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Nutcracker phenomenon with a daily persistent headache as the primary symptom: Case series and a proposed pathogenesis model based on a novel MRI technique to evaluate for spinal epidural venous congestion

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ABSTRACT

Objective: To determine if a specific population of patients with a daily persistent headache from onset have underlying nutcracker physiology and to propose a pathogenesis model for their headaches utilizing a novel MRI protocol.

Background: A single case report of a daily persistent headache associated with nutcracker syndrome was recently published. As the left renal vein has a connection to the spinal lumbar veins and secondarily to the spinal epidural venous plexus, one could hypothesize that renal vein compression could lead to persistent headache by altering spinal and cerebral venous pressure with secondary alterations in CSF pressure. The authors have published on a series of patients with a unique subtype of daily persistent headache from onset that appears to be caused by an abnormal reset of CSF pressure to an elevated state. The goal of the present study was to look for the presence of nutcracker physiology in this unique patient subgroup and to propose a pathogenesis model utilizing a novel MRI protocol to evaluate for retrograde lumbar vein flow and regional spinal epidural venous plexus congestion.

Materials and methods: Case series of patients with a daily persistent headache from onset, head pressure, and whose headaches worsened in the Trendelenburg position. Patients were imaged with a 3 T MRI in the supine position from the lower diaphragm to the top of the pelvis with a dynamic angiogram centered over the left L2 lumbar vein.

Results: 12 patients were studied of which 8 were positive for left renal vein compression, lumbar vein dilation and early spinal epidural venous plexus enhancement. All were women. Mean age of headache onset was 39 years. Six of the 8 patients had a lumbar puncture, and all had a normal opening pressure. All improved with CSF volume removal although pain resolution lasted from hours to 6 months. The patient's headaches were marked by holocranial pressure and the majority displayed migrainous associated symptoms although none had a prior headache history. They did not complain of typical symptoms or signs of nutcracker syndrome.

Conclusion: We suggest that patients with a daily persistent headache from onset who worsen in the Trendelenburg position may have underlying nutcracker physiology. From our imaging findings, it can be hypothesized that left renal vein compression leads to retrograde flow through the valveless lumbar vein which then leads to spinal epidural venous congestion and subsequently causes congestion of the cerebral venous system leading to an elevation of CSF pressure and to a daily headache. What appears to be unique about these patients is that a daily headache is their only manifestation of nutcracker physiology.

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1. Introduction

Recently, a single case report of a daily persistent headache associated with nutcracker syndrome (NCS) was published, in which the patient had alleviation of her treatment refractory headache after a kidney auto transplant [1]. NCS is a range of clinical symptoms and signs including micro or macroscopic hematuria, flank pain, pelvic congestion/varicocele, proteinuria and hypertension that result from the compression of the left renal vein (LRV) between the aorta and superior mesenteric artery (SMA) [2]. Nutcracker phenomenon (NP) is defined as nutcracker anatomy and physiology without classic nutcracker clinical symptoms. Treatment options for NCS include conservative "watchful waiting", endovascular stenting, and surgical options such as left renal vein bypass or auto transplant of the kidney In 2007, Scholbach hypothesized about a midline congestion syndrome evolving from left renal vein compression as a possible cause of headache and other somatic complaints in NCS [3]. Thus, could left renal vein compression (LRVC) be the etiology of a daily persistent headache in some NP/NCS patients and if so, what is the mechanism of headache induction? As the LRV has a connection to the spinal lumbar veins and secondarily to the spinal epidural venous plexus (EVP), it is possible that LRVC could lead to persistent headache by altering spinal and cerebral venous pressure with secondary alterations in CSF pressure (high and possibly low) [4].

The authors have already published on a series of patients with a unique subtype of daily persistent headache that appears to be caused by an abnormal reset of CSF pressure/volume to an elevated state [5,6]. These patients present with a daily headache from onset, which worsens immediately in the Trendelenburg position. Head-down tilt rapidly increases intracranial pressure [7,8]. For this subgroup, it is not an extreme alteration of CSF pressure/volume that is proposed to cause their headaches but a reset just above that individual's CSF pressure set point; but at a threshold that produces head pain. The underlying etiology for the abnormal CSF pressure reset is presently unknown. The authors' have suggested that a "tight or crowded posterior fossa" may contribute by intermittently obstructing CSF flow at the skull base [5]. This neuroanatomic issue is probably not the sole etiology however as many individuals have cerebellar ectopia without head pain.

The recent case report linking NCS to a daily persistent headache from onset and the past work by Scholbach suggested to the authors that our patients with an abnormal CSF pressure reset may indeed have nutcracker physiology (LRVC) as the underlying cause of their symptoms [1,3]. Thus, the goal of the present study was to look for the presence of LRVC in this unique patient population and then to propose a pathogenesis model by utilizing a novel magnetic resonance imaging (MRI) protocol to evaluate for retrograde lumbar vein flow and spinal regional epidural venous plexus enhancement/congestion.

2. Materials and methods

2.1. Case series

Patients with a unique subtype of daily persistent headache that appeared to be caused by an abnormal reset of CSF pressure/volume to an elevated state were studied. The eligible patients for the case series were evaluated by a headache neurologist at an academic headache center from 9/2019 to 4/2021. Each patient presented for headache consultation with a complaint of intractable daily headache. It was at the initial consultation that a diagnosis of a daily persistent headache from onset/new daily persistent headache (NDPH) was made. No patients were actively recruited for the study.

The following inclusion criteria were then used for diagnosing the abnormal reset of CSF pressure/volume subtype:

1. Daily headache from onset lasting >3 month thus meeting the International Classification of Headache Disorders-3 (ICHD-3) criteria for NDPH [9]
2. Headache described as a pressure sensation
3. Baseline daily head pain immediately worsened in the Trendelenburg position (10-15^{o} head down tilt using a mechanized table)
4. MRI brain and MR venogram were negative for space occupying lesions, Chiari malformation and/or cerebral vein thrombosis.
5. Patients responded to either CSF pressure/volume lowering medication (acetazolamide, spironolactone and/or indomethacin sustained release) or CSF volume removal via lumbar puncture (LP) with recurrence of daily headache either after tapering off the medication and/or after a certain time period post LP. This specific inclusion criteria was satisfied only after the patient was treated at the academic headache clinic.

The following exclusion criteria were used:

1. Patients with disc edema on fundoscopic examination, as that would suggest a diagnosis of idiopathic intracranial hypertension (IIH).
2. Individuals under 18 years of age as this was an adult headache study.

2.2. Imaging protocol

We utilized a novel contrast-enhanced magnetic resonance imaging (CE-MRI) protocol. Imaging was performed on 3 T Siemens Magnetom Skyra and Magnetom Vida systems (Siemens Medical Systems, Erlangen, Germany) with the patient in the supine position and from the lower diaphragm through the top of the pelvis using T1 (pre and post-contrast), T2, and a dynamic MRA sequence in the sagittal plane centered over the left L2 lumbar vein (LV) which focused on imaging blood flow around the spinal canal. MRI sequences were noted for LRV compression, superior mesenteric artery (SMA) angle, aortomesenteric distance, retrograde lumbar vein flow, and spinal EVP enhancement. Retrograde flow through the lumbar vein and EVP enhancement was evaluated with dynamic contrast-enhanced MRI throughout the arterial, venous, and delayed phases. Patients with evidence of early retrograde LV flow and EVP enhancement were considered positive for spinal epidural venous congestion (Figs. 1,2). The complete imaging protocol will be presented elsewhere. Of note doppler ultrasound (US) of the left renal vein is first line imaging for patients with suspected LRVC; however, US has several limitations including limited ability to visualize collateral veins and retrograde flow in the lumbar vein with inability to image the spinal EVP.

2.3. Statistical analysis

This was primarily a descriptive study; however, when statistical analysis was utilized to establish *p* values, the Chi-Square Test was used for calculating the *p*-value for the Beak Sign (see below) while the Independent *t*-test was used to calculate the p-value for the remainder of the variables including aortomesenteric distance and SMA angle.

Standard Protocol Approvals, Registrations, and Patient Consents.

The study was approved by the Mayo Clinic Florida Institutional Review Board (IRB# 20–006503). Informed consent was obtained from all participants in the study.

3. Results

We evaluated 12 patients of which 8 were positive for left renal vein compression, retrograde lumbar vein flow, and early spinal epidural venous plexus enhancement/congestion. (Table 1) All of the positive patients were women. Mean and median age of headache onset was 39 years (range of 14 to 55 years). Mean average duration of daily headache before diagnosis of nutcracker physiology was 3.5 years (range of 1.5 to 6 years). Mean average BMI was 26 (median: 24; range: 20 to 36). Two of the 8 positive patients were considered obese. No patient had a prior headache history. Headache location was holocranial in all and each

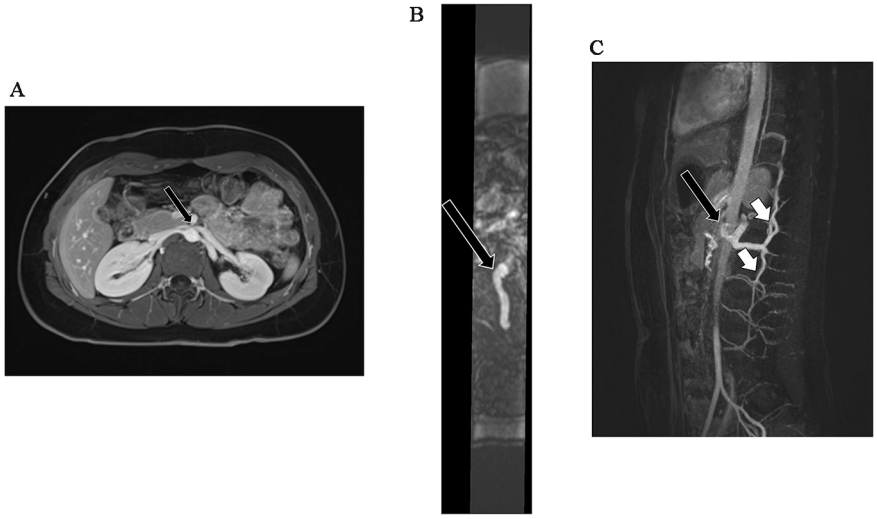

Fig. 1. 18-year-old woman with a 3-year history of a daily persistent headache from onset, worse in the Trendelenburg position, no response to CSF volume lowering medications, but improved with CSF volume removal with lumbar puncture A. Contrast-enhanced MRI Axial image demonstrates left renal vein compression between the aorta and superior mesenteric artery (black arrow). B. Reformatted axial image from time-resolved contrast-enhanced sagittal MR angiogram showing retrograde flow through a dilated lumbar vein (black arrow). C. Time-resolved contrast enhanced sagittal MR angiogram noting retrograde flow through the left renal vein (black arrow), dilated lumbar vein and early opacification of the spinal epidural venous plexus (white arrowheads).

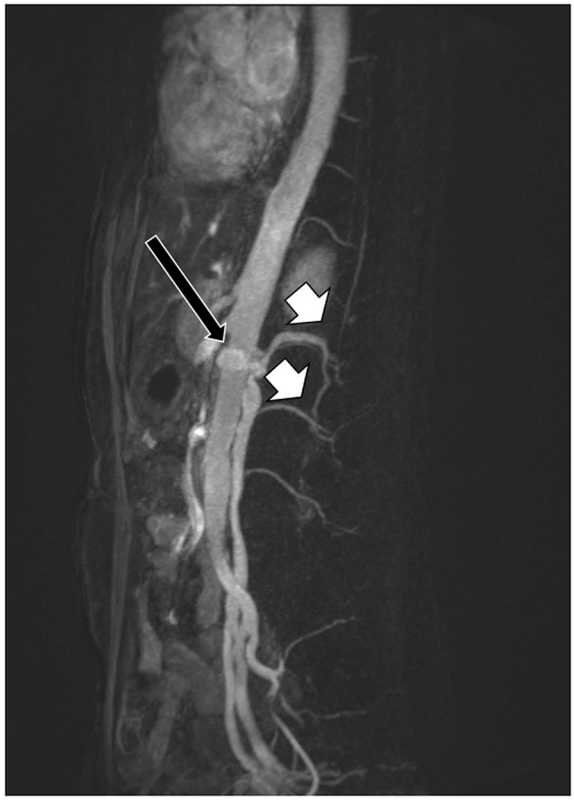

Fig. 2. 51-year-old woman with a 6-year history of a daily persistent headache from onset, worse in the Trendelenburg position, no response to CSF volume lowering medications.
Time-resolved contrast enhanced sagittal MR angiogram noting retrograde flow through the left renal vein (black arrow), dilated lumbar vein and early opacification of the spinal epidural venous plexus (white arrowheads).

stated the quality of the headache was pressure like. Migrainous associated symptoms including nausea and/or vomiting, photophobia or phonophobia were noted in 6 of 8 patients. Six of the 8 positive patients had a LP with a recorded opening pressure, and all were within the published norms of 10-25 cm H2O with a range of 17–21 cm H2O, a mean of 18.7 cm H2O and a median of 17.5 cm H2O. All the patients improved with CSF volume removal although pain resolution lasted from only hours to 6 months. The LPs were completed under fluoroscopy and the headache neurologist was alerted of the opening pressure and headache intensity at the initiation of the LP. CSF was then withdrawn. Initially 5 cc was removed. After CSF volume removal a repeat CSF pressure measurement was taken, and the patient was asked what their headache pain intensity level was at that moment. If the patient had not yet achieved pain freedom, an additional 5 cc of CSF were subsequently removed, with the patient then being asked their pain intensity level and documenting the CSF opening pressure. The goal was to try and get patients to as close to pain freedom as possible, with a maximum of 20 cc of CSF volume being removed in 5 cc increments. If the CSF opening pressure fell more than 15 cm H2O the procedure was also halted. Patients with the most symptom relief after LP, with improvement of headaches for months, developed a severe post LP headache for 5–7 days, but these patients never received an epidural blood patch. Suggesting they reset to their normal CSF pressure set point after CSF volume removal. Those who chose to get an epidural blood patch, immediately resumed their daily headache after the post LP headache resolved. One patient did not have a LP as she was planning for pelvic congestion surgery secondary to her NCS, while another patient decided she was doing well enough on acetazolamide and wanted to avoid a procedure. Study subjects who had subsequent LPs demonstrated consistent benefit. All patients failed at least 3 preventive medications while the majority failed 5 or more. These typically were migraine preventives including anti-epileptics (all failed topiramate), antidepressants and blood pressure medications, which were not likely to help their headaches as they were not truly having migraine. No patient was in medication overuse with abortive medication. After initial consultation at the headache clinic and meeting inclusion criteria, patients were tried on CSF volume lowering medications including acetazolamide, indomethacin sustained release and spironolactone. No patient had complete resolution of their headaches on these medications. Only acetazolamide showed any significant response with 1/8 patients having a 75% reduction in headache frequency. A partial response to acetazolamide was noted in 2 patients. 50% of the patients did not respond to any CSF volume lowering medication. (Table 1) Two patients had contraindications to CSF volume lowering medications including kidney stones or renal insufficiency. Most of our patients are still dealing with refractory chronic daily headache. Importantly, daily headache was only clinical symptom for the majority our patients, thus they were lacking the typical manifestations of NCS [4].

3.1. Patients with and without EVP enhancement/congestion

Regarding the patients who had a daily persistent headache with a positive Trendelenburg test but no secondary EVP congestion, there was

Table 1
Clinical characteristics of chronic daily headache patients with nutcracker physiology.

Headache diagnosis	Age of CDH onset (years)	Gender	BMI	Hypermobile	Duration of daily headache at diagnosis of NP	Pain Quality	Migrainous associated symptoms	Trendelenburg response (worsen, neutral, improve headache)	Fundoscopic exam *saw neuro-ophthalmologist	Headache Response to CSF removal N/A-never had LP Opening Pressure (OP cm H20)	Response to CSF pressure/ volume lowering medications Acetazolamide (A) Indomethacin (I) Spironolactone (S)	Imaging ES-empty Sella CF crowded Posterior Fossa MRV-B/L Transverse sinus Stenosis (Y/ N)
NDPH with EVP Enhancement												
Patient 1	14	F	23	Yes	5 years	Pressure	No	Worse	No disc edema*	Improved 17	A, I, S-no response	CF N
Patient 2	51	F	22	Yes	6 years	Pressure	Yes	Worse	No disc edema	Neutral to mild improve 18	A, I, S -no response	CF N
Patient 3	27	F	29	Yes	3 years	Pressure	Yes	Worse	No disc edema*	Improved 17	A, I, S-no response	CF N
Patient 4	54	F	20	Yes	5 years	Pressure	No	Worse	No disc edema	Improved 21	A-transient I,S no response	ES,CF N
Patient 5	42	F	25	Yes	4 years	Pressure	Yes	Worse	No disc edema*	N/A	A partially effective	CF N
Patient 6	36	F	36	Yes	1.5 years	Pressure	Yes	Neutral to worse	No disc edema*	Improved 22	A partially effective I-poor toleration	ES,CF N
Patient 7	34	F	21	Yes	1.5 years	Pressure	Yes, also cranial autonomic	Worse	No disc edema	N/A	For NDPH +HCI- 100% effective but bleeding issues A,S-contraindicated	ES, CF N
Patient 8	55	F	30	Yes	3 years	Pressure	Yes	Worse	No disc edema	Improved 17	A helped	ES, CF N
NDPH without EVP Enhancement												
Patient 1	53	M	23	Yes	4 years	Pressure	Yes	Worse	No disc edema	Neutral to mild improve 18	A, I-no response Onabotulinum toxin A treatment effective 90%+	ES, CF N
Patient 2	32	F	31	Yes	1 year	Pressure	Yes	Worse	No disc edema	N/A	A-no response S-90% effective	CF N
Patient 3	46	F	31	Yes	1.5 years	Pressure	Yes	Worse	No disc edema	Improved 23	A-90-100% response	ES N
Patient 4	23	F	22	Yes	14 years	Pressure	Yes	Worse	No disc edema	N/A	A-no response Onabotulinum toxin A treatment effective 90%+	ES, CF N

one male and 3 females. (Table 1, Fig. 3) Two of the four had LRVC. The average BMI for this subgroup was 27. Interestingly, this group had a positive response to treatment with two having headache reduction and pain-free time with CSF volume lowering medications, while two having consistent pain free time with Onabotulinum toxin A treatment.

In regard, to anatomical differences noted on MRI, the spinal EVP enhancement positive patients demonstrated a greater percent decrease in renal vein diameter, decreased SMA angle, and decreased aortomesenteric distance compared to those without EVP congestion, although none of these findings were statistically significant. The beak sign (defined as the sudden narrowing of the left renal vein between the aorta and superior mesenteric aorta with proximal dilatation of the LRV) was 75% specific for identifying retrograde lumbar vein flow with regional EVP enhancement.

We have also tested our MRI protocol on three patients with IIH (all with an elevated BMI) as well as two overweight and two normal weight chronic migraine patients with pressure like headaches. All were negative for both nutcracker physiology and for spinal EVP congestion.

3.2. Case presentation

A representative case is presented.

A 56-year-old woman consulted for a persistent headache of two years duration. The headache started daily from onset. She had no prior headache history. The initial headache awoke her from sleep at about 2 am. There was no overt triggering event as she denied a flu like illness, stressful life event, travel and/or surgical procedure. She was on an estrogen patch for post-menopausal issues. Past medical history was significant for Raynaud's phenomenon and Hashimoto's thyroiditis which was diagnosed one year into her headache history. The headache was holocranial in location and described as a pressure sensation. It was at its lowest intensity at the time of awakening and would typically peak just before lunch time. She however could be awakened from sleep with severe pain. The baseline pain intensity was a 5/10 on a visual analog scale while peak intensity was 10/10 and this could last hours to days and be of varying frequency. She denied any migrainous or cranial autonomic associated symptoms. She had been given a diagnosis of chronic migraine. She failed multiple preventive treatments including topiramate (150 mg/day), valproic acid (1000 mg/day), amitriptyline (100 mg/day), nortriptyline (100 mg/day), duloxetine (90 mg/day) and amlodipine (5 mg/day which was also being used for her Raynaud's). Abortively, triptans and combination analgesics were of no benefit. She also had no response to occipital nerve blocks and sphenopalatine ganglion injections. Her evaluation included two MRI brain scans which were not available to look at but were read as normal. She was completely disabled by her head pain syndrome. Examination at consultation was non focal except she had both cervical and systemic hypermobility and she immediately worsened in the Trendelenburg position. The patient was diagnosed with a daily persistent headache from onset and as she had a pressure like headache and worsened in the Trendelenburg position, an abnormal CSF pressure reset to an elevated state was considered. A repeat MRI brain with and without gadolinium and MR venogram were ordered. The brain MRI was read as normal but on further inspection she appeared to have a crowded posterior fossa and a partial empty sella. The venogram noted a dominant right cerebral venous system with no stenosis, however the non-dominant left transverse sinus had a prominent arachnoid granulation which was felt to be an incidental finding as it involved the non-dominant transverse sinus. Acetazolamide was started and at a dose of 250 mg 3× per day she was 80% improved, however after several months this improvement waned even with an elevation of dose up to 500 mg extended release 2× per day. Thus, she was switched first to spironolactone without benefit and then indomethacin sustained release but never recaptured the initial improvement she had on acetazolamide. To try and quell her pain, a high volume suboccipital injection (9 cc of 1% lidocaine and 1 cc of triamcinolone 40 mg/ml) was completed and gave partial pain relief for 2 months but overall, her headaches were worsening. She would remark it felt as if her head was going to “blow off” from pressure. A lumbar puncture was then completed (15 months after the patient's initial consultation). The procedure was done in the prone position with an opening pressure of 21 cm H2O. A closing pressure of 11 cm H2O was documented after 20 cc of CSF volume was removed. Her initial headache was 7/10 in intensity and was 3/10 after the procedure. CSF analysis was normal. Within 24 h the patient developed an orthostatic headache but after 5 days of conservative therapy her baseline headaches basically ceased, and she did very well (pain free) for 4 weeks and had sustained improvement for about 5 months with the pressure headache slowly worsening over time. Acetazolamide was restarted up to 1500 mg per day without much benefit. A second LP was completed 6 months after the first LP, this time on acetazolamide 250 mg per day. Opening pressure of 14 cm H2O with a headache intensity of 10/10 which was decreased to 4/10 with removal of 10 cc of CSF volume and a closing pressure of 9 cm H2O. Once again, the patient developed a post procedure orthostatic headache for 4 days then her headaches did well again for about 2 months with eventual recurrence. She again had no response to an escalating dose of acetazolamide. Furosemide was then tried to lower CSF volume but without relief. Around this same time the daily persistent headache and NCS manuscript had been published and as the patient had a pressure-based headache, it was decided to study her for renal vein compression. Our specialized MRI protocol was

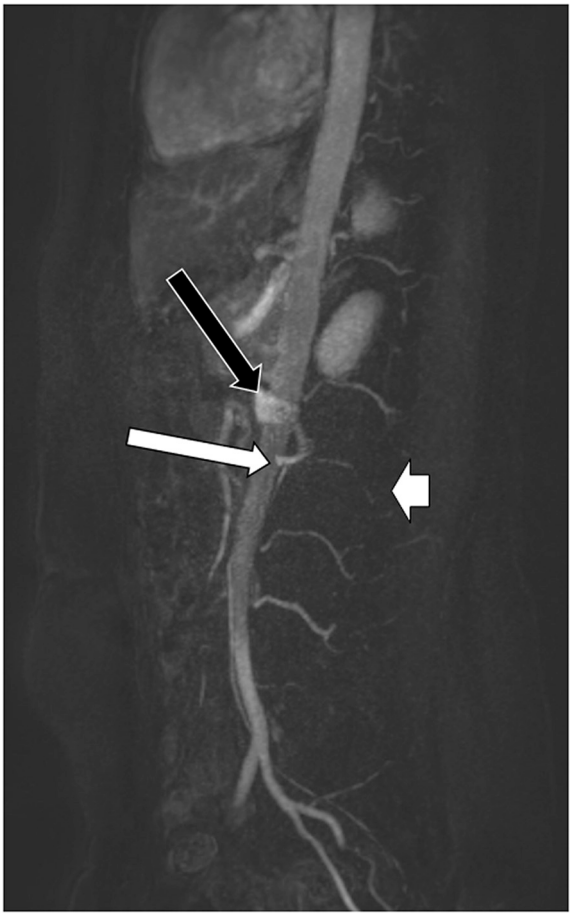

Fig. 3. 36-year-old woman with a 4-year history of a daily persistent headache from onset, worse in Trendelenburg position, possibly CSF pressure-based vs post-infectious subtype. Improved on CSF volume lowering medication.
Time-resolved contrast-enhanced sagittal MR angiogram showing renal vein (black arrow), a non-dilated lumbar vein (white arrow) and no early opacification of the spinal epidural venous plexus (white arrowhead). The lumbar vein circles downwards and empties into the inferior vena cava.

completed, and the patient showed a narrowing of the left renal vein by the SMA with associated retrograde flow into the lumbar plexus and opacification of the epidural venous plexus. Thus, the patient indeed had nutcracker physiology with spinal EVP congestion as a possible etiology for her headaches. Her crowded posterior fossa was felt to also be involved in her abnormal CSF pressure reset. It has now been one year since her imaging. Sadly, she remains with daily persistent pressure like headaches. As we are deciding how to safely treat these patients, we have started Onabotulinum toxin A treatment with moderate response. Patient is completely disabled by her pain syndrome.

4. Discussion

A venous congestion theory for headaches in NCS patients was first hypothesized by Scholbach in 2007 [3]. With our novel MRI technique we are now able to demonstrate spinal EVP congestion in patients with nutcracker physiology and a daily persistent headache. From these imaging findings, it can be hypothesized that LRVC leads to retrograde flow through the valveless lumbar vein which then leads to spinal epidural venous congestion and subsequently causes congestion of the cerebral venous system leading to an elevation of CSF pressure (just above someone's set point) and to a daily headache. The venous anatomy of the spinal cord and cerebral cortex allows us to make this hypothesis. The spinal EVP is valveless and capable of retrograde flow and secondary congestion. Part of spinal venous drainage is into the LRV via connections with the ascending lumbar vein system. The lumbar veins are connected to the spinal EVP while superiorly at the skull base the EVP forms connections with the dural venous sinuses (occipital and sigmoid) and inferior petrosal sinus, as well as the occipital and vertebral veins [10]. Thus, any obstruction leading to congestion of the ascending lumbar veins could reflux into the epidural venous plexus causing engorgement [3]. In addition, the vertebral venous plexus of the spine which includes the EVP not only drains the spinal cord and vertebrae but also accomplishes CSF reabsorption through arachnoid granulations in the spinal nerve roots [11]. This process may be disrupted by the EVP congestion and be another reason for increased CSF pressure in patients with nutcracker physiology. It appears that patients with the greatest percent decrease in renal vein diameter, SMA angle, and aortomesenteric distance are the most likely to develop spinal EVP congestion but this needs verification in a larger study population. Interestingly, our patients with LVRC and spinal epidural venous congestion did not readily respond to CSF pressure/volume lowering medications but those without spinal EVP congestion had a higher likelihood of a positive response. This could suggest that the spinal EVP congestion issue cannot be altered by a slow reduction of CSF volume with medication but can be transiently changed with an acute volume loss during a LP.

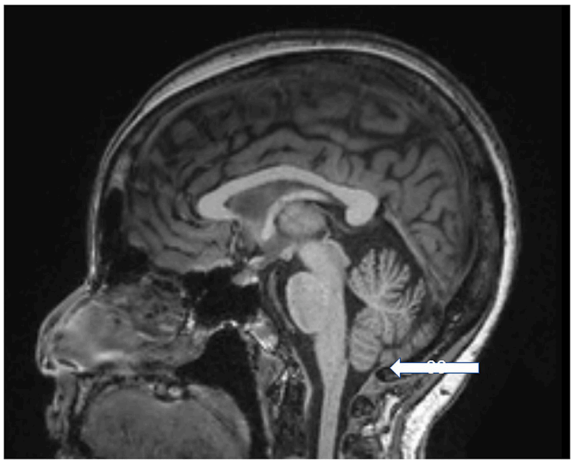

Fig. 4. Representative case of low-lying cerebellar tonsils/crowded posterior fossa (white arrow)

As the majority of our patients had a crowded posterior fossa on MRI (Fig. 4), this neuroanatomic issue may also be required along with spinal EVP congestion to produce an abnormal CSF pressure reset headache picture [5]. The presumed intermittent CSF obstruction that occurs in these patients secondary to their neuroanatomy most likely sets their CSF pressure on the higher side and then the nutcracker physiology reaches a critical threshold point where the renal vein is compressed enough that it causes retrograde flow through the lumbar vein leading to spinal EVP congestion, which then raises CSF pressure above the pain threshold point to cause a daily headache. A crowded posterior fossa has also been noted in patients with primary cough headache [12]. It has been proposed that temporary CSF obstruction set up by the neuroanatomy along with a valsalva maneuver such as a cough will raise CSF pressure/intracranial pressure high enough to cause head pain. Other possible risk factors for an abnormal reset high of CSF pressure would be bilateral transverse sinus stenosis (which was not present in any our patients) and an elevated BMI. (Table 1) Four of our 8 positive patients had a BMI of 25 and above so increased bodyweight may play a role in some. However, 50% of our patients were of normal weight. An elevated BMI is thus probably not a primary risk factor for developing daily persistent headache with nutcracker physiology. In our patients who were Trendelenburg positive but with no spinal EVP congestion, two were obese (both responding to CSF volume lowering medications), while two were of normal BMI (both responding to Onabotulinum toxin A). Of note, nutcracker phenomenon is typically noted in thin patients because they have loss of the fat pad around the SMA which then causes it to compress the LRV between the SMA and aorta.

Venous congestion has already been established as a potential etiology for distinct headache syndromes including exertional headache, cough headache, headache with idiopathic intracranial hypertension and even new daily persistent headache, but the venous pathology is typically in the neck (jugular) or cerebral venous system itself [13–16]. Spinal epidural venous congestion, based on our study, could be another potential etiology for atypical persistent headache syndromes as well as for short lived headaches such as Valsalva or exercise induced head pain.

The clinical characteristics of a daily persistent headache from onset associated with NP and spinal EVP congestion appears to be marked by holocranial head pressure and associated “migrainous symptoms”. The headache worsens immediately in the Trendelenburg position which has previously been shown to be a sensitive test for predicting CSF pressure related headache syndromes (high or low) [17,18]. Overall, this patient population has been treatment-refractory. They appear to not respond to CSF volume lowering medications in a consistent manner and have only transient relief with CSF-volume reduction with LP. CSF opening pressures were in the normal range for all case patients, but some were on the higher side of normal. The hypothesis is that all individuals have their own unique range/set point of CSF pressure/volume that they are adjusted too and anything that alters that range (high or low), even by minimal amounts, can produce a headache [5]. Thus, for our study patients, even though their CSF opening pressure was in the “normal range” we hypothesize that it was too elevated for that individual patient, not high enough to cause optic disc edema, but just high enough to produce a persistent headache.

No subject had a prior migraine history, thus a chronification of migraine is not the suggested etiology of headache in these patients. “Migrainous” associated symptoms were common in this small subset of patients but these symptoms can be seen in primary headache syndromes outside of migraine including cluster headache, hemicrania continua and new daily persistent headache as well as in secondary headaches including IIH (another elevated CSF pressure-based syndrome); suggesting these symptoms are more reflective of trigeminal nerve activation and not headache syndrome specific [19–22].

4.1. Treatment

For severe cases of true NCS with failure of two years of conservative management, left renal vein transposition and auto transplant of the kidney are surgical treatment options that can be considered. Auto transplant, which theoretically should correct the spinal EVP congestion issue, has already shown efficacy in a single reported case patient whose daily persistent headache ceased after surgery. We do not however have published spinal EVP imaging for that case patient to prove cause and effect [7]. In our patient population with nutcracker phenomenon, open surgery would seem excessive solely for headache treatment, thus non-surgical options are being considered.

Potential Non-Surgical Treatments:

1. Lumbar vein occlusion with coiling or embolization: in essence this would shunt blood away from the spinal EVP and hopefully reset the spinal/cerebral venous congestion issue and thus alleviate headache.
2. Treating with veno-constrictors: Dihydroergotamine (DHE) is a potent veno-constrictor utilized in the abortive care of migraine patients. Interestingly, DHE has been successful at treating pelvic congestion syndrome which is a potential secondary consequence of nutcracker physiology [23]. Thus, oral dihydroergotamine may have potential use in this population.

4.2. Limitations

One limitation of our study is that the MRI protocol only images EVP enhancement/congestion in the lumbar spine and may image a portion of the lower thoracic spine. We have yet to image consistently above these spinal levels. Thus, we can only propose that there are secondary alterations in spinal and cerebral venous flow/pressure above our imaging protocol which is leading to increased CSF pressure and then headache. The time resolved MRA sequences suffer from artifact in the cervical spine region, making it more difficult to image with this technique. Further study of these patients could entail cerebral venous pressure measurements with conventional venography. It would be best to do this study three separate times: before a LP, after a LP and after treatment of the EVP congestion issues. Even if we complete dural sinus venous manometry studies, the small changes we are suggesting may not be apparent. The symptomatic worsening in the Trendelenburg position which rapidly increases intracranial CSF pressure helps to support our hypothesis. Importantly, we have studied only a small number of patients thus our study results need to be verified in a larger study population. Finally, there was no true control population for our study as it was more case series/proof of concept. However, we did have study patients with no spinal EVP congestion on imaging which suggests that this imaging finding may be a specific pathophysiologic issue for patients with NP and with a daily headache from onset. Based on our negative MRI results in IIH patients and chronic migraine patients with an elevated BMI, the imaging finding of spinal EVP congestion does not appear to be secondary to an elevated BMI alone nor from having elevated CSF pressure from etiologies other than nutcracker physiology. It would have been preferable to study a control group of healthy individuals (age, gender, and BMI matched) without a headache history and verify that our findings are unique to this daily persistent headache subgroup. However, the specific imaging sequence developed in this study (which images the blood flow patterns in the left renal vein, lumbar vein, and epidural venous plexus) requires a precisely timed contrast injection followed by multiple imaging sequences focused on a limited field of view. Due to these specific parameters, it is not possible to add this sequence to other MRIs of the abdomen and pelvis being completed in non-headache patients and still obtain all the necessary images. Furthermore, this is complicated by the fact that even in healthy volunteers with nutcracker physiology there will probably be a subset of patients with retrograde blood flow through the lumbar vein and the epidural venous plexus. However, these findings will not cause headaches in all patients, as some may have compensated for the abnormal retrograde flow and congestion. We see a similar phenomenon when nutcracker physiology results in retrograde flow through the gonadal veins and the pelvis but does not necessarily cause pelvic congestion syndrome. In either case, normative data on the flow patterns in the lumbar vein and epidural venous plexus would be very helpful because it would suggest there are other added factors that lead to persistent daily headache in patients with nutcracker physiology in addition to spinal EVP congestion. In the future we plan to image a control group of healthy individuals with no headache history under a separate IRB protocol.

5. Conclusion

Based on our findings we propose that nutcracker phenomenon may present with a daily headache from onset as the sole or primary clinical symptom. This headache may be the result of an abnormal reset of CSF pressure to an elevated state caused by secondary spinal epidural venous congestion. Further research in larger patient cohorts to assess for nutcracker physiology as a possible etiology for daily headache is needed. Future studies should also focus on providing an effective but safe treatment plan which will correct the spinal venous congestion issues.

Declarations of Competing Interest

None for all authors.

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