New Daily Persistent Headache in Children and Adults

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New daily persistent headache (NDPH) is frequently seen in young patients with chronic daily headache. NDPH begins with a sudden onset, often associated with an infection or other physical stress. This headache syndrome is difficult to treat and may persist for years. This review discusses the epidemiology, comorbid symptoms, evaluation, and treatment of this disorder.

Introduction

The diagnosis of chronic daily headache (CDH) is based on the presence of headache for at least 15 days in a 1-month period over a period of 3 consecutive months and with no underlying organic pathology [1,2]. CDH has presented in nearly 30% of the patients observed in headache specialty clinics [3]. The prevalence of CDH in the general adult population is approximately 4% [4,5]. In a population-based sample of middle-school children, CDH had a prevalence of 2.4% in girls and 0.8% in boys [6]. Silberstein et al. [7] have defined four different categories of CDH on the basis of symptoms: transformed or chronic migraine, chronic tension-type headache (TTH), new daily persistent headache (NDPH), and hemicrania continua.

NDPH is a Unique Form of Chronic Daily Headache

NDPH was first described in 1986 [8]. According to the criteria of the International Headache Society, the defining characteristic of NDPH is a daily, unremitting headache from very soon after the onset of the initial headache (within 3 days at most). The pain is typically bilateral, pressing or tightening, and of mild to moderate intensity. This condition occurs in a patient with no significant prior headache history. Patients with NDPH may describe their headaches as having either migrainous or tension-type features [9].

NDPH Occurs More Frequently in Young Patients

NDPH is a more frequent diagnosis in children than in adults. In studies looking primarily at adult patients, the frequency of NDPH has been estimated to be 1.7% to 10.8% of patients with CDH [10]. In contrast, studies in children have found NDPH to occur more frequently, with a frequency of 13% to 35% [11–13]. In a study of 56 patients with NDPH, Li and Rozen [14] observed that the peak age at onset was in the second and third decades in women and in the fifth decade in men.

From a patient's perspective, the abrupt onset is quite remarkable. In this author's experience, most patients will remember the day (and sometimes the specific hour) in which the headaches began. With such a dramatic onset to the headaches, it is difficult for both the patient and the practitioner to accept that there is no definable abnormality on neuroimaging studies or other laboratory testing to explain the headaches.

How are NDPHs Triggered?

The pathophysiology of NDPH is unknown. Li and Rozen [14] identified viral infections, extracranial surgery, and stressful life events as triggers for the new onset of headache, primarily in adult patients. However, up to 40% of their patients did not have a known trigger. In addition to the risk factors previously mentioned, the transformation of an episodic headache into a chronic headache (or the onset of NDPH) in adults has also been associated with hypothyroidism, hypertension, consumption of alcohol more than 3 times per week, analgesic overuse, daily consumption of caffeine [15], multiple types of infections [16], and stressful life events [17]. A particularly interesting observation is that many patients will wake up after extracranial surgery (such as an appendectomy) with NDPH [13,18,19].

A previous study by this author [13] asked what factors are associated with the onset of a NDPH in children. It

demonstrated that NDPH occurred in 23% of the patients (18 years or younger) with CDH. Factors associated with the onset of NDPH included febrile illness, minor head trauma, high-altitude climbing, and extracranial surgery. Some patients had no identifiable inciting factor.

Infections are the factor most frequently associated with NDPH. Diaz-Mitoma et al. [20] noted that 84% of patients with NDPH had evidence of "active" Epstein-Barr virus infection. However, other infections can also provoke NDPH [16], and 43% of the patients in the childhood NDPH study reported some type of infection at the onset of symptoms [13]. Meineri et al. [18] reported NDPH associated with recent seroconversion to herpes simplex virus or cytomegalovirus. Taken together, these data suggest that NDPH is not the result of a specific infectious agent, but may reflect a nonspecific response to infection or physical stress.

Rozen and Swidan [21] found that NDPH patients, as well as those with chronic migraine, have elevated levels of tumor necrosis factor (TNF)-α in their cerebrospinal fluid. TNF is a proinflammatory cytokine, potentially involved both in inflammation and pain. The presence or absence of a precipitating infection, however, did not affect the TNF levels. This is a fascinating finding, but its significance remains to be determined.

The same phenomenon of an abrupt onset of CDH may also occur in patients with episodic migraine. This author [13] found that 30% of chronic migraine patients reported an abrupt onset to their chronic migraine, reminiscent of NDPH. These patients would often exhibit inciting factors, such as infection, that are similar to those of patients with NDPH.

The exact pathophysiology of how these events result in NDPH is unknown. The temporal relationship of a seroconversion on viral titers or head trauma to the onset of the headache is often impressive and striking, but certainly that close temporal relationship does not prove causation. These factors may not "cause" the headache, but they may aggravate an underlying predisposition to headaches. This author speculates that these physiologic stressors result in the initiation of the headache in a predisposed individual. Unanswered questions include why there is such a persistence of the headache, even after the inciting factor has resolved, and why do only certain individuals develop NDPH? These phenomena may relate to as yet unidentified host factors.

What could be the potential host factors? Rozen et al. [22] reported that cervical joint hypermobility may be a predisposing factor for NDPH. Similar observations have been hypothesized in other childhood pain syndromes. In this author's anecdotal experience, patients with NDPH seem to frequently have a family history of migraine. We may be dealing with a combination of host factors related to the immune system, connective tissue structure, and the familial nature of migraine.

Headache Symptoms in NDPH

Li and Rozen [14] reported that most (79%) patients had a continuous headache, often with symptoms of nausea (68%), photophobia (66%), phonophobia (61%), and lightheadedness (55%). This was a female-predominant disorder. Gladstein and Holden [11] reported that many children that they diagnosed with NDPH have a pattern of severe intermittent migraines with an underlying continuous TTH.

In this author's experience, most pediatric patients will complain of at least two distinct types of headaches. These children will describe episodes of severe intermittent headaches that are migraine-like. These are often associated with nausea during the most severe times, and the patient will frequently have photophobia, phonophobia, and osmophobia. Sleep will sometimes help, but they will still have persistent headache when they awaken. These severe headaches will typically occur multiple times a week.

The pediatric patient with NDPH may also complain of a continuous headache that is present 24 hours a day, 7 days a week. This continuous headache may wax and wane in severity, often being worse either in the morning or at the end of the school day. Some patients may also describe this constant headache as having features of TTH, with the pain being band-like or crushing rather than throbbing. Although one may characterize the severe type of headache as migraine, and the continuous type of headache as TTH, if you directly ask the child to compare these two headache types, the child will frequently say that the two headache types are the same in quality, and their only difference is in severity.

Comorbid Symptoms in NDPH

Mack and Terrell [23] have found that the frequency of comorbid symptoms in pediatric patients with NDPH is similar to pediatric patients with chronic or transformed migraine. Sleep is disrupted in at least two thirds of the patients who have NDPH. A common sleep disturbance is a delayed onset in sleep, and often times these individuals will not be able to fall asleep for 30 minutes to several hours after they go to bed. In these patients, it was unclear if the poor sleep is causing chronic headaches, or if the headaches are not allowing the patients to get good sleep. It is my opinion that at the start of the CDH cycle, the poor sleep is often due to the severe headache pain. However, as the CDHs persist, usually the sleep problem becomes multifactorial and may include pain issues, poor sleep hygiene, and a natural tendency for teens to want to be "night owls." Improvement in sleep is seen after better headache control, improved sleep hygiene, and avoidance of caffeine. The use of some preventatives, such as amitriptyline, gabapentin, or topiramate, may help sleep. Melatonin, given before sleep, can also be helpful.

Many CDH patients have symptoms of dizziness. The dizziness often occurs during times when the headaches are more severe. The dizziness is associated with feeling weak and unsteady, and with changes (blurring or loss of) in vision. When the dizziness is primarily related to the severe headache, then improvement will occur once the headache control is improved.

At times, however, patients may notice dizziness between the episodes of severe headaches. This latter dizziness is often positional, and patients will complain of syncope or near syncope after standing. The dizziness is particularly prominent in the morning after they first wake up. The patient often experiences mild symptoms of this dizziness if standing for several minutes in the office. One may see either a significant tachycardia with standing (postural orthostatic tachycardia syndrome [POTS]) and/or a decrease in blood pressure. A tilt table test will help confirm these findings. Some patients will have developed the sudden onset of POTS and a chronic (NDPH) headache at the same time. In children, these orthostatic symptoms can be treated by increasing the child's fluid and salt intake, or when necessary, with the use of β-blockers (such as metoprolol) when there is significant orthostatic tachycardia, and/or pressors (such as midodrine) when there is an orthostatic drop in blood pressure.

Mood problems and anxiety frequently coexist with CDH. The mood problems may precede or follow the onset of the headache. In some patients, it is possible to resolve the problems with mood without affecting the headache; in other patients, it is possible to improve the headaches without improving the mood problem. It is common for patients to first develop a headache, and then, after months of unrelenting symptoms, develop sadness because of the pain and frustration with their situation. CDH and NDPH should be considered a primary headache syndrome and not a mood disorder. The symptoms of headache and mood both need to be addressed.

In some patients, pain can also occur at other body sites. This can include nonspecific abdominal pain, back pain, neck pain, and diffuse muscle and joint pain. Often times, no additional organic etiology is found to explain these additional pain symptoms. The longer the duration of the CDH syndrome, the more prominent these symptoms seem to become. These additional areas of pain seem to be part of a much more diffuse pain syndrome. One can speculate that brainstem centers that relay pain become more effective in their role as time goes on. Over time, sensations that are not typically painful are perceived as pain and involve wider areas of the body than just the head.

How Should NDPH Patients be Evaluated?

The evaluation of a patient with NDPH should include a thorough history and physical examination, as well as consideration of a neuroimaging study, and in the occasional patient, a lumbar puncture. In selected patients, tilt table testing or sleep studies may also be of value.

In children, the most useful role of the neuroimaging study in CDH is to reassure the patient and family. An imaging study is most likely to be significantly abnormal if there are focal deficits on examination or if there is a history of seizures in the patient [24]. Occasionally, white matter abnormalities, arachnoid cysts, or pineal cysts will be seen that are generally believed to be of no clinical significance to CDH [25]. If a patient has had a significant history of head or neck trauma, particularly at the onset of CDH, then magnetic resonance angiography of the neck should also be considered to rule out a possible carotid dissection. When pseudotumor cerebri is a strong consideration, then magnetic resonance venography should also be considered because sinus thrombosis can cause increased intracranial pressure.

Idiopathic intracranial hypertension (IIH) is a constellation of symptoms and signs that include increased intracranial pressure with a normal MRI scan. A patient with IIH may complain of a headache, diplopia, tinnitus, and eye pain. On examination, the patient may have papilledema and a sixth nerve palsy. Although the diagnosis is easy to make when all these signs and symptoms are present, there are some rare patients who may have IIH without showing significant papilledema. If a lumbar puncture is performed, care should be taken to make sure the spinal fluid pressure is taken while the patient is relaxed, and the legs extended for an accurate measurement. Some obese patients may normally have slightly higher pressures. Unfortunately, many patients with NDPH seem to be prone to getting a postlumbar puncture headache. Although a lumbar puncture can be a valuable diagnostic tool, one should be judicious about its use because it can make a patient with a headache significantly worse rather than better.

The most informative serum studies may include thyroid studies [26]. As many as 4% of adults with chronic headache have thyroid abnormalities, although this is less frequently observed in children. Sedimentation rates could be used to look for signs of an arteritis, although this is a fairly nonspecific test and false-positives and false-negatives are common. If there are other clinical signs of lupus in addition to headache, then antinuclear antibody (ANA) levels in the blood should be measured. When headache is the only symptom, then measuring ANA levels can add more confusion rather than clarity to the situation.

Because many patients will transition from a headache-free period or from episodic migraines to chronic migraines during an infection, physicians should consider testing for Epstein-Barr virus, West Nile virus, and Lyme disease. Although some of the viral etiologies have no specific treatment, many patients and their families appreciate knowing there was a physiologic underpinning for the transition to a chronic headache.

Practical Implications for Therapy

Expert opinion suggests that NDPH is a very treatment–refractory headache disorder [18,19,27]. However, there is no direct comparative data in the primary literature to support or refute the view that this is any more difficult to treat than other CDH syndromes. Many of the initial series on this disorder came from tertiary referral centers, as opposed to population-based samples, resulting in a potential selection bias.

Comments by the International Headache Society note that NDPH may take either of two subforms: a self-limiting subform that typically resolves without therapy within several months, or a refractory subform that is resistant to aggressive treatment programs [9]. In the original paper describing NDPH by Vanast [8], it was noted that 86% of patients were headache-free at 24 months.

This author tends to use either amitriptyline, propranolol, or topiramate as an initial medication in the treatment of CDH, including NDPH. Amitriptyline is helpful for many of my patients with sleep difficulties, and a starting dosage is typically 0.5 mg/kg per day (25 mg in a teenager), increasing to 1–3 mg/kg per day (50–150 mg/day in a typical teenager or adult) as a target dosage. Nortriptyline seems to be better tolerated by adult patients. Sleep seems to improve first, followed by a reduction in the severe headaches, followed by an improvement in the "24/7" continuous headaches. If that is ineffective or poorly tolerated, then I try propranolol at 1 mg/kg per day. For teenagers, this comes in a once-daily, sustained-released form at 60 mg or 80 mg. In younger children, I will use atenolol at a 25 mg or 50 mg tablet, also given once daily. A typical adult dosage of propranolol will be between 60–120 mg a day. Finally, one can consider topiramate. This could be started at 25 mg every evening (0.5 mg/kg/day) and titrated weekly upward by 25 mg per week. A typical target dosage would be between 50–200 mg per day [28•].

It is important to state the expectations of preventative therapy to the patient and the family. Preventative therapy may improve the headaches but it will not eliminate the headaches in the short-term. After 1 month of an effective therapy, a reasonable expectation would be to have less frequent severe headache episodes and a decrease in the intensity of the all-the-time, 24/7 headache.

It is rare to see complete resolution of the headaches after a short period of time. It is usually the severe headaches that are keeping children out of school, rather than the 24/7 headache. Improvement of the severe headaches usually allows the patient to return to school. In my experience, when the continuous 24/7 headache is rated as less than "5" (on a 10-point scale), patients are able to become more functional in all of their activities. Once a trend toward improvement is seen, the dose of medication is adjusted for optimal control of the headaches, and the patient is continued on the preventative for at least 6 months of good (but rarely complete) symptom control.

These symptoms are indeed a challenge, and some patients will not respond to medications. In such a situation, one should consider alternative approaches, including the use of biobehavioral strategies, physiotherapy, trigger point injections, and botulinum toxin.

Conclusions

Pediatric patients with or without a previous headache history can abruptly transform into a CDH syndrome. Treating physicians should be aware of the multiple factors that are associated with this transition and offer appropriate counseling and therapies to their patients.

Disclosure

No potential conflict of interest relevant to this article has been reported.

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