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HEADACHE (R. HALKER SINGH, SECTION EDITOR)

New Daily Persistent Headache: a Diagnostic and Therapeutic Odyssey

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Abstract

Purpose of Review New daily persistent headache (NDPH) is a rare primary headache disorder, which often has a refractory clinical course. This narrative review seeks to highlight what is known about the development of NDPH, to outline a diagnostic approach to a patient with new daily headache, and to explore management considerations and potential future therapies for patients diagnosed with NDPH.

Recent Findings Interval work at the level of case series and cohort studies has identified novel triggering factors (e.g., Valsalva), subgroups with unique temporal profiles (e.g., thunderclap onset), psychophysical profiles (e.g., increased pain catastrophizing), and potential treatment options.

Summary The approach to the diagnosis and treatment of NDPH remains individualized, driven by clinical features and challenging in most cases. Earlier identification of patients (e.g., prediction of patients with status migrainosus destined to develop NDPH) may allow for more effective treatment.

Keywords New daily persistent headache · Status migrainosus · Refractory headache · Intractable headache · Migraine

Introduction

New daily persistent headache (NDPH) is a perplexing and challenging clinical disorder, where refractory chronic head pain emerges within a single day, often in the absence of traditional chronic pain risk factors. The disorder is recognized by the International Classification of Headache Disorders 3rd Edition (ICHD-3) as a primary headache disorder which is present for at least 3 months and has become continuous and unremitting within 24 h [1]. If the criterion for the 3-month duration has not yet been satisfied, an interval diagnosis of probable NDPH can be given. Of course, a history of a new daily progression of persistent headache naturally evokes the question of "what happened?" Accordingly, the diagnosis mandates that other diagnostic considerations be excluded, such as disorders of intracranial pressure, cervical artery dissection, and cerebral venous sinus thrombosis [2]. Because NDPH is often refractory to standard therapies, it is essential that an evaluation for secondary etiologies be thoughtful and comprehensive. In this narrative review, we will highlight a diagnostic approach to the patient with a new daily progression of persistent headache and explore management considerations for patients ultimately diagnosed with NDPH.

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Epidemiology and Clinical Features of NDPH

NDPH is a descriptive diagnosis and almost certainly a heterogeneous disease category unified by a common temporal profile and often refractory clinical course [3]. The disorder is uncommon in the general population, with an estimated prevalence of 0.1% (95% confidence interval 0.02 to 0.43) [4]. In a population-based study from Norway including individuals aged 30–44, the 1-year prevalence of NDPH was 0.03%, which was comprised of three men and one woman [5]. As a point of reference, the population prevalence of chronic daily headache is about 5% [4]. Despite the relative rarity of NDPH, it remains a commonly encountered differential

diagnosis among patients presenting to specialty clinics with chronic daily headache. In clinic-based series, NDPH tends to be reported more often in women than in men and has been observed across the lifespan [6, 7].

While earlier diagnostic criteria for NDPH recognized a tension-type phenotype alone, it is now widely recognized that migraine-like presentations may actually comprise the majority of cases. In one clinic-based series of 56 patients with NDPH, 68% reported nausea, 66% photophobia, and 61% phonophobia [6]. In another series, 14 of 18 NDPH patients reported migrainous accompanying symptoms [8]; similarly, in a large pediatric series, most patients with NDPH had associated migrainous features [9]. Current ICHD-3 criteria for NDPH do not require presence or absence of specific headache characteristics, but the headache must be daily and unrelenting from within 24 h of onset and cannot meet criteria for hemicrania continua [1]. A prior history of tension-type or migraine headaches does not preclude the diagnosis of NDPH; however, due to the rarity of NDPH, it is not clear whether comorbidity with another primary headache disorder is coincidental or has pathophysiological significance.

Approximately half of patients with NDPH identify a trigger or inciting event associated with the onset of their headache. A number of triggers have been reported in the literature, with viral illness being the most common in most series. In a clinic-based study of 97 patients with NDPH, 53% could not identify a trigger, 22% had an infection or flu-like illness, 9% had a stressful life event, 9% had a preceding surgical procedure with intubation, and 7% had another recognized trigger [10••]. In a series of 63 patients in India with NDPH, 54% could remember a trigger, which was infection (primarily respiratory) in 29% and injury in 11% [11]. There has also been a case series of patients with NDPH triggered by a single Valsalva event [12].

Clues to NDPH Pathophysiology

The heterogeneity of NDPH likely reflects differences in underlying pathophysiology, which is reflected in the variable triggers of the condition and differences in headache phenotype.

Broadly, we could consider that there are two main categories of NDPH based on the phenotype of the headache itself: chronic migraine (NDPH-CM) and chronic tension-type headache (NDPH-CTTH) subtypes. Some studies have suggested that these variants have similar prognosis [13], while others have demonstrated poorer outcome or worse symptoms in patients with NDPH-CM [14, 15•]. Given the high percentage of patients with NDPH with migrainous features, as well as some patients having a history of episodic migraine, NDPH-CM may exist along a temporal spectrum of acute and persistent migraines [16] (Fig. 1). The feature that distinguishes NDPH-CM from chronic migraine is the ability to pinpoint a particular day of onset of the continuous headache, without preceding escalation in frequency or severity of headaches. However, shortly after the onset of NDPH, the syndrome can be clinically indistinguishable from status migrainosus. The same persistent headache in a patient with a history of episodic migraine might be deemed status migrainosus at 72 h, probable NDPH at 2 months, and NDPH if it remains unremitting at three or more months from onset. Viewing NDPH from the perspective of a continuum of acute headache allows for novel questions of potential clinical significance [16]. It is not known, for example, whether patients with a history of status migrainosus are more likely to develop NDPH or if patients with status migrainosus can be risk stratified to identify those at greatest risk for impending NDPH diagnosis. Early identification of patients destined to develop NDPH may allow for early, aggressive preventive approaches.

Another potential method of categorizing patients with NDPH is by the temporal profile of the onset of symptoms. By definition, patients with NDPH have had onset of unremitting headache within 24 h of the start of the headache, but the time course can vary from a thunderclap onset [17] within seconds to minutes, to a more subacute presentation where the headache gradually develops and builds to its maximal intensity over hours to days. This difference may reflect differences in etiology, with acute presentations perhaps more likely to represent vascular etiology such as vasospasm, dissection, thrombosis, or related to other sudden shifts in fluid dynamics as would be seen with spontaneous intracranial hypotension. Subacute presentations could suggest the possibility of an infectious or inflammatory etiology. There has not yet been a clinical study attempting to categorize and compare patients with NDPH on the basis of such temporal features.

Finally, triggering events and comorbid conditions may be yet another way to subdivide patients with NDPH. Patients who develop NDPH after a viral infection may have a different underlying etiology than those who develop NDPH after a stressful life event or after surgical procedures with intubation. However, a common susceptibility may exist as the age and sex distributions appear indistinguishable when subgroups are compared with different trigger categories [10••]. Studies have yet to compare prognosis and/or treatment outcomes on the basis of recognizable triggers.

The subset of patients with a thunderclap onset of NDPH may represent a distinct subgroup. In a case series of seven patients with onset of thunderclap headache after a single Valsalva event, all patients had worsening of symptoms when placed in the Trendelenburg position and none had papilledema. Out of the seven patients, five had greater than 90% improvement in headache with CSF pressure/volume–lowering medication, such as acetazolamide, spironolactone, or indomethacin, and three were eventually able to taper off medication without recurrence [12]. There has also been a

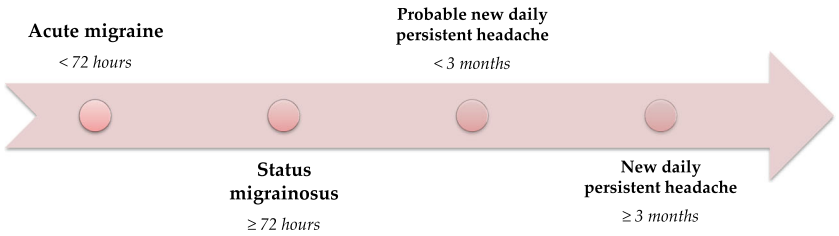

Fig. 1 Temporal continuum of acute and persistent migraines. A history of migraine may be present in patients presenting with status migrainosus and new daily persistent headache; therefore, a temporal continuum likely exists

published case report of a patient who had thunderclap headache and acalculia [17], with complete response to nimodipine, an agent that both inhibits cerebral artery vasospasm and reduces tumor necrosis factor alpha (TNF-α) levels.

Prior infection is one of the more commonly identified triggers for NDPH. This raises the possibility that NDPH is a post-infectious immune disorder. Specific viruses, particularly Epstein-Barr virus (EBV), have been previously implicated as potentially contributing to NDPH. An early study [18] showed that 27 of 32 patients with NDPH and only 8 of 32 controls had evidence of active EBV infection, as demonstrated by EBV excretion in the oropharynx or by elevated early antigen titer. A study of 40 children with NDPH found that 17 had onset of headache during or closely following an infection, with over half of these showing positive EBV serology at symptom onset [19]. Another study of 56 adults showed positive EBV titers suggesting past infection in 71%, although it did not specify baseline community rates of positive testing for past infection [6]. Finally, a study of 18 patients with NDPH found serological evidence for recent HSV infection in 42%, recent CMV in 11%, and no recent EBV [8].

Another possible mechanism for NDPH is cervical injury, particularly in patients with hypermobility. Studies have shown that the association of non-cranial surgeries with NDPH is in cases where patients were intubated during the procedure, suggesting the possibility that hyperextension of the neck during intubation and/or extubation could predispose to the development of NDPH [9, 10••]. To additionally support this theory, NDPH has been associated with joint hypermobility, with 10/12 patients in a small series found to have evidence of widespread joint hypermobility as assessed by physical therapist using the Beighton scale and 11/12 having evidence of cervical spine hypermobility [20]. A pediatric study identified minor head trauma as a trigger for NDPH, which may also cause subtle disruption of cervical structures as a mechanism for leading to NDPH [19]. There are reports of resolution of NDPH with osteopathic manipulation and cervical facet injections [10••, 21].

Multiple psychiatric and somatic comorbidities have been identified. As compared with patients with chronic migraine or chronic post-traumatic headaches, patients with NDPH are more likely to have asthma, allergies, and hypothyroidism [22]. Patients with NDPH as compared with patients with chronic low back pain with a similar average pain level are more likely to have depression, generalized anxiety, and pain catastrophizing; out of 55 patients with NDPH, 51 (92.7%) had evidence of generalized anxiety disorder, 49 (89.1%) had evidence of significant depression, 47 (85.5%) had significant pain catastrophizing, and 18 (32.7%) met criteria for somatoform disorder [15•]. The subgroup of patients with NDPH-CM had increased depression and pain catastrophizing scores as compared with the NDPH-CTTH subgroup. In children, NDPH is more likely to start in September or January, months associated with the start of the school semester and possibly associated with increased stress [23].

It is unclear whether having these other disorders predisposes to the development of NDPH, whether having NDPH increases development of psychiatric disorders, or whether both the psychiatric symptoms and headache are manifestations of a single disorder. A small case series from Brazil suggests that treating patients with panic disorder and NDPH simultaneously for both disorders can lead to a good response to treatment, perhaps indicating that there is a benefit to treating the psychiatric condition as it may improve response of headache to treatment as well [24].

Neurophysiology of NDPH is not yet well understood. Elevation of TNF-α levels in the CSF has been described in NDPH and treatment-refractory CM, which may support a role of CNS inflammatory response in the development of these disorders [25]. This is also supported by suggestions that therapies targeting inflammation such as montelukast, doxycycline, or steroids may be of benefit; however, there are no controlled trials [26, 27]. An ongoing open-label study is evaluating the use of low-dose naltrexone, which is both an anti-inflammatory agent and analgesic through its actions on glial cells within the nervous system, in the treatment of pediatric NDPH (NCT0344782). There is another ongoing study that is attempting to further shed light on the biology of NDPH by comparing serum levels of calcitonin gene-related peptide (CGRP) and nerve growth factor (NGF) levels in NDPH, chronic migraine, and healthy controls.

Imaging in NPDH is typically performed to exclude secondary headache mimics. Imaging is typically normal in NDPH. In a study of 97 NDPH patients, 84 patients had no white matter lesions on MRI. Of these, 36% had vascular risk factors and 44% had history of migraine [28]. The group of

patients with white matter lesions was significantly older and more likely to have had a post-surgical trigger for the NDPH.

Diagnosis of NDPH: How Far Should it Go?

Secondary headaches can mimic NDPH and should be considered in the differential diagnosis for a new-onset continuous headache. Headaches that most commonly present similarly to NDPH include high and low pressure–related headaches, such as idiopathic intracranial hypertension (IIH), idiopathic intracranial hypertension without papilledema (IIHWOP), and spontaneous intracranial hypotension (SIH). Other mimics can include venous thrombosis, cervical artery dissection, sinusitis, neuralgias, trochlear headache, post-traumatic headaches, meningitis, neoplasia, headaches secondary to hypothyroidism, and cervicogenic headache. In evaluating a patient for NDPH, it is crucial to perform careful evaluation to rule out secondary cause for the headache, as well as primary headaches such as hemicrania continua and primary trochlear headache, which have different treatments than do NDPH. Trochlear headaches are reported to have a new daily from onset progression in 88% in one series [29].

Clues in the patient history may lead to further investigations. For example, a headache that worsens when lying down might suggest increased intracranial pressure, while a headache that worsens when standing might suggest disorders associated with low intracranial pressure. A history of hypercoagulability or the presence of procoagulable state, such as exogenous estrogen use, pregnancy, or cancer, should lead to consideration of cerebral venous sinus thrombosis and evaluation by venous imaging. A report of unilateral pulsatile tinnitus, or a bruit on exam, might suggest the possibility of a dural arteriovenous fistula, which has been reported to present with a unilateral NDPH-like headache, and prompt arterial imaging [30]. History of trauma to the neck and/or hypermobility could suggest an arterial dissection. A history of neck pain preceding onset of headache and muscular pain and spasm of the neck musculature on exam suggests cervicogenic headache. Tenderness in the trochlear area and exacerbation of pain with reading could suggest trochlear headache. History of pain in an area innervated by a single nerve might suggest neuralgia.

On exam, it is crucial to evaluate for the more likely causes of persistent headache. Careful fundoscopy should be performed to look for signs of papilledema. Patients can be positioned in Trendelenburg to evaluate for positional effects on the headache [31]. Evaluation for signs of meningeal irritation should be performed. The head and neck should be palpated to evaluate for focal areas of tenderness that might suggest neuralgia or musculoskeletal dysfunction. Cranial and cervical auscultation for bruits should be performed.

Additional testing with laboratory studies or imaging is often needed. Ideally, MRI with and without contrast would be performed, as many secondary causes of persistent headache can be associated with MRI abnormalities. Dural thickening and enhancement would suggest low-pressure headache, which could be further evaluated with myelography or lumbar puncture, and CSF leak potentially treated with a blood patch or with surgery [31, 32]. Signs of increased pressure on MRI may also suggest need for LP to evaluate for increased pressure, even in absence of papilledema. MRI could also potentially show evidence of sinusitis even in absence of fever or rhinorrhea; an NDPH-like headache that resolved with antibiotic therapy has been reported in two Korean patients with isolated sphenoid sinusitis on MRI without other signs/symptoms to suggest infection [33]. Likewise, MRI imaging would be an appropriate evaluation for tumors that can cause new persistent headache. Some patients may benefit from MRV or MRA imaging to evaluate for vascular causes of the headache.

Viral titers may be positive in NDPH and could suggest a post-infectious inflammatory cause for the NDPH. TSH and thyroid antibodies may also be checked to rule out hypothyroidism-related headache.

Treatment of NDPH: How Far Should it Go?

The most commonly prescribed medications for NDPH include antidepressants such as amitriptyline or SSRIs, antiepileptic drugs such as topiramate or divalproex, and muscle relaxers, although most studies show a poor treatment response as compared with migraine [7, 8, 34]. Treatment should be phenotype driven. Patients with onset after Valsalva or with evidence of increased intracranial pressure may respond to agents such as acetazolamide and indomethacin, which lower CSF pressure.

It is reasonable to consider anti-inflammatory or immune-modulating treatments in patients with an infectious trigger for the headache. A case series of nine patients in India with post-infectious headache found that all patients had improvement with a 5-day course of IV methylprednisolone, in some cases followed with oral prednisolone, with all but two patients having near-complete improvement within 2 weeks. However, only four of those patients had duration of more than 3 months at time of evaluation. In a retrospective study of 63 patients in India, 37 patients were treated with combination of steroid (IV followed by oral), sodium valproate (IV followed by oral), and tricyclic antidepressant, with or without Naprosyn, and 46% had an excellent response (less than one headache a month) and 30% had a good response (> 50% reduction in headache frequency), while the remainder had a fair or poor response. The rate of excellent response was better in patients with a preceding history of infection and in patients

with shorter duration of symptoms at time of treatment [11]. Doxycycline and montelukast have been reported to show some success in post-infectious patients, but no controlled trials have been completed [26, 27].

In patients with cervical hypermobility or post-surgical onset of headache, some patients respond to cervical blocks by pain anesthesia. Physical therapy may also be helpful in these patients [10••, 27, 35].

Some studies have looked at onabotulinumtoxinA in NDPH. A retrospective review of a small number of patients showed decreased headache frequency in 50% of patients at 6 months and decreased severity in seven out of nine patients at 12 months [36•]. There are multiple additional case reports of improvement with onabotulinumtoxinA [37, 38].

Nerve blocks for NDPH have shown some immediate improvement in symptoms, but have not been associated with a sustained response in several retrospective service evaluations [39–41]. A single case of sustained relief of NDPH from surgical decompression of the occipital nerves has been reported [42].

Other less common therapies have been investigated. Subanesthetic doses of IV ketamine have been shown to improve symptoms in patients with migraine in a retrospective chart review, with 8 of the 14 patients with NDPH showing improvement with the treatment [43]. Mexiletine was shown in a small series of three patients with NDPH to lead to reduced pain but can be associated with side effects [44]. IV dihydroergotamine (DHE) does not tend to be effective in patients with NDPH; in one series, only 2 out of 11 patients with NDPH treated with DHE reported even mild benefit [45].

Advice for Caring for Patients with NDPH

We recommend referral of patients with suspected NDPH to a headache specialist for careful review for potential secondary etiologies and for longitudinal management, anticipating a potentially refractory treatment course. Early involvement of a multidisciplinary team, including efforts to bolster self-efficacy and self-management strategies and address comorbidities, is very important.

Patients with NDPH often have significant distress from their headaches. Often, multiple treatment types are trialed, and each patient may require a unique approach to their management. It is important to maintain an open mind when caring for patients with NDPH. Patients with this diagnosis are in special need of physicians who are empathetic, optimistic, and determined.

Conclusions

NDPH is a heterogeneous disorder defined by abrupt onset of an unrelenting headache that persists for at least 3 months and is often refractory to treatments. A thoughtful evaluation of patients with new onset of constant headache is critical to rule out secondary etiologies. At this time, a phenotypically driven approach (e.g., migraine, cervicogenic) to treatment is reasonable. In some cases, NDPH may represent a post-infectious immune/inflammatory phenomenon, which may respond to steroid treatment. In cases with features suggesting an elevated intracranial pressure (e.g., Valsalva as a trigger or aggravation with lying flat), CSF-lowering measures may prove beneficial. Patients with a thunderclap onset may respond to nimodipine. However, due to the rarity of this disorder, there are no randomized trials investigating treatments. Future research should interrogate novel approaches to categorizing patients (e.g., based on temporal acuity) and focus on early identification of cases, which may be initially diagnosed as status migrainosus at first presentation.

Compliance with Ethical Standards

Conflict of Interest Jonathan H. Smith reports royalties for the articles "Acute treatment of migraine in adults" and "Preventive treatment of migraine in adults" from UpToDate and a speaking fee (January 2019) from AMGEN, outside the submitted work. Emily J. Riddle declares no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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