Resolution of new daily persistent headache by a tumor necrosis factor alpha antagonist, Venlafaxine

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Abstract
New daily persistent headache is a continuous, unremitting headache, notorious for its unresponsiveness to aggressive medical interventions. The underlying pathophysiology of new daily persistent headache is poorly understood resulting in unending, chronic pain. However, a prior study identified elevated tumor necrosis factor alpha within the cerebral spinal fluid of new daily persistent headache patients. Herein, we report on a patient who suffered with headache for 6 years failing to respond to over 20 different medical treatments, but found drastic improvement and eventual resolution with Venlafaxine. This drug binds to the 5-HT2A receptor inhibiting tumor necrosis factor alpha signaling. Therefore, we hypothesize a chronic inflammatory mechanism driving new daily persistent headache pathology.

Keywords
New daily persistent headache, headache, NDPH, TNF-alpha, tumor necrosis factor alpha, Venlafaxine, 5HT-2a, serotonin

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Introduction
New daily persistent headache (NDPH) is an unremitting headache disorder without any specific treatment. Aggressive medical intervention yields minimal if any results, making it one of the most treatment-refractory conditions. The etiology of NDPH is unclear with multiple potential triggering factors including surgical procedure, stressful life events, and viral infection. Some patients experience spontaneous remission, but many go on to experience an unremitting headache for years and decades, greatly diminishing quality of life.

Interestingly, tumor necrosis factor alpha (TNF-α) has been shown to be elevated in this condition and may provide insight into this poorly studied ailment. Herein, we report on an NDPH patient who failed to find relief from over 20 different treatments, but found resolution with Venlafaxine, a known TNF-α inhibitor. Venlafaxine is traditionally used for major depressive disorder (MDD) patients, but its binding to 5-HT2A receptor allows for downstream inhibition of TNF-α. This observation in addition to other reports lends credence to a chronic inflammation within the central nervous system driving NDPH pathology.

Case report
A 24-year-old male presented with a 6-year-long continuous headache characterized by constant, bilateral pressure emanating from his temple. There was no family or pertinent past medical history. The pain had a pulsatile nature, and pain intensity was mostly constant at 8–9, on a self-reported numerical pain scale, with periods of increased pain reaching up to a 10.2 The pain was associated with exhaustion, nausea but not vomiting, position sensitivity, or photophobia. His symptoms led to difficulty in schoolwork and social interactions. From onset, the headache took a day to reach both 24/7 constancy and peak intensity. He could specifically recall the
moment of headache onset, noting that it slowly built in intensity over a 24 h, making it inconsistent with a thunder-clap onset. The patient sought medical evaluation and treatment from over 12 medical professionals including several headache specialists.

The patient self-administered Excedrin, Ibuprofen, and Acetaminophen without any benefit prompting a visit to his local neurologist. He was then administered Topiramate which was ineffective. The constancy of headache and associated nausea prompted a magnetic resonance imaging (MRI) study with contrast, in order to rule out any brain abnormalities, and found nothing of note. A sleep study was also conducted in order to rule out sleep apnea, which has been associated with chronic daily headache, and found no sleep abnormalities. Eventually, the patient sought out a headache specialist who found potentially elevated cerebral spinal fluid (CSF) pressure (24 cm H₂O) via lumbar puncture. A second puncture did not find elevation, and neither puncture improved the patient’s headache. Both punctures were taken in the lateral decubitus position. CSF analysis showed no evidence of meningitis, encephalitis, or any other abnormalities. Fundoscopic examination identified no papilledema which in conjunction with both lumbar punctures ruled out pseudotumor cerebri. Failure of headache responsiveness to Indomethacin ruled out hemicrania continua. Sustained pain and continued difficulty in school work led to a neuropsychiatric evaluation. Two areas of significant impairment were identified including immediate and delayed recall within stories (Wechsler Memory Scale-Revised (WMS-R)) and notably slow manual speed and dexterity in non-dominant left hand. Based on this history, he met the criteria for NDPH as outlined by International Classification of Headache Disorders (ICHD-3) beta. Further physical examination identified cervical hypermobility, a trait associated with NDPH irrespective of triggering event. Patient also exhibited discomfort over the auriculotemporal nerve distribution and tenderness over the greater occipital nerve region.

The patient cited a stressful life event as the triggering factor of the headache. Unlike other reported cases, our patient identified a prolonged period of stress associated with his transition to college life, rather than a singular triggering event. He was also heavily involved in academic research work, adding another layer of stress and workload. Directly prior to onset, patient reported period of biphasic sleep, high stress, and long “work” hours. The patient denied usage of alcohol or any illicit drug. There was no associated fever or chills. Patient also denies usage of any medications prior to onset or during treatment, other than those prescribed ruling out a medication-overuse headache. In total, over 20 medications/treatments were administered with no long-term benefit to headache pain (Table 1). However, we found that daily administration of Venlafaxine resulted in reduction of pain along with improving other symptoms such as nausea, exhaustion, and neuropsychiatric deficiencies.

The patient was administered 37.5 mg of Venlafaxine and instructed to incrementally increase dosage by 37.5 mg every week if no adverse side effects occurred. We found that a dosage of 300 mg resulted in a predictable attenuation of headache pain with the average pain score decreasing to a 3. After 3 months of treatment, we tried to see if removal of Venlafaxine would allow for retention of improvement. Following a 3 week washout, there was a rise in headache pain back to baseline along with accompanying symptoms. Readministration and titration of Venlafaxine once again ameliorated symptoms. Interestingly, 6 more months of Venlafaxine treatment resulted in resolution of pain.

Discussion

NDPH is considered one of the most treatment-refractory headache conditions with few, if any, established treatment options. There exist two subforms of NDPH, one which spontaneously resolves within months, and another which is unremitting and refractory to aggressive treatment. Those afflicted with the illness often suffer from a biphasic, never-ending headache. Many patients suffer for decades leading to significant reduction in quality of life. Here we report a patient who failed to find benefit from over 20 different medical interventions including many traditional migraine medications and newer treatments such as botulinum toxin injections. Despite these previous failures, the patient showed responsiveness to Venlafaxine, a serotonin-norepinephrine reuptake inhibitor generally used for the treatment of MDD.

NDPH is a disorder with multiple associate triggers including surgical procedure, stressful life event, and viral infection. Interestingly, the only clue to a common mechanism appears to be an increase in the inflammatory cytokine TNF-α. This increase in TNF-α is localized specifically to the CSF and is not present within blood serum. Prior reports have shown Venlafaxine to reduce TNF-α production within microglial cells in vitro following lipopolysaccharides stimulation as well as in sera of MDD patients. In addition, Venlafaxine binds to the 5-HT2A receptor which has been shown to cross talk with tumor necrosis factor receptor 1 (TNFRI) inhibiting its signaling. Normally, TNF-α binds to TNFR1 recruiting tumor necrosis factor receptor type 1-associated death domain protein (TRADD) and Receptor-interacting serine/threonine-protein kinase (RIPK). This causes phosphorylation and degradation of IkBα allowing for NF-κB nuclear translocation and activity driving inflammation. The 5-HT2A receptor binds to serotonin/Venlafaxine leading to a G-protein-coupled pathway. Protein Kinase C, downstream of G-protein, inhibits phosphorylation and degradation of IkBα preventing NF-κB nuclear translocation and activity. We hypothesize that this inhibition of TNF-α by Venlafaxine is driving amelioration.

In another case of NDPH, a patient with a proposed thunder-clap onset subset of NDPH had complete remission of headache
following administration of Nimodipine.9 Nimodipine is a calcium channel blocker traditionally used in treating cardiovascular diseases, but now mostly used in the management of subarachnoid hemorrhage. It also appears to inhibit TNF-α production by microglial cells, through inhibition of NADPH preventing superoxide production.10 In addition, Nimodipine inhibits cerebral artery vasospasm, a known downstream effect of TNF-α.11,12 This patient was administered Nimodipine, but found no major relief. To some, this may point to a non-TNF-α method of activity for Venlafaxine treatment. However, the mechanism of action for both drugs is different. We speculate that NDPH is a cluster of diseases driven by chronic inflammation via TNF-α within the CSF explaining heterogeneity in specific drug responsiveness, but homogeneity in ultimate drug activity. Other NDPH case reports also suggest an inflammatory pathogenesis.1,9,13,14

There are several caveats to a TNF-α based mechanism. The original study identifying TNF-α has never been replicated and did not analyze the full array of cytokine signals, biasing current interpretations of NDPH toward TNF-α.2 We did not measure TNF-α within the CSF of our patient either pre or post treatment. Had there been a downward trend due to Venlafaxine treatment, there would be some direct evidence supporting our hypothesis. We can only claim that Venlafaxine treated this singular patient. It remains to be seen whether other patients will benefit from Venlafaxine, and whether TNF-α plays a pathogenic role in NDPH or even a subset of NDPH cases. We are aware of one other NDPH case where Venlafaxine was administered without any reported benefit.15 However, in this other case the patient was given a maximal dosage of 150 mg for 2 months.15 We found a 150 mg dosage to be ineffective, and instead used a daily dosage of 300 mg Venlafaxine XR for a period of 3 months instead of 2 months. Furthermore, pain resolution occurred 6 more months following a washout period.

Conclusion
Overall, Venlafaxine should be considered specifically as a potential treatment for patients with NDPH. In addition, there appears to be a growing opinion that NDPH etiology is driven by chronic inflammation via TNF-α. Therefore, it has become critical to repeat the CSF TNF-α experiment to assure that we are moving in the right direction.

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Table 1. Patient medication list.

| Medication                                      | Dosage   |
|------------------------------------------------|----------|
| Topiramate                                      | 100 mg   |
| Nonsteroidal anti-inflammatory drugs            | N/A      |
| Furosemide                                      | 20 mg    |
| Zolof                                           | 100 mg   |
| Neurontin                                       | 900 mg   |
| Butalbital                                      | 200 mg   |
| Desipramine                                     | 10 mg    |
| Baclofen                                        | 10 mg    |
| Nortriptyline                                   | 50 mg    |
| Escitalopram                                    | 10 mg    |
| Indometacin                                     | 150 mg   |
| Verapamil                                       | 240 mg   |
| Amitryptiline                                   | 25 mg    |
| Sumatriptan                                     | 200 mg   |
| Valproate                                       | 1000 mg  |
| Clonazepam                                      | 1 mg     |
| Diamox                                         | 2000 mg  |
| Tizanidine                                      | 24 mg    |
| Botox trigeminal nerve injection                | N/A      |
| Cefaly TENS device                              | N/A      |
| Occipital nerve block                           | N/A      |
| Nimodipine                                      | 120 mg   |
| Cognitive behavioral therapy                    | N/A      |
| Doxycycline                                     | 100 mg   |

N/A: not applicable.
A list of failed medications that were discontinued due to ineffectiveness at therapeutic dosages or intolerable side effect.
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