Case report: Therapeutic response for new daily persistent headache by a tumor necrosis factor alpha antagonist, lithium

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Abstract
New daily persistent headache (NDPH) is an uncommon, treatment-resistant primary headache disorder that was first described by Vanast in 1986 as a benign syndrome. Elevated TNF-alpha levels on CSF of NDPH patients as a possible cause of this disease. TNF-alpha inhibitors like doxycycline, venlafaxine and montelukast have been used in the past with relative good success. Lithium, used in Cluster Headache, has anti-inflammatory effects by inhibition of glycogen synthase kinase-3 (GSK3). This mechanism of action reduces production of inflammatory IL-6, IL-1 beta and TNF-alpha production by microglia, astrocytes and other immune cells. We report a NDPH patient that responded successfully to the administration of lithium after trying multiple treatments. We propose lithium, a TNF-alpha Inhibitor, as an effective treatment for refractory cases of NDPH.

Keywords
chronic daily headache, lithium, NDPH, TNF-alpha inhibitor

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Introduction
New daily persistent headache (NDPH) is an uncommon, treatment-resistant primary headache disorder that was first described by Vanast in 1986 as a benign syndrome,¹,² combining features of common migraine and tension headache that occurs daily from the first day the headache begins. Since then, triggering events have been associated to NDPH related to headache onset such as cervical injury, viral infections or a stressful life event. Furthermore, multiple studies have linked an active Epstein-Barr virus infection to NDPH patients. The 1-year population prevalence of NDPH has been reported to be 0.03%² to 0.1%.³ Rozen et al. found elevated TNF-alpha levels on CSF of NDPH patients as a possible cause of this disease. TNF-alpha inhibitors like doxycycline, venlafaxine and montelukast have been used in the past to treat NDPH patients, with relative good success.

It has been described that lithium, used in Bipolar disorder and Cluster Headache, has anti-inflammatory effects by inhibition of glycogen synthase kinase-3 (GSK3). This mechanism of action reduces production of inflammatory IL-6, IL-1 beta and TNF-alpha production by microglia, astrocytes and other immune cells.⁴ We report a NDPH patient that responded successfully to the administration of lithium after trying multiple treatments.

Case report
Clinical findings
A 59-year-old, right handed, female patient presents to our office with 10 years of continuous daily headache

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characterized by constant dull pain, sharp in nature when it increased in intensity lasting for hours, involving the right side of her head from the auricular region, radiating through her right eye and reaching her jaw. The patient gave written inform consent for publishing this case.

The patient could specifically recall the moment of the headache onset following a Mononucleosis infection. The pain intensity was 3–4/10 with periods of increased pain reaching up to 10/10 spontaneously or related to loud noises or stress. There was no associated aura, nausea or photophobia. In some of her headache event, tearing was present. She recalls that 2 months after the mononucleosis infection, she developed Hashimoto disease and was treated with prednisone for 4 months, having remission of her pain. Once discontinued, she started again with her daily headache. The persistent pain led to difficulty in her daily activities and personal relationships which led to anxiety and depression that required psychiatric treatment and psychotherapy.

The patient sought previous medical evaluation. Neurological exam was reported as normal. A brain MRI study ruled out any brain abnormalities and a lumbar puncture was performed with normal cerebral spinal fluid (CSF) pressure. The lumbar puncture did not relieve the patient’s headache and CSF analysis was normal.

She was diagnosed with Trigeminal Neuralgia and treated with carbamazepine at increasing doses with no response. Of note she had no vessel contact on neuroimaging.

She tried over 10 different treatments including valproic acid, lamotrigine, verapamil, amitriptiline, topiramate, pregabalin, indomethacin at standard doses and high doses of morphine, with no long-term benefit.

Based on the clinical history and ruling out all other possible causes, the patient met the clinical criteria for NDPH described in the ICHD-3 beta.

Due to the fact that she had pain that started on the auricular region and radiated to the right eye, had autonomic features in some episodes and responded in the past to prednisone, we decided to start treatment as NDPH described in the ICHD-3 beta.

One month later, she was admitted to the Hospital. Montelukast was increased to 10 mg bid. We performed a lumbar puncture and TNF-alpha levels on CSF were normal, although the lab performing the test did not typically run CSF studies for TNF-alpha questioning sensitivity of the test.

After this admission (and 2 months after discontinuing lithium), added to the fact of constant ER visits and debilitating daily headaches, the patient decided to restart Lithium at increasing doses.

She started with 300 mg qd and increased to 300 bid in 5 days. Side effects started again and Lithium was tapered down to 300 mg daily.

The patient, once again, dramatically dropped her headache days 4 days after Lithium started and to date, (90 days of Lithium), the patient is headache free in 97% of days (Table 1).

### Timelines

The patient started her Headaches in 2009 after an Infectious Mononucleosis and was diagnosed as Trigeminal Neuralgia in 2010. She received several treatments before she came to our office on September 2019: We started Prednisone, Verapamil and Lithium as the core treatment under the clinical suspicion of Chronic Cluster Headache. On November 2019, after reviewing in detail her clinical history, we changed the diagnosis to NDPH.

### Discussion

NDPH is an under-recognized and heterogenous disorder and its exact pathogenesis remains unknown. Some authors have associated NDPH to Epstein-Barr virus infection with patients having positive EBV serology, proposing that NDPH might develop in response to the release of pro-inflammatory cytokines, like TNF-alpha, during a CNS inflammation. Other studies have even found elevated levels of TNF-alpha in CSF of NDPH patients and suggest that TNF-alpha inhibitors may have an important role in NDPH treatment.

When we first received this patient, and due to the fact that there was a response to steroids in the past, we thought it could be a case of Chronic Cluster Headache. Having failed to most of the classic treatments for cCH, we decided to start Lithium as a preventive treatment associated to Prednisone 50 mg/day and Verapamil 240 mg/day. In the next 3 weeks,
the patient developed side effects to the 900 mg/day dose. Initially we kept the dose due to the good response in headache free days, but we then tapered and discontinued it.

Headaches came back in the next 48 hours while still on Verapamil 240 mg/day and Prednisone 50 mg/day.

In our case, the past history of headache associated with Infectious Mononucleosis, clearly marking that day as when the headache started, continuous headache with exacerbations, although dosing of indomethacin did not exceed 150 mg per day, but lack of indomethacin response at 150 mg makes diagnosis of HC, less likely. Our patient was tested recently for EBV infection with elevated titers of IgG. The pain exacerbation periods were too long in duration, the patient did not have multiple attacks per day and the lack of consistent cranial autonomic symptoms with pain exacerbations ruled out chronic cluster headache.

Lithium is an established inhibitor of GSK3. Lithium and other GSK3 inhibitors, are remarkably effective in reducing inflammation. Therapeutic levels of lithium inhibit GSK3 directly and indirectly that causes an increased inhibitory action to GSK3. GSK3 inhibition has shown to have an anti-inflammatory effect, reducing IL-6, IL-1β and TNF-alpha by 67–90%.

There are two points that came to our attention in this case: we started 900 mg of lithium and there was a good headache response, dropping Headache free days to 59/84 days (70%) which she had never experienced before. She visited the ER 6 times out of 84 days (7%).

When we discontinued lithium, because of side effects, headaches returned within 48 hours with a pattern of 44 free headache days out of 77 total days, but ER visits increased to 31 visits in 77 days (40%), showing this the intensity in pain exacerbation.

Due to this fact, we restarted Lithium, this time at a low dose of 300 mg/day to avoid side effects, 4 days later headaches were gone, going back to 90 out of 94 headache free days and two visits to the ER due to exacerbations, in that period of time.

Given the favorable results we had after starting lithium in our patient, we postulate the possible efficacy of lithium as a treatment for NDPH resulting from its anti-inflammatory effects with inhibition of the GSK3 and consequently TNF-alpha.

Venlafaxine, reported as effective for NDPH patients was started at 300 mg dose 2 weeks prior to re installing Lithium. Tariq et al. report that effect starts 6 months after increasing Venlafaxine at that dose. Rozen has described the effect of Montelukast 10 mg twice daily with good results after 2 months. Our patient response was earlier that 2 months.

**Conclusion**

We propose lithium as an effective treatment for refractory cases of NDPH. This case report could be a stimulus for future larger studies on the efficacy of this therapy and other TNF inhibitors in NDPH.

**Clinical implications**

- New daily persistent headache (NDPH) is an uncommon, treatment-resistant primary headache disorder.
- Elevated TNF-alpha levels on CSF of NDPH patients as a possible cause of this disease.
- TNF-alpha inhibitors have been used in the past to treat NDPH patients, with relative good success.
- Lithium, has anti-inflammatory effects by reducing production of inflammatory IL-6, IL-1 beta and TNF-alpha.
- We report a NDPH patient that responded successfully to the administration of lithium after trying multiple treatments.

**Declaration of conflicting interests**

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Ethic approval and patient consent**

The patient was provided with the medical treatment plan and signed our informed consent form.

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