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The Pathophysiology of Headache and its treatment-Part II

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The International Headache Society (INH) now divides headache into two broad categories, primary headache disorders and secondary headache disorders. Headaches that are symptoms of another disease are known as secondary headaches. Headache diagnosis may be difficult, since many disorders have overlapping characteristics. It is based mainly on a complete medical history and general physical and neurological examination. Moreover, changing concepts of headache pathogenesis have helped develop new headache treatments. This article discusses the secondary headache disorders and the treatment of the various primary and secondary headache disorders.

Head and face pain, similar to pain elsewhere in the body, occurs in an almost infinite variety of syndromes. How accurately to classify patient groups suffering from headache is a taxing problem. the overwhelming majority of patients with recurrent headaches, suffer from what are usually called varieties of migraine or tension (muscle contraction) headache. The headaches symptomatic of specific diseases (headache secondary to ear, nose, throat disease, and to trauma) will be discussed here and they usually do not present long term diagnostic problems. The headaches in this small group of patients are difficult to control with the usual drugs. These patients require treatment with exotic drugs (perhaps not usually used for headache) or high doses of narcotic analgesics. In addition there is a group of patients in whom headache is but a symptom of another, perhaps more serious disease. It has been estimated that approximately 2% of headache patients have an underlying organic disorder as the cause[1]. While it is well to keep these possibilities in mind, they are only rare causes of headache.

CLASSIFICATION OF HEADACHE

The classification of the secondary types of headaches modified from that prepared by the ***American Medical Association's Ad Hoc Committee on Classification of Headache*** is as follows[1] :

1) Combined Headache : Vascular and Muscle Contraction
2) Headache of Delusional, Conversion of Hypocondriachal states
3) Non Migrainous Vascular Headache
   a) Systemic infection
   b) Caffeine withdrawal
   c) Hangover reaction
   d) Early morning hypertensive headache
4) Traction headache
   a) Malignant tumors
   b) Hematomas
   c) Abscesses
   d) Lumbar Puncture
5) Headache due to diseases of the eyes, ears, nose, sinus, throat and teeth.
6) Headache due to allergic states
7) Cranial Neuralgias
8) Analgesic rebound Headache.

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1. Combined Headache

This is a case in which, the muscle contraction appears to be a reflex response to vascular pain. When pain is produced around the vascular bed of the head, skeletal muscles in adjacent areas may contract. If the pain stimulus is brief, the muscle contraction is also short. However, if the painful stimulus persists, long lasting contraction of the muscles of the head and neck and even of the jaws and face may take place. Such sustained contraction results in pain and tenderness of the affected tissues. Muscle contraction as short as two minutes can be painful according to Lewis[2].

Moreover, sustained contraction of the muscles of the head and neck can result from overall reaction to prolonged anxiety, emotional conflict or tension. Since the headache itself may cause emotional tension there is a vicious cycle of painful headache creating the tension response which tends to perpetuate the pain[3]. The muscle contraction by itself is not so violent as to resemble the cramp like pain of the muscle spasm of the leg etc. However, the degree of contraction is such that the flow of blood is cut down with resulting pain and ischemia. This is a steady dull ache rather than the throbbing pain of the vascular headache.

2. Headache of Delusional or Hypochondriachal States

This term has been vaguely defined. The term is used to refer to the headache of overtly or neurotic patients, who complain of characteristically continual pain. The pain complained by these patients is analogous to other somatic disturbances in hysterical patients, for example paralyses or impaired special senses. However, unlike the others, the pain presents no findings on examination. Hence it can simply be stated that the patients complain of unusual, frequently continual headache and is severely neurotic. There is no criteria except psychiatric by which the diagnosis of conversion headache can be made. A more definite psychiatric entity is the uncommon complaint of bizarre headache heard from the psychotic patients. In these patients the headache is part of an overtly expressed delusional system[4].

3. Non Migrainous Vascular Headache

a) Hangover Headache

As many people have experienced, a headache usually follows an alcoholic binge. It is most likely that the alcoholic metabolite, acetaldehyde directly irritates the meninges and causes intracranial pain as it is toxic to the tissues[5].

b) Caffeine Withdrawal

It is a known that the enzyme, phosphodiesterase, is inhibited by caffeine which is present in small amounts in coffee. Hence caffeine prolongs or intensifies the activity of noradrenaline by decreasing the rate of breakdown of c-AMP by phosphodiesterase. This produces a marked increase in cerebral vascular resistance and reduce cerebral blood flow and the CSF pressure. It is this constriction that is believed to be responsible for the relief of hypertensive headache. Hence withdrawal of regular intake of caffeine will result in rebound headache[6].

c) Early Morning Hypertensive Headache

It probably does occur in patients with diastolic blood pressure over 120 to 130 mm of Hg. The headache occurs in the morning upon arising and subsides during the day. It is due to production of cerebral edema. Hypertension does not with any degree of uniformity produce headache and in community studies there is no consistent relationship between levels of blood pressure and presence or absence of headache[7,8]. Some studies have shown that rapidly advancing hypertension which causes cerebral edema might result in headache, dulling of consciousness and focal neurological signs[9]. This was further confirmed by a study in which headache was found to be associated with a diastolic pressure of over 130 mm Hg and that a reduction of blood pressure in hypertensive patients was associated with alleviation of headache[10].

d) Systemic Infections and Constipation

Constipation causes headache in many people. Because it has been shown that constipation headache can occur in persons whose spinal cords have been cut, we know that this type of headache is not caused by nervous impulses from the colon. Therefore it possibly results from adsorbed toxic products or from changes in the circulatory system resulting from loss of fluid into the gut[5].

4. Traction Headache

a) Tumor

Headache frequently but not universally occurs in association with increased intracranial pressure. In general the tendency to headache increases with the rising pressure. Increased pressure may result from intracanial masses of various sorts. The headache resulting from increased intracranial pressure is almost always either continual or occuring at frequent intervals. It is frequently associated with nausea or vomitting and may be localised or generalized. The location of a tumor or other masses does not seem to correlate well with the presence or absence of headache although lesions of the posterior fossa of the skull are particularly productive of severe headache. Speed of the tumor growth seem to be somewhat correlated with headache[4].

b) Hematomas and Abscess

Non neoplastic space occupying lesions are often acute and surrounded with edema. They usually present with signs on the neurologic examination and often with impaired state of consciousness, but the patient with subdural hematoma occassionally present with headache as the only finding[11].

c) Lumbar Puncture

Removing as little as 20 ml of fluid from the spinal canal particularly if the patients remain in the upright position often causes intense intracranial headache. Removing this quantity of fluid removes the floatation for the brain that is normally provided by CSF. Therefore the weight of the brain stretches the various dural surfaces and thereby elicits the pain which causes the headache[5].

5. Headache Due to diseases of Eyes, Ears, Nose and Sinus

The mucus membrane of the nose and also of all the nasal sinuses are sensitive to pain, but not intensely so. Nevertheless, infection or other irritative processes in widespread area of the nasal structure usually summate and cause headache that is referred behind the eyes, or in the case of frontal sinus infection to the frontal surface of the forehead or skull. Also pain from the lower sinuses such as the maxillary sinuses will be felt in the face. Similarly otitis, mastoiditis, pharyngitis and other localised diseases of the ear or pharynx rarely present with generalised headache. Acute sinusitis does produce in addition to tenderness of the involved sinuses, generalized head pain; the patients are, of course, acutely ill with systemic signs. *Chronic sinusitis* is usually a vaguely defined entity. Headache does occur in patients with evidence of chronic congestion of the nasal sinuses and over-growth of sinus mucosa, but it is a rarely defined cause of headache and the headache symptom rarely responds to treatment of the sinusitis. In addition, a variety of ophthalmic diseases, such as iritis, and conjunctivitis, may produce headache but they are rarely diagnostic problems.

Difficulty in focusing one's eye clearly may cause excessive contraction of ciliary muscles in an attempt to gain clear vision. This causes retroorbital headache. Also excessive attempts to focus the eyes can result in reflex spasms in various facial and extra-ocular muscles which is a possible cause of headache[4].

6. Headache Due to allergic States

Severe headache may occur during various kinds of allergic reactions. Exposure to certain exogenous agents seems to be a major source of headache in some individuals for example nitrites in food or environmental gases, ingested sodium glutamate or large amounts of vitamin A. Whether a disturbance of the immunologic mechanism is an etiologic factor in recurring headache is much disputed and remains controversial. It has been claimed that immunologic complexes occur in migraineurs without neurologic symptoms and only at the begining of the attack does complement activation occur[12]. Another study could find no evidence of the presence of immune complexes during migraine or any difference in complement components or immunoglobin levels between times of migraine and headache free periods[13]. The most vigorous and persuasive case for the importance of allergy in migraine has been made for the role of food allergy. A variety of foods have been implicated such as cereals, chocolates and dairy products.

7. Cranial Neuralgia

Neuralgia is a condition of paroxysmal pain in the distribution of a nerve without demonstrable neurologic deficit, and more specifically, cranial neuralgia designates a neuralgia confined to the head.

If pathologic anatomic changes are found which, in the opinion of the observer, are responsible for pain, the

neuralgia is called symptomatic or secondary : if, however, such structural changes cannot be demonstrated, the neuralgia is labelled as primary or idiopathic. When laceration occurs over one side of the face in the sensory distribution area (or part of the area) of the fifth or nineth nerve the phenomenon is called tic douloureux (trigeminal neuralgia or glossopharyngeal neuralgia). The pain feels like sudden electric shocks and it will appear for only a few seconds at a time or may be almost continuous. The trigeminal or glosspharyngeal pathway has been found to be damaged in many instances, most often by only a slight mechanical encroachment upon a ganglion or analogous vessels. In case of trigeminal neuralgias, the damage may be caused by too close a contact with the carotid artery or by slight stretching of the root as it crosses the petrous apex. It is remarkable that as minimal an impingement as that is produced by the pulsation of adjacent arteries may be responsible for the neuralgias. The pain may be caused because of the presence of an exceedingly sensitive trigger areas on the surface of the face, in the mouth or in the throat. Hence, instead of a pain stimuli a mechanoreceptive stimulus will set off the pain. For instance, when the patient swallows a bolus of food, as the food touches a tonsil it might set off a severe lancinating pain in the mandibular portion of the fifth nerve. Mild compression of the trigeminal root may lead to demyelination of its fibres with consecutive short circuiting of sensory impulses[14].

8. Analgesic Rebound Headache

Pain medications worked well when used occasionally, but most produce analgesic rebound headache and an escalation of the headache syndrome when used frequently. Thus excessive use of pain medications can turn intermittent headaches into chronic daily headaches. They also lead to psychological and physiological dependency like an addiction. If the patient tries to stop the medication, it gets worsened[4].

PHARMACOTHERAPY OF HEADACHE

1. Non Narcotic Analgesics

The mechanism of action of non narcotic analgesics is not clear, but they probably decrease inflammation by inhibiting the enzyme cyclooxygenase, thus inhibiting prostaglandin synthesis. Aspirin,acetaminophen and NSAIDS are used for acute (and prophylactic) treatment of migraine and Tension type headache (TTH). NSAIDS are particularly useful in menstrual migraineurs. Generally use of aspirin should be avoided in order to prevent rebound headaches. To date, NSAIDS have not been shown to be superior to aspirin; however, long acting NSAIDS may not be associated with rebound headache[15].

2. Narcotic Analgesics

The analgesic action of opioids is related to their action at the μ k and δ opioid receptors located on neurons at the supraspinal and spinal levels. Opioids are useful for patients with intractable menstrual migraine, those who fail or have contraindications to other migraine medications, and patients who require rescue medications, especially in the middle of the night. These agents are less frequently prescribed than other medications, due to the fear of abuse. The most commonly used narcotic analgesics include butorphanol, hydromorphone, meperidine and morphine[15].

3. Serotonin Agonists

Serotonin agonist decrease headache symptoms by decreasing inflammation in the dura mater of the brain by activating prejunctional 5-HT heteroreceptors on the trigeminal nerve. Activation blocks the release of neurokinins such as SP, CGRP, and neuropeptides[15].

Sumatriptan : A serotonin analog that selectively binds to 5-HT_{1A}, 5-HT_{1B} and 5-HT_{1D} receptors is used in acute treatment of migraine headache. Significant pain relief begins within 10 minutes following injection, and the pain was reduced or completely relieved in 70% of the patients within 1 h and 56% of the patients within 2 h. It also ameliorates associated symptoms such as nausea, vomiting, photophobia and phonophobia. The use of sumatriptan in patients with TTH is poorly documented[15].

Ergot alkaloids : ergotamine and dihydroergotamine (DHE) : Ergotamine tartarate and DHE are ergot alkaloids that are nonspecific serotonergic (5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1F} and 5-HT_{2C}), adrenergic (α –agonist and antagonist), and dopaminergic receptor agonist. Stimulation of adrenergic and serotonergic receptor constricts arteriole smooth muscle. Ergot also causes venoconstriction, decreases platelet aggregation and decreases neurogenic inflammation. Ergot is used as both prophylactic and acute treatment of migraine and cluster headaches. Prophylactic

use however, should be reserved for patients with menstrual migraine and for cluster patients at the begining of the cycle. DHE inhibits the baroreceptor circulatory reflex and has a greater effect on venous capacitance than on resistance vessels. Ergotamine effectively reduces the intensity and duration of attacks and is used to treat moderate to severe migraine when simple analgesics fail[15].

4. Corticosteroids

They are thought to decrease perivascular inflammation and are used in status migrainosus and episodic and chronic cluster headaches. In combination with neuroleptics, narcotics, metoclopramide, or DHE, intravenous corticosteroids may be used to treat refractory migraine headache. They are effective even when patients have had symptoms for a few days and have not responded to other migraine medications. Corticosteroids like prednisone and dexamethasone are the fastest acting of the cluster headache prophylactic therapies, with responses occuring within one to two days. Prednisone may decrease cluster headache in patients who failed therapy with methysergide, verapamil, ergotamine and lithium. However steroids are only used as initial therapy for less than a month to break the cycle while waiting for other medications to take effects[15].

5. Neuroleptics :

Phenothiazines are the neuroleptics most commonly used to treat acute migraine and TTH. These agents antagonize dopamine, decrease 5-HT reuptake, produce anticholinergic effects and block α - adrenergic receptors. The dopaminergic blockade is responsible for the drugs beneficial antiemetic effect and undesirable extrapyramidal symptoms. But their use should be limited in pregnant or lactating patients[15].

6. β-Blockers

The mechanism of action of β-blockers in the preventive treatment of migraine is most likely related to the inhibition of β_1-receptors with secondary effects on serotonin. However when given prophylactically, β-blockers are 60% to 80% effective in producing a 50% reduction in attack frequency and severity of migraine episodes. They are contraindicated in patients with asthma, hypotension, Raynauds disease or diabetes[15].

7. Antidepressants

Tricyclic antidepressants (TCAs) increase the availability of synaptic norepinephrine or serotonin by inhibiting reuptake. However the antinociceptive efficacy is unrelated to antidepressant action. Plausible explanations for the anti nociceptive efficacy of antidepressants include decrease in β-receptor density and norepinephrine mediated cAMP response, upregulation of $GABA_B$-receptors, and down regulation of 5-HT_2-receptor and 5-HT reuptake inhibition may be most crucial. They are useful in patients with concurrent depression, anxiety, insomnia or pain disorder and are 40 to 70% effective in reducing migraine and TTH frequency[15].

8. Calcium Channel Blockers

Excessive levels of intracellular calcium under ischemic conditions can produce neuronal damage and cell death. Flunarizine, a novel calcium channel blocking agent with antiepileptic properties, exhibit non specific antagonism to sodium as well as type T and N slow voltage sensitive Ca^{+2} channels, may therefore have significant advantages in terms of cerebral cell protection and lack of cardiovascular effects[15].

9. Serotonin Antagonists

Methysergide, a semisynthetic ergot 5-HT_{1D} receptor agonist and 5-HT_{2A} 5-HT_{2C} antagonist, decreases platelet aggregation, inhibits neurogenic plasma extravasation and inflammation and produces vasoconstriction in the carotid vascular bed. It is not useful in the treatment of acute cluster headache and migraine attacks but is primarily used as a preventive agent. Anticonvulsants such as valproic acid and phenytoin are also effective in decreasing pain in patients with migraine and cluster headache[15].

CONCLUSION

Headaches are very common, but many headache sufferers do not seek medical attention. Patients need an adequate evaluation to rule out medical and medication causes of headache.

Treatment involves pharmacological and non pharmacological measures and this effect may be synergistic. Pharmacological treatment may be abortive

or preventative. The goal of abortive treatment is to relieve headache pain and associated symptoms with minimal drug related adverse effects. Complete remission is an unreasonable expectation, as headache will recur. Thus, end point for preventative treatment include decreasing severity, duration and frequency of headache with minimal drug related adverse effects. There is a delicate balance between headache improvement and adverse effects. Some patients prefer the balance to tilt towards less headache improvement because they are unable to tolerate the adverse effects, while others are willing to tolerate more adverse effects in order to achieve better headache relief. Patients also need to be well informed about their therapy and take an active part in their management by avoiding headache trigger factors and evaluating the effects of their therapy.

REFERENCES

1. Closson, R.G., Neurological and Psychological Disorders, 1963, 10, 602.
2. Tauter, M.L., and Ferris, A.J., **Aspirin in modern technology,** 1969, 43.
3. Wolff, H.G., **Headache and Other Head pain,** 1963, 352.
4. Dewey, Z., **Neurology,** 1985, 1, 406.
5. Guyton, A.C., Textbook of Medical Physiology, 8th Ed, W. B Saunders Company, London 1991, 528.
6. Satoskar, R.S. and Bhandarkar, S.D., Pharmacology and Pharmacotherapeutics, 13th Ed, Popular prakashan Pvt Ltd, Mumbai 1993, 159.
7. Waters, W.E., **Br Med J,** 1971, 2, 77.
8. Weiss, W.S., **New Eng J Med,** 1972, 287, 631.
9. Ziegler, D.K., Zosa, A., and Zileli, T., **Arch Neurol,** 1965, 12, 472.
10. Badran, R.H.A.I., and Weir, R.J., **Scot Med J,** 1970, 15, 48.
11. Cameron, M.M., **J. Neural Neurosurg psychiatry,** 1978, 41, 834.
12. Lord, G.D.A., and Duckworth, J.W., **Headache,** 1970, 18, 255.
13. Behan, W.M.H., and Behan, P.O., **Headache,** 1981, 21, 55.
14. Malis, L.T., **Suppl J Neurosurg,** 1967, 26 (Part II), 163.
15. Herfindal, E.T., and Gourley, D.R., Textbook of therapeutic Drug and Disease Management, 6th Ed, William and Wilkins, A Waverly Company, U.S.A. 1996, 983.