

# New Daily Persistent Headache

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New daily persistent headache (NDPH), which is the acute onset of headache within 3 days and is persistent for 15 days or more each month for at least 3 months, is a predominantly female heterogeneous subtype of chronic daily headache, typically with migraine features of unknown etiology. NDPH may be a presentation of other primary headaches such as new onset migraine, tension, or benign thunderclap headache. The headaches can be difficult to treat. The diagnosis is one of excluding the many secondary types or NDPH mimics, which is especially critical early in the course of the disease when a secondary etiology is more likely. NDPH mimics include postmeningitis headache, NDPH with medication rebound, neoplasms, temporal arteritis, chronic meningitis, chronic subdural hematoma, post-traumatic headaches, sphenoid sinusitis, hypertension, subarachnoid hemorrhage, low cerebrospinal fluid pressure syndrome, cervical artery dissections, pseudotumor cerebri without papilledema, and cerebral venous thrombosis.

## Introduction

The term new daily persistent headache (NDPH) was coined by Vanast [1••] in 1986. Table 1 provides the International Headache Society proposed 2003 criteria for NDPH, based on an earlier proposal by Silberstein *et al.* [2]. There is no information on the prevalence and incidence of NDPH in the general population. This article presents two typical case histories, reviews NDPH, and discusses secondary causes of daily headache with an acute onset within 3 days (NDPH mimics).

## Case Studies

### Case 1

A 37-year-old woman was seen for evaluation of a new-onset daily headache that lasted 36 days. At the onset of the headache, she also had a sore throat without fever for 3 days. An ear, nose, and throat physician administered an antibiotic. She described a rather constant, generalized pressure and squeezing sensation with light sensitivity,

which was severe intermittently during the day. Two weeks before the evaluation, she experienced nausea. She did not have a fever and, other than the initial sore throat, did not experience any systemic symptoms. Her family physician prescribed Fioricet (Qualitest Pharmaceuticals, Huntsville, AL; two to three daily for 2 weeks, which dulled the headaches), naproxen, and citalopram. Three years before evaluation, she had frequent, mild, bifrontal, pressure-type headaches for approximately 1 year, which resolved after she quit her job. She also had two bad headaches during the previous 2 years, which consisted of a visual aura followed by a bifrontal throbbing with light sensitivity that resolved with sleep.

Medical history included resection of a noninvasive melanoma 10 months before evaluation. General and neurologic examinations were normal.

A magnetic resonance imaging (MRI) scan of the brain with and without contrast was normal. Routine blood studies were normal. A lumbar puncture revealed a normal opening pressure and normal cerebrospinal fluid (CSF). After 2 days of treatment in the hospital with intravenous metoclopramide, dihydroergotamine, and valproate every 8 hours, the headaches resolved completely.

The patient was placed on 25 mg of nortriptyline at bedtime, which was increased to 50 mg after 1 month. The headaches decreased gradually in frequency from three weekly to one weekly and then fewer. During the follow-up 4 months later, she reported only one migraine without aura during the past 7 weeks, which responded to oral sumatriptan [3].

### Case 2

A 24-year-old woman previously had only occasional mild headaches. On October 18, 2001, she was at a carnival when she developed a mild headache, which became severe within a few hours. She had daily headaches until the middle of January 2002. From then until July 2002, when she was evaluated initially, the headaches were occurring 4 to 5 days each week. The headaches were described as a severe, left-sided fronto-temporal-parietal, nonthrobbing pain associated with light and noise sensitivity and sometimes blurred vision. Each headache could last from 1 to 3 days. The headaches could be triggered by stress.

She was treated initially by a primary care physician. A computed tomography (CT) scan of the brain 2 months after the onset of headache was negative. She was administered various preventative medications, including propranolol, amitriptyline, and topiramate without benefit.

**Table 1. Proposed 2003 International Headache Society criteria for new daily persistent headache**

- A. Headache frequency of 15 days or more each month (on average) for 3 months
- B. Duration of headache 4 or more hours daily
- C. Acute onset of headache in less than 3 days
- D. Excludes trigeminal autonomic cephalgias\*
- E. At least one of the following
  - 1. Excludes sections 5 through 12†
  - 2. Disorders in section I are excluded by appropriate investigations
  - 3. If a disorder from Section I exists, it is unlikely to account for the new headache

\*Trigeminal autonomic cephalgias make up Section 3 of the revised International Headache Society classification previously called cluster headache and related symptoms.

†Refers to the International Headache Society classification categories.

Midrin (Elan Pharmaceuticals, Princeton, NJ), Imitrex tablets (GlaxoSmithKline, Research Triangle Park, NC) and subcutaneous injections, Amerge (GlaxoSmithKline, Research Triangle Park, NC), and Fiorinal (Novartis Pharmaceuticals, East Hanover, NJ) did not help. Cafergot (Novartis Pharmaceuticals, East Hanover, NJ) reduced the intensity of the headaches. Medical history was negative.

Her neurologic examination was normal. An MRI scan of the brain was normal. She was administered 75 mg of Effexor XR (Wyeth, Madison, NJ) daily. Three months later, the headache frequency was decreased to three to four each month.

These two cases are typical of NDPH. For the first patient, the headaches followed pharyngitis. In the second, the headaches did not have an obvious precipitant and the patient could pinpoint the exact day and circumstances when the headaches began.

## Clinical Features of New Daily Persistent Headaches

### Vanast's series: the first

There are only two patient series defining the clinical features of NDPH. Vanast [1••] reported on 45 patients, 19 men (80% of the ages were 26 to 45 years) and 26 women (ages 16 to 35 years), who were seen in the course of 24 months in Edmonton, Alberta, Canada. The headache pain was described as steady in 72% of the patients, pounding in 28%, and unilateral in 38%. Associated symptoms included nausea (57% of the men and 53% of the women), vomiting (5% of the men, 19% of the women), light sensitivity (26% of the men and 42% of the women), and noise sensitivity (21% of the men, 53% of the women). The neurologic examination, blood tests, and CT scans of the brain were always normal. Headaches disappeared without treatment for many of the patients. The percent of men and women, respectively, whose headaches disappeared at various time intervals was 30% and 30%, respectively, at 3 months, 68% and 52%, respec-

tively, at 6 months, 80% and 58%, respectively, at 12 months, and 86% and 73%, respectively, at 24 months.

### Li and Rozen's series

Li and Rozen [4••] described the clinical characteristics of 56 patients with NDPH (40 women and 16 men) who were identified from a retrospective 3-year chart review and seen at the Jefferson Headache Clinic in Philadelphia. The age of onset ranged from 12 to 78 years, with a peak age of onset during the second and third decade of life for women and during the fifth decade for men. Eighty-two percent of the patients were able to report the exact day when the headache started. The onset was associated with a cold or flu-like illness in 30% of the patients, extracranial surgery (*eg*, hysterectomy) in 12%, and a stressful life event in 12%. There was a history of headache in 38% of the patients. At the time of presentation at Jefferson, the duration of NDPH was at least 6 months in all of the patients and more than 5 years in many of the patients. The duration of the daily headaches, which were bilateral in 61%, ranged from 1.5 hours to 24 hours, with 79% of the headaches being continuous. Baseline average pain intensity was moderate in 61% of the patients and severe in 21%. Associated symptoms included nausea in 68%, photophobia in 66%, phonophobia in 60%, and lightheadedness in 55%. Laboratory test results and neuroimaging, except for Epstein-Barr titers, which were positive in five of seven patients tested, were normal in all of the patients. Lumbar puncture and cerebrospinal fluid examinations were normal in the 23 patients who were tested.

### Can new daily persistent headache have an infectious etiology in some cases?

Based on these two studies, NDPH is a female predominant, heterogeneous subtype of chronic daily headache with typically migrainous features of unknown etiology. NDPH may be a presentation of other primary headaches such as migraine, tension-type, and benign thunderclap headache (Table 2). However, there may be an infectious etiology for NDPH in a subset of patients.

#### Epstein-Barr virus

Diaz-Mitoma *et al.* [5] identified oropharyngeal secretion of the Epstein-Barr virus (EBV) by nucleic acid hybridization in 20 of 32 patients with NDPH compared with four of 32 age- and sex-matched control subjects. A history of infectious mononucleosis was identified in 12 of the patients with NDPH. Eighty-four percent of the patients with NDPH were thought to have active EBV infection. Santoni and Santoni-Williams [6] identified evidence of systemic infection in 108 patients with new daily headaches, including *Salmonella*, adenovirus, toxoplasmosis, herpes zoster, EBV, and *Escherichia coli* urinary tract infections. The small sample of Li and Rozen's patients [4••] tested also reflected a possible link to EBV infection. It is unknown how an infection could cause NDPH.

**Table 2. Differential diagnosis of new daily headaches**

New daily persistent headache	New daily persistent headache mimics
Chronic migraine	Postmeningitis headache
Chronic tension-type headache	Chronic meningitis
Combined features	Primary with medication rebound
Benign thunderclap headache	Neoplasms
	Temporal arteritis
	Chronic subdural hematoma
	Post-traumatic headache
	Sphenoid sinusitis
	Hypertension
	Subarachnoid hemorrhage
	Low cerebrospinal fluid pressure syndrome
	Cervical artery dissections
	Pseudotumor cerebri
	Cerebral venous thrombosis

#### *Postmeningitis headache*

Another consideration is postmeningitis headache. It is possible that some of the patients with NDPH actually had a viral meningitis that was not diagnosed and then had persistence of the headache or postmeningitis chronic daily headache. If a CSF examination was performed later, the CSF could certainly have become normal again. Support for this idea comes from the study by Neufeld *et al.* [7], who interviewed 70 patients with viral (53 patients) or bacterial meningitis (17 patients) after a mean time of 5 years later. After recovery from meningitis, new onset headache occurred in 19 patients (migrainous in six); seven of 13 patients with a history of headaches reported increased severity of their headaches. Those who developed headaches were younger than those who did not. They found no relationship among gender, family history, type of meningitis, and the development of headaches. Neufeld *et al.* [7] concluded that, through an unknown mechanism, there was an association of meningitis and persistent recurrent migrainous or nonmigrainous headaches.

#### Evaluation and Treatment

New daily persistent headache is a diagnosis based on excluding the many secondary causes of new daily headaches, which are discussed in the next section, as appropriate for the individual patient [8••,9,10]. Although Vanast [1••] described a disorder that resolved without treatment in most cases, Evans and Rozen [3] and Goadsby and Boes [11] reported that these patients were refractory to treatment. However, it is possible that this opinion of intractability may reflect selection bias based on the treatment of patients seen in tertiary headache clinics. The treatment is the same as it would be for other chronic daily headaches.

Similar to treating other chronic daily headaches, the possibility of medication overuse or rebound is a concern when treating NDPH.

#### Secondary Causes: New Daily Persistent Headache Mimics

Table 2 lists some of the secondary causes of a new daily headache, which can be NDPH mimics. Some of these secondary disorders may have a thunderclap or sudden onset of severe headache; others may develop over 1 to 3 days and meet the onset period criteria for NDPH. One possible presentation of NDPH, which may have a good prognosis if untreated (as suggested by Vanast [1••]), is that it transformed into a medication rebound type headache by overuse of symptomatic medications. This may be a frequent scenario when patients with NDPH are seen in headache clinics. New onset daily headaches with a normal neurologic examination could also result from various other causes (particularly when seen within the first several months after onset) including postmeningitis headache, chronic meningitis, brain tumors, leptomenigeal metastasis, temporal arteritis, chronic subdural hematomas, post-traumatic headaches, sphenoid sinusitis, and hypertension. When the headaches have been present for more than 3 months with a normal neurologic examination, the yield of testing is very low.

#### Subarachnoid hemorrhage

Subarachnoid hemorrhage (SAH) with a normal or near normal examination is always a potential concern when evaluating NDPH early in the course. Perhaps 50% of SAHs will present with a Hunt and Hess grade I (no symptoms or minimal headache, slight nuchal rigidity) or grade II (moderate to severe headache, no neurologic deficit other than cranial nerve palsy). Linn *et al.* [12] reported a series of 42 alert patients without focal findings with headache resulting from aneurysmal SAH. The headache had an onset that was almost instantaneous in 50% of the patients, more than 2 to 60 seconds in 24%, and more than 1 to 5 minutes in 19%. Twelve percent had a feeling of a "burst." The headaches were of moderate to severe intensity. Nineteen percent had a prior headache resembling the acute headache. Transient loss of consciousness ranging from 1 to 10 minutes was reported by 26% of the patients. The duration of the headache is almost always 1 hour or longer [13]. Sentinel or warning leak headaches usually subside in 1 or 2 days, but can last for 2 weeks in some cases [14].

#### Benign thunderclap headache

After SAH has been excluded, benign thunderclap headache is a consideration [15]. The headache, which is sudden and reaches maximum intensity within 30 seconds, usually lasts up to several hours, but a less severe headache may persist for weeks. Episodes of thunderclap headache

may occur repeatedly during a 7- to 14-day period. In up to one third of patients, the headache may recur over subsequent months to years. This acute and recurring form may be a type of migraine called crash migraine.

#### **Low cerebrospinal fluid pressure syndrome**

Low CSF pressure syndrome is an important treatable cause of NDPH with manifestations ranging from headache alone (which may or may not be orthostatic) to coma [16,17]. This syndrome may be a result of spontaneous CSF leaks of unknown cause, meningeal diverticulae, weak, attenuated dura, connective tissue disorders, spondylitic-dural tear, and trivial trauma. The syndrome also can result from traumatic leaks (head and spine trauma or surgery) and overdraining CSF shunts. The risk of postlumbar puncture headaches, which can persist for up to 1 year, can be reduced dramatically by the use of atraumatic lumbar puncture needles such as the Sprotte or Whitacre (PNA Medical Systems, Glens Falls, NY) [18,19••]. Unfortunately, use of the atraumatic needle, especially for patients who are at high risk for postlumbar puncture headaches (eg, younger women and those with a history of headaches) is sparse. Many physicians are not aware of the class I evidence on this issue.

Spontaneous intracranial hypotension can be a difficult diagnosis, especially when the orthostatic component is minimal or absent. The orthostatic worsening can be absent early in the clinical course and with chronicity. MRI abnormalities, which usually are (perhaps in 90% of the cases), but not always present, include diffuse pachymeningeal enhancement, sagging of the brain, subdural fluid collections, decrease in size of the ventricles, enlarged pituitary, engorged venous sinuses, and elongation of the brainstem in the anteroposterior plane. The CSF opening pressure and analysis can be normal, although there may be a decreased opening pressure, elevated protein level, presence of red blood cells, and a lymphocytic pleocytosis in many cases.

#### **Cervical artery dissections**

Cervical artery dissections can be a rare cause of new daily headaches [20]. Headache is a symptom in more than 75% of those with internal carotid artery dissections and 90% of those with symptomatic vertebral artery dissections. Headache can be the initial manifestation in almost 50% of those with internal carotid artery dissections. Occasionally, the headaches can persist intermittently for months, even years, and can lead to a pattern of chronic daily headaches, especially after cervical carotid artery dissection [21].

#### **Pseudotumor cerebri without papilledema**

Pseudotumor cerebri (PTC) can be a cause of new daily headaches and is easily suspected when papilledema is present. However, PTC without papilledema [22] can occur rarely and should be considered as the cause of NDPH, especially in obese women who account for 90% of the

cases of pseudotumor. Conversely, PTC can be present with papilledema and normal CSF opening pressure [23]. Papilledema can be present initially in PTC and then, rarely, resolve even though the intracranial pressure remains elevated [24]. Caution should be taken to avoid misdiagnosis (pseudo-pseudotumor cerebri) [25]. Although the CSF opening pressure can be up to 25 cm of water in obese patients, the pressure can be fictitiously elevated if the patient is not relaxed, the legs are flexed, and the abdominal muscles are contracted. Cerebral venous thrombosis also can be misdiagnosed as PTC when the appropriate neuroimaging study is not obtained.

#### **Cerebral venous thrombosis**

Headache is present in up to 90% of the patients with cerebral venous thrombosis (CVT) and often is the initial symptom. The headache can be unilateral or bilateral in any location, mild to severe, and intermittent or constant. The onset usually is subacute, but can be sudden or thunderclap. In more than 95% of the cases, the headache is associated with a variety of neurologic signs in the following percentages of patients: papilledema, 51%; seizures, 42%; focal deficits, 39%; encephalopathy, 31%; multiple cranial nerve palsies, 11%; bilateral cortical signs, 4%; and cerebellar signs, 3% [26]. CVT can be a mimic of PTC.

Neuroimaging studies have variable sensitivities in diagnosing CVT. CT diagnoses only approximately 20% of the cases of CVT when demonstrating the hyperdensity of the thrombosed sinus on plain images and the  $\delta$  sign seen with superior sagittal sinus thrombosis after contrast administration. Helical CT venography is a very sensitive diagnostic method. CVT may be missed on routine MRI of the brain, although echo-planar T2\*-weighted MRI may increase the sensitivity [27]. Magnetic resonance venography (MRV) increases the sensitivity of magnetic resonance, especially within the first 5 days of onset or after 6 weeks. CVT also can be demonstrated on conventional angiography.

Quattrone *et al.* [28••] investigated the occurrence of CVT in a series of 114 consecutive patients with chronic daily headache without papilledema by using MRV. CVT was detected in 9.6%. The CSF pressure was greater than 25 cm of water in only two of 11 patients diagnosed with CVT. Almost all of the patients with CVT were overweight (mean body mass index, 31.4; SD = 6.1). This intriguing study raises the question of whether MRV should be performed routinely in the evaluation of overweight patients with chronic daily headache. However, there are potential pitfalls in the diagnosis of CVT. For example, lack of flow in the proximal portion of the transverse sinus because of hypoplasia of the sinus, which is a normal variant, can simulate thrombosis on MRV. Anecdotally, based on the author's and other headache specialists' experience in obtaining MRV studies in patients with chronic daily headaches, 9.6% seems much too high. Confirmation by another prospective series would be of interest.

## Conclusions

New daily persistent headache is an interesting entity of uncertain etiology. NDPH may be a presentation of another primary type such as migraine, tension, or benign thunderclap headache. An infectious trigger may be present in some of the cases. There is little information available on the epidemiology and clinical features. Better treatments are needed. It can be a challenge to identify secondary causes of headache, which mimic NDPH.

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Is it possible that 9.6% of patients with chronic daily headaches without papilledema have CVT? Read the paper and judge for yourself and then decide whether you should routinely obtain MRI and MRV studies on overweight patients with CDH.