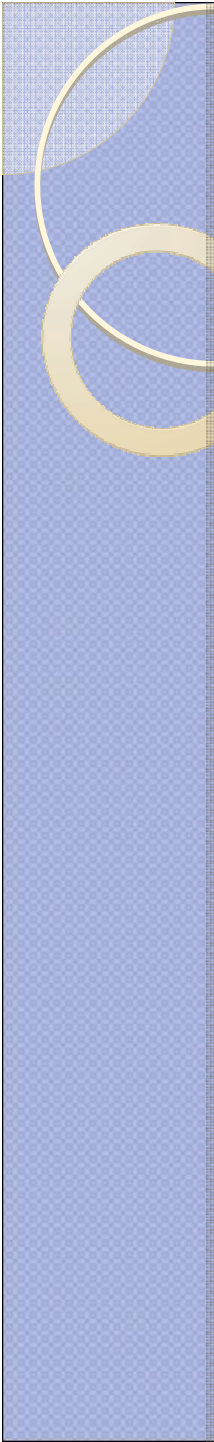



New Daily Persistent Headaches in Adolescents



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Q. My daughter, who is about to turn 14, has been suffering from headaches virtually daily for a couple of years now. She is miserable and making the family miserable, too, because she has mild to moderate headaches most of the time. She doesn't seem to have them upon waking, but sometimes they begin when she gets up. Sometimes rest and darkness help, sometimes not. The headaches are mostly around the temples and front parts of her head, particularly around her eyes. She is also extremely sensitive to bright or flashing lights and noises. Yet we're told she does not have migraines because the pain is fairly constant, rather than sudden and severe, she's not nauseous, and she probably doesn't have aura. She has tried all the over-the-counter medications we could think of, which do nothing. We were told it should not be caused by eyestrain.



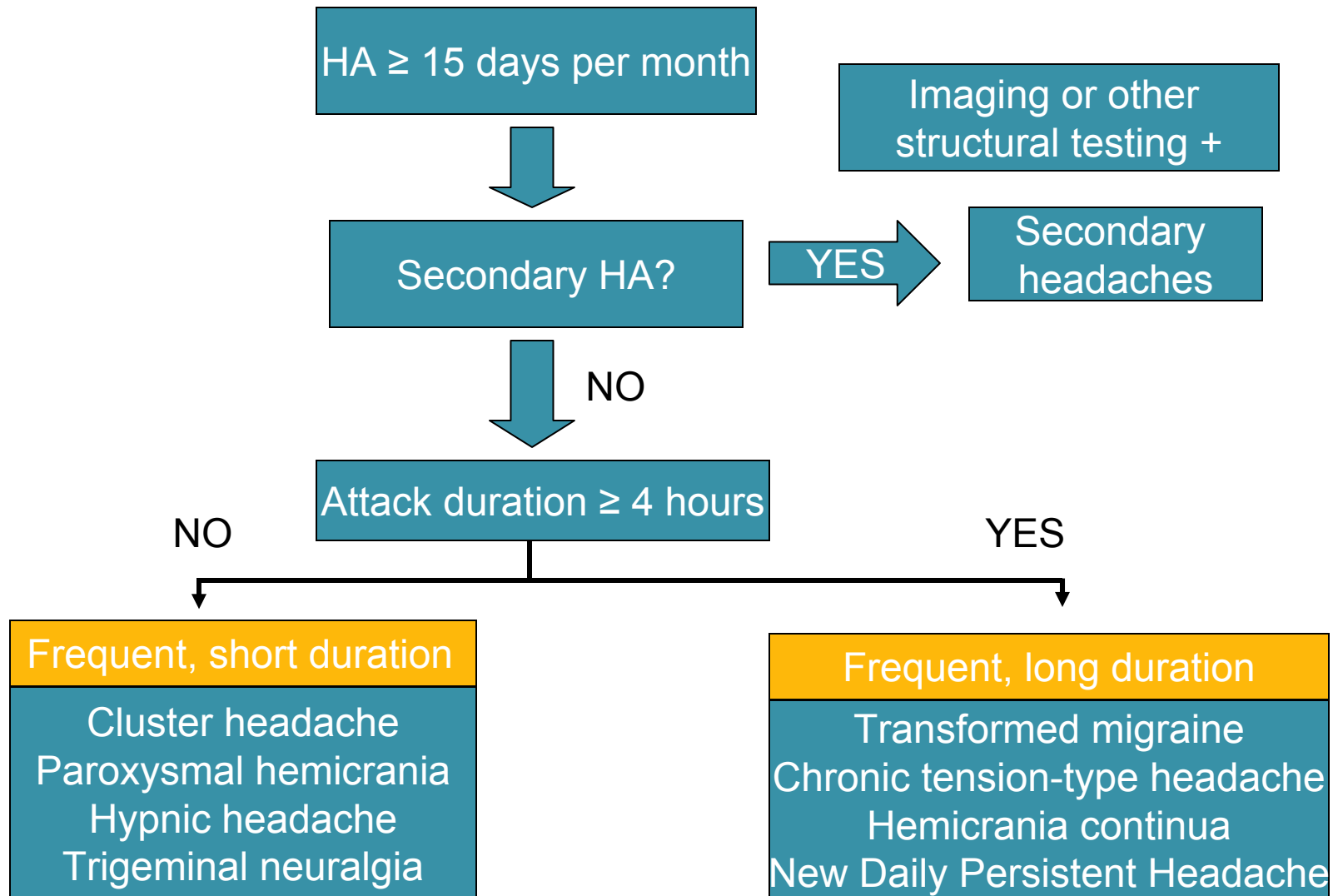
(continued) She has been to our family doctor repeatedly, who did some blood tests then sent her to the headache clinic connected to a children's hospital 100 miles away. The doctor there ordered an MRI to rule out life-threatening possibilities, then told her she had chronic daily headaches, which was common for kids her age, and commenced trying to treat her by prescribing one medication after another, hoping to find one that worked. She only saw him that once, and then we talked to the nurse via telephone after that, playing prescription roulette. Many of the medications he had her on were for other medical problems, from depression to epilepsy. None helped; some made things worse.

Otherwise, my daughter is very bright (top student in her grade), reliable, competent, and responsible.

If any of this rings any distant bells, I'd be grateful to be pointed in the right direction.

—A Concerned Dad

What kind of chronic daily headache does this teenager have?





Differential diagnosis of long-duration chronic daily headaches

- **Chronic migraine (CM)**
 - Associated nausea or vomiting or photo- and sonophobia
 - Gradually develops from episodic migraine
- **Chronic tension-type headaches (CTTH)**
 - No migrainous associated features
- **Hemicrania continua (HC)(very rare)**
 - Side-locked hemicranial pain
- **New daily persistent headaches (NDPH)**
 - Daily from onset of headaches



Differential diagnosis of NDPH: secondary mimics

- Headache attributed to low CSF pressure
 - Post-dural puncture headache
 - CSF fistula headache
 - Spontaneous or idiopathic low CSF pressure
 - Postural exacerbation may fade with time
- Headache attributed to cerebral venous thrombosis
- Arterial dissections: internal carotid, vertebral
- Cerebral arteritis
 - Giant cell arteritis
 - Primary or secondary CNS angiitis
- Another primary headache: Hemicrania continua
- Chronic headache attributed to lymphocytic meningitis
 - Not an IHS category: must resolve within 3 months

The syndrome of New Daily Persistent Headache: Then

- First described in 45 patients by Vanast in an abstract in 1986
 - “Definition of a Benign Syndrome”
 - “combining features of common migraine and tension headache”
 - “occur daily from the first day the headaches begin”
 - “without prior history of headache”
 - “without precipitants such as trauma or psychologic tension”
 - Uniformly negative neurological examination, blood tests (including Mono slide test), CT scans
 - “Treatment is usually ineffective”
 - Headaches disappeared without treatment in 73%-86% in 3-24 months
- “In drug studies, NDPH patients should be avoided for they improve regardless of therapy. In practice, NDPH is a welcome relief from the tedium of intractable headache syndromes.”

Vanast was from Edmonton, Alberta, so this makes NDPH a Canadian headache syndrome

W.J. Vanast, New Daily Persistent Headaches Definition of a Benign Syndrome, *Headache* 1986, 26:318 (abstract).



The syndrome of New Daily Persistent Headache: and Now

- NDPH is the opposite of benign
 - It is possibly the most refractory of all headache syndromes
 - Most patients fail multiple aggressive trials of outpatient and inpatient therapy
- Diagnostic criteria still in state of flux: competing criteria
 - Silberstein 1994
 - Li & Rozen 2002, 2003
 - ICHD-II 2004 (excludes any migrainous features)



“Silberstein” criteria for NDPH

(Silberstein et al. , *Headache* 1994, 34: 1-7.)

- A. Average headache frequency > 15 days/mo. for > 1 mo.
- B. Average headache duration > 4 hrs/day (untreated).
Frequently constant without medication, but may fluctuate.
- C. No Hx of TTH or migraine that increases in frequency and decreases in severity in association with the onset of NDPH (over 3 months).
- D. Acute onset (developing over < 3 days) of constant unremitting headache.
- E. Headache is constant in location.
- F. Does not meet criteria for hemicrania continua.
- G. Not attributed to another disorder (negative laboratory and imaging studies).

Note that presence or absence of symptoms of migraine are not required for the diagnosis: severity, nausea/vomiting, photo-/phonophobia, disability.

ICHD-II Criteria for NDPH

- A. Headache for >3 mo fulfilling criteria B-D
- B. Headache is daily and unremitting from onset or from <3 d from onset
- C. At least two of the following pain characteristics:
 - 1. bilateral location
 - 2. pressing/tightening (non-pulsating) quality
 - 3. mild or moderate intensity
 - 4. not aggravated by routine physical activity
- D. Both of the following:
 - 1. not >1 of photophobia, phonophobia or mild nausea
 - 2. neither moderate or severe nausea nor vomiting
- E. Not attributed to another disorder




ICHD-II criteria conceive of NDPH as suddenly-developing chronic tension-type headache. This is not supported by any evidence.



Various patterns of NDPH

- Three types now recognized
 - Self-limited type—resolves without therapy in most patients (described by Vanast)
 - Refractory type—resistant to outpatient and inpatient aggressive treatment (Li and Rozen 2002, Rozen 2004)
 - Transformed type—evolves abruptly from episodic migraine or tension-type headache (Mack, Ped Neurol 2004, 31:122-125)
 - Fourth type has been observed but has not yet been reported—NDPH evolves abruptly from chronic migraine (may be very common but occult)
- 3 severity patterns observed
 - Mild: daily headache is like CTTH
 - Moderate: sawtooth pattern, good days like TTH & bad days like severe migraine
 - Severe: disabling continuous high-level pain 24/7



Epidemiology of Chronic Daily Headaches (CDH)

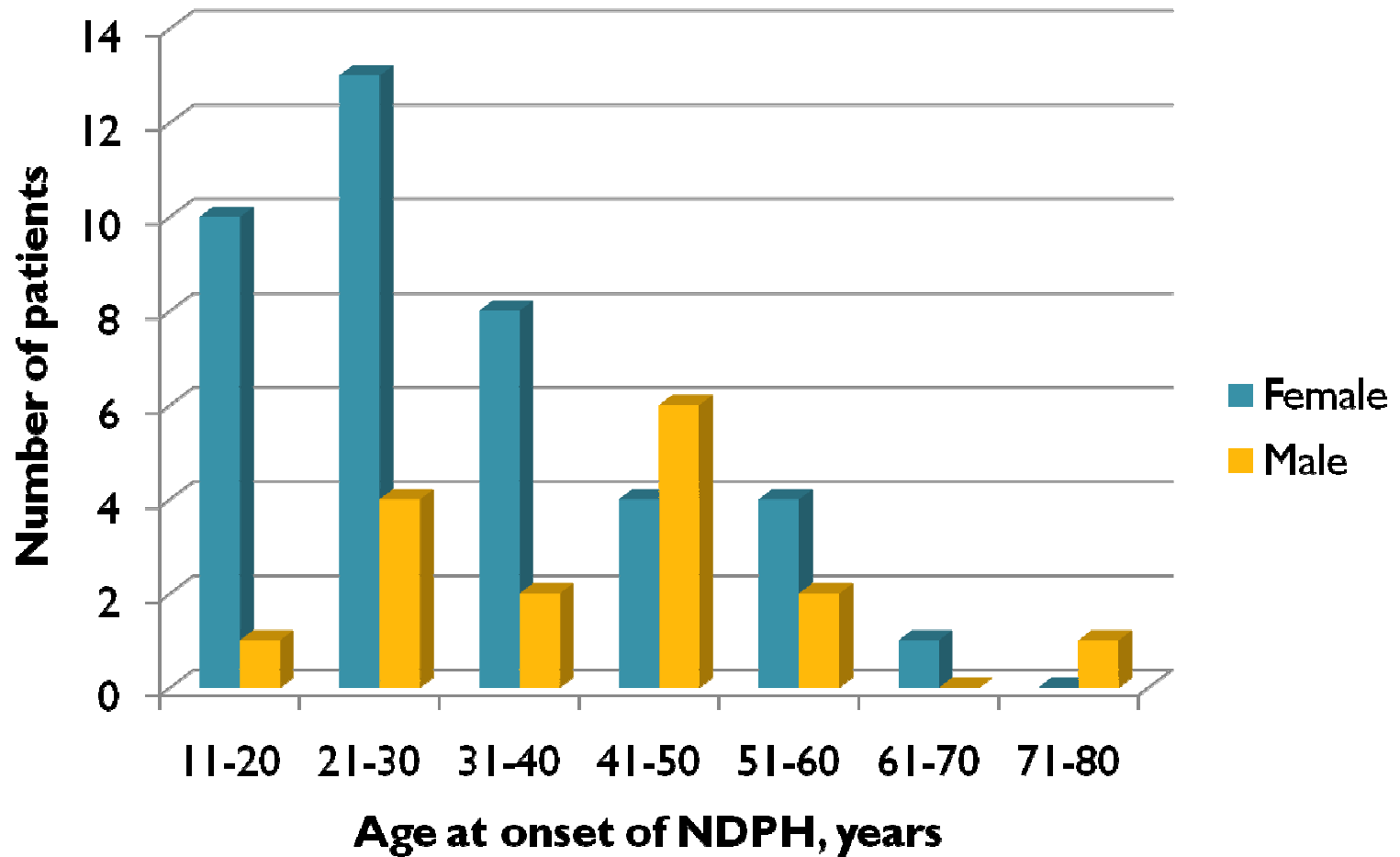
- Case definition: 15+ headache days per month
 - CDH Prevalence ~4%
 - CDH in 4.7% of 2252 patients in Spain
 - NDPH Prevalence
 - 0.1% of 2252 Spanish patients had NDPH (Castillo et al. 1999)
 - 10.8% NDPH patients of 638 CDH patients (Bigal et al. 2002)
- CDH Phenotype
 - Frequent 68% (some headache-free days)
 - Daily 15% (every day, but some headache-free hours)
 - Continuous 17% (never any headache free hours)

Epidemiology of primary chronic daily headaches in children and adolescents

	N	% chronic migraine	% NDPH	% CTTH
Kung et al. 2008	187	42.2	36.1	12.2
Cuvellier 2008 (France)	34	61.8	21.9	12.5
Bigal et al. 2004	170	68.8	21.1	10.1
Mack 2004	175	54	23	35
Koenig et al. 2002	174	64	23	13
Gladstein et al. 1996 (45% not classifiable)	37	15	35	5

Note much higher prevalence than in adults.

Age of onset of NDPH (N=56)



Li & Rozen, *Cephalalgia*, 2002, 22:66-69.

Clinical features of NDPH

(N=56, onset 12 – 78 years)

Prior headache history	38%
episodic migraine	19%
episodic TTH	2%
unspecified headache	14%
headaches increasing just prior to onset of NDPH	0%
Duration of daily headache	1.5 – 24 hours/day
Continuous throughout the day, never pain-free	79%
Over 80% were able to pinpoint the exact day that NDPH started.	
Mean pain intensity (10-pt VAS): Moderate (4-6) = 61%, severe (7-10)= 21%	
Location: bilateral 64%, occipitonuchal 60%, retro-orbital 44%, global 18%	
Quality: throbbing 53%, pressure-like 54%, stabbing 45%, dull 37%, tight 36%, burning 23%	

Note frequency of migraine symptoms in above table.

Li & Rozen, *Cephalalgia*, 2002, 22:66-69.



Clinical features of NDPH

(N=56, onset 12 – 78 years)(continued)

Li & Rozen, *Cephalalgia*, 2002, 22:66-69.

- Headache exacerbated by:
 - Stress 40%, physical exertion 32%, bright light 29%
- Headaches relieved by:
 - Rest 66%, dark room 48%, massage 23%, sleep 9%
- Associated symptoms
 - Nausea 68%, photophobia 66%, phonophobia 61%, dizziness 55%, sore/stiff neck 50%, blurred vision 43%, vomiting 23%, osmophobia in 23%, vertigo 11%
- Aura-type symptoms
 - Visual photopsia 9%, teichopsia 5%
- Family History + for headache in 29%

Note frequency of migraine symptoms in above table.

Clinical features of CDH in adolescents (N=306)


Mean:	TM	NDPH	CTTH
Age at onset, years	13.9	14.2	15.1
Female/male ratio	3.1	1.8	5.0
HA-days per month	27.0	27.5	29.1
Severe HA-days per month	10.9	10.8	1.5
IHS Migraine days per mo.	18.7	18.5	0.6
Non-migraine days per mo.	8.2	9.0	28.5
% attacks with nausea	42	39	3
% attacks with photophobia	67	69	6
% attacks with phonophobia	61	63	5

Kung E, Tepper SJ, Rapoport AM, Sheftell FD, Bigal ME. *Cephalalgia*, 2008, 29:17-22.



Etiology of NDPH (age-mixed groups)

- Related to systemic infection
 - +EBV titers for past infection in 5 of 7 NDPH pts (Li & Rozen 2002)
 - 62.5% have + EBV in nasal secretions vs. 12.5% in matched controls (Diaz-Mitoma et al. *Lancet* 1987, 1:411-415.)
 - “evidence of systemic infection” in 108 NDPH patients (Salmonella, adenovirus, toxoplasmosis, herpes zoster, EBV, E. coli UTI) (Santoni et al. *Intern Med* 1993, 32:530-533.)
 - Chronic meningitis has not been found in CSF of NDPH patients (Rozen, *Current Pain Headache Reports* 2003, 7:218-223.)
 - It is unknown how an infection can induce NDPH
- After non-cranial surgery 12% (Li & Rozen 2002)
- Related to stressful life event 12%
- 40% of NDPH patients = no apparent trigger



Inciting factors of NDPH in children and adolescents

(N=186, Mack, *Ped Neurol* 2004, 31:122-

125.)

- 43% had a febrile illness at onset
 - > 50% had + EBV serology
- 23% after minor head trauma
- 10% idiopathic intracranial hypertension
 - NDPH persisted after IIH treated or ruled out
- 10% after non-cranial surgery
- 2% related to high-altitude camping
- 12% no inciting factor identified



Etiology: elevation of TNF α in CSF

- Background & hypothesis
 - Possibly persistent systemic or CNS inflammation causes NDPH
 - Tumor Necrosis Factor (TNF) α is a pro-inflammatory cytokine involved in brain immune and inflammatory responses as well as in initiation of pain
- Goals
 - Analyze TNF α levels in CSF of inpatient NDPH patients (N=20)
 - Compare to inpatient controls with refractory chronic migraine (N=16) and post-traumatic headache (N=2)



Results: elevation of TNF α in CSF

- CSF levels of TNF α were elevated in 19 of 20 patients
 - Range 8.8 – 16.7 pg/mL (normal < 8.2 pg/mL)
 - \uparrow serum levels of TNF α in only 3/14 NDPH pts
- Control patients not any different
 - CSF TNF α was elevated in 16/16 chronic migraine patients (range 10.2--16.1 pg/mL)
 - CSF TNF α was elevated in both post-traumatic headache patients (mean 12.0 pg/mL)
- Other CSF values normal in all patients
 - Cell counts, total protein, glucose, cultures, significant increase CSF pressure



Significance of the study results

- These may be significant findings because a significant proportion of NDPH begins after an infection or illness, which are known stimulators of cytokines.
 - Little is known about stimulation and regulation of CSF cytokines, but laboratory triggers include infection, stress and surgery, the same as for NDPH.
 - Recent evidence that $\text{TNF}\alpha$ can induce CGRP production (see Rozen's article for full discussion).



Significance

- This study has no true control group—all the “controls” also showed the abnormality.
 - This implies that elevated $\text{TNF}\alpha$ may contribute to causing intractable chronic migraine and post-traumatic headaches.
- Research should focus on finding $\text{TNF}\alpha$ inhibitors or receptor antagonists that pass the blood-brain barrier into CSF
 - Current antagonists such as infliximab are monoclonal antibodies and will not penetrate BBB.



Treatment of NDPH

- The benign form of NDPH is self-limited and usually does not need therapy
- Refractory form can continue for decades and fail to respond to the most-aggressive outpatient and inpatient treatment (Rozen, 2004)
- Some patients may respond to topiramate > 100 mg/day or gabapentin > 2700 mg/day but reports are anecdotal only.



Current recommendations for therapy of NDPH in adolescents

- From New England Regional Headache Center
 - All patients should be monitored with daily headache diary
 - To start: riboflavin (vitamin B2) 200 mg bid for minimum 6 w.
 - Next: topiramate increased 15 – 25 mg/week up to 200mg/day, minimum 8 weeks at Dmax.
 - Next: add gabapentin 400 – 600 mg weekly, up to 3000 mg/day (split doses improve absorption).
 - Next: botulinum toxin A (BoNTA) 100 units per injection sequence every 10 weeks for 3 rounds of treatment.
 - To end: trial of occipital nerve stimulator
- If headaches substantially improve or stop, then maintain last level of treatment X 6 months, then taper.



The case of the 14yo girl with NDPH: The physician answers

- Adolescents are at risk for primary headache disorders
 - Not caused by underlying illnesses
 - Often occur daily in teenagers
- New Daily Persistent Headache (NDPH) is a form of Chronic Daily Headache (CDH)
 - It begins suddenly and remains daily
- Treatment is difficult
 - Involves drug & non-drug therapy
 - Tx with drugs=antidepressants or anticonvulsants
 - Tx non-drug=biofeedback, relaxation & cognitive therapy
 - Treatment best delivered in specialized Headache Clinic, sometimes including inpatient hospitalization

A multi-disciplinary headache unit is often the best place to get this double-barreled approach, and sometimes adolescents with severe and difficult to treat NDPH require inpatient hospitalization as well. I wish I could say that there is a magic bullet for this condition, but the usual approach is to try and try again, always using multiple therapies, both drug and non-drug.

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