Curr Neurol Neurosci Rep (2014) 14:425
DOI 10.1007/s11910-013-0425-5

HEADACHE (R HALKER, SECTION EDITOR)

New Daily Persistent Headache and Potential New Therapeutic Agents

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Published online: 9 January 2014

Abstract New daily persistent headache is a form of a chronic daily headache with a unique temporal profile. Patients can recall the exact day when their headache started. It can be one of the most refractory types of headache to treat. Recent publications have highlighted different subtypes and heterogeneity in presentation. Referring to it as a syndrome versus a distinct disorder has also been suggested. Several different classes of medications have been used for the treatment, with mixed results. The underlying pathophysiology of new daily persistent headache is unclear, but tumor necrosis factor may play a role. The clinical features, differential diagnosis and potential new therapeutic agents will be discussed.

Keywords New daily persistent headache · Chronic daily headache · Tumor necrosis factor

Introduction

New daily persistent headache (NDPH) was first described in a series of 45 patients by Vanast in 1986 [1•] as a "benign syndrome, combining features of common migraine and tension headache and occurs daily from the first day the headache begins". It is currently recognized as a form of chronic daily headache (CDH). One of the most unique features of NDPH is the temporal profile, as it starts abruptly and is daily from onset. A large proportion of patients will remember the exact day of onset, and are often able to recall what they were doing at the time of onset.

CDH is defined as a headache occurring 15 or more days per month. Secondary CDH can be produced by many central nervous system (CNS) or systemic causes, or by exogenous causes such as trauma. Primary CDH, for which no imaging or laboratory testing can demonstrate an underlying cause, is separated into frequent headaches of short duration and frequent headaches of long duration. Short-duration headaches include cluster headache (both chronic type and episodic type), paroxysmal hemicrania, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing/short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNCT/SUNA), and hypnic headache. Long-duration headaches are comprised of chronic migraine (CM), chronic tension-type headache (CTTH), hemicrania continua (HC), and NDPH.

Of the frequent long-duration headaches, CM has associated features, which are mandatory for the diagnosis under the International Classification of Headache Disorders (ICHD-3-Beta) [2]. These include nausea/vomiting or photophobia and phonophobia. CTTH is characterized by its frequent occurrence and absence of migrainous features. HC is a very rare type of headache that is continuous, side-locked with ipsilateral autonomic features, and is reputedly absolutely responsive only to indomethacin. NDPH may have features of all of these types except that it begins abruptly and continues on a daily basis from the very onset.

Epidemiology

The prevalence of NDPH has been estimated to be 0.1 % in a study conducted in Spain involving 2,253 patients with a CDH prevalence of 4.7 % [3]. The age of onset ranges from 12 to 79 years [4]. Comparatively, the prevalence of CDH in the United States is about 4 % [5].

This article is part of the Topical Collection on *Headache*

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Diagnosis

The diagnostic criteria for NDPH have evolved over time. Little heed was paid to Vanast's description until NDPH was included in the Silberstein Lipton classification of CDH in 1994, the Silberstein–Lipton CDH criteria [5]. In this first attempt at standardizing criteria, NDPH was described as occurring more than 15 days/month for more than 3 months, lasting longer than 4 h per day and beginning abruptly over fewer than 3 days, without being preceded by increasing frequency of migraine or tension-type headache.

In 2004, the ICHD-II excluded any migrainous features [6]. The International Headache Society (IHS) defined NDPH as an abruptly-developing headache with CTTH features with or without mild nausea. In clinical practice, NDPH can be one of the most refractory of all headache syndromes. Most patients fail multiple aggressive trials of outpatient and inpatient therapy. The notion of NDPH having primarily CTTH features also contradicted an earlier view, in 2002, when Li and Rozen [4] had proposed that the absence of migrainous features should not be required for the diagnosis.

In 2008 Kung et al. [7] proposed a more simplified criteria that did not stipulate whether migrainous features were present or not. For the first time, it was recognized that NDPH could mimic chronic migraine, with all the migrainous features that are diagnostic of migraine.

The new IHS classification, to be finalized in 2014, has accepted this definition. The ICHD-3-Beta describes NDPH as a primary headache disorder with a distinct and clearly remembered onset, pain becoming daily and unremitting within 24 h, and persisting for greater than 3 months [2].

Clinical Features

Different patterns of onset, time course, and severity of NDPH have been observed. NDPH typically starts abruptly in previously headache-free individuals. It seems as if anyone is at risk for developing this type of headache, regardless of whether they have a prior personal or family headache history. According to ICHD-3-Beta, patients with a history of migraine or tension-type headache are not excluded from the diagnosis of NDPH, but the NDPH headache should take on a sudden daily frequency without any gradual crescendo [2].

Regarding response to treatment, there are two sub-types of NDPH. The remitting type usually resolves without any treatment in most patients, as first described by Vanast [1•]. Remissions may occur in up to 20 % of patients within 2 months to 2 years after onset [3]. A persistent refractory type is resistant to multiple outpatient and inpatient treatments.

The severity ranges from a mild daily headache pattern akin to CTTH to a severe disabling continuous high-level constant daily pain akin to severe chronic migraine.

Robbins et al. [8••] have suggested further dividing the groups based on prognosis: 1) persistent type with a continuous headache from onset; 2) remitting type with complete resolution of headaches that occurs fewer than 5 days per month for 3 months; and 3) relapsing–remitting type with pain-free breaks between bouts of continuous headache.

Li and Rozen [3] studied 56 patients and reported several clinical findings. About 38 % had a prior headache history, of which 19 % had episodic migraines. Almost 80 % reported a continuous pain 24 h a day. More than 80 % were able to pinpoint the exact day when NDPH started. Most of the headaches were located bilaterally and in the occipital-nuchal region. A significant proportion of these patients reported having migrainous features such as nausea, photophobia, and phonophobia. This was the first study to highlight triggering events such as flu-like illness (30 %), extracranial surgery (12 %), and stressful life events (12 %). However, > 40 % of the patients could not identify a triggering event. The retrospective nature of the triggering events lends itself to recall bias, and should be taken into consideration before making a diagnosis of NDPH.

The heterogeneity of NDPH has also been highlighted in a set of three cases presented by Robins and Evans [9], two of which involve thunderclap headache at the onset of NDPH with a thorough negative secondary cause evaluation. The first was of a 42-year-old woman who developed a right nuchal-occipital 10/10 severe headache at onset that persisted for 3 weeks. This was followed by a variable intensity headache in the same locations with some migrainous features. There was only a remote history of a 3-week headache after a head injury. The second case was of a 39-year-old man who had a 10/10 abrupt headache at onset that persisted for 3.5 months. There were no classic migrainous symptoms, but there were some autonomic features. The third case was of a 29-year-old woman with a prior history of headaches with migrainous features and good response to sumatriptan. At some point she suddenly developed a daily headache with variable intensity for about 3.5 months. The authors concluded that NDPH is likely a heterogeneous disorder, in which some of the patients may, in reality, have another primary or secondary disorder.

Goadsby [10••] has asserted that NDPH is a syndrome rather than a discrete disorder with primary or secondary subtypes. He argues that it should be used as an "umbrella description", which should invite better characterization.

Differential Diagnosis

There are several differential diagnoses for a headache with daily frequency. Among the primary headache disorders, CM is different from NDPH in that it progressively evolves from episodic migraine. CTTH similarly develops from episodic

tension-type headache, and lacks migrainous features. HC is a rare, side-locked headache with associated ipsilateral autonomic features. Like NDPH, HC is daily from onset [5].

There are several NDPH mimics. Low intracranial pressure headaches can result from several different etiologies. Postdural puncture headaches following lumbar puncture or epidural anesthesia tend to resolve spontaneously, but persistent low-pressure headaches can be chronic. Other causes of intracranial hypotension include a cerebrospinal fluid (CSF) fistula, ruptured congenital Tarlov cysts, whiplash/trauma, and even trivial movements like looking over the shoulder while driving. The postural component that is observed with low CSF pressure may disappear over time, leaving only a daily form of headache.

Cerebral venous thrombosis can also present with a daily headache. However, clinical features present with a venous thrombus such as seizures, focal neurological deficits, and an abnormal fundoscopic examination are not found in NDPH. Internal carotid and vertebral dissections can produce headaches acutely from onset. Clinical features include ipsilateral pain in the head, neck, and/or face, which can be of gradual or sudden onset. Other features may include a Horner's syndrome and/or a cervical bruit.

Primary or secondary CNS angiitis or giant cell arteritis can also present with a continuous headache. Giant cell arteritis must be ruled out in any new onset headache in persons over the age of 50 years. Features that further suggest this diagnosis include ipsilateral visual deficits and jaw pain/fatigue with chewing consistent with claudication. Chronic headaches can be produced by lymphocytic meningitis, including Mollaret's Syndrome, which is recurrent herpes simplex virus meningitis.

Other mimics of NDPH include sinusitis, slowly accumulating subdural hematomas, and contact-point headache. Contact point headache is a headache that is thought to be due to contact between the lateral nasal wall and the nasal septum. These headaches have been noted to respond to a septoplasty [11], but recent studies have demonstrated that the presence of a contact point does not necessarily imply the presence of a headache, and decompression does not frequently have favorable results [12].

NDPH is similar in some ways to chronic post-traumatic headache (CPTH) in that they both can be daily from onset, refractory to treatment, and variable in their presentation. In both types of headache, the mechanism(s) that perpetuate chronic daily head pain are unclear. In clinical practice, both CPTH and NDPH can have migrainous or tension-type features. As such, treatment is often based upon headache features.

Another mimic was recently reported by Rozen [13] in a case of a 19-year-old woman who presented to a specialty headache clinic with a 3-month headache that she just woke up with one day. There was no prior history of significant headache or clear antecedent triggering event such as a flu-like illness or a stressful life event. The headaches were described as sharp and throbbing in quality, located in the bi-frontal and temporal region. The headaches had some migrainous features. She also had two spells involving of loss of consciousness. Around the same time, she was also experiencing episodes of staring spells and lip-smacking. It is not clear if her seizure-like activity occurred in the context of a severe headache. Her medical history was only significant for bipolar disorder, which was well controlled on carbamazepine. Physical examination was only significant for tenderness to palpation in the occipito-nuchal and temporal regions. Gabapentin was added for headache and she subsequently developed generalized tonic–clonic seizures with an electroencephalography (EEG) pattern consistent with juvenile myoclonic epilepsy. She was tapered off the carbamazepine and started on lamotrigine. After a 9-month follow up, she remained without any headache or seizures. The author suggests including EEG evaluation in suspected NDPH patients with similar presenting symptoms.

A recent report noted a radiologically isolated syndrome in a multiple sclerosis (MS) patient who met the diagnostic criteria for NDPH. The authors hypothesized that headache in MS may be a result of an inflammatory process, and pointed out that pro-inflammatory cytokines have been identified in CSF of both patients with NDPH and MS [14].

Pathophysiology

The underlying pathophysiology of NDPH remains unknown. A significant portion of patients have a febrile illness at the onset of headache [3]. In one study, more than 50 % of 186 NDPH patients had positive Epstein–Barr virus (EBV) serology [15]. In another study, 84 % of 32 patients with NDPH and 25 % of 32 controls had evidence of EBV virus infection [16]. However, secondary causes for NDPH may not have been adequately ruled out. Not enough information regarding the clinical history is presented in the article to determine whether an alternative diagnosis may have been present. Evidence of systemic infections such as salmonella, adenovirus, toxoplasmosis, herpes zoster, EBV, and *Escherichia coli* urinary tract infections were identified in a study of 108 NDPH patients [17]. Evidence of chronic meningitis was not found in the CSF of NDPH patients [18].

Joint hypermobility/laxity has also been observed. Rozen et al. [19] examined a group of 12 patients with NDPH who all had a similar body habitus with tall stature and long necks. He postulated that cervical afferent input to the trigeminal nucleus caudalis may result in head pain. However, there was no control group and no analysis of CSF pressure. This was also pointed out by Goadsby [10••]. A possible connection could be that such patients actually have low CSF pressure from

minor head or neck trauma causing rupture of congenital CSF containing cysts. This population, especially if they have confirmed connective tissue disorders such as Ehlers–Danlos syndrome (EDS), is prone to spontaneous CSF leaks [20].

EDS is a type of inheritable disorder resulting in abnormal collagen production. Out of six subtypes, type IV more often leads to neurovascular complications. Bilateral carotid and vertebral dissections have been reported in this population by Jacome [21], who collected data on 18 patients with EDS and chronic headache for at least 2 years. He diagnosed his patients with CM with and without aura, CTTH, and CPTH. He concluded that chronic headaches might be the only presentation of EDS in the absence of structural, congenital, or acquired CNS lesions. He hypothesized that EDS patients may be more prone to migraine owing to "inherent disorders of cerebrovascular reactivity or cortical excitability".

Inflammation likely plays a significant role in the genesis and perpetuation of NDPH. Tumor necrosis factor (TNF)-α is a pro-inflammatory cytokine, which is involved in brain immune and inflammatory responses, as well as in the initiation of pain. In one study, CSF levels of TNF-α were elevated in 19/20 NDPH patients (8.8–16.7 pg/mL, normal <8.2 pg/mL), but levels were also elevated in 16/16 CM and CPTH patients used as the control group (10.2–16.1 pg/mL) [22]. However, these results have not been replicated.

It is not clear at this time if increased CSF TNF-α is a consistent finding unique to NDPH, as it may be elevated in other headache disorders. If this study is confirmed, then it may promote the future development of TNF antagonists that could pass the blood–brain barrier, unlike the large monoclonal antibodies used to treat peripheral TNF-α disorders such as rheumatoid arthritis.

Treatment

The prognosis of NDPH was initially presumed to be benign. In the original studies by Vanast [1•], 30 % of the men were headache free at 3 months, and 86 % at 2 years. Thirty percent of the women were headache free at 3 months and 73 % were pain free at 2 years [1•]. However, in a study performed by Robbins et al. [8••], > 50 % with the persistent subtype had a daily headache for 2 years. Of the group that remitted, 63 % did so within 24 months. In the relapsing–remitting subgroup, the first remission was within 24 months. These patients were not studied beyond 24 months [8••].

Just as NDPH starts abruptly, it may also end abruptly. Unfortunately, refractory forms can continue and fail to respond to inpatient and outpatient treatments. Owing to this variable and unpredictable course, there have been no well-designed prospective placebo-controlled studies published regarding NDPH treatment.

Most headache specialists prefer to treat the patient based upon the phenotype of the headache pattern. If the patient has a migrainous phenotype, then migraine abortive and preventative drugs such as sumatriptan and topiramate may be used. If the pattern is more consistent with tension-type headache, then drugs such as naproxen and amitriptyline can be used. If the pattern is more neuralgic, then neuropathic pain drugs such as gabapentin or amitriptyline can be used. The use of several agents with complementary adverse effect profiles is often seen.

Some treatment regimens have been recommended based on the triggering events such as infections, stressful life event, and surgery [23].

Methylprednisolone

In one study, intravenous and oral steroids improved the headache in a few patients with postinfectious NDPH [24]. Nine patients were given intravenous methylprednisolone 1,000 mg daily for 5 days followed by a brief oral prednisone taper for 2–3 weeks. Six patients were given oral steroids alone for 2–3 weeks. Seven patients had almost complete relief within 2 weeks, and two patients showed complete improvement between 6 and 8 weeks after initial treatment. However, these patients were treated only a few weeks after onset, which does not meet the 3-month criteria for NDPH. NDPH patients rarely present to headache specialists so early in the course of their headaches.

There are two case reports of good response to onabotulinum toxin type A (BTX). Spears [25] presented a case of a 67-year-old man who had complete response for 8–12 weeks after each of three rounds of 100 units of BTX. Tsakadze and Wilson [26] presented an abstract in which three patients treated with 100 units of BTX every 3 months had> 75 % relief, and one patient had 100 % relief.

Doxycycline

Doxycycline is a drug that can block the TNF-α receptor. In a small, open-label trial, four patients with NDPH and elevated CSF TNF-α were given 100 mg doxycycline twice daily [27]. All of these patients had failed at least five preventive agents, and three patients had an antecedent infection. All patients had a positive response after 3 months. Two patients became pain-free, one had an 80 % improvement, and one had>50 % reduction of severe headache episodes. Rozen [27] hypothesize that NDPH may result from CNS inflammation caused by the release of TNF-α from glial activation. As doxycycline can cross the blood–brain barrier, it may serve to inhibit the production of TNF-α and prevent microglial activation.

Mexilitine

In a study evaluating the use of mexilitine (600–1,500 mg/day) in three treatment-refractory NDPH patients, some improvement in pain severity and limited reduction in headache frequency was observed [28]. However, side effects were prominent, such as dizziness, nausea, and lack of coordination.

Topiramate and Gabapentin

Small case series have suggested some response to topiramate and gabapentin. Rozen [29] presented five cases with successful treatment with either gabapentin or topiramate.

Potential New Therapeutic Agents for NDPH

Naltrexone

Naltrexone is a potential NDPH therapeutic agent. Its mechanism of action involves competitive antagonism of opioid receptors, and it has been shown to attenuate the production of inflammatory cytokines and neurotoxic superoxides via suppressive effects on CNS microglia cells. It has been postulated that the neuroprotective effects of naltrexone are due to modulation of mitochondrial apoptotic pathways [30].

Naltrexone has also been shown to block acute endotoxic shock by inhibiting the production of TNF-α [31]. Septic shock is hypothesized to result from over activation of the immune system by bacterial toxins. This results in the release of pro-inflammatory cytokines such as TNF-α, interleukin (IL)-1, and IL-6. TNF-α is a mediator for tissue damage, organ failure, hypotension, and septic shock. Naltrexone has been reported to reverse some of these effects. Greeneltch et al. [31] conducted animal studies which showed not only naltrexone's protective effects against septic shock, but also identified a mechanism of indirect inhibition of TNF-α production in vivo.

Fibromyalgia (FM), like NDPH, is a chronic pain disorder due to chronic central sensitization of the nervous system. In a placebo crossover study, a group of ten FM patients given naltrexone 4.5 mg/day for 8 weeks showed 30 % reduction in their pain scores compared with a 2.3 % reduction in the placebo-treated patients [32]. Another small placebo-controlled trial showed 27 FM patients treated with 4.5 mg/day naltrexone had an almost a 50 % reduction in their pain scores compared to placebo ($p = 0.006$) [33]. There was a 48 % pain reduction with naltrexone versus 27.4 % with placebo ($p = 0.021$). These results are better than FM pain reduction reported for the Food and Drug Administration-approved drugs pregabalin, duloxetine, and milnacipran. These positive findings for the use of naltrexone for the treatment of fibromyalgia suggest its utility in the treatment of NDPH.

Naratriptan

Rapoport et al. [34] retrospectively reviewed 27 cases of treatment refractory chronic daily headaches who had received treatment with 2.5 mg naratriptan taken twice daily for more than 2 consecutive months. The majority of these patients may have had NDPH (personal communication to HGM). Sixty-five percent of 20 patients who took naratriptan for 6 months had reverted to an episodic pattern of headache. When followed up at 12 months, 55 % continued to experience episodic headaches, 5 % relapsed to chronic migraine, and 2 % were lost to follow up. The authors recommended that naratriptan be used as a long-term preventative treatment for CM. They also suggested the possibility of using daily naratriptan as an adjunctive agent during detoxification of medication overuse from acute abortive medications.

These findings were replicated by a prospective pilot study when 30 intractable CDH patients were treated with naratriptan 2.5 mg twice daily for 3 months. There was a reduction in mean headache frequency from 27.1 days to 19.0 at 3 months ($p < 0.001$). Also the mean numbers of rescue medications was reduced from 17.7 to 9.7 at 3 months ($p < 0.001$). Of 22 patients who completed the protocol, 54 % converted from a chronic daily to an episodic pattern [35].

Others have also shown similar improvements in patients treated with daily naratriptan, especially a 1-year treatment regimen with naratriptan, which produced excellent results and no significant adverse effects [36]. These positive findings for the use of naratriptan for the treatment of CDH, including some cases that may have been NDPH, suggest its utility in the treatment of NDPH.

Prazosin

Prazosin is a presynaptic alpha-adrenergic receptor antagonist usually used to manage hypertension. In recent years it has been used by psychiatrists to treat anxiety, insomnia, and post-traumatic stress disorder.

In a study conducted by Ruff et al., a trial of prazosin resulted in a relatively long-term improvement of headache in 126 veterans with mild traumatic head injury caused by a blast injury [37]. Patients were offered sleep counseling along with increasing doses of oral prazosin. The authors felt that treating sleep impairment would reduce headache frequency. Prazosin was chosen because it has been shown to prevent nightmares in patients with stress disorders. Surprisingly, peak headache pain (0–10 scale) decreased from 7.28 to 4.08. The number of headaches per month decreased from 12.4 to 4.77. Montreal Cognitive scores improved from 24.5 to 28.6. These improvements were maintained 6 months later. The authors speculate that the chronification of CPTH could be caused by "sympathetically maintained pain", which is a possible reason that an

alpha-adrenergic receptor antagonist like prazosin demonstrated some efficacy in the treatment of CPTH, and could potentially be effective for the treatment of NDPH.

Conclusion

NDPH is a headache disorder that is under-recognized, heterogeneous in presentation, and often refractory to conventional headache treatment. A careful search for secondary causes for headache should be conducted. Although multiple medications are used in clinical practice, there are limited data to favor any particular agents. As such, further studies are needed to elucidate the pathophysiology of NDPH and to establish more consistent treatment paradigms.

Compliance with Ethics Guidelines

Conflict of Interest Shivang G. Joshi, Paul G. Mathew, and Herbert G. Markley declare that they have no conflict 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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