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Glucagon-Like Peptide-1 Analogue In The Management Of Rebound Intracranial Hypertension: A Case Report

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Abstract

Background: Rebound intracranial hypertension (RIH) is a possible complication of epidural blood patching used in the management of spontaneous intracranial hypotension (SIH). RIH has been reported to occur in up to 27% of patients after SIH treatment and is characterized by elevated intracranial pressure, resulting in severe headache, nausea, and vomiting. Although it typically resolves spontaneously, treatment may be warranted for symptom control. While acetazolamide is the most commonly used agent for RIH, there are side-effects, and its efficacy remains inconclusive. Recently, novel glucagon-like peptide-1 (GLP-1) analogues have been found to modulate CSF secretion and consequently reduce intracranial pressure.

However, there are no studies that have evaluated the use of these agents in the treatment of RIH. We report of a case of a 46 year old female patient with persistent RIH after CSF leak repair that was refractory to pharmacologic and interventional treatments. The patient was treated with Semaglutide, an oral GLP-1 analogue and experienced immediate and sustained benefit of her symptoms.

Conclusion: RIH is a common complication after successful patching of a CSF leak, a proportion

of patients suffer from persistent and debilitating headaches. Our case report showed that GLP-1 agonist Semaglutide appeared to reduce symptoms in this one patient with refractory RIH symptoms. The use of GLP-1 agonists in the treatment of RIH should be evaluated in controlled studies to establish its safety and efficacy in this population.

Abbreviations

BBB = Blood Brain Barrier
CSF = cerebrospinal fluid
EBP = epidural blood patch
GLP = glucagon like peptide
ICP = intracranial pressure
IIH = idiopathic intracranial hypertension
RIH = rebound intracranial hypertension
SIH = spontaneous intracranial hypotension

Introduction

Spontaneous intracranial hypertension (SIH) is characterized by orthostatic headaches due to CSF hypovolemia that occurs due to a spinal CSF leak. The most common causes responsible for a CSF leak include nerve root diverticula, cerebrospinal fluid-venous fistulas, or CSF leak-osteophyte spurs. [1] Patching of a CSF leak can be achieved by patching the leak with blood or fibrin, and if unsuccessful surgical repair may be indicated. Unfortunately, one fourth of patients who undergo a CSF leak patch will suffer from rebound intracranial hypertension (RIH). [2] RIH presents as a headache but in contrast to an SIH headache, RIH improves in upright position and worsens when lying down. Further, patients complain of nausea, vomiting, and other associated symptoms such as blurry vision. Whereas patients with SIH mostly present with positional occipital headaches, RIH usually causes frontal or periorbital headaches. [3] Patients that are younger, female, and had extradural CSF collection on spinal imaging appear to be at greater risk of RIH. [2]

The mechanism of RIH after epidural blood patching/surgical leak repair is not fully understood. Multiple theories have been suggested to explain the increased intracranial pressure: 1) displacement of CSF after injecting volume (blood) in the confined epidural space; 2) failure of reversal of the compensatory SIH mechanisms; 3) disrupted CSF reabsorption. [3] Patients with SIH who before epidural patching show greater levels of intracranial venous sinus stenosis appear to be at increased risk of developing RIH. These data suggest that elevated intracranial venous pressure and impaired resorption of CSF may play an important role in developing RIH. [2]

While RIH is usually mild and spontaneously resolves within several days, patients can suffer for months and infrequently for years. As such, treatment options are often considered for symptom control until RIH headaches improve. The typical treatment of RIH is acetazolamide, a carbonic anhydrase inhibitor. Acetazolamide can offer pain relief by temporarily decreasing CSF production. [2] Unfortunately, some patients are refractory to acetazolamide or cannot tolerate side-effects, which include nausea, vomiting, diarrhea, fatigue, and paresthesia. Other pharmacologic agents such as topiramate or furosemide can provide varying degrees of relief but are also associated with their own side-effects. Rare reports of the use of ventriculo-peritoneal shunt to manage RIH when accompanied by papilledema exist, but this is an invasive procedure and its effectiveness in conditions such as Idiopathic Intracranial Hypertension (IIH) to reduce pain is uncertain. [4, 5] As such, there is a need to identify novel

therapeutics that are effective, safe, and well tolerated to assist in the management of RIH.

Pre-clinical studies using animal data suggest that novel glucagon-like peptide-1 receptor (GLP-1) analogues, used in the treatment of type 2 diabetes and obesity [6], can reduce intracranial pressure by modulating CSF secretion through the reduction of ion transport and consequently water across choroid plexus.[7] GLP-1 analogues have been evaluated for the treatment of idiopathic intracranial hypertension (IIH) in a phase-II randomized controlled trial (reported on a pre-print server prior to peer review) and showed significant and persistent reductions in intracranial pressure for up to 12 weeks with no serious adverse events. [8] While there are ongoing studies evaluating GLP-1 analogues for IIH, there is little clinical data on the utility of these agents in the management of RIH.

Here, we report a case of a patient with persistent RIH refractory to pharmacologic and interventional treatment options that found significant improvements with a trial with a GLP-1 agonist.

Case Report

A 46 years old woman presented with a classic orthostatic headache in 2016 beginning after a brief history of coughing spells. Brain and spine MRI failed to show a CSF leak, but two and she failed to have prolonged relief from two empiric epidural blood patches. The first epidural blood patch was performed as non-targeted (level unknown) and provided some benefit. The second epidural blood patch was performed at T8-9 level given that an initial cervical and thoracic CT spine with contrast demonstrated enhancement posterior to the thoracic cord from T5 to T8.

Then, in late 2016, a digital subtraction myelogram was performed and identified dynamic leakage of CSF underneath the left T10 pedicle. Opening pressure was too low to be measured. She had repeat blood and fibrin patching performed at T10 level for symptomatic relief, and in total, she had four epidural blood patches and seven fibrin patches each followed by recurrent symptoms. Eventually, she underwent definitive surgical repair in July 2017.

The procedure resolved her classic orthostatic headaches, however she eventually developed new type of headache characterized by a diffused head pressure in the frontal area, behind her eyes and at the top of her head. She also described a burning sensation around her nose and sinuses and a numbness feeling in the posterior occipital area. Headaches now had a paradoxic positional component in which they were now worse in the supine position and with quick movements (fast walking), household chores (vacuuming), and lifting arms above her head. Valsalva maneuver however was not associated with an increase in headache intensity. She would often wake up in the middle of the night after a few hours of sleeping with severe headaches associated with nausea and vomiting. In the mornings, she would also report symptoms of her ears feeling plugged, decreased hearing, blurry vision, and pain in her sinuses.

Given the patient's constellation of symptoms, a diagnosis of RIH was made and she was treated empirically with acetazolamide and furosemide. While she initially responded, improvements waned over time despite increasing doses of both medications. She required approximately 200 mg every 2 hour of acetazolamide and 90 mg of oral furosemide twice a day. These high doses resulted in significant side-effects and required serial electrolyte monitoring. Additional pharmacological agents were trialed for further symptom control which included acetaminophen, diclofenac powder, gabapentin, pregabalin, desipramine,

topiramate, almotriptan, low dose naltrexone, and amlodipine. We also trialed a number of interventional procedures including ultrasound-guided bilateral occipital nerve blocks (not effective) and PREEMPT botox injections (modest benefit). A VP shunt was considered but was declined by the patient. Despite these management options, she remained debilitated with her symptoms, unable to work, and enjoy leisure activities.

Given pre-clinical data of GLP-1 analogues for reducing intracranial pressure, and its safety in the diabetic and weight loss populations, patient agreed to undergo a trial with oral Semaglutide. We sought consultation with an endocrinologist that specializes in diabetes and weight-loss prior to initiation. After consulting, the oral formulation of Semaglutide was suggested for this patient as it appears to be associated with less weight gain, which is a side-effect of Semaglutide which we aimed to avoid. We discussed the risks associated with the medication and weaned her off furosemide prior to initiation. Prior to trial of oral Semaglutide, she was taking approximately 2400 mg of acetazolamide a day. We initiated Semaglutide at an oral dose of 3 mg daily on November 3, 2021. Her weight at that time was 57.7 kg. Prior to the trial she would rate the severity of her morning headaches (when it was worst) as being 6 on a 0 to 10 numeric rating scale (NRS). In the first day of taking this medication, she reported some dizziness which resolved the day after. After the first week, she already noticed substantial improvements in terms of the severity and frequency of her headaches. She found much less pressure and head fullness and substantially reduced her acetazolamide dose to 1500 mg a day (250 mg every 4 to 5 hours). We decided to titrate her dose in an attempt to obtain further benefits. After one month, the oral dose of Semaglutide was increased to 7 mg once daily and after three months to 14 mg once daily.

Two months after starting Semaglutide, she would experience several mornings per week with her morning headaches being rated as either a 0 or 1 on the NRS scale. She substantially reduced her acetazolamide use to either 125 mg once or twice a day (250 mg daily on average). On day 65 after initiation of Semaglutide, she reported the first day ever that she did not require any acetazolamide. At six months after Semaglutide initiation, she reported to experience a remarkable improvement of her symptoms, specifically with respect to her head fullness and painful sensation in the morning, as well as her morning nausea. Sleep substantially improved and she no longer wakes from sleep in the middle of night with pain and nausea. Her quality of life substantially improved as she was able to increase her daily activities, return to work on a part-time basis, and take her first vacation with her family after several years. Her weight stayed relatively constant throughout these months and was noted as 56 kg at 6 months after treatment initiation.

The patient currently still remains on oral Semaglutide on a daily basis.

Discussion

This case report describes the use of a GLP-1 agonist for the treatment of rebound intracranial hypertension- a condition with limited treatment options. In this case, a patient with RIH refractory to extensive medical and interventional management options found substantial benefit with a GLP-1 agonist in reducing severity and frequency of headaches, improving function and quality of life, and allowing the patient to wean from acetazolamide.

Although RIH is infrequently reported, is it not an uncommon complication of epidural blood patching (EBP). Approximately 7-27% of the patients undergoing an EBP for SIH are noted to

develop RIH, with RIH being a recognized complication since 1990.[9] It is characterized by frontal headaches, that worsen in supine position. RIH is often accompanied by nausea, vomiting, blurry vision and diplopia. These symptoms often develop early, within the first 36 hours after seal of the CSF leak but can be delayed and become chronic as well. [9] The diagnosis of rebound hypertension headache following treatment of SIH is a clinical diagnosis, and while a dural puncture opening pressure could provide definitive evidence, concerns exist in this patient population about intentionally creating another CSF leak.

RIH can be divided in either early RIH, where symptoms occur immediately after EBP, and delayed RIH, that may develop days to weeks following the EBP. Persisting intracranial venous distension after repair of the CSF leak is a possible explanation for early RIH. Whereas delayed RIH is thought to arise from upregulation of CSF production and maladjusted CSF reabsorption during the period of the CSF leak.[9]

Glucagon-like peptide-1 (GLP-1) is a neuropeptide, produced and secreted by intestinal endocrine cells, with known effects on blood glucose homeostasis. These agents are becoming increasingly used in diabetes and as an effective weight-loss agent. Obesity appears to be linked to increased intracranial pressure and weight gain is a risk factor for Idiopathic Intracranial Hypertension (IIH) or pseudotumor cerebri. [7] As such, weight loss plays a key role in IIH management and may explain one mechanism by which GLP-1 analogues could reduce ICP. In this case report, the patient's weight stayed relatively constant, despite significant clinical improvement. Another mechanism, supported by preclinical animal studies suggest that GLP-1 analogues lower ICP by modulating receptors at the choroid plexus that are involved in the production of cerebrospinal fluid.[10] Human and rodent choroid plexus epithelium express GLP-1 receptors and stimulation of these receptors have resulted in reduced CSF secretion, via Na+- and K+-dependent adenosine triphosphatase activity, a key regulator of CSF secretion, eventually reducing ICP. An almost 50% reduction in ICP in hydrocephalic rats could be seen after treatment with Exenatide, a GLP-1 analogue, which is a remarkable reduction and not seen at clinically relevant doses of acetazolamide.[11] In another study by Hakon et al, treatment with the GLP-1 analogue Liraglutide, significantly reduced cerebral edema after experimental TBI in rats. Liraglutide is thought to cross the BBB and to have anti-inflammatory effects on cerebral endothelial cells and astrocytes. [12]

A recent randomized controlled trial posted on a preprint server by Mitchell et al. provides clinical evidence on the potential benefit of GLP-1R in reducing ICP. [8] This trial evaluated Exenatide in fifteen women with active IIH defined as ICP >25 cm CSF and papilledema. Investigators found that Exenatide significantly lowered ICP at all timepoints, with a meaningful reduction in monthly headache days but without significant change in headache severity. Despite the favorable findings, there were no definite change in body weight at 12-weeks in the treatment arm, hypothesizing that the ICP reduction was probably mediated by a reduction in CSF secretion, rather than through weight loss. [8]

These data suggest that GLP-1 analogues may have a direct or indirect effect to reduce ICP and thus, may be a promising candidate for improving symptoms associated with RIH. While our report is an early indication for this possible use for GLP-1 analogues, there are several limitations to this case report. First, there are the biases inherent to case report such as the impossibility to deduce causality, overinterpretation and other methodological limitations.[13] The subjective character of

outcome data, lack of validated questionnaires and a tool to objectively proof correlation between GLP-1 and improvement as well as to rule out other confounders, are critical elements to take into account. Second, there might be a possibility that RIH and secondary headaches improved due to the natural course of the disease itself. Moreover, a placebo effect cannot be ruled out, however given the durability of improvement, and lack of response to multiple other previous oral agents make the role of an expectancy effect less likely.

Lastly, the patient currently still remains on oral Semaglutide on a daily basis. Given the chronic nature of rebound intracranial hypertension and the novel use of this medication in this context, we were concerned about return of her symptoms if we discontinued the Semaglutide. Further prospective research will be needed to understand whether improvement of symptoms with Semaglutide will result in persistent effects despite discontinuing use.

Conclusion

RIH is a common complication after successful patching of a CSF leak, and while RIH is most often a mild and self-limiting process, a proportion of patients suffer from persistent and debilitating headaches. The GLP-1 agonist Semaglutide appeared to reduce symptoms in this one patient with refractory RIH symptoms. The use of GLP-1 agonists in the treatment of RIH should be evaluated in controlled studies to establish its safety and efficacy in this population. Specific consideration in future studies should be paid to how symptom improvement correlates, or fails to correlate, with measurements of CSF pressure, and also to the role concomitant weight loss plays in symptom relief.

Declarations/Disclosures

Consent/Permission/Ethics Approval: Informed consent was obtained from the patient for the publication of this case report.

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References

1. Houk J, Dennison JV, Kranz PG and Amrhein TJ. Spontaneous Intracranial Hypotension: A Review of Pathogenesis, Presentation, Diagnosis, and Treatment. *Advances in Clinical Radiology*. 2022;4((1)):231-241. doi:https://doi.org/10.1016/j.yacr.2022.04.015
2. Schievink WI, Maya MM, Jean-Pierre S, Moser FG, Nuno M, Pressman BD. Rebound high-pressure headache after treatment of spontaneous intracranial hypotension: MRV study. *Neurol Clin Pract*. Apr 2019;9(2):93-100. PubMed PMID: 31041122; PubMed Central PMCID: PMCPMC6461412. doi:10.1212/CPJ.0000000000000550
3. Kranz PG, Amrhein TJ, Gray L. Rebound intracranial hypertension: a complication of epidural blood patching for intracranial hypotension. *AJNR Am J Neuroradiol*. Jun 2014;35(6):1237-40. PubMed PMID: 24407273; PubMed Central PMCID: PMCPMC7965157. doi:10.3174/ajnr.A3841
4. Sinclair AJ, Kuruvath S, Sen D, Nightingale PG, Burdon MA, Flint G. Is cerebrospinal fluid shunting in idiopathic intracranial hypertension worthwhile? A 10-year review. *Cephalalgia*. Dec 2011;31(16):1627-33. PubMed PMID: 21968519. doi:10.1177/0333102411423305
5. Yoshimoto S, Takai K, Takahashi K, Yasui T, Taniguchi M. Intracranial hypotension and hypertension: reversible Chiari malformation due to dynamic cerebrospinal fluid abnormalities in Gorham-Stout disease. Case report. *J Neurosurg Pediatr*. Nov 1 2018;22(5):508-512. PubMed PMID: 30074451. doi:10.3171/2018.5.PEDS1859

6. Nauck MA, Quast DR, Wefers J, Meier JJ. GLP-1 receptor agonists in the treatment of type 2 diabetes - state-of-the-art. *Mol Metab*. Apr 2021;46:101102. PubMed PMID: 33068776; PubMed Central PMCID: PMCPMC8085572. doi:10.1016/j.molmet.2020.101102
7. Eftekhari S, Westgate CSJ, Uldall MS, Jensen RH. Preclinical update on regulation of intracranial pressure in relation to idiopathic intracranial hypertension. *Fluids Barriers CNS*. Nov 26 2019;16(1):35. PubMed PMID: 31767019; PubMed Central PMCID: PMCPMC6878629. doi:10.1186/s12987-019-0155-4
8. Mitchell JL, Lyons HS, Walker JK, et al. The effect of GLP-1RA exenatide on idiopathic intracranial hypertension: a randomized clinical trial. *Brain*. May 2 2023;146(5):1821-1830. PubMed PMID: 36907221; PubMed Central PMCID: PMCPMC10151178. doi:10.1093/brain/awad003
9. Jafari E, Karaminia M, Togha M. Early and Delayed Rebound Intracranial Hypertension following Epidural Blood Patch in a Case of Spontaneous Intracranial Hypotension. *Case Rep Neurol Med*. 2022;2022:5637276. PubMed PMID: 35340426; PubMed Central PMCID: PMCPMC8956435. doi:10.1155/2022/5637276
10. Mollan SP, Tahrani AA, Sinclair AJ. The Potentially Modifiable Risk Factor in Idiopathic Intracranial Hypertension: Body Weight. *Neurol Clin Pract*. Aug 2021;11(4):e504-e507. PubMed PMID: 34484948; PubMed Central PMCID: PMCPMC8382420. doi:10.1212/CPJ.0000000000001063
11. Botfield HF, Uldall MS, Westgate CSJ, et al. A glucagon-like peptide-1 receptor agonist reduces intracranial pressure in a rat model of hydrocephalus. *Sci Transl Med*. Aug 23 2017;9(404)PubMed PMID: 28835515. doi:10.1126/scitranslmed.aan0972
12. Hakon J, Ruscher K, Romner B, Tomasevic G. Preservation of the blood brain barrier and cortical neuronal tissue by liraglutide, a long acting glucagon-like-1 analogue, after experimental traumatic brain injury. *PLoS One*. 2015;10(3):e0120074. PubMed PMID: 25822252; PubMed Central PMCID: PMCPMC4379006. doi:10.1371/journal.pone.0120074
13. Nissen T, Wynn R. The clinical case report: a review of its merits and limitations. *BMC Res Notes*. Apr 23 2014;7:264. PubMed PMID: 24758689; PubMed Central PMCID: PMCPMC4001358. doi:10.1186/1756-0500-7-264