LETTER TO THE EDITOR

To The Editor

Chronic Cannabis Use and Treatment Failure of Onabotulinum Toxin A for Chronic Migraine

Keywords: Onabotulinum toxin A, Chronic migraine, Chronic cannabis use, Cannabis

A 27-year-old female with a history of headache since age 13 presented to the headache clinic with ongoing daily headaches. Her headaches were described as holocephalic and moderate to severe in intensity, with associated nausea, vomiting, photophobia, and phonophobia. She would see flashing and flickering spots prior to the onset of her headaches. In the setting of life stressors, hormonal changes, and poor lifestyle habits, she experienced chronification of symptoms over time and was having daily headaches by her early 20s. Her past medical history was unremarkable and her brain magnetic resonance imaging was reported as normal. At that time, she was diagnosed with chronic migraine (CM) with visual aura. She was treated with multiple preventative medications including amitriptyline, propranolol, and valproic acid, but they were discontinued due to ineffectiveness and/or intolerance. She was later treated with onabotulinum toxin A (BTX) (PHASE III Research Evaluating Migraine Prophylaxis Therapy protocol – 155 units in 31 sites) which decreased her headache frequency to 8-days/month after the first cycle. She had similar response for the next two cycles of treatment (1 cycle is every 12 weeks). She was not taking abortive or other preventive medications during this period. Unfortunately, BTX treatment was stopped after three cycles due to loss of insurance coverage and her headaches returned to her previous state (daily severe headaches). With this progression, she started smoking recreational cannabis (tetrahydrocannabinol and cannabidiol combination, unknown ratio and strain), up to 2 grams twice daily, to manage her headaches. She reported that the cannabis was helping her sleep and appetite, but no effect on the headaches. She did not take other abortive therapies. Four years later, her insurance coverage was reinstated for BTX and treatment was resumed. However, in the setting of ongoing daily cannabis use, she experienced no improvement with her headaches after two cycles of treatment. We suspected her treatment response was affected by her chronic cannabis use, thus, we advised her to stop using it. She was able to immediately stop all cannabis use and BTX was restarted 12 weeks later. After the first cycle of BTX, she had a significant decrease in headache frequency and severity, similar to her previous response prior to cannabis use, down to 8-headache days/month. Similar response was seen for the next 2 years with BTX treatments.

This is a unique case as there is no medical literature on the effect of chronic cannabis use in chronic migraineurs who are on BTX concurrently. Chronic cannabis use may have put this patient at risk of medication overuse headache (MOH), and the presence of medication overuse could have rendered standard migraine therapies such as BTX to be ineffective, possibly due to central sensitization and alteration to pain threshold and/or modulation.

Cannabis has not been established as a standard treatment for headache disorders. Both recreational and medicinal cannabis are being used by patients as acute or preventive treatments for various headache disorders, including migraine, despite the lack of high quality research evidence.[1]

Does chronic cannabis use act similarly to other abortive therapies in causing MOH? The pathophysiology of MOH is still not fully understood, but genetic polymorphism, drugs of choice and duration all play a role in alteration of the central pain sensitization pathway and neurotransmitter metabolism, such as the serotoninergic and endocannabinoid systems.[2] In animal models, it has been shown that cannabinoid receptor agonists produce a state of latent sensitization characterized by increased sensitivity to stress[3] and overuse of cannabinoids including cannabis may increase the risk of MOH. In addition, chronic use of cannabis has been shown to affect the endocannabinoid system by downregulation of brain cannabinoid receptor type 1, and this may affect the modulation of neuropathic, visceral, and inflammatory pain.[1,4] It has been demonstrated that chronic migraineurs with or without MOH responded well to BTX treatment similarly and in the chronic migraineurs with MOH group, they started to decrease their daily abortive medications overtime due to their response to BTX.[5] However, this was not seen in our case and some plausible hypotheses include an alteration to the pain and treatment threshold with chronic cannabis use and/or a drug interaction between BTX and cannabis.[3,6,7]

This case was limited by the unknown, specific composition of the cannabis product that the patient was using. There is currently significant heterogeneity in the unregulated products that patients have access to, which reflects the real world setting. Each species of cannabis has a unique biochemical composition or cannabinoid profile of varying amounts of more than 400 compounds.[8] Different strains, compositions, dosages, ratios, or route of administration may have different effects for headache disorders. The lack of response to BTX could indicate the development of neutralizing antibodies to BTX over time, but this would be unlikely as the patient responded to BTX subsequently when cannabis was discontinued. Some other variables may have impacted treatment response, such as financial or mental stressors, not reported by the patient.

Although there is an increasing usage of cannabis for headache disorders, it is important to note that chronic cannabis use could render standard CM therapies such as BTX to be ineffective. In addition, chronic cannabis use may put patients at risk of MOH. This is the first report in the medical literature presenting with treatment failure to BTX in the context of chronic cannabis use. Providers should be vigilant in asking their patients about cannabis use before deeming treatment failure. In addition, it is prudent to advise patients to discontinue cannabis use before initiating additional treatments to avoid polypharmacy and potential drug–drug interactions. This case provided an observation and allowed us to generate hypotheses on the potential interaction between chronic cannabis use and headache disorders. The endocannabinoid system is an important system in modulating endogenous pain processing pathways and further research is required to elucidate the association between acute versus chronic cannabis use with headache disorders, interaction between cannabis and other headache treatments, the effect on pain modulation from different composition of cannabis, and risk of developing MOH from chronic cannabis use in human models.

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Statement of authorship

NZ examined the patient. Both authors wrote and revised the manuscript.

Disclosures

The authors have no conflicts of interest to delcare. Informed consent was obtained from the patient.

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References

1. Rhyne DN, Anderson SL, Gedde M, Borgelt LM. Effects of medical marijuana on migraine headache frequency in an adult population. Pharmacotherapy. 2016;36(5):505–10.
2. Diener H-C, Holle D, Solbach K, Gaul C. Medication-overuse headache: risk factors, pathophysiology and management. Nat Rev Neurol. 2016;12(10):575–83.
3. Kopruszinski CM, Navratilova E, Vagnerova B, et al. Cannabinoids induce latent sensitization in a preclinical model of medication overuse headache. Cephalalgia. 2019 Jul 16; 333102419865252.
4. Ceccarini J, Kuepper R, Kemels D, van Os J, Henquet C, Van Laere K. [18F]MK-9470 PET measurement of cannabinoid CB1 receptor availability in chronic cannabis users. Addict Biol. 2015 Mar; 20(2):357–67.
5. Negro A, Curto M, Lionetto L, Crialesi D, Martelletti P. OnabotulinumtoxinA 155 U in medication overuse headache: a two years prospective study. Springerplus. 2015;4:826.
6. Kraft B, Frickey NA, Kaufmann RM, et al. Lack of analgesia by oral standardized cannabis extract on acute inflammatory pain and hyperalgesia in volunteers. Anesthesiology. 2008 Jul;109(1): 101–10.
7. Wallace M, Schulteis G, Atkinson JH, et al. Dose-dependent effects of smoked cannabis on capsaicin-induced pain and hyperalgesia in healthy volunteers. Anesthesiology. 2007 Nov;107(5): 785–96.
8. Baron EP. Comprehensive review of medicinal marijuana, cannabinoids, and therapeutic implications in medicine and headache: what a long strange trip it's been .... Headache. 2015 Jun;55(6):885–916.

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