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Expert Opinion

The Challenge of New Daily Persistent Headache

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New daily persistent headache is a rare chronic daily headache of long duration characterized by the abrupt onset of persistent headache that generally develops over less than 3 days and does not remit. While it was initially thought to be a benign, self-limiting disorder, further research has shown that a significant percentage of patients continue to suffer for many years, often experiencing pain that is refractory to treatment. This article reviews the symptoms, pathophysiology, diagnostic criteria, diagnostic testing, treatment, and prognosis.

Key words: new daily persistent headache, chronic daily headache, diagnostic testing, treatment

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One of the most common and often difficult to treat headache disorders seen by headache specialists is chronic daily headache of long duration which occurs on at least 15 days per month with untreated headache lasting longer than 4 hours for more than 3 months with primary types (not related to structural dysfunction or other illness) diagnosed after the exclusion of the many possible causes of secondary headaches by history, examination, and testing, as indicated.[1] About 4% of the adult population have one of the primary types which include chronic migraine, chronic tension-type headache, hemicrania continua, and new daily persistent headache (NDPH). These 2 cases exemplify an uncommon type.

CASE 1

This 17-year-old girl is seen with a 4-year history of constant and daily headaches from the onset described as a pressure and throbbing with an intensity ranging from 3-9/10 with an average of 8/10 with intermittent nausea, light and noise sensitivity, and vomiting (once a month) but no visual symptoms. She reported no prior history of headaches. She is currently taking no preventive or symptomatic medications. At the onset of the headache, she had a low-grade fever, chills, myalgias, nausea, and fatigue for about 1 week.

Valproic acid, topiramate, venlefaxine, duloxetine, sertraline, gabapentin, pregabalin, memantine, methylergonovine maleate, and botulinum toxin injections either did not help or were discontinued because of side effects. Meloxican, naproxen sodium, ibuprofen, tramadol, a butalbital combination, zolmitriptan, eletriptan, rizatriptan, sumatriptan, zolmitriptan, frovatriptan, hydrocodone, and propoxyphene did not help. An intravenous regimen in the hospital including dihydroergotamine, metoclopramide, and valproic acid had no effect on the pain. Chiropractic treatment and acupuncture were of no benefit. She saw a psychologist and was felt to be depressed over her headaches. Biofeedback has been of perhaps mild help.

Five magnetic resonance imaging (MRI) scans of the brain including one with contrast and a lumbar

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puncture and cerebrospinal fluid examination with opening pressure were normal. Blood work was normal including Epstein Barr titers. She has been seen by 5 prior neurologists. Past medical history was otherwise negative. She was being homeschooled for 2 years due to the headaches and was 1 year behind. Neurological examination is normal.

CASE 2

This 37-year-old woman presented for a headache consultation with a 4-month history of daily constant headaches, constant since onset, with no prior history of headaches. She described a generalized pressure and throbbing with an intensity of on a visual analogue scale of 3-5/10 with nausea, light and noise sensitivity but no vomiting or visual symptoms. The headache was not better supine. There was no antecedent infection, stressful life event, surgery, or head trauma. She had tried ibuprofen, naproxen sodium, tizanidine, metaxalone, and combinations of acetaminophen/aspirin/caffeine, isometheptene, and butalbital/acetaminophen/caffeine without benefit. Physical therapy did not help.

She initially went to an emergency room where a computed tomography (CT) of the brain was negative. She then saw 2 neurologists, an ears, nose, throat (ENT) physician, and an endocrinologist who all found normal examinations. An MRI of the brain with and without contrast and a CT of the paranasal sinuses were negative. Extensive blood tests were normal. Neither neurologist considered the diagnosis of NDPH.

Past medical history was negative. Neurological examination was normal. There was tenderness to palpation over both greater occipital nerves.

Bilateral greater occipital nerve blocks were performed with lidocaine without benefit. She declined hospitalization for an inpatient dihydroergotamine regimen. She was treated with topiramate for 2 months (titrated up to 100 mg daily) and then venlafaxine extended release (titrated up to 150 mg daily) for 2 months without benefit. Baclofen 10 mg tid prn did not help. She became depressed over the persistent headaches with no prior history of significant depression. She was next placed on escitalopram 10 mg daily with a significant decrease in the intensity of the pain. (On 20 mg daily, the headaches were no less and she complained of sweating.) One year after initial consultation, the headaches were still daily and constant but were a generalized pressure, tightness, and fullness without associated symptoms with an intensity of 1/10 for which she was taking no symptomatic medication and the depression was better.

Questions: What is the diagnosis, pathophysiology, and diagnostic criteria? What testing is indicated and what treatment is effective?

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Both cases are consistent with NDPH which was first described by Vanast in 1986[2] but not defined by the International Headache Society (IHS) until 2004. In order to meet the diagnostic criteria as defined by the IHS, the headache must occur daily and be unremitting from within 3 days of onset.[3] The onset is often so striking that most patients can identify the exact day that their headache disorder began.[4,5] The headaches can vary greatly in their clinical presentation and duration. Eighty percent of patients experience a constant headache throughout the day with no pain-free period.[6] For most patients, the baseline level of pain is mild to moderate in intensity and bilateral in up to 94%.

The headaches are typically described as throbbing and/or pressure-like, generalized or localized to any head region, although migraine symptoms such as nausea, photophobia, phonophobia, and lightheadedness occur in over 50% with occasional vomiting..[7,8] Cranial autonomic symptoms occur with painful exacerbations in 21% and cutaneous allodynia may be present in 26%.[8] There are rare reports of an associated visual aura and unrelated frequent episodic bilateral facial flushing with painful exacerbations (usually lasting for a few minutes).[8]

The age of onset ranges from 6 to greater than 70 years old, with a mean of 35 years.[6,8] NDPH is more common in women with a 2.5:1 ratio in adults[8] and 1.8:1 ratio in children.[9] NDPH is rare. A population-based cross-sectional study of 30,000 persons aged 30-44 years found a 1-year prevalence of 0.03%.[10] In patients with chronic daily headache seen in tertiary headache clinics, NDPH is diagnosed more often in children and adolescents (13-35%)[11] than in adults

(1.7-10.8%).[9] In one study, 25% had a preexisting history of a primary headache disorder (episodic tension-type headache in 18.3% or episodic migraine 7%).[8]

Both patients in the case became depressed with their persisting headaches. In a study of 71 patients, there was a history of prior depression or anxiety in 51% and symptoms of current depression in 62%.[8] There is a report of co-morbidity with panic disorder in a study of 9 patients.[12]

Anecdotally, many general neurologists, as in this case, are not familiar with NDPH and misdiagnose the disorder as chronic tension-type headache or chronic migraine. Non-neurologists are typically not familiar with the diagnosis and may additionally misdiagnose the headaches as sinus headaches, temporomandibular joint disorder, due to eye strain, chronic Lyme disease, etc. It is common for NDPH patients to see numerous physicians in different specialties, dentists, psychologists, and chiropractors in a dizzying and depressing musical chairs of expensive misdiagnoses and sometimes potentially harmful treatments. Or patients may see numerous neurologists and headache specialists seeking help for their intractable headaches as in the 2 cases.

Pathophysiology.—The pathophysiology of NDPH is still very much a mystery. There have been several studies postulating a link between a preceding flu-like or upper respiratory infection in 14-30%,[7,8] a stressful life event in 10-12%,[6-8] or extracranial surgery in 7-12%.[6,7] Cervical joint hypermobility[13] and defective internal jugular venous drainage[14] have also been suggested as causes.

The suggestion of a link between infection or life stressors and the onset of NDPH has led to several studies trying to find the pathogen underlying the disorder. While one study of 32 patients found evidence of active Epstein-Barr virus (EBV) infection in 85% of those with NDPH as compared to 25% of the controls,[15] another study found only 13% of 56 NDPH patients with evidence of past exposure to EBV and none with an active infection.[7] In a retrospective analysis of 18 NDPH patients, 6 had a recent exposure to herpes simplex virus and 2 patients had recent exposure to cytomegalovirus but none tested positive for EBV.[16]

Two related studies also suggest a possible causal connection between infection and NDPH. In a study of 108 patients with new headaches with a duration of 3-60 days (not NDPH), evidence of a variety of systemic infections was found including *Salmonella*, adenovirus, toxoplasmosis, herpes zoster, EBV, and *Escherichia coli* urinary tract infections.[17] A mean 5-year retrospective analysis of 53 patients with a history of viral meningitis and 17 patients with a history of bacterial meningitis showed an increased onset of subsequent new onset headache and increased severity of those with prior primary headaches.[18] Finally, one study found elevated levels of tumor necrosis factor alpha, a proinflammatory cytokine, in the cerebrospinal fluid but not the serum of patients with NDPH, chronic migraine, and post-traumatic headaches suggesting inflammation as the cause of the headaches.[19]

Diagnostic Criteria.—The International Classification of Headache Disorders 2nd edition (ICHD-2) has provided diagnostic criteria for NDPH (see Box 1).[3] The most critical aspect of the diagnosis is

Box 1.—New Daily Persistent Headache Diagnostic Criteria (From Headache Classification Subcommittee of the International Headache Society[3])

1. Headache is daily and unremitting from within 3 days of its onset
2. Headache occurs for more than 3 months
3. Headache has at least 2 of the following characteristics:
   - Bilateral location
   - Non-pulsating quality
   - Mild to moderate intensity
   - Does not worsen with routine physical activity such as walking
4. Only has one of the following 3 characteristics: photophobia, phonophobia, mild nausea
5. Does NOT include moderate to severe nausea or vomiting
6. Is not secondary to another disorder

the daily and unremitting headache from within 3 days of its onset. However, this definition is overly restrictive because it excludes the presence of more than 1 migraine feature which are often present in children and adults with abrupt onset chronic daily headaches. In one study of 71 children and adults, 56.3% did not meet the ICHD-2 criteria because they had too many migraine features.[8]

Robbins et al have proposed a revised version of ICHD-2 criteria, creating an NDPH-ICHD subset (the current guidelines) and an NDPH-mf subset (those with migraine type features).[8] They further divided these groups into 3 prognostic subgroups: persisting type with a continuous headache from onset, a remitting type where the headache either resolves completely or occurs less than 5 days per month for at least 3 months, and a relapsing-remitting type where pain-free periods are interspersed among times of continuous headaches. The authors found that the 2 subtypes (NDPH-ICHD and NDPH-mf) had very similar demographic, clinical, and prognostic features.

Diagnostic Testing.—NDPH is a diagnosis of exclusion.[20,21] Some of these secondary disorders may have a thunderclap or sudden onset of severe headache whereas others may develop gradually over 1-3 days and meet the onset period criteria for NDPH. New onset daily headaches with a normal neurological examination could also be due to various other causes particularly when seen within the first 2 months after onset including postmeningitis headache, chronic meningitis, brain tumors, leptomeningeal metastasis, temporal arteritis, chronic subdural hematomas, posttraumatic headaches, sphenoid sinusitis, and hypertension. When the headaches have been present for more than 3 months with a normal neurological examination, the yield of testing is low. Box 2 lists some primary and secondary causes of new daily headaches present for more than 3 months.

Blood tests may be indicated including a cbc (headache may be a symptom of a decrease of hemoglobin concentration by half or more and due to thrombotic thrombocytopenic purpura), thyroid-stimulating hormone because headache may be a symptom in 14% of cases of hypothyroidism, a chemistry profile (renal failure and hypercalcemia can cause headaches), and collagen vascular and infectious etiology studies as appropriate (such as erythrocyte sedimentation rate, antinuclear antibody, Lyme antibody, and HIV test). Lumbar puncture may also be indicated in selected cases such as patients who are immunocompromised, suspected subacute or chronic meningitis, and a low or high cerebrospinal fluid pressure syndrome. The yield of neuroimaging in patients with new daily headaches and then a few examples of secondary causes will be discussed.

Box 2.—Differential Diagnosis of New Daily Headaches Present for More Than 3 Months

Primary headaches
New daily persistent headache
Chronic migraine
Chronic tension-type
Hemicrania continua

Secondary headaches (new daily persistent headache mimics)
Medication overuse
Postmeningitis headache
Chronic meningitis
Sphenoid sinusitis
Neoplasms
Chronic subdural hematoma
Posttraumatic headaches
Hypertension
Low cerebrospinal fluid pressure syndrome
Pseudotumor cerebri (idiopathic and secondary intracranial hypertension)
Cervical artery dissections
Cerebral venous thrombosis
Arteriovenous malformation
Dural arteriovenous fistula
Unruptured intracranial saccular aneurysms?
Chiari malformation
Temporal arteritis
Cervicogenic
Temporomandibular joint dysfunction

Subacute or Chronic Headaches and a Normal Neurologic Examination.—A number of studies have reported the yield of neuroimaging in headaches

present for 1 month or more mostly with a normal neurological exam but none specifically with patients meeting criteria for NDPH. Tsushima and Endo[22] retrospectively reviewed the clinical data and magnetic resonance (MR) studies of 306 adult patients (136 men and 170 woman) referred for MRI evaluation of chronic or recurrent headache with a duration of 1 month or more, no other neurologic symptoms or focal findings at physical examination, and no prior head surgery, head trauma, or seizure with the following results: 55.2% had no abnormalities, 44.1% had minor abnormalities, and 0.7% (2) had clinically significant abnormalities (pituitary macroadenoma and subdural hematoma). Neither contrast material enhancement (n = 195) nor repeated MRI (n = 23) contributed to the diagnosis.

Sempere and colleagues[23] reported a study of 1876 consecutive patients (1243 women, 633 men) aged 15 years or older, with a mean age of 38 years, with headaches that had an onset at least 4 weeks previously who were referred to 2 neurology clinics in Spain. One-third of the headaches were new onset, and two-thirds had been present for more than 1 year. Subjects had the following types: migraine (49%), tension (35.4%), cluster (1.1%), posttraumatic (3.7%), and indeterminate (10.8%). Normal neurological examinations were found in 99.2% of the patients. CT scan was performed in 1432 patients and MRI in 580; 136 patients underwent both studies.

Neuroimaging studies detected significant lesions in 22 patients (1.2%), of whom 17 had a normal neurological examination. The only variable or "red flag" associated with a higher probability of intracranial abnormalities was an abnormal neurological examination with a likelihood ratio of 42. The diagnoses in these 17 patients were pituitary adenoma (n = 3), large arachnoid cyst (n = 2), meningioma (n = 2), hydrocephalus (n = 2), Arnold-Chiari Type I malformation, ischemic stroke, cavernous angioma, arteriovenous malformation, low-grade astrocytoma, brain stem glioma, colloid cyst, posterior fossa papilloma (one of each). Of these 17 patients, 8 were treated surgically: hydrocephalus (n = 2), pituitary adenoma, large arachnoid cyst, meningioma, arteriovenous malformation, colloid cyst and papilloma (one of each).

The rate of significant intracranial abnormalities in patients with headache and normal neurological examination was 0.9%. Neuroimaging studies discovered incidental findings in 14 patients (75%): 3 pineal cysts, 2 intracranial lipomas, and 8 arachnoid cysts. The yield of neuroimaging studies was higher in the group with indeterminate headache (3.7%) than in the migraine (0.4%) or tension-type headache (0.8%) groups. The study does not provide information on white matter abnormalities in migraineurs. MRI performed in 119 patients with normal CT revealed significant lesions in 2 cases: a small meningioma and an acoustic neurinoma. No saccular aneurysms were detected; MR angiography was not obtained.

However, the studies do not give information about the detection of paranasal sinus disease, which may be the cause of some headaches. For example, sphenoid sinusitis may cause a severe, intractable, new-onset headache that interferes with sleep and is not relieved by simple analgesics. The headache may increase in severity with no specific location. There may be associated pain or paresthesias in the facial distribution of the fifth nerve and photophobia or eye tearing with or without fever or nasal drainage. The headache may mimic other causes such as migraine or meningitis.[24]

Wang et al[25] retrospectively reviewed the medical records and MRI images of 402 adult patients (286 women and 116 men) who had been evaluated by the neurology service with a primary complaint of chronic headache (a duration of 3 months or more) and no other neurologic symptoms or findings. Major abnormalities (a mass, caused mass effect, or was believed to be the likely cause of the patient's headache) were found in 15 patients (3.7%) including a glioma, meningioma, metastases, subdural hematoma, arteriovenous malformation, 3 with hydrocephalus, and 2 Chiari I malformations. They were found in 0.6% of patients with migraine, 1.4% of those with tension headaches, 14.1% of those with atypical headaches, and 3.8% of those with other types of headaches.

Finally, Lewis and Dorbad[26] retrospectively reviewed records of children aged 6-18 years with migraine and chronic daily headache with normal examinations. Of 54 patients with migraine who

underwent either CT (42) or MRI (12) scans, the yield of abnormalities was 3.7%, none clinically relevant. Of 25 patients with chronic daily headache who underwent either CT (17) or MRI (8) scans, the yield of abnormalities was 16%, none clinically relevant.

Secondary Headaches (NDPH Mimics).— Spontaneous intracranial hypotension (SIH) syndrome often presents with a headache that is present when a patient is upright but is relieved by lying down, or by an orthostatic headache. However, as SIH syndrome persists, a chronic daily headache may be present without orthostatic features. SIH syndrome may also present with other types of headaches, including exertional or cough without any orthostatic features, acute thunderclap onset, paradoxical orthostatic headaches (present in recumbency and relieved when upright), intermittent headaches due to intermittent leaks, and the acephalgic form with no headaches at all.[27] Neck or interscapular pain may precede the onset of headache in some cases by days or weeks. MRI abnormalities of the brain and spine are variably present in perhaps 90% of cases. An MRI scan of the brain may reveal diffuse pachymeningeal (dural) enhancement with gadolinium without leptomeningeal (arachnoid and pial) involvement and, in some cases, subdural fluid collections, which return to normal with resolution of the headache.[28]

Cervical artery dissections, which can present with headache or neck pain alone,[29] can be a rare cause of new daily headaches.[30] Occasionally, the headaches can persist intermittently for months and even years and can lead to a pattern of chronic daily headaches especially after cervical carotid artery dissection. MR angiography is the study of choice for detection as carotid ultrasound is operator dependent and less sensitive.[31]

Cerebral venous thrombosis (CVT) is a rare disease (3-4 cases/million people/year) which can present with headache in up to 90% of cases, is often the initial symptom,[32] and can be the only symptom with a normal neurological examination in 32%.[33] The headache can be unilateral or bilateral in any location, mild to severe, intermittent or constant, and even resemble migraine with aura. The onset is usually gradual over several days but can be thunderclap and become chronic. The headache can be associated with other neurological signs such as papilledema, focal deficits, seizures, disorders of consciousness, or cranial nerve palsies. Although CVT can be a mimic of idiopathic intracranial hypertension, there is controversy over whether raised intracranial pressure can be the cause of venous obstruction with resolution by lowering the cerebrospinal fluid pressure.[34]

Neuroimaging studies have variable sensitivities in diagnosing CVT. CT only diagnoses about 30% of 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. CVT may be missed on routine MRI of the brain although echo-planar T2*-weighted MRI increases the sensitivity.[35] The addition of MR venography increases the sensitivity of MR further especially within the first 5 days of onset or after 6 weeks. Helical CT venography is a very sensitive diagnostic method. Digital subtraction venography can be performed when the diagnosis is still uncertain.

Chiari I malformation is a typically congenital malformation of cerebellar tonsillar herniation at least 5 cm below the foramen magnum. The headache attributed to Chiari I malformation is occipital or nuchal-occipital with occasional radiation unilaterally to frontotemporal or shoulder regions and sometimes generalized.[36] The pain may be dull, aching, or throbbing and may last less than 5 minutes to several hours to days. Pain may be precipitated by neck flexion or palpation or coughing.

In an imaging study of children with headaches aged 2-18 years,[37] Chiari type I malformation was identified in 14 of 241 (5.8%) patients. Five of 14 (35.7%) patients with Chiari I malformation had headaches secondary to their malformation. Three patients had surgical decompression with significant headache relief in 2. The other 9 patients were diagnosed with migraine (35.7%) and tension-type (28.6%) headaches. In adults, one study found an association of chronic migraine with Chiari I.[38] Although headache is the most common presenting complaint of Chiari I malformation, the malformation is typically an incidental finding on MRI studies done for primary headaches.

Secondary pathology should be especially considered when NDPH occurs over the age of 50. In a study of those over 65 years of age with new-onset headaches, the prevalence of secondary headaches due to serious pathology was 15%.[39] Temporal arteritis should always be considered but the diagnosis is often delayed, especially in those under the age of 70. Temporal arteritis rarely occurs under the age of 50 with most biopsy proven large series having no patients under the age of 50.[40] As the rare exception, in a Canadian study of 141 consecutive patients presenting to a neuro-opthalmology practice, there was 1 patient under the age of 50 (age 47).[41] New onset stabbing headache (ice pick headache) has also been reported accompanying the new onset headache in temporal arteritis.[42]

Rarely, a dural arteriovenous fistula can also mimic NDPH and present with a unilateral headache alone followed later with ipsilateral tinnitus[43] or a unilateral headache associated with ipsilateral popping noises and tinnitus.[44] The MRI of the brain may be negative or show subtle abnormalities which may be overlooked. An MR or computerized tomographic angiogram may reveal the fistula but a catheter angiogram is the gold standard for diagnosis.

Finally, one possible cause of secondary NDPH which might be further explored is unruptured saccular aneurysm. Two studies have found patients with chronic headaches (unspecified, tension-type, or migraine) whose headaches improved after treatment of an unruptured aneurysm.[45,46]

Treatment.—Takase et al in Japan reported the largest uncontrolled series of 30 patients who met ICHD-II criteria for NDPH (17 men) were first administered muscle relaxants (baclofen or tizanidine).[6] If no effect was observed, tricyclic antidepressants (amitriptyline in 23 patients), selective serotonin reuptake inhibitors (SSRIs) (fluvoxamine or paroxetine in 12 patients), valproic acid (9 patients), and beta-blockers (in addition to tricyclics in 2 patients) were subsequently administered. Drug treatment was rated as very effective by 27% of patients, moderately effective by 3%, mildly effective by 20%, and ineffective by 50%. Some patients with long duration headache responded. Rozen opined that response rates are higher during the first year than if the patient has been static for 10-20 years.[47]

In a retrospective study of 18 patients tried on amitriptyline (16), fluoxetine (7), and valproic acid (7), no drug was reported as effective.[16] There are case reports and small series of efficacy of topiramate, venlefaxine, and nortriptyline;[48] gabapentin and topiramate;[49] and mexiletine.[50] There are no reports on the efficacy of escitalopram for NDPH as suggested in the case presented although the drug might be effective for migraine prevention.[51] In a small series of patients, Grosberg has found clonazepam 0.5 mg qhs up to 1 mg bid with an extra 0.5 mg-1 mg prn for breakthrough pain effective (Brian Grosberg, MD, personal communication). For some patients, headache escalations may respond to triptans.[8]

Two studies have tried immunosuppression for NDPH. Doxycycline (which is a tumor necrosis factor alpha inhibitor) 100 mg bid for 2 months has been reported as effective in 4 patients.[52] (However, my own anecdotal experience has been negative.) Intravenous methylprednisolone (1000 mg daily for 5 days) in 9 patients followed by oral steroids (60 mg of prednisolone daily) for 2-3 weeks in 6/9 was reported as producing complete resolution in all patients with NDPH and a history of antecedent extracranial infection but 0/2 without. However, only 4/9 cases had the NDPH for 3 months or longer. Further confirmation of both of these studies in larger series would be of interest.

In practice, NDPH is typically treated empirically using the same preventive medications for chronic tension-type[53] or chronic migraine alone or in combinations. In children and adolescents, the most commonly used medications include the tricyclic antidepressants (amitriptyline) and antiepileptics (topiramate, valproic acid, gabapentin) and less often propranolol, selective serotonin reuptake inhibitors and muscle relaxants.[54] Alternative therapies are sometimes tried without evidence of efficacy including riboflavin, butterbur, coenzyme Q10, magnesium, massage, acupuncture, exercise, physical therapy, chiropractic manipulation, weight loss, and yoga. Some patients undergo surgical procedures such as septoplasty and occipital nerve decompression without reports of efficacy. Although neuromodulation especially occipital nerve stimulation may be of benefit for

some primary headaches,[55] I can find no reports of efficacy for NDPH although this would be of interest.

According to 2 reports of 12[56] and 9[57] patients, an inpatient regimen of an intravenous regimen of dihydroergotamine may produce at least temporary improvement in some cases. Intravenous haloperidol[58] and intravenous magnesium[18] might be of some benefit. Although continuous opioid therapy is sometimes used for refractory headaches including NDPH, this therapy is usually not effective and needs to be carefully monitored by experienced physicians for adverse events.[59]

Greater occipital nerve blocks might be effective for NDPH based upon a series of 16 injections in 10 patients, 4 who had a complete temporary response and 6 with a partial response.[60] Sensitivity around the greater occipital nerve was significantly associated with a response to injection. Another study also suggests benefit.[8] A single case report suggests the possible efficacy of botulinum toxin.[61] Anecdotally, some patients may have reduced pain with cervical trigger point injections and physical therapy.[32]

Medication overuse was present in 45% of mainly adults in one study[8] and 12.5% in a child and adolescent study.[9] Medication overuse may increase the level of pain and may make patients less responsive to preventive medications where drug withdrawal is recommended by some experts[62] but not another.[30] However, there are no prospective studies investigating the effects of medication overuse in worsening and maintenance of NDPH or in resistance to therapy.

Prognosis.—Vanast's initial series suggested a self-limiting disorder, with 86% of men and 73% of women being headache free at 2 years.[2] Another series found 66% headache free at 2 years.[31] However, other studies have demonstrated the intractable chronic nature of NDPH for many with headaches persisting for decades in some cases. A 5-year study of 30 patients found a poor prognosis for recovery where patients had headaches at study entry with a mean of 3.3 years (and up to 27 years).[6] Robbins et al's study of 71 patients found 3 prognostic categories of NDPH patients: 76.1% with persistent headaches, 15% with remission (time to remission ranged from 4 months to 54 years with a median duration of 21 months), and 8% with a relapsing-remitting type (range to first remission 3-24 months).[8]

In a study of 28 children and adolescents, 20/28 continued to have headache 6 months to 2 years later and only 8/28 were headache-free (3 within 1 year and 4 within 2 years).[63] However, 79% had migraine disability assessment (MIDAS) scores indicating normal function in school/home. Risk factors for chronification of NDPH in children and adolescents may include female sex, straight-A report cards, excess extracurricular activities, poor sleep, a disordered home life, medication overuse, obesity, caffeine, poor diet, stressful life events, head injury, and insufficient exercise and fluids.[36]

New daily persistent headache is often one of the most difficult to treat headache types which can result in impairment and disability. More studies are needed to answer questions about all aspects of this challenging disorder and provide better treatments for our patients.

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