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The Three T's of NDPH (How Clinical Observations Have Led to Improved Treatment Outcomes)

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Even though it was only first described in 1986, and thus is very "new" in the pantheon of known headache disorders, new daily persistent headache (NDPH) has already been established as one of the more treatment refractory of all head pain conditions. Partly or wholly, this reflected our true lack of understanding of the pathogenesis of this disorder. Where it seemed early on as if almost no one with NDPH ever improved, unless they had the remitting subtype, a change in thinking has offered a much better outlook both for the understanding of the etiology of NDPH and for positive treatment outcomes. The key has been the recognition that NDPH is not a single entity, but a disorder caused by multiple disparate conditions. These varying disorders which the author suggests can be subtyped by the "Three Ts Model": Triggering event, Trendelenburg response, and Thunderclap headache (define the first ever headache that heralded NDPH) allows us to place NDPH patients within subgroups.[1-3] Those in the same subgroup most likely have similar if not the same underlying pathogenesis and based on that presumed knowledge a specific effective treatment regime can be established.[1] A short review of what we have learned recently about NDPH based on the Three Ts model will be presented with specific treatment options based on the model.

THREE TS MODEL OF NDPH (TABLE 1)

Triggering Events.[1]—The headache history for NDPH patients should truly focus on finding any possible triggering event that may have correlated with headache onset. As over 50% of NDPH sufferers cannot recognize a triggering event, specific questions that one may utilize are presented.[1] Start by asking about a viral prodrome (sinus-based issues are included as most acute sinus infections are viral), a single stressful life event and/or did the patient have any surgical procedure requiring intubation or any procedure in which their neck was put in a prolonged extension or flexion position (typically otolaryngology and/or dental). Post-procedural triggered NDPH is now deemed a cervicogenic-based syndrome.[1] A non-cervical spine-related intervention that the author has noted to trigger NDPH is eye-related surgery (LASIK, cataract). This normally has head pain side locked to the surgery site and is from a presumed nerve-based compression syndrome (supraorbital/supratrochlear or trochlear).

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In this scenario, the head pain may start immediately after the procedure but it also can initiate several weeks after.

As the majority of NDPH patients have cervical and systemic hypermobility, and especially if no triggering event can be ascertained, specific questions about events/actions that may have caused irritation to the upper cervical spine are needed.[4] This patient population, based on their mobile or "floppy" neck, has presumed upper cervical spine/facet and even atlantoaxial irritation at baseline. This population can thus easily reach the activation threshold for the trigemino-cervical complex (TCC) with seemingly innocuous events. Once the TCC is activated, a daily persistent headache can initiate. For younger patients (teens or younger), physicians should ask specifically about sleep over events at friends (laying/sleeping on the floor) or going to overnight summer camp as events surrounding NDPH onset. With these scenarios, the patient is not sleeping in their own bed or utilizing their own pillows leading to abnormal neck positioning and upper cervical spine irritation with presumed TCC activation and cervicogenic-based head pain. In all patients ask about long car rides, airplane travel, hotel stays, and visiting amusement parks (the author has noted multiple patients developing NDPH after roller coaster rides and without concomitant arterial dissection), again looking for any triggering event that could cause cervical spine irritation. Always ask about vacations or trips just prior to NDPH onset. If the patient did indeed travel then ask about the altitude of their destination, as not only can the cervical spine be irritated by travel, but a condition of an abnormal reset of cerebrospinal fluid (CSF) pressure/volume to an elevated state can also occur when patients travel to an altitude higher than that of their home location. In women who develop NDPH immediately post-partum, asking about epidural anesthesia and positional headache assessing for a CSF leak is necessary, as well as inquiring about a thunderclap headache which could indicate the presence of the reversible cerebral vasoconstriction syndrome (RCVS) or a cerebral vein thrombosis. If NDPH starts several months post-partum then one must consider this being a neck based pain syndrome as typically these women have cervical hypermobility issues and the neck irritation that takes place with caring for a newborn is substantial (holding baby with fixed neck position for long periods of time along with breastfeeding with fixed neck position).

Always ask about other more rare triggers including toxin exposure (pesticides, refrigerants), syncope, SSRI withdrawal, and vaccinations. There is already an established linkage to the HPV vaccine, while the author has also noted NDPH with other viral based vaccinations.[1,5] Finally, if the patient was in the armed forces or a firefighter/first responder when they developed NDPH then ask about potential chemical exposure and/or non-direct blast injuries as these could lead to cytokine activation and/or alterations in CSF pressure/volume through alteration of the cerebral vein system.[6-9]

Trendelenburg Test.—The use of the Trendelenburg test (head down tilt 10-20° for 1-2 minutes) should be utilized in all patients who present with NDPH.[10,11]

Immediate Worsening in the Trendelenburg Position may Suggest a State of Elevated CSF Pressure/Volume.—This will then require neuroimaging to look for secondary issues like cerebral vein thrombosis and space occupying lesions. Look very closely, however, at "normal imaging" as seemingly incidental findings such as a crowded posterior fossa, partial empty sella, slightly enlarged ventricles, mega cisterna magna, presence of a cavum septum pellucidum or cavum vergae, incidental venous anomalies can all be neuroanatomic risk factors for the development of elevated CSF pressure/volume. These neuroanatomic issues could potentially place these patients at a CSF pressure/volume level higher at baseline than in those without these imaging findings and thus more easily pushed over the CSF pressure/volume pain threshold with simple triggering events like a trip to a higher altitude, a plane ride, after a valsalva event, or after recent weight gain; all of which raise CSF pressure/volume on their own. Patients with hypermobility issues appear to develop tonsillar ectopia and a secondary crowded posterior fossa more often than non-hypermobile patients (most likely from ligament laxity leading to the tonsillar descent),thus this population, even though on average are of normal to low BMI, can also develop a state of elevated CSF pressure/volume. Once the elevated CSF pressure/volume pain threshold is reached their neuroanatomic issues may not allow a CSF pressure/volume reset and thus a daily persistent headache develops. The positive news is that most of these patients improve on CSF pressure/volume-lowering medications (see below).

Table 1.—Three Ts Model for NDPH Question's Checklist

1. Triggering events

Suggested Questions

a. Ask specifically if had a viral illness, single stressful life event or surgical procedure with intubation prior to NDPH onset
b. If negative: ask specifically if had a dental, ENT or any other procedure leading to prolonged cervical extension/flexion positioning
c. If negative: ask specifically about a single Valsalva event, toxin exposure, syncope, SSRI withdrawal, and vaccinations prior to NDPH onset
d. If no triggering event can be ascertained from above questions and especially if patient has cervical hypermobility on examination, the following questions should be asked:

Younger population: did they have any event leading to abnormal neck positioning such as sleep over events at friends, going to overnight summer camp or class trips

In all hypermobile patients: ask about long car rides, airplane travel, hotel stays, and visiting amusement parks

– If went on vacation then ask about the altitude of their destination

In women: If NDPH starts immediate post-partum: ask about epidural anesthesia/positional headache and/or a thunderclap headache onset – if positives then will require further investigation

– If NDPH starts several months post-partum: then investigate the upper cervical spine as NDPH generator

2. Trendelenburg position (10-20° head – down tilt) – ask about alteration in headache

a. Headache worsens (typically immediate): consider a state of elevated CSF pressure/volume relook at MRI Brain for "abnormal"/normal findings that could potentially raise CSF pressure/volume
   – Further questions: ask about Valsalva event just prior to NDPH onset, ask about if lying supine worsens headaches or if awakens from sleep with headache
b. Headache improves or alleviates: evaluate for intracranial hypotension
c. Neutral response look for other causes outside of CSF pressure/volume as NDPH etiology

3. Thunderclap Headache

Questions about initial onset of NDPH

– Always ask about the temporal profile of original headache-how quickly did it peak?
– if maximum intensity without latency consider RCVS spectrum disorder and use of nimodipine
– Always ask about when original headache began: out of sleep or during the day. If during the day then at what time did NDPH begin? If awoke with original headache and morning is always the worst time for NDPH then consider raised CSF pressure as etiology. If began later in day and headache worsens as day goes on then consider intracranial hypotension as etiology

Headache Improvement in Trendelenburg.—This may suggest a state of CSF hypotension/hypovolemia thus evaluation for a CSF leak should be initiated.[2]

Neutral Headache Response (thus no Worsening or Improvement).—This would suggest against a CSF pressure/volume-dependent headache issue.

It is important to note that being on a CSF pressure/volume-altering medication (eg, topiramate, spironolactone, acetazolamide, and furosemide) may provide a false negative or positive response to the Trendelenburg test. In addition, if past CSF modulatory procedures have been completed like an epidural blood patch and/or fibrin glue administration; this also may alter the validity of the Trendelenburg response.

One has to also remember that the Trendelenburg position can affect the upper cervical spine with cervical facet/vertebral body loading/unloading, thus cervical spine irritation could worsen or even improve in head down tilt (acting as a traction maneuver). It is also possible that sphenoid sinus issues and nasal contact points may alter in Trendelenburg, as well as blood pressure related syndromes that are comorbid with headache (POTS, orthostatic hypotension).

Thunderclap Headache at Onset.—Always ask NDPH patients about their original headache. What was the temporal profile of onset of the first ever headache. If maximum intensity without latency or a "thunderclap" this may be an RCVS spectrum disorder headache (see below).[12] Did the initial headache start while the patient was awake and if so what time or did the patient awaken with it. Is it worst first thing in the morning or evenings and is there a positional/orthostatic component. Finally, what month or time of year did it start as there is a newer recognition of circadian periodicity to NDPH onset.[12,13] It is possible that patients may only develop NDPH at certain times of the year and

if they had been exposed to the same triggering event outside of those times period, NDPH would not have developed.

UPDATE ON SPECIFIC TREATMENTS BY NDPH SUBTYPE BASED ON THE 3Ts MODEL

Triggering Events.—*NDPH after a Single Valsalva Event*.—Daily headache from onset after a prolonged single Valsalva event (coughing fit, vomiting, lifting a heavy object). An abnormal reset of CSF pressure/volume to an elevated state is the presumed pathogenesis and may relate to the patient's baseline neuroanatomy of a crowded posterior fossa. Worsening in the Trendelenburg position is a probable diagnostic test. Very responsive to CSF pressure/volume lowering medications.[13]

Post-Infectious NDPH.—To make the diagnosis of post-infectious NDPH, the headache should initiate during the time of a presumed illness/infection. The author will order serum viral titers (IgG, IgM) for cytomegalovirus (CMV), parvovirus B19, and Epstein Barr virus (EBV) on all patients who present with NDPH triggered by a supposed infection. At present, the exact mechanism by which these patients develop headache is unknown.

Two Possible Treatments.—*Early Onset Post-Infectious NDPH*.—Prakash and Shah reported on 9 patients.[14] All were given high-dose intravenous methylprednisolone for 5 days, while 6 patients were given oral corticosteroids for 2-3 weeks. All patients improved, with 7 individuals achieving almost complete pain freedom within 2 weeks, while 2 patients needed between 6 and 8 weeks to improve. The results are promising but none of the patients met the ICHD-3 criteria for NDPH because they were treated only several weeks after the headaches began. It is conceivable that some or all of these patients had the remitting form of NDPH and would have improved on their own even without treatment. However, treating presumed post-infectious NDPH early on in the course with high-dose corticosteroids maybe a very efficacious treatment modality.

Chronic Post-Infectious NDPH.—The most common recognized triggering event for NDPH is a flu-like illness. Many of these patients will present months to years after headache onset. At present, there is nothing noted in the literature for the treatment of chronic post-infectious NDPH. A small case series of patients evaluated by the author at an academic headache clinic is now presented. All patients were determined by history to have the post-infectious variant of NDPH. Each had high enough IgG viral titers (as determined by the author from previous experience) to be treated: parvovirus >6.0 U/mL (lab positive >1.1 U/mL), CMV > 2 U/mL (lab positive >.0.7 U/mL), EBV >750 U/mL (lab positive >21.99 U/mL). Each patient was placed on famciclovir 125-250 mg bid for 2 months with follow-up. If improvement was noted, the dose could be adjusted upward. Those with improvement continued therapy. Fifty patients with NDPH were reviewed over a 3-year time period. Eleven patients were diagnosed with the post-infectious subtype but only 6 were included in the analysis as 5 patients did not have adequate follow after initial consultation. There were 3 females and 3 males. Average age of headache onset was 35 years (females 30 years, males 41 years, range 15-76 years). The majority of patients (5/6) developed their NDPH during the months of October-February. Average length of headache duration prior to consultation was 28 months (range 7-84 months). The suspected viral infectious pathogen based on positive titers were: parvovirus alone in 3 patients, CMV alone in 1 patient, and possible co-infection in 2 patients (CMV and parvovirus, CMV, and EBV). All patients were deemed treatment refractory failing at least 3 preventives but some failed more than 10. 5/6 patients did well on treatment with improvement of 95% or greater in all responders and pain freedom in 4/5 patients. The lone patient with the youngest age of onset did not improve. Dosing ranged from 125 mg bid to 500 mg bid of famciclovir.

Post-Surgical/Procedure NDPH.—This NDPH patient subtype typically has minimal to no head pain history prior to their procedure, although they may have intermittent to chronic neck pain. Almost immediately after the procedure (which is not typically being done for neck or head pain) they recognize a new headache. If they underwent an invasive surgical procedure all patients had endotracheal intubation.[1] This is a significantly older subgroup of NDPH sufferers, thus this patient population has a higher likelihood of having underlying cervical arthritis and upper cervical

facet irritation at baseline. Their headache is speculated to be the result of an exacerbation of this underlying upper cervical facet syndrome induced by the cervical hyperextension occurring during intubation and the neck positioning during surgery. In younger patients who develop this subtype of NDPH, they are more likely to have an underlying cervical hypermobility syndrome and thus secondary underlying cervical facet irritation and/or atlantoaxial irritation going into their procedure. The same situation occurs with dental and otolaryngology procedures and even at the hairdresser where neck extension for prolonged periods leads to trigeminocervical activation in those individuals who already have baseline cervical facet/atlantoaxial irritation. This NDPH subtype on examination should demonstrate significant upper cervical facet, GON, and sometimes C1-2-based irritation. This NDPH subtype has shown a significant improvement with cervicogenic-based treatments including: medications (muscle relaxants combined with anti-inflammatories), onabotulinum toxin A injections, and directed high cervical spine-based pain anesthesia procedures including: upper cervical facet injections (C2-4), C2 dorsal root ganglia injections, and C1-2 localized injections.[1]

Trendelenburg Response.—*NDPH Presenting in Older Female Population*.—This NDPH subtype has only been noted to occur in women who are typically in perimenopause or early into menopause with an average age of 57 years.[11] They typically awaken one day out of sleep with a headache and normally have headache exacerbation when they try to lay supine. Immediate worsening in Trendelenburg appears to be a diagnostic test for the syndrome. Some of these patients present with a paradoxical orthostatic headache, thus better lying supine and worse as the day progresses. Worsening in the Trendelenburg position helps to sort out it is high rather than a low CSF pressure state.[11] This NDPH syndrome appears to be caused by an abnormal reset of CSF pressure/volume to an elevated state. Hypothesized that a combination of an elevated BMI and the presence of cerebral venous insufficiency (possibly induced by estrogen loss) leads to this form of daily headache. Very responsive to CSF pressure/volume lowering medications.[11]

Thunderclap Temporal Profile.—*NDPH Starting With a Single Thunderclap Headache at Onset*.—There are now 4 published cases for this NDPH subtype.[12] It is probably a subform of the reversible cerebral vasoconstriction syndrome. It is most likely caused by persistent or intermittent cerebral artery vasospasm. Key to diagnosis is asking about the temporal profile of onset of the first ever NDPH headache. These patients normally have neurologic symptoms at the time of headache onset which is atypical for other NDPH subtypes.[12] Nimodipine is very effective in treating this head pain syndrome.

CONCLUSION

NDPH is still an overall enigma. We can certainly continue to learn more about the disorder and this will hopefully lead to a better understanding of the underlying etiology, which can then lead to more effective treatment. Recognizing that NDPH is not a single entity but multiple disparate disorders, has already led to better treatment outcomes when triaging NDPH patients into different subtypes. The other recognition that NDPH is probably not a primary headache syndrome but a secondary condition caused by multiple underlying etiologies, some known (CSF pressure (high or low), cytokine activation, cervicogenic irritation, hyperimmune response to viruses, and cerebral artery vasospasm) and some unknown, should push discussion further about this disorder. As a physician who gets to see many patients with NDPH, at present they are overall very frustrated by multiple failed medicine trials and a lack of understanding about their condition. We have to remember a large majority of these patients (>50%) never had a headache prior to NDPH onset and now they have daily unremitting pain sometimes for years.[1] As headache specialists we need and can do better for this population.

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