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Single Case – Headache

A Possible Newly Defined and Treatable Secondary Cause of Early Morning Wake-Up Headaches in an Older Hypermobile Woman: Nutcracker Physiology with Spinal Epidural Venous Congestion

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Keywords
Morning headache · Nutcracker physiology · Left renal vein compression · Spinal epidural venous congestion · Hypermobile Ehlers-Danlos syndrome

Abstract
Introduction: Left renal vein compression (nutcracker physiology) with secondary spinal epidural venous congestion is a newly recognized cause of daily persistent headache. Presently, only women with underlying symptomatic hypermobility issues appear to develop headache from this anatomic issue. The hypothesized etiology is an abnormal reset of the patient's cerebrospinal fluid (CSF) pressure to an elevated state. Headaches that occur during sleep can have a varied differential diagnosis, one of which is elevated CSF pressure. We present the case of an older woman who began to develop severe wake-up headaches at midnight. She was found to have left renal vein compression and spinal epidural venous congestion on imaging. After treatment with lumbar vein coil embolization, which alleviated the spinal cord venous congestion, her headaches alleviated. ***Case Report:*** A 61-year-old woman with a history of hypermobile Ehlers-Danlos syndrome began to be awakened with severe head pain at midnight at least several times per week. The headache was a holocranial, pressure sensation, which worsened in the supine position. The headaches were mostly eliminated with acetazolamide. Because of her hypermobility issues and pressure-like headache, she was investigated for

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underlying nutcracker physiology and spinal epidural venous congestion. This was confirmed using magnetic resonance (MR) angiography and conventional venography, and after lumbar vein coil embolization her wake-up headaches ceased. ***Conclusion:*** The case report suggests a possible new underlying and treatable cause for early morning, wake-up headaches: nutcracker physiology with secondary spinal epidural venous congestion. The case expands on the clinical headache presentation of nutcracker physiology.

Introduction

Sleep-associated wake-up headaches can be very alarming to a patient. There are some primary headache disorders that are typified by awakening from sleep including cluster and hypnic headaches, but as these are rare headache syndromes, evaluating for an underlying secondary etiology is suggested [1]. In many instances, however, neuroimaging and laboratory tests fail to define an underlying cause. An elevation of cerebrospinal fluid (CSF) pressure/volume is one important etiology of wake-up headaches [2]. The authors have recently defined a new secondary cause of elevated CSF pressure leading to a daily persistent headache from onset, which is left renal vein (LRV) compression or nutcracker physiology (NP) with retrograde flow through the left second lumbar vein (L2LV) resulting in regional spinal epidural venous plexus (EVP) congestion [3]. We hypothesized that the spinal cord EVP led to a secondary congestion of the cerebral venous system, which then caused an elevation of CSF pressure above the individual's "head pain triggering CSF pressure set point" leading to a daily headache from onset (shown in Fig. 1) [3, 4]. We have also recently shown that coil embolization of the L2LV in these patients not only abolishes the spinal EVP congestion but leads to either complete alleviation or substantial improvement of the underlying headaches [5]. Thus far, a daily persistent headache from onset is the only headache clinical phenotype that has been noted to occur in patients with NP and spinal EVP [3, 5, 6]. In addition, the syndrome appears to only arise in women and is preferential to those with underlying hypermobility syndromes such as Ehlers-Danlos syndromes (EDSs) including hypermobile EDS (hEDS) and hypermobility spectrum disorder (HSD) [3, 5].

The authors have also defined a unique population of older women who began to develop daily headaches out of the blue with the initial headache awakening them from sleep with no definable secondary cause being noted on neuroimaging [7]. As they all responded to CSF pressure/volume lowering medications, a presumed abnormal reset of CSF pressure to an elevated state was hypothesized to be the underlying etiology, but the cause of this abnormal reset was never defined.

We now present a case of an older woman with early morning wake-up headaches who was found to have NP and spinal EVP on imaging and whose headaches have been alleviated with lumbar vein coil embolization. Our findings help to define a possible new secondary cause of wake-up headaches and expand on the clinical presentation of headache associated with LRV compression with spinal EVP.

Methods: Case Report

A 61-year-old woman with a history of hEDS presented with a 4-week complaint of new-onset early morning wake-up headaches. She was well known to our practice as we had been treating her for the past 3 years for chronic migraine with onabotulinumtoxin A. Her baseline

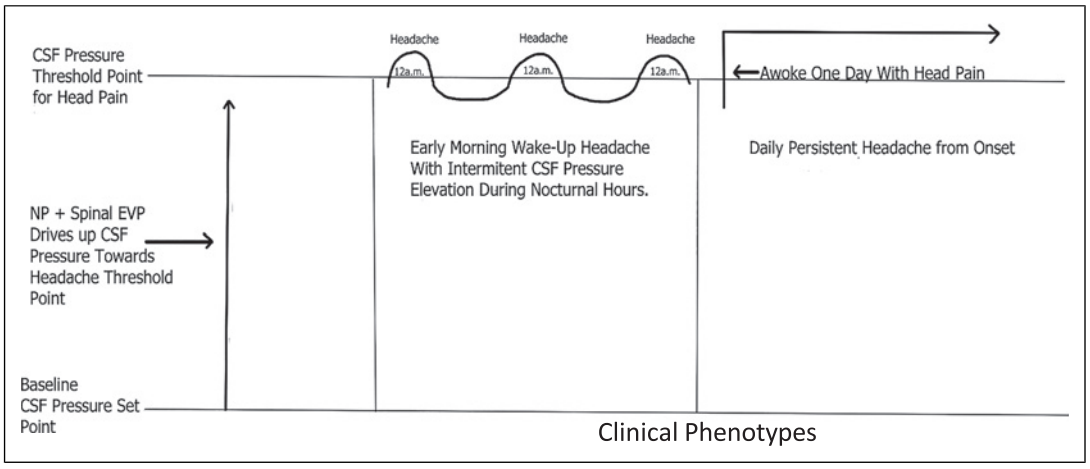

Fig. 1. Clinical headache presentation of NP with spinal epidural venous congestion. NP, nutcracker physiology (LRV compression); EVP, epidural venous plexus congestion; CSF, cerebrospinal fluid.

headaches were very well controlled with this treatment. She began with migraines in her 20s and had evolved into chronic migraine by her 40s. She was diagnosed with hEDS at an academic hypermobility specialty clinic utilizing the 2017 International Classification of the Ehlers-Danlos Syndromes criteria.

Suddenly during the spring season, she started to awaken around 12:00 a.m. with severe holocranial head pressure, 10/10 on the visual analog scale. These headaches lacked any associated symptoms including vertigo, dizziness, and tinnitus. They were completely unlike her migraine headaches. She had never experienced nocturnal-based head pain prior to this occurrence. She denied any triggering event for the new sleep-associated headaches such as travel, excessive Valsalva maneuvers, change in medication, or a viral illness. She did not snore and was never observed to have apnea spells. She had been underweight most of her life. From the outset, she would have early morning headaches 2–3× per week. She could not predict the nights that they would occur as she went to sleep those evenings without head pain or pressure. She typically went to bed about 10:30–11:00 pm and the headache would initiate 60–90 min post-sleep. She slept on one pillow and had not changed this routine. What was very evident was the positionality of the pain. If she remained in bed, the pain would continue to worsen, but if she got up from the supine position and either walked around or sat upright the pain would eventually dissipate, sometimes taking several hours to do so. Having her head hang off the bed or just trying to lie back down would exacerbate the head pressure. Sometimes she would take over-the-counter medications or a triptan or a ketorolac which she had as a rescue medication for her migraines, but they did not relieve her symptoms. Eventually she began to sleep upright in a lounge chair to prevent the headaches from occurring, which worked on most occasions.

Her neurologic examination was normal and there was no evidence of papilledema on fundoscopic examination, which was verified by ophthalmology. Her BMI was 15.7. She demonstrated cervical and systemic hypermobility consistent with her diagnosis of hEDS. She underwent neuroimaging to rule out secondary pathology including MRI brain with and without gadolinium, MR angiography of the intra- and extracranial blood vessels as well as an MR venogram and all these studies were negative. As the headaches awoke her from sleep and worsened laying down, the possibility of elevated CSF pressure as the underlying cause was suggested, with a less likely paradoxical presentation of intracranial hypotension especially with no imaging findings to suggest this diagnosis [2]. She also checked her blood pressure

during attacks and there was no evidence of nocturnal hypertension. It was also feasible this was an atypical presentation of hypnic headache. She was started on indomethacin 75 mg sustained release at bedtime, and this helped reduce the frequency for a short period of time but did not completely abolish the headaches and eventually the headaches broke through this dose. The dose could not be increased as she developed gastrointestinal intolerance, so indomethacin was stopped. Acetazolamide was then prescribed, initially a low dose of 125 mg at bed with an increase every 5 days if headaches continued. Eventually on 500 mg extended release at bedtime, her headaches basically ceased. In addition, she purchased an adjustable bed and kept her head elevated while sleeping, which also seemed to improve her symptoms. She had some side effects from acetazolamide (paresthesias, shortness of breath), but she wanted to remain on the medication as the wake-up headaches were very disabling. She would try to taper off at least several times per year but always with headache recurrence.

About 2.5 years into this new headache syndrome, our group had become interested in the role of NP and spinal EVP in hypermobile women with daily persistent pressure-like headaches. Our case patient did not have persistent head pain, but she was very reminiscent of our other patients. Thus, we decided to evaluate her for LRV compression and possible spinal EVP congestion with a novel time resolved abdominal MRI [4]. This study demonstrated moderate compression of the LRV by the aorta and superior mesenteric artery (shown in Fig. 2a) with retrograde flow through the L2LV and opacification of the spinal EVP suggesting congestion (shown in Fig. 2b–d). Eventually 4 years after the onset of her early morning headaches, the patient underwent conventional venography that confirmed NP with spinal EVP congestion (shown in Fig. 2e). The L2LV was then coil embolized and a follow-up venogram from the LRV demonstrated no further flow into the L2LV or the EVP (shown in Fig. 2f). Prior to the venogram, the patient gave consent for the coil embolization procedure. On the morning after the embolization, she awoke completely head pressure free. What she then recognized was that at some point maybe 1–2 years after the onset of her early morning wake-up headaches she had probably transitioned into having a persistent low-grade head pressure sensation all the time and that she could only recognize that now because the sensation was completely gone after the procedure. During the next month, she slowly tapered off acetazolamide experiencing days of complete pain freedom, while on other days she experienced some headaches reflecting high CSF pressure, and on other days the symptoms of intracranial hypotension (better supine and worse upright). She was alerted that this CSF pressure adjustment phase had been observed in other patients after lumbar vein coil embolization [5]. She is now 7 months post-coil embolization and 6 months off acetazolamide and her headaches (wake-up and persistent head pressure) are completely gone. Her migraines remain well controlled on onabotulinumtoxinA. She had no procedure-related side effects. Physically, she recovered within 48 h post-procedure. She was very happy with the response and reported it as “life changing.” Of note, she had been offered coil embolization 1 year prior, but she wanted to see how our other patients did with the procedure before undergoing it herself. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000537705).

Discussion

We present a possible newly defined secondary cause of early morning wake-up headache, which is NP with spinal EVP. We presume this was the underlying etiology of our patient’s sleep-associated headaches as they completely alleviated after lumbar vein coil embolization, which stopped the spinal cord venous congestion from occurring.

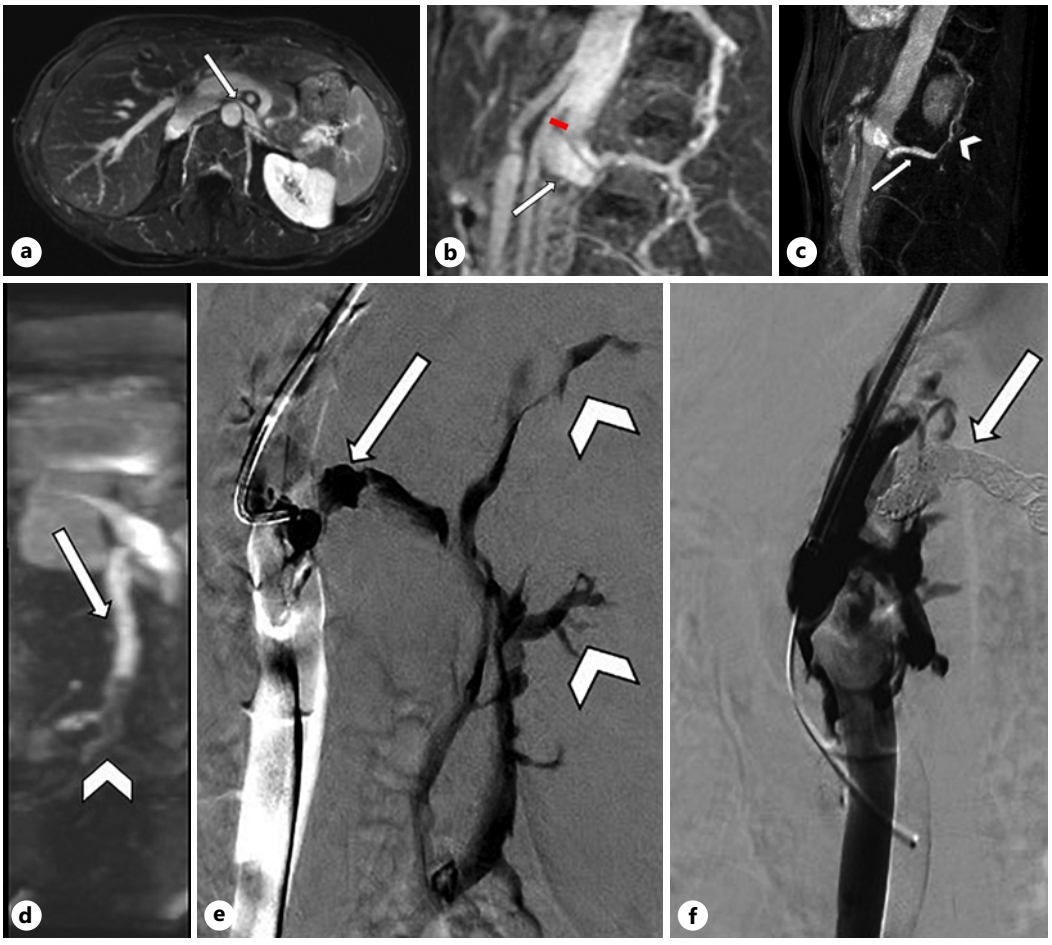

Fig. 2. a Time-resolved contrast-enhanced axial magnetic resonance angiography (MRA) demonstrates a beak sign (arrow) secondary to severe LRV narrowing between the aorta and superior mesenteric artery. **b** Time-resolved contrast-enhanced sagittal MRA demonstrates retrograde flow through the LRV (arrow) and a decreased aortomesenteric distance (red line). **c** Time-resolved contrast-enhanced sagittal MRA demonstrates an enlarged L2LV (arrow) and a congested spinal EVP (arrowhead). **d** Axial reformat of the dynamic time-resolved MRA demonstrates retrograde flow through the enlarged L2LV (arrow) with enhancement and congestion of the spinal EVP (arrowhead). **e** Left second lumbar venogram demonstrates retrograde flow through the L2LV (arrow) with congestion of the spinal EVP (arrowheads). **f** Left renal venogram post-embolization demonstrates complete coil occlusion of the L2LV (arrow) with no further flow into the spinal EVP.

Wake-up headache has a differential diagnosis that can vary by the timing of when the pain awakens the individual from sleep. Cluster headache has a peak wake-up time of 2:00 am, which has been consistently reported by studies across different continents [8]. Cluster headache is easily recognized by its short headache duration, severe intensity, multiple attacks per day, and cranial autonomic associated symptoms with agitation. Hypnic or alarm clock headache appears to have a varied peak time incidence from 12:00 a.m. to 4:00 a.m., although the actual true timing of attacks in population studies is not well documented [9]. A recent meta-analysis noted that hypnic headache has an average age of onset of around 60 years with a small female predominance and is typified by bilateral head pain of moderate to severe intensity with a pressing quality and a duration of about 2 h [9]. It is conceivable that some hypnic-like headaches are secondary to abdominal venous congestion syndromes,

especially if they have a positional component. Thus, evaluation for NP should be considered in treatment refractory or atypical cases.

Awakening in the morning at the patient's typical arousal time with a headache also has a noted differential diagnosis including cervicogenic etiologies (arthritic/facet issues), a consequence of obstructive sleep apnea, nocturnal hypertension, or may be part of a primary chronic daily headache chronification process such as in chronic migraine or medication overuse headache [10]. Elevated CSF pressure should be considered in the differential diagnosis of any headache that occurs during sleep [2]. Studies have suggested that intracranial pressure rises during night hours in both animals and humans [11]. A recent investigation demonstrated a 30% increase in ICP in humans at night and this was deemed to be caused by an increase in CSF secretion [11]. Thus, as intracranial pressure rises during evening hours one could infer that a patient who awakens early in the sleep cycle with a severe headache must have a CSF pressure at baseline very close to their "headache pain threshold point" and that threshold is quickly surpassed when CSF pressure/volume rises during sleep (shown in Fig. 1). On the other hand, those who develop a headache only upon arising at their normal wake time are further from the "CSF pressure headache threshold point" at baseline, and thus it takes longer to reach the pain threshold during nocturnal hours. Certainly, the position of the patient's body during sleep (no pillows vs. head elevation with pillows and prone vs. supine) will also affect timing of headache onset as being completely supine, which alters cerebral venous outflow, and/or prone, which increases abdominal pressure and secondarily ICP, will both potentially cause a quicker rise in CSF pressure during sleep than in someone who elevates their head on multiple pillows, for example [12, 13].

All patients with new-onset wake-up headaches need neuroimaging to rule out potential secondary underlying causes that could lead to CSF pressure/volume elevation such as a large or obstructive tumor, colloid cyst, or cerebral vein thrombosis [2]. One should also evaluate for idiopathic intracranial hypertension based on patient BMI and fundoscopic exam. Our patient had normal neuroimaging, a low BMI, and normal ophthalmologic evaluation; thus, no overt neurologic secondary cause could be identified. A sleep study was considered but not completed because of her low BMI and lack of any witnessed snoring or apnea spells. A lumbar puncture was also considered but not completed because of patient preference and because the prior patients we studied with NP and spinal EVP never showed elevated CSF opening pressures [3, 5].

As stated previously, our group has recently documented on a special population of hypermobile women with new-onset daily persistent headaches with underlying NP and spinal EVP and that treating these patients with lumbar vein coil embolization, which abolishes the spinal EVP congestion, greatly improves or resolves their underlying headaches [5]. Lumbar vein coil embolization is a minimally invasive outpatient procedure unlike the standard surgical treatments for NP including renal auto-transplant and renal vein transposition, which can carry significant morbidity [5]. These patients were deemed hypermobile by physical therapists specializing in this condition and were given a diagnosis of hEDS or HSD at an academic hypermobility clinic utilizing specific EDS criteria. As our current case patient had hEDS, we evaluated her for NP theorizing that unlike our daily persistent headache patients who we surmised had a persistent abnormal reset of their CSF pressure above their pain threshold point, she only episodically went above the pain threshold during sleep hours and once she positioned herself upright her CSF pressure fell below the pain threshold level and her headaches alleviated (shown in Fig. 1). Eventually, pretreating with CSF volume-lowering medications prevented the nocturnal rise in ICP and protected her from the wake-up headaches. Lumbar vein coil embolization then alleviated the headaches without the need of medication.

Before the acknowledgment of NP as a possible secondary cause of headache, the authors had published a study on a group of older women (average age 57 years) who began to develop a daily persistent headache out of the blue with their first headache occurring upon awakening from sleep and being at its peak intensity first thing in the morning before arising [7]. One patient also had distinct early morning wake-up headaches. All the patients did well on CSF volume-lowering medications suggesting that they had an abnormal reset of their CSF pressure to an elevated state. As their neuroimaging and testing was negative, no underlying secondary etiology was identified. The patients were grateful that medication helped them but frustrated that when they tried to taper off the medication that the headaches would recur, and many had significant side effects; thus, quality of life was diminished. With our current case patient, it can be surmised that at least several if not more of these patients, many of whom have been lost to follow-up, may have had underlying NP with spinal EVP that would have been greatly helped by lumbar vein coil embolization.

Our overall prior findings as well as the findings of this current case report suggest that looking for NP with spinal EVP should be part of the evaluation of female patients who present with a daily persistent headache from onset or with sleep-associated headaches and have symptoms suggesting elevated CSF pressure and who have no other secondary causes noted on neuroimaging. As abdominal venous compression disorders like nutcracker syndrome appear to occur more commonly in patients with symptomatic hypermobility disorders like hEDS and HSD, further research should be conducted in this group of patients who frequently suffer from headache and migraine [14, 15].

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Statement of Ethics

This was approved by the Mayo Clinic Institutional Review Board (IRB number: 19-002635). Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors declare that there are no conflicts of interest.

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Author Contributions

T.D.R., Z.D., B.D., D.F., and K.B.: conceptualization, formal analysis, investigation, methodology, writing – original draft, and writing – review and editing.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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