

Expert Opinion

Etiology and Treatment of New Daily Persistent Headache

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Abbreviations: NDPH new daily persistent headache, CDH chronic daily headache, EBV Epstein-Barr virus

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The onset of a headache which persists and is not relieved by usual headache medications can pose a difficult management problem.

CLINICAL HISTORY

A 37-year-old woman was seen for evaluation of a new-onset daily headache of 36 days' duration. At the onset of the headache, she also had a sore throat without fever for 3 days. An ear, nose, and throat physician started her on an antibiotic. She described a rather constant generalized pressure and squeezing sensation with light sensitivity which was intermittently severe any time of the day. On one occasion 2 weeks previously, she had nausea. She had no fever and other than the initial sore throat, no systemic symptoms. Her family physician prescribed Fioricet (two to three per day for 2 weeks) which dulled the headaches, naproxen, and citalopram. Three years prior to evaluation, she had frequent, mild, bifrontal, pressure-type headaches for about a year, which resolved after quitting her job. She also had two bad headaches during the prior 2 years which consisted of a visual aura followed by a bifrontal throbbing with light sensitivity which resolved with sleep.

Past medical history included resection of a non-invasive melanoma 10 months previously. General and neurological examinations were normal.

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

Questions.—Could the upper respiratory infection without apparent meningitis have triggered new-onset daily headache? How often are causes of new daily persistent headache (NDPH) identified? What treatment do you recommend?

EXPERT COMMENTARY

This patient had a history of migraine with aura and tension-type headaches. She presented with a daily headache that started when she had a sore throat. The headache, which was daily from onset, was described as a generalized pressure and squeezing sensation. She also had some photophobia.

New daily persistent headache is a type of chronic daily headache (CDH) that starts acutely and continues as a daily headache from onset. Many patients can pinpoint the exact day their headache began. The term *new daily persistent headache* was first coined by Vanast in 1986.¹ Even though NDPH has probably been around for centuries, the literature is sparse, and it has only recently been diagnosed as an entity separate from chronic tension-type headache, hemi-crania continua, and transformed migraine. It is not always easy to diagnose NDPH, as most patients who have the disorder are already overusing analgesics by

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the time they see a physician. When taking a CDH history, it is important to ascertain whether the chronic headache started before or after the start of analgesic overuse. With NDPH, the headache starts suddenly without any history of prior medication use. Silberstein et al² have proposed criteria for NDPH, which include average headache frequency greater than 15 days a month for more than 1 month; average headache duration greater than 4 hours a day if untreated; no history of tension-type headache or migraine that increases in frequency and decreases in severity in association with the onset of NDPH; the acute onset of a constant, unremitting headache that develops over less than 3 days; and headache that does not meet the criteria for hemicrania continua.

There are no large case series dedicated to NDPH; most published studies involve only several case reports. In the first-ever study of NDPH, Vanast¹ identified 45 patients (26 women, 19 men) over a 2-year period. Seventy-two percent of patients had constant headaches that could occur in any region of the head. Some patients experienced associated migrainous symptoms: 50% had nausea, 10% had vomiting, and photophobia occurred in about 30%. At the Jefferson Headache Center, we have seen over 100 patients with NDPH. It seems to be a female-predominant disorder that can occur at any age, but typically occurs in the second decade in women and in the fourth decade in men. The head pain is continuous throughout the day, is typically bilateral, and can occur anywhere on the head. Many patients have occipitonal discomfort. Sixty percent of our patients with NDPH have migrainous symptoms (nausea, photophobia, and phonophobia).

Many patients with NDPH have no prior personal or family history of headaches; this is their first-ever headache. Patients with NDPH seen at the Jefferson Headache Center and those from other case studies frequently develop NDPH in conjunction with a concurrent illness. In our population, 30% of patients developed NDPH after an episode of influenza or a cold. The patient under discussion began having daily headaches around the time of a sore throat. Typically, there appears to be an illness (often a very mild one) and a concomitant headache. The illness is self-limited, but when it resolves, the patient is left

with a CDH. If there has been an illness surrounding the headache onset, one needs to question if there is still an ongoing infection perpetuating the daily headache, such as a chronic indolent meningitis or even Lyme disease. The physician also needs to inquire about explosive coughing episodes along with the illness. We have identified several patients who developed spontaneous CSF leaks, and thus NDPH, from dural tears after repetitive Valsalva events. At the time of presentation, these patients no longer had positional headaches, so questions about what happened at the time of headache onset led to the discovery of their CSF leaks.

The evaluation of NDPH should include laboratory investigations (complete blood count, sedimentation rate, vasculitis screen, Lyme titer), imaging studies (MRI brain scan with gadolinium to identify pachymeningeal enhancement for a possible CSF leak), and even a lumbar puncture to rule out a chronic indolent infection or CSF hypovolemia. Anecdotally, laboratory studies are usually normal.

There appears to be a possible infectious etiology for NDPH in a subset of patients. This patient developed NDPH with a sore throat. Diaz-Mitoma et al³ identified oropharyngeal secretion of Epstein-Barr virus (EBV) by nucleic acid hybridization in 20 of 32 patients with NDPH compared with 4 of 32 age- and sex-matched controls. A history of infectious mononucleosis was identified in 12 of the patients with NDPH. Eighty-four percent of the patients with NDPH were felt to have active EBV infection. Santoni and Santoni-Williams⁴ identified evidence of systemic infection in 108 patients with new daily headaches, including Salmonella, adenovirus, toxoplasmosis, herpes zoster, EBV, and E. coli urinary tract infections. How an infection causes NDPH is unknown. One may hypothesize an activated autoimmune response setting up possible persistent neurogenic inflammation.

There are no published studies on the treatment of NDPH. The patients with NDPH at the Jefferson Headache Center appear to be some of the most treatment-refractory patients we see. Multiple preventive drugs, the same agents used in patients with CDH, including antidepressants and antiseizure agents, have provided very little pain relief. Anecdotally, gaba-

pentin has been somewhat beneficial in a few of my patients and appears to have broken the cycle in at least one patient. Even if a patient with NDPH presents in analgesic overuse and the overuse cycle is broken, the headaches generally do not greatly improve, even with preventative medication. New daily persistent headache has also shown a very poor response to abortive therapy, such as around-the-clock dosing of dihydroergotamine, valproate, methylprednisolone, intravenous magnesium sulfate, or neuroleptics, in our patient population. The patient under discussion responded to repetitive therapy of metoclopramide, dihydroergotamine, and valproate. A large number of patients with NDPH have cervical trigger points and even cervical facet inflammation on examination. The neck appears to play a large role in NDPH. It has been my experience that agents that reduce neck irritation, including anti-inflammatory agents in combination with muscle relaxants and aggressive physical therapy, reduce the daily intensity of the pain. If patients improve with cervical trigger point injections, cervical facet blocks can reduce pain intensity even further.

The true long-term prognosis for NDPH is not known. Vanast¹ found that his patients improved spontaneously without any intervention. Thirty percent of men were headache-free at 3 months, and 86% were headache-free at 2 years. Thirty percent of women were headache-free at 3 months, while 73% were pain-free at 2 years. The patients with NDPH that I have seen appear to be refractory to our typical treatment schemes for transformed migraine, chronic tension-type headache, and hemicrania continua. Although some patients do demonstrate decreased headache intensity with therapy, it is difficult to achieve any prolonged headache-free time in this patient popula-

tion. Since the Jefferson Headache Center is a tertiary headache referral center, it may be that we only see the patients with NDPH who do not spontaneously remit; thus, by selection, we are seeing the most refractory patients with NDPH. Further research must be invested into studying NDPH, as it is being diagnosed more frequently and appears to be refractory to many of our known CDH preventative and abortive agents.

REFERENCES

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FOLLOW-UP

She was placed on nortriptyline, 25 mg, at bedtime which was increased to 50 mg after 1 month. The headaches gradually decreased in frequency from three per week to one per week and then less. On follow-up 4 months later, she reported only one migraine without aura during the prior 7 weeks which responded to oral sumatriptan.