.[19,20]

The pathophysiology of MH is complex and there are multiple theories (2 described below) as to what is actually generating the pain/symptoms associated with migraines. One theory is the neurogenic inflammation theory. Once afferent nerve endings in the trigeminal nerve are activated, they send stimuli to the pons and this sends signals to the posterior cortex and causes the wave of cortical spreading depression.[19,20,23] Cortical spreading depression, newly described as cortical spreading depolarization, is thought to be the phenomenon related to auras.[24] Cortical spreading depolarization is a focal neurologic disturbance that commonly starts in the visual cortex, explaining why the majority of auras are visual in nature.[20] In this theory, cortical spreading depolarization is thought to activate the trigeminal nerve that activates the release of neurotransmitters such as substance P, neurokinin A, and calcitonin gene-related peptides (CGRP). These neurotransmitters cause vasodilation and sterile inflammation, contributing to head pain.[19,20,23] However, migraine aura can commonly occur without head pain and most migraine attacks do not include aura, indicating that this might not be a primary component of a migraine attack but rather just one component, which highlights the variable dysfunction of the nervous system in migraineurs.[24] Once neurotransmitters are released, the resulting inflammation will then cause the reactivation of the trigeminal nerve (first order neurons), causing normally non-noxious stimuli, such as a pulsing cerebral artery, to become throbbing pain. This also helps explain why normal physical activity, such as walking around the house, aggravates migraine pain. The activation of the trigeminal nerve contributes to peripheral sensitization.[19,20,23] The trigeminal nerve then brings the signal back to the brain stem at the trigeminal nucleus caudalis; the signal then travels to the thalamus and then the somatosensory cortex. If the peripheral sensitization is unsuccessfully treated, then the second and third order neurons extending from the midbrain to the thalamus and up to the cerebral cortex are continuously stimulated; this can lead to central sensitization. Clinically, central sensitization is characterized by allodynia, phonophobia (sensitivity to sound), and photophobia (sensitivity to light).[19,20,23]

Another theory of migraine pathophysiology involves the dura and its blood vessels. According to this theory, once the trigeminocervical complex in the brainstem is activated, the dura and its blood vessels release neurotransmitters, specifically