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Case 2: Chronic daily headache in a teenager

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Case 1: Altered mental status – a state of confusion

A nine-year-old boy is brought to the emergency department by his mother after she found him lying on the bathroom floor vomiting. She explained that her son has had fever for five days accompanied by episodic nonbloody, nonbilious vomiting. Today, she found her son to have a temperature of 40°C and noticed that he began to act 'very sleepy'. Furthermore, she described several recent instances during the current illness when he was delirious and 'not acting himself'. He has had minimal relief of symptoms with ibuprofen and acetaminophen. He denied taking any other medications (such as acetylsalicylic acid) or using any recreational drugs, and reported no recent travel.

The patient was a healthy child with occasional 'strep throats'. He was briefly hospitalized three years previously for dehydration and vomiting. His mother and sister were both recently ill with viral symptoms that included fever and vomiting, but neither had any change in mental status. He lived at home with his mother, father, two siblings and two grandparents.

In the emergency department, the patient was slow to respond and would occasionally become confused when asked a few questions. According to the mother, he was drowsy and markedly less active, but was able to follow commands with a lot of encouragement. He appeared mildly dehydrated and had normal vital signs except for a temperature of 39.4°C. His neurological examination showed normal cranial nerve functions. His pupils were 3 mm in size and briskly reactive to light. The remainder of the examination produced no additional findings.

Due to the change in mental status, a more thorough evaluation was undertaken. Initial findings included normal blood chemistries, urinalysis and head computed tomography. His urine toxicology screen was negative. A complete blood count showed mild neutropenia. Cerebral spinal fluid (CSF) revealed a white blood cell count of 2×10^6/L, a red blood cell count of 7×10^6/L, protein of 0.23 g/L and glucose of 3.6 mmol/L. The patient was then admitted to the hospital for further evaluation and management.

Case 2: Chronic daily headache in a teenager

A 16-year-old boy presented to a paediatric neurology clinic with a six-month history of daily headaches. The headache developed fairly suddenly with no antecedent events. There was no aura preceding the headache pain. The headache was consistently left-sided with a constant feeling of pressure in the left temple, radiating into the left eye and neck, and rarely toward the right eye. The headache was described at times as stabbing and aching. Intermittently, above the continuous pain, he would have more severe exacerbations during which his left eye would become watery and light sensitive, associated with clear rhinorrhea. The exacerbations could last 30 min to 3 h, and could be triggered by positional change and exercise. Exacerbations occurred at any time of the day and even in the middle of the night. The patient used ibuprofen and acetaminophen with some relief, and gradually developed a pattern of frequent daily analgesic use. There had been no clear antecedent event before the onset of headache.

Medical history was significant for recurrent otitis media with tympanostomy tubes in early childhood, two mild concussions and multiple fractures from sports injuries. He had a comorbid diagnosis of obsessive-compulsive disorder for which he was on fluvoxamine. Despite his mental health difficulties, no recent psychosocial stressors were described. He had environmental allergies. A positive family history for migraine in the mother and maternal grandmother, and a younger sister with transient neonatal seizures was noted.

His vital signs and general physical examination were normal. He gave the impression of being in mild chronic pain. Mental status examination was normal. Cranial nerve examination showed no abnormalities including fundoscopy. Motor strength, tone and reflexes were normal. Sensory examination was normal and no balance or coordination changes were seen. A computed tomography (CT) of the head was normal.

An initial diagnosis of chronic daily headaches from analgesic overuse was made, and he was taken off all analgesic medications with no resolution of symptoms after four weeks. On establishing that he did not have medication-overuse headache, he was started on a medication that alleviated his symptoms and clarified the diagnosis.

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CASE 1 DIAGNOSIS: ACUTE ENCEPHALOPATHY CAUSED BY INFLUENZA INFECTION

A general assessment of a child with altered mental status leaves the treating practitioner with an extremely broad differential diagnosis. The etiology of acute-onset altered mental status can be divided into conditions arising from central nervous system (CNS) pathology (such as trauma, seizures, infection, neoplasm, vascular disorder and hydrocephalus) and those conditions that secondarily affect the brain and CNS (such as hypoxia, intoxication, metabolic abnormalities, dehydration and psychiatric conditions) (1). Narrowing the differential diagnosis can be accomplished by rapid assessment of the airway, breathing and circulatory functions, as well as the vital signs. In addition, obtaining an accurate history and performing a thorough physical and neurological examination will provide further clues to the etiology.

Although rheumatological and oncological conditions should also be considered, the presence of fever makes infectious etiologies more likely. Bacterial meningitis remains one of the leading infectious causes of diminished level of consciousness. The most common organisms cultured are *Streptococcus pneumoniae*, *Neisseria meningitidis* and to a lesser extent *Haemophilus influenzae*. Viral meningitis and encephalitis can also cause alterations in mental status. The most common viruses implicated as causes of altered mental status are herpes simplex virus, nonpolio enteroviruses, mumps, the arboviruses and Epstein-Barr viruses.

During his hospital stay, cultures of the throat, blood, and CSF were all negative. Parvovirus titres as well as CSF polymerase chain reaction for enteroviruses and herpes were also negative. The neutropenia resolved within a few days. Because the patient presented during the winter (February) season and influenza was present in the community, rapid viral antigen testing was performed, revealing a positive result for influenza B. Because this was the seventh day of illness, antiviral therapy was not instituted. The patient's symptoms gradually improved, with the change in mental status believed to be secondary to an influenza infection.

While viruses are well known to cause changes in mental status, influenza specifically is often overlooked as a potential cause. However, recent studies (2-5) suggest that influenza-associated neurological involvement is more common than originally believed. In a 2008 study (2) from Toronto, Ontario, 5% of children with acute childhood encephalitis/encephalopathy were found to have evidence of current influenza infection. Fever was found to be the most common prodromal symptom occurring in all patients, followed by cough and vomiting (2,4). A broad array of neurological manifestations can be observed such as altered mental status, seizures, cranial nerve abnormalities, hallucinations, abnormal behaviour and persistent irritability (2-5). With the ongoing novel influenza A (H1N1) pandemic, the Centers for Disease Control and Prevention (USA) has already reported several cases of neurological complications associated with this virus (6).

The pathogenesis of influenza-associated neurological manifestations remains unclear. The two proposed mechanisms include direct viral invasion of the CNS and the sustained systemic immune response or hypercytokinemia incited by the virus (2-4). The onset of neurological symptoms within a few days of the respiratory symptoms suggests an acute process rather than a postinfectious process. However, the majority of studies, except for a few cases, have not reported detection of the virus in the brain or in the CSF by polymerase chain reaction (2-4). Support of the second mechanism is suggested by the high levels of proinflammatory cytokines in the serum and CSF of children with influenza-associated encephalopathy (2,3). Whether this state is the cause of or a result of the severity of the disease remains to be determined.

Several poor prognostic findings in patients with influenza-associated encephalopathy have been observed: fever greater than 41.0°C, hyperglycemia, severely elevated transaminase levels, thrombocytopenia, and hematuria or proteinuria (5). Among Japanese patients, the mortality rate in patients with neurological symptoms can be as high as 30% (5). Antiviral therapy, if initiated within 48 h of the onset of the infection, has been shown to shorten the duration of symptoms by 24 h to 36 h and may reduce the complications associated with influenza infection (4,6). Its effectiveness in preventing or altering the course of neurological complications, once present, is unknown. However, the Centers for Disease Control and Prevention recommends that antiviral treatment be initiated as soon as possible for any hospitalized patients at high risk for developing complications, including those with neurological manifestations, caused by seasonal influenza or novel influenza A (H1N1) (7).

Recommendations on the particular antiviral medications to be used should depend on the specific circulating strain and the susceptibility pattern observed in the community.

CLINICAL PEARLS

- Influenza should be considered in patients presenting with fever and altered mental status if it is known that influenza viruses are circulating in the community and as more common or more life-threatening causes are eliminated.
- Given the appropriate clinical setting, rapid antigen testing for influenza should be obtained early in the course of patients with fever and altered mental status because it is easy to collect, can aid in the diagnosis and can rule out multiple causes right away.
- In patients seen early in the influenza illness or with complicated cases of influenza infection, treatment with antiviral medication should be considered to reduce the time course and the potential for further complications.

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CASE 2 DIAGNOSIS: HEMICRANIA CONTINUA

The boy was started on a trial of indomethacin at a dose of 25 mg three times daily, with complete resolution of his headaches within two days. He had no further headaches and remained on indomethacin treatment for four months, and then gradually tapered off with no further recurrences. This dramatic and complete response to indomethacin solidified the diagnosis of hemicrania continua.

Headaches are a common problem in children and adolescents. The incidence of headaches in children aged seven years and older is approximately 33%. However, they occur on a frequent basis in approximately 2.5% of the paediatric population. The incidence of headaches in those aged 15 years and older is slightly higher at approximately 50%, with frequent occurrences in approximately 15% of that population. Headaches are known to be more common in boys before puberty, with higher female preponderance postpuberty. General population studies suggest that headaches account for 10% of all school absences. Chronic daily headache presents a particular challenge to the health care provider because several primary and secondary etiologies can have a similar manifestation. Table 1 lists the more common considerations for children presenting with frequent or daily headaches (1).

Indomethacin-responsive headaches (IRHs) are uncommon in paediatrics, but of importance given their rapid and complete response to indomethacin. In fact, the response to indomethacin is effectively diagnostic as well as therapeutic, and may eliminate the need for other more expensive or invasive tests if considered early. The true IRHs seen in the paediatric population are hemicrania continua and paroxysmal hemicrania. With these headaches, a complete response to indomethacin is part of the diagnostic criteria. Exertional headaches and primary stabbing headaches are also highly responsive to indomethacin but do not require a response for diagnosis. Diagnostic criteria for these headache syndromes are itemized in Table 2. Atypical patterns of hemicrania continua and paroxysmal hemicrania, such as bilateral head pain, lack of autonomic features, and temporomandibular and otic pain, do occur in paediatric patients. Consideration should be given for a trial of indomethacin in the setting of persistent daily headache or paroxysmal headaches of short duration that do not fit the typical diagnostic criteria for migraine and/or tension-type headache. However, this needs to be within the context of a normal neurological examination and all secondary causes of headache should be ruled out.

TABLE 1
Causes of chronic daily headaches in children

Primary headache	Secondary headache
Long-duration headaches:	Medication overuse headache
Chronic migraine	Raised intracranial pressure
Chronic tension-type headache	(eg, benign intracranial hypertension)
Hemicrania continua	Space-occupying lesion
New daily persistent headache	Sinus thrombosis
Short-duration headaches:	Infectious origin:
Chronic cluster headache	Chronic postinfection headache
Chronic paroxysmal hemicrania	Chronic postbacterial meningitis
Primary stabbing headache	headache
	Sinus infection
	Post-traumatic origin:
	Chronic post-traumatic headache
	Chronic headache attributed to other head or neck trauma

In hemicrania continua, most cases occur in female patients and the age of onset ranges from 10 to 58 years. Patients treated with indomethacin report complete relief of symptoms between 24 h to 72 h after starting treatment. Doses can vary from 50 mg/day to 300 mg/day, with an average of 75 mg/day in divided doses needed for most paediatric patients. A starting dose of 25 mg three times daily is recommended. The dosage should be increased to 50 mg three times per day if the patient has not responded within 48 h. A dose of 100 mg three times daily should be achieved for a week before eliminating the possibility of an IRH. Typically, patients are maintained on indomethacin for at least three months before weaning, but may need a longer term of therapy to avoid headaches (2). Indomethacin was discovered in 1963 for its potent anti-inflammatory, analgesic and antipyretic properties via cyclooxygenase inhibition and prevention of prostaglandin synthesis. The main mechanism in controlling headaches stems from its function as a potent cerebral vasoconstrictor, which is a special property of indomethacin differing from other nonsteroidal anti-inflammatory drugs (NSAIDS). It is known to reduce cerebral blood flow by 18% to 50%, while leaving cerebral metabolism unchanged. Indomethacin also acts as a free

TABLE 2
Indomethacin-responsive headaches in children

Hemicrania continua	Paroxysmal hemicrania	Primary exertional headache	Primary stabbing headache
A. Headache for more than three months fulfilling criteria B to D	A. At least 20 attacks	A. Headache specifically brought on by and occurring during or after physical exercise	A. Head pain occurring as a single stab or a series of stabs
B. All of the following characteristics: unilateral (one-sided pain without side shift), daily and continuous, without pain-free periods; and moderate intensity, but with exacerbations of severe pain	B. Attacks of severe unilateral orbital, supraorbital and/or temporal pain always on the same side lasting 2 min to 30 min	B. Pulsating in nature	B. Exclusively or predominantly felt in the distribution of the first division of the trigeminal nerve
C. At least one of the following autonomic features occurs during exacerbations and ipsilateral to the side of pain: conjunctival injection and/or lacrimation; nasal congestion and/or rhinorrhea; ptosis; and/or miosis	C. Attack frequency more than five per day for more than half of the time (periods with lower frequency may occur)	C. Lasts from 5 min to 48 h	C. Stabs last for up to a few seconds and recur with irregular frequency ranging from one to many per day
D. Complete response to therapeutic doses of indomethacin	D. Pain associated with at least one of the following signs/symptoms on the symptomatic side: conjunctival injection, lacrimation, nasal congestion, rhinorrhea, ptosis and/or miosis and eyelid edema	Note: This is often worse in hot, humid weather or high altitude	D. No accompanying symptoms
	E. Absolute effectiveness of indomethacin in therapeutic doses		E. Not attributed to another disorder
	Note: Episodic and chronic variants are recognized depending on the presence of remission-free periods of greater than one month		

The diagnostic criteria include no other secondary explanation for the headaches. Data adapted from reference 3

radical scavenger and interferes with calcium transport. There is good oral absorption of indomethacin, with a 2 h delay in plasma concentration when consumed with meals. It is 90% plasma bound with 60% renal excretion in 48 h. It is available both orally and rectally.

It is important to recognize the high incidence of side effects with chronic use of indomethacin. Gastrointestinal side effects including dyspepsia, nausea, vomiting, vertigo and gastric bleeding are commonly reported. To prevent gastric adverse effects, antacids, an H_2 antagonist or proton pump inhibitor may be co-administered when indomethacin is being used for longer periods. An indomethacin suppository is another option for gastric intolerance or when a higher dose (eg, 300 mg/day) is needed. Interestingly, frontal headache has been reported as a side effect as well. Other rare side effects include hypersensitivity reactions, suicidal behaviour and severe depression, psychosis, and renal impairment. Patients should be cautioned against using other NSAIDs while on indomethacin to avoid potentiating any gastrointestinal side effects. Patients should also be cautioned against using other medications such as anticoagulants, diuretics, methotrexate, cyclosporine and antihypertensive agents. The main contraindication remains in patients in whom acute asthmatic attacks, urticaria or rhinitis are precipitated by administration of this drug or known to have a similar reaction to other NSAIDS.

CLINICAL PEARLS

- IRH syndromes are uncommon in the paediatric population and so may be easily overlooked in clinical practice due to lack of knowledge.
- IRH syndromes have a rapid and dramatic response to indomethacin soon after administration.
- A trial of indomethacin for headaches not responding to conventional medication may be warranted provided secondary causes of intractable headache have been ruled out and the neurological examination is normal. In these cases, a short course of indomethacin is beneficial as a diagnostic procedure.
- At least three months of treatment are recommended before trying to wean the medication.

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