Clinical Reasoning: An underrecognized etiology of new daily persistent headache

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Section 1

A 66-year-old man with no headache history presented with a new daily and persistent headache that began acutely 1 year ago without any clear provoking features. The pain was mild, constant holocephalic pressure with associated photophobia and phonophobia. He denied nausea/vomiting or migraine aura–like symptoms. Previously failed preventive migraine medications included onabotulinumtoxinA injections, nortriptyline, gabapentin, and metoprolol. The patient's neurologic examination including funduscopic evaluation was normal.

Questions for consideration:

1. What is your differential diagnosis of new daily and persistent headache?
2. What additional clinical or examination features would help narrow the differential?

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Section 2

New daily persistent headache (NDPH) is a unique primary headache disorder in which headache begins one day and does not remit, with patients invariably being able to identify the exact date their headache started.[1] While some patients are able to identify triggers prior to the onset of headache, no trigger seems to have a cause-effect relationship with NDPH and the pathophysiology of NDPH remains poorly understood.[2] An awareness of the primary and secondary headache disorders that may be mistaken for NDPH is crucial to avoid misdiagnosis. Table 1 provides a comprehensive differential diagnosis of NDPH with clinical clues and neuroimaging features that may be seen.

A careful history is essential for narrowing this differential diagnosis with particular attention paid to the classic red flags or worrisome historical features (table 2).

On further questioning, our patient reported that he would experience abrupt onset, instantly severe exacerbation of headache with Valsalva maneuver and bending forward. The Valsalva-induced headaches could last up to 1 hour and were improved within 15–30 minutes of recumbency. There was no history of head or neck trauma.

Questions for consideration:

1. What diagnosis should be considered with the new historical information provided?
2. What are typical MRI findings expected in this condition?

Table 1 Differential diagnosis of new daily persistent headache

Diagnosis	Possible clinical clues for diagnosis	Possible neuroimaging features[a]
Arteriovenous malformation	Seizure Focal neurologic deficit	Intracranial hemorrhage Tangle of blood vessels
Brain tumor	Progressive headache Seizure Focal neurologic deficit Signs of increased intracranial pressure[b]	Well circumscribed mass(es) that enhance ± surrounding edema
Carotid or vertebral artery dissection	Tearing neck pain with ipsilateral headache Ischemic stroke Horner syndrome (25% of cases) Tinnitus, audible bruit Cranial neuropathies Thunderclap or subacute headache	Angiogram (MRA/CTA): String sign Tapered stenosis or flame-shaped occlusion
Cerebral venous thrombosis	Signs of increased intracranial pressure[b] Seizures Encephalopathy Thunderclap or subacute headache	Empty-delta sign on postcontrast imaging MRV showing nonvisualized venous sinuses or filling defect Venous infarcts
Chronic meningitis	Signs of increased intracranial pressure[b] Low-grade fevers Neck stiffness/meningismus	Leptomeningeal enhancement Basal exudates Hydrocephalus Ring-enhancing lesions (if associated with abscess)
Chronic subdural hematoma	Elderly patient or history of alcoholism History of mild head trauma Minor behavioral changes or gait abnormalities Urinary frequency/urgency	Unilateral/bilateral subdural hematoma with/without mass effect
Giant cell arteritis	Headache starting at age over 50 Temporal tenderness Jaw claudication Visual disturbances Unexplained fever or anemia Symptoms of polymyalgia rheumatica Elevated ESR/C-reactive protein	Temporal artery MRA or ultrasound may assist investigations; temporal artery biopsy is gold standard
Hemicrania continua	Unilateral headache (side-locked to one side) Ipsilateral autonomic features Absolute response to indomethacin is diagnostic	Normal imaging Should exclude pituitary abnormalities as a secondary cause of trigeminal autonomic cephalalgia
Idiopathic intracranial hypertension	Signs of increased intracranial pressure[b]	Empty sella sign Flattened posterior optic globes; vertically tortuous optic nerves; perioptic nerve sheath distension MRV/CTV with bilateral distal transverse cerebral venous sinus stenoses
Leptomeningeal metastasis	Multifocal involvement (multiple cranial neuropathies) Altered mental status Cerebellar dysfunction Radiculopathy/cauda equina syndrome	Thin, diffuse leptomeningeal contrast enhancement Cranial nerves may be abnormally thickened and enhancing
Posttraumatic headache	Associated postconcussive symptoms including the following: Dizziness Sleep disturbance Personality change, irritability, anxiety or depression Difficulty with memory/concentration	Often normal Hemorrhage (subarachnoid, subdural/epidural, intraparenchymal) Chronic signs: Cystic degeneration or bony fractures DTI showing traumatic axonal injury
Sphenoid sinusitis	Nasal congestion ± mucopurulent drainage Facial pain, pressure, fullness Reduced/loss of smell if other sinuses involved	Sphenoid sinus mucosal thickening bilaterally
Spontaneous spinal CSF leak	Orthostatic headache Valsalva-induced headache Hearing changes Cognitive or gait changes Thunderclap headache	Pachymeningeal enhancement Brain sagging Subdural fluid collections Engorgement of the venous structures Pituitary hyperemia

Continued

Table 1 Differential diagnosis of new daily persistent headache *(continued)*

Diagnosis	Possible clinical clues for diagnosis	Possible neuroimaging features[a]
Spontaneous subarachnoid hemorrhage	Worst headache of life, thunderclap headache Signs of increased intracranial pressure[b] Neck stiffness/meningismus	CT scan with acute blood usually visible SWI sensitive in detecting blood in subarachnoid spaces MRA/CTA may show aneurysm

Abbreviations: CTA = CT angiography; DTI = diffusion tensor imaging; ESR = erythrocyte sedimentation rate; MRA = magnetic resonance angiography; MRV = magnetic resonance venography; SWI = susceptibility-weighted imaging; TVO = transient visual obscurations.
[a] Neuroimaging features typically best seen on MRI unless specifically noted.
[b] Increased intracranial pressure may be associated with 6th nerve palsy, papilledema, TVOs, headache worse supine/early morning, pulsatile tinnitus.

Table 2 Red flags for headache history

Older age at onset (>50 y)
Acute onset (thunderclap) headache
Significant change in the characteristics of prior headaches
Signs or symptoms of systemic illness (fever, chills, weight loss)
Neurologic symptoms not consistent with typical migraine aura symptoms
Known systemic illnesses predisposing to secondary headache (e.g., cancer, HIV)
Positional headache
Precipitated by Valsalva maneuvers

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Section 3

In the absence of a history of lumbar puncture, an orthostatic headache that occurs with an upright position and is relieved by lying down is suggestive of a spontaneous CSF spinal leak, a condition often referred to as spontaneous intracranial hypotension (SIH). Nomenclature of SIH is somewhat misleading as patients with this condition tend to have normal CSF pressure.[3] Therefore, terms including CSF hypovolemia and spontaneous spinal CSF leak have been proposed as alternative nomenclature. Although much has been learned about this condition since it was first described in 1938,[4] an estimated 46%–55% of patients with SIH have no identifiable confirmed site of leak and effective management can be difficult.[5] SIH remains an important differential in NDPH.[4]

The classic manifestation of SIH is an orthostatic headache generally occurring or worsening within 15 minutes of upright posture, although this can be variable, with some patients experiencing worsening after hours of upright posture. Improvement in headache within 15–30 minutes of lying down is typical. Clinical description of headache in SIH is variable and may be throbbing or nonthrobbing, diffuse or localized, most commonly to the occipital or suboccipital regions, and severity varies greatly. The onset is generally subacute although some patients may describe a thunderclap headache.[4]

Although orthostatic headaches are prototypical of SIH, this orthostatic component may become less apparent with time, and some patients may have no postural component to their headache from onset. Other patients report prominent Valsalva-induced headaches, second half of the day headaches, or rarely paradoxical headaches that worsen while lying down.[4] A wide range of symptoms has been reported in SIH, including neck pain or meningismus, altered hearing, tinnitus, imbalance, and cognitive decline or mental fogginess.[6]

Additional diagnoses that should be considered in the context of an orthostatic headache include autonomic dysregulation (e.g., postural orthostatic tachycardia syndrome), postsurgical Chiari decompression, cervicogenic headache, and third ventricle colloid cysts.[6]

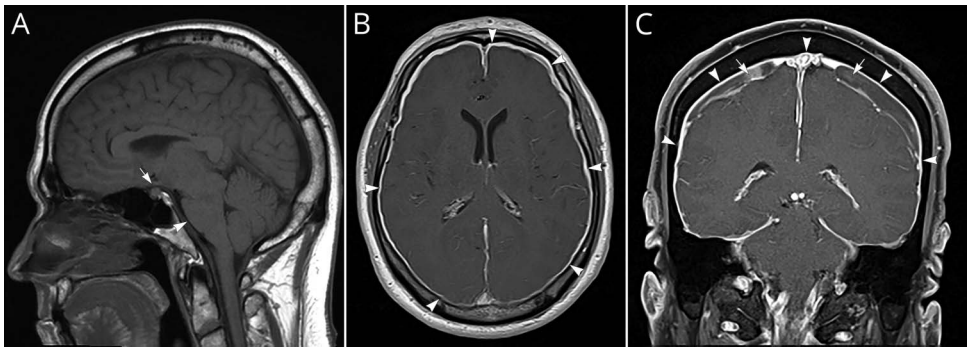
Characteristic features on MRI seen in SIH can be remembered by the mnemonic SEEPS: (1) subdural fluid collections, (2) enhancement (diffuse) of the pachymeninges, (3) engorgement of venous structures, (4) pituitary hyperemia, and (5) sagging of the brain (figure 1).[4] Sagging of the brain can be recognized by descent of the cerebellar tonsils at or below the foramen magnum (sometimes mimicking Chiari type 1 malformation), effacement of prepontine or perichiasmatic cisterns with bowing of the optic chiasm over the pituitary fossa, flattening of the anterior pons, and crowding of the posterior fossa.[4,6] Such imaging findings are related to compensatory changes in response to CSF volume loss.[6,7]

Our patient's initial MRI brain without contrast done at an outside facility was read as normal but per our review showed possible subtle brain sag. MRI of the entire spine did not show epidural fluid collections suggestive of a CSF leak.

Question for consideration:

1. What treatment or additional neuroimaging studies would you consider at this time?

Figure 1 Characteristic features of SIH on brain MRI



(A) Sagittal T1-weighted image demonstrates brain sagging in spontaneous intracranial hypotension. The prepontine cistern is narrowed (arrowhead). Note downward displacement of optic chiasm and optic tracts (arrow). (B) Axial T1-weighted postcontrast image demonstrates diffuse smooth dural (pachymeningeal) enhancement (arrowheads). (C) Coronal T1-weighted postcontrast image demonstrates diffuse smooth dural (pachymeningeal) enhancement (arrowheads) and bilateral subdural fluid collection (arrows). Used with permission of Mayo Foundation for Medical Education and Research. All rights reserved.

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Section 4

Treatment of a suspected spinal leak based on clinical presentation or MRI findings is highly variable. Conservative approaches include bed rest, hydration, increased caffeine intake, and use of an abdominal binder. Furthermore, cases of SIH may resolve spontaneously without any specific therapy. While purely conservative approaches may be effective for some, many patients are debilitated from this condition and additional treatment may be considered. The effectiveness of steroids, IV caffeine, and theophylline is limited.[6] The most commonly employed treatment involves an epidural blood patch (EBP). EBPs can be blind or targeted at suspicious areas of interest and a fibrin sealant may be considered if the site of leak is known. In a retrospective review of 25 patients treated with EBP, 9 patients (36%) responded well to the first patch, 5 patients (33%) became asymptomatic after the second patch, and of 8 patients who received 3 or more EBP (mean 4), 4 patients (50%) responded well.[8] Intrathecal saline or artificial CSF may provide temporizing relief until a leak can be permanently repaired in more severe cases. Surgical treatment is indicated in patients in whom nonsurgical measures have failed and an accurate CSF leak location has been established.[4]

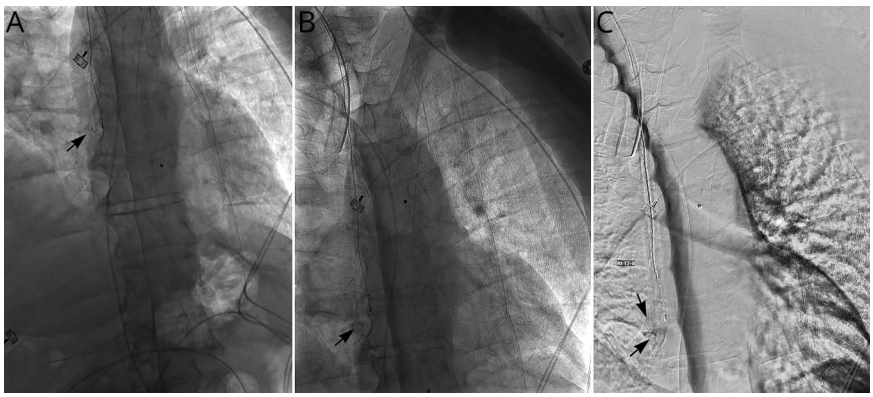
In cases of diagnostic uncertainty, when there is clinical suspicion of CSF leak but no convincing evidence on MRI, radionuclide cisternogram may be considered to identify presence of a leak, although it will not usually identify the site of leak. In this procedure, intrathecal radioisotope is injected via lumbar puncture and its dynamics are followed by sequential scanning at various intervals up to 48 hours. Cisternography findings in SIH include early accumulation of tracer in the kidneys and bladder, slow ascent of tracer along the spine, and paucity of activity over the cerebral convexities.[4]

Our patient underwent a L1/L2 EBP and was headache-free for 24 hours. When headaches returned, they were reduced in severity and the duration of the Valsalva-induced headaches was shorter. A second L1/L2 EBP and third bi-level T10/T11 and L4/L5 EBP produced no noticeable benefit. Amitriptyline provided only mild improvement in the severity of Valsalva-induced headaches. A cisternogram was obtained and revealed incomplete distribution or flat top appearance over the convexities. MRI brain with and without contrast showed similar mild brain sag and mild pachymeningeal enhancement, though it was unclear if this was related to the lumbar puncture at the time of cisternogram. Our patient's headaches spontaneously worsened 4 months later and repeat MRI brain with and without contrast revealed increased pachymeningeal enhancement and prominence of brain sagging.

When SIH is suspected from clinical history and brain neuroimaging findings, and conservative measures (e.g., EBPs) fail, the next step is identifying the site of leak. MRI of the spine is routinely utilized and may identify dilated epidural or intradural veins, dural enhancement, meningeal diverticula, extrathecal CSF collections, syringomyelia, and retrospinal C1/2 fluid collections, but only occasionally identifies leak location.[4] CT myelography is the diagnostic study of choice for identifying the location and extent of a CSF leak.[9] However, in 46%–55% of patients with SIH, a site of leak is not identified on myelography.[5] In such cases, digital subtraction myelography may be helpful in identifying evasive leaks.

In our patient, CT myelogram failed to identify a site of leak but showed prominent paravertebral veins at T3-4/T4-5. Targeted patching with fibrin glue did not provide improvement. Digital subtraction myelography was then pursued, revealing prominent leakage of contrast into the right paraspinal region in the region of T7-8, indicating the presence of a slowly flowing CSF-venous fistula (figure 2). He underwent surgical ligation of the right T7/T8 nerve root with complete resolution of headaches immediately after the procedure and remained headache-free on 6-month follow-up.

Figure 2 Digital subtraction myelogram (DSM) of our patient



DSM is a dynamic form of imaging that employs intrathecal injection of contrast under fluoroscopy with the ability to subtract a precontrast image to enhance the view of the contrast. DSM may be helpful for rapid leaks, ventral spinal leaks, and slow-flow leaks (as in the case of CSF venous fistula).[11] Our patient's DSM (A–C) shows prominent leakage of contrast into the right paraspinal T7-T8 region (arrows), indicating the presence of a slowly flowing subtle CSF-venous fistula. Used with permission of Mayo Foundation for Medical Education and Research. All rights reserved.

Discussion

SIH is an important cause of new daily and persistent headache that remains an elusive diagnosis even among experienced neurologists given the varied presenting clinical and radiographic manifestations, often leading to misdiagnoses including migraine, tension type headache, medication overuse, or malingering. This patient's case highlights the importance of recognition and awareness of SIH secondary to CSF-venous fistula as often these may not be evident on more commonly utilized neuroimaging modalities, including CT myelogram. There is some evidence that the presence of a hyperdense paraspinal vein on CT myelogram may provide a diagnostic clue to this entity.[5] CSF-venous fistulas appear relatively unresponsive to EBP, further emphasizing the importance of a correct diagnosis as in our experience they are exquisitely amenable to surgical interventions including sacrificing a nonappendicular nerve root or venous communication obliteration.[10,12] Such treatments may provide complete pain relief for patients whose pain was otherwise intractable.

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Jaclyn R. Duvall, MD	Mayo Clinic, Rochester, MN	Author	Data collection and analysis, drafting and revision of manuscript, involved in clinical care of the patient
Carrie E. Robertson, MD	Mayo Clinic, Rochester, MN	Author	Revision of manuscript for intellectual content
Mark A. Whealy, MD	Mayo Clinic, Rochester, MN	Author	Revision of manuscript for intellectual content, involved in clinical care of the patient
Ivan Garza, MD	Mayo Clinic, Rochester, MN	Author	Revision of manuscript for intellectual content, involved in clinical care of the patient

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