Indomethacin-Responsive Headaches in Children and Adolescents

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Headache is a common symptom in childhood and adolescence. Effective therapy for this symptom is based on the specific headache syndrome. This article presents examples of the four recognized indomethacin-responsive headache syndromes encountered in pediatrics including exertional headache, cyclic-cluster migraine, chronic paroxysmal hemicrania, and hemicrania continua. Although uncommon conditions, successful treatment depends on recognition of these indomethacin-responsive headache syndromes.

Headaches are a common problem in children and adolescents. Significant headaches affect 25% of school children younger than 15 years of age and account for 10% of school absences. About 6.8% of children between ages 7 and 15 years have recurrent nonmigrainous headaches. Treatment is usually based on the specific headache syndrome (ie, migraine vs. chronic nonprogressive headaches). We review four syndromes that are uncommon in pediatric practice and usually are not well recognized. These syndromes are specifically responsive to indomethacin and include exertional headaches, cyclic (cluster) migraine, chronic paroxysmal hemicrania, and hemicrania continua. In this review, four patients are presented, each with one of the four forms of indomethacin-responsive headaches.

CASE REPORTS

Case 1: Exertional Headache

A 14-year-old boy was seen for evaluation of headaches and had been essentially well until 2 years before consultation when he developed a "flu" with a fever of 103°F that lasted for 1 day. He ran in a track meet afterwards where he participated in three events. Ten to 15 minutes after his last event, he developed blurry vision out of the corner of one eye and a severe frontal headache. Riding in the bus made it worse. He had no associated symptoms. The headache continued until he went to bed. It awakened him in the middle of the night, and he took several ibuprofen tablets which helped. Two days later, he participated in another track meet. Ten to 15 minutes after a one-mile relay event, he again could not see out of the corner of one eye and developed a severe frontal headache without associated symptoms that lasted 1 to 2 hours. He took ibuprofen before running another event in the afternoon and felt better. The following day, he woke up with a right frontal headache, took ibuprofen, and although he felt better, the headache continued for 2 days. These events continued for the next 2 years.

The history was significant for the placement of polyethylene tubes and surgical correction of an aneurysmal bone cyst. He was allergic to penicillin.

The family history revealed two brothers with occasional nonmigrainous headache. His mother had severe headaches during menstruation without nausea and vomiting. There was a positive family history of mental illness.

The review of systems revealed a mild head injury at 3 years of age without residua, frequent upper respiratory symptoms secondary to allergy, and a healed fracture of his leg.

His general physical examination and a detailed neurologic examination were normal. Laboratory studies, including a normal complete blood count and chemistry panel, as well as lupus erythematosus (LE) prep, erythrocyte sedimentation rate, and antinuclear antibody (ANA), were normal. EKG and echocardiogram were normal. An magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) were normal.

Treatment consisted of 50 mg of indomethacin taken the night before and the morning of each race. He was able to race without experiencing headaches or treatment side effects. His headaches disappeared 1 year later and have not returned to date.

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**Case 2: Cyclic (Cluster) Migraine**

A 16-year-old boy presented with headaches that occurred daily for 4 weeks and then disappeared for 3 months. The cycle repeated itself two to three times yearly. During the headache period, he would have five severe headaches weekly at any time, which were usually unilateral and described as pounding. He had no associated symptoms, save some nausea and pallor, and the headache lasted an average of 6 hours. Exercise and noise worsened the pain. Prior treatment with acetaminophen, aspirin, ibuprofen, amitriptyline, and propranolol had been unsuccessful.

His medical history and review of systems were noncontributory. His family history was positive for headaches, type unknown. His mother had headaches during her 20s.

His complete general physical and neurologic examinations were normal. Laboratory studies, including a complete blood count, chemistry panel, ANA, and erythrocyte sedimentation rate, were normal. An MRI scan was normal.

He was treated with indomethacin 50 mg three times daily, and the headaches decreased to one to two per week during his cycle. They lasted less than 1 hour and were mild. Follow-up 3 years later revealed that the headaches had disappeared, and the use of indomethacin was no longer needed.

**Case 3: Chronic Paroxysmal Hemicrania**

A 4-1/2-year-old girl presented with headaches that had been occurring for the previous 5 months. The headaches had been increasing in frequency, awakened her from sleep, and caused her to cry with pain. They would occur at noon and again between 2:00 AM and 4:00 AM. They were left-sided without aura. They were accompanied by fatigue and irritability. She would hold her head and wanted to sleep. They were made worse by exercise and adversely impacted her usual daily activities. Acetaminophen modified the headaches but did not completely relieve the pain.

Her medical history was significant for Kawasaki’s disease that had been treated with aspirin and intravenous immune globulin. Her family history was negative for migraine, although her mother did have occasional headaches.

Her general physical examination and a detailed neurologic examination, as well as an ophthalmologic examination, were normal. Laboratory testing, including complete blood count and chemistry panel, erythrocyte sedimentation rate, and ANA, was unremarkable, save a hemoglobin of 10.3 g/dL. MRI showed an incidental pineal cyst without any mass effect or hydrocephalus and opacification of the sphenoid sinuses.

She was treated with amoxicillin and clavulanate potassium (Augmentin), which resolved the sinusitis. The nature of her headache did not change. The headaches continued to occur daily and to awaken her at night. During the day, her headache worsened when the acetaminophen wore off. Aspirin was tried but did not relieve her headaches. Indomethacin 6 mg three times daily was initiated, and the headaches disappeared completely within 48 hours.

Her mother noted that when she did not give the indomethacin, the headaches recurred. On telephone follow-up 3 years later, she has been off indomethacin for 1 year and had been headache-free, except for mild headaches not requiring medication.

**Case 4: Hemicrania Continua**

This case was reported by Zuckerman in 1987. This case illustrates a case of hemicrania continua that had its onset during adolescence.

A 42-year-old woman developed a unilateral left-sided headache at the age of 11 years. The headache was throbbing and of variable intensity (usually low to moderate) and occurred daily. She had rare headache-free periods of 10 to 15 days. Occasional exacerbations would occur, during which the pain could be more severe. Exacerbations could be precipitated by strong odors or exertion and lasted from 5 to 10 hours. They were most likely to occur during the afternoon. The pain was severe enough to awaken her at night. During periods of relatively intense pain, she had some nausea, slight bilateral nasal stuffiness, facial flushing, and tearing, more pronounced on the left side. No ocular congestion, rhinorrhea, facial sweating, ptosis, or pupillary asymmetry was observed. The headaches became continuous, more severe, and required hospitalization.

Analgesics gave partial relief. Some relief was obtained after taking any of the following medications separately or in various combinations: phenacetin, caffeine, diphenhydramine, aspirin, butalbital, dihydroergotamine, ergotamine tartrate, propiphenazone, and paracetamol.
Her medical history was significant for occipital and frontal head traumas at ages 5 and 11 years. She had mild arterial hypertension, controlled by diet. The family history revealed her mother and sister had chronic headaches.

Her general physical and neurologic examinations were normal. Complete blood count, sedimentation rate, ANA, electroencephalogram, lumbar spinal fluid examination, and four-vessel cranial angiography showed no abnormalities. After angiography, she had a 2-day period of total visual loss that slowly resolved. Two days after angiography, a computed tomographic (CT) scan was done and showed a small hypodense lesion in the left internal capsule. Roentgenograms of the cervical spine showed minimal osteoarthrosis.

Indomethacin at 75 mg per day substantially reduced the headache and with 100 mg per day, the headache was barely noticeable. During hospitalization, indomethacin was withdrawn, and the headache recurred. Indomethacin was readministered at a dosage of 150 mg per day, and the headache disappeared completely. Indomethacin withdrawal was attempted several times, and invariably the severe headaches recurred.

**DISCUSSION**

The headache syndromes described in these cases share several features. They are uncommon; differ in character from both migraine and "tension" headaches; respond rapidly and dramatically to indomethacin; are rare in children and adolescents; are more common in females, and tend to be unilateral, severe, and chronic. All patients had been seen by several physicians, and a prolonged period of time had elapsed before the specific diagnosis was made. Table 1 lists the indomethacin-responsive headache syndromes.

**Exertional headaches** are typically precipitated by exertion. This type of headache is well documented and is seen with coughing, sexual intercourse, and most frequently with sports. For the athlete, headaches may interfere with training, practice, and performance. With the increase in sexual activity and emphasis on athletic activities in the adolescent population, exertional headaches may be encountered with increasing frequency. The headaches occur during or after the activity and may be associated with nausea and vomiting. They may be generalized or sharply localized, are usually severe and usually brief, but may last up to 16 hours. Although most exertional headaches are benign, Rooke found 10% of patients to have an underlying intracranial disease. It is especially important to rule out an occult Arnold-Chiari malformation. Prognosis for complete remission is generally good.

The mechanism underlying exertional headache is not clear. One proposed mechanism suggests an increase in intrathoracic pressure, and a sudden increase in blood pressure leads to extracranial vasodilation. Action, such as head rotation and jumping, "may also be implicated because of traction of the intracranial contents." Predisposing factors include high altitude, heat, humidity, and lack of athletic training. One author believed that the cause of these headaches may be similar to that of altitude headaches. Indomethacin has been shown to completely control these headaches in 86% of the patients.

Evaluation of these patients includes a thorough history and general and neurologic examinations, as previously outlined. There should be no symptoms of increased intracranial pressure or progressive neurologic disease. The examinations should be normal. We believe that an MRI and MRA are necessary to rule out structural intracranial pathologies.

**Cyclic (cluster) migraine** comes in cycles (clusters) but is not related to and has no features of true cluster headache. The headache cycle occurs as groups of headaches separated by periods free or relatively free of headache. There are usually 1 to 12 cycles yearly. During the cycle, the headache occurs at a rate of four to seven times per week. Auras or scintillating scotomas or other focal neurologic symptoms are frequent in cyclic migraine, but certainly not in cluster headaches. A frequent symptom during the cycle was a constant low intensity, unilateral or bilateral headache between the actual migraine attacks. Most patients were female and the usual age of onset ranged from 7 to

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**Table 1. Indomethacin-Responsive Headache Syndromes**

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<th>Exertional headaches</th>
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<td>Benign effort headache</td>
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<td>Benign cough headache</td>
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<td>Benign coital headache</td>
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<tr>
<td>Cyclic (cluster) migraine</td>
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<tr>
<td>Paroxysmal hemicrania (episodic and chronic)</td>
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<tr>
<td>Hemicrania continua (episodic and chronic)</td>
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42 years. Many may have a positive family history of migraine. The headaches are accompanied by autonomic and central nervous system (CNS) symptoms, the most common being nausea and photophobia.

Cyclic migraine has been best controlled over the long term with indomethacin or lithium carbonate. It does not respond well to standard antimigraine therapy. Acute treatment with the triptans may be helpful but daily administration of these medications is contraindicated. If indomethacin treatment fails, lithium should be tried.

Chronic paroxysmal hemicrania (CPH) was first described in 1974 by Sjaastad and Dale.\textsuperscript{17} It may occur in an episodic form as well. CPH is characterized\textsuperscript{18} by multiple daily attacks, lasting 5 to 30 minutes each. They are unilateral, do not shift sides, and are excruciatingly severe with autonomic phenomena and a female preponderance. They can be precipitated by head movement and, at times, by alcohol or applying firm manual pressure to certain sensitive points in the neck.\textsuperscript{19} More than 100 cases have been reported, with the youngest patient being 3 years of age\textsuperscript{20-22}.

The pathogenesis of chronic paroxysmal hemi- crania is unclear. Certain similarities to cluster headaches suggest that there may be an abnormality of the hypothalamic regulation of circadian rhythms.\textsuperscript{23}

Medical evaluation should include an MRI and MRA with special views of the orbits.

The indomethacin dosage necessary for successful treatment ranges from 25 to 300 mg per day, with an average of 100 mg per day. The beneficial effects appear within 2 days (range, 1 to 5 days). On discontinuation, headache reappears in about 3 days (range, 1 to 14 days). Long-lasting remissions after discontinuation of indomethacin have been reported. Kudrow and Kudrow\textsuperscript{24} have reported successful abolition of the headache in a 9-year-old with aspirin prophylaxis.

Hemicrania continua was first described by Sjaastad and Spiering in 1984.\textsuperscript{25} It is an uncommon form of headache characterized by a steady, nonparoxysmal hemicrania localized anteriorly or anteroposteriorly and not associated with nausea. There are few accompanying symptoms.\textsuperscript{26} There are no known precipitating mechanisms.\textsuperscript{27} The pathogenesis is unclear, and this disorder is differentiated from CPH by its continuous nonparoxysmal pattern of pain. Most patients are female, and the onset ranges from 10 to 58 years of age.\textsuperscript{28} No family history has been reported. All patients were treated with indomethacin; the dosage varied from 50 mg to 150 mg per day with an average of 75 mg per day. Headache relief was obtained between 24 and 72 hours after starting treatment in most cases.

Several other headache syndromes have been reported to be indomethacin responsive. However, sufficient data regarding the syndromes of hypnic headache and chronic bilateral headache have not been accumulated, so these syndromes are not further discussed. Sunct another newly described short-lasting headache is not Indomethacin responsive.

Indomethacin, discovered in 1963, was approved initially to treat rheumatoid arthritis and related disorders.\textsuperscript{29} It is a potent anti-inflammatory analgesic with antipyretic activities, and its use has been expanded to the treatment of other disorders, including fever and headaches. It has properties similar to the salicylates. It is rapidly and almost completely absorbed after oral administration. The plasma concentration is attained within 2 hours if the patient has been fasting but is delayed when the medication is taken with or after meals. It is 90% plasma-bound and has a low concentration in the cerebrospinal fluid. Sixty percent is excreted in the urine within 48 hours.

A high incidence of side effects is associated with its chronic use. Serious side effects are seen in 10% of patients and, therefore, indomethacin should not be routinely used as an analgesic or antipyretic. Most side effects are dose-related and involve the gastrointestinal tract and CNS. The most frequent gastrointestinal side effect is nausea with or without vomiting and dyspepsia. Other gastrointestinal problems include diarrhea, abdominal distress or pain, constipation, anorexia, flatulence, rectal bleeding, ulcerative stomatitis, and gingival ulcers. It may reactivate latent peptic or intestinal lesions resulting in gastrointestinal bleeding. The most frequent CNS effect and also the most common side effect overall, ironically, are severe frontal headaches that occur in 25% to 50% of patients with chronic administration. Dizziness, vertigo, lightheadedness, and mental confusion may also occur. Severe depression, psychosis, hallucination, and suicides have occurred during chronic indomethacin treatment. Adverse hematologic, ocular, and otic side effects, including renal function impairment and renal failure,
occur in less than 1% of patients. Hypersensitivity reactions may also occur.\textsuperscript{30}

Indomethacin's usefulness as a specific headache therapy began in 1984 when Sjaastad and Dale\textsuperscript{17} characterized chronic paroxysmal hemicrania. The mechanism by which it exerts its effect is not known, but inhibition of prostaglandin synthesis has been implicated.\textsuperscript{31-33} Two other properties may also explain its effectiveness; it is a vasoconstrictor and decreases cerebrospinal fluid pressure.\textsuperscript{34} No effect on arterial blood pressure or PaCO\textsubscript{2} has been identified.\textsuperscript{31} One special property of indomethacin that is not seen with other nonsteroidal anti-inflammatory agents is its capability to decrease cerebral blood flow.\textsuperscript{35,36} It may affect cerebral flow by directly acting on smooth muscle and acting as a free-radical scavenger or interfering with calcium transport.\textsuperscript{37}

The indomethacin dosage for the described headache syndromes ranges from as little as 25 mg per day to 150 mg per day. An average dosage of 100 mg per day is usually required. Symptoms usually abate within 48 to 72 hours.

We believe that increased awareness of the specific symptoms of these uncommon headache syndromes will lead to their earlier recognition, treatment, and relief of symptoms. The natural history of these syndromes is not well known. If indomethacin is started, a response should occur within 72 to 96 hours. If no significant change is noted with the maximum dosage of indomethacin after 2 weeks, the diagnosis should be reconsidered and the drug discontinued. If the patient responds well to indomethacin, a periodic attempt to reduce the dosage that provides maximum relief should be initiated. The patient should be carefully monitored for gastrointestinal, hematologic, renal, and hepatic side effects.

CONCLUSION

The indomethacin-responsive headache syndromes can be recognized by their uncommon presentation. They are easily distinguished from migraine and tension headaches. Proper identification of these uncommon headache syndromes in children and adolescents is essential if appropriate therapy is to be instituted. Specific therapy will decrease pain rapidly and dramatically. Both physician visits and number of school days missed will decrease. The psychosocial impact of chronic pain on the child and the family will be diminished. The treatment plan, therapeutic limitations, and side effects should be explained in detail to both the patient and parents. Treatment must be monitored, the diagnosis reconsidered, and therapy changed if results are not rapid or side effects appear.

REFERENCES