

Cervicogenic Headache Responsive To Galcanezumab In Patients With Comorbid Migraine: A Case Series.

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Abstract

Introduction

Cervicogenic headache (CH) is a chronic headache that is referred to the head from the cervical spine that typically starts or worsens with neck movement. The pain typically presents posteriorly with anterior radiation. Nociceptive input from structures innervated by the upper three cervical spinal nerves can theoretically exacerbate primary headache disorders like migraine. We present three cases of CH related to C1-C2 joint arthropathy that significantly improved after treatment with calcitonin gene-related peptide (CGRP) antibodies initiated for chronic comorbid migraine.

Case Descriptions

We describe a case series of 3 patients with comorbid CH and migraine that were treated with CGRP antibodies. All three patients had significant improvement in their migraines with C1-C2 joint injections and subsequently CGRP antibodies

provided a greater than 50% benefit in each patient preventing the need for repeat injections.

Conclusions

The diagnosis of CH in patients is confirmed when treatment of the cervical spine lesion alleviates pain significantly. While CH itself has not been shown to be associated with elevated serum CGRP as has been demonstrated in migraine, animal models of osteoarthritis have shown reduction of hyperalgesia with galcanezumab. An upregulation in CGRP related to nociceptive input from degenerative changes in the cervical spine could lead to potentiation and sensitization which could potentially respond to systemic administration of CGRP antibodies. As a result, the presence of features suggestive of CH in patients with migraine may be a predictor of a positive response to CGRP antibodies. For patients with comorbid migraine and CH, CGRP antibodies could prevent the need for invasive injection treatments.

Introduction

Cervicogenic headache (CH) is pain referred to the head from the cervical spine. It is typically a chronic and recurrent headache that starts or worsens with neck movement and is usually associated with neck pain and a reduced range of motion of the neck.¹ CH is confirmed when the headache is abolished following diagnostic blockade of a cervical structure or its nerve supply.² CH typically presents with tension phenotype, but patients can present with comorbid migraine and have accompanying migrainous features to the headache presentation.³ There is limited evidence that treatments directed at the cervical spine can provide some benefit in patients with migraine.⁴ The nociceptive input from structures innervated by the upper three cervical spinal nerves can theoretically interact at the level of the trigeminal cervical complex to exacerbate primary headache disorders like migraine.⁵ We report three cases of CH related to C1-2 joint arthropathy that significantly improved after implementation of a preventive strategy with calcitonin gene-related peptide (CGRP) antibodies.

Methods

This was a retrospective case series of patients seen at an academic headache clinic. A diagnosis of CH was suspected clinically and supported by imaging with at least 50% improvement in headache severity after intraarticular C1-2 joint injections.

Case Descriptions

Case 1

A 65-year-old man presented to our clinic with 4 years of headaches. He had a past medical history of a right posterior cervical sarcoma that was resected 14 years prior, but no other history of head or neck trauma. His headaches did not have a distinct day of onset, but rather retrospectively was appreciated by the patient to have had a gradual onset and progression. At time of presentation, his headaches were chronic and daily without any

periods of headache freedom. The pain fluctuated in severity. The pain was located bilaterally in the occipital regions (right worse than left) with radiation anterior to the temporal regions. The pain was a dull constant pressure but when severe could be throbbing with photophobia and worsened with exertion fulfilling International Classification of Headache Disorders (ICHD) criteria for probable migraine. Head rotation, more than cervical spine flexion and extension, provoked the pain. He had a history of acephalic migraine aura described as flashing lights throughout his visual field that lasted for five minutes. This occurred twice a year since early adulthood. The patient had done adequate medication trials of amitriptyline, gabapentin, and botulinum toxin for presumed chronic migraine prior to his initial consult without significant relief of his pain along with no evidence of medication overuse. Rizatriptan was ineffective at aborting his migraines. A right C1-C2 facet joint injection with steroid was performed (**Figure 1**). The patient had almost immediate relief of his pain for a few hours with moderate sustained relief ten days after the injection that continued until his follow up visit 4



Figure 1: Pre- and post-facet injections of right C1-C2. Lateral and anterior-posterior views of patient's cervical spine demonstrating mild-moderate degeneration of the right C1-2 joint (A, B). Lateral and anterior-posterior views of patient's cervical spine receiving right C1-C2 facet joint injection (C, D).

months later. With the tension phenotype, occipital distribution, provocation of pain with head rotation, degenerative changes of the right C1-2 joint, and response to right C1-2 joint injection, his constant background headache fulfilled ICHD diagnostic criteria for CH. At that time, the patient was prescribed a CGRP antibody, galcanezumab. Three months after starting the CGRP antibody, the patient had a gradual reduction over weeks in his baseline headache pain of 4/10 in severity to 1-2/10 in severity based on the numeric rating scale (NRS). In addition, he had a reduction in the severe headache pain which typically occurred with neck movements from a 7-9/10 to 4-6/10 in severity. Overall, the patient reported a greater than 50% improvement in his headache severity.

Case 2

A 52-year-old woman with a past medical history of episodic migraine that transformed to chronic migraine presented to our clinic with daily headaches since her 30s. She had severe headaches twelve days out of the month. The pain was located unilaterally in the right frontal and retro-orbital area with involvement of the right ear and suboccipital region. The pain was an explosive pressure sensation. She had photophobia, phonophobia, and nausea. She developed severe neck pain two years prior to her presentation. Turning her head right and neck extension provoked pain. The patient had done numerous medication trials including verapamil, topiramate, gabapentin, propranolol, amitriptyline, nortriptyline, venlafaxine, and botulinum toxin prior to her initial consult without significant relief of her pain. Given the fixed unilateral location and intractable nature of the headache along with provocation of pain with neck movements, it was elected to pursue diagnostic and potentially therapeutic upper cervical spine injections for probable cervicogenic headache. Based on the suboccipital referral pattern, she underwent right C2-3, C3-4 facet injections which provided good relief for a few days, but the pain quickly returned to baseline. A right C1-C2 joint injection provided 5 months of significant improvement in pain, but repeat injections provided diminishing benefit over time (3-4 months of pain relief with second injection and no

response from the third injection). At this time, the patient was prescribed a CGRP antibody, galcanezumab. At three months follow up, the patient stated her headaches significantly improved to where she only had 5 severe headache days per month. The patient reported a greater than 50% improvement in her headache severity along with improved range of motion with neck movements.

Case 3

A 65-year-old woman with no past medical history of migraine had left sided posterior neck pain that in the past had responded to periodic radiofrequency denervation of the left C3-4, C4-5, C5-6 facet joints. In the past, she had been treated with nortriptyline up to a dose of 50 mg taken for 10 years, but was able to taper off the nortriptyline as pain was well controlled with the radiofrequency ablations and it was unclear if the medication was providing any benefit. Over the past two years she developed a severe daily headache. The pain was now in the bilateral occipital distribution (left greater than right). The pain had posterior to anterior radiation to her eyes with 90% of the pain involving the left side. The headaches were characterized as a "clamp-like" pressure sensation, but with the most severe headaches, they would be throbbing in nature and accompanied by photophobia and phonophobia. The headaches worsened with exertion. She had a restricted range of motion of her neck to 30 degrees and provocation of pain with flexion/extension and axial rotation of the head. She was trialed on gabapentin titrating up to 600 mg three times daily for a year with no significant benefit. MRI of the cervical spine showed multilevel degenerative changes with hypertrophic degenerative changes of the C2-3 facet joints. She had short lived responses to bilateral C2-C3 facet injections with at most 10 days of pain relief. She had positive diagnostic bilateral third occipital nerve blocks and bilateral third occipital nerve ablations resulted in about two months of pain relief. During one of the radiofrequency ablations she developed a temporary post-ablation neuritis for several weeks following the procedure. Following a left C1-2 joint injection, she had about 3 months of significant

pain relief. Repeat left C1-2 joint injection provided 1-2 months of pain relief. Based on the tension phenotype, occipital distribution, provocation of pain with neck movements, advanced degenerative changes in the cervical spine, and response to C1-2 joint injection, it was felt the constant background headache was consistent with CH. The severe exacerbations of headache fulfilled diagnostic criteria for episodic migraine without aura. With the severe exacerbations consistent with migraine, a trial of galcanezumab was pursued. At follow up three months later, she reported improvement 4-5 days after initiation of the new medication. She stated that she went from having daily severe headaches to no severe headaches at all. She would be headache free for the first two weeks, but then develop a mild headache two weeks before she was due for the next injection of the CGRP antibody. When she was headache free, she no longer had pain limiting the range of motion in the neck with rotation and flexion/extension of the neck.

Discussion

Cervicogenic headache is a clinical syndrome of headache with posterior to anterior radiation, typically unilateral and pain is worsened with neck movements. In some cases, people will have reduced movement of their neck or pain to palpation of the cervical structures.¹ The clinical syndrome is supported by imaging and a response to treatments directed at structures of the cervical spine.² CH by itself has been shown not to be associated with elevated serum levels of CGRP.⁵ CGRP is however implicated in the pathogenesis of migraine and a number of other chronic pain conditions.^{6,7} In CH, tissue injury or inflammation related to degenerative changes can potentially result in peripheral sensitization by decreasing the firing thresholds of peripheral nociceptors which subsequently increases the production of CGRP. The commercially available CGRP monoclonal antibodies are molecules that are too large to cross the blood brain barrier and the mechanism of action is likely through CGRP inhibition of the peripheral trigeminal and cervical afferents.^{8,9} In animal models of osteoarthritis, the use of galcanezumab was effective in blocking the

behavioral signs of hyperalgesia. In patients with CH, potentially an upregulation in CGRP related to nociceptive input from degenerative changes in the cervical spine could lead to peripheral sensitization which could in turn cause a new onset of a primary headache disorder with a cervicogenic trigger or exacerbate a prior known primary headache disorder.⁵ Conversely, patients with CH and clinical features suggestive of sensitization (e.g. cutaneous allodynia) would theoretically respond to systemic administration of CGRP antibodies as peripheral sensitization is in part mediated by CGRP.^{7,10} The presence of features suggestive of CH in patients with migraine may have specificity for responders to CGRP antibodies as this would indicate the presence of nociceptive input that would promote sensitization, but the sensitivity of the clinical findings may not be adequate to identify all responders in migraine. For patients with migraine and a component of CH, the use of CGRP antibodies could prevent the need for periodic invasive injections as typically treatments directed at CH have a self-limited response due to regrowth of nerves with denervation procedures and limited duration of action with intraarticular steroids. It is not uncommon for some patients to have diminished efficacy with intraarticular steroid injections and this could be related to either progression of degenerative changes or manipulation of the joint inherent from the injection. The decreased responsiveness over time occurred in Case 2 and the CGRP antibodies provided an alternative treatment option after the loss of efficacy. All of the patients from this series have not required repeat C1-2 joint injection for at least 6 months following the implementation of galcanezumab. Clinical trials should be done in the future to explore the efficacy of CGRP antibodies in patients with CH and comorbid migraine and also in patients with CH alone.

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