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NEW DAILY PERSISTENT HEADACHES

Chronic daily headache of long duration

- Occurs on at least 15 days/month with untreated headache lasting >4 hrs for more than 3 months with primary types diagnosed after exclusion of secondary causes
- Chronic migraine
- Chronic tension-type headache
- Hemicrania continua
- New daily persistent headache (NDPH) which was first described by Vanast in 1986

ICHD-2 2004 criteria

1. Headache is daily and unremitting from within 3 days of its onset
2. Headache occurs for more than 3 months
3. Headache has at least 2 of the following characteristics:
 - Bilateral location
 - Non-pulsating quality
 - Mild to moderate intensity
 - Does not worsen with routine physical activity such as walking
4. Only has one of the following 3 characteristics: photophobia, phonophobia, mild nausea
5. Does NOT include moderate to severe nausea or vomiting
6. Is not secondary to another disorder

ICHD-2 is overly restrictive

- However, about 56% of patients have migraine features and do not meet the criteria
- Robbins et al propose creating a new subset including those with migraine features which has similar demographic, clinical, and prognostic features to ICHD-2 NDPH

Robbins MS, Grosberg BM, Napchan U, et al. Clinical and prognostic subforms of new daily-persistent headache. *Neurology*. 2010;74:1358-1364.

Proposal for Diagnostic Criteria for New Daily Persistent Headache (Goadsby)

New Daily Persistent Headache – Primary

- A. Headache for more than 3 months fulfilling B-D
- B. Daily head pain or discomfort from the onset without remission of more than a day, and coming on within one day
- C. The headache, or worsenings of the headache, either
 - I. Are associated with any one of: throbbing pain, aggravation of pain with movement, nausea, vomiting, photophobia, phonophobia, or osmophobia
 - II. Have no associated features such as in I. above
- D. Not attributed to another disorder

The patient may recognize their head does not feel “normal” although the pain or discomfort level may be low from time to time. To fulfill criterion D, hemicrania continua should be excluded.

Goadsby PJ. New daily persistent headache: a syndrome not a discrete disorder. *Headache*. 2011 Apr;51(4):650-3.

Additional time based subdivision: duration (Evans)

- Acute (0-14 days)
- Subacute (14 days to 3 months)
- Chronic (more than 3 months)
- What is the prognosis of NDPH presenting at these times?
- What testing should be done?
- No prospective studies

Clinical features of NDPH

- Most pts can identify the exact day of onset
- 80% have a constant headache
- The baseline pain level is mild to moderate for most
- Bilateral pain for 90%, unilateral in 10%
- Throbbing and/or pressure-like, generalized or localized to any head region
- Migraine features in over 50% such as nausea, light and noise sensitivity, lightheadedness, and occasional vomiting

Evans RW, Seifert TD. The challenge of NDPH. *Headache* 2011; 51:145

Clinical features (contd)

- Cranial autonomic symptoms with painful exacerbations in 21% and cutaneous allodynia in 26%
- Rare reports of associated visual aura and unrelated frequent episodic facial flushing usually lasting a few minutes with painful exacerbations

Takase Y, Nakano M, Tatsumi C, Matsuyama T. Clinical features, effectiveness of drug-based treatment, and prognosis of new daily persistent headache (NDPH): 30 cases in Japan. *Cephalalgia*. 2004; 24:955-959; Robbins MS, Grosberg BM, Napchan U, et al. Clinical and prognostic subforms of new daily-persistent headache. *Neurology*. 2010;74:1358-1364.

Demographics of NDPH

- Age of onset ranges from 6 to more than 70 years with a mean of 35 years
- Female:male 2.5:1 in adults and 1.8:1 in children
- Rare: one-year prevalence of 0.03% in persons ages 30-44 years
- Among pts with CDH in tertiary headache clinics, NDPH accounts for 13-35% of pediatric and 1.7-10.8% of adult cases

Kung E, Tepper SJ, Rapoport AM, et al. New daily persistent headache in the paediatric population. *Cephalalgia*. 2009;29:17-22

Grande RB et al. Prevalence of new daily persistent headache in the general population. The Akershus study of chronic headache. *Cephalalgia*. 2009;29:1149-1155.

Co-morbidity of NDPH

- 25% have a pre-existing history of a primary headache disorder: episodic tension-type in 18% or episodic migraine in 7%
- Prior depression or anxiety in 51% and current depression in 62%
- Panic disorder may be co-morbid

Misdiagnosis of primary NDPH is common

- Anecdotally, many general neurologists misdiagnose NDPH as chronic migraine or CTTH
- Many non-neurologists are not familiar with NDPH and misdiagnose sinus headaches, TMD, eye strain, chronic Lyme disease, cervicogenic headaches
- Common for patients to see numerous physicians in numerous specialties or numerous neurologists and headache specialists

NDPH vs Chronic Migraine (CM)

- 2.5% of those with episodic migraine progress to CM yearly gradually
- 30% of peds with CM reported an abrupt transition from episodic migraine (Mack K. What incites new daily persistent headache in children? *Pediatr Neurol.* 2004;31:122)
- Robbins et al excluded pts with preexisting migraine frequency of ≥ 4 days of headache monthly and no clear escalation of headache frequency prior to daily headache onset (*Neurology.* 2010;74:1358)
- Could those with prior history of EM and migraine features just have CM then with an abrupt onset? Yes. But prognosis with treatment is worse.
- Same argument for chronic tension-type headache

Hemicrania Continua

- Unilateral with varying intensity; rarely bilateral or alternating sides; female : male, 1.6:1; rare; first described by Sjaastad and Spierings in 1984; 88% of cases unremitting or continuous and 12% remitting
- 75% have exacerbations of severe throbbing or stabbing pain, lasting 20" to several days which can be associated with photophobia (59%), phonophobia (59%) [often unilateral], nausea (53%), and vomiting (24%); visual aura rare
- Exacerbations can last from 20" to several days with pain awakening 1/3 of patients. Autonomic features are present in up to 75% with tearing and then conjunctival injection the most common

Hemicrania continua (contd)

- Primary stabbing HA or jabs and jolts in 41% especially in exacerbations; some report a feeling of sand in the eye
- RX: Absolute response to indomethacin 50-300 mg/d divided doses, usually 150 mg/d or less; Trial 25 tid x 3 d, 50 tid x 3 d, 75 tid x 3 d-stop at effective dose; if not effective at 75 tid, not HC
- Less other nsaids, melatonin 6-12 mg hs, Botox, topiramate, verapamil, gabapentin, occipital nerve stimulation, iv steroids
- Definitely consider in unilateral NDPH but even in intractable bilateral cases and try indomethacin

Cittadini E, Goadsby PJ. Hemicrania continua: a clinical study of 39 patients with diagnostic implications. Brain 2010;133(Pt 7):1973

Pathophysiology of primary NDPH

- Unknown
- Preceding flu-like or upper respiratory infection in 14-30%, a stressful life event in 10-12%, or extracranial surgery in 7-12%
- Cervical joint hypermobility and defective internal jugular venous drainage suggested as causes

Pathophysiology of primary NDPH (contd)

- One positive and one negative study of active EBV infection and a variety of other infections
- One study found elevated levels of tumor necrosis factor alpha (a proinflammatory cytokine) in the csf but not the serum of pts with NDPH, CM, and PTH

Rozen TD. New daily persistent headache: clinical perspective. *Headache*. 2011 Apr;51(4):641-9

Goadsby PJ. New daily persistent headache: a syndrome not a discrete disorder. *Headache*. 2011 Apr;51(4):650-3.

Differential Diagnosis of New Daily Headaches Present for More Than 3 Months: Primary

- NDPH
- Chronic migraine and chronic tension type: not daily from within 3 days of onset
- Hemicrania continua

Differential Diagnosis of New Daily Headaches Present for More Than 3 Months: Secondary or NDPH Mimics

- Medication overuse, postmeningitis HA, chronic meningitis, sphenoid sinusitis, neoplasms, chronic subdural hematoma, posttraumatic, hypertension, spontaneous intracranial hypotension, idiopathic intracranial hypertension, cervical artery dissection, reversible cerebral vasoconstriction syndrome, cerebral venous dissection, AVM, dural arteriovenous fistula, unruptured intracranial saccular aneurysm?, Chiari malformation, temporal arteritis, cervicogenic, temporomandibular joint dysfunction

Blood tests and lumbar puncture

- CBC: headache due to 50% or more decrease of hemoglobin or TTP
- TSH: HA in 14% of cases of hypothyroidism
- CMP: HA in renal failure and hypercalcemia
- As appropriate: esr, ANA, mono spot, Lyme antibody, HIV
- Lumbar puncture: low and high csf pressure, subacute or chronic meningitis

Neuroimaging: no studies just for NDPH

Retrospective review of MRI scans of 306 adults with chronic or recurrent headaches for 1 month or more with no other neuro sx's and normal exams

- 55% no abnormalities, 44% minor abnormalities, .7% (2) abnormal-pituitary macroadenoma and subdural hematoma
- Neither contrast enhancement nor repeated MRI contributed to the diagnosis

Tsushima Y, Endo K. MR imaging in the evaluation of chronic or recurrent headache. *Radiology*. 2005;235:575

Neuroimaging (contd)

- 1876 consecutive patients age 15 or older (mean age 38) with headaches with onset at least 4 wks before referred to 2 neuro clinics in Spain; 1/3 new onset, 2/3 present >1 yr; migraine 49%, TTH 35%, cluster 1%; normal exam 99%
- CT scans in 1432, MRI in 580, 136 had both
- Significant lesions in 1.2% with normal neuro exams in 17/22

Sempere AP, Porta-Etessam J, Medrano V, et al. Neuroimaging in the evaluation of patients with non-acute headache. *Cephalalgia*. 2005;25:30

Neuroimaging (contd)

- Retrospective review of 402 adults with headache present for 3 months or more and no other neuro symptoms or findings
- Major abnormalities in 15 patients (3.7%) including a glioma, meningioma, metastases, subdural hematoma, arteriovenous malformation, hydrocephalus (three patients), and two Chiari I malformations.
- Found in .6% with migraine, 1.4% with TTH, 14% atypical HA, and 3.8% others.

Wang HZ, Simonson TM, Greco WR, et al. Brain MR imaging in the evaluation of chronic headache in patients without other neurologic symptoms. *Acad Radiol.* 2001;8:405

Neuroimaging (continued)

- Retrospective review of children ages 6-18 with migraine and chronic daily headache and normal exams
- 54 with migraine had CT (42) or MRI (12): 3.7% clinically not relevant findings
- 25 with CDH had CT (17) or MRI (8): 16% clinically not relevant findings

Lewis DW, Dorbad D. The utility of neuroimaging in the evaluation of children with migraine or chronic daily headache who have normal neurological examinations. *Headache*. 2000;40:629

Sphenoid sinusitis

- Can cause severe new onset HA that interferes with sleep with no specific location
- Can have associated pain or paresthesias in the facial distribution of V and photophobia or tearing with or without fever or nasal drainage
- Can mimic migraine and meningitis

Spontaneous Intracranial Hypotension

- Headache types: orthostatic, chronic daily without orthostatic features, exertional, cough, acute thunderclap onset, paradoxical (present recumbent and relieved upright), intermittent, or acephalgic (no headache). Neck or interscapular pain may precede the onset of headache in some cases by days or weeks.
- MRI abnormalities of the brain and spine are variably present in approximately 90% of cases. Most CSF leaks occur at the thoracic or cervicothoracic junction.
- An MRI scan of the brain may reveal diffuse pachymeningeal (dural) enhancement with gadolinium without leptomeningeal (arachnoid and pial) involvement and, in some cases, subdural fluid collections, which return to normal with resolution of the headache-can be normal in up to 20% of cases.

Cervical internal carotid or vertebral artery dissections

- Headache most frequent presenting symptom of cervical artery dissection occurs in ~70% of patients with both carotid and vertebral artery dissection. Neck pain in about 50% of vertebral dissections and 25% of carotid. Incidence of dissections is 2.6/100,000/yr
- 8% can present with unilateral or bilateral headache or neck pain alone (Arnold et al. JNNP 2006;77:1021)
- Usually gradual onset but thunderclap onset in 20%. Rare cause of new daily headaches especially after cervical ica dissections.
- ICA dissection can mimic migraine with aura-visual ± sensorimotor ± dysphasia sequentially. Migraine is a risk factor for dissections (OR 2.15)
- MRA, CTA, cerebral arteriogram-MRA preferred by most-carotid ultrasound operator dependent, less sensitive (Debette and Leys. Lancet Neurol 2009; 8:668)

Cerebral venous thrombosis (CVT)

- Headache is present in up to 90% of cases of CVT, often the initial symptom, presenting symptom in 15%, and occasionally the only symptom (Cumurciuc et al. JNNP. 2005; 76:1084). The headache can be unilateral or bilateral in any location, mild to severe, and intermittent or constant. The onset usually is subacute but can be thunderclap.
- The headache almost always is associated with other neurologic signs, such as papilledema, focal deficits, seizures, disorders of consciousness, or cranial nerve palsies. Mimic of idiopathic intracranial hypertension.
- CT will diagnose only approximately 20% of cases of CVT when demonstrating the hyperdensity of the thrombosed sinus on plain images and the delta sign seen with superior sagittal sinus thrombosis after contrast administration. Helical CT venography is a sensitive diagnostic method.
- May be missed on routine MRI imaging of the brain although echo-planar T₂*-weighted MRI may increase the sensitivity. MRV increases the sensitivity of MR especially within the first 5 days of onset or after 6 weeks.
- Can be demonstrated on digital subtraction venography.

Chiari I malformation (CMI)

- Congenital malformation of cerebellar tonsillar herniation at least 5 mm below the foramen magnum
- Headache is occipital or nuchal-occipital with occasional radiation unilaterally to frontotemporal or shoulder regions and sometimes generalized. The pain may be dull, aching, or throbbing and may last less than 5" to several hours to days. Pain may be precipitated by neck flexion or palpation or coughing.
- Imaging study of children (2 to 18 yrs) who had headaches, CMI identified in 14/241 (5.8%). 5 out of these 14 (35.7%) had headaches secondary to their malformation. Three patients had surgical decompression with significant headache relief in 2 (Schwedt. Headache 2006; ;46:387).
- Can be associated with chronic migraine (Kaplan. Clin Neurol Neurosurg 2008;110:818) but usually incidental finding.

Can unruptured saccular aneurysm contribute to chronic headaches?

- 32 patients with chronic headaches who underwent Guglielmi coil embolization of unruptured aneurysm.
- Headaches not classified using IHS criteria: many of the patients clearly had features of migraine with and without aura.
- After treatment, 59% reported improvement in the severity of their headaches, and the headaches were less frequent.
- Selection bias? No control group

Qureshi et al. Headache 2003, 43:1090

Can unruptured saccular aneurysm contribute to chronic headaches? (contd)

- 49/81 (61%) with unruptured saccular aneurysms had chronic headaches before surgery (clipping or coil): chronic tension type in 23, chronic migraine in 19; 57 women, 24 men, mean age 57 years
- Post-op: 44 (89.8%) reported headaches were improved (slightly in 12 and markedly in 32) with no difference between the coil and surgical group (50% in each). Improvement in 1st week post-op. No difference between different types of headache, size, and location of aneurysms.
- Retrospective history of headaches, placebo effect, no controls

Hong et al. Headache. 2007;47:693

Can unruptured saccular aneurysm contribute to chronic headaches? (contd)

- Prospective study of 44 patients treated including 38 with coils, 5 clipping, 3 liquid embolic agent infusion
- 90 day frequency decreased from an average of 31 days prior to treatment to 17 days following treatment
- Those with pre-treatment migraine less likely to improve

Schwedt TJ, Gereau RW, Frey K, Kharasch ED. Headache outcomes following treatment of unruptured intracranial aneurysms: A prospective analysis. *Cephalalgia*. 2011;31:1082

Reversible cerebral vasoconstriction syndromes (RCVS)

- Thunderclap headache (TCH), normal or near-normal cerebrospinal fluid, and reversible cerebral segmental vasospasm involving arteries of the circle of Willis. Female:male=1.8:1
- TCH may occur in isolation or in conjunction with other symptoms, such as altered mental status, motor deficits, sensory deficits, seizures, visual changes, ataxia, speech abnormalities, and nausea/vomiting. Throbbing headaches, visual blurring, scotomas, and cortical blindness are the most common symptoms.
- Spontaneous 1/3. Secondary 2/3: history migraine, pregnancy, vasoactive drug exposure (ergotamine, triptans, SSRIs, pseudoephedrine, cocaine, amphetamines, ecstasy, cannabis, and bromocriptine)
- TCH only symptoms in 76% with multiple TCH in 94% (range 2-18) lasting 5"-36 hours, exacerbated with Valsalva, lasting for weeks
- 1/3 have blood pressure surges (systolic >160) with headache-may be due to pain, eclampsia, or drugs such as cocaine.
- Usually resolution spontaneously over 2-6 weeks-often benign course-rare severe strokes, brain edema, and even death

RCVS (contd)

- Can cause chronic and/or continuous HA (Hastriter et al. Headache prognosis in RCVS. Neurology 2011; 76 (9;suppl 4):A266.
- RCVS manifest as alternating segments of vasoconstriction and dilation or alternating areas of vasoconstriction and normal vascular caliber in the proximal and distal branches of the circle of Willis.
- Brain MRA/MRI may be normal or have abnormalities consistent with posterior reversible leukoencephalopathy or watershed infarctions in the distal vascular territory of cerebral vessels with severe spasm (Chen et al. Ann Neurol. 2010;67:648). Cortical SAH in 22%, intracerebral hemorrhage in 6%, reversible posterior leukoencephalopathy in 9%, and cerebral infarcts in 4% (Ducros et al. Brain. 2007;130(Pt 12):3091).

Dural arteriovenous fistula

- Rare mimic of NDPH
- Can present with a unilateral headache alone followed later with ipsilateral tinnitus
- Or can present with unilateral headache with ipsilateral popping noises and tinnitus
- MRI of brain may be negative or show subtle changes
- MRA of CTA may show fistula; angio gold standard

Evans RW, Schiffman JS. Headache as the only symptom of a spontaneous dural carotid-cavernous fistula. *Headache*. 2005;45:1256

Idiopathic intracranial hypertension (IIH; pseudotumor cerebri)

- Can present without papilledema in 6% of cases of IIH with following features: lower OP (mean 309 vs 373 with papilledema), photopsias 20%, non-physiologic VF constriction 20%, visual auras in 55%, and SVPs present in 75% (Digre KB, et al. A comparison of idiopathic intracranial hypertension with and without papilledema. *Headache*. 2009;49:185)
- “Normal pressure pseudotumor”: 13 pts with refractory headache and normal OP with HA relief with LP or shunt (Vargas B et al. Normal Pressure Pseudotumor: A Case Series (abstract). *Headache*. 2011;51:74)

NDPH over the age of 50

- The prevalence of headache decreases with older age
- Although 90% of headaches in younger patients are of the primary type, about 66% of those in the elderly are primary
- About 2% of those with migraine and 10% with tension type have the onset over the age of 50 years
- NDPH can have onset over age 50

Temporal arteritis

- **Criteria for the diagnosis of temporal arteritis of the American College of Rheumatology**
 - 1. Age at least 50 years**
 - 2. New onset of localized headache**
 - 3. Temporal artery tenderness or decreased pulse**
 - 4. Erythrocyte sedimentation rate of least 50 mm/h**
 - 5. Positive histology**

Temporal arteritis (contd)

- Approximately 50% of patients with TA have polymyalgia rheumatica and about 15% of patients with polymyalgia rheumatica have TA
- Both conditions occur almost exclusively in patients over the age of 50, with a mean age of onset of about 70 with female to males, 3:1
- Most biopsy-proved large series have no patients under age of 50. Of 141 consecutive patients presenting to a Canadian neuro-ophthalmology practice, there was one patient under age 50 who was age 47 (Ramstead. Can J Ophthalmol 2007;42:295)

Temporal arteritis (contd)

- Headaches are the most common symptom reported by 60 -90% of patients
- The pain is most often throbbing although many patients describe a sharp, dull, burning, or lancinating type of pain. The pain may be intermittent or continuous and is more often severe than moderate or slight.
- Location: 25%, only the temple; 54%, the temple either exclusively or inclusively; 29%, not involving the temple at all; and 8%, generalized
- Intermittent jaw claudication in 38%

Diagnosis of temporal arteritis

- Westergren erythrocyte sedimentation rate (ESR)
For elderly patients, the ESR range of normal may vary from <20 mm/h to 40 mm/h
A formula for the upper limits of normal for the ESR which includes 98% of healthy persons is as follows: age in years divided by 2 for men and age in years plus 10 divided by 2 for women
TA with a normal ESR has been reported in 10 to 36% of patients
When abnormal, the ESR averages 70 to 80 and may reach 120 or even 130 mm/h
- CRP is not influenced by various hematologic factors or age and is more sensitive than the ESR for the detection of TA
- The ESR and CRP combined give the best specificity, 97%
- False-negative rate of temporal artery biopsies ranges from 5-44%.
7-13% with negative unilateral bx, have + bx on other side.
- Pathologic evidence of TA persists for at least 4 to 5 days after the start of corticosteroid treatment
- Also contrast enhanced MRI of STAs

Treatment

- No prospective RCT
- Uncontrolled series of 30 pts meeting ICHD-II criteria (17 males)

First given baclofen or tizanidine

If no benefit, tricyclic (amitriptyline for 23), SSRI, valproic acid (9), and beta blockers (2).

Very effective 27%, mod effective 3%, mildly effective 20%, and ineffective 50%

Takase Y et al.

Clinical features, effectiveness of drug-based treatment, and prognosis of new daily persistent headache (NDPH): 30 cases in Japan. *Cephalalgia*. 2004; 24:955

Treatment (continued)

- Retrospective series of pts on amitriptyline (16), fluoxetine (7), and valproic acid (7): none effective
- Case reports and small series reporting efficacy of topiramate, venlafaxine, nortriptyline, gabapentin and topiramate, mexiletine, and clonazepam

Treatment: immunosuppression

- Doxycycline 100 mg bid for 2 months: reported as effective in 4 pts ($\frac{3}{4}$ with antecedent infections)±montelukast 10 mg bid: needs further confirmation

(Rozen. Headache 2008;48:549)

- Cohort with a history of antecedent extracranial infection in India: IV methylprednisolone 1000 mg daily for 5 days then 60 mg of prednisolone daily for 2-3 wks for 6/9-complete resolution of HA in 6/9 but HA was present for 3 months or longer in only 4/9 cases: needs further confirmation

Prakash S, Shah ND. Post-infectious new daily persistent headache may respond to intravenous methylprednisolone. J Headache Pain. 2010;11:59

Treatment (continued)

- Typically treated empirically using the same medications used for chronic migraine or tension type based on clinical features
- Two reports of 12 and 9 patients of temporary efficacy of inpatient DHE regimen
- IV haloperidol and iv magnesium might be effective
- Continuous opioid therapy usually not effective
- Greater occipital nerve blocks may be helpful
- Trigger point injections and PT might be helpful
- Cervical facet , atlantoaxial, auriculotemporal, supraorbital/trochlear, DRG blocks/RF ablation-anecdotal
- There is a single case report using botulinum toxin
- Medication overuse a potential risk: 45% in a mainly adult study and 12.5 % in a pedi study

Prognosis

- Vanast (1986): 86% males, 73% females headache free at 2 years
- Most studies since have found a poor prognosis for improvement
- 71 pts: 76% with persistent HA, 15% with remission (4 months to 54 years with median of 21 months), and 8% with a relapsing-remitting type (range to first remission 3-24 months)

Robbins et al. Clinical and prognostic subforms of new daily-persistent headache. *Neurology*. 2010;74:1358

- Might the RR type be episodic daily migraine?

Evans RW. Thomas Jefferson's headaches: Episodic daily migraines. *Headache*. 2006;46:1210

Prognosis: children and adolescents

- 20/28 HA still present 6 months to 2 years later
- 8/28 headache free: 3 within 1 year and 4 within 2 years
- 79% had MIDAS scores indicating normal function in school/home
- Risk factors for chronic HA: female sex, straight-A report cards, excess extracurricular activities, poor sleep, a disordered home life, medication overuse, obesity, caffeine, poor diet, stressful life events, head injury, and insufficient exercise and fluids.

Wintrich S, Rothner D. New daily persistent headaches—follow up and outcome in children and adolescents. *Headache*. 2010;50(Suppl. 1):s23.