Headach. Med. Con. 2021;1(1):1–4

Headache Medicine Connections

The Official Journal of the World Headache Society

Classification of Head, Neck, and Face Pains First Edition (WHS-MCH1): Position paper of the WHS Classification Committee

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ARTICLE INFO

Article history:
Received 01.08.2021
Accepted 05.08.2021
Published 20.08.2021

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https://doi.org/10.52828/hmc.v1i1.classifications

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ABSTRACT

The WHS classification of Head, Neck and Face pain, Edition 1 Version 1 (WHS-MCH1) is the official document of the World Headache Society. It was conceptualized and developed by the Society's Classification Committee. The work began with a clean slate to create a comprehensive, updated and holistic classification of headache disorders; where 'headache' was defined as any pain above the shoulders, thus including head, neck and face pain. This new classification reflects a scientifically robust understanding of disease and also places patient experience in the qualia of pain. It is a training manual to be used at the bedside and office as an aid to the diagnosis and management of headache disorders. The dynamic nature of this first ever live classification of headaches also means that ultra-rapid updates, or versions, will be available electronically. It is not a disease criteria but a classification criteria [(1)] and is useful to pick extended spectra and 'mimickers' of diseases. Although increased sensitivity usually comes at the expense of reduced specificity, an expanded spectrum of diseases in this case also means increased specificity. WHS-MCH1 is a syndromic classification. A syndrome is a recognizable complex of symptoms and physical findings which may have more than one aetiology. Although disease is nominalist and culture-relativistic [(2)], a syndrome based approach reflects the discipline of first widening the view of possibilities before analysing each to formulate a diagnostic hypothesis. Such an approach provides a useful framework for organizing the complexity of clinical experience in order to derive inferences about outcome and guide decisions about treatment. WHS-MCH1 has a vertical grouping designed for use by clinicians of all levels of experience; this is linked to the horizontal groupings which are syndrome-based. The syndrome groups are also interlinked to one another. This design enables clinicians to efficiently create the 'big picture' so as not to miss any diagnosis. Axis 1 and 2 are the vertical and horizontal grouping categories, respectively. Axis 3 is the patient narrative of bothersome symptoms and level of impairment. Axis 4 are biomarkers that may be derived from investigations and this is the best example of the continuum of better understanding of disease defining markers. Axis 5 is an objective impairment scale that clinicians may choose based on availability.
The World Headache Society hopes that the use of such a robust and inclusive framework will lead to better patient outcomes and improved patient and clinician satisfaction with the investigative and diagnostic process.

Keywords: Classification; Syndromes; Headache disorders; Neck pain; Facial pain; Aaxis classification; Head pain; Face pain; Headache; Multiaxis

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1 KEY POINTS

- Multiaxial classification of head, face and neck pain
- Updated understanding of pain and disease mechanisms
- Incorporates live electronic updates as 'versions'
- Clinician's tool for better patient care
- Framework for national and regional registries
- Holistic in approach

2 PREAMBLE

2.1 Who is this classification for?

This classification is intended to be used by any licensed medical professional who may see a patient complaining of head, neck or face pain. This includes, but is not limited to: general practitioners, family physicians, internists, paediatricians, geriatricians, neurologists, neurosurgeons, ophthalmologists, ENT specialists, emergency physicians, paramedics, critical care physicians, psychiatrists, headache specialists, dentists, orthopaedics, sleep specialists, physical therapists, indigenous alternative medicine system practitioners, psychologists, nurses, physiotherapists and pharmacists.

2.2 Rationale

Classification is an essential component of all scientific activity. The rapid development of medicine reshapes classifications from time to time, and it also points to several philosophical, linguistic and logical problems. Philosophically it is related to the questions about the ontological nature of medical entities. The linguistic problem arises with conventions and the language used to describe medical phenomena, and the logical aspect is related to the problem of reasoning over facts [3].

A diagnostic category is useful because it allows the clinician to make inferences and predictions about patients assigned to the diagnostic category. It has been demonstrated that expert clinicians begin the diagnostic process by generating a list of diagnostic hypotheses using intuitive, nonanalytic reasoning. Analytic reasoning then allows the clinician to test and verify or reject each hypothesis, leading to a diagnostic conclusion. However, in ill-defined, complex cases, pattern recognition and past experience may not be sufficient, and experts will adapt by relying more on analytic reasoning based on causal or conceptual knowledge [4]. There is a similar challenge when a clinician is faced with new or unusual situations - which can lead to less efficient hypothesis generation. In all cases where a comprehensive method isn't followed there is a risk of excluding a potential syndrome through subconscious bias, misapplied experience, lack of knowledge or simple human error.

For this reason it is important to have a classification system that is useful to all clinicians of varying levels of experience and inherently practical in application; and so the project was started with this aim. It is important to differentiate between the theoretical parts of a classification and the practical parts because an efficient classification needs to be more than a scientifically solid basis of classification. It must also be easily applicable by practitioners because the best classification system is futile if it is too complicated, thus raising the question how to define and evaluate the right way to use a classification system. This point addresses practical, methodological and educational issues, and these have important epistemological and ethical implications [5]. Classifications can also be diagnostic manuals and guide diagnosis.

3 METHODOLOGY

The Classification Committee adopted a classification that is not disease defining. As several scholars have noted, this issue is closely related to the question whether it is possible to define disease [6]. There is also a focus on the difference between non-normal states and pathological ones due to the ability of biological organisms to adapt to new norms [7]. It is also difficult to compare normativity that is ascribed to an organism ('biological normativity') and normativity that refers to socio-cultural norms [8].

We designed an actionable classification that implies a call for action: diagnosis of a disease (conceptualised and classifiable as such), entailing a treatment decision, that is to say, a physician ought to do something, 'something' being broadly construed, including also to inform the patient and not further treating him or her at all.

4 DIFFERENCES OF NOTE

1. There is no division between primary and secondary headaches in WHS-MCH1 for three reasons.

    (a) It is a vestige clinging on from a preimaging era when diseases were classified as primary/secondary, idiopathic/symptomatic, organic/non-organic. Medical science has progressed to now understand that every one of these headaches have a pathophysiological basis, making primary and secondary redundant.

    (b) The criteria for primary headaches gives several check-list criteria and junior clinicians often have a false assurance that they are primary-although it is mentioned that all secondary headaches can behave like a primary. In practice, treatments for primary and secondary also overlap making their divide even less important. For example, migraine-like headaches in other conditions are treated with migraine medications.

(c) It is important to have a mechanistic classification for all headaches and that would identify all the contributory causes if multiple axes are applied diligently.

2. There is no divide between episodic and chronic in WHS-MHC1 for, again, three reasons.

   (a) The usefulness of such divisions are more in socioeconomic domains than in the scientific domain. Using arbitrary numbers to divide and further subdivide may have a negative impact or even be discriminatory to some patients, by directly or indirectly influencing their treatment options.
   (b) It is applied at an individual, but is never a true reflection of the individual burden of disease. An individual has different levels of impairment or disability based on the impact on that individual, and that is very person-specific. It is not based on the number of days. Such norm and value pushes away the individual experience of the individual in front of the clinician. Such numbers are useful from an epidemiology standpoint and to assess a societal burden. WHS-MHC1 includes that impact assessment in each patient, for every visit. It would not discriminate against patients based on numbers, nor will it encourage a provider or beneficiary to document differently. It is our objective that, as imaging technology is increasingly able to assess burden indirectly, future WHS-MHC editions would incorporate these biomarkers wherever possible.
   (c) It is understood that the progression and regression between the acute and chronic states is fluid. Also, other comorbid chronic pain disorders such as fibromyalgia, back pain and chronic regional pain syndrome may co-exist, adding to the burden and thus again the burden of chronic pains need to be assessed holistically.

3. Classifications based on response to treatments are not included in WHS-MCH1
   Although it may be a starting approach, it has outlived its utility. The variability of response to even reliable treatments precludes a treatment-based diagnosis. It also does not say what to do with identical patients who do not respond to such treatment. Such a classification is simplistic, rudimentary and incomplete in as much as they do not know what to do with the non-responders.

5 A MULTIAXIAL MODEL

The axis model gives multiple layers of insight into a patient's condition. It does not restrict itself to a descriptive classification. It includes pathophysiology and aetiology where possible. Where relevant it also describes clinical neuroanatomical localisation that may be supported by imaging.

6 THE WHS FIVE AXIS MODEL

Axis 1: Headache description based on one or more WHS vertical groups.

Each patient who presents with a headache can be placed into one of these broad categories. Abbreviations may be used for convenience.

1. Headaches associated with Dizziness (HaD)
2. Headaches associated with Postural Variation (HaPV)
3. Headaches associated with Fever (HaF)
4. Headaches associated with a Metabolic Abnormality (HaMA)
5. Headaches associated with Inflammation (HaI)
6. Headaches associated with Strokes (HaSt)
7. Headaches associated with Seizures (HaS)
8. Headaches associated with Cognitive or Behavioural Impairment (HaCBI)
9. Headaches associated with Ophthalmic Involvement (HaOI)
10. Headaches associated with Sleep Disorders (HaSD)
11. Headaches associated with Intracranial Space-occupying Lesion (HaSoL)
12. Headaches with no associated symptoms (HnAS)
13. Non-headache symptoms associated with headache disorders (nHS)

Axis 2: Headache syndrome chosen from one or more WHS horizontal groups.

Clinical medicine in general, and neurology in particular, starts with a syndromic approach leading to a presumptive diagnosis. A syndrome is a cluster of symptoms and signs which has more than one cause. The exact aetiology may unfold only later and it is therefore important to have a broad syndromic approach initially. Each horizontal group/syndrome is discussed later as a separate section in this document.

1. Syndrome of Migraine (SyM)
2. Syndrome of Trigeminal Autonomic Cephalalgias (SyTAC)
3. Syndrome of Exertional Headaches (SyExH)
4. Syndrome of Sleep-related Headaches (SySrH)
5. Syndrome of Environment-related Headaches (SyEnvH)
6. Syndrome of Traumatic Headaches (SyTrH)
7. Syndrome of Vascular Headaches (SyVH)
8. Syndrome of CSF Dysregulation Headaches (SyCDH)
9. Syndrome of Infection-related Headaches (SyInfH)

10. Syndrome of Hormone and Chemical-related Headaches (SyHCH)
11. Syndrome of seizure-related headaches (SySH)
12. Syndrome of facial pain (SyFP)
13. Syndrome of neck pain (SyNP)
14. Syndrome of ocular pain (SyOcP)
15. Syndrome of ear pain (SyEP)
16. Syndrome of oral pain (SyOrP)
17. Syndrome of neuralgias (SyNeu)
18. Syndrome of worst ever headache (SyWEH)

Axis 3: Patient narrative of bothersome symptoms and level of impairment.

Patients may have several symptoms which they would present to the clinician. However, each patient is different and to know the impact of the symptoms, the clinician should ask what is/are the most bothersome symptom(s). They may also be asked what are the impairments due to these symptoms and note any activities the patient is prevented from doing.

Axis 4: Headache biomarkers: Imaging, genetic study, biopsy, serum or body fluid.

This includes structural and functional imaging studies including resting state Magnetic Resonance Imaging (MRI), Diffusion Tensor Imaging (DTI), Positron Emission Tomography (PET), Single Photon Emission Computed Tomography (SPECT), electrophysiology, serum and cerebrospinal fluid (CSF markers), and, if any, functional biomarkers such as sensory hypersensitivity. The clinician is expected to document the findings on investigations in this axis.

Axis 5: Impairment scale.

This incorporates commonly used and validated scales such as HIT6, HAD, MIDAS, Migraine Aura Complexity Score [9]. Clinicians are encouraged to develop and validate culturally appropriate assessment scales.

7 HOW TO USE WHS-MCH1

The WHS-MCH1 is based on a cross-talk between the vertical groups and the horizontal groups.

The thirteen vertical groups are headaches with an associated problem and are convenient and easy way to initially access the classification. This group is linked to the horizontal groups and would guide on appropriate referrals and management based on the syndromes they are linked to. There is no reason why an experienced clinician could not start with the syndromic grouping/horizontal groups. Individual diseases and their mechanisms are given an overview in each syndrome. The horizontal groups are also interlinked with each other like links of a chain. Every detail of the disease is beyond the scope of this document and users are encouraged to read more about the disease if required. Some of the disease entities are described in more than one section. This ensures that each section can stand complete in its own right and can be read with just the foreward/preamble for context; this is for completeness and also ease of use as it reduces the need to navigate to cross-references. This document does not mention treatments and clinicians are advised to refer to trusted sources after formulating a differential diagnosis based on this manual.

8 TEAM WORKSHARE

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9 ACKNOWLEDGEMENTS

The authors wish to thank

- Dr Madhav Raje for reviewing this classification in its entirety and contributing their expertise through the addition of psychiatry related commentary.
- Miss Kris Castle for their assistance in compiling and editing of the classification.

Funding sources: None
Competing interest: None

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Headache Medicine Connections

The Official Journal of the World Headache Society

Section 1 : Horizontal Group 1, Syndrome of Migraine (SyM)

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ARTICLE INFO

Article history:
Received 01.08.2021
Accepted 05.08.2021
Published 20.08.2021

https://doi.org/10.52828/hmc.v1i1.classifications

ABSTRACT

Migraine is understood to be a disease of abnormal sensory processing, with abnormal brain electrochemical activity. It is likely that migraine-like headaches are the end-stream effects of other headache syndromes. For example what is currently labelled a 'tension-type' headache could more properly be part of an extended spectrum of migraine with similar clinical features and shared aetiology.[1,2]. Grouping them together extends both the spectrum and the combined disability associated of both conditions. Adopting the approach of 'a migraine spectrum' will also ameliorate the discrimination some patients face after being diagnosed with 'tension headache'; which sadly some clinicians still be believe to be an emotional disorder as opposed to what they see as a the physical disorder of migraine.

Keywords: Migraine; Tension-type headache; Migraine-like headache; Migraine spectrum; Headache; Mental health; Discrimination; Disability; Chronic pain

1 CLINICAL FEATURES, MECHANISMS AND ASSOCIATED CONDITIONS

1. Abnormality in the trigeminovascular system and its connections.
   The headache in migraine can be focal headache/focal headache becoming generalised. This is understood to be due to cortical spreading depression (CSD)-associated nociceptive information transmitted through the trigeminovascular system to the brainstem and subsequently to thalamic and cortical areas to produce the sensation of pain[3].
2. Abnormality in thalamus and thalamocortical connections.
   The trigemino-thalamo-cortical pathway, is a relay network for transmitting information to the cerebral cortex and receiving feedback information from other areas. This may result in hypersensitivity to non-painful and painful skin stimuli (allodynia and hyperalgesia)[4] over many areas in the head and neck region. There is sensitisation of the thalamus during migraine, which evolves over 2–4 hours. This also causes extracephalic allodynia wherein patients are hypersensitive to touch and pain[5].
3. Abnormal sensory perception; This causes:
   (a) Sensitivity to light: Aversion to bright light[6]
   (b) Sensitivity to sound: Aversion to loud sounds[7]
   (c) Sensitivity to smell/taste: Aversion to strong odour[8]
   (d) Sensitivity to motion: Prefers to avoid movement[9]
4. Abnormality of the cortex
   They manifest as auras. Multiple auras may occur in the same individual but they usually follow one after other. CSD can predispose to epileptic activity and vice-versa. Migraine aura can be mistaken for a stroke as areas of hypoperfusion can be evidenced during migraine aura[10]. Depending on the cortical region, the manifestations vary.

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(a) Occipital lobe and connections This can occur in epilepsy as well [11]

i. Bright white zig-zag lines, Flashing colourful lights.
ii. Scotoma: dark and grey areas in the visual field.
iii. Visual noise/snow: Tiny dynamically flickering dots in the entire visual field resembling the static noise of television. Sometimes as a heat wave off a hot pavement.
iv. Palinopsia: Consists of recurrent or persistent images following removal of the visual stimulus.
v. Entoptic phenomena: Floaters, blue field entoptic phenomenon, spontaneous photopsia.
vi. Diplopia (Parieto-occipital) Cerebral diplopia or polyopia is associated with a dysfunction of the primary or secondary visual cortex [12].

(b) Temporal lobe and connections

i. Hippocampus Memory disturbances including transient global amnesia [13,14].
ii. Prosopagnosia, and visual agnosia.
iii. Dysphasia.
iv. Tinnitus [15]

(c) Parietal lobe and its connections

i. Paraesthesia [16]
ii. Detachment from the environment (spaced out feeling).
iii. Visual illusions of Alice in Wonderland syndrome: Metamorphopsia-lilliputian (too small) or brobdingnagian (too large) hallucinations, misperceptions of distances. Telopsia, when objects appear further and pelopsia, from objects appear nearer.
iv. Derealization, depersonalization.
v. Somatopsychic duality (the idea that the person is split into two, often vertically in the middle).
vi. Alteration in the judgment of time is part of Alice in Wonderland Syndrome [17]

(d) Frontal lobe and its connections

Cognitive process takes place at the medial prefrontal cortex and the dorsolateral prefrontal cortex, its neural connectivity with each other and with the thalamus, limbic system, hippocampus, and other regions. Commonest reversible cognitive dysfunction observed is dysfunction of executive function. Cognitive process slows down during migraine as a result of lowered connectivity. Lower connectivity with Default Mode Network (DMN) is observed from visual cortex to frontoparietal & posterior insular network. Migraine is consistently associated with decreased volume of frontal lobe which may account for symptoms of frontal lobe dysfunction. Loss of appetite is explained by activation of 'trigeminal-parabrachial-hypothalamic circuits'.

i. Executive dysfunction/lack of attention and concentration. Other cognitive symptoms are visual & verbal memory deficit, slow speed of processing of information, short attention span, difficulty in new-learning, emotional dysregulation, lack of goal directed behaviour, impairment in set shifting.
ii. Motor dysphasia [18]
iii. Depression and anxiety [19,20]
iv. Limb weakness [21,22]

(e) Hypothalamus [23]

i. Yawning
ii. Tiredness and mood changes
iii. Attacks are linked with hormonal status and the menstrual cycle
iv. Food cravings
v. Nausea

(f) Brainstem symptoms with probable cortical involvement

i. Vertigo
ii. Tinnitus: elementary auditory hallucination generated by the neocortical temporal lobe, notably within Heschl's gyrus [24]
iii. Impaired hearing
iv. Ataxia
v. Confusion [25]
vi. Loss of consciousness [26]

5. Genetic

(a) Family history of migraine [27]
(b) Familial Hemiplegic migraine is the only type of migraine in which monogenic mode of inheritance with autosomal dominance is clearly established. Some of the patients of sporadic hemiplegic migraine (SHM) have a similar monogenic mode of inheritance. Clinical picture of SHM along with migraine headache comprises aura of SHM presents with temporary weakness or temporary hemiparesis, confusion, drowsiness, difficulty in speech along with flashes of light, scotomas. Some patients of SHM present with fever, prolonged weakness, seizures & coma.

6. Childhood migraine precursors [28,29]

(a) Cyclic vomiting
(b) Abdominal migraine
(c) Benign paroxysmal vertigo
(d) Paroxysmal torticollis of infancy
(e) Infantile colic

7. Psychobiology[30–32]
   Serotonergic dysfunction is common in both migraine & depression. Plasma levels of serotonin are lowered during Interictal phase & increased during migraine. Ovarian hormones like oestrogen have an impact over serotonin & sympathetic flow. The hypothalamopituitary axis was dysregulated in both depression & migraine. Panic disorder, phobia, and subclinical obsessive compulsive disorder features are commonly associated with migraine. Panic disorder is more commonly observed than others. Interictal symptoms of migraineurs may also be contributed by obsessive compulsive spectrum disorder comorbidity. Serotonergic dysfunction is a common factor that underlies association of OC features & migraine symptoms. Common risk factors are environment, genetic disposition, and dysfunctional serotonin.

2 THE SYNDROME OF MIGRAINE CAN BE ASSOCIATED WITH THE FOLLOWING CONDITIONS

1. Migraine with aura and without aura
   This is the most common disease entity with a worldwide prevalence and is a leading cause of disability.
2. Tension-type headache[33]
   There are several overlapping features between tension-type headaches and migraines and may represent a spectrum of the same disease.
3. Trigeminal autonomic cephalalgias (TACs)[34]
   Migraines can co-exist with TACs. Although aura symptoms have been described in TACs, migraine-like auras have not been reliably associated with it.
4. Exercise headache[35]
   Exercise can trigger migraine attacks.
5. Headaches associated with sexual activity[36]
   There is a significant comorbidity with migraine.
6. Cold-stimulus headache
   Cold stimulus headaches are more common in migraineurs.
7. External pressure headache
   If the stimulus causing the pain is prolonged, then the local area pain may lead to a more severe migrainous headache in predisposed individuals.
8. New daily persistent headache (NDPH)
   Migrainous features were common in patients with NDPH[37]
9. Post-traumatic headache
   Some of them have migraine or tension-type headache features. They may be generalized, bifrontal, bitemporal, cap-like, occipital-nuchal or with a headband distribution. Migraine-like headaches of recurring nature with possible vasospasm sequelae like hemiparesis, somnolence, irritability, vomiting, confusional state, transient blindness, and brainstem signs can be precipitated.
10. Post Stroke headache
    Varies upon the type of stroke. In a cohort of patients with ischemic stroke, 30% had photophobia, 24% phonophobia, and 28% nausea or vomiting.
11. Headache linked to vasculitis[38]
    These may be associated with severe headache, scalp tenderness, and blurry vision.
12. Headache linked to vascular malformations
    Migraine-like headache with occipital arteriovenous malformations (AVMs) with ipsilateral localization of pain is most commonly reported finding. Occipital AVMs may also present with a hemianopic scintillating scotoma with or without jagged fortifications in the contralateral visual field to the AVM. Headaches associated with AVM are typically ipsilateral with intermittent visual symptoms and pulsatile character.
13. Headache linked to arterial dissection
    They can present with orbital, facial and neck pain and pulsatile tinnitus.
14. Headache linked to cerebral venous thrombosis
    They may be associated with Nausea and/or vomiting, phonophobia and tinnitus.
15. Headache linked to reversible cerebral vasoconstriction syndrome
    Headache is typically bilateral, with a posterior onset followed by a diffuse pain, with a severe to very severe intensity, sometimes excruciating, with agitation, shouting and yelling, often associated with nausea, vomiting, photophobia and phonophobia.
16. Headache linked to Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL)
    CADASIL which occurs due to mutations in the NOTCH3 gene, is characterised by recurrent strokes, neurocognitive impairment and migraine. The prevalence of migraine in CADASIL is slightly higher than the general population. Migraine with and without aura, migraine aura without headache, hemiplegic migraine and migraine with brainstem symptoms have been described in patients with CADASIL. Status migrainosus has also been reported. The prevalence of migraine with aura is higher. Aura in these patients may be atypical. Possible mechanisms leading to higher prevalence of migraine with aura is increased susceptibility or altered expression of cortical spreading depression and there may also be involvement of the brainstem. The NOTCH3 gene may itself behave as a migraine susceptibility gene.
17. Headache attributed to Mitochondrial Encephalopathy, Lactic Acidosis and Stroke-like episodes
    The recurrent attacks of severe pulsatile headaches with vomiting resemble those of migraine. Some patients

with migraine have been reported to suffer ischaemic stroke as a sequel, with motor or sensory deficits, speech disturbances, or much more commonly, visual field defects which have been named migrainous stroke.

18. Headache attributed to Moyamoya angiopathy
The headache is more commonly with tension-type features and associated with photophobia. Migrainous headaches in Moyamoya disease are often refractory to treatment. Studies have supported the role of cerebral artery nociceptors in the generation of headache.

19. Migraine-like aura attributed to cerebral amyloid angiopathy
Transient focal neurological symptoms or 'amyloid spells' are characteristically described as stereotyped and recurrent, with spreading paraesthesias lasting several minutes. Both positive (e.g. visual symptoms) and negative (e.g. paresis, dysphagia) transient symptoms have been described similar to migrainous auras [39].

20. Headache attributed to syndrome of retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations
Retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations (RVCL) is an autosomal dominant small vessel disease due to mutations in the TREX1 gene. Up to 59% of these patients may have migraines [40].

21. Headache linked to pituitary disease
Chronic (46%) migraine and episodic (30%) migraine were the predominant complaints in pituitary adenoma [41]. Headache and visual field defects seem to be the most common presenting clinical features, in 64% and 55%, respectively [42].

22. Headache linked to increased cerebrospinal fluid (CSF) pressure
It has been postulated that the underlying disorder causing migraine symptoms is a disturbance of CSF circulation at the convexity of the brain, resulting in an accumulation of CSF in the posterior fossa, basal cisterns and frontal areas. If the CSF pressure reaches a certain level, it may cause a spasm or stenosis of the vertebral arteries at the site of entry into the intradural space in the cervical region, followed by cerebral ischemia in the region of the vertebral and basilar artery. This usually results in transient neurological symptoms such as a visual aura. A spasm of the carotid artery will occur as a result of increased CSF pressure in the parasellar cisterns, may lead to neurological deficit from the MCA territory (hemiplegic migraine) [43]. Around 52% of idiopathic intracranial hypertension patients have been classified as migraine while 16% as probable migraine. About 22% patients have tension type headache while 4% being classified as probable tension type [44].

23. Headache linked to low cerebrospinal fluid (CSF) pressure
Bilateral posterior head pain is the most common complaint but it may be unilateral or any location of the head. It can mimic migraines [45].

24. Headache linked to non-infectious inflammatory intracranial disease
In Sturge-Weber syndrome prevalence of recurrent headache was 44%, including migraine (28%), chronic tension-type headache (4%) [46].

25. Headache attributed to intracranial neoplasm
In a nested case-control study, it was found that among patients with and those without brain tumors, 554 (4.89%) and 235 (2.08%) individuals, respectively, were identified as having a prior migraine diagnosis [47].

26. Headache attributed to epileptic seizure
Patients with postictal headaches have features of migraine, like photophobia, or phonophobia or vomiting. Vasodilatation following seizures has been implicated [48].

27. Headache attributed to Chiari malformation type I (CM1)
Cough headache can be due to raised intracranial pressure if there is posterior fossa CSF obstruction. They may present with occipital headaches [49]. When there is a Chiari malformation causing obstruction, there is a difference in pressure between the ventricles and the lumbar subarachnoid space. The difference in pressure displaces the tonsils into the foramen magnum. Pain caused by Valsalva manoeuvres may thus be caused by traction on pain-sensitive structures in the arachnoid space or on the blood vessels surrounding the tonsils [50].

28. Alcohol-induced Headache
Headaches linked to alcohol may either be hangover headaches or migraine attacks triggered by alcohol. All types of alcohols can potentially trigger migraine attacks, in 80% of cases within 3 hours [51].

29. Headache linked to nitrates
Nitrate-containing compounds often act as migraine triggers. Nitrate-induced headaches may be immediate, within 1 hour of ingestion; these have mild to moderate severity and are mediated by NO-induced vasodilation. They may also be delayed, occuring 3-6 hours after ingestion, severe and migrainous [52].

30. Headache linked to Monosodium glutamate
Monosodium glutamate (MSG) is the sodium salt of glutamic acid used as a flavoring agent. It has been considered to be a food trigger of migraine. The association was not certain in a systematic review. MSG may increase craniofacial muscle pain sensitivity and pericranial muscle tenderness [53]. Headaches due to MSG intake are described to be tightening or burning pains, and may be pulsatile.

31. Headache linked to caffeine withdrawal
Sudden caffeine withdrawal may trigger migraine attacks [54].
32. Headache linked to hormones
Increased association between migraine and several endocrine disorders such as hypothyroidism, endometriosis, PCOD.
33. Headache linked to infection
Post meningitis headaches can have migrainous characteristics. Headaches may precede the meningitis with migrainous nature in some of them.
34. Headache linked to hypoxia and hypercapnia
Hypoxia may be a trigger for migraines [55].
35. Headache linked to arterial hypertension [56]
Headache, usually bilateral occipital and pulsating, caused by persistent blood pressure elevation accompanied by lethargy and visual disturbances.
36. Headache linked to fasting
Fasting or skipping meals are well-characterized migraine triggers [57].
37. Cardiac cephalalgia
They are associated with migraine-like headaches that occur during myocardial ischemia. High myocardial oxygen consumption can occur during exertion. Proposed mechanisms include convergence of nerve fibers within the spinal cord, increased intracranial pressure secondary to decreased venous return from the brain.
38. Reversible Cerebral Vasoconstriction Syndrome
Reduced cerebral blood flow due to vasoconstriction can cause cortical ischemia inducing Cortical spreading depression and migraine symptoms [58,59].
39. Cervicogenic headache
These may be unilateral, starting from posterior head and neck, spreading frontally to even involve the eyes. There may also be ipsilateral arm discomfort, nausea or vomiting, dizziness, phonophobia, photophobia, blurred vision, and difficulties in swallowing [60].
40. Headache linked to sinusitis
Headache due to sinusitis is characterised by facial pain, pressure, congestion and fullness, nasal discharge, nasal obstruction, purulence, hyposmia/ anosmia, fever. Because of location of the headache, some migraines and tension-type headaches are thought to be due to sinusitis [61]. Sphenoid sinusitis can present with a vertex headache. The headaches can be worse on movement, or coughing. There may be periorbital pain, and more than 50% patients have fever. These features, along with presence of a continuous increasing headache, trigeminal distribution pain, photophobia, and eye tearing may be a clue [62].
41. Headache linked to tooth disorders
Dental disorders often coexist with other headache syndromes such as migraine. Dental pain may mimic the episodic throbbing pain of migraine. Although typically migraine pain occurs in the V1 territory, it may involve the V2 or V3 distribution, and hence may mimic dental pain, and may lead to dental treatment, which does not relieve this pain of migraine. Dental interventions may also initiate migraine pain. Injury in the V1 and V2 distribution may lead to central sensitisation, and relocate the pain due to migraine, called 'remapped migraine' [63].
42. Headache linked to temporomandibular disorder
Temporomandibular disorders include abnormalities of temporomandibular joint and attached masticatory muscles and associated structures. Migraine is frequently reported in individuals with temporomandibular disorder [64]. Temporomandibular disorders may trigger or precipitate migraines [65]. These may serve as nociceptive stimuli or lower the central pain threshold in migraine.

3 HORIZONTAL AXIS GROUPS WHICH MAY BE INTERLINKED WITH THE SYNDROME OF MIGRAINE

Table 1: Horizontal groups linked to syndrome of migraine

ID	Abbr	Syndrome	Linked?
HG1	SyM	Syndrome of Migraine	
HG2	SyTAC	Syndrome of Trigeminal Autonomic Cephalalgias	✓
HG3	SyExH	Syndrome of Exertional Headaches	✓
HG4	SySrH	Syndrome of Sleep-related Headaches	✓
HG5	SyEnvH	Syndrome of Environment-related Headaches	✓
HG6	SyTrH	Syndrome of Traumatic Headaches	✓
HG7	SyVH	Syndrome of Vascular Headaches	✓
HG8	SyCDH	Syndrome of CSF Dysregulation Headaches	✓
HG9	SyInfH	Syndrome of Infection-related Headaches	✓
HG10	SyHCH	Syndrome of Hormone and Chemical-related Headaches	✓
HG11	SySH	Syndrome of seizure- related headaches	✓
HG12	SyFP	Syndrome of Facial Pain	✓
HG13	SyNP	Syndrome of Neck Pain	✓
HG14	SyOcP	Syndrome of Ocular Pain	✓
HG15	SyEP	Syndrome of Ear Pain	✓
HG16	SyOrP	Syndrome of Oral Pain	✓
HG17	SyNeu	Syndrome of Neuralgias	✓
HG18	SyWEH	Syndrome of Worst Ever Headache	✓

ID = Identifier / Serial number, Abbr = Abbreviation, Linked? = check mark / tick mark denotes links between horizontal groups

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Headache Medicine Connections

The Official Journal of the World Headache Society

Section 2 : Horizontal Group 2, Syndrome of Trigeminal Autonomic Cephalalgias (SyTAC)

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ARTICLE INFO

Article history:
Received 01.08.2021
Accepted 05.08.2021
Published 20.08.2021

https://doi.org/10.52828/hmc.v1i1.classifications

ABSTRACT

The Trigeminal autonomic cephalalgias (TACs) are characterized by strictly one-sided headache disorders commonly associated with unilateral autonomic features. The features are characteristic enough to enable reliable separation from migraine. The autonomic features in Cluster Headache (CH) are commonly marked [(1)] whereas in migraine autonomic features, while not uncommon, are often bilateral and not as intense.

The superior salivary nucleus is the origin of the parasympathetic output (which is increased during attacks), via the greater superficial petrosal nerve and sphenopalatine ganglion. Ptosis and miosis are thought to be due to an ocular sympathetic deficit. The reduced sympathetic output is due to dysfunction of postganglionic (third-order) sympathetic neurons which originate in the superior cervical ganglion and travel in the wall of the internal carotid artery. The mechanism of the deficit is unknown. The sympathetic outflow starts in the hypothalamus. There is no migraine-cluster (hybrid) attack and use of this term is discouraged.

Subjects with both migraine and cluster headache can easily separate the two, and so should the practitioner [(2)]. There are 4 constituent groups described below. Patients may exhibit more than one TAC and in such cases it is often helpful to identify one anchor TAC and then associated disorders.

The term 'cluster-tic syndrome' has been used for the occurrence of both CH and ipsilateral trigeminal neuralgia (TN). Associations have also been made between the other TACs and TN. However TACs are brain disorders and TN is a focal nerve disorder. The relationship between the two (if any) has yet to be conclusively defined. All TAC syndromes may on occasion be associated with a focal lesion seen on imaging thought etiologic. Disciplined history taking is stressed.

Associated clinical features of TACs may include features present in other headache disorders such as migraine and does not imply another headache disorder or a hybrid disorder. Much is unknown about the nature of the biological vulnerability to TACs, why these syndromes start, triggers to active periods and triggers to individual attacks.

Keywords: Trigeminal autonomic cephalalgias; cluster headache; paroxysmal hemicrania; hemicrania continua; SUNCT; SUNA

1 CLINICAL FEATURES, MECHANISMS AND ASSOCIATED CONDITIONS

1.1 Cluster Headache [(2)]

Cluster headache (CH) attacks are strictly unilateral short lived (< 3 hours) and severe in intensity (untreated) although the intensity may vary. Attack onset is rapid, within a few minutes to severe pain, often accompanied by 'shadow' sensations on the painful side between attacks when the CH is active. More than 90% of attacks are accompanied by unilateral autonomic features, most commonly tearing, but also a blocked nasal passage and running nostril all on the painful side. CH is the most prevalent TAC. Patients are typically active for a number of weeks (or months) and often multiple attacks are experienced a day. Most patients with CH experience frequent breaks of months or years between active periods. Alcohol is a reliable trigger when CH is active. Multiple separate sleep attacks in the same night dramatically increase the likelihood of CH. Less than 10% of CH patients only have sleep-related headaches.

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1.2 Paroxysmal Hemicrania[3]

Much less common than CH. Attacks are very similar to CH but shorter (<30 minutes) and more frequent. More common in women, with no preponderance of sleep-related attacks. Occasionally neck movements can trigger an attack.

1.3 Short-lasting Unilateral Neuralgiform Headache Attacks (SUNA)[4]

The rarest TAC. Very brief (seconds to a few minutes) repeated attacks (can be hundreds) occurring with or without conjunctival injection and tearing.

1.4 Hemicrania Continua[5]

Side-locked chronic headaches present all the time to a greater or lesser extent. Typically experiences exacerbations which are migraine-like often resulting in presentation to medical care and unilateral autonomic features are helpful in making the diagnosis. Strictly one-sided migraine may look similar.

2 FURTHER CLINICAL FEATURES

- Left or Right Side
  For descriptive purposes the affected side should be recorded. TACs may switch sides but would not be expected to do this commonly.
- Shadow sensations
  Most commonly seen in CH, they constitute non-pain or minimal pain sensations in the geographic area of active CH attacks interictally. Shadow sensations last a variable amount of time but typically far longer than CH attacks. Such sensations may herald the onset of a cluster period and disappearance of shadows is consistent with resolution of a cluster period.
- Unilateral Autonomic Activation with Pain[6]
  Features are tearing, nasal discharge, blocked nostril, one-sided facial sweating and sometimes ptosis and miosis. Typically these features are most prominent when the pain is most severe.
- Associated with demonstrated structural abnormality on the same side that may be etiologic[7].
  Imaging for new presentations in particular may demonstrate a mass lesion in the region of the trigeminal nerve on the painful side. More likely in newly developed headache syndromes.
- Associated with demonstrated contralateral structural abnormality or pituitary lesion[8]. Some studies have suggested a greater chance of a pituitary lesion in those with TACs.
- Associated with raised intracranial pressure[9]
  Raised ICP may be associated with TACs.
- Associated with endocrinological abnormalities[10]. Some hormone abnormalities may be associated with CH such as low testosterone.
- Gastrointestinal activation
  Nausea/vomiting may occur due to the pain.
- Abnormal sensory perception
  Photophobia may occur. Interestingly photophobia may be perceived ipsilateral to the pain.
- Neck pain
  Some patients with TAC report a lot of neck pain with attacks.
- Aura
  In contrast to some published series, migraine-like aura is not reliably associated with CH. Those with migraine-like aura and CH invariably experience aura separate from CH.
- Functional imaging studies may demonstrate abnormalities in the posterior hypothalamus in CH (and all TACs)[10,11].
- In the last 12 calendar months how many months have had at least one attack? Useful metric to reflect level of activity.

3 SYNDROME OF TACS CAN BE ASSOCIATED WITH THE FOLLOWING CONDITIONS

3.1 Hypnic headache

A syndrome not to be confused with cluster headache. Hypnic headache (HH) is defined by recurring attacks only during sleep, typically occurring in those over 50 years of age[12]. Mostly one attack a night, typically lasting 15-240 minutes. Intensity of attacks is typically mild or moderate and a minority of attacks are severe. Most attacks are bilateral and less than 10% exhibit autonomic features. Unilateral HH may be mistaken for CH and even contain other CH characteristics resulting in what would best be identified as a separate entity under HH. Clinical Features that help separate unilateral Hypnic Headache (HH) from Cluster headache (CH):

1. HH less severe, even when experiencing severe attacks, have plenty of less than severe attacks
2. HH preponderance of moderate severity attacks
3. HH tends to be longer duration (64% over 2 hours)
4. HH attack later at night (>50% 4-6am)
5. HH may still have some bilateral headache
6. Smaller number of attacks per night (HH 94% 1 or 2 attacks/night
7. HH starts at an older age
8. Most CH is episodic and goes away completely for months

3.2 Obstructive sleep apnea[13]

Obstructive sleep apnea (OSA) is thought to be more common in the CH population, with several but not all controlled studies demonstrating this finding.

3.3 Depression/suicidal thoughts[14]

More common in the most severely affected, particularly with chronic CH.

4 HORIZONTAL AXIS GROUPS WHICH MAY BE INTERLINKED WITH SYNDROME OF TACS

Table 1: Horizontal groups linked to syndrome of migraine

ID	Abbr	Syndrome	Linked?
HG1	SyM	Syndrome of Migraine	✓
HG2	SyTAC	Syndrome of Trigeminal Autonomic Cephalalgias	
HG3	SyExH	Syndrome of Exertional Headaches	✓
HG4	SySrH	Syndrome of Sleep-related Headaches	✓
HG5	SyEnvH	Syndrome of Environment-related Headaches	
HG6	SyTrH	Syndrome of Traumatic Headaches	✓
HG7	SyVH	Syndrome of Vascular Headaches	✓
HG8	SyCDH	Syndrome of CSF Dysregulation Headaches	✓
HG9	SyInfH	Syndrome of Infection-related Headaches	
HG10	SyHCH	Syndrome of Hormone and Chemical-related Headaches	✓
HG11	SySH	Syndrome of seizure- related headaches	
HG12	SyFP	Syndrome of Facial Pain	✓
HG13	SyNP	Syndrome of Neck Pain	✓
HG14	SyOcP	Syndrome of Ocular Pain	
HG15	SyEP	Syndrome of Ear Pain	
HG16	SyOrP	Syndrome of Oral Pain	
HG17	SyNeu	Syndrome of Neuralgias	✓
HG18	SyWEH	Syndrome of Worst Ever Headache	✓

ID = Identifier / Serial number, Abbr = Abbreviation, Linked? = check mark / tick mark denotes links between horizontal groups

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Headache Medicine Connections

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Section 3 : Horizontal Group 3 - Syndrome of Exertional Headaches (SyExH)

Section Lead: Pravin Thomas

ARTICLE INFO

Article history:
Received 01.08.2021
Accepted 05.08.2021
Published 20.08.2021

https://doi.org/10.52828/hmc.v1i1.classifications

ABSTRACT

This includes headaches which occur during or immediately following exertion. This may be of abrupt onset and moderate to severe in intensity. They may last from minutes to hours. Multiple mechanisms have been postulated in exertional headaches. It is important to recognise them as there may be underlying sinister and life-threatening causes that need immediate attention.

Keywords: Exercise; Exertion; Exertional; Headache; Pain; RCVS; Cardiac; Ischemic Heart Disease; Migraine

1 CLINICAL FEATURES, MECHANISMS AND ASSOCIATED CONDITIONS

- Moderate to severe pulsatile or throbbing head pain
- Nausea, vomiting, scotomas, and photophobia [1]
- Neck pain as an initial symptom [2]
- Migraine as a final common pathophysiological pathway in exertional headaches [3]
- Abnormality in cerebrovascular regulation [4]
- Incompetence of internal jugular valve in patients with primary exertional headache has been implicated in exertional headaches.
- Abnormality of CSF pressure regulation
  Physical exertion may cause transient rise of intracranial pressure. This may result in venous or arterial distention which triggers the pain pathways and headache [5–7].
- Abnormal cardiac output
  A reduction of cardiac output and an increase in right atrial pressure occur in myocardial ischemia. The associated reduction in venous return may increase intracranial pressure, which could produce headache**.** Myocardial ischemia releases serotonin, bradykinin, histamine, and Substance P which may stimulate nociceptive intracranial receptors and produce headache [8].
- Abnormal metabolism
  Vigorous exercise may influence the hypocretin pathway to theoretically initiate attacks [9].
  Anaerobic exercise results in the by-product lactate. Higher migraine frequency is related to increased brain lactate levels as demonstrated by magnetic resonance spectroscopy [10].

2 THE SYNDROME OF EXERTIONAL HEADACHES CAN BE ASSOCIATED WITH THE FOLLOWING CONDITIONS

2.1 Exercise headache

A headache that is precipitated by strenuous exercise. It may last from a few minutes to several hours [11]. It may have a throbbing or non-throbbing nature and can present as pain in the neck or occipital region or any other part of the head. It can begin within 30 minutes or in some cases up to 2 hours after exercise; the intensity of the pain will depend on the fitness level of the individual. Many of these headaches are precipitated while exercising in hot weather [12].

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They may be benign or associated with an underlying sinister causes like cervical artery dissection, subarachnoid hemorrhage, Chiari malformation, reversible cerebral vasoconstriction syndrome (RCVS), space-occupying lesions, sinusitis, and pheochromocytoma. [13]

2.2 *Headache associated with sexual activity*

These may be mild, moderate pressure-like headaches or explosive headaches which increase in intensity with sexual excitement that occurs just before or at the time of orgasm. It can last from a few minutes to several hours [14]. It may herald aneurysmal subarachnoid haemorrhage and may be a symptom of dissection of the basilar and middle cerebral arteries, arteriovenous malformations and reversible cerebral vasoconstriction. Valsalva manoeuvre during orgasm may transiently increase intracranial pressure, leading to headache.

2.3 *Headache linked to reversible cerebral vasoconstriction syndrome (RCVS)*

A headache that presents with thunderclap-nature and explosive headaches with reversible vasoconstriction of intracranial arteries. These headaches can be spontaneous or exertional. Triggers include exertion, coughing, defecation, sexual activity, and bathing [15]. They are also associated with head and neck surgery, carotid endarterectomy, use of illicit drugs, immunosuppressant drugs, catecholamine excess, vasoactive or blood products, pregnancy and postpartum, head and neck trauma, and cervical artery dissection [16]. They may have residual mild to moderate headaches following the explosive headaches. Studies showed dysfunction of the autonomic system [17] and cerebral vasomotor reactivity [18] in patients with RCVS.

2.4 *Cardiac cephalalgia*

These are associated with migraine-like headaches that occur during myocardial ischemia. High myocardial oxygen consumption can occur during exertion. Convergence of nerve fibers inside the spinal cord is a proposed mechanism. Decreased venous return from the brain can also increase intracranial pressure. Abnormal hypothalamic functional connectivity has also been demonstrated. There may also be associated RCVS and autonomic dysreflexia. Reduced cerebral blood flow due to vasoconstriction causes cortical ischemia which induces cortical spreading depression and migraine symptoms [19,20].

2.5 *Migraine*

Exercise can trigger migraine attacks [21–24].

3 HORIZONTAL AXIS GROUPS WHICH MAY BE INTERLINKED TO THE SYNDROME OF EXERTIONAL HEADACHES

Table 1: Horizontal groups linked to syndrome of migraine

ID	Abbr	Syndrome	Linked?
HG1	SyM	Syndrome of Migraine	✓
HG2	SyTAC	Syndrome of Trigeminal Autonomic Cephalalgias	
HG3	SyExH	Syndrome of Exertional Headaches	
HG4	SySrH	Syndrome of Sleep-related Headaches	✓
HG5	SyEnvH	Syndrome of Environment-related Headaches	
HG6	SyTrH	Syndrome of Traumatic Headaches	
HG7	SyVH	Syndrome of Vascular Headaches	✓
HG8	SyCDH	Syndrome of CSF Dysregulation Headaches	✓
HG9	SyInfH	Syndrome of Infection-related Headaches	
HG10	SyHCH	Syndrome of Hormone and Chemical-related Headaches	
HG11	SySH	Syndrome of seizure- related headaches	
HG12	SyFP	Syndrome of Facial Pain	
HG13	SyNP	Syndrome of Neck Pain	✓
HG14	SyOcP	Syndrome of Ocular Pain	
HG15	SyEP	Syndrome of Ear Pain	
HG16	SyOrP	Syndrome of Oral Pain	
HG17	SyNeu	Syndrome of Neuralgias	
HG18	SyWEH	Syndrome of Worst Ever Headache	✓

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Headach. Med. Con. 2021;1(1):18–20

Headache Medicine Connections

The Official Journal of the World Headache Society

Section 4: Horizontal Group 4 - Syndrome of Sleep-related Headaches (SySrH)

Section Lead: Brian E McGeeney

ARTICLE INFO

Article history:
Received 01.08.2021
Accepted 05.08.2021
Published 20.08.2021

https://doi.org/10.52828/hmc.v1i1.classifications

ABSTRACT

Headaches that are associated with sleep refer to headaches starting only or predominantly during sleep. The term sleep-related headache is expected to be more precise than nocturnal or night headaches. Often attacks would occur during the day if asleep. Those experiencing frequent headaches may worsen at night and present as a sleep-related headache. Attempts to sleep during the day or sleeping upright in a comfortable chair can separate out the core inciting event.

The trigger to an attack may be the sleep itself, time of day, a mechanical mechanism with sustained recumbency or medication/substance related. Any cause of raised intracranial pressure can result in worsening headache while lying down, reflecting the sensitivity to a natural increase in intracranial pressure (ICP) with recumbency [1]. Headaches may be bilateral, unilateral or occipital-predominant and be variable in length of time. Care is taken to identify headaches that wake a person up from those that are noticed during natural awake times during the night. Both can reflect sleep-related headaches.

Keywords: Nocturnal; Night; Sleep; Headache; Hypnic; Migraine; Obstructive Sleep Apnoea; Hypertension; Raised intracranial pressure; Respiratory Failure; Caffeine withdrawal; Medication Withdrawal

1 CLINICAL FEATURES, MECHANISMS AND ASSOCIATED CONDITIONS

1.1 Hypnic headache [2]

Defined by recurring attacks only during sleep, typically occurring in those over 50 years old. Mostly one attack a night, typically lasting 15-240 minutes. Intensity of attacks is typically mild or moderate and a minority of attacks are severe. Most attacks are bilateral and less than 10% exhibit autonomic features.

Clinical Features that help separate unilateral Hypnic Headache (HH) from Cluster headache (CH).

- HH is generally less severe, generally with only a minority of attacks deemed severe
- HH preponderance of moderate severity attacks
- HH tends to be longer duration (64% over 2 hours)
- HH attack further into sleep period (>50% 4-6am)
- HH may still have some bilateral headache
- Smaller number of attacks per night (HH 94% 1 or 2 attacks/night
- HH starts at an older age
- Most CH is episodic and goes away completely for months
- HH may be prevented by nightly caffeine unlike CH

1.2 Migraine [3]

Migraine attack onset can be when asleep. Typically the patient will awaken at or near normal waking times with the attack and not early in the night. Invariably there are also attacks during the day and the diagnosis is typically not in question.

1.3 Trigeminal Autonomic Cephalalgias

The strictly unilateral cluster headache (CH) but not other trigeminal autonomic cephalalgias (TACs) has a predilection for attacks while asleep. Other TACs may develop while asleep but are not thought to have any increased likelihood when asleep. While sleep-related attacks are thought to be related to circadian and other natural body rhythms for which the hypothalamus is implicated, underlying mechanisms remain largely unknown. Multiple separate

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sleep attacks in the same sleep period dramatically increase the likelihood that the diagnosis is CH. Less than 10% of CH patients exclusively have sleep-related attacks. There is no consistent relationship between CH attacks and specific sleep stages or arousals. CH attacks typically occur 60–90 min after falling asleep. As the trigger is the sleep cycle more than time of day, sleep during the day would be expected to increase the risk of an attack also. Functional imaging studies may demonstrate abnormalities in the posterior hypothalamus in CH (and all TACs)[4,5].

1.4 Obstructive sleep apnea[6,7]

Obstructive sleep apnea is a mechanical obstruction of the airways when lying down often associated with obesity or naturally short neck/jaw. Headache related to obstructive sleep apnea (OSA) is typically a mild morning headache which disappears within a few hours. Most of even the most severe OSA is not accompanied by headache. One would not expect severe headache or all day headache to be related to OSA. Correcting the OSA should then stop the OSA related headache. Separately, the chronic disrupted sleep associated with OSA may make other headaches more likely.

1.5 Cervical spine and occipital pathology

Arthritis and cervical myofascial pain can present with pain when recumbent. While lying down the spine loses the gravity load and resultant small mechanical changes may result in pain. Imaging or other testing often demonstrates arthritis but identifying a causative lesion is challenging. Any tenderness or sensitivity to pressure (from neuralgia or soft tissue tenderness) can result in pain when the head is resting on a pillow.

1.6 Raised Intracranial Pressure (any cause)[8,9]

Lying down naturally increases venous and arterial pressure to the brain and is normally expected to result in an increase in ICP. For those who already have raised ICP this may result in or worsen headache. There may or may not be an intracranial mass. The "classic" presentation of tumor headache –a severe head pain on awakening, with a dull, constant character with nausea and vomiting occurs in far less than half of all those with intracranial tumors. In children with intracranial tumor, nocturnal and morning headaches are more common, as are nausea and vomiting. An example of raised ICP without mass would be idiopathic intracranial hypertension.

1.7 Hypertension[10]

Severe hypertension is typically accompanied by headache of any intensity. Sleep-related headache is a common experience of untreated severe hypertension. With recumbency brain blood pressure normally increases, and this moderate change may be significant when the person already has severe untreated hypertension. Adequate treatment is expected to result in cessation of headache.

1.8 Hypercapnic respiratory failure

Such as seen in obesity hypoventilation syndrome, and in marked kyphoscoliosis. The retained CO2 causes venous vasodilation and can result in raised ICP.

1.9 Low CSF volume/pressure and paradoxical headache[11,12]

Uncommonly the well characterized orthostatic headache present with low CSF volume (pressure) is paradoxically reversed. The patient then experiences a headache when lying down. The mechanism for this is unknown but may be related to leaks of CSF higher up the neuraxis possibly associated with less leaking when upright. The increased venous pressure when lying down may be involved also.

1.10 Ingestion of Ethanol[13]

Ethanol is a common trigger for migraine. Evening ingestion may result in migraine developing when asleep.

1.11 Analgesic and caffeine withdrawal

Use of frequent analgesics for any reason, including chronic headache can be associated with sleep related headache due to relative withdrawal symptoms. This includes caffeine.

1.12 Exploding Headache Syndrome

An experience of sudden loud noise or sense of explosion occurring at the wake-sleep transition or during sleep, followed by immediate arousal often with a sense of fright, and without significant pain [14].

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2 HORIZONTAL AXIS GROUPS WHICH MAY BE INTERLINKED WITH SLEEP-RELATED HEADACHES

Table 1: Horizontal groups linked to syndrome of migraine

ID	Abbr	Syndrome	Linked?
HG1	SyM	Syndrome of Migraine	✓
HG2	SyTAC	Syndrome of Trigeminal Autonomic Cephalalgias	✓
HG3	SyExH	Syndrome of Exertional Headaches	
HG4	SySrH	Syndrome of Sleep-related Headaches	
HG5	SyEnvH	Syndrome of Environment-related Headaches	
HG6	SyTrH	Syndrome of Traumatic Headaches	✓
HG7	SyVH	Syndrome of Vascular Headaches	✓
HG8	SyCDH	Syndrome of CSF Dysregulation Headaches	✓
HG9	SyInfH	Syndrome of Infection-related Headaches	
HG10	SyHCH	Syndrome of Hormone and Chemical-related Headaches	
HG11	SySH	Syndrome of seizure- related headaches	
HG12	SyFP	Syndrome of Facial Pain	
HG13	SyNP	Syndrome of Neck Pain	✓
HG14	SyOcP	Syndrome of Ocular Pain	✓
HG15	SyEP	Syndrome of Ear Pain	
HG16	SyOrP	Syndrome of Oral Pain	
HG17	SyNeu	Syndrome of Neuralgias	
HG18	SyWEH	Syndrome of Worst Ever Headache	✓

ID = Identifier / Serial number, Abbr = Abbreviation, Linked? = check mark / tick mark denotes links between horizontal groups

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Headach. Med. Con. 2021;1(1):21–24

Headache Medicine Connections

The Official Journal of the World Headache Society

Section 5 : Horizontal Group 5 - Syndrome of Environment-related Headaches (SyEnvH)

Section Lead: Pravin Thomas

ARTICLE INFO

Article history:
Received 01.08.2021
Accepted 05.08.2021
Published 20.08.2021

https://doi.org/10.52828/hmc.v1i1.classifications

ABSTRACT

This includes headaches which are related to changes in the external environment, that induce pathophysiological mechanisms related to headache. They may pose significant challenges to certain occupations. Occupational health physicians should consider these while assessing patients with headaches.

Keywords: Occupational Health; Cold; Pain; Brain Freeze; Ice Cream Headache; Mask Headache; Mountain Sickness; Barotrauma; Diving Headache; Space Headache; Airplane Headache

1 CLINICAL FEATURES, MECHANISMS AND ASSOCIATED CONDITIONS

1.1 Cold stimulus headache

This includes headaches that are precipitated by ingestion, inhalation or external application of a cold stimulus. Cold stimulus headaches appear to be more common in migraineurs[1]. This may be because of the triggering of migraine headaches by the cold[2]. The duration is between a few seconds to a few minutes and are typically stabbing in nature, frontal and temporal[3].

Transcranial doppler ultrasonography in patients who developed headache following cold stimulus has demonstrated reduced mean cerebral blood flow velocities of the middle cerebral arteries following cold stimulus, while no such reduction was noticed in patients without the headache[4]. Lacrimation observed during cold stimulus headaches indicates that the trigeminal-autonomic reflex is involved[5]. Inadequate thermal protection of divers can lead to a cold-stimulus headache[6].

1.2 External pressure headache

This includes headaches resulting from prolonged compression of the scalp and forehead. They are mostly mild to moderate, non-pulsating headaches felt most in the area subjected to pressure. It often increases over minutes and disappears within 1 h of removing the causative stimulus[7]. If the stimulus causing the pain is more prolonged, then the local area pain may lead to a more severe migrainsous headache in predisposed individuals[8]. They result from wearing various types of headgear and tight bands around the head, swimming goggles, headsets, and helmets[9]. More recently, mask-associated 'de novo' headaches have been observed during the COVID-19 pandemic[10].

1.3 Headache linked to hypoxia or hypercapnia

Hypoxia causes secondary headaches associated with low oxygen pressure, such as high-altitude headache and headache due to acute mountain sickness[11]. High altitude headaches tend to have a pulsatile-burst type quality[12]. Many of them have a bilateral headache, with moderate intensity, and aggravated by movement, exertion and straining[13]. Retinal venous distension on ophthalmologic exam and radiographic narrowing of transverse sinus may predict hypoxemia and risk of HAH[14].

At altitudes over 4500 m, headache is extremely common especially with rapid ascent. There is a lesser chance in pre-acclimatized individuals[15]. The body acclimates to higher altitudes by increasing respiration, producing more red blood cells to carry oxygen, and increasing pressure in pulmonary capillaries[16]. Unacclimatized persons who have reached an altitude above 2500 m developed features of acute

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mountain sickness. Along with headache, they may also have fatigue, insomnia, dizziness, anorexia, nausea or vomiting. They can also cause transient ischemic attacks and stroke, transient global amnesia, cerebral venous thrombosis, seizures, high-altitude syncope, cranial nerve palsies, retinal haemorrhages, and sleep disturbances [13]. Hypoxia may be a trigger for migraines [17]. Hypoxic mechanisms have also been postulated in cluster headaches [18].

Intentional breath holding, shallow or intermittent breaths and strenuous underwater exertion may predispose to hypoxia and hypercapnia, which results in headaches [19].

1.4 Barometric pressure-related headache

These headaches are related to changes in barometric pressure and/or barotrauma. This includes headaches linked to migraines, airplane travel, diving headache and space headache.

Barometric pressure is the force exerted by the atmosphere per unit area. The normal barometric pressure is around 1013 mb. Barometric pressure may be high on sunny days and drops down on windy days [20].

When a gas-filled body space such as the lungs and middle ear) fails to equalize its internal pressure as adjustment to changes in ambient pressure, there is tissue damage [21].Changes in barometric pressure may trigger migraines. Many people report weather changes and rainfall as a trigger for their migraines [22].

In a study that included 7054 patients assessed in the emergency department over 7 years, there was an increased risk of acute headaches following a drop in the barometric pressure in the preceding 48 to 72 hours [23].

There was also increased headache with high barometric pressure and lower wind speeds. [24].

Barometric pressure also changes when a flight takes off [25]and with altitude [26].

Headache linked to airplane travel typically presents as a sudden onset of severe jabbing, stabbing, shooting, bursting pain in the head, usually unilateral, orbital, supraorbital, temporal or occipital. It may be associated with eye watering of eyes, nasal congestion and stuffiness [27].

Pre-existing pathology of the nose, sinuses or ears may predispose to increased sensitivity of trigeminal nerve endings and defective adaptation to pressure variation during airplane travel. Hence precipitating attacks of headache occur [28].

Paranasal barotrauma can be the result of ascent or descent causing a During air travel if there is a sudden drop in cabin pressure, especially during ascent or descent, there is barotrauma due to paranasal sinus expansion. A person with structural abnormalities may be unable to equalize pressure which in turn can cause inflammation of paranasal sinuses from vacuum effect, subsequently leading to fronto-orbital pain [25]. Fear and stress raises cortisol levels which in turn facilitates stimulation of triggers in nerve endings of the trigeminal nerve to cause pain.

1.5 Dive-Related Barotrauma and headaches

Divers are constantly exposed to alterations of surrounding pressure during descent and ascent.

Sinister causes of headache during diving include, decompression sickness, carbon monoxide contamination of scuba tank, arterial gas embolism, otic or sinus barotrauma with rupture have all been implicated [21].

Very rarely, cervical artery dissection has been implicated [29].

In a case series of 200 patients, 45.6% reported experiencing identical headache during or shortly after ascent from free diving, snorkelling, or SCUBA diving [30].

1.6 Space Headache

Headache attributed to space travel is common and may also be due to increased ICP from fluid and pressure shifts in microgravity. Microgravity alone is capable of inducing hypoxia and subsequently increased ICP. Many astronauts describe the pain as “exploding” or “heaviness” [31].

Motion sickness in space usually begins within the first hours or days of transition from gravity on earth to microgravity in space. According to the sensory conflict theory there is a conflict between the visual and vestibular systems. It explains why headaches occur along with other accompanying symptoms of motion sickness [32].

Mathematical modelling of intracranial pressures under microgravity conditions tested the hypothesis that intracranial hypertension can be a cause of microgravity-induced headache [33,34].

Headache due to high altitude/hypoxia/hypercapnia are associated with mental status changes, cognitive decline and mood irregularities. Initially hypoxia induces euphoria like mood, however persistent hypoxia/hypercapnia causes irritability, low mood, vigour, fatigability. Cognitive functions like memory, attention, reasoning, complex task performance, reaction time, vigilance, mental skills significantly affected. Mechanism involved behind these changes is thought to be due to irregularities of neurotransmitters. Synthesis of all neurotransmitters depends upon oxygen, however Acetylcholine (Ach) suffers the most significant impairment of all. Ach is responsible for learning memory, hence executive function aligned with learning & memory is impaired [35,36].

2 SYNDROME OF ENVIRONMENT-RELATED HEADACHES CAN BE ASSOCIATED WITH THE FOLLOWING CONDITIONS

1. Migraine [2,8,17]
2. Headaches with cranial autonomic symptoms [5,27]
3. Cluster headache [18]
4. Idiopathic intracranial hypertension [33,34]
5. Cervical artery dissection [29]

3 HORIZONTAL AXIS GROUPS WHICH MAY BE INTERLINKED

Table 1: Horizontal groups linked to syndrome of migraine

ID	Abbr	Syndrome	Linked?
HG1	SyM	Syndrome of Migraine	✓
HG2	SyTAC	Syndrome of Trigeminal Autonomic Cephalalgias	✓
HG3	SyExH	Syndrome of Exertional Headaches	✓
HG4	SySrH	Syndrome of Sleep-related Headaches	
HG5	SyEnvH	Syndrome of Environment-related Headaches	
HG6	SyTrH	Syndrome of Traumatic Headaches	✓
HG7	SyVH	Syndrome of Vascular Headaches	
HG8	SyCDH	Syndrome of CSF Dysregulation Headaches	✓
HG9	SyInfH	Syndrome of Infection-related Headaches	
HG10	SyHCH	Syndrome of Hormone and Chemical-related Headaches	
HG11	SySH	Syndrome of seizure- related headaches	
HG12	SyFP	Syndrome of Facial Pain	
HG13	SyNP	Syndrome of Neck Pain	
HG14	SyOcP	Syndrome of Ocular Pain	✓
HG15	SyEP	Syndrome of Ear Pain	
HG16	SyOrP	Syndrome of Oral Pain	
HG17	SyNeu	Syndrome of Neuralgias	
HG18	SyWEH	Syndrome of Worst Ever Headache	✓

ID =Identifier / Serial number, Abbr =Abbreviation, Linked? =check mark / tick mark denotes links between horizontal groups

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Headach. Med. Con. 2021;1(1):25–29

Headache Medicine Connections

The Official Journal of the World Headache Society

Section 6 : Horizontal Group 6 - Syndrome of Traumatic Headaches (SyTrH)

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ARTICLE INFO

Article history:
Received 01.08.2021
Accepted 05.08.2021
Published 20.08.2021

https://doi.org/10.52828/hmc.v1i1.classifications

ABSTRACT

This group encompasses headaches following injuries to the head, face and neck with temporal association suggesting the causality of trauma. They range from mild headaches to life threatening ones. Many of them present to the emergency department in the acute phase. Brain imaging may be normal and yet the pain continues to contribute to morbidity even after the local tissue injuries have healed. They result from accidents, assault, sports injuries and occasionally self-inflicted harm. Long term manifestations of traumatic headaches are also linked to cognitive and behavioural impairments. Some of these headaches have migraine-like symptoms but they are resistant to conventional treatment. They are also a cause of long-term disability and need a multidimensional approach to treatment.

Keywords: Traumatic Headache; Trauma; Injury; Whiplash; Cough Headache; Concussion; Hematoma; Ischemic Stroke; Migraine; Spinal Cord Injury; Intracerebral Haemorrhage; Tensiontype Headache

1 CLINICAL FEATURES, MECHANISMS AND ASSOCIATED CONDITIONS

1.1 Superficial tissue trauma

In superficial traumatic injury leading to lacerations, there is tear to the pial membrane which is often associated with underlying bruising called a contusion. Contusions are commonly due to a contrecoup injury and coup injury, the latter of which usually underlies a fracture. Contusions are usually asymptomatic, but can be a cause for epilepsy[(1)]. There is evidence of inflammatory changes in deep cranial structures suggesting that in the acute phase post-minimal traumatic brain injury (TBI), the headache may originate from peripheral rather than from central or supraspinal pain pathways. Injury to peripheral structures, including blood vessels, nerve fibers and bone, as well as the initiation of an inflammatory cascade results in the persistent traumatic headache post minimal TBI resulting from laceration[(2)].

1.2 Daily tension-type headaches

Daily tension-type headaches with occipital, bifrontal, bitemporal, cap-like, headband distribution or generalized types are the most common type of headaches in this syndrome.[(3)]

1.3 Migraine like headaches

Migraine-like headaches of recurring nature with possible vasospasm sequelae like hemiparesis, somnolence, irritability, vomiting, confusional state, transient blindness, and brainstem signs can be precipitated by trauma[(3)].

1.4 Neuralgias

Neuralgias due to entrapments of nerves like occipital, supraorbital, infraorbital nerve with shooting, tingling or burning pain along with decreased or altered sensation and decreased sweating from the nerve territory. Occipital neuralgia which is the most common of the neuralgias following traumatic brain injury does not necessarily arise from the occipital nerve and does not usually have a neuralgic quality but presents with a throbbing or aching nuchal pain[(3)].

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1.5 Whiplash

Whiplash of the neck resulting in pain at the time of trauma is characterised by triad of pain and restricted mobility of neck with throbbing and/or pressure-like unilateral pain from occipital region extending to temporoparietal area [3].

1.6 Trivial trauma

Coughing, lifting, minor falls, or pushing are considered as trivial trauma. Cerebrospinal fluid leak resulting from intracranial hypotension from trivial trauma can cause headaches [3,4].

1.7 Post-concussion headache

Post-concussion headache presents as a symptom complex that includes dizziness, fatigue, irritability, anxiety, insomnia, loss of concentration and memory, and noise sensitivity [5].

1.8 Hematomas

Subdural and epidural hematomas both may be associated with headache due to the associated space-occupying abnormalities [5].

1.9 Headache in traumatic subarachnoid haemorrhage (SAH)

Sudden severe headache that reaches maximum intensity at the onset [6]. Subdural hematoma and contusion can occasionally be seen with SAH due to spreading of blood outwards around penetrating injuries and lacerations. Ventral surface of the brain stem can sometimes be affected by traumatic SAH [7]. The headache intensity can be moderate. Prompt consideration of SAH should be done in the presence of any acute-onset headache regardless of severity or prior headache history [8]. Altered level of consciousness, cranial neuropathies, focal weakness, and meningism are the additional features [8].

Pain is thought to be caused by the chemical irritation caused by the blood on the meninges and in the subarachnoid space along with immune activation, infiltration of immune cells and inflammatory cytokines [9,10].

Development of headache after SAH is also contributed by the accompanying hypertension in the patient. The sequelae of SAH like cerebral vasospasm and hydrocephalus also results in headaches after SAH [10].

A significantly higher pain scores is seen those who develop cerebral vasospasm early after SAH [10].

Fever after SAH has infection as a cause in 75% but may be central or neurogenic in etiology in the rest and is significantly associated with an increased risk of symptomatic vasospasm and with poor outcome [11]. Seizures and epilepsy are well-known complications following aneurysmal SAH [12].

Reversible cause of blindness following severe headache in SAH due vitreous haemorrhage can be recognized only with high index of suspicion [13].

Thunderclap headache associated with severe back pain, root pain or findings of spinal cord dysfunction all point to a spinal cause of SAH, such as a spinal arteriovenous malformation, aneurysm or hemangioma [14].

1.10 Headache attributed to ischemic stroke following trauma

Headache associated with ischemic stroke usually has acute onset headache associated with focal neurologic signs [15] or persistent headache attributed to a past ischemic stroke.

About 2.5% of moderate to severe TBI patients develop acute ischemic stroke. Higher-velocity events are a more common cause of dissections due to TBI in cervical dissection patients who experience ischemic stroke after TBI [16].

Commonest pattern is a bilateral headache of tension type pattern which is of mild to moderate nature, not associated with nausea, vomiting, photophobia, or phonophobia which improves over time [17].

Infarction at the territory of posterior cerebral artery was found to be associated most commonly following a trauma [18].

Headache at the onset of stroke is more commonly seen in posterior circulation strokes than in strokes affecting other vascular territories. Headache is more common in major stroke than in minor stroke as well as in cortical than in subcortical lesions and is a rare symptom in lacunar stroke [19].

The onset of headache on the day the stroke initiated occurred in 87% of the patients, and in the remaining patients, onset occurred between days 2 and 5. The headache mostly behaved in a continuous manner, but decreased in frequency and intensity over the days [17].

Extensive cerebral infarctions with mass effect and structural herniation, the displacement and compression of pain-sensitive structures such as the meninges and the proximal segment of the intracranial arteries may cause headache [17].

Trigeminovascular system activation by the cortical spreading depression (CSD) triggered by cerebral ischemia and release of prothrombotic, inflammatory, and excitotoxic substances may play a role [17].

The edema and haemorrhagic transformation causing mass effect and trigeminovascular system activation could be an added pathophysiology for headache occurring in acute ischemic stroke [15].

Localization of pain is in such a manner that the pain arising from supratentorial structures are referred frontally and that arising from the infratentorial structures are localized to the occipital regions [20].

The central sensitization of nociceptor inputs after stroke may cause persistence of the pain. Organization of the infarction and further structural changes leads to stretching of pain sensitive structures and may also disrupt central pain pathways localized in the brainstem, insula, or somatosensory cortex.

The trigeminovascular system densely innervates the vertebrobasilar system than the carotid system, and this may contribute to the increased frequency of headaches [17].

1.11 Headache associated with intracerebral haemorrhage following trauma

Headache occurs at the onset in about 57% of intracerebral hematomas.

New-onset headaches occurred in a tenth of the patients and were usually of the tension-type but on the other hand a similar number of patients who had pre ICH headaches became symptom free following bleeding [21].

Intracranial bleeding may modify the responses of trigeminal neurons to the usual triggers of migraine and other headache types. When the haemorrhage is small, headache may be entirely absent

Increased intracranial pressure headache is observed in 51.5% of patients with ICH. Focal neurologic deficit that develops within minutes to hours is the additional neurological manifestation in ICH patients [22].

Headache is usually severe in thalamic and putaminal haemorrhages, and is thought to be caused by the subarachnoid and intraventricular extension of the hematoma.

Headache is ipsilateral, but it may generalize if there is hydrocephalus and elevated ICP [23].

Headache intensifies when there is rupture of the hematoma into the subarachnoid space and will be associated with neck stiffness and other signs of meningeal irritation [23].

It can be associated with vomiting and also the patient may have depression [22], [21].

The intraparenchymal mass stretches the pain-sensitive vascular, meningeal, and neural structures and as hematoma enlarges there is increase in ICP due to CSF flow obstruction [23].

Cerebellar hemorrhages are characterised by occipital headaches followed rapidly by vomiting, impaired consciousness, and brainstem, cerebellar or cranial nerve dysfunctions [23].

The pathophysiology of mild TBI is multifactorial with partly neurometabolic origin associated with release of excitatory neurotransmitters. The axons are not sheared at the time of injury in mild TBI, but instead undergo a series of changes that may result in a secondary axotomy within 24 hours [3].

Whiplash is sudden acceleration and deceleration of the neck and the specific mechanism involves the merging of cervical and trigeminal afferents inside the trigeminocervical nucleus [24].

Chronic post-traumatic headache is the headache which continues for months after incurrence of the injury and is the most prevalent type of pain after mild TBI, with a prevalence rate of 47–95%, compared to about 20– 38% in moderate–severe TBI [25].

The most frequent painful region was the temple, followed by the forehead, neck, back of head, eyes, and vertex [25].

Tension-type like chronic headache patients suffer from bilateral pain of mild to moderate intensity of pressing and dull quality which is aggravated by emotional stress [25].

Migraine type like chronic headache patients suffer from unilateral pain of moderate to severe intensity, pounding, throbbing, drilling, and piercing in quality, which is aggravated by physical activity and may complain of sensitivity to bright light or noise [25].

Mixed headaches with overlapping headache types including cluster-like headache features characterized by excruciating unilateral pain can also be present [25].

Individuals with whiplash injuries also present with headache features similar to tension-type and migraine-type headaches as well as cervicogenic headaches [25].

Frequency of headache can vary from daily, weekly or monthly headaches and during an episode it was reported to gradually increase, reaching very high intensities and was described as a misery [25].

Chronic headache following trauma can have neck pain mainly in the posterior aspect , which is described as a feeling of muscle spasm in the neck [25].

Structures innervated by pain receptors which are connected to C and A-delta fibers, convey impulses from the nociceptors to the nociceptive neurons in the spinal cord. Spinothalamic tracts then convey these impulses onto brain regions so that various aspects of the pain experience could be processed [25].

Release of cytokines and chemokines near the injured tissue results in monocyte cellular activation, glial cell activation, and release of nociceptive neuropeptides. This neuroinflammation causes vascular disruption and nociceptors adjacent to the injury region gets activated and sensitized, and become hyper responsive to stimuli spontaneous pain, as well as hypersensitivity to noxious and innocuous stimuli [25].

Nociceptive input from cervical segments reaching the trigeminal nucleus might be a source of referred pain to neck if cervical damage occurs during the TBI [26].

Direct damage to the trigeminal nerve during the trauma may lead to neuropathic pain. Trigeminal neuropathic pain results from the abnormal compression of the trigeminal nerve by a vein or artery, leading to deterioration of myelin sheaths [27].

Central pain occurs after severe TBI and less commonly with moderate and mild injury, which was diffusely located in the hemi body contralateral to the TBI site including the head and face have also been reported [28].

Deafferented neurons in the thalamus and somatosensory cortex undergo plastic changes and become hyper-excitable and hyper-reactive. The complaints of pain coincide with the spontaneous burst of neurons with an epileptiform discharge. This could also be a pathophysiology for underlying mechanism for spontaneous pain in chronic post traumatic headache [25].

Hyperalgesia and allodynia in chronic post traumatic headache is caused by impairment in supraspinal modulation of nociceptive inputs due to prolonged peripheral nociceptor activation [25].

Post-traumatic stress disorder may also affect headache post trauma due to severe depression [25].

1.12 Headache following spinal cord injury

Headache is a common symptom of a clinical condition known as autonomic dysreflexia following spinal cord injury. This is characterised by episodes of extreme hypertension usually accompanied by headache, upper body flushing and slow heart rate, that may be provoked by stimuli.

Consequences of untreated episodes of this syndrome include intracranial hemorrhage, seizures, retinal detachments ,myocardial infarction, pulmonary edema, coma and sometimes death. The pathogenesis of headache is not clear in this syndrome but suggested to be due to vasomotor nature. Also headache resulting from autonomic dysreflexia may result from passive dilation of cerebral vessels or increased circulating prostaglandin E2.

1.13 Headache following Post craniotomy

Headaches that occur initially after craniotomy is characterised by superficial pain resulting from somatic pain in the muscles of the pericranium and soft tissues rather than a visceral pain [29].

Headache in a post craniotomy patient is associated with depression, anxiety, and temporomandibular disorders [29].

Frontal craniotomies have less pain than craniotomies done for treating lesions of the posterior fossa [29].

Adherence of the musculature to the dura mater is an important mechanism for Post craniotomy headache [29].

Another cause of post craniotomy headache is the circulation of bone debris caused by bone drilling may cause aseptic meningitis [29].

Post acoustic neuroma craniotomy was found to have a neuralgic pattern in about 43% of the patients [29].

Presence of a neurinoma in the scar has been suggested as a cause or contributory factor for Post craniotomy headache [29].

Persistence of the pain following surgery is favoured by the process of central sensitization of nociceptor inputs after acute surgical trauma [30].

2 SYNDROME OF TRAUMATIC HEADACHES CAN BE ASSOCIATED WITH THE FOLLOWING CONDITIONS

1. Migraine like Headaches
2. Neuralgias
3. Tension-type headache
4. Post Stroke headache
5. Headache linked to CSF dysregulation
6. Headache attributed to intracranial neoplasm
7. Cervicogenic headache

3 HORIZONTAL AXIS GROUPS WHICH MAY BE INTERLINKED

Table 1: Horizontal groups linked to syndrome of migraine

ID	Abbr	Syndrome	Linked?
HG1	SyM	Syndrome of Migraine	
HG2	SyTAC	Syndrome of Trigeminal Autonomic Cephalalgias	
HG3	SyExH	Syndrome of Exertional Headaches	✓
HG4	SySrH	Syndrome of Sleep-related Headaches	✓
HG5	SyEnvH	Syndrome of Environment-related Headaches	
HG6	SyTrH	Syndrome of Traumatic Headaches	
HG7	SyVH	Syndrome of Vascular Headaches	✓
HG8	SyCDH	Syndrome of CSF Dysregulation Headaches	✓
HG9	SyInfH	Syndrome of Infection-related Headaches	
HG10	SyHCH	Syndrome of Hormone and Chemical-related Headaches	
HG11	SySH	Syndrome of seizure- related headaches	
HG12	SyFP	Syndrome of Facial Pain	✓
HG13	SyNP	Syndrome of Neck Pain	✓
HG14	SyOcP	Syndrome of Ocular Pain	
HG15	SyEP	Syndrome of Ear Pain	✓
HG16	SyOrP	Syndrome of Oral Pain	
HG17	SyNeu	Syndrome of Neuralgias	
HG18	SyWEH	Syndrome of Worst Ever Headache	✓

ID = Identifier/ Serial number, Abbr =Abbreviation, Linked? =check mark / tick mark denotes links between horizontal groups

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Headach. Med. Con. 2021;1(1):30–42

Headache Medicine Connections

The Official Journal of the World Headache Society

Section 7 : Horizontal Group 7 - Syndrome of Vascular Headaches (SyVH)

Section Lead: H Ahamed Subir

ARTICLE INFO

Article history:
Received 01.08.2021
Accepted 05.08.2021
Published 20.08.2021

https://doi.org/10.52828/hmc.v1i1.classifications

ABSTRACT

This encompasses headache disorder symptoms ranging from mild diffuse headaches to life-threatening thunderclap headaches with associated symptoms caused by diseases of blood vessels or situations arising out of their subsequent complications.

Keywords: Vascular Headache; Thunderclap Headache; Ischemic Stroke; Transient Ischemic Attack; Subarachnoid Hemorrhage; Aneurysm; AV malformation; Vasculitis; Hypertension; Hypertensive; CADASIL; MELAS; Cavernoma; Sturge Weber Syndrome; Sentinal headache

1 CLINICAL FEATURES, MECHANISMS AND ASSOCIATED CONDITIONS

1.1 Headache attributed to ischemic stroke or transient ischemic attack (TIA)

Ischemic strokes usually have acute onset headaches associated with focal neurologic signs or may have persistent headaches attributed to a past ischemic stroke[1]. Commonest pattern of headache is a tension type pattern with mild to moderate bilateral headache which is not associated with vomiting, nausea, phonophobia, or photophobia and which improves over time[2]. Headaches at the onset of stroke are more often seen in posterior circulation strokes than in strokes affecting other vascular territories. Headache is associated more with major strokes than with minor strokes as well as in cortical than in subcortical lesions and is a rare symptom in lacunar stroke[3].

Headache on the day the stroke initiated occurred in 87% of the patients, and in the remaining patients, onset occurred between days 2 and 5. The headache mostly behaved in a continuous manner, but decreased in frequency and intensity over the days[2].

In lacunar infarctions, the headache was described by most patients as having started at the same time as the focal neurologic deficit, and was described as mild, poorly localized, and with a pressure-like pain[3].

Extensive cerebral infarctions having mass effect and structural herniation, the displacement and compression of pain-sensitive structures such as the meninges and the proximal segment of the intracranial arteries may cause headache[2]. The activation of the trigeminovascular system by the cortical spreading depression (CSD) triggered by cerebral ischemia and release of prothrombotic, inflammatory, and excitotoxic substances may play a role[2]. The central sensitization of nociceptive inputs after stroke may cause persistence of the pain. Organization of the infarction and further structural changes leads to stretching of pain sensitive structures and may also disrupt central pain pathways localized in the brainstem, insula, or somatosensory cortex.

The Trigeminovascular system is more densely packed in the vertebrobasilar system than the carotid system, and this may contribute to the increased frequency of headaches in strokes occurring in this region[2].

The pathophysiology of headache in lacunar infarctions are more linked to neurotoxic effects than mechanical effects[3].

The atherosclerotic mechanisms as well as uncomplicated cerebral infarction are painless[3].

The oedema and haemorrhagic transformation causing mass effect and activation of the trigeminovascular system could be an added pathophysiology for post-acute ischemic stroke headache[1].

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Pain arising from supratentorial structures are referred frontally and that arising infratentorial is localized to the occipital regions [4].

Occurrence of headache during TIA is as puzzling as the nature of TIA itself and has multiple hypotheses involving trigeminovascular and neuroexcitotoxic factors [5]. Persistent headaches have been observed in up to 23% of patients after ischemic or haemorrhagic stroke. The persistent headaches are of tension-type nature and are more frequent and severe than the headaches which occur following acute strokes [6].

Central pain modulation in the brainstem, insula, or somatosensory cortex is disrupted by infarction. Chronic tension-type headache and migraine occurs due to functional and structural alterations in previously mentioned regions regions, as well as orbitofrontal and cingulate cortex. Persistence of headache in acute stroke is also contributed by central sensitization of nociceptive pathways. Poor posture or altered biomechanics following stroke is an additional mechanism for chronic tension-type headache, which triggers sensitization of second-order spinal and supraspinal central neurons. Comorbid depression, fatigue, and sleep apnea may exacerbate or perpetuate the headaches. [6]

1.2 Headache associated with intracerebral hemorrhage

Headache occurs at the onset in about 57% of intracerebral hematomas and a few patients also mention about a sentinel headache which is an unusual headache in the weeks preceding the event.

New-onset headaches occurred in a tenth of the patients and were usually of the tension-type but on the other hand a similar number of patients who had pre intracerebral hemorrhage (ICH) headaches became symptom free following bleeding. [7]

Intracranial bleeding may modify the responses of trigeminal neurons to the usual triggers of migraine and other headache types. When the haemorrhage is small, headache may be entirely absent.

Additional clinical manifestations of ICH include focal neurologic deficit that develops within minutes to hours. [8]

Headache is ipsilateral, but it may generalize in the presence of hydrocephalus and elevated ICP. [9]

Increased intracranial pressure headache is observed in 51.5% of patients with ICH.

Headache is usually severe in putaminal and thalamic haemorrhages and is caused by the intraventricular and subarachnoid extension of the hematoma.

Headache intensifies when there is rupture of the hematoma into the subarachnoid space will be associated with neck stiffness and other signs of meningeal irritation. [9]

It can be associated with vomiting, and patient may have depression. [7,8], spontaneous non traumatic ICH is presumably an end result of small vessel diseases which include arteriolosclerosis, lipohyalinosis, and cerebral amyloid angiopathy. [8]

The intraparenchymal mass stretches the pain-sensitive vascular, meningeal, and neural structures and as hematoma enlarges there is increase in intracranial pressure (ICP) due to obstruction of CSF flow. [9]

Cerebellar hemorrhages are characterised by occipital headaches followed rapidly by vomiting, impaired consciousness, and brainstem, cerebellar or cranial nerve dysfunctions. The headache is often acute and may be maximal at onset and severe, mimicking a subarachnoid hemorrhage SAH. [9]

Acute severe headaches may also be caused by acute distension of the ventricular system through engorgement of the ventricles with blood under arterial pressure or as acute hydrocephalus produced by obstruction of the aqueductus or of the fourth ventricle as in case of occasional pontine or cerebellar haemorrhages.

The ipsilateral and occasional bilateral location of pain and the increased frequency of headaches in the presence of occipital and cerebellar hematomas may be explained by the trigeminovascular system organization. Location, size of the haemorrhage, and rate of evolution determines the occurrence and severity of headache.

Tension type headaches are the common type of chronic post-ICH headaches and occur in association with depression.

Post ICH headaches are usually less frequent and severe than pre-ICH headaches. Some headaches, especially migraines, remitted after ICH.

Intracranial bleeding may modify the responses of trigeminal neurons to the usual triggers of migraine and other headache types.

1.3 Headache in ruptured and unruptured aneurysms

Sudden severe headache that is at maximum intensity at onset. [10]

The headache intensity can be moderate. The presence of any acute-onset headache regardless of severity or prior headache history should prompt consideration of SAH. [11]

Altered level of consciousness, cranial neuropathies, focal weakness, and meningism are the additional features. [11]

Aneurysmal subarachnoid hemorrhage headache pain was not instantaneous in half of the patients and may take up to minutes in one-fifth of cases. [12]

Pain is thought to be caused by the chemical irritation caused by the blood on the meninges and in the subarachnoid space along with immune activation, infiltration of immune cells and inflammatory cytokines. [13,14]

Development of headache after SAH is also contributed by the accompanying hypertension in the patient. The sequelae of SAH like cerebral vasospasm and hydrocephalus also results in headaches after SAH. [14]

Significantly higher pain scores is seen those who develop cerebral vasospasm early after SAH [14]

Fever after SAH has infection as a cause in 75 % but may be central or neurogenic in aetiology in the rest and is significantly associated with an increased risk of symptomatic vasospasm and with poor outcome. [15]

Seizures and epilepsy are well-known complications following aneurysmal SAH. [16]

Reversible cause of blindness following severe headache in SAH due to vitreous haemorrhage can be recognized only with a high index of suspicion. [17]

Thunderclap headache associated with severe back pain, radicular pain, or symptoms and signs of spinal cord dysfunction all point to a spinal cause of SAH, such as a spinal arteriovenous malformation, aneurysm, or hemangioma. [18]

The non-aneurysmal perimesencephalic SAH is characterised by headache that occurs in minutes rather than seconds, loss of consciousness is exceptional, and focal neurologic abnormalities are generally not found. The possible cause is mostly of venous rupture into the cisterns surrounding the midbrain. [18]

Headache in unruptured saccular aneurysm has a new acute headache which includes, sentinel or thunderclap headache and or painful third nerve palsy with other evidences of the unruptured aneurysm. [19]

The intracranial arteries, especially the proximal portions of the major vessels, are innervated by sensory nerves that could potentially be activated by aberrant blood flow and/or structural changes of the vessel wall. [19]

A markedly increased prevalence of migraine without aura was present in patients with unruptured saccular intracranial aneurysms. Saccular intracranial aneurysm of the internal carotid artery results in severe pain around the eye with the pain radiating to the head due to the compression of the third nerve. Headaches can occur in giant aneurysms as they can cause compression or distortion of intracranial structures. Headaches are a common finding in aneurysms compressing cranial nerves or other structures but usually will not have characteristics of a migraine headache. Migraine in unruptured aneurysm occurs as a result of input from perivascular sensory nerve terminals around the aneurysm which acts as a stimulus that increases sensitization in the central nervous system. [20]

1.4 Headache in AV malformations (AVM)

Headache was the initial manifestation in one fourth of the patients.

Migraine-like headache with occipital AVM with ipsilateral localization of pain is most commonly reported finding. [21]

Occipital AVMs can have hemianopic scintillating scotoma with or without jagged fortifications in the contralateral visual field to the AVM. [21]

Headaches were ipsilateral and associated with intermittent visual symptoms and has a pulsatile character. The absence of nausea and autonomic dysfunction differentiates AVM-associated headache from migraine. [21]

Increased intracranial pressure (ICP) is thought to activate the trigeminovascular system which is composed of blood vessels as well as trigeminal afferents and their central projections. High-flow arteriovenous shunting associated with AVM may result in cerebral steal phenomena and ischemia that initiates headache. [21]

The hemodynamic changes like the steal phenomena or the mechanical effects due to AVM can trigger cortical spreading depolarisation and the trigeminovascular system. [22]

AVM nidus acts as an “irritative focus” that initiates CSD, there by determining lateralization of headache and aura in patients who are already predisposed to migraine. [21]

1.5 Headache in Dural AV fistulas (DAVF)

The clinical course of DAVFs varies widely and ranges from benign with spontaneous remission to fatal due to cerebral haemorrhage. [23]

Migraine-like headache seems to be a typical characteristic of dural AV fistulas not associated with carotico-cavernous fistulas and can have headache, tinnitus and progressive neurologic deficits as associated symptoms. [24,25]

Carotico-cavernous fistulas are characterised by non-migraine-like headache and is often associated with ocular symptoms, due to increased venous sinus pressure occurring due to the reversal of flow in the ophthalmic veins. [24]

Very aggressive symptoms such as haemorrhage, seizures, focal neurological deficits, cranial nerve palsies, myelopathy or intracranial hypertension signs were observed in about forty percentage of patients. DAVF location and the pattern of the venous drainage determines the symptoms. [24]

Headache which was initially localized to the same site of the lesion becomes generalized as a result of the dural stretching. [25]

Increase in vascular pulsatility in the arteriolar and venous territories may lead to an increased activity of the perivascular sensory terminations present at the DAVFs level. As a result, there is release of neuropeptides from the trigeminal sensitive nerve peripheral endings at the meningeal level, triggering components of the neurogenic inflammation causing migraine-like headache in DAVFs. [24]

1.6 Headache in cavernous malformations

Cavernous malformations or angiomas are usually benign symptomatic vascular lesions which when becomes symptomatic presents with headache, seizure, impaired consciousness, or new/worsened focal neurologic deficit pointing to the anatomical location. [26] Chronic headache is common in patients with cavernous malformations [27]. Rarely migraine-type headaches can occur. [28]

Traction headache for increased intracranial pressure, followed by activation of trigeminal vascular system secondary to bleeding. [28]

Headaches may be caused by increased intracranial pressure, followed by activation of trigeminal vascular system secondary to bleeding.

Frontal lobe cavernomas can provoke psychiatric signs, mostly those involving the prefrontal region. [28]

1.7 Headache in leptomeningeal angiomatosis

All the headaches reported in patients with Sturge–Weber syndrome (SWS) appear to have migrainous features, with reversible focal neurological symptoms. [29]

Epilepsy and mental retardation are the most common symptoms, migraine like headache is an important phenotypic spectrum of leptomeningeal angiomatosis. [27]

Prevalence of recurrent headache was 44%, including migraine (28%), headache related to glaucoma (8%), chronic tension-type headache (4%), episodic tension-type headache (1%) and unclassifiable headache (3%) reported in a study. [30]

Chronic focal oligaemia and ensuing tissue hypoxia might precipitate migraine-like headaches and severe, prolonged neurological deficits, without cerebral infarction. As well known, cortical spreading depression is the suggested mechanism for migraine visual aura. [29]

Hypoxia decreases the threshold for cortical spreading depression and thus increase the susceptibility for initiation of headache. [31]

Recurrent small leaks from leptomeningeal angiomatosis, venous anomalies, occipital lobe seizure, reperfusion hyperaemia, focal encephalitis, and the activation of the trigeminovascular system are the probable causes for migraines. [32]

Once the trigeminovascular system is activated by an unknown trigger as in migraine, augmented reaction develops particularly in the area of leptomeningeal angiomatosis and increases vasogenic plasma leakage and leakage of neuropeptides into the subarachnoid space.

Neuropeptides further activate or sensitize the peripheral trigeminovascular fibers, causing migraine features and vasodilatation in the corresponding cortex. The augmented vasogenic leakage which is presumably caused by trigeminovascular activation, can result in prolonged aura and probably migraine. [32–34]

The main theories on the pathogenesis of glaucoma in SWS includes a congenital malformation of the anterior chamber angle leading to high aqueous humor outflow resistance, an increase in episcleral venous pressure due to arteriovenous shunts into the episcleral hemangioma, fluid hypersecretion by either the ciliary body or the choroidal hemangioma and abnormal hemodynamics of the episclera and the anterior chamber angle due to premature aging of the trabecular meshwork–Schlemm's canal complex. [35]

Narrow-angle glaucoma can cause severe headaches and may occasionally be accompanied by pain in the forehead or eyes. [35]

1.8 Headache due to vasculitis

Vasculitis may present primarily with headache symptoms and also can be associated with neurological deficits and cerebrospinal fluid lymphocytosis. [36]

Primary CNS vasculitis, granulomatous vasculitis, systemic necrotizing arteritis, and systemic collagen diseases are the most common types of vasculitis that are associated with headaches. [36]

Granulomatous giant cell and epithelioid cell inflammation with necrotizing arteritis of cerebral vessels causes headaches. [36]

Headache and encephalopathy are the most frequent initial symptoms and stroke or focal symptoms develop in less than 20% at the onset of disease in primary CNS vasculitis. [37]

Children can also present with seizures, cognitive deficits, cranial nerve deficits and decreased alertness. [38]

Headaches occur in as many as 63% of patients with primary angiitis of the central nervous system (PACNS), are indolently progressive, and usually are not severe enough to warrant emergency evaluation for subarachnoid haemorrhage. [37]

Vasculitis affects the blood vessels of the brain and the meninges. For pain to appear, substance P, calcitonin gene related peptide (CGRP) and other cytokines must be released in the trigeminal nerve–innervated structures. Vasculitis can also produce headaches indirectly if it is associated with complications such as intracerebral haemorrhage or subarachnoid haemorrhage. [36]

Giant cell arteritis is associated with headache (70-90%), jaw claudication (40-60%), transient ischemic attack (4%), neck pain, scalp tenderness, and visual disturbances. [39]

Headaches present as a dull pain that may be diffuse or localised, and is most commonly located in the temporal region. The pain may also be described as severe, sharp, or burning and can also be localized to the occipital, parietal, or periorbital regions. The pain and scalp tenderness can be resistant to analgesic treatment and so severe that it may interfere with sleep or wearing glasses, owing to scalp tenderness. [40]

Inflammation of the large size arteries is thought to be the cause of GCA. Inflammatory cells can form multinucleated giant cells that can surround fragmented elastic lamina. Inflammation leads to smooth muscle layer injury and intimal layer hyperplasia and sometimes causes vessel occlusion that can subsequently cause stroke and other vascular complications. [40]

Secondary vasculitis due to CNS infections can injure blood vessels in multiple ways which includes infection of endothelium, or trigger of immune response that indirectly affects vasculature and subsequent blood vessel injury that may reflect the sequela of a direct infection, compressive inflammatory exudate, septic emboli, or formation of mycotic aneurysms.

Vascular complications typically occur early and focal neurologic findings may be present in the acute phase of bacterial meningitis. [41]

Headache incidence was found to be ranging from 50-100% in tubercular meningitis in most of the case series. Chronic meningitis like TBM resulting in headaches can be acute, subacute, or chronic and occurs as a result of the involvement of the meninges and other inflammatory changes that produce hydrocephalus and stroke. These inflammatory changes may be irreversible, such as a communicating hydrocephalus. [42]

Involvement of small vessels by deposition of immune complexes in intracranial blood vessels is the mechanism of drug-induced vasculitis and these can lead to infarctions and/or haemorrhages causing further potential complications leading to headaches. [36]

Parenteral drug users can have necrotizing arteritis of the polyarteritis type in cerebral arteries and arterioles. Ischemic strokes and intracerebral haemorrhage secondary to the arteritis causes headaches in such patients. [43]

1.9 Headache in Reversible Cerebral Vasoconstriction Syndrome (RCVS)

Presents with sudden onset, recurrent and severe worst ever headaches occurring often over days to weeks. [44]

RCVS headaches have an explosive onset followed by a monophasic course usually without any new complications after 4 weeks which helps differentiate this clinical entity from the rarer primary CNS angiitis. [45]

It has a typical bilateral pain of usually posterior onset followed by a diffuse headache with a severe intensity, sometimes excruciating, with agitation, shouting and yelling, often associated with some features of migraine like nausea, vomiting, photophobia and phonophobia which subsides in hours and recur over days. [45]

In RCVS, some deficits begin progressively and successively including transient ischemic attacks occurring in a few minutes, and can include positive visual as well as sensory symptoms, mimicking auras of migraine and may evolve into persistent focal deficits revealing a stroke. [45]

Migraine sufferers who had suffered RCVS distinguished the thunderclap headaches as totally different from their usual migraine attacks. [45]

Trigger factors like sexual activity, straining, sudden emotion, exertion, coughing, sneezing, urinating without effort, bathing or showering, or sudden bending down are found in majority headache episodes associated with RCVS. [45]

Generalized tonic-clonic seizures are reported in about 20% of patients at the time of presentation, recurrent seizures are rare. [45]

RCVS is found in association with pregnancy, postpartum state, exposure to medications and illicit drugs, pheochromocytoma, hypercalcaemia, sexual intercourse and exercise. This history from the patient aids in diagnosing RCVS headaches. [46]

Majority of headaches in RCVS occur in the postpartum period or post exposure to vasoactive substances and are generally self-limited. [44]

Cerebral vascular tone is transiently dysregulated leading to arterial constriction and dilation at multiple sites. The catecholamines, endothelin-1, calcium, serotonin, nitric oxide and prostaglandins are then involved in the pathophysiology of vasoconstriction in RCVS. [44]

Vascular receptor activity and sensitivity are dependent on vascular tone. A sudden or evoked central vascular discharge may underlie the alteration and reversible nature of RCVS and contribute to the acute severe headaches. [44]

1.10 Cognitive, psychiatric aspects of RCVS

Most of the patients with RCVS recover without sequelae. Pathophysiology of RCVS is unknown, however sympathetic overtones play a role. Potential complications of RCVS are alarming and fatal. [47]

A rare case where grief caused severe headache with RCVS affirms the role of sympathetic overtone as a causal factor in RCVS. [48]

The clinical presentation in some patients of RCVS is cognitive dysfunction, where headache is just one of the symptoms and is not so severe.

Though thunderclap headache is a hallmark of clinical presentation of RCVS not all patients fall under the category of 'worst ever headache' or thunderclap headache but their

major clinical presentation is that of cognitive impairment, seizure, focal neurological deficit, coma. RCVS is diagnosed with radiological investigations like angiograms in these patients. [49]

RCVS causes distinct cognitive impairments and dementia due to lower cerebral blood flow, and these may slowly recover over 1 to 4 years.

Serotonin syndrome and Serotonergic antidepressants can trigger RCVS headache. [50]

Acute stress disorder, physiological increases of stress, including pregnancy, heightened emotions, grief, post traumatic stress disorder, high altitude and substance abuse may trigger RCVS. Serotonergic and sympathetic pathways with catecholamine surge are implicated in RCVS headache.

Thunderclap headache with cognitive impairment and memory deficit of sudden onset may indicate RCVS. [51]

Combination of serotonergic agent like fluoxetine and antihistamine like loratadine and maijuana causes RCVS. [52]

A rare case report of spinal cord injury resulting in quadriplegia revealed that use of Midodrine, vasospastic agent, alpha adrenergic agonist caused RCVS with thunderclap headache when Foley's catheter was flushed. Massive sympathetic response was caused by noxious stimuli (manipulation of Foley's catheter) resulting in cerebral vasoconstriction giving rise to thunderclap headache with RCVS. [53]

1.11 Cervical artery dissection

Headache due to vertebral and carotid artery dissection ranges from migraine-like or hemicrania-like headaches to severe thunderclap headaches.

New onset pain of the head and neck and occasional associated horner's syndrome is the commonest presentation of a dissection, especially the extracranial type. [54]

New unilateral headache especially in the anterior head region along with oculosympathetic paresis is suggestive of internal carotid artery dissection . Unilateral headache with delayed focal cerebral ischemic events is seen in internal carotid artery dissection. [54]

Dysgeusia, amaurosis fugax, pulsatile tinnitus, and cranial nerve pain are seen but cranial nerve palsies are less common. [54]

Dysgeusia in internal carotid artery dissection has been reported and is indicative of chorda tympani or a glossopharyngeal nerve involvement. [55]

The haemorrhage into the carotid wall in carotid dissection, could lead to intimal injury and these hematomas may form as the dissection progresses into the media, which can further occlude the lumen leading to amaurosis fugax, transient ischemic attacks and strokes. [56]

The sound of non-laminar blood flow being transmitted to the inner ear is probably the mechanism for the pulsatile tinnitus in case of cervical artery dissection. [57]

Direct or indirect neck trauma may cause cervical artery dissections. [54]

Vertebral artery dissection pain is commonly a constant aching, pressing or sharp in quality pain rather than pulsating pain. It can be either ipsilateral or bilateral and typically distributed over the posterior head region interpreted as muscle contraction headache. [54]

Frontotemporal headaches and orbital, facial, and ear pain in patients with ICAD supports the observation that stimulation of the carotid artery bifurcation can produce pain referred to these areas. [54]

Half of patients with vertebral artery and a quarter of patients with carotid artery dissections have neck pains associated with the episodes. [58]

Predominantly occipital distribution of headache in vertebral dissection is explained by the upper cervical nerves innervating the vasculature of the posterior fossa. [59]

Isolated thunderclap headache as initial manifestation along with delayed stroke can be a presentation of vertebral artery dissection. [60]

Carotid artery is surrounded and accompanied by cervical sympathetic plexus of nerves and this supplies the intracranial vasculature, the pupil and the levator palpebrae oculi. The skin over the face is supplied by the trigeminal nerve and that of the neck is innervated by the second and third cervical nerves. The occurrence of headache in carotid dissection is a classic example of referred pain. [60]

Visual phenomena of migraine are rarely seen at onset and have a characteristic march and usually last less than 1 hour, but these features can occur in a carotid artery dissection. The mechanisms causing this are embolism to the ophthalmic artery and its retinal branches, retinal hypoperfusion, or embolism to a foetal posterior cerebral artery with involvement of post-chiasmal visual pathways. Another mechanism suggested is the ischemia to the retina resulting in transient depolarization of nerve cells which corresponds to the positive visual phenomena in carotid dissection. [61]

Carotid artery morphological variations (CAMV) are implicated for mild cognitive impairment (MCI) with attention deficit. CAMV causes low cerebral perfusion and chronic cerebral ischemia, leading to MCI. Vertebral artery dissection (VAD) deteriorates quality of life leading to post-traumatic stress symptoms, depression, and anxiety. [62]

1.12 Cerebral venous sinus thrombosis

Cerebral venous sinus thrombosis (CVT) has headache as a predominant symptom with varying character and with neurological signs.

It is usually characterised by subacute onset headache with rapid worsening and variable severity but sometimes can mimic subarachnoid haemorrhage, migraine, and idiopathic intracranial hypertension. [63]

They may present with subacute onset and persistent headaches, but at times they can also be initially intermittent, worsening over time and one tenth can have thunderclap headaches. [64]

Headaches in CVT may be refractory to common analgesics and may persist through the night. It may be exacerbated by physical activity or valsalva maneuver and may get worsened with recumbency due to raised intracranial pressure. Nausea and/or vomiting, phonophobia are the most frequent associations. [64]

Sigmoid sinus thrombosis can present with unilateral tinnitus or unilateral headache mimicking migraine with or without aura or cluster headache. [64]

All of the processes that determine the inflammation, distension, or traction of any of the intracranial pain sensitive structures can result in headaches. [64]

Headache in patients of CVT without intracranial hypertension, was suggested to be due to an irritation of the nerve fibres in the walls of the occluded sinus. [64]

Intracranial hypertension secondary to the obstruction of large venous sinuses has a clinical picture as that of symptomatic intracranial hypertension.

Distension of veins and sinuses due to venous sinus occlusion caused by thrombosis determines the distension of pain-sensitive structures of both veins and sinuses. Venous infarction due to obstacle to the blood reflux causes cortical hematic infarcts and this results in subsequent cortical irritation and inflammation. [64]

Cerebral venous thrombosis (CVT) causes significant cognitive impairment in some cases. Cognitive impairment included impairment of memory, language, visuospatial orientation, and constructional ability. Cognitive impairment persists longer in around 1/3rd of cases of CVT to attribute leading to failure to return to work. Direct sinus involvement and persistent parenchymal lesion were implicated in cognitive impairment. [65]

1.13 Headache in Hypertensive states

Headache is seen in 20% of hypertensive urgency, and is bilaterally throbbing. They may be precipitated by activity in patients with a hypertensive crisis presenting without encephalopathy. [66]

The headache is usually occipital and is pulsating in nature. It is accompanied by symptoms of encephalopathy like confusion, lethargy, visual disturbances or seizures and improves as soon as the blood pressure normalises. [67]

Thunderclap headache should be listed as a potential early presentation of hypertensive encephalopathy. [67]

A sudden rise in blood pressure induces disruption of cerebral vascular auto-regulation, mostly in the posterior cerebral vasculature, causing leakage of fluid into the brain parenchyma. [68]

Diffuse vascular constriction caused by humoral factors is the trigger for the hypertensive process and the consequence is vascular endothelial injury and activation of coagulation factors leading to fibrinoid necrosis of the arterioles.

High blood pressure impairs the integrity of the blood brain barrier leading to cerebral hyperperfusion which finally causes brain edema and this sequence of activity results in the clinical presentation of hypertensive encephalopathy patients. [66]

In preeclampsia the neurologic signs and symptoms are common presentations of the disorder, including severe persistent headache (bilateral throbbing type), visual defects such as blurred vision, diplopia, or floating spots, confusion, depression of consciousness, and finally may lead to seizures or eclampsia. [66]

Pathophysiology is similar to hypertensive encephalopathy, with cerebral hyperperfusion due to failure of autoregulatory response. [69]

Headache is a common symptom of a clinical condition known as autonomic dysreflexia following spinal cord injury. This is characterised by episodes of extreme hypertension usually accompanied by headache, upper body flushing and slow heart rate that may be provoked by stimuli.

Intracranial hemorrhage, coma, myocardial infarction, retinal detachments, pulmonary edema, seizures and death are the consequences of untreated episodes of autonomic dysreflexia.

Headache pathogenesis is not clear in this syndrome but suggested to be due to vasomotor nature. Also headache attributed to autonomic dysreflexia may result from passive dilation of cerebral vessels or increased circulating prostaglandin E2. [70]

Headache is a feature of the severe spectrum of preeclamptic disease and a potential precursor of eclampsia. The headache is typically diffuse, constant, throbbing, and mild to severe in intensity. Blurred vision, photophobia, and confusion and alteration in the level of consciousness may occur. [71]

The suggested pathophysiology are marked vasospasm in the cerebral vasculature in response to elevated systemic blood pressure resulting in ischaemia and vasoconstriction of vessels in the brain followed by reflex vasodilation leading to overdistension, extravasation of fluid and cerebral oedema. In normal individuals , the cerebral autoregulation protects against sudden fluctuations in blood pressure, but if the systolic blood pressure exceeds 150 mmHg, then the autoregulation fails and results in hypertensive encephalopathy. [71]

1.14 Headache due to pheochromocytoma

These are usually short-duration, frontal or occipital intense headaches. These may be pulsatile or constant. Associated features include anxiety, palpitation, sweating, pallor, angor animi, chest pain, tachycardia and vomiting. Headaches are typically short-duration. [72]

Headaches in pheochromocytoma are related to adrenaline surges, and correspond with sudden rise in blood pressure by the pressor effect of secreted amines. It may present as a thunderclap headache.

Pheochromocytoma presenting as thunderclap headache in the absence of hypertension has also been reported. [73]

1.15 Headache associated with diagnostic and therapeutic vascular procedures

Headache during intracranial vascular stimulation is characterized by a sudden onset, short duration, non-throbbing and a unilateral, focal, localized nature. [74]

Headache occurred instantly or within seconds after balloon inflation and after intra-arterial glue injection. In cases of balloon inflation, headache disappeared as the pressure inside the balloon was decreased and reappeared with reinflation. [74]

Pain originating from intracranial arteries was referred to the cutaneous area of the ophthalmic branch of the trigeminal nerve. [74]

Pain was stereotyped and started suddenly in all patients reaching maximum intensity at once or within seconds and lasts for several minutes. Disappearance of pain was gradual. Intensity was rated as moderate to severe in most cases. Some cases had excruciating pain and the patients were in great distress. The pain was variously described as ”pain”, ”hot”, ”pinprick”. [74]

Headache was always focal and well localized. Its site did not change in each single episode. Headache was unilateral in all cases. [74]

Direct stimulation of the arterial wall at the site of arterial occlusion is the mechanism that explains the close relation between the onset of pain and manoeuvres irritating the vascular wall, and the relief of pain by the end of such procedures. It also explains the sudden onset of pain and the constant topographic pattern depending upon the stimulated artery. [74]

Although vasogenic edema could account for some of the late occurring pain it is difficult to explain a transient, short-lasting pain by such a phenomenon and studies had ruled out hypertension in this scenario as the cause of acute pain. [74]

Possible reasons for temporary headaches after endovascular therapy include local inflammation due to placement of foreign objects like stents, coils or glue, as well as mechanical stimulation of the arterial wall. [75]

A change in flow dynamics after EVT causes the release or the stress of a venous overload possibly leads to post-procedural headaches. [75]

Vasospasm due to catheter and reaction to contrast material was also not likely for the pain. [74]

About 35.4% of patients had headaches, 24 hours after angiography without any specific characteristics for these headaches. Cerebral endovascular procedures rarely trigger a migraine. Angiography does not seem to influence the occurrence of chronic recurrent headaches. [76]

Contrast material is known to trigger migraine headaches during angiography. Contrast material may trigger headaches more easily in patients with tendency to headaches. [77]

Case reports of post angiography migraine speculate arterial stimulation as a possible mechanism. This may trigger migraine-like headaches due to cortical spreading depression. There may also be focal neurological symptoms, depending on the regions where blood flow changes occur. [78]

Headache and hypertension, with or without seizures and focal neurological signs, developing within days of successful carotid endarterectomy is the characteristic feature of post-carotid-endarterectomy cerebral hyperperfusion syndrome. [79]

Hypertension and hyperperfusion with changes in middle cerebral arterial flow have been implicated in the syndrome. [79]

As far as pathogenesis of post-endarterectomy headache is concerned, mechanical stretching of the artery and vasodilatation could be responsible for the pain but involvement of the sympathetic system has also been postulated. [80]

1.16 Headache due to Pituitary apoplexy

Presents as acute onset headaches with ophthalmoplegia, diminished visual acuity, and altered mental status caused by the sudden haemorrhage or infarction of a pituitary gland.

Severe acute headache with maximum intensity at onset with visual disturbances, nausea, and or vomiting is the characteristic feature of pituitary apoplexy. [81]

Head trauma, pregnancy, hypotension, anticoagulants, surgery, pituitary dynamic testing, irradiation and hypertension are the precipitants for apoplexy. Rapid enlargement results in increased pressure of the intrasellar contents. [81]

There has also been reports of status migrainosus like presentation with gradual onset, unremitting throbbing headache with nausea, phonophobia, and mild photophobia of several weeks duration. [82]

Meningeal irritation is caused by dural stretching by mass effect, and extravasation of blood and necrotic tissue into the subarachnoid space. [81,83]

Pressure increase in sella turcica causes superior compression of the optic tracts, chiasm or nerves and brain stem leading to altered levels of consciousness. Lateral compression of the oculomotor cranial nerves causes diplopia. [84]

Transient hemiplegia secondary to vasospasm of the intracavernous carotid artery can also occur in pituitary apoplexy. [84]

Cognitive dysfunction in patients of Pituitary apoplexy (infarction in pituitary) does not occur uniformly. Causes of cognitive dysfunction are pressure effects, i.e. third ventricle & diencephalic structures, dysfunction of hormonal secre-

tion, treatment modality especially radiotherapy. Radiotherapy was considered a major factor behind memory loss. Most of the cases showed anterograde memory loss. Most of the patients preserve premorbid intelligence quotient. [85]

Endocrine dysfunction plays an important role in cognitive impairment, and may be reversible after surgical intervention. [86]

1.17 Headache due to genetic vascular disorders

1.17.1. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)

Various types of migraine headaches have been reported in 20–40% of patients with CADASIL, including migraine with typical aura, which accounts for the majority of cases, migraine without aura, migraine aura without headache, basilar migraine, hemiplegic migraine, acute onset aura without headache, migraine with acute onset aura, migraine with prolonged aura and retinal migraine. [87]

The symptoms are stroke or transient ischaemic attacks in 43% of patients, migraine in 40%, depression in 9%, cognitive impairment in 6% and epilepsy in 2%. [88] CADASIL is a vascular disease with decreased blood flow and cerebrovascular reactivity and consistent with the classical vascular theory for migraine, migraine aura could be a result of episodic ischemia. [89]

In CADASIL there is an increased cortical susceptibility to cortical spreading depression, which could be caused by chronic vascular brain damage or acute episodes of hypoperfusion. [89]

1.17.2. Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like episodes (MELAS)

Recurrent attacks of prolonged migrainous headache and repeated vomiting, epileptic seizures with bouts of status epilepticus, and migrating stroke-like episodes with cortical blindness or deafness are the characteristic features of this distinct mitochondrial syndrome of MELAS. [90]

The recurrent attacks of severe pulsatile headaches with vomiting resemble those of migraine. Some patients with migraine have been reported to suffer ischaemic stroke as a sequel, with motor or sensory deficits, speech disturbances, or much more commonly, visual field defects which has been named migrainous stroke. [90]

Another mitochondrial syndrome named MERRF (Myoclonic Epilepsy with Ragged-Red Fibers) is sometimes associated with hemicranial headaches. [91] The energy for the brain is produced by mitochondria in the form of ATP, and disturbance in its supply can result in an increased susceptibility to migraine attacks. [92]

Case reports of typical cluster headaches with other associated features of MELAS has also been reported. [93]

Acidosis has been suggested as being a trigger of cluster headache, by peripheral or central mechanisms. [93]

1.17.3. Moya moya angiopathy

The headache was more commonly pressing, mild to moderate in severity, unchanged by physical activity and associated with photophobia. [94]

Presents as migrainous headaches refractory to both prophylactic and abortive medical therapies. [94]

The role of cerebral artery nociceptors in generation of headache is supported by studies where stretch of intracerebral vasculature produced nausea and referred pain in regions typically involved in the migraine attacks. [94,95]

Enlarging aneurysm resulted in stimulation of trigeminal nociceptors due to stretch. Both cerebral aneurysms and arteriovenous malformations found in moyamoya disease will cause this mechanical effect. Sentinel aneurysmal bleed into the subarachnoid space, manifesting as pulsating headaches accompanied by photophobia, nausea or vomiting may also be seen in Moya moya disease. [94]

Neurogenic inflammation seen in moyamoya disease causes the stretch of perivascular nociceptors innervating intracranial vasculature and leads to a release of pronociceptive mediators. This in turn activates the nociceptors producing both generation and maintenance of the headache. [94]

An intracranial oligemic state is induced by cerebral hypoperfusion in case of moyamoya disease as a result of progressive intracranial stenosis. This hypoperfusion has been described as an aetiology of headache as well. [96]

1.17.4. Cerebral amyloid angiopathy

Cerebral amyloid angiopathy (CAA) is a type of cerebrovascular disorder characterized by the accumulation of amyloid beta-peptide within the leptomeninges and small to medium-sized cerebral blood vessels and is usually asymptomatic. [97]

The clinical presentations of CAA include spontaneous lobar ICH, cognitive impairment and dementia and transient focal neurological episodes often associated with acute convexity subarachnoid haemorrhage or cortical superficial siderosis. [97]

It can cause hemiplegia and decreased consciousness if the bleeding is large, while smaller haemorrhage may cause more focal deficits, headaches, or seizures. The haemorrhages are more likely to occur in the posterior brain.

Memory impairment in CAA is more similar to the pattern seen in classic vascular cognitive impairment than in the Alzheimer's disease. CAA has executive dysfunction and impaired processing speed with relatively preserved episodic memory. White matter ischaemic lesions are responsible for impaired processing speed in cerebral amyloid angiopathy. Cerebral microbleeds, cortical microinfarcts, and altered structural connectivity results in CAA-related dementia and vascular cognitive impairment. Vascular function and physiology are significantly affected in CAA and this might result in more widespread brain injury. [97]

Hereditary Dutch-type CAA called Hereditary Cerebral Haemorrhage with Amyloidosis-Dutch type is a hereditary variant of CAA, caused by a mutation in the Aβ region of the APP (amyloid precursor protein) gene. Cerebral Amyloid Angiopathy- Dutch type (D-CAA) patients suffer from recurrent ICH from the age of 50. [98]

More than half of D-CAA patients had migraines with aura. Migraine attacks preceded the first symptomatic haemorrhage in the majority of the carriers.

Beside haemorrhagic events and cognitive decline, transient focal neurological deficits are a common symptom of CAA. Migraine aura attacks are thought to be a result of cortical spreading depression. [98]

The presence of migraine in angiopathies such as CADASIL, Retinal Vasculopathy with Cerebral Leukoencephalopathy and Systemic Manifestations (RVCLS) and D-CAA suggests that it may be caused by vascular changes associated with damage to the intracerebral small vessels leading to impaired vasoreactivity and increased susceptibility for cortical spreading depression. [98]

1.17.5. Retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations

Retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations is a small-vessel disease.
RVCL-S affects highly vascularized tissues including the retina, brain, liver, and kidneys.

Common findings are decreased visual acuity or visual field defects and the neurologic manifestations may include hemiparesis, facial weakness, aphasia, as well as hemianopsia. Migraines and seizures are described in this syndrome.

In a study, migraine occurred in 24 out of 41 individuals in whom other manifestations of the disease like retinal vasculopathy and/or brain lesions were present. The association of migraine with RVCL-S is reminiscent of the association of migraine with another neurovascular disorder like CADASIL. Similar to CADASIL, migraine is highly prevalent and precedes the typical disease features by many years in RVCLS. [99]

2 HORIZONTAL AXIS GROUPS WHICH MAY BE INTERLINKED

Table 1: Horizontal groups linked to syndrome of migraine

ID	Abbr	Syndrome	Linked?
HG1	SyM	Syndrome of Migraine	✓
HG2	SyTAC	Syndrome of Trigeminal Autonomic Cephalalgias	✓
HG3	SyExH	Syndrome of Exertional Headaches	✓
HG4	SySrH	Syndrome of Sleep-related Headaches	
HG5	SyEnvH	Syndrome of Environment-related Headaches	
HG6	SyTrH	Syndrome of Traumatic Headaches	✓
HG7	SyVH	Syndrome of Vascular Headaches	
HG8	SyCDH	Syndrome of CSF Dysregulation Headaches	✓
HG9	SyInfH	Syndrome of Infection-related Headaches	✓
HG10	SyHCH	Syndrome of Hormone and Chemical-related Headaches	✓
HG11	SySH	Syndrome of seizure- related headaches	✓
HG12	SyFP	Syndrome of Facial Pain	✓
HG13	SyNP	Syndrome of Neck Pain	✓
HG14	SyOcP	Syndrome of Ocular Pain	✓
HG15	SyEP	Syndrome of Ear Pain	
HG16	SyOrP	Syndrome of Oral Pain	
HG17	SyNeu	Syndrome of Neuralgias	
HG18	SyWEH	Syndrome of Worst Ever Headache	✓

ID =Identifier / Serial number, Abbr =Abbreviation, Linked? =check mark / tick mark denotes links between horizontal groups

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Headach. Med. Con. 2021;1(1):43–47

Headache Medicine Connections

The Official Journal of the World Headache Society

Section 8 : Horizontal Group 8 - Syndrome of CSF dysregulation (SyCSF)

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ARTICLE INFO

Article history:
Received 01.08.2021
Accepted 05.08.2021
Published 20.08.2021

https://doi.org/10.52828/hmc.v1i1.classifications

ABSTRACT

Cerebrospinal fluid (CSF) dysregulation syndrome is primarily of two types, High CSF pressure syndrome and Low CSF pressure syndrome. Both the conditions share clinical characteristics among each other along with various other headache disorders. They also present as new daily headaches. In longstanding, delayed presentation, may pose a significant challenge in making diagnosis. A detailed history and neurological examination is required to detect these conditions. Signs and symptoms of what has historically been called low CSF pressure are really driven by low CSF volume. Interestingly, high CSF pressure syndromes are not necessarily accompanied by high CSF volume. The normal range of CSF opening pressure is 10-25 cmH20.

Keywords: High CSF pressure; Idiopathic intracranial hypertension; Pseudotumor cerebri; Secondary intracranial hypertension; Low CSF pressure; Low CSF Volume; Spontaneous intracranial hypotension; Monro Kellie

1 CLINICAL FEATURES, MECHANISMS AND ASSOCIATED CONDITIONS HIGH CSF PRESSURE HEADACHE SYNDROME

Raised intracranial tension may be associated with various pathological conditions like space occupying lesion, stroke either ischemic or haemorrhagic, cortical venous thrombosis, intake of various drugs or hormones and pseudo tumor cerebri or idiopathic intracranial hypertension. We are going to discuss various conditions as well as its clinical manifestation due to high CSF pressure syndrome

Low CSF pressure headache after treatment can become high CSF pressure headache due to obstruction of constant pressure release [(1)].

Several conditions may result in high CSF pressure states like Cerebral venous sinus thrombosis (CVST), jugular vein thrombosis, superior vena cava syndrome, increased right heart pressure, AV fistulas, previous infection or subarachnoid haemorrhage hampering CSF absorption from arachnoid villi [(2)].

Various drugs and hormones are also responsible for pseudotumor cerebri syndrome like quinolones, steroid, danazol, tetracycline class antibiotics, vitamin A, thyroxine, nalidixic acid, tamoxifen, contraceptive implants, growth hormones and some H2 blockers [(3)].

Endocrine abnormalities that may result in high CSF pressure states are hypothyroidism, hyperthyroidism, addison's disease, adrenal insufficiency, cushing's syndrome, and hypoparathyroidism [(2)].

1.1 Space occupying lesions

Intracranial tumors either primary or secondary, hematoma either extradural, subdural or intracranial, abscesses, cyst, arterio-venous malformation, congenital cysts can presents with raised intracranial tension.

The Monro Kellie doctrine stated that intracranial volume is fixed, as the entire brain and spinal cord are enclosed by in expansible bony cavity, hence expansion of their contents by a space-occupying lesion (SOL) leads to compression and distortion of the pain sensitive tissues. Rapid enlargement can cause a brisk rise in pressure in the affected compartment from the normal level and herniation of the soft parenchymal tissue into adjacent compartments where the pressure is lower [(4,5)].

1.2 Frontal or retro-orbital pain

Headaches without any characteristic feature is a common presentation in idiopathic intracranial hypertension or pseudotumor cerebri. It may be unilateral, bilateral,

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holocranial, anterior or posterior distribution. Character may also vary from band-like, pulsatile, dull, stabbing with or without nausea, vomiting, photophobia, and phonophobia. This broad spectrum of clinical features make it difficult to diagnose.

Conditions causing decreased CSF outflow (through the arachnoid granulations and other structures) or venous obstruction lead to increased intracranial pressure. Stretching of pain sensitive structures like dura, pial arteries, nerve roots, large veins, and venous sinuses, are proposed mechanisms [6].

Due to highly variable headache symptomology it may be confused with other headache disorders.

1.3 Migraine & Tension type headache

Around 52% of IIH patients have been classified as migraine and a further 16% as probable migraine. About 22% patients have tension type headache while 4% being classified as probable tension type [7]. Clinical features commonly seen are, worse in the morning or no fluctuation, nocturnal awakening, worsening with Valsalva, exercise or bending over, worsening with consumption of caffeine or no response, worsening with lying flat, and worsening on high altitude [6].

1.4 Pulsatile tinnitus

Unilateral or bilateral synchronous pulsatile tinnitus is the 2nd most common symptom.

It was thought that the sound is nothing but a transmission of amplified vascular pulsations under high CSF pressure. Blood may have turbulence from relative venous stenosis secondary to venous sinus collapse due to high intracranial pressure [8].

1.5 Transient Visual Obscuration

Transient episodes of vision loss in one or both eyes with high intracranial tension lasting for seconds due to transient ischemia of optic nerve head, secondary to raised ICP [9].

1.6 Diplopia

Double vision is another important clinical symptom that occurs secondary to compression/stretching of the 6th cranial nerve due to raised intracranial pressure [10].

1.7 Papilledema

There is unilateral or bilateral optic disc edema due to direct or indirect pressure on the optic nerve, secondary to raised intracranial tension. In long standing untreated cases it may lead to vision loss [11].

1.8 Neck and back pain

Patients may report neck pain, shoulder and back pain due to radicular involvement. The mechanism is probably due to filling of spinal dural root sheaths by CSF under high pressure [12].

1.9 Sleep disturbance

Obstructive sleep apnea risk was found to be high in a cohort of patients with Idiopathic intracranial hypertension (IIH) [13].

IIH is also associated with depression, anxiety and decreased quality of life [14].

2 CLINICAL FEATURES, MECHANISMS AND ASSOCIATED CONDITIONS, LOW CSF PRESSURE HEADACHE SYNDROME

Headache is the most common clinical presentation with characteristic orthostatic (worsening in standing and improvement in lying down) features. Bilateral posterior head pain is another common complaint, it may sometimes be unilateral or may be located at other sites on the head [15]. Headache is often posteriorly located but it may be variable, worsen as day progresses, with or without nocturnal awakening.

It can mimic migraines with or without aura, tension type headache, new daily persistent headache (NDPH), trigeminal autonomic cephalgia in clinical presentation. Postural variation is very peculiar for this condition as it worsens with uprightness and is usually relieved by lying flat [16].

Low CSF pressure may be due to various reasons like decreased production of CSF by the choroid plexus, increased absorption of CSF or by CSF leakage from small tears. A notable etiology for spontaneous intracranial hypotension is CSF leakage from a ruptured arachnoid membrane. The most acceptable mechanism for pain is downward stretching of pain sensitive cervical and cranial structures like meninges, ligaments, nerve roots and decreased CSF volume, compensatory vasodilation. [17]

These patients may have previous history such as:

- Trivial trauma/fall
- Heavy weight lifting, Gym, Yoga, Kayaking, coughing, straining, tennis, golf
- Previous spinal surgery or spinal anaesthesia
- Lumbar puncture
- Calcified herniated disc
- CSF AV fistula

These conditions may increase the CSF leak through spinal defects and further exacerbate intracranial hypotension [17].

2.1 Tinnitus

Tinnitus is relatively rare, if present it is non-pulsatile. It can also be associated with ear pain. Possibility of thickened pachymeninges resulting in venous distension and nerve entrapment [18].

2.2 Joint Hypermobility

In various connective tissue disorders and degenerative disc conditions, there is a possibility of hypermobility which may lead to dural weakness and tears, following which CSF leaks into epidural space [19]. Connective tissue disorders with this predisposition include : [20]

- Ehlers-Danlos syndrome type II
- Marfan syndrome
- Autosomal dominant polycystic kidney disease
- Personal or family history of non-rheumatic valvular diseases
- Aneurysm, and vascular dissection
- It increases the risk of low CSF volume/pressure headache and its complications

2.3 Chest and back pain (Coat hanger headache)

Stretching of cervical nerve roots, and also due to fluid collection at extra-arachnoid space causing chronic pressure on the ventral aspect of the cord, may mimic bibrachial amyotrophy [21,22].

2.4 Diplopia, blurred vision, hearing abnormalities

Stretching of multiple cranial nerves results in various clinical manifestations like, diplopia, vision difficulty, hearing and balance problem by involvement of oculomotor, vestibular nerve and cochlear nerve respectively [23–25].

2.5 Cognitive and mental status changes, including dementia

Exact pathophysiology of cognition change and dementia in spontaneous CSF hypotension is uncertain but the most likely explanation is compression of the frontal and temporal cortices caused by caudal brain sagging due to loss of hydrologic support [26,27].

2.6 Hyperkinetic, hypokinetic movement disorders and Ataxia

Various hyperkinetic and hypokinetic movement disorders may occur as long term complications of spontaneous intracranial hypotension (SIH). Reversible parkinsonism related to SIH has been reported, probably due to pressure on the midbrain or other deep brain structure from SIH-related brain sagging and herniation at the tentorium, and which reversed after correction of intracranial hypotension by appropriate treatment. [28–31].

2.7 Galactorrhea

The traction and the increased vascularity may produce enlargement of the pituitary gland. Hyperprolactinemia and galactorrhea have been reported in association with spontaneous intracranial hypotension [32,33].

2.8 Subdural fluid collections & Subdural haemorrhage

Due to decrease in CSF volume, brain buoyancy will decrease and the brain will sag toward the posterior fossa and foramen magnum. This leads to fluid accumulation over the cerebral convexity and development of subdural hygroma , which causes further pressure effect on the cerebrum.

Due to sag toward the posterior fossa there is traction of the bridging veins within subdural space that may rupture and produce subdural hematomas [34,35].

2.9 Posterior reversible encephalopathy syndrome (PRES)

PRES is characterized by reversible vasogenic edema in different parts of brain. This clinically manifests as progressive worsening postural headache, nausea, photophobia followed by rapidly worsening of sensorium with new neurological deficits like diplopia, hemiplegia, hemianesthesia, loss of consciousness, with or without seizures. CSF hypovolemia leading to PRES has an entirely different pathophysiologic mechanism which includes arterial hyperperfusion along with venous dysfunction [36,37].

2.10 Facial pain

This may present with trigeminal neuralgiform pain due to stretching of cranial nerve roots [38].

2.11 CSF overdrainage

High CSF pressure headache, after treatment with shunt surgery can become low CSF pressure headache due to over drainage of CSF [39].

3 HORIZONTAL AXIS GROUPS WHICH MAY BE INTERLINKED

Table 1: Horizontal groups linked to syndrome of migraine

ID	Abbr	Syndrome	Linked?
HG1	SyM	Syndrome of Migraine	✓
HG2	SyTAC	Syndrome of Trigeminal Autonomic Cephalalgias	✓
HG3	SyExH	Syndrome of Exertional Headaches	✓
HG4	SySrH	Syndrome of Sleep-related Headaches	✓
HG5	SyEnvH	Syndrome of Environment-related Headaches	✓
HG6	SyTrH	Syndrome of Traumatic Headaches	✓
HG7	SyVH	Syndrome of Vascular Headaches	✓
HG8	SyCDH	Syndrome of CSF Dysregulation Headaches	
HG9	SyInfH	Syndrome of Infection-related Headaches	
HG10	SyHCH	Syndrome of Hormone and Chemical-related Headaches	✓
HG11	SySH	Syndrome of seizure- related headaches	
HG12	SyFP	Syndrome of Facial Pain	✓
HG13	SyNP	Syndrome of Neck Pain	✓
HG14	SyOcP	Syndrome of Ocular Pain	✓
HG15	SyEP	Syndrome of Ear Pain	✓
HG16	SyOrP	Syndrome of Oral Pain	✓
HG17	SyNeu	Syndrome of Neuralgias	✓
HG18	SyWEH	Syndrome of Worst Ever Headache	✓

ID = Identifier / Serial number, Abbr = Abbreviation, Linked? = check mark / tick mark denotes links between horizontal groups

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Headach. Med. Con. 2021;1(1):48–51

Headache Medicine Connections

The Official Journal of the World Headache Society

Section 9 : Horizontal Group 9 - Syndrome of Infection Related Headaches (SyInfH)

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ARTICLE INFO

Article history:
Received 01.08.2021
Accepted 05.08.2021
Published 20.08.2021

https://doi.org/10.52828/hmc.v1i1.classifications

ABSTRACT

Infectious headaches are headaches that occur in temporal correlation to a localized or a systemic infection. Localised infections include infections of adjacent structures such as the eye, nose, throat, sinuses. Systemic infections may affect the central nervous system (CNS). CNS infections include meningitis, encephalitis or their combination (meningo-encephalitis), brain abscess or parasitic or fungal infections. These typically present with excruciating headache and may have symptoms of raised intracranial pressure, such as projectile vomiting, visual impairment, and even focal neurological deficits. Systemic infections may also lead to headache along with other widespread features of infection. Headache due to infectious causes may indicate a sinister underlying cause, and hence, presence of fever must alert the clinician to this possibility. A thorough examination must be conducted to ascertain features of meningeal irritation and raised intracranial pressure. Treatment of the underlying infection usually will lead to remission of the headache, although chronic headache may also develop. Mechanism of headache development is related to meningeal inflammation, elevated intracranial pressure, and release of inflammatory mediators.

Keywords: Infection; Meningitis; Brain Abscess; Meningoencephalitis; Sinusitis; COVID19; Fungal Infection

1 CLINICAL FEATURES, MECHANISMS AND ASSOCIATED CONDITIONS

1.1 Meningeal inflammation

Stimulation of sensory nerve endings in the meninges because of infection or inflammation due to the infection.

As a result of infection or inflammation focal headache may develop into a generalised headache with neck stiffness and clinical features of meningeal irritation.

1.2 Increased intracranial pressure

Trigemino-thalamo-cortical pathway, is regarded as a relay route region for transmitting information to cortical areas and receiving feedback information from them.

The clinical manifestations of elevated intracranial pressure due to meningitis or meningo-encephalitis include headache, papilledema, vomiting. The headaches are described as throbbing or bursting and increases in severity with factors that raise intracranial pressure such as coughing, sneezing, Valsalva maneuver. These headaches are typically worse in the morning.

1.3 Inflammatory mediators

Bacterial endotoxins, interleukins (IL-1, IL-6), bradykinins, prostaglandins, cytokines, induce pain sensitization and neuropeptide release.

2 THE SYNDROME OF INFECTIOUS HEADACHE CAN BE ASSOCIATED WITH THE FOLLOWING CONDITIONS:

2.1 Headache due bacterial meningitis or meningoencephalitis

This is an acute and severe holocranial headache, accompanied by other features including those of meningeal irritation, stiff neck, fever, altered mental state, and seizures.

Typically, headache due to bacterial meningitis remits with treatment or resolution of the underlying infection. [(1)]

Post-infection headache may be diagnosed when infection resolves or is treated efficiently, but headache endures beyond 3 months.

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Chronic post-infection headache includes chronic post-bacterial meningitis headache. In this group, the headache is a direct continuation of headache attributed to bacterial meningitis. [1]

Cluster headache developing after meningitis has also been described. [2]

Post meningitis headache can have migrainosus characteristics. In a study conducted by Neufeld et al. : 70 patients with the diagnosis of meningitis' were compared to a control population. There was a history of headache preceding the meningitis in 13 patients (19%), with migrainous nature in eight of them. Among the control group, 18 patients (26%) experienced headache. This headache was migrainous among eight of these patients. Following meningitis, 7/13 patients who had pre-existing headache reported worsening pain. Headache subsequent to meningitis occurred in 19 patients; it was migrainous in 6/19. In terms of intensity, headaches were of mild-moderate intensity in 15 patients and severe in four. Among four patients, headaches appeared in the first year following the meningitis. [3]

2.2 Headache due to viral meningitis or encephalitis

Viral Encephalitis is an acute, diffuse inflammatory process affecting the brain due to viral etiology. Headache, fever and altered mental status are classical features.

Focal features such as memory impairment, aphasia, behavioural issues, and focal seizures are typical of herpes simplex encephalitis (HSE). However, these features are not indicative of a particular etiology among viral infections per se. [4]

It has recently been recognised that about 20% of HSE cases may be relatively mild and atypical without the typical focal features. [5]

Raised intracranial pressure may also accompany this syndrome in later stages.

2.3 Headache due to localised brain infection (abscess)

An abscess is a focal intraparenchymal collection which may arise due to multiple causes, including local ear infection, sinusitis, trauma, hematogenous dissemination.

Headache is severe, progressive in intensity, usually focal and refractory to analgesia (ipsilateral to the abscess).

Associated features include altered mental status, focal neurological deficits including aphasia, hemiparesis, nausea, vomiting, high grade fever, seizures, papilledema.

2.4 Headache due to systemic infection (bacterial, viral or other infections

Systemic infections can also be associated with headache, and systemic features including myalgia, malaise, coryza, cough, dysuria. fatigue, eye pain etc.

2.5 Headache related to COVID-19 infection

COVID-19 infection has been reported to lead to headache.

A cross-sectional study of 172 individuals with COVID-19 infection and headache reported that diffuse headache was reported by 52.9% of patients. It was pressing in character at 40.7%, median intensity of 7 (on VAS) and median frequency of 7 days/week.

Patients who had pre-existing primary headache (52.9%) had significantly more frequent COVID-19 related headache than those without (47.1%) ($p = 0.001$).

Patients with dehydration suffered more COVID-19 related headaches.

Patients who had accompanying fever (69.8%) had significantly more frequent and severe intensity of COVID-19 related headache compared to afebrile patients(30.2%) ($p = 0.003, 0.012$).

Patients who had comorbid illnesses (19.8%) had significantly more frequent and intense headaches than those without (80.2%) ($p = 0.006, 0.003$).

In regression analysis, underlying primary headache, dehydration and comorbidities were predictive of COVID-19 related headache.

Fever and dehydration were predictors of pain intensity. [6]

2.6 Headache due to rhinosinusitis

Perception of nasal mucosal pain is mediated by A delta fast mechanoreceptor pain fibers and slower unmyelinated C fibers. These nerve fibers release tachykinins, including substance P, and neurokinins. Sympathetic stimulation is associated with neuropeptide Y, along with norepinephrine, and parasympathetic fibers cause release of acetylcholine and related mediators. [7]

Stimulation of trigeminal nerves in the nasal mucosa, via relay to the trigeminal medullary sensory nucleus, and parasympathetic vagus neurons may lead to vagal symptoms. [8]

Patients with sphenoid sinusitis experience headache which exacerbates on Valsalva maneuvers such as standing, straining, or coughing. There may be associated periorbital pain. Patients may also develop fever. An important pointer to sphenoid sinusitis is the presence of a progressively worsening headache, pain along the trigeminal nerve, eye pain and suffusion, lacrimation, photophobia and pain is usually refractory to pain medications. Additionally, the pain may disrupt sleep. [9]

Headache due to sinusitis is characterised by facial pain, pressure, congestion and fullness, nasal discharge, nasal obstruction, purulence, hyposmia/ anosmia, fever. Migraine and tension-type headache may be mistaken for sinusitis due to similar location of the headache. [10]

2.7 Headache due to localised infections of the ear, nose, throat and dental structure

Infections in these areas may present with referred pains and local spread of the infection.

2.8 Headache due to trigeminal neuropathy due to herpes zoster

Pain due to herpes zoster infection in the trigeminal nerve usually begins in the prodromal phase. It may continue for nearly 30 days after the rash settles.

In most cases, it leads to burning sensation or itching, piercing, cutting, shooting and paroxysmal pain.

Some patients have pain accompanied by fever, headache, or malaise.

The prodromal period is the time it takes to activate the latent virus infection and penetrate the varicella-zoster virus along the nerve trunks from roots and sensory ganglia into nerve ends in the skin and mucous membranes.

A characteristic feature of painful herpetic neuropathy is allodynia, a pain that occurs under an ordinary non-noxious stimulus.

The occurrence of allodynia is predictive of postherpetic neuropathy development.

The subacute phase of painful herpetic neuropathy begins after the end of the acute phase and lasts until the onset of postherpetic neuropathy. Constant pain, termed postherpetic neuropathy (PHN), is a debilitating feature of herpes zoster.
Four kinds of pain are described with PHN:

1. Continuous, deep, dull, pressing or burning pain;
2. Paroxysmal, sharp, shooting pain
3. Allodynia
4. Intense pruritus and burning

The theory of "hyperactive pathological determinant structures" with. The flow of signals through myelinated fibers is reduced due to their changes at the periphery, and the flow of signals to the dorsal root ganglia (DRG) through poorly myelinated fibers begins to predominate. In the DRG, generators of "pathologically enhanced excitation" arise among a certain group of neurons. This "generator" activates the reticular formation of the brainstem, the mesencephalic region, thalamus, limbic system and the cerebral cortex. This leads to a pathological pain-generating system with high excitability and responding to afferent stimuli with paroxysms of pain.[11]

2.9 Headache due to nervus intermedius neuropathy due to herpes zoster

In nervus intermedius neuropathy due to herpes zoster, previously known as Ramsay-Hunt syndrome, pain occurs inside the auditory canal, auricle or region of the mastoid process.

It is dull, continuous, pain. It is located deep inside the ear.

Brief paroxysmal episodes of pain also occur, but these are not prominent.

Other cranial nerves, including auditory, glossopharyngeal, vagal and spinal accessory nerves, may also be affected concomitantly and lead to associated symptoms.

2.10 Headache due to parasitic and fungal infections

Cerebral toxoplasmosis may lead to recurrent headaches. Associated symptoms include nausea, vomiting, altered sensorium, confusional state.[12]

Neurocysticercosis (NCC) is a common cause of headache. Even calcified NCC is associated with headache.

These may occur due to raised intracranial pressure due to cysticercal encephalitis, hydrocephalus or giant extrapyramidal cysts.[13]

Migraines may also be a feature of NCC. Calcified NCC contain remnants of the parasitic membrane These remnants come in contact with the host immune system due to remodelling within the calcified lesion. This leads to inflammation in the adjacent brain parenchyma, breach of the blood-brain barrier, edema, and NO and free radical liberation. This further leads to CGRP release and activation of the trigeminothalamic system, triggering migraine attacks.[13]

Intracranial infections due to fungi including aspergillosis, mucormycosis, histoplasmosis, cryptococcosis, blastomyces, Coccidiodes etc. may also cause headaches due to meningo-encephalitis or raised intracranial pressure.

3 HORIZONTAL AXIS GROUPS WHICH MAY BE INTERLINKED

Table 1: Horizontal groups linked to syndrome of migraine

ID	Abbr	Syndrome	Linked?
HG1	SyM	Syndrome of Migraine	✓
HG2	SyTAC	Syndrome of Trigeminal Autonomic Cephalalgias	
HG3	SyExH	Syndrome of Exertional Headaches	
HG4	SySrH	Syndrome of Sleep-related Headaches	
HG5	SyEnvH	Syndrome of Environment-related Headaches	
HG6	SyTrH	Syndrome of Traumatic Headaches	
HG7	SyVH	Syndrome of Vascular Headaches	✓
HG8	SyCDH	Syndrome of CSF Dysregulation Headaches	✓
HG9	SyInfH	Syndrome of Infection-related Headaches	
HG10	SyHCH	Syndrome of Hormone and Chemical-related Headaches	✓
HG11	SySH	Syndrome of seizure- related headaches	
HG12	SyFP	Syndrome of Facial Pain	✓
HG13	SyNP	Syndrome of Neck Pain	✓
HG14	SyOcP	Syndrome of Ocular Pain	✓
HG15	SyEP	Syndrome of Ear Pain	✓
HG16	SyOrP	Syndrome of Oral Pain	✓
HG17	SyNeu	Syndrome of Neuralgias	✓
HG18	SyWEH	Syndrome of Worst Ever Headache	✓

ID = Identifier / Serial number, Abbr = Abbreviation, Linked? = check mark / tick mark denotes links between horizontal groups

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Headache Medicine Connections

The Official Journal of the World Headache Society

Section 10 : Horizontal Group 10 - Syndrome of Hormone and Chemical-related Headache (SyHCH)

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ARTICLE INFO

Article history:
Received 01.08.2021
Accepted 05.08.2021
Published 20.08.2021

https://doi.org/10.52828/hmc.v1i1.classifications

ABSTRACT

These include headaches that occur in association with excess or low hormonal levels or other chemical substances. A multitude of hormonal excesses are associated with headache. An important factor among women is the cyclical changes that occur during menstruation. Estrogen withdrawal is the main pathogenetic mechanism responsible. Pituitary tumors are also associated with headache, either due to mass effect, raised intracranial pressure or secretory/ biochemical mechanisms. Migraine, cluster headache, tension type headache (TTH) are associated with several endocrinological abnormalities. Headache due to chemicals is another large group, which may be associated with intoxication or withdrawal of specific chemicals or drugs, such as alcohol, carbon monoxide, nitrates.

Keywords: Hormone; Hormonal; Chemical; Menstruation; Period; Estrogen; Pituitary; Tumour; Prolactinoma; Migraine; Cluster Headache

1 CLINICAL FEATURES, MECHANISMS AND ASSOCIATED CONDITIONS

1.1 Secretory/ biochemical mechanisms

Prolactin hypersecretion: Migraine may be triggered by menstrual dysfunction that occurs due to prolactin oversecretion.[1] Cavestro et al. have suggested an association between high prolactin levels and migraine chronification.

In growth hormone oversecretion, headache may occur in 13-60% of patients.[2] There is improvement in headache after pituitary surgery for acromegaly leading to decline in growth hormone levels, and recurrence with recurrent tumor.[3]

1.2 Mechanical effects

Pituitary tumor enlargement may lead to traction on pain-sensitive structures such as the dural meninges, cranial nerves and blood vessels.

Rise in intrasellar pressure may also be subsequent to pituitary tumor enlargement, leading to pain.[4]

Cystic changes in the pituitary may also lead to headache.[5]

1.3 Raised intracranial pressure

Endocrine disorders like Addison's disease, adrenal insufficiency, Cushing's syndrome, hypothyroidism or hyperthyroidism and hypoparathyroidism, may leads to raised intracranial pressure symptoms.[6]

2 THE SYNDROME OF HEADACHE DUE TO HORMONES AND CHEMICALS CAN BE ASSOCIATED WITH THE FOLLOWING CONDITIONS

2.1 Migraine

Shortly before a migraine attack begins, hypothalamic functional connectivity is altered. Hence, the hypothalamus plays a significant role in migraine attack generation. Hypothalamic nuclei communicate directly with the trigeminohypothalamic tract (THT) to receive pain stimuli. The hypothalamus also processes several key migraine symptoms, including mood, fatigue etc. possibly driven by dural nociceptive input.[7] A correlation between migraine and several endocrine disorders exists for example hypothyroidism, endometriosis, PCOD.

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Hypothyroidism: Described in the section below in 'headaches due to hypothyroidism'. Endometriosis: Patients with endometriosis have increased small unmyelinated C fibers in the endometrium. These produce calcitonin gene-related peptide (CGRP), which may mediate migraine.[8] Activation of sensory fibers in endometrial tissue leads to central nervous system hyperexcitability. It is also posited that mast cells in the endometriosis can provoke the release of several inflammatory mediators. Inflamamtory mediators, in turn, hypersensitise meningeal nociceptive neurons, eventually triggering migraine attacks. There is significant association between endometriosis and increased risk (49%) of migraine.[9] PCOD: The mechanism of headache may be the effect of high levels of testosterone and dehydroepiandrosterone on cerebral vasculature.[10,11]

2.2 *Menstrual migraine*

Menstruation may be a trigger factor among women with migraine.

Patients may either have migraine related to menstruation, or may have pure menstrual migraine

Menstrual migraine tends to occur on days -3 to +5 of menstruation. In pure menstrual migraine, migraine attacks are confined to this perimenstrual period. In migraine related to menstruation, attacks may occur even outside the perimenstrual period.

Decline in serum estradiol level, or estrogen withdrawal, is believed to be the underlying reason for the development of menstrual migraine.[12]

Decreased estrogen levels are associated with decreased threshold for trigeminal activation.

A decrease in estrogen level increases vulnerability to prostaglandins, which are increased during menstruation. Prostaglandins further lead to increased production of neuropeptides including substance P and CGRP which mediate pain.

The CGRP system is also affected by endogenous and exogenous steroid hormones.[13]

Within the CNS, estrogen receptors are distributed in the thalamus, periaqueductal grey matter, amygdala, and hence, estrogen influences other symptoms of migraine, including allodynia, and food cravings.

However, some studies have not found a significant difference in the rate of decline of estrogen among individuals with and without acute headache.

Women with menstrual migraine may have inherent neuroendocrine susceptibility leading to migraine attacks.

A link between menstrual migraine and Single nucleotide polymorphisms (SNPs) in TNF-alpha, SYNE1 gene and NRP1 gene has also been suggested.[14,15]

Menstrual migraine is usually more painful, resistant to therapy, more disabling and longer lasting than non-menstrual migraine.[16]

2.3 *Ovulation and migraine*

Although ovulatory or post-ovulatory migraine has been reported, with post-ovulatory estrogen-withdrawal being the likely mechanism, several studies have not been able to corroborate this association.[17]

2.4 *Headache and oral contraceptive pills*

Nearly 70% of users of oral contraceptive pills experience headache during the placebo week of the pill cycle. This is due to an abrupt decline in levels of exogenous estrogen along with an increase in neuronal nociceptive sensitivity.[16,18]

Migraine patients have variable experience. 50% experience no change of the headache pattern, 15% experience improvement, and 28% report worsening.[19]

In progestin-only methods, headache occurs frequently at initiation of therapy but improves subsequently. Worsening of migraine with progestin-only methods has not been reported. In fact, migraine can significantly improve with this type of contraception.

Regimens that reduce the hormone-free period or altogether eliminate it are associated with decreased frequency of headache.

This correlates with the degree of suppression of ovarian activity.

These headaches usually peak on the day three of the pill withdrawal week.

2.5 *Headache and hormonal changes in pregnancy*

During pregnancy, the level of estrogen hormone increases multifold whereas progesterone levels decline, eventually rising towards the end of pregnancy.

Many pregnant women report improvement in migraine attacks during pregnancy, especially if they had menstrual migraine or migraine without aura. A smaller fraction may experience worsening or new onset migraine during pregnancy.[20]

This improvement in migraine frequency may be attributed to lack of hormonal fluctuations during pregnancy.

Production of endorphins during pregnancy could also be a contributory factor.

Recurrence usually occurs in the first postpartum week due to an abrupt decline in estrogen and endorphin levels.[21]

2.6 *Tension-type headache (TTH)*

A large proportion of patients with pituitary adenomas (37·5–70%) suffer from headache, primarily presenting as migraine or TTH.[22]

2.7 Trigeminal autonomic cephalalgias

Cluster headache may be associated with pituitary tumours.

Disruption of the hypothalamic-pituitary axis leads to dysautonomia, accounting for the episodic characteristic of headaches. [23]

Dura mater stretch may be a mechanism of this group of headaches. [24]

Invasion of the cavernous sinus: Cavernous sinus contains the first and second branches of the trigeminal nerves in the lateral wall and the internal carotid artery in the centre, which are structures that can generate pain

Role of "nociceptive peptides" such as CGRP, substance P is also posited. [25]

SUNCT or SUNA associated with pituitary micro- or macroadenoma: Chitsantikul et al. identified six patients with such forms of headache (5 SUNCT, 1 SUNA). Patient with SUNCT (five patients) had headache on the same side as the pituitary tumour; tumour removal led to significant pain relief in three patients. [26]

2.8 New Daily Persistent Headache

New daily persistent headache has been reported to have association with hypothyroidism. [27]

2.9 Headache due to pituitary apoplexy

Pituitary apoplexy that occurs within a pre-existing pituitary tumour leads to an abrupt increase in size of the pituitary tumour, leading in turn to abrupt rise in intrasellar pressure. This leads to abrupt onset of severe and pulsatile headaches. [28]

Pituitary apoplexy usually presents with a sudden-onset headache (92–100%). Features of meningeal irritation such as neck stiffness may also be present. Hence, it closely resembles subarachnoid haemorrhage or meningitis. Concomitant features include altered sensorium, bitemporal hemianopia, restriction of oculomotor movements, and projectile vomiting. [29,30]

2.10 Headache due to excess of growth hormone

In growth hormone oversecretion, headache may occur in 13-60% of patients.

There is improvement in headache after pituitary surgery for acromegaly leading to decline in growth hormone levels, and recurrence with recurrent tumor. [31,32]

2.11 Headache associated with lymphocytic hypophysitis

Among 38 patients with granulomatous hypophysitis, the most common clinical feature was headache. [33] Other features may include those due to pituitary dysfunction such as diabetes insipidus, hyperprolactinemia, etc.

2.12 Headache due to hypoglycemia

Headache due to fasting is commonly diffuse in character. It may be bifrontal. The pain is usually non-pulsatile. The intensity may be mild to moderate.

The probability of developing a fasting headache tends to increase with the duration of fasting.

Patients with pre-existing headache are more likely to develop fasting headaches compared to those who have no history of headache. [34]

Hypoglycemia and withdrawal of caffeine may be possible reasons for fasting headache. [34,35]

2.13 Headache due to pheochromocytoma

These are usually short-duration, frontal or occipital intense headaches. These may be pulsatile or constant. The patient may have concomitant anxiety, palpitation, sweating, pallor, angor animi, chest pain, tachycardia, vomiting etc. Headaches are typically of short-duration (15 minutes to one hour).

Headaches in pheochromocytoma are related to adrenaline surges, and correspond with sudden rise in blood pressure by the pressor effect of secreted amines. [36]

It may present as a thunderclap headache. [37]

Pheochromocytoma presenting as thunderclap headache in the absence of hypertension has also been reported. [38]

2.14 Headache due to hypothyroidism

Pituitary growth associated with high TSH levels and a possible "mass effect" (compression of painful intrasellar structures) may be one of the mechanisms of headache.

Hypothyroid patients may have high prolactinemia, which can aggravate headaches.

Additionally, patients with hypothyroidism may also have enlarged pituitary glands which may contribute to headache via "mass effect." [39]

The headache due to hypothyroidism is continuous, bilateral, and nonpulsatile. It occurs with the development of hypothyroidism, and relieved with optimisation of thyroid status. [40]

Headache is among the commonest symptoms amongst patients with hypothyroidism, occurring in nearly one third of patients with hypothyroidism.

History of pre-existing migraine is elicited in 58% of these patients.

Patients with subclinical hypothyroidism may also present with similar headaches and respond in a similar manner to levothyroxine supplementation.

78% of patients with headache report an improvement after correction of their hypothyroid status due to supplementation with thyroxine.

Increased cases of hypothyroidism among patients with migraine and Tension-type headache (TTH) has been reported although the exact relationship remains unclear. [41]

Increased association of NDPH and hypothyroidism has also been reported. [42]

Treatment with levothyroxine may cause headaches due to raised intracranial pressure. [43]

How levothyroxine leads to IIH is unclear. Hypothyroid patients possibly have decreased ability to clear free water. Levothyroxine normalises tissue composition and excess water is excreted. This could lead to altered CSF dynamics and predispose to IIH. [44]

2.15 Headache due to hyperthyroidism

Hyperthyroidism may also be linked with chronic headache. [45]

Headache in hyperthyroidism may also occur due to raised intracranial pressure. [46]

2.16 Headache due to Cushing's syndrome

Cushing syndrome may presents with headaches due to raised ICP.

The mechanism involves cerebrospinal fluid dynamics, which are influenced by both inflammatory mediators and 11ß-hydroxysteroid dehydrogenase type 1. [47]

2.17 Headache due to adrenal insufficiency

Adrenal insufficiency may present with raised ICP-related headache. [48]

2.18 Headache due to testosterone

Men with chronic migraine may have lower testosterone levels. [49]

Use of exogenous testosterone may lead to headaches as a side effect, a possible mechanism for this effect may be cause of secondary arterial hypertension. [50] Raised intracranial pressure may be another potential mechanism.

2.19 Headache due to obesity

Obesity is linked with increased risk for chronic headache in general. [51]

Also linked with increased risk for migraine. Risk may be highest among individuals in the reproductive age group.

Obesity is considered to be a contributory mechanism accounting for chronification of episodic migraine. [52]

Among patients with migraine, hypothalamic modulation may lead to hyperphagia and weight gain (Cause or effect?) [53]

There are multiple hypothalamic peptides and neurotransmitters that can lead to migraine pathophysiology: for example serotonin, orexin, adipokines. [54]

There is less data assessing the relationship between obesity and tension-type headache (TTH). Three population based studies have varied findings. Two studies found an increase in risk for both episodic and chronic TTH with obesity while one study found no increase in risk. [55–57]

Raised intrathoracic pressure, secondary to increased abdominal obesity, may also increase the risk of Idiopathic Intracranial Hypertension (IIH). [57]

Apart from absolute weight, recent weight gain is also a risk factor for IIH (5-15% of baseline weight over the preceding 12 months). [57]

2.20 Headache linked to nitrates

Headache is amongst the most frequent side effect of nitrate use. This occurs due to cerebral arterial vasodilation due to activation of the nitric oxide-CGMP pathway. [58]

Nitrate-containing compounds often act as migraine triggers. Nitrate-induced headaches may manifest in one of two ways:

2.20.1. Immediate headaches

Occur within an hour of medication ingestion; these have mild to moderate severity. These are mediated by NO-induced vasodilation. [59]

2.20.2. Delayed headaches

These occur 3-6 hours after ingestion; these are more severe and are migrainous in character. These occur due to release of CGRP, CGMP and s-nitrosylation mediated changes in cerebral function. These are also more frequent among patients with family history of migraine. [60]

2.21 Headache linked to phosphodiesterase (PDE) inhibitors

Headache is a highly common side effect of PDE inhibitors. PDE5 inhibitors include sildenafil, tadalafil, vardenafil, avanafil.

The mechanism is vasodilatation induced by them. [61]

Associated features of vasodilatation, including flushing, dyspepsia, nasal congestion or rhinitis, may occur. These side effects tend to dissipate with time.

The headache may resemble either tension type headache or migraine with a pulsatile quality.

Paroxysmal hemi-crania like headache may also occur. [62]

Headache has also been reported with PDE3 inhibitor, cilostazol. Delayed migraine-like attacks may occur, after a median 6 hours of intake.

Cyclic increase in cAMP is the underlying mechanism. [63]

Headache after theophylline intake due to PDE3 inhibition has also been reported. [64]

2.22 Headache linked to Carbon Monoxide

Carbon monoxide (CO) is an endogenously produced signalling molecule that has a role in nociceptive processing and cerebral vasodilatation. [65]

Headache due to acute CO intoxication is classically diffuse and throbbing.

In a series, the most common location was frontal, although more than one location may be affected. The nature of pain may be dull or sharp. It may be throbbing, continuous or intermittent. [66]

2.23 Headache linked to alcohol

Alcohol behaves as a migraine trigger, in about one-third of migraine patients. [67]

Familial hemiplegic migraine (FHM) may be triggered by alcohol in 15%.

Hemicrania continua is usually triggered within 3 hours of intake of alcohol.

Alcohol may also trigger tension-type headaches. [68]

Headaches linked to alcohol may either be hangover headaches or migraine attacks triggered by alcohol.

All alcohols may trigger migraine attacks, in 80% of cases within 3 h, and consistent with other studies, red wine is frequently incriminated. [69]

Above 50% patients indicate alcohol triggers of cluster headache (CH) attacks in chronic CH and in episodic CH only during bouts. [70]

Alcohol withdrawal syndrome also has headache as a prominent complaint.

2.24 Headache linked to cocaine

Cocaine is a highly vasoactive drug.

Central nervous system effects of cocaine abuse include headache, seizures, ischemic/hemorrhagic stroke, aneurysm formation and subarachnoid hemorrhage. [71]

Sympathetic activation leads to vasoconstriction.

It also causes decreased reuptake of noradrenaline and adrenaline and release of these amines from the adrenal gland.

It also leads to release of dopamine which further enhances vasoconstriction.

Other mechanisms leading to vasoconstriction include endothelial activation, smooth muscle calcium influx and mediators such as benzoylecgonine and ecgonine which mediate vasoconstriction. [71]

Patterns of headache following cocaine use may be immediate or delayed. Immediate headache occurs due to synaptic blockade of noradrenaline uptake and acute vasoconstriction. This resembles migraine. Delayed headache may develop 40 to 90 minutes after cocaine use.

Cocaine may also have pain-relieving properties in patients with cluster headaches. This occurs due to anesthetising properties of cocaine on the sphenopalatine ganglion. However, presynaptic serotonin depletion leads to rebound headache.

Cocaine can also trigger RCVS which can cause severe acute headaches.

Cocaine-induced headache occurs commonly in younger individuals, and among females.

Chronic cocaine users may present with one of three groups of headaches:

2.24.1. Group I

In these, headaches immediately follow cocaine use. This is usually bilateral or occipital, lasts 2-48 hours, may have associated emesis, nausea, photophobia. The manner of cocaine use is inhalation or intravenous.

2.24.2. Group II

This occurs in crack users (snorting) or smoking. This group presented with a frontal pulsatile headache, associated with nausea and vomiting.

2.24.3. Group III

These patients present with a headache a few days after cocaine abstinence. These patients present with bifrontal throbbing headache. Associated nausea, vomiting and photophobia may also occur.

Uncommonly, vertebral or cervical artery dissection may occur due to cocaine use.

In patients who develop a sudden and severe headache, the possibility of intracerebral hemorrhage or RCVS may be considered. [71]

2.25 Headache due to histamine

Histamine plays an important pathogenetic role in migraine. It maintains the neurogenic inflammation pathway and sensitises the trigeminal afferents and ganglia. [72]

It is an inducer of migraine attacks by its action on extracerebral H1 receptors. [73]

Histamine headache is immediate or delayed. Migraine, TTH and cluster headache may follow histamine exposure. [73]

2.26 CGRP-induced headache

CGRP is a central molecule in migraine pathophysiology.

Intravenous infusion of CGRP leads to migraine attacks in patients with migraine without aura. It may also trigger auras. [74]

2.27 *Headache linked with exogenous acute pressor agent*

Headache may occur due to an increase in blood pressure triggered by an exogenous agent.

These may include amphetamine, cocaine, monoamine oxidase inhibitors, or withdrawal of alcohol, alpha agonists and beta blockers. [75]

2.28 *Headache due to non-headache medication or other substances*

Several drugs may lead to headaches: These include atropine, digitalis, disulfiram, hydralazine, imipramine, nimodipine, nifedipine, sildenafil.

The headache is usually diffuse, non-throbbing.

2.29 *Medication overuse headache*

Medication-overuse headache (MOH) develops usually in patients suffering from chronic headaches (migraine or tension type), who may use medications on a chronic basis to obtain symptom relief.

The medications associated with MOH risk, from lowest to highest are NSAIDs and acetaminophen, triptans/ ergot compounds, combinations containing opioids or barbiturates.

Central sensitisation plays a key role. [76]

Genetic susceptibility may play a role. Insertion/ deletion polymorphisms occurring in angiotensin converting enzyme (ACE) may enhance susceptibility to MOH. [77]

2.30 *Substance withdrawal headache*

Headaches may occur due to withdrawal of opioids, alcohol, caffeine and estrogen.

3 HORIZONTAL AXIS GROUPS WHICH MAY BE INTERLINKED:

Table 1: Horizontal groups linked to syndrome of migraine

ID	Abbr	Syndrome	Linked?
HG1	SyM	Syndrome of Migraine	✓
HG2	SyTAC	Syndrome of Trigeminal Autonomic Cephalalgias	✓
HG3	SyExH	Syndrome of Exertional Headaches	
HG4	SySrH	Syndrome of Sleep-related Headaches	✓
HG5	SyEnvH	Syndrome of Environment-related Headaches	
HG6	SyTrH	Syndrome of Traumatic Headaches	
HG7	SyVH	Syndrome of Vascular Headaches	✓
HG8	SyCDH	Syndrome of CSF Dysregulation Headaches	✓
HG9	SyInfH	Syndrome of Infection-related Headaches	✓
HG10	SyHCH	Syndrome of Hormone and Chemical-related Headaches	
HG11	SySH	Syndrome of seizure- related headaches	✓
HG12	SyFP	Syndrome of Facial Pain	
HG13	SyNP	Syndrome of Neck Pain	
HG14	SyOcP	Syndrome of Ocular Pain	
HG15	SyEP	Syndrome of Ear Pain	
HG16	SyOrP	Syndrome of Oral Pain	
HG17	SyNeu	Syndrome of Neuralgias	
HG18	SyWEH	Syndrome of Worst Ever Headache	✓

ID = Identifier / Serial number, Abbr = Abbreviation, Linked? = check mark / tick mark denotes links between horizontal groups

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Headach. Med. Con. 2021;1(1):60–62

Headache Medicine Connections

The Official Journal of the World Headache Society

Section 11 : Horizontal Group 11 - Syndrome of Seizure-related Headaches (SySRH)

Section Lead: Pravin Thomas

ARTICLE INFO

Article history:
Received 01.08.2021
Accepted 05.08.2021
Published 20.08.2021

https://doi.org/10.52828/hmc.v1i1.classifications

ABSTRACT

Migraine and epilepsy share many close resemblances, yet they have pathophysiological differences. It is very important to recognise both conditions and treat them appropriately. Failure to recognise and control one of them may mean a trigger for the other and added disability. There are situations where both overlap and are associated with disorders of awareness and consciousness. This includes headaches that precede (pre-ictal), accompany (ictal) and proceed a seizure attack (postictal). Seizure may also follow a prolonged migraine aura. There are several conditions which may present with headaches and seizures but this section is for seizure-related headaches only.

Keywords: Seizure; postictal; ictal; preictal; epilepsy; migraine; convulsions; migralepsy

1 CLINICAL FEATURES, MECHANISMS AND ASSOCIATED CONDITIONS

The prevalence of headaches is high in patients with epilepsy. It is likely that various pathophysiologic mechanisms converge into a common final pathway hallmarked by neuronal membrane hyperexcitability, manifesting as a seizure or a migraine [1].

Post ictal headache is common in generalized epilepsy [2] Postictal headaches have migraine symptoms like vomiting, photophobia, or phonophobia. Seizures are often followed by vasodilation and this may also be connected to the headaches [3].

A likely pathophysiological link between headache and epilepsy, is a slowly propagating wave of strong neuronal depolarization which induces fleeting, but intense spike activity. This is followed by a neural suppression which lasts for several minutes. Along with depolarization there is also an increase in cerebral blood flow regionally. However, during the phase of decreased neural activity, there is also a reduction in brain perfusion. Cortical spreading depression activates the trigeminovascular system, triggering a cascade of inflammatory molecules leading to the headache phase. Cortical spreading depression (CSD) and epileptic focus are now understood to be phenomenon that are able to facilitate each other; albiet to a variable degree. Often, a minimum threshold is to be reached before depolarisation starts, but the threshold required is presumably lower for a cortical spreading depression than for an epileptic discharge, even though both facilitate each other at the onset. So in all probability it would be more likely to find a patient with epilepsy having peri-ictal headache than a patient with headache leading to an epileptic attack. Depolarization and dysexcitability are the destinations of these closely related pathways [4].

1.1 Familial hemiplegic migraine (FHM and benign familial infantile convulsions (BFIC)

Mutation in the Na + −K + ATPase pump gene has been associated with both FHM and BFIC. Defects in the Na + −K + ATPase pump alter cortical excitability, This can lead to the phenotypic manifestations of both migraine and epilepsy-(CSD) (for migraine) and inhibitory postsynaptic potential (IPSP) (for epilepsy) [5].

A study using transcranial magnetic stimulation (TMS) to assess cortical excitability in migraine compared with control subjects and patients with epilepsy demonstrated that cortical excitability increases in migraine. This also suggested involvement of intracortical inhibitory circuits and may account for some of the similarities observed in both migraine and epilepsy [6].

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1.2 Aura mimics of migraine and epilepsy

In migraine, visual phenomena are the most common aura and include scintillating patterns and dark scotomata. Most are black and white, although they may be coloured. They slowly move across the visual field to encompass a hemi-field. This suggests a cerebral origin, although purely monocular auras have been described. The latter are probably retinal in origin and may be related to vasospasm and ischemia. Complex patterns and distortions of vision are also common. These include "fortification spectra".Other migraine auras include disturbances of taste and smell, dizziness, paresthesias both unilateral or bilateral, and varying degrees of altered consciousness [(7)].

1.3 Confusional Migraine

Change in mental state is the principal sign or symptom of migraine. The term "confusional migraine" may not be an ideal one, but it is important to recognise that alterations in consciousness may rarely be seen in migraines. There may be bilateral EEG abnormalities [(8)]. They may thus be a subclinical epilepsy or an overlap syndrome of migraine and epilepsy.

1.4 Cyclic Vomiting Syndrome

It is commonly seen in young children who have episodes of nausea and vomiting, often with no other associated symptoms, but may also develop headaches and epileptic seizures, either later in life, or at the same time as the episodes of nausea and vomiting [(7)].

1.5 Headache heralding a seizure

A headache may be a sign that a seizure is approaching. These headaches are called pre-ictal because they occur before the seizure activity starts. They are sometimes considered a manifestation of the epileptic aura, warning an impending seizure. These headaches are usually short-lasting and have a throbbing or sharp quality. One-fifth of patients with epilepsy are noted to have pre-ictal headaches. It has also been hypothesized that the migralepsy sequence may not exist at all and that the initial part of the "migralepsy" may merely be preictal headache that is followed by other ictal autonomic, sensory, motor and psychic symptoms or signs, being labelled "hemicrania epileptica" [(9)].

It is therefore advisable to perform an EEG especially in children who may have subclinical seizure manifestations, if their headaches do not respond to anti-migraine therapy [(10)].

1.6 Post ictal headaches (PIH)

These are prevalent, moderate to severe in intensity, last many hours, and frequently features of migraine. Young adults with a history of interictal headaches are at an increased risk of developing PIH [(11)].

1.7 Interictal headaches

In uncontrolled epilepsy, if one seizure of closely followed by another, there may be postictal headaches which merge with the preictal headaches of the next seizure. There may also be interictal headaches in infrequent seizures. In a given individual, the headache characteristics may also be stereotyped. [(12)].

1.8 Rolandic epilepsy

Migraine tends to cluster not only in epileptic patients, but also in their close relatives without epilepsy. This may suggest a common susceptibility gene, for example, in siblings of children with Rolandic epilepsy [(13)].

2 HORIZONTAL AXIS GROUPS WHICH MAY BE INTERLINKED

Table 1: Horizontal groups linked to syndrome of migraine

ID	Abbr	Syndrome	Linked?
HG1	SyM	Syndrome of Migraine	✓
HG2	SyTAC	Syndrome of Trigeminal Autonomic Cephalalgias	
HG3	SyExH	Syndrome of Exertional Headaches	
HG4	SySrH	Syndrome of Sleep-related Headaches	✓
HG5	SyEnvH	Syndrome of Environment-related Headaches	✓
HG6	SyTrH	Syndrome of Traumatic Headaches	✓
HG7	SyVH	Syndrome of Vascular Headaches	✓
HG8	SyCDH	Syndrome of CSF Dysregulation Headaches	✓
HG9	SyInfH	Syndrome of Infection-related Headaches	✓
HG10	SyHCH	Syndrome of Hormone and Chemical-related Headaches	
HG11	SySH	Syndrome of seizure- related headaches	
HG12	SyFP	Syndrome of Facial Pain	
HG13	SyNP	Syndrome of Neck Pain	
HG14	SyOcP	Syndrome of Ocular Pain	
HG15	SyEP	Syndrome of Ear Pain	
HG16	SyOrP	Syndrome of Oral Pain	
HG17	SyNeu	Syndrome of Neuralgias	
HG18	SyWEH	Syndrome of Worst Ever Headache	✓

ID = Identifier / Serial number, Abbr = Abbreviation, Linked? = check mark / tick mark denotes links between horizontal groups

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Headach. Med. Con. 2021;1(1):63–68

Headache Medicine Connections

The Official Journal of the World Headache Society

Section 12 : Horizontal Group 12, Syndrome of Facial Pain (SyFP)

Section Lead: Anand Kumar

ARTICLE INFO

Article history:
Received 01.08.2021
Accepted 05.08.2021
Published 20.08.2021

https://doi.org/10.52828/hmc.v1i1.classifications

ABSTRACT

The area of the face extends from the forehead up to the chin. The patients often find it difficult to know which is the appropriate medical speciality for acute or chronic pain felt in the facial region. Sometimes general physicians refer patients to dental and oro-maxillofacial surgeons, otolaryngologist, neurologist or pain medicine expert [1]. The subsequent approach to diagnosis and treatment may vary depending on the selected speciality. Little is known about the exact incidence of face pain in the general population. A few older studies by general practitioner (GP)-databases showed a considerably higher incidence rate of trigeminal neuralgia compared to estimations from hospital data in the early 90s (26.8–28.9 per 100,000 person years (PY) versus 4.7 per 100,000 persons) [2].

Keywords: Facial migraine; Lower half facial migraine; Gradenigo's Syndrome; Sluder's Neuralgia; Contact point headache; Vacuum Headache; Eagle's Syndrome; Raeder's Syndrome; Persistent idiopathic facial pain

1 CLINICAL FEATURES, MECHANISMS AND ASSOCIATED CONDITIONS

1.1 Facial pain in migraine

Facial involvement in migraine is rare but not uncommon, it is referred to as facial migraine or lower half facial migraine. The mechanism is the same as other migraines involving the trigeminal neurovascular structures and vasoactive peptides such as calcium gene-related peptides [3–6].

1.2 Facial pain in tension-type headache

This is classically mild to moderate with bilateral sensation of muscle tightness or pressure lasting hours to days. It is not associated with nausea or vomiting. Hyperexcitability of peripheral neurons of head, face and neck muscles is the most acceptable mechanism for episodes of infrequent tension-type headache [7].

1.3 Facial pain in cluster headache

Classical severe periorbital stabbing pain may radiate to adjacent areas of the face near by hemifacial region. Facial involvement is common up to 50% in upper teeth, 45% in jaw and cheeks. Isolated involvement of maxilla and mandible are leave as is. In cluster headaches attention drawn to the facial location of pain can cause delay in diagnosis [8].

1.4 Facial pain in paroxysmal hemicrania

Classically it is a severe pain involving unilateral orbital, supraorbital or temporal regions. Rarely it can involve V2, V3 dermatomal distributions, teeth and jaw [9].

1.5 Facial pain in hemicrania continua

It usually affects the temporal, orbital, frontal, and/or parieto-occipital region, but it can also cause pain in distribution of V2 and V3 dermatones (infraorbital, maxillary, teeth, and jaw) [10,11].

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1.6 Facial pain in SUNCT and SUNA

Facial pain in short-lasting unilateral neuralgi form headache attacks with conjunctival injection and tearing (SUNCT) & short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA) is moderate to severe unilateral headache, with orbital, supraorbital, temporal and/or other trigeminal distribution. In a few cases it can also involve V2 and/or V3 even radiating to the maxilla [12].

1.7 Facial pain related to sinuses, ear, nose, and oral cavity

1.7.1. Sinuses

Maxillary, ethmoid and frontal sinus infection leads to pain at the facial region along with other signs and symptoms of infection like redness, swelling, mucopurulent discharges and fever [6].

Sinusitis is the most frequent misdiagnosis given to patients with migraine, which leads to delay in diagnosis and unnecessary treatment. In a study of 130 migraine patients, 106 (81.5%) were misdiagnosed as sinusitis. The mean delay in time for diagnosis of migraine was (7.75 ± 6.29 years) [13].

1.7.2. Vacuum Headache

If the frontonasal duct is blocked transiently, air in the sinus may get absorbed and create a vacuum-type pull on the frontal sinus mucosa which results in pain from the stimulation of pain sensitive structures carrying sensation by afferent nerve fibres from division of trigeminal nerve. This pain is relieved after surgical intervention and equalization of pressure in the sinus to external atmosphere [14].

1.7.3. Facial pain related to ear

The most common causes of primary otalgia are otitis media and otitis externa. Other causes are foreign body, barotrauma, malignant (necrotizing) otitis externa, Ramsay Hunt syndrome (herpes zoster oticus), cellulitis/chondritis/perichondritis, relapsing polychondritis, trauma, mastoiditis, tumors or infected cysts in auricle or ear canal, wegener's granulomatosis, viral myringitis. Referred pain from temporomandibular dysfunction, dental caries or related diseases, and cervical spine diseases may sometime present as facial pain [15].

1.7.4. Gradenigo's Syndrome

Characterized by the classical triad of otorrhea, facial pain and diplopia, related to otitis media [16].

1.7.5. Facial pain related to nose

Acute inflammatory processes in the paranasal sinuses and chronic rhinitis can cause facial pain. When the nasal mucosa gets infected or irritated, it secretes neurotransmitter peptide like substance P, which is a recognized neurotransmitter in nociceptive fibers [17].

1.7.6. Nasal polyposis

If it blocks the sinus ostia and coexisting infection results in purulent discharge it can cause facial pain, if there is coexisting infection with a purulent discharge [18].

1.7.7. Sluder's Neuralgia (sphenopalatine neuralgia)

Sluder's Neuralgia presents with ipsilateral, boring, burning facial pain which starts from lateral side of the nose to the eye, forehead, orbit, temporal, and mastoid regions. Pain may be constant or paroxysmal, sometimes associated with lacrimation, rhinorrhea, injected conjunctiva, with involving the cheek. It is likely that cases described under this syndrome represent cluster headache [19,20]. Many author consider it different type of frontal pain which could produce ocular symptoms, and the pain is relieved by use of astringents in the middle meatus area [21].

1.7.8. Contact point headache

Contact point headaches are attributed to the intranasal contact area between two opposing mucosal surfaces inside the nasal cavity. This clinical entity was described by Morgenstein and Krieger in 1980 and was called the "middle turbinate headache syndrome." In their study, they mentioned that "headache is a most trying differential diagnosis, possibly because of contact between the septum and middle turbinate, or bulla ethmoidalis, or the uncinate processes." After this study many surgeons advocated endoscopic modified sinus surgery to relieve headaches, even in migraine without aura. By removing the two opposing surfaces, including the medial walls of the ethmoid sinuses and the superior turbinates inside the nose, the pressure point is eliminated and so are the headaches in a good number of patients [22].

1.7.9. Facial pain related to oral cavity

- Odontalgia (dentine- enamel defects, pulpitis, peripheral periodontitis and abscess, fractured tooth). Dental pain represents the most common example of orofacial pain syndrome. Common causes of dental pain are caries, pulpitis, apical periodontitis. Tooth pulp is a soft connective tissue, densely innervated by a number of trigeminal sensory fibers, and stimulation of the pulpal nerves results mainly in pain sensations [23].
- Glossodynia and sore mouth (burning tongue or oral dysethesia).
  This is a completely intraoral condition clinically manifested as burning, discomfort of the tongue and

oral mucosa without any local or systemic causes. Electrophysiological testing and histopathology of tongue biopsy showed peripheral nerve involvement with abnormal perception of temperature but functional MRI studies also point towards changes in central pain processing [24,25].

- Intraoral non dental pain
  Oral mucosal lesions like recurrent oral ulceration, lichen planus, blistering conditions can cause chronic pain. Salivary stones or salivary gland infection can also cause acute pain, as well as chronic pain, frequently associated eating and sometimes even with the thought of food [26].

1.7.10. Atypical odontalgia, phantom tooth pain

Characterised by persistent oral pain without any local disease [27].

1.7.11. Temporomandibular pain

Temporomandibular arthralgia or masticatory myofascial pain is one of the important differential of facial pain syndrome. Pain can involve temporomandibular joint pericranial muscles, masticatory muscles and can radiate to nearby facial structure. Even persistent peripheral pain can sensitize and become chronic central pain [28,29].

1.8 Facial pain due to other direct and indirect causes

Other causes like trauma, surgery, soft tissue infection like, skin, cartilage or bony involvement, carcinoma of skin, soft tissue, blood vessels, nerve fibre can produce pain by various direct or indirect mechanisms [30].

1.8.1. Skin pain

- Facial cellulitis
  Facial pain can be associated with suppurative or non-suppurative facial cellulitis along with other features like redness, swelling or pus discharge [31].

1.8.2. Nerve pain

- Trigeminal neuralgia
  Facial pain is restricted to one or more divisions of the trigeminal nerve; sudden severe, short lasting, electrical sensation like pain, more commonly in second (maxillary) or third (mandibular) division of the trigeminal nerve. Most common aetiology is intracranial vascular compression of the trigeminal nerve root. The most commonly responsible vessel is the superior cerebellar artery. Other diseases such as multiple sclerosis or a tumor in the cerebellopontine angle can cause trigeminal neuralgia. In approximately 10% of patients, no apparent cause was identified and they were considered as idiopathic trigeminal neuralgia [32].
- Glossopharyngeal Neuralgia (IX Nerve)
  Intermittent lancinating pain involving posterior tongue, pharynx, ear. Commonly due to inflammation, entrapment or compression of glossopharyngeal nerves [33].
- Neuralgia of Superior Laryngeal nerve (Vagus nerve Neuralgia)
  Paroxysms of unilateral lancinating pain radiating from the side of the thyroid cartilage or pyriform sinus to the angle of the jaw and occasionally to the ear [34].

1.9 Facial pain due to ocular causes

Various ophthalmic conditions can lead to acute or chronic facial pain syndrome [35,36].

1. Conjunctival diseases (conjunctivitis, dryness, trauma, ulcer)
2. Corneal diseases (trauma, ulcer, keratitis)
3. Scleral diseases (infection, trauma)
4. Diseases of eyelid like chalazion, folliculitis, mass, abscess
5. Optic neuritis, Retinitis, Glaucoma, Cellulitis, Panophthalmitis
6. Orbital diseases like mass, infection, trauma
7. Intra-orbital or intracranial mass
8. Idiopathic inflammatory conditions
9. Nasolacrimal duct infections, like dacryocystitis, obstruction

1.10 Vascular causes

1.10.1. Giant cell arteritis

Classically presented as facial pain, headache and neck pain symptoms. They are seen in chronic vasculitis of the large and medium vessels, involving the extracranial branches of the carotid arteries, in particular, the temporal artery. Inflammation of arterial wall leads to blood stasis causing luminal occlusion and further tissue ischemia responsible for all pain and other various clinical manifestations [37].

1.10.2. Cavernous sinus thrombosis

Cavernous sinus thrombosis classically presents as pain in the head, face and eye region along with redness of eye and diminution of vision. Other striking signs of CVT are orbital abnormalities such as proptosis, facial erythema, lid swelling and chemosis. Causes other than infections include various systemic diseases, intracranial tumors, pregnancy, puerperium, contraceptives pills, and coagulopathic disorders. In about 30% of cases, aetiology cannot be identified. Cavernous sinus thrombosis hampers drainage from the facial vein and superior and inferior ophthalmic veins resulting in facial and periorbital venous congestion leading to edema, ptosis, proptosis, chemosis, discomfort and pain to adjacent structures [38,39].

1.10.3. Acute coronary syndrome

Myocardial infarction may refer to pain radiating from the left chest, neck up to the orofacial region, the throat and the teeth [40–42]. About 6% of total subjects had craniofacial pain as the only complaint of coronary ischaemia while an additional 32% experienced craniofacial pain concomitant with pain in other regions. Thoracic cardiac branch of the left vagus nerve stimulation in acute coronary syndrome can produce pain originating from the left sided of the neck, face, teeth and jaw. This hypothesis suggests that vagus nerve transmits pain to the ipsilateral head-neck-face region in acute coronary syndrome [43].

1.11 Tumor

Craniofacial pain secondary to neoplasm is rare.
Primary tumors like Schwannoma, pontine tumors [44], lymphoma directly interfering with the trigeminal nerve can lead to facial pain. Metastatic carcinoma from breast and renal may presents as facial pain. [45,46]. Chemotherapy related facial pain has also been reported [47].

1.11.1. Stylohyoid Process Syndrome (Eagle's Syndrome)

This leads to pain predominantly at the lateral side of neck and mandible and or floor of mouth. After trauma or tonsillectomy there may be compression or irritation of nearby pain sensitive structure by the styloid process. Symptoms vary greatly in location severity, ranging from mild head-neck pain symptoms to serious cerebral ischemia [48].

1.11.2. Superior Pulmonary Sulcus Syndrome (Pancoast Tumor)

This leads to progressively pain in neck, shoulder and ulnar side of the arm along with Horner's syndrome due to neoplasm. Primary cause is due to involvement of nearby nerve roots and brachial plexus involvement [49].

1.11.3. Raeder's Syndrome (Raeder's Paratrigeminal Syndrome)

Also known as painful postganglionic Horner's syndrome. It may be associated with multiple cranial nerves and require detail clinical and radiological evaluation for detection of any primary or metastatic tumor in middle cranial fossa [50].

1.12 Idiopathic facial pain [Persistent idiopathic facial pain) (PIFP)]

Pain is mostly deeply situated, but it can be superficial. It is dull, ill localized, mostly unilateral but can be bilateral too. Pain described as various different characteristics like throbbing, aching, burning and often stabbing with severity, ranging from mild to severe. It may aggravate in emotional stress and is most often associated with minor surgery or invasive dental or otolaryngologic procedures. There is no evidence of neurovascular compression of trigeminal nerve complexes.

Recent studies showing increased neuronal excitability at the brainstem level in patients of PIFP [51,52].

1.13 Pain from the jaw bones

Jaw pain occur due to various etiologies which can cause acute or chronic facial pain syndrome [53–59].

- Trauma: mandible fracture, chin lacerations
- Infection: bacterial, viral (herpes zoster, fungal (*Aspergillosis, mucormycosis*)
- Benign neoplasm: giant cell tumour, osteoid osteoma and osteoblastoma
- Malignant neoplasm: osteosarcoma, Langerhans' cell histiocytosis, non-Hodgkin lymphoma and multiple myeloma, metastatic deposits
- Therapy-related: Medication-related osteonecrosis of the jaw (MRONJ), Osteoradionecrosis, alveolar osteitis
- Systemic disease: sickle cell disease, Gaucher's disease and Paget's disease

2 HORIZONTAL AXIS GROUPS WHICH MAY BE INTERLINKED

Table 1: Horizontal groups linked to syndrome of migraine

ID	Abbr	Syndrome	Linked?
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HG4	SySrH	Syndrome of Sleep-related Headaches	
HG5	SyEnvH	Syndrome of Environment-related Headaches	
HG6	SyTrH	Syndrome of Traumatic Headaches	✓
HG7	SyVH	Syndrome of Vascular Headaches	✓
HG8	SyCDH	Syndrome of CSF Dysregulation Headaches	
HG9	SyInfH	Syndrome of Infection-related Headaches	✓
HG10	SyHCH	Syndrome of Hormone and Chemical-related Headaches	
HG11	SySH	Syndrome of seizure- related headaches	
HG12	SyFP	Syndrome of Facial Pain	
HG13	SyNP	Syndrome of Neck Pain	✓
HG14	SyOcP	Syndrome of Ocular Pain	✓
HG15	SyEP	Syndrome of Ear Pain	✓
HG16	SyOrP	Syndrome of Oral Pain	✓
HG17	SyNeu	Syndrome of Neuralgias	✓
HG18	SyWEH	Syndrome of Worst Ever Headache	✓

ID = Identifier / Serial number, Abbr = Abbreviation, Linked? = check mark / tick mark denotes links betweenhorizontal groups

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Headach. Med. Con. 2021;1(1):69–73

Headache Medicine Connections

The Official Journal of the World Headache Society

Section 13 : Horizontal Group 13, Syndrome of Neck Pain (SyNP)

Section Lead: Anand Kumar

ARTICLE INFO

Article history:
Received 01.08.2021
Accepted 05.08.2021
Published 20.08.2021

https://doi.org/10.52828/hmc.v1i1.classifications

ABSTRACT

Syndrome of neck pain includes pain in the neck region and both anterior and posterior neck. A commonly used term is cervicogenic headache which incorporates pain originating from the posterior aspect of the neck. It can be unilateral, start from the head and neck posteriorly, and radiating to the front of neck and eyes and even associated with ipsilateral arm pain and discomfort. It may be associated with nausea, vomiting, dizziness, phonophobia, photophobia, blurred vision, and difficulties in swallowing. They cause considerable impact on individuals and their families, society, and health. In one study the annual incidence of neck pain is about 10-21% with higher incidence in office going and computer working population. The prevalence of neck pain in general population ranges from 0.4% to 86% [1].

Keywords: Whiplash; Temporal arteritis; Coat hanger headache; Myofascial pain; Necktongue syndrome; Fibromyalgia pain; Vagus nerve Neuralgia; Raeder's Syndrome; Thoracic outlet Syndrome; Carotidynia

1 CLINICAL FEATURES, MECHANISMS AND ASSOCIATED CONDITIONS

The syndrome of neck pain can be associated with the following conditions.

1.1 Migraine

Migrainous headache can be associated with neck pain, either as a trigger or a part of the migraine attack [2].

1.2 Tension-type headache

Pericranial tenderness by manual palpation is abnormal sign in patients with tension-type headache. Involvement of splenius, sternocleidomastoid, and trapezius muscles leads to constant neck pain [3].

1.3 Cluster Headache

In 10% of cluster headache patients, pain is experienced in the neck, along with typical orbitotemporal pain. In 37% patients, pain radiates from the orbit or temple to the ipsilateral neck. Neck pain and stiffness was reported in 40% of patients while tenderness was reported in 29% during headache attack. Neck flexion can precipitate cluster headache in 9% of patients [4].

1.4 Hemicrania continua

Most of the patients have side-locked headache, predominantly located in the first division of the trigeminal nerve i.e. orbital, supraorbital, or temporal location. It may sometimes radiate to involve occiput, retro & peri auricular region, neck, shoulder, arm, cheek, jaw, ear, nose, and oral cavity [5,6].

1.5 Post traumatic headache

Post-traumatic headache patients can present with persistent low back pain, neck pain and with headache which may present with a variable time delay. The most widely accepted mechanism is an acceleration/deceleration injury that is often related with whiplash-related symptomatology [7].

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1.6 Temporal arteritis

Also known as giant cell arteritis. It is an autoimmune vasculitis commonly affecting elderly individuals over 50 years of age. It involves medium and large arteries of the head, neck, and upper parts of the body. Branches of external or internal carotid arteries are primarily involved leading to the classical clinical manifestations of intermittent or sometimes permanent visual loss, headache, tenderness of scalp, with or without jaw claudication. Mechanism of neck pain is due to ischemia of muscles supplied by branches of the external carotid artery[8].

1.7 Low CSF pressure associated Neck pain (Coat hanger headache)

Low CSF pressure causing constant stretching of cervical nerve roots leads to persistent boring type of neck pain with or without headache[9].

1.8 Post Lumbar-puncture headache

Bilateral headache along with neck pain that develop usually within hours but may be delayed up to several days after lumbar puncture. Constant leak of CSF from the subarachnoid space from puncture site during lumbar puncture, results in fall of intracranial CSF volume and CSF pressure[10].

1.9 Myofascial pain

Traumatic or micro traumatic events like overload, postural deviations, repetitive activity involving the same muscles and maintenance of the same posture for prolonged periods of time can act as direct stimuli. Indirect stimuli can lead to development of secondary points in muscles, which are not subjected to traumatic or micro traumatic events. These indirect stimuli are sites of pain referral from distant structure which are either visceral or somatic[11].

1.10 Fibromyalgia pain syndrome

Symptoms of diffuse body pain associated with multiple pain points predominantly around the neck. In genetic predisposed individuals, altered central processing of nociceptive stimuli exacerbates the pain response[12].

1.11 Congenital anomalies

Various congenital conditions can lead to neck pain like occipitalization of the atlas, atlantoaxial dislocation, and separation of the odontoid[13].

1.12 Neck-tongue syndrome

Acute unilateral occipital pain aggravated by jerky movement of the head, with sensation of numbness in the ipsilateral half of the tongue. Subluxation of a lateral atlantoaxial joint can cause pain, while numbness of the tongue is due to impingement, or stretching of the ventral ramus of C2 against the subluxated articular process edge[14,15].

1.13 Pain related with fracture of bony structure in neck

Pain due to fracture can be localised due to pain sensitive periosteum involvement, or diffuse due to muscle spasm, radicular pain due to nerve root entrapment or stretching or by disc prolapse. Pain may be of sudden onset, axial, sharp, variable in intensity, aggravated by change in posture, rotation of neck or bending forward. Fracture dislocation can also lead to nearby nerve root injury and neck pain[16,17]. The following conditions are related with fracture of different structure of neck leading to neck pain syndrome.

- Fracture of vertebral body
- Fracture of spinous processes (Clay shoveler's fracture)
- Fracture of Transverse process
- Fracture of Articular pillar
- Fracture of superior and inferior articular process
- Fracture of Lamina
- Fracture of Odontoid process
- Fracture of Anterior and posterior Arch of Atlas
- Bust fracture of Atlas

1.14 Pain related to infection

Neck pain associated with infection may have following characteristics: nocturnal pain, malaise, generalized fatigue, depressed appetite along with fever and axial pain. Pain may be due to the direct extention of infection into epidural space or due to compression of adjacent pain sensitive structures[18–23].

- Infection to vertebral body (Osteomyelitis)
- Septic Arthritis of Zygapophysial joint
- Radicular Pain related to Infection
- Septic Arthritis of Atlantoaxial joint
- Infection of Paravertebral muscles or Space
- Infection of Intervertebral disc (Diskitis)
- Infection of Epidural Space (Epidural Abscess)
- Infection of Spinal Meninges (Meningitis)
- Acute Herpes Zoster, Post herpetic Neuralgia
- Syphilis (Tabes Dorsalis and Hypertrophic Pachymeningitis)

1.15 Pain attributed to Tumors

Pain associated with tumors may be localised, due to pain sensitive periosteum involvement, or diffuse due to muscle spasm, radicular pain due to nerve root entrapment, direct cord involvement or stretching or by disc involvement[24].

- Primary tumor of Vertebral body
- Primary tumor of any part of vertebra other than its body
- Primary tumor of Zygapophysial joint, Atlantoaxial joint, Paravertebral muscles or Space
- Primary tumor of Epidural fat (Lipoma
- Primary tumor of Epidural vessels (Angioma)
- Primary tumor of Meninges (Meningioma)
- Primary tumor of Spinal nerve (Neurofibroma)
- Primary Tumor of spinal cord (Glioma)
- Metastatic tumor affecting vertebra, vertebral canal

1.16 Pain related to metabolic bone diseases

Discogenic pain mediated by intervertebral disc related pathologies like deformity in external contour, protrusion, extrusion and breakdown of degenerative disc [25–27].

- Osteoporosis due to Age, and other causes
- Hyperparathyroidism
- Paget's disease of bone

1.17 Pain related to cervical trauma

Excessive stress, trauma, overuse of neck musculature, postural related and any direct or indirect injury to muscle, ligament, bone, tendon, nerve roots [28–30].

- Traumatic Avulsion of nerve roots
- Traumatic Prolapse of cervical disc
- Traumatic Cervical Ligament Sprain
- Traumatic cervical muscle Sprain
- Traumatic Discogenic pain
- Traumatic Zygapophysial pain

1.18 Pain related to arthritis

Pathophysiology of pain in various arthritis are different. It can be due to direct bony involvement, bony erosion, spinal stenosis, inflammation of nearby tissue, pannus formation, fracture dislocation of various joints. Nature of pain and severity can vary as per structure involvement. It can be dull aching, constant boring pain, or sharp shooting radicular pain. It can be acute and severe in onset in case of fracture dislocation. The following various arthritis are commonly responsible for neck pains.

- Rheumatoid arthritis [31]
- Ankylosing arthritis [32]
- Osteoarthritis [33]
- Seronegative spondylarthropathy [34]

1.19 Neck Pain due to Neuralgia

1.19.1. Glossopharyngeal Neuralgia (IX Nerve)

Characterized by intermittent, lancinating pain involving the pharynx, posterior tongue and ear. Commonly due to inflammation, entrapment or compression of glossopharyngeal nerves [35].

1.19.2. Neuralgia of Superior Laryngeal nerve (Vagus nerve Neuralgia)

Paroxysms of unilateral lancinating pain radiating from the side of the thyroid cartilage or pyriform sinus to the angle of the jaw and occasionally to the ear. Superior laryngeal nerve is superficially located so that any regional inflammation or further local trauma can produce localized neuritis and can cause the throat pain [36]

1.19.3. Occipital Neuralgia

Pain in the distribution of the greater or lesser occipital nerves, irritation or compression of the greater occipital nerve or even the C2 spinal nerve [37].

1.19.4. Raeder's Syndrome (Raeder's Paratrigeminal Syndrome)

It may include sinister lesions such as middle cranial fossa tumor. Clinically may mimic benign conditions such as unilateral headache and neck pain syndromes also known as painful postganglionic Horner's syndrome. There is involvement of multiple parasellar cranial nerves requiring detail clinical examination and radiological evaluation to detect occult primary or metastatic middle cranial fossa tumor [38].

1.20 Visceral pain in neck

Visceral neck pain can be due to direct or indirect trauma, infection, malignancy primary to neck structures. Metastatic deposition to various neck structures, secondary to lymph nodes involvements infection or malignancy either by stretching of the fibrous capsule, compression of pain sensitive structures like major vessels and nerve roots.

- Carcinoma of Thyroid [39]
- Carcinoma of Larynx [40]
- Carcinoma of Pharynx [41]
- Acute traumatic injury to Larynx [42]
- Riedel's Thyroiditis [43]
- Acute or chronic Pharyngitis [44]

1.21 Carotidynia

Pain in the neck, radiating to the face and head predominantly temporal or mastoid area, usually on one side. Head and neck movement, swallowing, coughing, may precipitate the pain. Mechanisms include cranial arterial wall inflammation known as cranial arteritis or by dilatation causing pressure effects secondary to carotid body tumor [45].

- Suboccipital and cervical musculoskeletal disorder
- Stylohyoid Process Syndrome (Eagle's Syndrome)
  Pain occurs predominantly at the lateral side of neck, mandible, floor of mouth. The syndrome generally follows trauma or tonsillectomy. Compression or irritation by the styloid process, causing symptoms may vary in location and severity ranging from mild to severe head and neck pain to disabling ischemic stroke [46].

1.22 Pancoast Tumor

Progressive pain in neck, shoulder and ulnar side of the arm, associated with sensory and motor deficits and Horner's syndrome due to neoplasm. Primarily due to involvement of nearby nerve roots and brachial plexus [47].

1.23 Thoracic outlet Syndrome, Cervical rib/Malformed first thoracic rib

Pain in the root of the neck, head, shoulder, which may radiate to the arm and hand. Pain due to pressure and stretching of brachial plexus by hypertrophied muscle, congenital bands, post-traumatic fibrosis, cervical rib or band, or malformed first thoracic rib [48]

1.24 Cognitive deficit in neck pain syndrome

Various degree of cognition decline like attention deficit, memory impairment, comprehension and other parameters are frequently related with chronic pain syndromes. Studies showing atrophy of grey matter at hippocampus, dorsolateral prefrontal cortex is associated with decrease in pain tolerance. Some of them even correlated the atrophy with reduced pain threshold [49].

2 HORIZONTAL AXIS GROUPS WHICH MAY BE INTERLINKED

Table 1: Horizontal groups linked to syndrome of migraine

ID	Abbr	Syndrome	Linked?
HG1	SyM	Syndrome of Migraine	✓
HG2	SyTAC	Syndrome of Trigeminal Autonomic Cephalalgias	✓
HG3	SyExH	Syndrome of Exertional Headaches	✓
HG4	SySrH	Syndrome of Sleep-related Headaches	✓
HG5	SyEnvH	Syndrome of Environment-related Headaches	✓
HG6	SyTrH	Syndrome of Traumatic Headaches	✓
HG7	SyVH	Syndrome of Vascular Headaches	✓
HG8	SyCDH	Syndrome of CSF Dysregulation Headaches	✓
HG9	SyInfH	Syndrome of Infection-related Headaches	✓
HG10	SyHCH	Syndrome of Hormone and Chemical-related Headaches	
HG11	SySH	Syndrome of seizure- related headaches	
HG12	SyFP	Syndrome of Facial Pain	✓
HG13	SyNP	Syndrome of Neck Pain	
HG14	SyOcP	Syndrome of Ocular Pain	✓
HG15	SyEP	Syndrome of Ear Pain	✓
HG16	SyOrP	Syndrome of Oral Pain	✓
HG17	SyNeu	Syndrome of Neuralgias	✓
HG18	SyWEH	Syndrome of Worst Ever Headache	✓

ID = Identifier / Serial number, Abbr = Abbreviation, Linked? = check mark / tick mark denotes links betweenhorizontal groups

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Headach. Med. Con. 2021;1(1):74–79

Headache Medicine Connections

The Official Journal of the World Headache Society

Section 14: Horizontal Group 14, Syndrome of Ocular Pain (SyOcP)

Section Lead: Chaithra D Aroor

ARTICLE INFO

Article history:
Received 01.08.2021
Accepted 05.08.2021
Published 20.08.2021

https://doi.org/10.52828/hmc.v1i1.classifications

ABSTRACT

Headache is a common symptom, presenting to medical practitioners in all arenas and specialties. Ophthalmologists are often the first physicians to evaluate patients with headaches, eye pain, and headache-associated visual disturbances [1]. Pain involving the eye has multiple etiologies and evaluating these are a challenge for clinicians. This classification summarizes the causes of ocular pain, which are classified into periocular, intraocular, retroocular, extraocular and intraorbital causes.

Keywords: Ocular; Ophthalmic; Red eye; Orbital; Periorbital; Refractive Error; Trochlear; Glaucoma; Dacryocystitis; Neuropathic ocular pain

1 CLINICAL FEATURE, MECHANISMS AND ASSOCIATED CONDITIONS

The syndrome of ocular pain can be associated with the following conditions

1.1 Periocular Causes

1.1.1. Trochleodynia

Several disorders are characterized by pain in the trochlear region. The structures which cause pain in this region can include: the superior oblique (SO) muscle, the cartilaginous trochlea, the fibrovascular sheath, the SO tendon, the supraorbital nerve and the supratrochlear nerve. [2]

'Trochlear migraine' refers to ipsilateral trochlear pain along with migraine symptoms. Trochleitis may trigger or sustain the pain of chronic migraine in susceptible individuals. [3]

There are three probable etiologies of the pain experienced in trochleodynia: neuropathic, neuromuscular, and inflammatory. Repeated trauma to the supratrochlear and supraorbital nerve which runs in proximity to the trochlea causes pain that is perceived in the periorbital and frontal areas. Myofascial trigger point in the superior oblique muscle leads to increased frequency of nociceptive input from supraorbital or supratrochlear nerves toward the spinal trigeminal nucleus caudalis. Inflammation in this region may be idiopathic or secondary to a systemic inflammatory disease. Bilateral inflammation is almost always secondary to a systemic inflammatory condition. Histopathologic features of perivascular lymphocytic infiltration of connective and adipose tissue adjacent to trochlear cartilage with invasion of the SO myofibrils is indicative of inflammatory pathophysiology. [2] Symptoms include severe pain in the trochlear region and pain with eye movements or while performing near work. The pain can be continuous or paroxysmal, or continuous with paroxysmal exacerbations. Extra-trochlear pain is usually retro-orbital and sometimes supra-orbital [2]. Clinical signs that can be elicited are tenderness in the trochlear region and increased pain on elevation in abducted position or depression in adducted position.

1.1.2. Herpes Zoster Ophthalmicus

Herpes zoster ophthalmicus (HZO) is a reactivation of the varicella-zoster virus after a period of dormancy in the dorsal root ganglion. HZO affects the dermatomal distribution of the first branch of the trigeminal nerve. [4]

It is characterized by a vesicular eruption on the skin accompanied by severe pain. The pain of HZO is described as burning, aching, stabbing, shooting, or throbbing. The pain may precede the skin eruption by days.

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1.1.3. Headache attributed to Eyelid and adnexal pathologies

- This can be caused by functional abnormalities of the meibomian gland, which can be congenital or acquired. They manifest as ocular and eyelid discomfort, altered tear film and dry eyes. Patients with meibomian gland dysfunction (MGD) report dry eye symptoms and ocular pain (like foreign-body sensation, photophobia, and conjunctival injection). MGD can lead to inflammation and hyperosmolarity of the tears. This results in ocular pain caused by mechanical friction between the eyelids and globe[(5)]. In ocular surface disorders photophobia is presumably due to direct irritation of the trigeminal afferents that innervate the cornea and eye[(6)].

- A hordeolum is an acute bacterial infection found in the lid of the eye. The most common organism that infects the hair follicle of the eyelash is Staphylococcus aureus. There are two types of hordeolum's, internal and external. The external hordeolum is caused by a blockage of the sebaceous (Zeis) glands or sweat (Moll) glands. They present as red painful swelling that may develop into a pustule. Whereas an internal hordeolum is caused by a blockage of the meibomian glands, forming pustule on the inner surface of the eyelids. There is a robust local inflammatory response and abscess formation.[(7)] The usual complaint is that of an insidious onset, slowly progressive painful, red, and swollen eyelid with no history of trauma or foreign body.

- The eyelids are involved in 10% of cases of skin cancer, and the vast majority are basal cell carcinomas (BCC). Destruction of the eyelid architecture and loss of lashes may suggest malignancy.[(8)] Also, an enlarging destructive lesion, with induration or ulceration may indicate malignancies like basal cell carcinoma, sebaceous and squamous cell carcinoma.

- Dacryocystitis is an inflammation of the nasolacrimal sac often caused by an obstruction in the nasolacrimal duct or sac. This results in stagnation of tears and infection in the lacrimal sac. The most common organisms causing acute dacryocystitis are Staphylococcus and Streptococcus species. The obstruction can be at any level of the nasolacrimal system. There will be swelling in the inferomedial portion of the orbit and the medial canthus is erythematous and tender.[(9)]

1.1.4. Headache attributed to Ptosis

The levator aponeurosis and the Müller muscle elevate the eyelid. The occipitofrontalis muscle can also assist in lifting the eyelid with its connectivity to the orbicularis fascia.

In patient with ptosis, mechanoreceptors in the Müller muscle may stimulate a tonic reflex, leading to contraction of the occipitofrontalis muscle. Persistent contraction of this muscle can trigger tension type headache or a migraine[(10)].

1.2 Intraocular causes

1.2.1. Headache attributed to refractive errors

Uncorrected refractive errors are associated with frontal or occipital headache.[(11)] Various studies on headache have reported the role of visual anomalies like refractive error and vergence deficiencies. Hypermetropia can cause sustained effort of accommodation and thereby induce headache due to painful ciliary muscle contracture. Myopia may cause headache by increasing the squinting of eyelid and forehead in an effort to achieve pinhole effect. The mechanism causing headache in astigmatism is not fully understood, but in all likelihood, is related to visual blur.[(12)] One hypothesis might be that astigmatic errors of refraction cause changes to visual perception that alter the hyperexcitability in the visual cortex of the brain of some migraine sufferers perhaps because astigmatic blur may exacerbate the perception of striped patterns thought to be important in the visual triggers of migraine.[(13)] This can lead to asthenopia and headache which is mild with persistent brow ache, aggravated by prolonged visual tasks, particularly at the distance where vision is most impaired. Headache is relieved by the correction of refractive error or if the visual task is discontinued.[(14)]

1.2.2. Headache attributed to dry eye disease (DED)

The exact mechanism underlying the relationship between migraine headaches and DED is unclear. Inflammatory processes have been implicated in both dry eye disease and migraine. There are increased levels of neurogenic inflammatory mediators and cytokines, such as C-reactive protein and interleukin that causes plasma extravasation which in turn increases trigeminal ganglion neuronal hypersensitivity and progression of migraines. T-lymphocyte–mediated inflammation in dry eye disease may also trigger similar events in neurovascular tissue, again leading to propagation of migraines. Excessive dryness of the ocular surface can trigger reflex tearing via the trigeminal nerve, which could potentially trigger migraines.[(15)]

1.2.3. Neuropathic ocular pain (NOP)

This can present with burning or shooting pain in one or both the eyes. This can be associated with increased sensitivity to light or any mechanical stimuli associated with or without ocular surface abnormalities. Ocular surface pain may be nociceptive or neuropathic. Causes of nociceptive pain are structural abnormalities of the eyelids, conjunctiva, cornea, poor tear film, and environmental factors such as pollution and low humidity. Dysfunctional corneal nerves and their central connections may lead to neuropathic ocular pain.[16]

Symptoms include foreign body sensation, burning sensation, dryness, shooting pain, grittiness, throbbing or stabbing pain. They can be triggered by light, wind or temperature changes. Symptoms can be insidious in onset or precipitated by trauma or surgery to the eye. Chronic pains may be experienced in a wider spread distribution radiating from the eye to the occipital region. This is postulated to be caused by peripheral sensitization which occurs at the corneal surface and central sensitization in the trigeminal sensory pathway, thalamus and cerebral cortex; this central sensitization manifests as hyperalgesia and allodynia.
If the symptoms are disproportionate to the signs of ocular surface disease, it is more likely to be neuropathic than nociceptive.

1.2.4. Corneal causes

Corneal abrasion is one of the most common eye injuries. They present with discomfort in the eye, congestion and photophobia. Corneal abrasions result from a disruption or loss of cells in the corneal epithelium. Corneal abrasions can be classified as traumatic, including foreign body-related and contact lens-related, or spontaneous. There may be foreign body sensation associated with the eye pain. Other common causes of ocular pain are a corneal foreign body and infectious keratitis. Infectious keratitis presents with severe ocular pain, congestion, foreign body sensation, reflex tearing and blurred vision[4].

1.2.5. Headache attributed to Scleritis

Scleritis can be idiopathic or caused by infectious or non-infectious conditions. Additionally, associations with malignancy, autoimmune diseases, and surgically induced or medication side effects are causative factors. The sclera comprises of an extracellular matrix of collagen, elastin, and proteoglycans resembling the components of joints, making it equally susceptible to inflammatory conditions such as rheumatoid arthritis. Scleritis is characterized by cellular infiltration and edema of the sclera[17].

Scleritis is characterized by ocular redness, which is a deep violet hue of deep vessels progressing a few days later to pain which is mild to moderate in nature that may radiate to the face and temple, which increases with eye movements.

1.2.6. Headache attributed to Uveitis

Inflammation in the uveal tract is termed as uveitis. Uvea comprises iris, ciliary body & choroid. Patients with anterior uveitis typically report photophobia and pain in or around the involved eye. Uvea is densely innervated with trigeminal fibres, and this can be a pain generator[6]. Any painful stimulus to these areas invariably causes photophobia. Patients with acute anterior uveitis present with severe ocular pain, photophobia and circumcorneal congestion[4].

Uveitis is characterized by the presence of cells, flare and signs of inflammation in the eye. The mechanism of the pain of uveitis seems to be related to a breakdown of the blood-aqueous barrier that allows the release of kinins and prostaglandin E1 from polymorphonuclear leukocytes, and the release of substance P and other polypeptides (as well as prostaglandin E2) from the iris itself. These substances are thought to stimulate chemoreceptors in the ciliary body nerve plexus[14].

1.2.7. Headache attributed to Glaucoma

Primary angle closure glaucoma results when resistance to aqueous flow occurs at the pupillary margin in patients with anatomically shallow anterior chamber[14]. Common precipitating factors include mydriasis due to stress, medications, and conditions of dim illumination. Acute angle closure presents with cloudy vision, colored halos, headache and eye pain which is severe[4]. Nausea and vomiting may accompany the headache. Corneoscleral stretch may trigger an oculo-trigemino-vago-abdominal (oculoabdominal) reflex which results in nausea, vomiting, and abdominal cramps[18]. Eye is hard and tender due to the raised intraocular pressure. The symptoms subside with intraocular pressure control.

1.2.8. Headache attributed to inflammation in the optic nerve / Optic neuritis

The inflammation in optic neuritis is mediated by delayed type IV hypersensitivity reaction. This reaction is induced by cytokines and other inflammatory mediators that are released by activated T-cells. These mediators can cross the blood brain barrier and cause destruction of myelin, axonal degeneration and neuronal cell death[19].

Optic neuritis can be retrobulbar with a normally appearing optic disc or can involve the optic nerve head, which is termed as papillitis where the optic disc appears swollen. The triad of symptoms are periocular pain, vision loss and dyschromatopsia. Painful ocular movements are present in patients with acute demyelinating optic neuritis. The pain may be mild, and rarely severe in some cases. It may precede or occur concurrently with vision loss, and is usually exacerbated by eye movement[19]. The pain associated with optic neuritis is mediated by trigeminal afferents within the blood vessels supplying the optic nerve and the dura covering the optic nerve[6].

1.3 Retroocular causes

1.3.1. Headache attributed to raised intracranial pressure (ICP)

Headache is often the first symptom and the characteristics of headaches are nonspecific. They are usually global, present behind the eyes which may be constant or intermittent. Headaches associated with raised intracranial pressure often worsen during a Valsalva manoeuvre (coughing, straining, etc.). The headache associated with increased ICP may be caused by stretching of the meninges or from distention of cerebral veins [14].

Headaches begin as an ache that occurs at the back of the head or behind the eyes, which in one third of the patients may wake them up from sleep. The pain starts as a dull, aching pain that worsens at night or in the morning. It can be associated with vomiting. Patients may also eventually develop visual difficulties which occur as a result of increased intracranial hypertension.

Transient visual obscuration is most likely attributable to transient compression and optic nerve ischemia [14].

Papilledema is due to an increased CSF pressure in the optic nerve sheath that causes a stasis of the axoplasmic flow at the optic nerve head. This further leads to intraneuronal ischemia and secondary vascular changes within the optic nerve. Early papilledema is usually asymptomatic. Even well-developed papilledema may produce minimal or no symptoms. Sometimes the only abnormality found on careful testing is mild to moderate enlargement of the physiologic blind spot. Some patients present with variable loss of visual acuity, visual field, or both [20].

Visual field defects-Concentric enlargement of the blind spot is the most common and frequently the only visual field defect in patients with papilledema. Compression, detachment, lateral displacement, acquired hyperopia (due to elevation of peripapillary retina by subretinal fluid) of the peripapillary retina appear to be the major reasons that the blind spot increases in size in patients with papilledema. Other visual field defects in papilledema, include concentric constriction, complete blindness, with the rest of the defects divided among homonymous hemianopia and central and arcuate scotomas.

Diplopia-Sixth nerve palsy is a classic example of a false localizing sign of raised ICP, and traditionally attributed to traction of the intracranial segment of the nerve due to brainstem shift, or compression of the nerve against the petrous ligament or ridge of the petrous temporal bone [21].

1.4 Orbital Causes

1.4.1. Headache attributed to retrobulbar/ extraocular/ intraorbital pathologies (Cavernous sinus syndrome, superior orbital fissure syndrome and orbital apex syndrome)

Broad categories of diseases involving the cavernous sinus, superior orbital fissure and orbital apex include bacterial or fungal infections, nonspecific inflammations like Tolosa Hunt syndrome, vascular lesions and neoplasms [22].

Headache can be described as sharp, shooting, stabbing, boring, severe, and intense. Pain is usually periocular or retroocular, with extension into the frontal and temporal areas [23]. Pain tends to be the presenting symptom and can precede ophthalmoplegia. Headache with painful ophthalmoplegia is the characteristic feature of retroocular inflammations.

1.4.2. Inflammatory lesions

Idiopathic orbital inflammatory disease (OID) may be idiopathic or secondary to systemic inflammatory disease like inflammatory bowel disease, sarcoidosis, systemic lupus erythematosus. It can occur at any age, presenting with acute, chronic, or recurrent symptoms and signs. The pain is severe, may worsen with eye movement and presents without external inflammatory signs [4].

1.4.3. Orbital masses and vascular malformations

They are characterized by rapidly expanding orbital lesions which are associated with proptosis, dystopia, blurring of vision and increased intraocular pressure. The orbital vascular lesions include arterial and arteriovenous malformations (AVMs), venous vascular malformations, capillary hemangiomas, venous lymphatic malformations. Orbital neoplasms include hemangiopericytoma, melanoma and hemangiomas. Orbital AVMs cause pain due to expansion of the mass and raised intraocular pressure. The conjunctiva typically shows corkscrew vessels.

Abnormal communications between the intracerebral vessels originating from the carotids and the low-flow intracranial arteriove-nous connections lead to dural shunts. They are less painful than traumatic high-flow fistulas or orbital malformations and commonly seen in middle aged women. They present with conjunctival injection, elevated intraocular pressure, proptosis and a subjective bruit. They may be misdiagnosed as chronic conjunctivitis but an orbital imaging reveals a dilated superior ophthalmic vein, which is diagnostic [4].

1.4.4. Orbital Cellulitis and Abscess

Orbital cellulitis may present with orbital pain and inflammatory signs like, periorbital edema and erythema, similar to idiopathic OID. In preseptal cellulitis, the superficial tissues are involved in contrast to orbital cellulitis which primarily involves the deeper structures. Patients with preseptal cellulitis present with eyelid erythema, edema and inflammation. Painful eye movements, limited ocular movements, relative afferent pupillary defect, blurring of vision, and proptosis are features of orbital cellulitis.

90% of cases of orbital cellulitis are associated with contiguous sinusitis[4]. Endogenous infections, dental infections, and trauma can also lead to orbital cellulitis. Both bacterial and fungi pathogens can be causative organisms, but fungi may be a prominent cause in immune-compromised hosts. Orbital cellulitis from mucormycosis can rapidly progress and deteriorate due to the underlying ischemic orbitopathy. Several cases of mucormycosis in patients with COVID-19 have been reported world-wide. The germination of Mucorales spores in COVID-19 is facilitated by hypoxia, hyperglycaemia, metabolic acidosis, hyperferritinemia and decreased white blood cell phagocytosis which are SARS-CoV-2 mediated. Treatment with steroids may be an additional cause for immunosuppression in these patients. Mechanical ventilators may also contribute to an increased risk of infection[24].

Orbital abscesses are diagnosed with radiologic imaging modalities, including CT or MRI with emphasis on orbital evaluation. Dystopia [non axial exophthalmos] and distortion of the contour of the globe are the clinical signs which may be appreciated on ultrasonography as well.

1.4.5. Thyroid eye disease

Thyroid eye disease is an autoimmune disease which presents with hyperthyroidism, orbital disease, pretibial myxedema and acropachy. There is inflammation and fibrosis of the extraocular muscles. It is the most common cause of unilateral proptosis in adults and thyroid function abnormalities may be absent initially. Pain and ocular discomfort may be the initial symptoms. The pain originates from dry eyes and exposure keratopathy, as a result of lacrimal gland dysfunction, eyelid retraction and proptosis[4]. Eyelid retraction, conjunctival flare, chemosis, proptosis, and restricted eye movements, leading to diplopia, exposure keratopathy, and compressive optic neuropathy are the clinical signs noted in this condition.

1.5 Ocular nerve palsy

Microvascular disease of the oculomotor (III), trochlear (IV), or abducens (VI) nerves, either individually or in combination is an important cause of diplopia in older individuals. Ipsilateral ocular pain is seen in approximately 40% of the cases[4]. The pain is mediated through the trigeminal sensory fibres and may precede, accompany, or follow the onset of ptosis or diplopia.

Recurrent painful ophthalmoplegic neuropathy (RPON), previously known as ophthalmoplegic migraine, is more common in children and young adults and manifests as headache and ophthalmoplegia[25]. The pathogenic mechanisms postulated are ischemia of the cranial nerves, recurrent demyelination-remyelination, infectious neuritis and schwannoma[26].

Ipsilateral headaches can start up to two weeks before the onset of third, fourth or sixth cranial nerve palsy and they may be recurrent.

2 HORIZONTAL AXIS GROUPS WHICH MAY BE INTERLINKED

Table 1: Horizontal groups linked to syndrome of migraine

ID	Abbr	Syndrome	Linked?
HG1	SyM	Syndrome of Migraine	✓
HG2	SyTAC	Syndrome of Trigeminal Autonomic Cephalalgias	✓
HG3	SyExH	Syndrome of Exertional Headaches	
HG4	SySrH	Syndrome of Sleep-related Headaches	✓
HG5	SyEnvH	Syndrome of Environment-related Headaches	
HG6	SyTrH	Syndrome of Traumatic Headaches	✓
HG7	SyVH	Syndrome of Vascular Headaches	✓
HG8	SyCDH	Syndrome of CSF Dysregulation Headaches	✓
HG9	SyInfH	Syndrome of Infection-related Headaches	✓
HG10	SyHCH	Syndrome of Hormone and Chemical-related Headaches	✓
HG11	SySH	Syndrome of seizure- related headaches	
HG12	SyFP	Syndrome of Facial Pain	✓
HG13	SyNP	Syndrome of Neck Pain	
HG14	SyOcP	Syndrome of Ocular Pain	
HG15	SyEP	Syndrome of Ear Pain	
HG16	SyOrP	Syndrome of Oral Pain	
HG17	SyNeu	Syndrome of Neuralgias	✓
HG18	SyWEH	Syndrome of Worst Ever Headache	✓

ID = Identifier / Serial number, Abbr = Abbreviation, Linked? = check mark / tick mark denotes links between horizontal groups

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Headach. Med. Con. 2021;1(1):80–82

Headache Medicine Connections

The Official Journal of the World Headache Society

Section 15 : Horizontal Group 15, Syndrome of ear pain (SyEP)

Section Lead: Pravin Thomas

ARTICLE INFO

Article history:
Received 01.05.2021
Accepted 05.08.2021
Published 20.08.2021

https://doi.org/10.52828/hmc.v1i1.classifications

ABSTRACT

Pains of the ear can be due to diseases of the ear or due to pain referred to the ears. Ear pain can be localised to the external ear, ear canal, or the middle ear. The embryological development of the ear is complex. The ear is innervated by or connected to several cranial and cervical nerves, which also innervate regions within the head, neck, chest, and abdomen. Therefore lesions in these regions can refer pain to the ear [(1)]. Additional symptoms such as ear discharge and localised tenderness suggest a disease of the ear. If there is no associated hearing loss, a non-otologic disease should be considered. Migraine often presents as aural fullness or tinnitus.

Keywords: Ear pain; Otalgia; Otitis; Otitis externa; Otitis media; Migraine; Tinnitus; Red Ear syndrome

1 CLINICAL FEATURES, MECHANISMS AND ASSOCIATED CONDITIONS

The external and middle ear are pain-sensitive structures. The medial part of the auricle is supplied by the auriculotemporal nerve. The lateral aspect of the ear is supplied by the greater occipital nerve (C2 and C3) and lesser occipital nerve. The concha and external auditory meatus are supplied by V3 division of the trigeminal nerve, cranial nerve VII and auricular branch of cranial nerve X. The tympanic membrane is supplied by cranial nerves VII, IX, and X; and the middle ear by cranial nerves V, VII, and IX. Lesions affecting any of these nerves can result in otalgia. Since these nerves also supply the other organs apart from the ear, any pathology of these organs leads to referred pain in the ear [(2)].

The trigeminal nerve supplies the face, paranasal sinuses, palate, teeth and the temporomandibular joint (TMJ). Diseases affecting the TMJ can also localise pain to the ears.

Glossopharyngeal nerve innervates the posterior one third of the tongue and oropharynx. The Vagus nerve innervates the thyroid gland, pharynx, larynx, heart, lung, and parts of the gastrointestinal tract. The posterior aspect of the head and neck and the cervical paraspinal muscles are supplied by the C2 and C3 through the posterior rami communicantes.

Pain from any of the structures listed above can be associated with pain in the ear [(3)].

2 THE SYNDROME OF EAR PAIN CAN BE ASSOCIATED WITH THE FOLLOWING CONDITIONS

2.1 External ear pain

1. Trauma
2. Acute folliculitis
3. Dermatitis
   (a) Contact dermatitis
   (b) Eczematoid dermatitis
   (c) Seborrheic dermatitis
   (d) Psoriasis
4. Infection
   (a) Bacterial
   (b) Fungal
   (c) Viral (herpes zoster)
5. Malignant otitis externa in diabetes or the immunocompromised

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6. Malignant neoplasm: malignant tumors of the ear:
    (a) Melanoma
    (b) Squamous cell carcinoma
    (c) Basal cell carcinoma
7. Non-infectious inflammatory: inflammation of the skin like;
    (a) Sweet syndrome
    (b) Cartilage-MAGIC syndrome
    (c) Granulomatous disorders
    (d) Chondrodermatitis nodularis helicis

2.2 *Middle Ear Pain*

1. Infection of the middle ear:
    (a) Acute otitis media due to Moraxella catarrhalis, Streptococcus pneumoniae, or Haemophilus influenzae
    (b) Chronic otitis media
    (c) Serous otitis media
2. Tympanic membrane infection: bullous myringitis
3. Barometric pressure-related earache: Sudden ascent or descent related
4. Eustachian tube dysfunction
5. Cholesteatomas: sense of fullness is more common than severe pain
6. Glomus tumor
7. Tumors of the middle ear

2.3 *Pain arising from structures outside the ear*[4]

1. Dural venous sinuses
    (a) Cavernous sinus/sigmoid sinus — Thrombosis
    (b) Infective causes: bacterial, fungal thrombophlebitis
2. Scalp
    (a) Temporal arteritis
3. Paranasal sinuses
    (a) Sinusitis
    (b) Nasal polyps
4. Temporomandibular joint
    (a) Temporomandibular joint arthritis
    (b) Bruxism
    (c) Jaw opening/jaw closing dystonia
5. Temporal bone
    (a) Petrous apicitis
    (b) Metastasis in the petrous apex
    (c) Lymphoma
    (d) Eagle syndrome (elongated styloid process
6. Red ear syndrome
    Manifests as pain and redness of one or both external ears. There may also be a burning sensation. Radiation of pain to the mandible, cheek, and occiput is not uncommon. Although the attacks can last for seconds to hours, it commonly lasts 30 min to an hour [5]
7. Neck
    (a) Carotidynia
    (b) Lymphadenopathy
    (c) Lymph node metastasis
8. Neuralgias
    (a) Geniculate
    (b) Trigeminal
    (c) Sphenopalatine
    (d) Glossopharyngeal
    (e) Occipital
    (f) Vagal
9. Retroauricular pain
    (a) Bell's palsy
10. Oropharyngeal disease
    (a) Oral cavity: Dental caries, impacted molars, squamous cell carcinoma of the tongue/mandible, buccal mucosa
    (b) Pharyngitis, parapharyngeal abscess, retropharyngeal abscess, laryngitis, laryngo-esophageal reflux disease, Globus pharyngeus, oropharyngeal dystonia, dysphagia, malignancies of the upper aerodigestive tract
    (c) Parotitis: Preauricular pain
11. Musculoskeletal
    (a) Myofascial pain, cervical dystonia, fibromyalgia, tension-type headache, cervical disc degeneration, cervical radiculopathy
    (b) Cricoarytenoid arthritis
12. Cardiac disease
    (a) Myocardial infarction
    (b) Myocarditis
13. Gastrointestinal disease
    (a) Gastroesophageal reflux disease (GERD)
    (b) Esophageal carcinoma
    (c) Achalasia cardia

3 HORIZONTAL AXIS GROUPS WHICH MAY BE INTERLINKED

Table 1: Horizontal groups linked to syndrome of migraine

ID	Abbr	Syndrome	Linked?
HG1	SyM	Syndrome of Migraine	
HG2	SyTAC	Syndrome of Trigeminal Autonomic Cephalalgias	
HG3	SyExH	Syndrome of Exertional Headaches	
HG4	SySrH	Syndrome of Sleep-related Headaches	
HG5	SyEnvH	Syndrome of Environment-related Headaches	✓
HG6	SyTrH	Syndrome of Traumatic Headaches	✓
HG7	SyVH	Syndrome of Vascular Headaches	
HG8	SyCDH	Syndrome of CSF Dysregulation Headaches	✓
HG9	SyInfH	Syndrome of Infection-related Headaches	✓
HG10	SyHCH	Syndrome of Hormone and Chemical-related Headaches	
HG11	SySH	Syndrome of seizure- related headaches	
HG12	SyFP	Syndrome of Facial Pain	✓
HG13	SyNP	Syndrome of Neck Pain	✓
HG14	SyOcP	Syndrome of Ocular Pain	✓
HG15	SyEP	Syndrome of Ear Pain	
HG16	SyOrP	Syndrome of Oral Pain	✓
HG17	SyNeu	Syndrome of Neuralgias	✓
HG18	SyWEH	Syndrome of Worst Ever Headache	✓

ID = Identifier / Serial number, Abbr = Abbreviation, Linked? = check mark / tick mark denotes links between horizontal groups

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Headach. Med. Con. 2021;1(1):83–86

Headache Medicine Connections

The Official Journal of the World Headache Society

Section 16 : Horizontal Group 16, Syndrome of Oral Pain (SyOrP)

Section Lead: Pravin Thomas

ARTICLE INFO

Article history:
Received 01.08.2021
Accepted 05.08.2021
Published 20.08.2021

https://doi.org/10.52828/hmc.v1i1.classifications

ABSTRACT

Syndrome of oral pain includes any pain originating from the oral cavity. The pain is commonly due to dental caries but several oral structures may be affected, with various etiologies ranging from causes such as aphthous ulcers to oral malignancies. This is sometimes included as orofacial pains when it includes the face. WHS-MCH1 has a section dedicated to facial pains and while we do know that there may be overlap, this section deals with oral pain only. The oral cavity starts from the lips and extends to the posterior fauces. The structures contained within are the teeth, gums, oral mucosa, tongue and the palate. These are innervated by a dense network of nerves- the trigeminal nerve, glossopharyngeal nerve, vagus nerve. Pain may be caused by lesions affecting the lips, salivary glands, oral mucosa, gingiva, periodontium or the pulp of the teeth. In certain cases, the pain from other causes such as pharyngeal or laryngeal pain, stimuli arising from the muscles of mastication, muscles of the floor of the mouth such as digastrics, mylohyoid can be perceived as pain arising from the teeth, gums, mandible or the buccal mucosa [(1)]. Muscle pains are covered in the syndrome of facial pains and neuralgias are covered in the syndrome of neuralgias.

Keywords: Oral pain; Orofacial; Dental; Dentoalveolar; Gingival; Pulp; Periodontal; Salivary gland; Lingual

1 CLINICAL FEATURES, MECHANISMS AND ASSOCIATED CONDITIONS

1.1 Pain arising from the Lips

1. Infection
    (a) Herpes labialis
    (b) Candida
2. Inflammation
    (a) Granulomatous cheilitis
    (b) Exfoliative cheilitis
    (c) Cheilitis simplex
    (d) Eczematous cheilitis
    (e) Drug induced cheilitis
    (f) Exfoliative cheilitis
    (g) Cheilitis glandularis
    (h) Angular cheilitis
    (i) Actinic cheilitis

1.2 Pain arising from the oral mucosa

1. Epithelial lesions
    (a) Erosion: Superficial mucosal epithelial cell loss
    (b) Ulcer: Deeper than erosion, with a base in submucosa
    (c) Vesicles
2. Adjacent structure involvement
    (a) Dentoalveolar pain
    (b) Underlying muscle
    (c) Periodontal disease
    (d) Periapical disease

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3. Etiologies
    (a) Infection
        i. Bacterial: Treponema pallidum, Neisseria gonorrhoeae, Selenomonas, B. melaninogenicus sp. intermedius and Fusobacterium sp [(2)], mycobacterium tuberculosis.
        ii. Viral: Herpes simplex virus, varicella zoster virus, human papillomavirus, cytomegalovirus, coxsackievirus, human immunodeficiency virus
        iii. Fungal: pseudomembranous candidiasis
    (b) Inflammation
        i. Chemotherapy
        ii. Autoimmune: Pemphigus, mucous membrane pemphigoid, Sjögren's syndrome
        iii. Hypersensitivity reaction: oral lichenoid drug reaction (OLDR)
        iv. Endocrine: hypothyroidism, diabetes mellitus, epulis of pregnancy
        v. Nutritional: deficiency of iron, vitamin B complex, zinc, folate
        vi. Blood dyscrasias: anaemia, gammopathies, haematinic deficiencies, leukaemia, myelodysplastic syndrome, neutropenia and other white cell dyscrasias
        vii. Gastro-oesophageal reflux disease
        viii. Miscellaneous: dermatitis herpetiformis, epidermolysis bullosa, linear IgA disease, and chronic ulcerative stomatitis
    (c) Tumour
        i. Primary: Squamous cell carcinoma
        ii. Secondary: metastatic deposits
    (d) Trauma
        i. Hot foods or drinks
        ii. Tooth brushing or flossing
        iii. Mandibular, maxillary or dentoalveolar fracture
        iv. Tooth root fracture
        v. Poorly fitting dentures
        vi. Over-erupted dentition
        vii. Parafunctional habits: habitual chewing
        viii. Bites due to dystonia or seizure
        ix. Surgical: Thermal injuries during the use of electrocauterization, surgical laser
        x. Chemical injuries: disinfectants, dental materials

1.3 Pain arising from the gingiva

1. Etiologies
    (a) Infection
        i. Bacterial: Treponema pallidum, Neisseria gonorrhoeae, Selenomonas, B. melaninogenicus sp. intermedius and Fusobacterium sp, mycobacterium *tuberculosis*.
        ii. Viral: Herpes simplex virus, varicella zoster virus, human papillomavirus, cytomegalovirus, coxsackievirus, human immunodeficiency virus, ECHO virus, enteroviruses, Epstein-Barr virus.
        iii. Fungal: Candida albicans, mucormycosis, aspergillosis, histoplasmosis, blastomycosis and paracoccidioidomycosis
    (b) Inflammation
        i. Radiation
        ii. Chemotherapy
        iii. Autoimmune: Pemphigus, mucous membrane pemphigoid, recurrent aphthous stomatitis, oral lichen planus, erythema multiforme, Sjögren's syndrome, Behçets disease, graft versus host disease, lupus erythematosus (systemic or discoid type), erythema migrans, Crohn's disease, ulcerative colitis and coeliac disease.
        iv. Hypersensitivity reaction
        v. Endocrine: hypothyroidism, diabetes mellitus
        vi. Nutritional: deficiency of iron, vitamin B complex, zinc, folate
        vii. Blood dyscrasias: anaemia, gammopathies, haematinic deficiencies, leukaemia, myelodysplastic syndrome, neutropenia and other white cell dyscrasias
        viii. Gastro-oesophageal reflux disease
    (c) Tumour
        i. Primary: Squamous cell carcinoma
        ii. Secondary: metastatic deposits
    (d) Trauma
        i. Mechanical
        ii. Surgical: Thermal injuries occur during use of electrocauterization and surgical laser
        iii. Chemical injuries: disinfectants, dental materials

1.4 Pain arising from the salivary glands

1. Etiologies
    (a) Infection
        i. Bacterial: Staphylococcus
        ii. Viral: mumps, HIV, CMV
    (b) Inflammation
        i. Autoimmune: Sjogren's syndrome
        ii. Hypersensitivity: Graft versus host disease
    (c) Obstruction
        i. Sialolithiasis
        ii. Mucus plug
        iii. Space-occupying lesion
    (d) Traumatic
    (e) Radioiodine ablation therapy

1.5 Dental Pain[3]

1. Etiologies of pulpal pain
    (a) Enamel crack
    (b) Dentine exposure
    (c) Hypersensitivity and central sensitisation
    (d) Abrasion
    (e) Trauma: Fracture of crown, root, root cementum, dentin
    (f) Developmental: amelogenesis imperfecta, dentinogenesis imperfecta, hypomineralization or hypomaturation of enamel
    (g) Dental procedures: Root canal treatment, temporary filling, restoration, prosthodontic replacement
    (h) Pulpitis: Reversible and irreversible
    (i) Cervical root resorption
    (j) Systemic: sickle cell anemia
2. Etiologies of periodontal pain
    (a) Inflammation
    (b) Trauma
    (c) Hyperocclusion
    (d) Hypermobility of tooth
    (e) Postoperative
    (f) Apical periodontitis
    (g) Extraradicular infection: Actinomyces and Propionibacterium
    (h) Plaque-induced
    (i) Haematological: acquired neutropenia, leukaemia
    (j) Genetic: leukocyte adhesion deficiency syndromes, Papillon–Lefèvre syndrome, Chediak–Higashi syndrome, hypophosphatasia, histiocytosis, familial neutropenia, glycogen storage disease, infantile genetic agranulocytosis, Down syndrome, Cohen syndrome, Ehler–Danlos syndrome (types IV and VIII)
    (k) Peri-implantitis

1.6 Lingual pain[4]

1. Etiologies
    (a) Infection
        i. Bacterial: mycobacterium tuberculosis, syphilis, scarlet fever
        ii. Viral: Human herpesvirus 4, Epstein-Barr virus causes hairy leukoplakia in immunocompromised
        iii. Fungal: pseudomembranous candidiasis, hyperplastic candidiasis, median rhomboid glossitis
    (b) Inflammation
        i. Recurrent aphthous stomatitis
        ii. Autoimmune: Pemphigus
        iii. Hypersensitivity reaction: lichenoid reaction
        iv. Nutritional: deficiency of iron, B12, niacin, riboflavin
    (c) Tumour
    (d) Primary: Squamous cell carcinoma
    (e) Secondary: metastatic deposits
    (f) Trauma
        i. Thermal
        ii. Physical
        iii. Chemical

2 HORIZONTAL AXIS GROUPS WHICH MAY BE INTERLINKED

Table 1: Horizontal groups linked to syndrome of migraine

ID	Abbr	Syndrome	Linked?
HG1	SyM	Syndrome of Migraine	
HG2	SyTAC	Syndrome of Trigeminal Autonomic Cephalalgias	✓
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HG4	SySrH	Syndrome of Sleep-related Headaches	
HG5	SyEnvH	Syndrome of Environment-related Headaches	
HG6	SyTrH	Syndrome of Traumatic Headaches	✓
HG7	SyVH	Syndrome of Vascular Headaches	
HG8	SyCDH	Syndrome of CSF Dysregulation Headaches	
HG9	SyInfH	Syndrome of Infection-related Headaches	✓
HG10	SyHCH	Syndrome of Hormone and Chemical-related Headaches	✓
HG11	SySH	Syndrome of seizure- related headaches	
HG12	SyFP	Syndrome of Facial Pain	✓
HG13	SyNP	Syndrome of Neck Pain	
HG14	SyOcP	Syndrome of Ocular Pain	
HG15	SyEP	Syndrome of Ear Pain	
HG16	SyOrP	Syndrome of Oral Pain	
HG17	SyNeu	Syndrome of Neuralgias	✓
HG18	SyWEH	Syndrome of Worst Ever Headache	✓

ID =Identifier / Serial number, Abbr =Abbreviation, Linked? =check mark / tick mark denotes links between horizontal groups

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Headach. Med. Con. 2021;1(1):87–89

Headache Medicine Connections

The Official Journal of the World Headache Society

Section 17 : Horizontal Group 17, Syndrome of neuralgias (SyNeu)

Section Lead: Pravin Thomas

ARTICLE INFO

Article history:
Received 01.08.2021
Accepted 05.08.2021
Published 20.08.2021

https://doi.org/10.52828/hmc.v1i1.classifications

ABSTRACT

Neuralgic pain is a syndrome in which the pain is located in the distribution of a particular nerve. They are described as sharp, shooting, burning or cold sensation occurring in paroxysms. They are short lasting. Persistent burning pains, tingling and sense of swelling and sensory loss in the distribution of the nerve are associated with painful neuropathies. Cutaneous sensory nerves of the head and neck as well as cranial nerves can cause neuralgias. Some patients may have a genetic predisposition to demyelination or nerve hyperexcitability. Pathologies affecting cranial nerves like glossopharyngeal, trigeminal, vagus, facial and branches of upper cervical nerves can manifest as both neuralgia and neuropathic pain in the head, neck and facial regions [(1)].

Keywords: Neuralgia; Trigeminal neuralgia; Glossopharyngeal neuralgia; Occipital neuralgia; Numb chin syndrome; Nervus intermedius neuralgia

1 CLINICAL FEATURES, MECHANISMS AND ASSOCIATED CONDITIONS

Several cases of neuralgic pain may be related to a vascular loop leading to ephaptic transmission which manifest as paroxysmal pain in the distribution of the nerve. When metastatic or lymphoma infiltration occurs in the nerve, ephaptic transmission leads to pain the region innervated by the nerve.

1.1 Trigeminal neuralgia

Is characterized by pain along the V1, V2 or V3 distribution of the trigeminal nerve. They present as sharp stabs of pain lasting usually less than 120 seconds. The pain is triggered by stimuli that activate the sensory or motor or divisions of the trigeminal nerve, such as touching the face or applying make-up, talking, chewing, brushing the teeth, shaving or cold wind blowing on the face. Patients are mostly asymptomatic between the paroxysms. During this refractory period even if there is an attack, it is usually mild. Sometimes there is a series of paroxysms that usually last less than an hour. Some patients develop a background pain between the attacks and this may even be continuous. Unless there is a neuropathy, trigeminal neuralgia alone does not present with sensory loss. However subclinical sensory deficits may be demonstrated with specialised tests [(2)]. The right trigeminal nerve is often more involved compared to the left. The V2 (maxillary) and V3 (mandibular) divisions of the trigeminal are more affected than the V1 (ophthalmic) division [(3)]. Bilateral trigeminal neuralgia is uncommon and should raise suspicion of conditions like multiple sclerosis [(4)]. V1 trigeminal neuralgia may present with mild autonomic symptoms like redness of the eye or tearing. However prominent autonomic symptoms are more likely to be a trigeminal autonomic cephalalgia. Trigeminal neuralgia may result from compression by blood vessels. Usually it is the superior cerebellar artery, but other vessels such as the anterior inferior cerebellar artery or veins may be the culprits. The trigeminal nerve is particularly vulnerable to injury at the root entry zone which is the first few millimetres where it enters the pons [(3)]. Vascular compression may cause focal demyelination which in turn results in trigeminal nerve hyperexcitability [(4)].

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Painful trigeminal neuropathy can be caused by inflammation, infection, trauma, neoplasm or metabolic insults. Iatrogenic trauma to nerve branches caused by dental procedure, salivary gland biopsy, or face-lift may result in mental neuropathy, inferior alveolar neuropathy or infraorbital neuropathy, respectively. The ganglion, nerve root or the entire nerve may be injured after avulsion injuries, chemical or radiofrequency ablative procedures for trigeminal neuralgia and surgical trauma.[1].

1.2 Numb chin syndrome

Isolated mental or inferior alveolar neuropathy may be the first symptom of an orofacial or systemic malignancy[5].

1.3 Glossopharyngeal Neuralgia (IX Nerve)

Characterized by intermittent, lancinating pain involving the pharynx, tonsillar fossa, posterior tongue, the angle of the jaw and ear. It may be provoked by coughing, yawning, swallowing and even talking. Attacks usually last between 2 seconds and 2 minutes[6].

Commonly due to inflammation, entrapment or compression of glossopharyngeal nerves[7]. Vagal symptoms such as bradycardia, syncope, hypotension, syncope leading to seizures, and even cardiac arrest may occur during an attack of glossopharyngeal neuralgia[6]. This is caused by neurovascular compression of the combined glossopharyngeal-vagal complex most often by the posterior inferior cerebellar artery and less commonly by the anterior inferior cerebellar artery or the vertebral artery[8]. Apart from compression any source of irritation, or infiltration along the glossopharyngeal nerve pathway by demyelinating lesions; oropharyngeal, laryngeal or skull base tumours; parapharyngeal abscess); carotid sheath trauma; or elongated/calcified styloid processes (Eagle syndrome) can cause pain[6].

1.4 Neuralgia of Superior Laryngeal nerve (SLNN)

Paroxysms of unilateral lancinating pain radiating from the side of the thyroid cartilage or posterolateral thyrohyoid space to the neck, angle of the jaw and occasionally to the ear. As the superior laryngeal nerve is quite superficial, any regional inflammation or local trauma may cause localised neuritis, resulting in throat pain. Displacement or stretch of the nerve as may occur with head movement or swallowing may precipitate the pain. Some patients experience pain on swallowing. Straining the voice may also trigger pain in some patients[9]. Point tenderness may be elicited in SLNN and also in carotidynia but in carotidynia it is located more lateral, over the carotid bifurcation. Patients will often present with throat pain, odynophagia, dysphagia, and anterolateral neck pain. Many patients have a history of tonsillectomy, with could possibly have resulted in scarring of the pharyngeal wall with involvement of the peristyloid tissue and glossopharyngeal nerve[10]. Palpation of the prelaryngeal muscles may elicit tenderness or tightness bilaterally, sometimes with nodularity, at the level of the anterior thyrohyoid space in patients with muscle tension dysphonia. However SLNN-associated pain is located farther posterior on the thyrohyoid membrane and is generally unilateral.

1.5 Occipital Neuralgia

Paroxysmal shooting pain in the distribution of the greater occipital, or third occipital nerves. This may be caused by irritation or compression of the greater occipital nerve or even the C2 spinal nerve[11]. There may be localised tenderness or trigger point, associated dysesthesia and/or allodynia. Occipital neuralgia can also be the result of lesions of the upper cervical cord, such as demyelination and cavernous malformations[12,13].

1.6 Raeder's Syndrome (Raeder's Paratrigeminal Syndrome

This is associated with a postganglionic, painful Horner's syndrome. Multiple cranial nerves can be affected in the parasellar region. They may also be associated with lesions such as metastatic tumours within the middle cranial fossa[14].

1.7 Nervus intermedius neuralgia

Pain in the auditory canal which occasionally radiates to the parieto-occipital region, or just behind the ear lasting for a few seconds. Similar to trigeminal neuralgia, it can be precipitated by touching the ear canal or the preauricular region. Even cold wind over the posterior wall of the auditory canal or periauricular region can precipitate pain and may be accompanied by a disorder of abnormalities of lacrimation, salivation or taste[15].

Inflammations and infections of the facial nerve and may be followed by nervus intermedius neuralgia, example, just after Bell's palsy or Ramsay Hunt syndrome[16].

1.8 Neck tongue syndrome (NTS)

Sudden neck movements can precipitate paroxysms of intense pain in the cervical or occipital areas associated dysesthesia of ipsilateral tongue. The most likely explanation is a temporary subluxation of the lateral atlantoaxial joint. The subluxation results in the ventral ramus of C2 impacting the articular processes on rotating the head[17].

The first three cervical spinal (C1–C3) nerves relay pain signals from the cervical structures to the trigeminocervical nucleus, which allows the bidirectional referral of painful sensations between the neck and trigeminal sensory receptive fields of the face and head[18]. Thus, 'cervicogenic headache' may result in facial pain. The afferent fibres from

the lingual nerve anastomose with the hypoglossal nerve and return to the C2 ventral ramus through the cervical plexus. In NTS, lingual pseudoathetosis may also occur and is presumed to be due to lingual deafferentation [19].

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HG8	SyCDH	Syndrome of CSF Dysregulation Headaches	
HG9	SyInfH	Syndrome of Infection-related Headaches	✓
HG10	SyHCH	Syndrome of Hormone and Chemical-related Headaches	
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HG13	SyNP	Syndrome of Neck Pain	✓
HG14	SyOcP	Syndrome of Ocular Pain	✓
HG15	SyEP	Syndrome of Ear Pain	✓
HG16	SyOrP	Syndrome of Oral Pain	✓
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HG18	SyWEH	Syndrome of Worst Ever Headache	✓

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Headach. Med. Con. 2021;1(1):90–99

Headache Medicine Connections

The Official Journal of the World Headache Society

Section 18 : Horizontal Group 18 - Syndrome of Worst Ever Headaches (SyWEH)

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ARTICLE INFO

Article history:
Received 01.08.2021
Accepted 05.08.2021
Published 20.08.2021

https://doi.org/10.52828/hmc.v1i1.classifications

ABSTRACT

This group characterised by excruciating headaches that stands out from any previously experienced headaches because of its increased severity. In broad terms, the worst ever headache can be divided into thunderclap and non-thunderclap varieties. "Thunderclap nature" is sometimes added to this headache syndrome as an adjective reflecting the rapidity to which it reaches its maximum intensity. Some thunderclap headache presentations may involve multiple or recurrent thunderclap episodes. Theoretically any nociceptive aetiology from the neck and above including the common headaches like migraine could present with the worst ever headache. While some entities only rarely present in a thunderclap manner, other disorders do so commonly. In some of the thunderclap variety headaches, the aetiology is not evident and they have been historically categorized as idiopathic, but it reflects just one end of this spectrum of disorder.

Keywords: Worst ever headaches; thunderclap headaches; Non thunderclap headaches; Subarachnoid Hemorrhage; Reversible cerebral vasoconstriction syndrome; Cerebral venous sinus thrombosis; Cervical artery dissection; Hypertensive emergency; Spontaneous intracranial hypotension; Pituitary apoplexy; Valsalva headaches; Cough headache

1 CLINICAL FEATURES, MECHANISMS AND ASSOCIATED CONDITIONS

1.1 Subarachnoid Haemorrhage (SAH)

SAH is usually characterised by sudden severe headache that is at maximum intensity at the onset.[1] But the intensity of headache can also be moderate. Any acute-onset headache regardless of its severity or prior history of headaches in a patient, particularly if persistent, should prompt the diagnosis of Subarachnoid haemorrhage (SAH).[2]

Headache in aneurysmal subarachnoid haemorrhage was not instantaneous in about half of the patients and was found to take up to minutes in about one-fifth of the cases in a study.[3]

Additional features include altered level of consciousness, cranial neuropathies, focal weakness, and meningism.[2]

Pain is thought to be due to the chemical irritation of the blood on the meninges and in the subarachnoid space. There is associated infiltration of immune cells, immune activation, and inflammatory cytokines, which have been suggested as the mechanism of headache.[4,5]

Headaches also occur due to post subarachnoid haemorrhage hypertension episodes, as may the evolution of cerebral vasospasm and hydrocephalus which may develop as a consequence of SAH.[5]

A significantly higher pain score is seen in those who develop cerebral vasospasm early after SAH.[5]

Febrile episodes after SAH has infection as a cause in about 75% of the patients but could have a central or neurogenic cause in the rest and has increased risk of symptomatic vasospasm and a poor outcome.[6]

A well-known complication of aneurysmal subarachnoid haemorrhage is the occurrence of seizures and epilepsy but the incidence of post-surgical epilepsy following ruptured intracranial aneurysms varies between 1% and 27.5%.[7]

Reversible blindness following severe headache in SAH due to vitreous haemorrhage can be recognized only with a very high index of suspicion.[8]

Severe back pain, root pain, or symptoms and signs of spinal cord dysfunction along with thunderclap headache all points towards a spinal cause of SAH, such as a spinal arteriovenous malformation, aneurysm, or haemangioma.[9]

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Venous rupture in the cisterns around the midbrain is the possible cause for the nonaneurysmal peri mesencephalic SAH, which has headache which occurs in minutes rather than seconds and the loss of consciousness is rare, and focal neurologic abnormalities are generally not found. [9]

SAH causes cognitive decline and fatigue with impaired daily and social activities almost equally. However, it is thought that aneurysmal SAH is a more debilitating disorder than that of perimesencephalic SAH.

Memory loss, especially declarative and non-declarative memory, executive function and language are affected. Long term cognitive impairment including dysfunctional cognitive flexibility is observed in patients of SAH. Patients find it difficult to resume previous job and lead a fully functional life. Inflammatory response to bleeding and pathological involvement of hypothalamus, frontobasal, temporal areas of brain, and damaged neural connectivity are implicated for symptoms. Along with cognitive impairment, anxiety, depression and fatigue is observed in aSAH. [10,11]

Memory impairment is seen within three months of an SAH. However, memory impairment can be as long as 6 months. Verbal memory is most frequently affected in 15 to 60% of patients. Visual memory gets affected in 15 to 50 % of patients. Factors responsible for verbal and visual memory loss are old age, illiteracy, rupture of aneurysm in anterior circulation, thick arachnoid bleed. Frontal lobe dysfunction detected in aSAH patients include impairment in planning, problem solving, inhibition, & cognitive flexibility. [12]

Rupture of internal carotid and middle cerebral artery causes aphasic, spatial and memory impairment. Anterior communicating artery (ACoA) rupture causes personality changes along with memory impairment. In a large number of patients rupture of ACoA can cause intellectual deterioration, severe amnesia which includes symptoms like confabulation; difficulty to learn concepts, temporal sequencing to the extent that patients cannot reach premorbid functioning level. [13] Statistically significant number of patients showed recovery from memory deficits after a couple of years (1 to 4 years) among patients who were surgically treated for ACoA rupture. Short and long term verbal – mechanical and visual memory recovered in large number of patients. Numerical and working memory recovered. Long term deficits in verbal – logical memory were found. [14]

1.2 Reversible Cerebral Vasoconstriction Syndrome

It is associated with recurrent, sudden-onset and severe worst ever headaches occurring often over days to weeks [15]

RCVS headaches have an explosive onset followed by a monophasic course usually without any new complications after 4 weeks which helps differentiate this clinical entity from the rarer primary CNS angiitis. [16]

It is characterised by a typically bilateral pain of usually posterior onset followed by a diffuse headache with a severe intensity, sometimes excruciating, with agitation, shouting, often associated with vomiting, nausea, phonophobia and photophobia which subsides in hours and recur over days. [16]

In RCVS, some deficits begin progressively and successively including transient ischemic attacks over a few minutes, and can include positive visual and/or sensory symptoms, mimicking migraine aura and may evolve into persistent focal deficits revealing a stroke. [16]

The migraine sufferers who had suffered RCVS distinguished the thunderclap headaches as entirely different from their usual migraine headaches. [16]

Trigger factors like sexual activity, straining, sudden emotion, exertion, coughing, sneezing, urinating without effort, bathing or showering, or sudden bending down is found in majority headache episodes associated with RCVS. [16]

Generalized tonic-clonic seizures are reported in up to 20% of patients, recurrent seizures are rare. [16]

Pregnancy, postpartum state, exposure to medications and illicit drugs, hypercalcaemia, pheochromocytoma, exercise and sexual intercourse are the associations found in RCVS. Thus history from the patient aids in diagnosing RCVS headaches. [17]

Majority of headaches in RCVS occur in the postpartum period or post exposure to vasoactive substances and are generally self-limited. [15]

Transient dysregulation of cerebral vascular tone, leads to multi-focal arterial constriction and dilation. The catecholamines, endothelin-1, calcium, serotonin, nitric oxide and prostaglandins are involved in the pathophysiology of vasoconstriction in RCVS. [15]

Vascular receptor activity and sensitivity are dependent on vascular tone. The alteration and reversible nature of RCVS is due to the sudden or evoked central vascular discharge and contribute to the acute severe headaches. [15]

Most of the patients with RCVS recover without sequelae. Pathophysiology of RCVS is not clear, however sympathetic overtones play a role. Potential complications of RCVS are fatal and alarming. [18] A rare case where grief caused severe headache with RCVS affirms the role of sympathetic overtone as a causal factor in RCVS. [19]

In some patients clinical presentation of RCVS is cognitive dysfunction, where headache is one of the symptoms but is not so severe.

Though thunderclap headache is a hallmark of clinical presentation of RCVS some patients don't fall under the category of 'worst ever headache' or thunderclap headache but instead their major clinical presentation is that of cognitive impairment, seizure, focal neurological deficit, coma, etc. along with probable presence of headache. RCVS is diagnosed with radiological investigations like angiograms among such patients. [20]

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RCVS causes distinct cognitive impairments and dementia because of lower cerebral blood flow which may recover after 1 to 4 years.

Serotonin syndrome and serotonergic antidepressants can trigger RCVS headache. [21]

Cognition related conditions like acute stress disorder, physiological situations exacerbating stress and sympathetic over activity, stress inducing conditions like pregnancy/high emotional mental states, grief, post-traumatic stress disorder, high altitude, substance abuse trigger RCVS. Serotonergic and sympathetic pathways with catecholamine surge are implicated for RCVS headache. Thunderclap headache with cognitive impairment and memory deficit of sudden onset indicate RCVS. [22]

Combination of serotonergic agent like fluoxetine and antihistamine like loratadine causes RCVS presenting with severe headache. SSRI, antihistamine, marijuana together have the potential to cause RCVS induced severe headaches. [23]

A rare case report of spinal cord injury resulting in quadriplegia revealed that use of midodrine, vasospastic agent, alpha adrenergic agonist caused RCVS with thunderclap headache when Foley's catheter was flushed. Massive sympathetic response was caused by noxious stimuli (manipulation of Foley's catheter) resulting in cerebral vasoconstriction giving rise to thunderclap headache with RCVS. [24]

1.3 Cervical artery dissection

Headache due to vertebral and carotid artery dissection ranges from migraine-like or hemicrania-like headaches to severe thunderclap headaches.

New onset pain of the head and neck and occasional associated horner's syndrome is the commonest presentation of a dissection, especially the extracranial type. [25]

New unilateral headache especially in the anterior head region along with oculosympathetic paresis is a pointer towards internal carotid artery dissection. One sided headache with delayed focal cerebral ischemic events is seen in internal carotid artery dissection. [25]

Dysgeusia, amaurosis fugax, pulsatile tinnitus, and cranial nerve pain are seen but cranial nerve palsies are less common. [25]

Dysgeusia in internal carotid artery dissection is indicative of chorda tympani or a glossopharyngeal nerve involvement as seen in case reports. [26]

The haemorrhage into the carotid wall in carotid dissection, could lead to intimal injury and these hematomas may form as the dissection progresses into the media, which can further occlude the lumen leading to amaurosis fugax, transient ischemic attacks and strokes. [27]

The sound of non laminar blood flow being transmitted to the inner ear is probably the mechanism for the pulsatile tinnitus in case of cervical artery dissection. [28]

Direct or indirect neck trauma may cause cervical artery dissections. [25]

Vertebral artery dissection pain is commonly a constant aching, pressing or sharp in quality pain rather than pulsating pain. It can be either ipsilateral or bilateral and typically distributed over the posterior head region interpreted as muscle contraction headache. [25]

Frontotemporal headaches and orbital, facial, and ear pain in patients with ICAD supports the observation that stimulation of the carotid artery bifurcation can produce pain referred to these areas. [25]

Half of patients with vertebral artery and a quarter of patients with carotid artery dissections have neck pains associated with the episodes. [29]

Predominantly occipital distribution of headache in vertebral dissection is explained by the upper cervical nerves innervating the vasculature of the posterior fossa. [30]

Isolated thunderclap headache as the initial manifestation along with delayed stroke can be a presentation of vertebral artery dissection. [31]

Carotid artery is surrounded and accompanied by cervical sympathetic plexus of nerves and this supplies the intracranial vasculature, the pupil and the levator palpebrae oculi. The skin over the face is supplied by the trigeminal nerve and that of the neck is innervated by the second and third cervical nerves. The headache occurrence in carotid dissection is a classic example of referred pain. [31]

Visual phenomena of migraine are rarely seen at onset and have a characteristic march and usually last less than 1 hour, but these features can occur in a carotid artery dissection. The mechanisms causing this are embolism to the ophthalmic artery and its retinal branches, retinal hypoperfusion, or embolism to a foetal posterior cerebral artery with involvement of post-chiasmal visual pathways. Another mechanism suggested is the ischemia to the retina resulting in transient depolarization of nerve cells which corresponds to the positive visual phenomena in carotid dissection. [32]

Carotid artery morphological variations (CAMV) are implicated for mild cognitive impairment mainly causing attention deficit. CAMV causes low cerebral perfusion leading to chronic cerebral ischemia which is responsible for MCI. MCI was assessed by Montreal cognitive assessment scale. [33]

Vertebral artery dissection deteriorates quality of life leading to post-traumatic stress symptoms, depression, anxiety. [34]

1.4 Cerebral venous sinus thrombosis

Cerebral venous sinus thrombosis (CVT) has headache as a predominant symptom with varying character with associated neurological signs.

It is usually characterised by subacute onset headache with rapid worsening and variable severity but sometimes

can mimic subarachnoid haemorrhage, migraine, and idiopathic intracranial hypertension. [35]

Headache of gradual subacute onset tending to be persistent, but at times it can also be initially intermittent, worsening over time and one tenth can have thunderclap headaches. [36]

CVT headache usually becomes refractory to common analgesics and may persist through the night. It is exacerbated by physical activity or valsalva maneuver and may get worsened with recumbency due to raised intracranial pressure. Nausea and/or vomiting, phonophobia are the most frequent associations. [36]

Sigmoid sinus thrombosis can present with unilateral tinnitus or unilateral headache mimicking migraine with or without aura or cluster headache. [36]

All of the processes that determine the inflammation, distension, or traction of any of the intracranial also sensitive structures can result in headaches. [36]

Headache in patients of CVT without intracranial hypertension, was suggested to be due to an irritation of the nerve fibres in the walls of the occluded sinus. [36]

Intracranial hypertension secondary to the obstruction of large venous sinus has a clinical picture as that of symptomatic intracranial hypertension.

Distension of veins and sinuses due to venous sinus occlusion caused by thrombosis determines the distension of pain-sensitive structures of both veins and sinuses. Venous infarction due to obstacle to the blood reflux causes cortical hematic infarcts and this results in subsequent cortical irritation and inflammation. [36]

Cerebral venous thrombosis [CVT] causes significant cognitive impairment in some cases disclosing the score of MMSE less than 17/30. Deeper the CVT more and long lasting is the cognitive impairment. Cognitive impairment included impairment of memory, language, visuospatial orientation, and constructional ability. Cognitive impairment persists longer in around 1/3rd of cases of CVT to attribute failure to return to work. Direct sinus involvement and persistent parenchymal lesion were implicated for cognitive impairment. [37]

1.5 Spontaneous intracranial hypotension

Postural headache briskly eased by lying down but worsened in the upright position caused by low cerebral spinal fluid pressure or volume and rarely can be of thunderclap nature.

Generalised throbbing headaches which are frontal or occipital in nature which can be associated with neck pain and may include neck stiffness, nausea and vomiting, horizontal diplopia, blurred vision, tinnitus or altered hearing. [38]

Postural nature is due to CSF leak and loss through the dura mater breach which results in downward displacement of the brain due to gravitation and causes traction or distortion of pain sensitive structures around the brain. Reflex homeostatic dilation of the cerebral veins and venous sinuses may contribute to pain. [39]

Orthostatic headaches are more common with spinal CSF leakage as compared to cranial CSF leakage and suggests an increase in compliance at the lower end of CSF spinal space whenever there is a spinal CSF leak thus the lack of equilibrium in the craniospinal elasticity precipitates orthostatic headaches. [40]

Patients with underlying weaknesses like connective tissue disorders may find that minor trauma results in dural tear and subsequent CSF leak. The diagnosis becomes more difficult when the initial orthostatic component after a few months often changes to daily headaches that occur in the second part of the day without orthostatic symptoms. [38]

Headache onset may be acute, mimicking a subarachnoid haemorrhage. There are even reports of neck pain, photo or phonophobia, diplopia, parkinsonism and even coma along with this condition. [39]

Patients with clinical and radiographic features of intracranial hypotension and who also have a skull base CSF leak should be evaluated to look for the presence of a spinal CSF leak as well, because CSF otorrhoea and rhinorrhoea do not cause positional headaches. [41]

Spontaneous intracranial hypotension [SIH] is commonly caused by CSF leak in spine leading to downward displacement of brain. SIH causes progressive cognitive impairment, clinical picture of frontotemporal dementia.

SIH should be suspected in patients with dementia, behavioral changes and headache. This is significant because it is one of the treatable cause. [42]

1.6 Headache with severe hypertension

Headaches in hypertensive encephalopathy are bilateral occipital and pulsating, and occurs due to persistent blood pressure elevation accompanied by symptoms of encephalopathy such as confusion, lethargy, visual disturbances or seizures and improves as soon as the blood pressure normalises. A potential early presentation of hypertensive encephalopathy is the thunderclap headaches. [43]

A sudden rise in blood pressure causes disruption of cerebral vascular auto-regulation, especially in the posterior cerebral vasculature, leading to leakage of fluid into the brain parenchyma. [44]

Diffuse vascular constriction caused by humoral factors is the trigger for the hypertensive process and the consequence is vascular endothelial injury and activation of coagulation factors leading to fibrinoid necrosis of the arterioles. High blood pressure impairs the blood brain barrier integrity leading to cerebral hyperperfusion which finally causes brain edema and this sequence of activity results in the clinical presentation of hypertensive encephalopathy. [44]

When hypertension disrupts the brain's auto-regulation, cerebral perfusion and causes infarct or ischemia of cerebral microbleed/ lacunar infarcts/hypertensive encephalopathy,

cognition gets affected. Symptoms similar to dementia are observed. [45]

Hypertensive encephalopathy can present with progressive cognitive impairment only for a couple of months; making physicians misdiagnose the condition. Radiological investigations helped diagnose cerebral lesions; leading to diagnosis of hypertensive encephalopathy. [46]

1.7 Pituitary apoplexy

Acute onset of headache with ophthalmoplegia, altered mental status and diminished visual acuity caused by the sudden haemorrhage or infarction of a pituitary gland. It is an uncommon clinical syndrome.

Severe acute headache with maximum intensity at onset with visual disturbances, nausea, and or vomiting is the characteristic feature of pituitary apoplexy. [47]

Head trauma, pregnancy, hypotension, surgery, anticoagulants, pituitary dynamic testing, hypertension and irradiation are the precipitants for apoplexy. Increased pressure of the intrasellar contents occurs due to rapid enlargement of pituitary. [47]

There has also been reports of status migrainosus like presentation with gradual onset, unremitting throbbing headache with nausea, phonophobia, and mild photophobia of several weeks duration. [48]

Meningeal irritation is caused by dural stretching by mass effect, and extravasation of blood and necrotic tissue into the subarachnoid space. [47] [49]

Pressure increase in sella turcica causes compression of the optic tracts from the superior side, chiasm or nerves and brain stem leading to disorientation. Diplopia is caused by lateral compression of the oculomotor cranial nerves. [50]

Transient hemiplegia secondary to vasospasm of the intracavernous carotid artery can also occur in pituitary apoplexy. [50]

Cognitive dysfunction in patients of pituitary apoplexy does not occur uniformly. Causes of cognitive dysfunction are pressure effects on third ventricle and diencephalic structures, dysfunction of hormonal secretion and treatment modality especially radiotherapy.

Radiotherapy was considered a major factor behind memory loss. Most of the cases showed anterograde memory loss. Most of the patients preserve premorbid IQ. [51]

Cause of significant cognitive impairment in functioning pituitary adenoma is hormonal, i.e. endocrine dysfunction plays a major role in cognitive impairment, which gets fully recovered after surgical intervention. [52]

1.8 Meningitis or meningoencephalitis

This causes an acute and severe holocranial headache, accompanied by other features including those of meningeal irritation, stiff neck, fever, altered mental state, and seizures.

A diagnosis of headache attributed to bacterial meningitis resolves or greatly improves after effective treatment or with spontaneous remission of the infection. Cluster headache developing after meningitis has also been described. [53]

Sometimes a patient referred with thunderclap headache turns out to have meningitis and CSF examination is essential for diagnosis. [9]

Headache is severe, progressive in intensity, usually focal and refractory to analgesia in cases of bacterial abscess.

When the intracranial infection is effectively treated or when it remits spontaneously, but headache persists for months, the diagnosis of chronic post-infection headache is made. [53]

Meningitis is associated with significant cognitive dysfunction in the areas of attention, psychomotor function and memory. Male sex and cranial nerve palsy are risk factors for cognitive impairment. [54]

1.9 Sinusitis

Sinusitis may also cause severe worst ever headaches of frontal location within seconds, especially during air travel when cabin pressures suddenly change. [9]

Extension of the inflammatory material outside the confines of the sinuses (especially sphenoid) resulted in thunderclap headache. Aseptic meningitis or bacterial meningitis or impending cavernous sinus thrombosis can also present with thunderclap headache in the setting of sphenoid sinusitis. [55]

Headache which is worse on standing, bending, movement, or coughing, with periorbital pain can be seen in patients having sphenoid sinusitis. About 50% of patients may have associated fever. Continuously increasing headache, pain and paresthesia in the distribution of trigeminal nerve, photophobia, and eye tearing along with the headache causing sleep interference not relieved by analgesics are the key clinical clues. [56]

Chronic sinusitis is implicated to cause cognitive impairment in the form of lack of attention, deficit in memory, and slowed thinking. [54] Chronic rhinosinusitis is implicated to cause cognitive impairment as a result of deteriorated quality of life, distress of illness and inflammation. [57]

1.10 Colloid cyst of third ventricle

Diffuse, generalized and episodic postural headaches enhanced by activity which raises the intracranial pressure due to CSF flow obstruction by colloid cyst.

Headache is intermittent or episodic, severe and intense, of short duration and located frontally and is relieved by lying down, which is a characteristic which is unusual for headaches caused by intracranial tumors and thus helps differentiate this entity which is a close differential diagnosis. [58]

Frontal and occipital headaches enhanced by activity like coughing, sneezing, defecating, or laughing are observed in this condition. Headache is accompanied by symptoms and signs of raised intracranial pressure, such as nausea, vomiting and rarely papilledema and tinnitus. Adolescents develop personality changes and impaired memory, behavioral disturbances and their school results grows worse and the headache is frequently intensified in the morning hours. A change in the position of the head may alleviate the headache, particularly in adults. [58]

Subtle signs or even lack of symptoms of increased intracranial pressure may prevent a timely diagnosis before the occurrence of deadly complications. [59]

When the cyst is still small, or when it is not yet compressed in Monro's foramen, a change in the position of the head may have a favourable effect on the so-called valve type of CSF flow disturbance. In the presence of a large colloid cyst entirely filling the lumen of the third ventricle, or in a case of compressed cyst, a change in the position of the head has no effect on the significantly decreased or interrupted CSF flow. [60]

Third ventricular colloid cysts should be recognized as a cause of acute neurological deterioration and sudden death as lumbar puncture may hasten death by increasing brainstem compression due to cerebellar tonsillar herniation. [60]

Cognitive impairment is observed in the colloid cyst of the third ventricle when fornix was found to be affected. [61]

1.11 Valsalva headaches

Valsalva headaches can manifest as 'worst ever' headaches. This includes headaches that are triggered by Valsalva maneuver like coughing, sneezing, nose-blowing, laughing, straining and lifting heavy objects.

They are characterised by explosive headaches. Elevated CBF velocities triggered by the Valsalva manoeuvre in symptomatic patients indicate reactive cerebral hyperaemia during the post-straining period which occurs due to the excessive vasodilation as the mechanism. Explosive headaches may be contributed by hyperaemia also. Cerebral autoregulation failure causes exaggerated vasodilation of cerebral vessels provoked by the Valsalva manoeuvre. [62]

Cough headache can be due to raised intracranial pressure if there is posterior fossa CSF obstruction. They may present with occipital headaches. [63]

If there is a Chiari malformation causing obstruction, it results in pressure difference between the ventricles and the lumbar subarachnoid space and displaces the tonsils into the foramen magnum and pain by coughing could therefore be caused by compression on pain-sensitive structures in the arachnoid space or blood vessels surrounding the tonsils. [64] The headaches can last between 1 second to up to 2 hours.

The lesional/symptomatic cough headaches can have a slight delay of seconds before the start of headache. [65]

Patients with migraine may also have cough headache. Protracted period of coughing due to chest infection, the use of drugs like angiotensin converting enzyme inhibitors, or may be due to frequent episodes of migraines that might lead to peripheral sensitisation, with reduced threshold for trigeminal activation. There may also be dysregulatory control of venous tone in the orbital venous plexus, which is dependent on sympathetic fibres carried in the ciliary nerves. The long ciliary nerves which are indirect branches from the first division of the trigeminal and carries both somatic sensory and sympathetic fibers, innervates the frontal part of cranium. Hence headache is most often frontally distributed. [66,67]

Low CSF pressure headaches due to spontaneous intracranial hypotension can also cause cough headaches. [64]

Valsalva manoeuvre can also induce cluster headaches. [68]

Other causes of cough headache include cerebral aneurysm, sphenoid sinusitis and subdural hematoma. Carotid disease can also cause cough headaches. [69,70]

Valsalva headache with underlying cerebral autoregulation failure is associated with minimal cognitive impairment. [71]

1.12 Ischemic stroke

Headache associated with ischemic stroke usually has acute onset headache associated with focal neurologic signs or persistent headache attributed to a past ischemic stroke. [72]

A headache with altered characteristics and a new type of headache are true sentinel headaches causally related to strokes. [73]

In ischemic stroke patients, the exact mechanism of sentinel headache is not established, but embolism is considered to be the most probable cause. Emboli blocks the arteries and affects the vascular endothelium of the brain resulting in liberation of cytokines which causes vasodilation and in addition have proinflammatory effects. This subsequently affect perivascular nerve endings and lead to pain. [73]

Trigeminovascular system's activation in the intracranial vessels seems to be essential for the production of post ischemic stroke headache. [74]

Thunderclap headache may be caused by direct activation of intracranial pain-sensitive structures, especially the cerebral blood vessels. Neuropeptide Y and noradrenaline-containing sympathetic afferents, which modulate vascular tone are present in the proximal portions of the intracranial arteries. [74]

Commonest pattern is a mild to moderate bilateral headache (tension type pattern) which is not associated with nausea, vomiting, photophobia, or phonophobia which improves over time.

The onset headache is more often seen in posterior circulation strokes than in strokes in other vascular territories Headache is more common in major stroke than in minor stroke as well as in cortical than in subcortical lesions and is a rare symptom in lacunar stroke. [75]

The onset of headache on the day the stroke initiated occurred in 87% of the patients, and in the remaining patients, onset occurred between days 2 and 5. The headache mostly behaved in a continuous manner, but decreased in frequency and intensity over the days. [76]

In lacunar infarctions, the headache was described by most patients as having started at the same time as the focal neurologic deficit, and was described as mild, poorly localized, and with a pressure-like pain. [75]

Extensive cerebral infarctions with mass effect and structural herniation, the displacement and compression of pain-sensitive structures such as the meninges and the proximal segment of the intracranial arteries may cause headache. [76]

The edema and haemorrhagic transformation causing mass effect and activation of the trigeminovascular system could be an added pathophysiology for headache in acute ischemic stroke. [72]

The activation of the trigeminovascular system by the cortical spreading depression [CSD] triggered by cerebral ischemia and release of prothrombotic, inflammatory, and excitotoxic substances may play a role. [76]

The central sensitization of nociceptive inputs after stroke may cause persistence of the pain. Organization of the infarction and further structural changes leads to stretching of pain sensitive structures and may also disrupt central pain pathways localized in the brainstem, insula, or somatosensory cortex.

The vertebrobasilar system is more densely innervated by the trigeminovascular system than the carotid system, and this may contribute to this difference of frequency. [76]

Pain arising from supratentorial structures are referred frontally and that arising infratentorially is localized to the occipital regions. [77]

The headache pathophysiology associated with lacunar infarction is probably suggested to be more of inflammatory or neuroexcitotoxic aspect than on mechanical aspects. [75]

The basic atherosclerotic process as well as uncomplicated cerebral infarction are painless. [75]

Prevalence of post-stroke cognitive impairment is quite high. Cognitive impairment impedes recovery of a patient. Hence psychological history & mental state examination need to be optimized. [78]

1.13 Intracerebral hemorrhage

Headache can be ipsilateral but may be holocranial in the presence of hydrocephalus and elevated intracranial pressure. [79]

New-onset headaches occurred in a tenth of the patients and were usually of the tension-type. [80] Additional clinical manifestations of ICH include focal neurologic deficit that develops within minutes to hours. [81]

Headache intensifies when there is rupture of the hematoma into the subarachnoid space and will be associated with neck stiffness and other signs of meningeal irritation [79]

It can be associated with vomiting and also that the patient may have depression. [80,81]

Spontaneous non traumatic ICH is presumably an end result of small vessel diseases which include arteriolosclerosis, lipohyalinosis, and cerebral amyloid angiopathy [81]

The intraparenchymal mass stretches the pain-sensitive vascular, meningeal, and neural structures and as hematoma enlarges there is increase in ICP due to obstruction of CSF flow. Cerebellar hemorrhages are characterised by occipital headaches followed rapidly by vomiting, impaired consciousness, and brainstem, cerebellar or cranial nerve dysfunctions. [79]

Acute severe headaches may also be caused by acute distension of the ventricular system through engorgement of the ventricles with blood under arterial pressure or as acute hydrocephalus produced by obstruction of the aqueductus or of the fourth ventricle as in case of occasional pontine or cerebellar haemorrhages. [82]

The ipsilateral and occasional bilateral location of pain and the increased frequency of headaches in the presence of occipital and cerebellar hematomas may be explained by the trigeminovascular system organization. Location, size of the haemorrhage and rate of evolution determines the occurrence and severity of headache.

Intracerebral haemorrhages commonly occur in Putamen. Putamen is associated with learning, cognitive functions, language, etc., thus intracerebral hemorrhage with headache do have cognitive dysfunctions. [83]

Patients who have psycho-bio-social vulnerability to phobia, acute stress disorder, thyroid disease, obsessive compulsive disorder, bipolar disorder, attention deficit hyperactivity disorder, dependent personality traits, can relatively suffer more from psycho-cognitive dysfunction. Hence it is imperative to ask appropriate questions to elicit psychiatric disorder or to detect traits of psychological aberrations while taking history of patients with the worst ever headache. [84]

Patients who experience the worst ever headache usually accept that 'locus of control' is 'external'; meaning thereby their next attack of headache is neither in their control nor can the doctor predict or control it. Under such conditions the possibility of developing depression or psychiatric disorder is greater in these patients. [85]

2 SYNDROME OF THUNDERCLAP VARIETY OF WORST EVER HEADACHES ARE ASSOCIATED WITH THE FOLLOWING CONDITIONS

1. Subarachnoid haemorrhage
2. Reversible cerebral vasoconstriction syndrome
3. Cerebral venous sinus thrombosis
4. Cervical artery dissection
5. Hypertensive emergency
6. Spontaneous intracranial hypotension
7. Meningitis and Sinusitis
8. Ischemic stroke
9. Intracerebral haemorrhage
10. Pituitary apoplexy
11. Colloid cyst of third ventricle
12. Valsalva headache

3 SYNDROME OF NON-THUNDERCLAP WORST EVER HEADACHES IS A LARGE LIST BUT THE COMMON TYPES SEEN IN PRACTICE ARE

1. Primary headache disorders like migraine, or cluster headaches
2. Meningitis and Encephalitis
3. Ruptured brain abscess
4. Glaucoma
5. Sinus-related headache
6. Systemic infections
7. Stroke or cerebral ischemia
8. Hypertensive disorders
9. Mass lesions
10. Cervical disc disease or arthritis
11. Dental pain
12. Middle ear pathologies
13. Trauma related headaches

4 HORIZONTAL AXIS GROUPS WHICH MAY BE INTERLINKED

Table 1: Horizontal groups linked to syndrome of migraine

ID	Abbr	Syndrome	Linked?
HG1	SyM	Syndrome of Migraine	✓
HG2	SyTAC	Syndrome of Trigeminal Autonomic Cephalalgias	✓
HG3	SyExH	Syndrome of Exertional Headaches	✓
HG4	SySrH	Syndrome of Sleep-related Headaches	
HG5	SyEnvH	Syndrome of Environment-related Headaches	
HG6	SyTrH	Syndrome of Traumatic Headaches	✓
HG7	SyVH	Syndrome of Vascular Headaches	✓
HG8	SyCDH	Syndrome of CSF Dysregulation Headaches	✓
HG9	SyInfH	Syndrome of Infection-related Headaches	✓
HG10	SyHCH	Syndrome of Hormone and Chemical-related Headaches	✓
HG11	SySH	Syndrome of seizure- related headaches	✓
HG12	SyFP	Syndrome of Facial Pain	✓
HG13	SyNP	Syndrome of Neck Pain	✓
HG14	SyOcP	Syndrome of Ocular Pain	✓
HG15	SyEP	Syndrome of Ear Pain	✓
HG16	SyOrP	Syndrome of Oral Pain	✓
HG17	SyNeu	Syndrome of Neuralgias	✓
HG18	SyWEH	Syndrome of Worst Ever Headache	

ID = Identifier / Serial number, Abbr = Abbreviation, Linked? = check mark / tick mark denotes links between horizontal groups

5 TEAM WORKSHARE

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ACKNOWLEDGEMENTS

The authors wish to thank:

1. Dr Madhav Raje for reviewing this classification in its entirety and contributing their expertise through the addition of psychiatry related commentary.
2. Miss Kris Castle for their assistance in compiling and editing of the classification.

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Headach. Med. Con. 2021;1(1):100–106

Headache Medicine Connections

The Official Journal of the World Headache Society

Section 19 : Vertical groups & Horizontal group links

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ARTICLE INFO

Article history:
Received 01.08.2021
Accepted 05.08.2021
Published 20.08.2021

https://doi.org/10.52828/hmc.v1i1.classifications

ABSTRACT

This section is a quick reference tool to link each vertical group with the horizontal groups/syndromes that they may be associated with.
As an example, if a patient presents with headache and dizziness, the clinician can link to all those syndromes which are linked with headaches and dizziness. Then the individual disease entities within the syndrome can be referenced, guiding the clinicians as to what they may be dealing with. This would also help to triage the patient into clinical pathways and referrals.

Keywords: Headache triage; Clinical pathway; Headache referral; Diseases causing headache; Head pain; Face pain; Neck pain

1 VERTICAL GROUPS

1.1 Vertical Group 1 — Headaches associated with Dizziness (HaD)

Dizziness is sometimes difficult for the patient to describe or categorise. For this classification, dizziness includes giddiness, vertigo and feeling of imbalance. Links to horizontal groups: Figure 1

1.2 Vertical Group 2 — Headaches associated with Postural Variation (HaPV)

This includes:

- Headaches which are made worse when the head is parallel to the ground, for example lying flat on a bed or stooping forwards.
- Headaches which are made worse when the head is perpendicular to the ground, example on standing upright.

Links to horizontal groups: Figure 2

1.3 Vertical Group 3 — Headaches associated with Fever (HaF)

Fever includes self-reported and documented fever. Links to horizontal groups: Figure 3

1.4 Vertical Group 4 — Headaches associated with a Metabolic Abnormality (HaMA)

This includes presentations with a documented metabolic abnormality or that which is suspected clinically. Links to horizontal groups: Figure 4

1.5 Vertical Group 5 — Headaches associated with Inflammation (HaI)

This includes either known local or systemic inflammatory diseases or those diagnosed on presentation. Links to horizontal groups: Figure 5

1.6 Vertical Group 6 — Headaches associated with Strokes (HaSt)

This includes headache presenting in a patient with an old or a new stroke. Links to horizontal groups: Figure 6

1.7 Vertical Group 7 — Headaches associated with Seizures (HaS)

This includes headaches in a patient with known seizures or suspected seizures. Links to horizontal groups: Figure 7

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1.8 Vertical Group 8 — Headaches associated with Cognitive or Behavioural Impairment (HaCBI)

This includes problems with memory, speech, mood or personality. Links to horizontal groups: Figure 8

1.9 Vertical Group 9 — Headaches associated with Ophthalmic Involvement (HaOI)

This includes headaches associated with symptoms or signs involving the eye. Links to horizontal groups: Figure 9

1.10 Vertical Group 10 — Headaches associated with Sleep Disorders (HaSD)

This includes headaches associated with lack of sleep, disturbed sleep or excessive sleep. Links to horizontal groups: Figure 10

1.11 Vertical Group 11 — Headaches associated with Intracranial Space-occupying Lesion (HaSoL)

This includes headaches in a patient with a known or suspected tumour or granuloma. Links to horizontal groups: Figure 11

1.12 Vertical Group 12 — Headaches with no associated symptoms (HnAS)

There are no other symptoms or signs to suggest any association. Links to horizontal groups: Figure 12

1.13 Vertical Group 13 — Non-headache symptoms associated with headache disorders (nHS)

These include auras which present without headaches and also non-headache clinical presentation in a patient who also has headaches. Links to horizontal groups: Figure 13

2 SUMMARY TABLE OF VERTICAL TO HORIZONTAL GROUP MAPPING

Figure 14

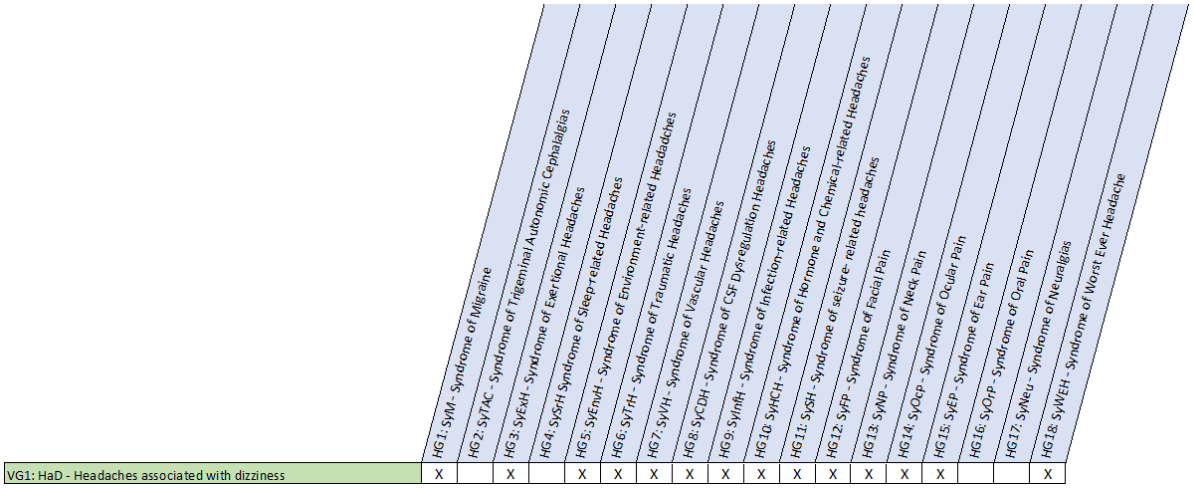


Fig. 1: Horizontal Associations for Vertical Group 1

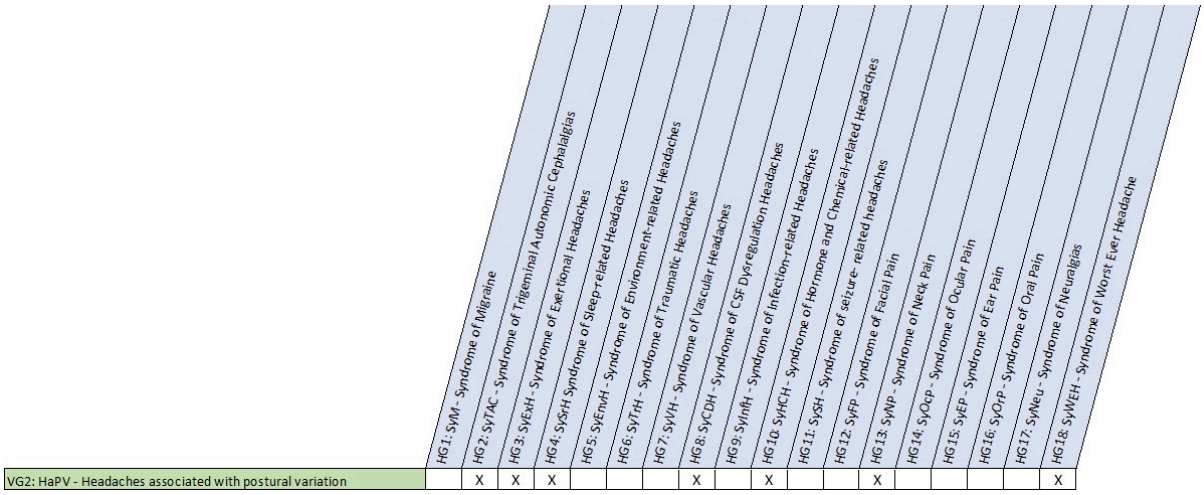


Fig. 2: Horizontal Associations for Vertical Group 2

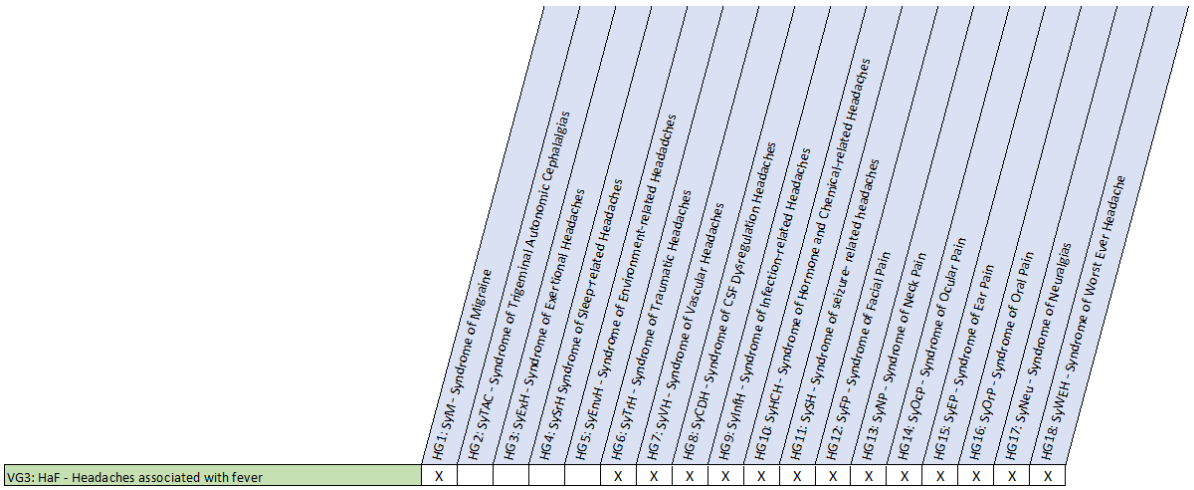


Fig. 3: Horizontal Associations for Vertical Group 3

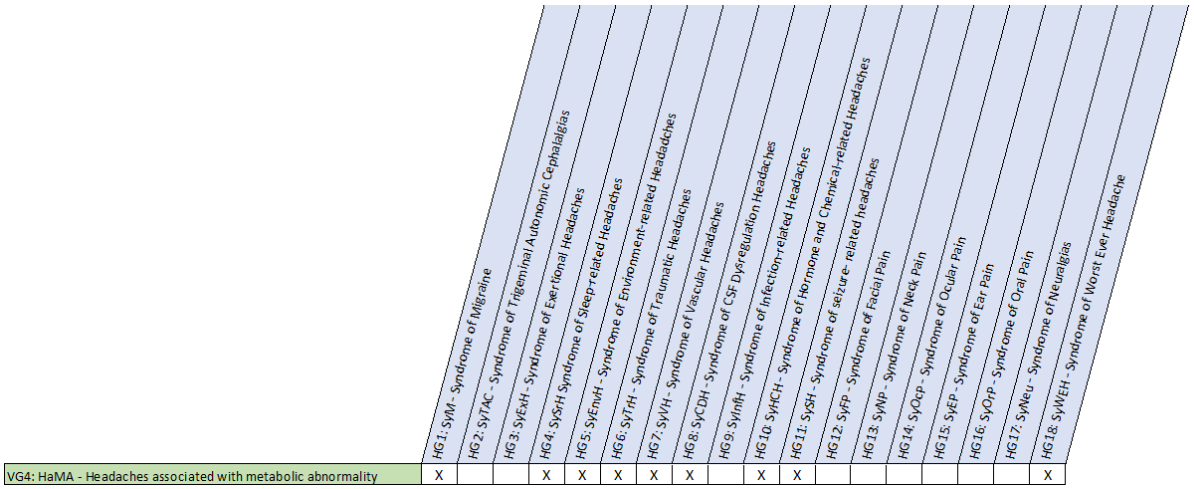


Fig. 4: Horizontal Associations for Vertical Group 4

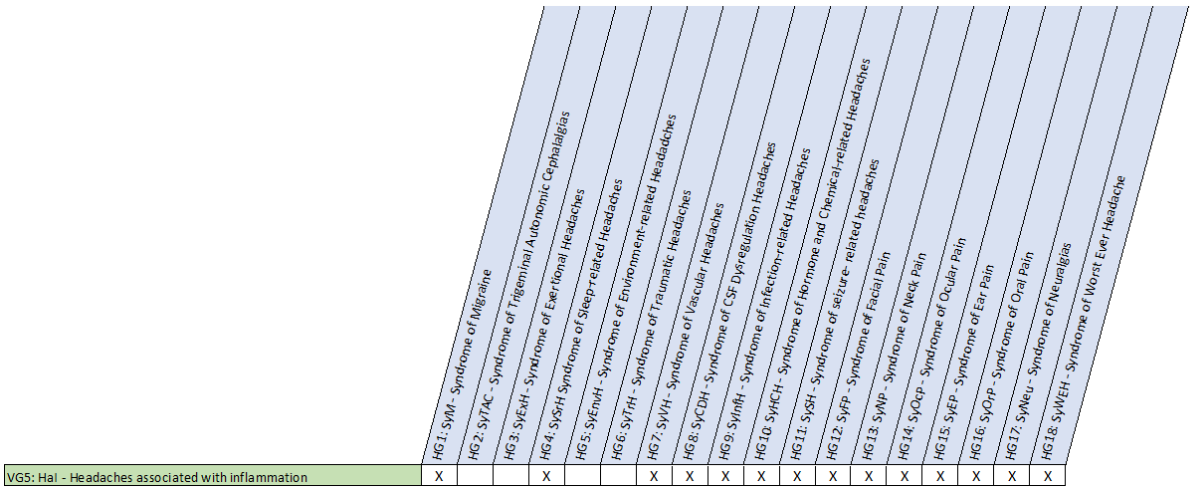


Fig. 5: Horizontal Associations for Vertical Group 5

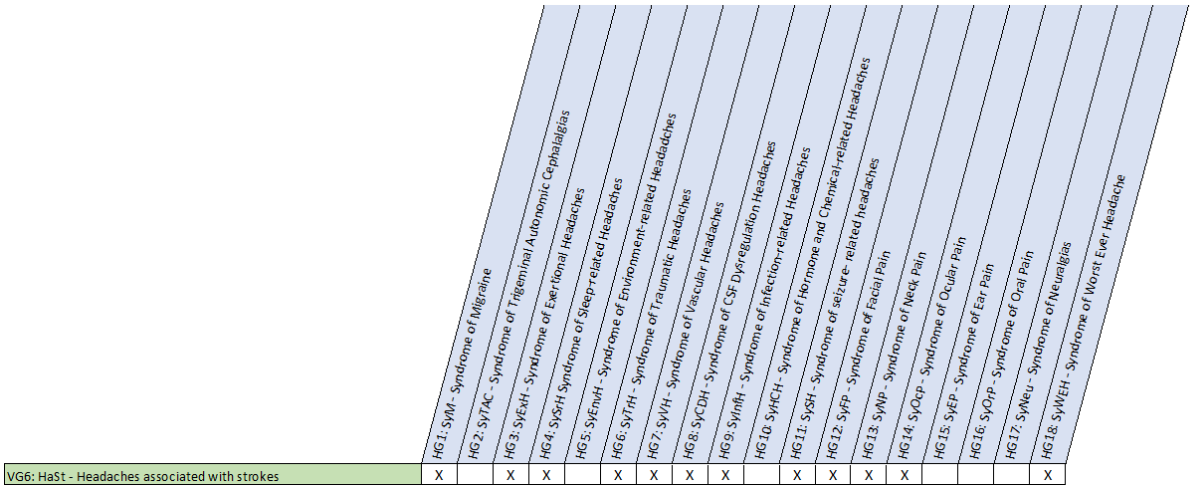


Fig. 6: Horizontal Associations for Vertical Group 6

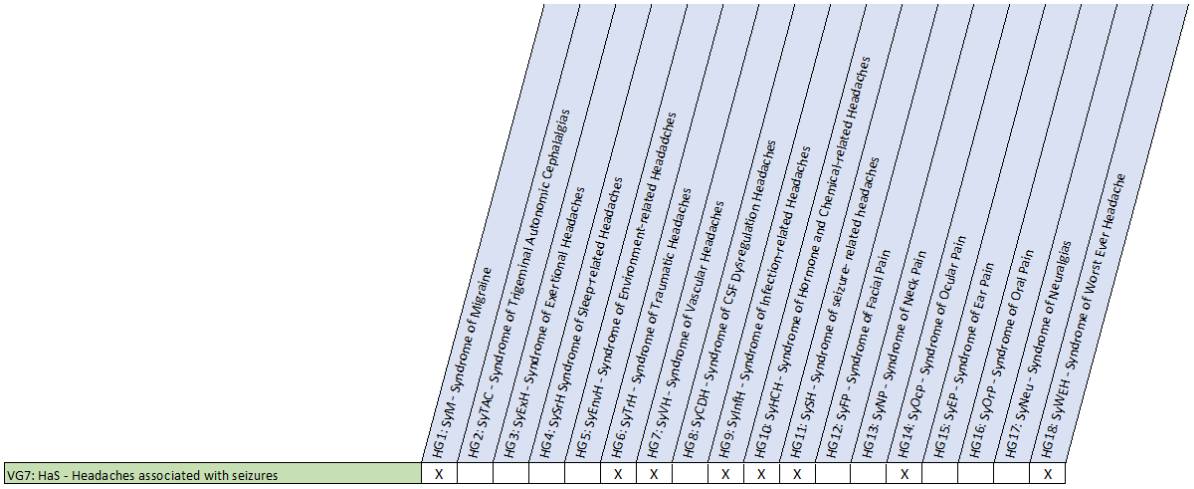


Fig. 7: Horizontal Associations for Vertical Group 7

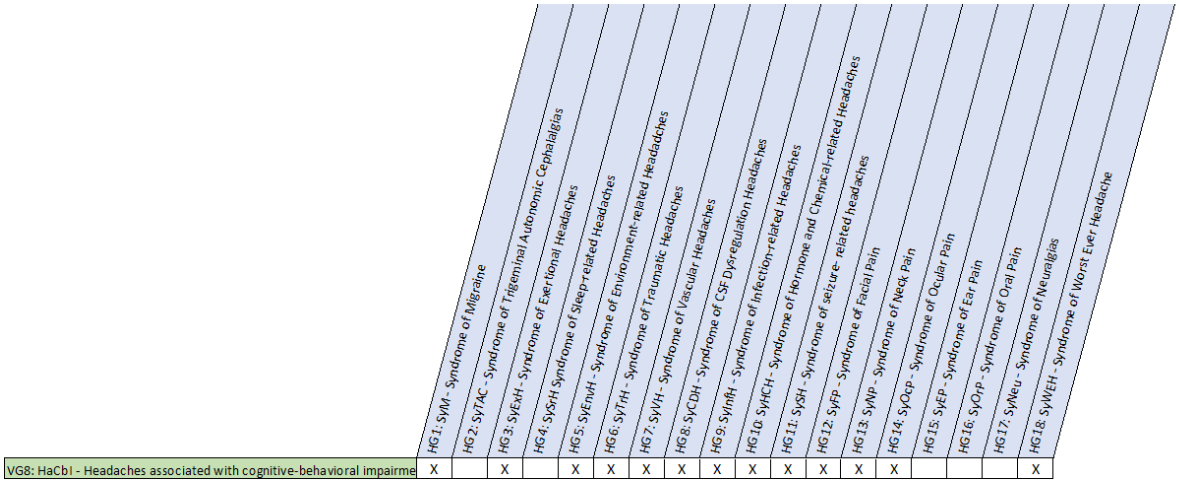


Fig. 8: Horizontal Associations for Vertical Group 8

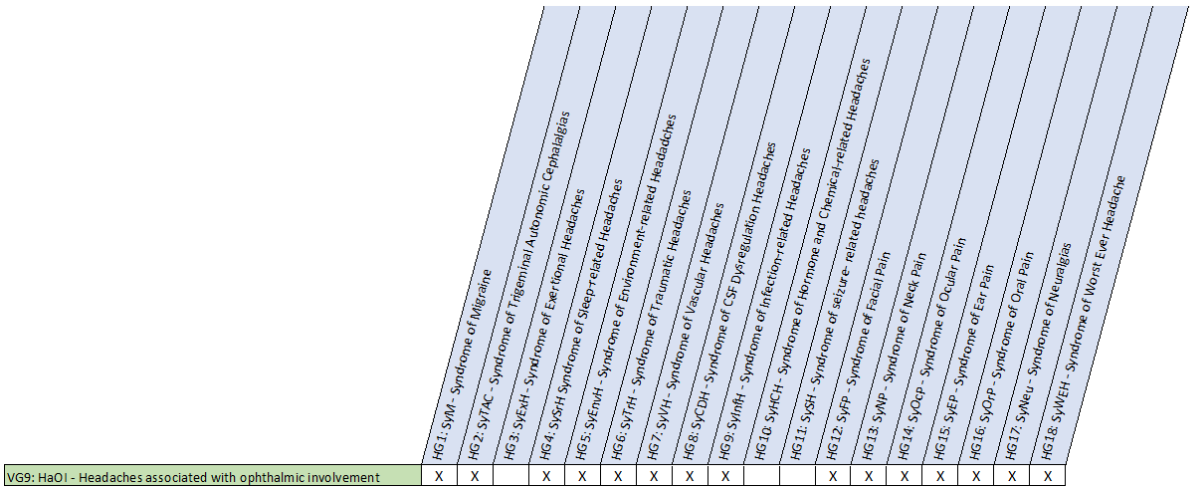


Fig. 9: Horizontal Associations for Vertical Group 9

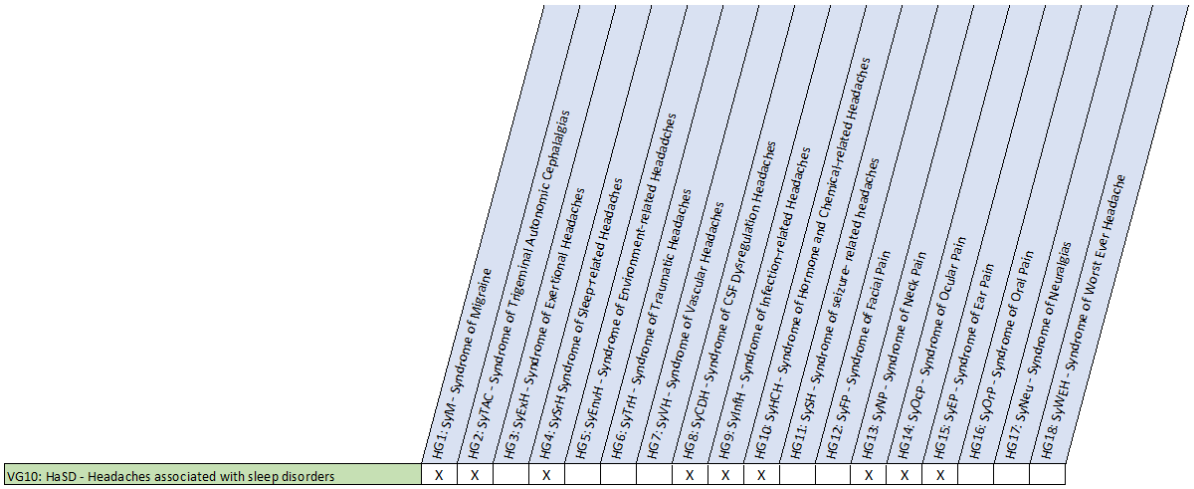


Fig. 10: Horizontal Associations for Vertical Group 10

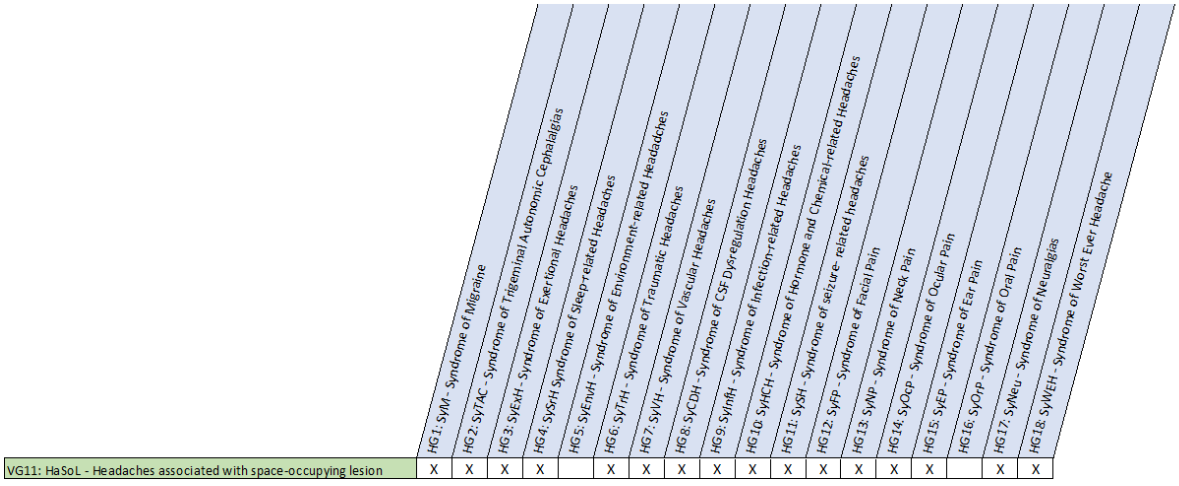


Fig. 11: Horizontal Associations for Vertical Group 11

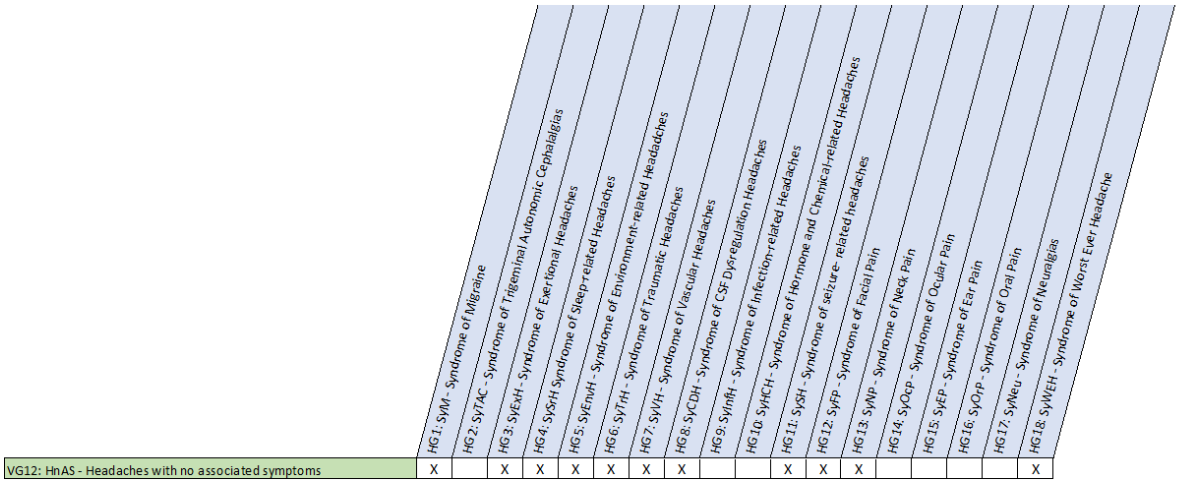
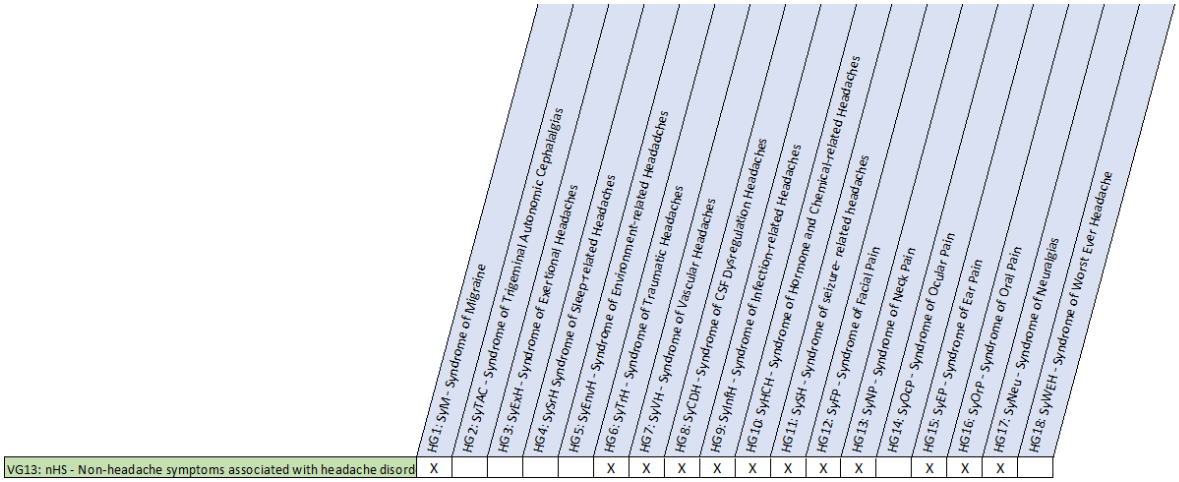
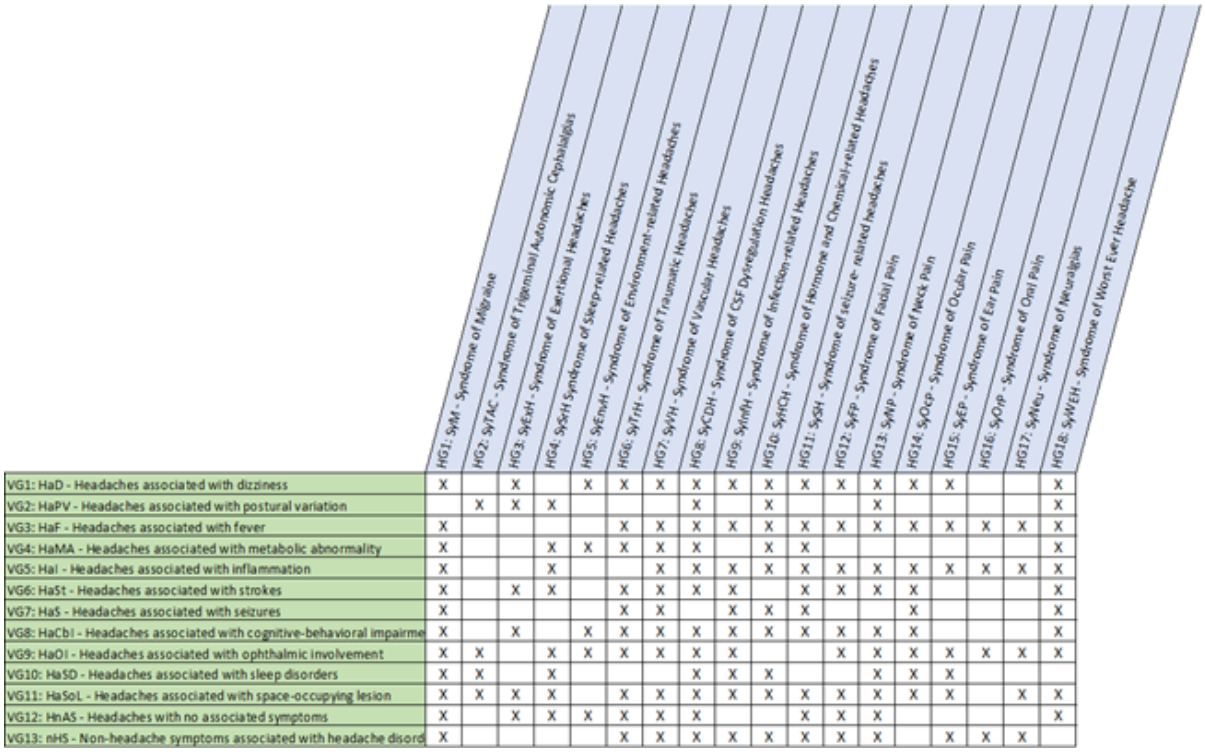


Fig. 12: Horizontal Associations for Vertical Group 12



	HG1: SyM - Syndrome of Migraine	HG2: SyTAC - Syndrome of Trigeminal Autonomic Cephalalgias	HG3: SyExH - Syndrome of Exertional Headaches	HG4: SySrH Syndrome of Sleep-related Headaches	HG5: SyEnvH - Syndrome of Environment-related Headaches	HG6: SyTrH - Syndrome of Traumatic Headaches	HG7: SyVH - Syndrome of Vascular Headaches	HG8: SyCDH - Syndrome of CSF Dysregulation Headaches	HG9: SyInfH - Syndrome of Infection-related Headaches	HG10: SyHCH - Syndrome of Hormone and Chemical-related Headaches	HG11: SySH - Syndrome of seizure- related headaches	HG12: SyFP - Syndrome of Facial Pain	HG13: SyNP - Syndrome of Neck Pain	HG14: SyOcp - Syndrome of Ocular Pain	HG15: SyEP - Syndrome of Ear Pain	HG16: SyOrP - Syndrome of Oral Pain	HG17: SyNeu - Syndrome of Neuralgias	HG18: SyWEH - Syndrome of Worst Ever Headache
VG13: nHS - Non-headache symptoms associated with headache disord	X					X	X	X	X	X	X	X	X		X	X	X	

Fig. 13: Horizontal Associations for Vertical Group 13



	HG1: SyM - Syndrome of Migraine	HG2: SyTAC - Syndrome of Trigeminal Autonomic Cephalalgias	HG3: SyExH - Syndrome of Exertional Headaches	HG4: SySrH Syndrome of Sleep-related Headaches	HG5: SyEnvH - Syndrome of Environment-related Headaches	HG6: SyTrH - Syndrome of Traumatic Headaches	HG7: SyVH - Syndrome of Vascular Headaches	HG8: SyCDH - Syndrome of CSF Dysregulation Headaches	HG9: SyInfH - Syndrome of Infection-related Headaches	HG10: SyHCH - Syndrome of Hormone and Chemical-related Headaches	HG11: SySH - Syndrome of seizure- related headaches	HG12: SyFP - Syndrome of Facial Pain	HG13: SyNP - Syndrome of Neck Pain	HG14: SyOcp - Syndrome of Ocular Pain	HG15: SyEP - Syndrome of Ear Pain	HG16: SyOrP - Syndrome of Oral Pain	HG17: SyNeu - Syndrome of Neuralgias	HG18: SyWEH - Syndrome of Worst Ever Headache
VG1: HaD - Headaches associated with dizziness	X		X		X	X	X	X	X	X	X	X	X	X				X
VG2: HaPV - Headaches associated with postural variation		X	X	X				X		X			X					X
VG3: HaF - Headaches associated with fever	X					X	X	X	X	X	X	X	X	X	X	X	X	X
VG4: HaMA - Headaches associated with metabolic abnormality	X			X	X	X	X	X		X	X							X
VG5: HaI - Headaches associated with inflammation	X			X			X	X	X	X	X	X	X	X	X	X	X	X
VG6: HaSt - Headaches associated with strokes	X		X	X		X	X	X	X		X	X	X	X				X
VG7: HaS - Headaches associated with seizures	X					X	X		X	X	X			X				X
VG8: HaCbI - Headaches associated with cognitive-behavioral impairme	X		X		X	X	X	X	X	X	X	X	X	X				X
VG9: HaOI - Headaches associated with ophthalmic involvement	X	X		X	X	X	X	X	X			X	X	X	X	X	X	X
VG10: HaSD - Headaches associated with sleep disorders	X	X		X				X	X	X			X	X	X			
VG11: HaSoL - Headaches associated with space-occupying lesion	X	X	X	X		X	X	X	X	X	X	X	X	X	X		X	X
VG12: HnAS - Headaches with no associated symptoms	X		X	X	X	X	X	X			X	X	X					X
VG13: nHS - Non-headache symptoms associated with headache disord	X					X	X	X	X	X	X	X	X		X	X	X	

Fig. 14: Complete Vertical to Horizontal Group mapping

Headach. Med. Con. 2021;1(1):107–108

Headache Medicine Connections

The Official Journal of the World Headache Society

SECTION 20: Real-world Application of WHS-MCH1

ARTICLE INFO

Article history:
Received 01.08.2021
Accepted 05.08.2021
Published 20.08.2021

https://doi.org/10.52828/hmc.v1i1.classifications

ABSTRACT

This case study demonstrates the application of WHS-MCH1 in a real-life scenario.
The thought process of the clinician is mentioned as noted below each axis that is being applied.
It also applies intuitive reasoning, which is a part of the clinical decision-making process, and is therefore not a pure algorithmic approach.

1 GRAPHICAL ILLUSTRATION OF WHS MCH1 APPLICATION TO SUPPORT PATIENT CONSULTATION (FIGURE 1)

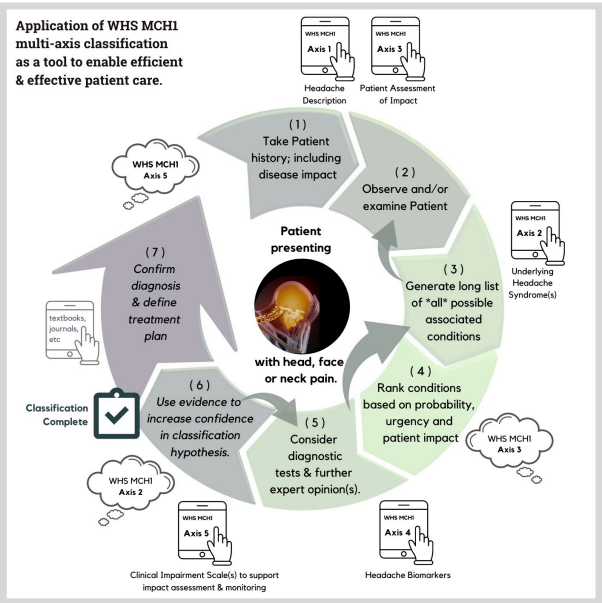


Fig. 1: Application of WHS MCH1 multi-axis classification as a tool to enable efficient and effective patient care

2 CASE SUMMARY (PATIENT AS SEEN IN AUGUST 2021 AT A NEUROLOGY CLINIC)

A 55-year-old female without any previously known comorbidities presented with neck pain, which started insidiously 5 years previously. She described it as a dull ache involving the whole neck, without any radiation to the head, limbs, or torso. She describes the pain as mild to moderate in intensity (Visual Analog Scale 5/10). No aura or cranial autonomic symptoms. No head or neck trauma, dizziness, fever, postural variation, or weight loss. On examination, there was terminal restriction of neck movement when turning to the left. The rest of the general and neurological exam were normal.

3 APPLYING WHS-MCH1

3.1 Axis 1: Headache description based on one or more WHS vertical groups.

Selection: Headaches with no associated symptoms (HnAS)

Explanation:

In WHS-MCH1, headache includes all pains of the head, including the neck and face. The clinician chooses a Vertical Group (VG) that best describes the patient symptom, which is VG12: Headaches with no associated symptoms (HnAS).

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3.2 Axis 2: Headache syndrome chosen from one or more WHS horizontal groups.

Selection: Syndrome of Neck pain (SyNP)

Explanation:

There are several Horizontal Groups (HG) that are linked with HnAS. The most appropriate choice in this case is to link to HG13, Syndrome of Neck Pain (SyNP). A focussed clinical examination is then done, keeping in mind the various conditions associated with the syndrome of neck pain that have been described in HG13. In the absence of trauma and infection and with the restriction of neck movements being the only abnormality, this points to either a deep somatic pain or a visceral pain. Deep somatic pain could be due to involvement of soft tissues or bone, like cervical joint or disc disease. Visceral pain is mediated by surrounding pain-sensitive structures.

3.3 Axis 3: Patient narrative of bothersome symptoms and level of impairment.

Patient narrative: "Constant, nagging, dull type of pain throughout the day". Clinician confirms: No limitations of daily activities and sleep is normal.

Explanation:

This patient did not consult any doctor earlier because the pain was mild, and she thought it is due to work-related muscle pain and would subside on its own. As it continued over the years, she decided to consult a doctor.

3.4 Axis 4: Headache biomarkers: Imaging, genetic study, biopsy, serum or body fluid.

Selection: MRI cervical spine

Result

Mild C5-6 intervertebral disc bulge, multilobular mass originating from the right lobe of the thyroid. Figure 2

Explanation: Based on the differential diagnosis derived from Axis 2, an MRI cervical spine was done with a hypothesis of a bony, muscular, or soft tissue lesion.

3.5 Axis 5: Impairment scale

Result: Pending.

Explanation:

The most applicable assessment scale would be HIT6; although it may be that development of a locally appropriate and validated impairment scale should also be pursued. Assessment was not completed on this initial visit due to practical constraints but will be completed at next available opportunity.

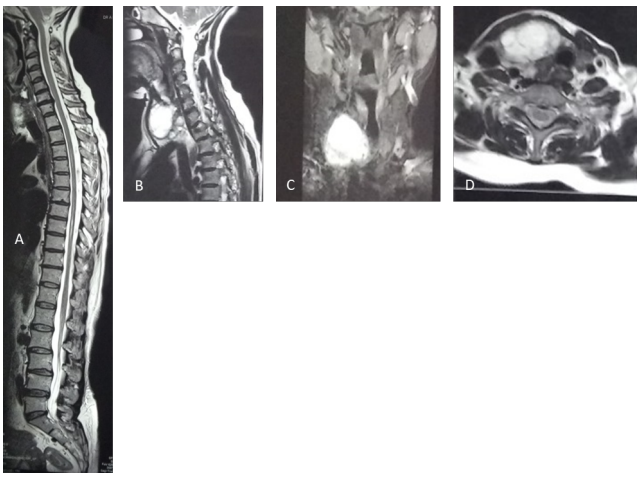

Fig. 2: MRI Results: A) T2 Sagittal screening of whole spine: Mild C5-6 & C6-7 intervertebral disc bulge producing indentation on thecal sac without any signal change in cord. B) T2 Parasagittal section: Hyperintense, lobulated masslesion seen originating from the right lobe of thyroid gland. C) T2 Coronal section: Hyperintense, lobulated mass seen originating from right lobe of thyroid gland. D) T2 Axial section: Hyperintense multi-lobular mass origination from right lobe of thyroid