Pathophysiology of Recurrent Headaches in Children and Adolescents

A. DAVID ROTHNER, MD

In dealing with headaches in children, physicians must consider both physical and psychological factors in determining the correct diagnosis. The pathophysiology of the specific headache type must be understood in order to select the optimal treatment program. The existing methods of classifying headache are based on the presumed location of the abnormality, the pathophysiology, or the symptom complex. For research purposes, the classification of the International Headache Society is used most frequently.\(^1\)

Clinically, I find it useful to classify headaches in an additional way, by their temporal pattern: acute, acute recurrent, chronic progressive, chronic nonprogressive, and mixed (Figures 1 and 2).\(^2,3\) An acute headache is defined as a single event with no history of a previous similar event. If this acute event is associated with neurologic symptoms or signs, an accurate diagnosis must be made quickly, as intervention may be life-saving. The differential diagnosis of the acute headache involves many disorders: systemic infection, central nervous system infection, toxins, postictal headaches, hypoxia, hypertension, postlumbar puncture, trauma, vascular thromboses, hemorrhage, collagen disease, and exertion. The history and physical examination help differentiate between these disorders. Acute recurrent headaches are events that recur periodically. If they are associated with nausea, vomiting, and the desire to sleep, and are separated by pain-free intervals, they are migrainous in most instances.

Chronic progressive headaches increase in severity and frequency over time. If other neurologic symptoms or signs are present, a structural disorder of the central nervous system should be suspected. Neuroimaging is needed frequently. Chronic nonprogressive headaches occur either several times weekly or

\(^{Dr} Rothner\) is from the Department of Pediatric Neurology, The Cleveland Clinic Foundation, Cleveland, Ohio. Address reprint requests to A. David Rothner, MD, The Cleveland Clinic F71, Cleveland, OH 44195.
daily or constantly without significant change in severity over time. They are usually not associated with neurologic symptoms or signs, and usually are related to stress. The mixed headache syndrome implies superimposition of acute recurrent headaches (migraine) on chronic nonprogressive headaches. The added dimension of time helps one determine the need for intervention and the urgency with which the intervention must be undertaken.

MECHANISMS OF HEAD PAIN

It is important to recognize which structures in the head are sensitive to pain and which nerves mediate pain. The classic work of Ray and Wolff helped elucidate many of these mechanisms. Both extracranial and intracranial structures may be sensitive to pain. Extracranial structures sensitive to pain include the skin, subcutaneous tissues, muscles, mucous membranes, and some of the larger vessels. Intracranial tissues sensitive to pain include the vascular sinuses, the larger veins, the dura surrounding these larger veins, dural arteries, and arteries at the base of the brain. Structures not sensitive to pain include the brain, the cranium itself, most of the dura, the ependymal lining, and the choroid plexus.

Pain from the extracranial and intracranial structures in and about the face and in the front half of the skull are mediated by way of the fifth cranial nerve and are referred to the front half of the skull and face. Smaller areas are innervated by branches of the seventh, ninth, and tenth cranial nerves. Pain from the occipital half of the skull and upper cervical area is mediated via the upper cervical nerves. Inflammation, irritation, displacement, traction, dilation, or invasion of any of these structures will cause pain. It should be noted that the location of the pain may be localizing, as in the case of an invasive hemispheric tumor; nonspecific, as in the case of vasculitis; or very specific, as in the case of occipital neuralgia. In many cases, however, the pain itself is of no localizing value. The perception of pain is modified by psychological factors, ethnic factors, age, and previous experience, and should not be taken as an absolute indication of the severity of the disease.

Pathogenesis of Migraine

Exciting new advances have been made in understanding the pathophysiology of migraine. Liveing, more than a century ago, suggested that "migrain" was similar to epilepsy and that the associated circulatory changes were secondary to neuronal discharges. Graham and Wolff documented that ergotamine reduced the pulsation and amplitude in the temporal artery and decreased the pain. These observations led to the vascular theory of migraine. It was postulated that during the initial phase, constriction of the intracranial vessels caused neurologic symptoms. In the second phase, vasodilation of the extracranial blood vessels associated with sterile inflammation surrounding the vessels caused the intense pain. Lauritzen et al reported that regional cerebral blood flow decreased an average of 25% to 30% prior to the onset of a classic migraine attack. The reduced perfusion spread in an occipitofrontal fashion at a rate of about 2 mm/minute, similar to the spreading depression of Leao, and was associated with deficits in the vasomotor regulatory apparatus. Therefore, concomitant focal ischemia and secondary cerebral edema seemed to account for the neurologic symptoms and the rare occurrence of cerebral infarction associated with migraine.

New technologies that have permitted measurement of regional cerebral blood flow, coupled with a better understanding of the chemistry of neurotransmitters, have blended to produce the primary neuronal hypothesis dominant today. This hypothesis considers migraine an inherited sensitivity of the trigeminal vascular system. Cortical, thalamic, or hypothalamic mechanisms initiate the attack secon-
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dary to internal or external stimuli. These structures stimulate the locus ceruleus and nucleus raphe dorsalis within the brainstem, which in turn project via serotoninergic and noradrenergic pathways back to the cortex to produce the spreading wave of neuronal depression and then to the cranial vasculature to produce a cascade of neurogenic inflammation and secondary vascular reactivity. Released vasoactive neuropeptides activate endothelial cells, mast cells, and platelets, which then increase extracellular amines, peptides, and other metabolites. This results in sterile inflammation of dural and pial blood vessels from which nociceptive afferents transmit centrally via the trigeminal nerve.10-12

When stimulated, the trigeminal nerve releases substance P and calcitonin gene-related peptide into dural and meningeal blood vessels. The release of substance P causes the degranulation of mast cells and the attraction of polymorphonuclear leukocytes. This leads to the mast cell release of histamine and platelet release of serotonin with resultant vasodilation and eduction of plasma into the tissues. The resulting inflammation and swelling of the blood vessels represents the so-called sterile arthritis described by Wolff half a century ago. The neurogenic inflammation and the release of substance P causes both distention of cranial arteries and headache pain.12

A major advance in improving our knowledge of migraine pathophysiology and therapy is related to the recent understanding of serotonin (5-HT) receptors. Several papers have reviewed this topic in detail.12,13 This article addresses only the issues salient to migraine.12,13 There are at least five serotonin receptor subtypes: 5-HT1A, 5-HT1D, 5-HT1C, 5-HT2, and 5-HT3. A number of drugs used to treat migraine are serotonin agonists or antagonists. Drug interactions with specific 5-HT receptor subtypes may be the basis for their efficacy in both abortive and prophylactic treatment of migraine. 5-HT1D receptors are implicated in the constriction of cerebral blood vessels and arteriovenous anastomoses. Several effective abortive agents, including dihydroxyergotamine and sumatriptan, have potent activity at the 5-HT1D receptor site. Drugs that affect these receptors, therefore, are useful in aborting migraine attacks. The 5-HT1A receptors have been shown to mediate serotonin-induced constrictions of the basilar artery in dogs. 5-HT1A receptor agonists inhibit raphe cell firing. Several antimigraine drugs have a moderate or high affinity for the 5-HT1A receptors, including methysergide, dihydroxyergotamine, sumatriptan, and propranolol. No obvious correlation appears to exist between drug affinity for this receptor and potency in terms of migraine relief.

A number of potent 5-HT2 antagonists have been shown to be effective prophylactic agents for migraine, including methysergide, cyproheptadine, amitriptyline, and verapamil. Beta-blockers are inactive at these sites. The 5-HT2 receptor has been shown to mediate smooth muscle contraction in many vascular beds. It may inhibit serotonin from inducing an inflammatory state.

The exact role of 5-HT1C and 5-HT1D receptors in migraine is not clear, but it is known that the 5-HT3 receptor antagonists have potent antiemetic effects. Some agents such as metoclopramide are useful in the acute treatment of migraine. Peroutka13 summarized the hypothetical role of serotonin receptor subtypes in migraine therapy by stating that acute migraine relief is generated by agonist activity at the 5-HT1D or 5-HT1A receptors while prophylactic activity was dependent on antagonist activity at 5-HT2 or 5-HT1C receptors.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are also effective abortive agents.14 The abortive effect of NSAIDs is most likely due to direct effects on vascular inflammation, rather than mediation of the trigeminal vascular system through serotonin receptors. The prophylactic effect of NSAIDs may be mediated through effects on serotonin receptors or through other anti-inflammatory mechanisms. Drugs that block the stimulation of the trigeminal vascular system and substance P release are useful for abortive migraine therapy; these include sumatriptan and ergotamine. Agents that inhibit trigeminal vascular stimulation are useful for migraine prophylaxis; these include beta-blockers, calcium-channel blockers, antidepressants, NSAIDs, and methysergide.

Headaches From Increased Intracranial Pressure
Increased intracranial pressure often is associated with headache.15 Two important concepts are to be stressed when evaluating patients with possible increased intracranial pressure. The first is the concept of intracranial volume in relation to intracranial pressure.16 The skull is a fixed structure, and the volume of the intracranial contents is comprised of three main components: the brain and associated structures, the blood vessels and dura, and the cerebrospinal fluid. The presence of a tumor is a nonphysiologic "fourth" content. An incremental increase in one component results in equal decrease in one of the other components. The intracranial vasculature is
“autoregulated,” meaning that increases in systemic blood pressure are met with a constriction of blood vessel diameter to maintain an acceptable intracranial pressure. Other physiologic processes also may change the blood vessel diameter; hypercarbia causes the vessels to dilate and hypocarbia causes constriction. Over most physiologic systemic blood pressures, hypocarbia causes vasoconstriction. Over most physiologic systemic blood pressures, the process of autoregulation maintains a normal intracranial blood pressure and intracranial pressure. The pressure-volume relationship is not maintained at dramatically elevated blood pressures.

The second concept is that of brain compliance: “the compressibility of the brain” that is determined by factors such as the presence of cerebral edema, hydrocephalus, scarring of the ventricular lining, and the presence of abnormal structures. In most physiologic and early pathologic conditions, there is a linear volume/pressure relationship: an increase in intracranial volume is met with predictable increase in intracranial pressure. This linear relationship is maintained to some degree by autoregulation and to some degree by the pliable nature of the brain. Under circumstances of poor brain compliance, as would be found in patients with brain tumors, head injuries, hydrocephalus, or purulent meningitis, the relationship between volume and pressure may not be linear. Therefore, a small increase in intracranial contents could result in a large increase in intracranial pressure.

The common clinical situation that exemplifies this situation is a child with shunted hydrocephalus being evaluated soon after the shunt malfunctions. The child has symptoms and often signs of increased intracranial pressure, but there is little or no change in the ventricular size as seen on imaging study. In fact, a small increase in ventricular volume can result in a dramatic increase in intracranial pressure, and the clinician therefore should never make an assumption of intracranial pressure based on ventricular size or change in ventricular size.

### SPECIFIC HEADACHE SYNDROMES

**Acute**

An isolated acute headache may represent a difficult diagnostic problem. These headaches may be separated into those with generalized pain and those in which the pain is localized.

**Acute Generalized.** Two percent to 6% of all emergency room visits are due to headaches. No data relating specifically to acute headaches in the pediatric and adolescent population are available. In a general emergency room population, 40% of the patients had non-central nervous system infections, 20% had tension headaches, 10% had traumatic headaches, 5% had vascular headaches, and 5% had headaches related to hypertension. The presence of altered consciousness, focal neurologic abnormality, or nuchal rigidity should result in rapid evaluation. Abnormalities including temperature elevation, hypertension, papilledema, retinal hemorrhages, and disturbed affect may aid in identifying the basic process.

Headache frequently accompanies febrile illness in children. Only a single article has dealt with these patients as seen in the pediatrician’s office. Bacteria and viruses can produce toxins and fragments that stimulate the release of endogenous pyrogens such as interleukin-1 and interferon. These cause vascular headaches by release of prostaglandins and vasoactive substances. Fever also can cause headaches because of cerebral blood flow changes. Treatment of the underlying infection, as well as the use of anti-inflammatory agents, such as ibuprofen, ameliorates fever and headache concomitantly.

**Acute Localised.** Sinusitis, otitis media, and orbital cellulitis are localized inflammatory disorders secondary to infection. Headache in these cases is caused by the mechanisms discussed above. Antibiotics as well as anti-inflammatory agents are needed. Ocular causes of headache include astigmatism, refractory error, and squints. The pathophysiology of these headaches is not clear, but the ophthalmic division of the trigeminal nerve innervates the eyes, as well as the surrounding structures. Inflammation of these structures such as in uveitis and retinitis also can cause pain. The ciliary body is innervated by the trigeminal nerve, and extensive contraction of this structure, as is seen with astigmatism or refractory error, can cause headaches.

**Occipital Neuralgia**

Occipital neuralgia is a specific disorder in which pain is localized to the occipital and upper cervical areas. It is characterized by unilateral or bilateral occipital and suboccipital headaches, scalp pain, and local tenderness. Paresthesia in the distribution of the 2nd cervical dermatome may be present. The pain may be related to congenital anomalies of the cervical spine or trauma. Intermittent subluxation and compression of the cervical root or entrapment of the
Chronic nonprogressive headaches are thought to be precipitated by or associated with emotional causes and have no organic substrate.

Acute Recurrent
Migraine is a specific genetic disorder characterized by episodic periodic paroxysmal attacks of vasoconstriction and vasodilation. The pathophysiology of this disorder has been discussed already. The disorder is inherited as an autosomal-dominant with greater penetrance in females. The episodes are triggered frequently by anxiety, stress, fatigue, head trauma, excitement, exercise, menses, travel, illness, diet, and medication. Chemospecific substances, including nitrates, phenylethylamine, and monosodium glutamate, also may trigger migraine headaches. Treatment, discussed elsewhere in this issue of Pediatric Annals, is individualized, depending on the age and reliability of the patient and the frequency and severity of attacks.

Chronic Progressive
Chronic progressive headaches include the disorders in which the pathologic process is within the cranial vault and increased intracranial pressure is usually present. Brain tumors, pseudotumor cerebri, hydrocephalus, brain abscess, and subdural hematomas may cause headaches that are progressive in severity and frequency. The rapidity with which the process progresses determines the slope of the curve (shown in Figure 1); temporary remissions of the headache may occur. Associated symptoms of increased intracranial pressure include nausea, vomiting, ataxia, weakness, lethargy, personality change, intellectual deterioration, visual disturbances, sensory abnormalities, and seizures. The type of pathological process and its location may result in varying combinations of cortical, pyramidal, extrapyramidal, cerebellar, and cranial nerve abnormalities. If the patient has increased intracranial pressure, and a structural abnormality of the central nervous system is suspected, magnetic resonance scanning is the procedure of choice.

If increased intracranial pressure is present, nontargeted treatment modalities include corticosteroids, diuretics, and glycerol. In the presence of a brain tumor, however, more definitive therapy requires surgery, chemotherapy, and radiotherapy. In the case of pseudotumor cerebri, repeated lumbar punctures, diuretics, and weight loss are useful. If vision is threatened, optic sheath decompression or lumbar peritoneal shunting is indicated. In the case of hydrocephalus, with ventricular enlargement, ventricular peritoneal shunting or third ventriculostomy are the treatments of choice. In the case of subdural hematoma, either due to head trauma, spontaneous rupture of vascular structures, or blood dyscrasia, drainage of the subdural by repeated subdural taps, external drainage, or shunting procedure is indicated. In the case of brain abscess, which is more commonly found in association with chronic ear infections, cyanotic congenital heart disease, or immunocompromised patients, the treatments of choice include antibiotics and surgical drainage.

Chronic Nonprogressive
Chronic nonprogressive headaches are thought to be precipitated by or associated with emotional causes and have no organic substrate. These may include so-called tension headaches, headaches associated with depression, and protracted post-traumatic headaches. The mechanism by which muscle contraction headache causes pain may be related to prolonged muscle contraction and resultant muscle ischemia. However, in those patients in whom no excessive muscle contraction can be demonstrated, and the pain is thought to be related to “stress,” the pathophysiology is unclear. In this author’s experience, these patients are best evaluated medically as outlined previously and psychologically using a structured psychological interview and questionnaires such as the Minnesota Multiphasic Personality Inventory-Adolescent Version and The Personality Inventory for Children. Treatment is tailored to the emotional factors that are causative and may include family counseling, individual counseling, biofeedback, and relaxation training. If the patient has had protracted absence from school, return to school is mandatory. Treatment modalities also can include pharmacologic agents. Narcotic analgesics, major tranquilizers and antianxiety agents are avoided. Antidepressants such as amitriptyline have been noted to be useful. The prognosis is unknown.

SUMMARY
The classification and pathophysiology of headache syndromes in children and adolescents is reviewed. The most important issues are classifying the headache type and determining the etiology of the child’s headache. This is best accomplished with a thorough history and physical examination, coupled with selected laboratory tests. The pathophysiology of the underlying headache as reviewed usually will allow the choice of appropriate treatment modalities.
REFERENCES