New Daily Persistent Headache: An Update

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Abstract New daily persistent headache is a primary headache disorder marked by a unique temporal profile which is daily from onset. For many sufferers this is their first ever headache. Very little is known about the pathogenesis of this condition. It might be a disorder of abnormal glial activation with persistent central nervous system inflammation and it may be a syndrome that occurs in individuals who have a history of cervical hypermobility. At present there is no known specific treatment and many patients go for years to decades without any improvement in their condition despite aggressive therapy. This article will present an up-to-date overview of new daily persistent headache on the topics of clinical presentation, treatment, diagnostic criteria, and presumed pathogenesis. It will also provide some of the authors own treatment suggestions based on recognized triggering events and some suggestions for future clinical trials.

Keywords New daily persistent headache · Chronic daily headache · Tumor necrosis factor alpha · Cytokines · Hypermobility

Introduction

New Daily Persistent Headache (NDPH) is a unique primary headache disorder first described by Vanast in 1986 [1]. Vanast felt this was the best form of daily headache a patient could develop because it would always go away without any treatment and he termed this a benign daily headache syndrome. In the headache clinic, however, NDPH is felt to be anything but benign and is considered one of the most treatment refractory of all primary headache conditions. It is definitely unique in its temporal profile compared with other disorders in that it begins daily from onset, typically in a patient population with no prior headache history and can continue for years unabated without any sign of alleviation, despite aggressive treatment. In many instances patients can actually name the date their headache began, sometimes the time it began, even if it was many years prior to their visit with the headache specialist. The objective of this review article is to discuss what is new in the medical literature about NDPH over the past few years in regard to headache characteristics, pathogenesis, treatment, diagnostic criteria, as well as commenting on possible future clinical trials, and the author’s current evaluation and treatment approach for the NDPH patient.

Clinical Features of NDPH

There have been 2 recent papers that have added to the literature defining the clinical characteristics of NDPH. In brief the hallmark of NDPH is a daily headache from onset that is continuous without breaks. It is bilateral in location, can be mild to severe in intensity, can occur anywhere on the head, and can have migrainous associated symptoms. Other defining features are listed in Table 1 which is compiled from previous studies of NDPH [2*, 3–5]. Robbins et al. [2*] in 2010 looked at NDPH in a headache specialty clinic population. Seventy-one patients met criteria for NDPH (allowing migraine features). Patients were predominantly white women with moderate to severe pain of bilateral location (89%), of throbbing quality (45%), and had migrainous associated symptoms which included nausea 48%, vomiting 13%,
Table 1 Clinical characteristics of NDPH (based on multiple published manuscripts) [2–5]

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Female predominant</td>
</tr>
<tr>
<td>Age of onset</td>
<td>Younger women (can be 2nd and 3rd decade), older males</td>
</tr>
<tr>
<td>Location</td>
<td>Bilateral in most but can occur anywhere on head; if 1-sided–should think hemispheric continuum</td>
</tr>
<tr>
<td>Intensity</td>
<td>Moderate to severe in most individuals</td>
</tr>
<tr>
<td>Pain duration</td>
<td>Constant pain</td>
</tr>
<tr>
<td>Associated symptoms</td>
<td>Migrainous features can be present</td>
</tr>
<tr>
<td>Recognized triggering event</td>
<td>In &lt;50%; known triggers: postinfectious, stressful life event, surgical (typically intubation involved), exposure (chemicals)</td>
</tr>
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NDPH: New Daily Persistent Headache

Photophobia 45%, and phonophobia 41%. The authors commented on 3 NDPH sub-forms: persistent 76%, remitting 16%, and relapsing–remitting 8.5%. Women with NDPH were slightly younger than males with the syndrome (woman 26 years vs males 28 years). A prior headache history was noted in 25%; episodic tension type headache (18.3%) and migraine (7.0%). Triggering events were noted in 46.5% with a flu-like or upper respiratory infection in 14%, stressful life event in 10%, and menarche in 4.2%. Two newly identified triggers were a tapering of an SSRI medication and after a human papillomavirus vaccination. Prakash et al in 2012 [6••] observed 63 patients with NDPH from a neurology institute in India. Age of onset ranged from 18-68 years. There was a female predominance for the syndrome (57%). Only 33% could recall the exact date of headache onset. Thirty-five percent of the patients had migrainous features. Triggers were noted in 54% with infection being the most common (29%) while others described trauma, stress, and surgery. A past history of headache was noted in 54% (migraine 25%, tension type 29%).

Etiology of NDPH

Sadly, there have been rare studies that have delved into the pathogenesis of NDPH. A main reason why physicians struggle in the treatment of NDPH is a lack of understanding of its pathogenesis. In brief, several of the possible mechanisms involved in the etiology of NDPH include the following.

1. Persistent central nervous system inflammation secondary to glial activation and increased tumor necrosis factor alpha levels in the CSF. As a certain percentage of NDPH patients have their headaches start after an infection or stressful life event the possibility of a persistent state of systemic or CNS inflammation comes into question. Tumor necrosis factor alpha (TNF alpha) is a pro-inflammatory cytokine involved in brain immune activities and inflammation. It is also pronociceptive. Rozen and Svidan [7] looked at TNF alpha levels in the CSF of primary NDPH patients from an inpatient headache unit from a large headache specialty clinic. Twenty patients were studied and TNF alpha levels were elevated in 19 samples. Based on their results the authors suggested a role for TNF alpha in the pathogenesis of NDPH. The thought is that NDPH patients in some manner have persistent glial activation after a viral illness or stressful life event with persistent cytokine production triggering a chronic inflammatory response. Many of the study patients had had their triggering infection 5–10 years prior to the CSF study but were still showing elevated CSF TNF alpha levels. As serum TNF alpha levels were not elevated in most NDPH patients, NDPH was not a disorder derived from systemic inflammation, but rather inflammation solely involving the CNS. There is evidence that TNF alpha will induce calcitonin gene-related peptide production, which is a known factor in the pathogenesis of other trigeminal based pain syndromes, thus, a mechanism by which NDPH pain may commence [8].

2. Cervical spine joint hypermobility as a predisposing factor for the development of NDPH. Rozen and colleagues [9] had noticed a similar body habitus in most of their NDPH patients of tall height, thin weight, and a long neck reminiscent of the physical characteristics seen in individuals with hereditary connective tissue disorders. On examination these patients also appeared to have hypermobility of both the cervical spine and systematically. Rozen et al [9] then studied for the presence of joint hypermobility in NDPH patients, hypothesizing that cervical spine hypermobility was a predisposing factor for the development of NDPH. Eleven of 12 NDPH patients investigated were found to have cervical spine joint hypermobility and 10 of 12 NDPH patients had widespread systemic joint hypermobility utilizing the Beighton score. Joint hypermobility in the cervical spine can theoretically lead to persistent daily headache as there is convergence of trigeminal and cervical afferents in the trigeminal nucleus caudalis (TNC) [10]. Cervical spine joint hypermobility may influence cervical afferent input into the TNC with the subsequent development of head pain. In essence patients with cervical spine hypermobility have years’ worth of wear and tear in their upper cervical facet joints and atlanto-axial joint prior to when they develop their daily headache out of the blue, they just have not reached the threshold yet to activate the TNC and have headaches. Once, however, that threshold is met (thus, new daily persistent headache) these patients can be very difficult to reverse based on their innate flexibility issues and cervical spine...
irritation issues, thus, the treatment refractory nature of NDPH.

**Treatment**

At present no specific treatment strategy can be suggested for primary NDPH based on clinical evidence. Most headache specialists will therapy NDPH with the same acute and preventative medications that they use to treat chronic migraine although based on nonresponse to most of these medications, NDPH and chronic migraine are 2 disparate syndromes.

What is New from the Medical Literature on NDPH Treatment?

**Tetracycline Derivatives**

A promising treatment reported by Rozen [11] in abstract form is the use of daily oral doxycycline which is a TNF alpha inhibitor and is based on his CSF study. Four patients with treatment resistant NDPH and elevated CSF TNF alpha levels were treated with doxycycline 100 mg BID in an open label fashion for 3 months. All patients had failed at least 5 preventative agents and thus, were deemed treatment refractory. Three of 4 patients also failed inpatient headache treatment. Duration of NDPH prior to doxycycline therapy ranged from 8 months to 3 years. All of the subjects had a positive response to doxycycline treatment; 2 became pain free while 1 patient had an 80% improvement in daily pain intensity and one had a >50% reduction in frequency of severe pain episodes with a much improved quality of life. Average time to see improvement was after 2 months of therapy and the 2 patients with the highest CSF TNF alpha levels were the ones who became pain free with doxycycline.

**Mexiletine**

Manura et al [12] looked at mexiletine in 3 patients with NDPH who had been deemed treatment refractory. All 3 patients showed a reduced severity of pain, but only 1 showed a reduced headache frequency. Significant side-effects were noted on this medication.

**IV Corticosteroids**

Prakash and Shah [13] reported on 9 patients with postinfectious NDPH. All patients were given high dose intravenous methylprednisolone for 5 days while 6 patients were given oral steroids for 2–3 weeks. All patients improved with 7 patients getting almost complete pain relief within 2 weeks, while 2 patients needed between 6 and 8 weeks. These results are very promising for NDPH but none of the patients would have fit the ICHD-2 criteria [14] for NDPH at the time because they were treated only several weeks after headaches began (and the criteria required 3 months of headache) plus some of these patients may have had the remitting form of NDPH and would have improved on their own even without treatment, thus, the efficacy of therapy comes into question. Most headache specialists rarely ever see NDPH until after it is has been ongoing for months to years, thus, high dose corticosteroids may work early in the course of NDPH but may not work as effectively in the more prolonged cases or more “real clinic” cases. This same author in another more recent publication [6••] also treated 37 patients with combination therapy using IV corticosteroids plus additional treatments—intravenous methylprednisolone 500–1000 mg per day for 3–5 days, followed by oral prednisolone 1 mg/kg body weight for 7 days plus sodium valproate (intravenous loading 15 mg/kg body weight, followed by 5 mg/kg Q8 hours for 3–5 days), followed by oral valproate (500–1500 mg daily) for 3–12 months plus an antidepressant (either amitriptyline 25–75 mg/day or dothiepin 25–75 mg/day) plus minus naprosyn 250–500 mg bid. An excellent response was noted in 46%, good response in 30%, fair in 16%, and poor in 8%. This response rate is fairly robust for NDPH, and as the valproate is given throughout many headache clinics IV, one has to wonder again if it is the high dose corticosteroid as the trigger here for success? It did not state, however, what percent of these patients received this combination therapy at what stage of their NDPH. What the author did state was that in patients with NDPH >2 years vs those at 3–6 months complete response of any treatment tried was noted in 26% vs 58% again showing how difficult it is to get NDPH patient’s better the longer they have the syndrome.

**Nerve Blockade**

As a number of NDPH patients appear to have cervical irritation signs on examination possibly relating to underlying cervical hypermobility, sending them for pain clinic evaluation for nerve block procedures is recommended when medication is not helping. Robbins et al [3] reported on peripheral nerve block responses in patients with NDPH. Greater and lesser occipital, auriculotemporal, supraorbital, and supratrochlear nerve blocks were tried. In the persisting subform of NDPH or the prolonged subform, 54% had an acute response to nerve blockade but that correlated to only 1 day of pain relief. No semipermanent procedures were tried like radiofrequency ablation.

**Diagnostic Criteria**

New daily persistent headache was originally included in the second edition of the International Classification of Headache Disorders criteria (ICHD-2) and there was tremendous
controversy over the criteria as basically NDPH was made out to be a daily form of tension-type headache which it was not from its clinical presentation in studies and in the clinic [14]. By ICHD-2 criteria there needed to be an almost absence of migrainous symptoms to make a diagnosis of NDPH. Clearly looking at the available descriptive studies migrainous symptoms was not only common in NDPH patients but they were almost as prevalent as that seen in migraine itself. Robbins et al [3] looked at patients with NDPH and utilized a revised ICHD criteria allowing migrainous symptoms. Of 71 patients who met the revised criteria only 43% of those met the ICHD-2 criteria, thus, demonstrating that the majority of NDPH patients do have migrainous symptoms along with their daily headache and if the current criteria stood it would have excluded most true patients with NDPH.

The recently published ICHD-3 beta criteria for NDPH does solve this issue but in reality the criteria is still quite lacking [15••]. Basically NDPH is now a headache that starts daily from onset and is nothing more, with no mention of headache location or type of associated features.

**Diagnostic Criteria**

1. Persistent headache fulfilling criteria B and C
2. Distinct and clearly remembered onset, with pain
3. Becoming continuous and unremitting within 24 hours
4. Present for >3 months
5. Not better accounted for by another ICHD-3 diagnosis.

It seems the committee could have done more but at least there is no issue if a patient does or does not have migrainous associated symptoms.

**What Can We Look Forward to in the Future?**

**Possible Clinical Trials**

Patients ask all the time if there are any clinical trials for NDPH. As federal funding is very limited for any form of pain trials, NDPH would seem to be very low on the priority list for suggested funds as it just has low prevalence, but for the individual the condition is devastating as these are not “professional pain/headache sufferers” like our chronic migraineurs, thus, they have very little coping mechanisms for chronic pain as they have had daily pain thrust upon them with minimal chance of therapeutic response. As this appears to be a syndrome of altered CNS inflammation one would think that immune modulation could be efficacious.

One proposal would be either intravenous immunoglobulin therapy or plasma exchange therapy for treatment. This is not without precedence as the author has a postinfectious NDPH patient in his practice who also had an immunoglobulin deficiency syndrome and after IVIG treatment her NDPH basically alleviated.

A second proposal would be a placebo controlled trial looking at glial/cytokine inhibitors like doxycycline or minocycline which we have been using in open label fashion with some success. The trial could involve priming with IV tetracycline treatment to start.

Third Proposal: Onabotulinumtoxin A for NDPH; anecdotally I have treated a number of NDPH patients with very positive results. It is important to recognize those patient’s with cervical hypermobility and, thus, not to put any Onabotulinumtoxin A in cervical paraspinals as this will make their cervical muscles much weaker and pain syndrome worse. Suggest physical therapy for neck strengthening before doing Onabotulinumtoxin A.

**Neuroimaging**

Does NDPH have a specific imaging signature? That would certainly help to decipher if this is a true unique syndrome and not just a bunch of disparate conditions that start daily from onset but have nothing else in common. Functional MRI or PET to study NDPH would be an exciting prospect as well as morphologic studies.

**How Should We Evaluate and Treat NDPH Patients**

**My Approach**

All patients should receive evaluation for secondary causes of daily persistent headache: the 2 most common-cerebral vein thrombosis and intracranial hypotension [16] One key point is if the patient has a vertex headache think sphenoid sinusitis or pituitary tumor and if periorbital pain do not forget nasal contact point headache which is easily demonstrated on brain MRI. All patients with NDPH should have viral titers drawn (IgG, IgM) for Epstein Barr virus, cytomegalovirus, human herpes virus type 6, and parvovirus. I rarely see acute infections but I am seeing very elevated chronic titers which I think could be causative.

Over the years I have always told my patients that if I meet them within a year of onset of NDPH then the odds of therapy working specifically intravenous therapy as with outpatient infusion, with an almost curative outcome, is very high but after 1 year of onset of headache the success with intravenous therapy precipitously drops as it does with oral preventive medication.

[1] Approach to NDPH of early onset—intravenous therapy like treating chronic migraine. Use same combination IV medications but if want to add high dose corticosteroids plus or minus IV doxycycline
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.

References

Papers of particular interest, published recently, have been highlighted as:

** Of major importance


Compliance with Ethics Guidelines

**Conflict of Interest** Todd Rozen declares that he has no potential conflicts of interest.