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Case report

High frequency migraine refractory to usual pharmacological therapy and anti-CGRP receptor antibody and responsive to broad-spectrum cannabidiol: a case report

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Abstract

The use of derivatives of *Cannabis* sp. in the treatment of certain medical conditions, such as neuropathic pain, epilepsy and multiple sclerosis, is well known. However, studies on its benefit in headache are low in scope, consisting, in majority, of reports and case series. We report the case of a 74-year-old male patient with high frequency migraine (2 to 3 times/week) for several years, presenting important functional limitation associated with several triggers, and using triptans for headache crisis only. The patient expressed intolerance to 2 prophylactic drugs (topiramate and propranolol). He performed 2 applications of erenumab 70 mg, wich promoted considerable initial improvement followed by a new increase in attacks' frequency after the second application, leading to interruption of this therapy. Nutraceuticals were tried for 6 months, but there was not any improvement. After the introduction of cannabidiol oil, migraine attacks reduced in frequency (1 episode/month) and intensity, with a record interval of 30 consecutive days without pain, associated with elimination of triggers. Preclinical studies evaluating the relationship between endocannabinoid system and migraine pathophysiology point to *Cannabis* sp. derivatives as potential weapons for the treatment of this condition. However, the role of these derivatives as prophylaxis of migraine attacks is still speculative, thus requiring controlled studies for further definition.

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Introduction

Headache is among the most disabling diseases in the world. Data from the Global Burden of Disease 2017 reveal that headache is the second leading cause of years lived with disability worldwide and is a condition that carries high individual and social costs.[1,2]

Migraine is among the most frequent primary headaches, but it is a generally neglected, underdiagnosed, and undertreated disease. Despite the existence of specific and effective treatments, less than half of the migraine sufferers are good responders and end up developing the chronic form of the disease throughout their lives. Thus, it is imperative to search for other treatment options, both prophylactic and abortive, for migraine with good tolerability and efficacy in refractory cases.[2,3]

The medicinal use of cannabis derivatives in clinical conditions such as epilepsy, multiple sclerosis, and neuropathic pain is ratified by prospective studies with a high level of evidence. However, research on the application of these derivatives in migraine and other headache disorders, despite showing benefits, are mostly case reports and case series, telephone questionnaires, and retrospective analyses.[3,4]

We present the case of a patient with migraine refractory to various treatment strategies, but responsive to broad-spectrum cannabidiol oil (CBD).

Case Report

A 74-year-old male with high-frequency migraine (2-3 times/ week) for several years, living with significant functional limitation associated with various triggers, such as wine, chocolate, and physical activity in the sun. He takes only sumatriptan or naratriptan during his crisis, with no significant improvement. Previously tried prophylactic treatments (topiramate and propranolol) were not tolerated due to their adverse effects. A monoclonal antibody (erenumab 70 mg) was proposed monthly and guidance on the correct use of naratriptan, since sumatriptan caused drowsiness.

Days after the second application of the antibody, he presented a notable reduction in the frequency and intensity of migraine crisis, with a total of 3 episodes in the last 30 days. However, one month after the second application, crisis returned in a frequency of two episodes a week, and no new applications were made. Riboflavin was prescribed for 3 months, with no improvement in the frequency of crisis, and coenzyme Q10 and magnesium were associated, again with no result.

The use of venlafaxine was discussed, but the patient preferred a more natural treatment. The patient opted for a broad-spectrum cannabidiol oil (containing 20% CBD and <0.3% TCH), obtained by mixing hemp extract in medium chain triglyceride oil, at a concentration of 6 mg CBD per drop, with a dosage of 5 drops 12/12 hours. Two months later, there was an important improvement in the frequency and intensity of pain, with 4 episodes in the last month, in addition to having been able to drink wine without feeling headaches, something unheard of until then. The treatment dose was doubled, and after 3 months the frequency of days with pain reduced to 3 per month. In the following quarter, it was further reduced to 1 day per month, with a record interval of 30 pain-free days in a row. The patient was very satisfied with the treatment, reporting that the pain he eventually presents is much milder and he perceives that the painkiller is more effective, in addition to the elimination of the triggers of wine, chocolate, and physical activity in the sun.

Discussion

Historically, the first clinical publications regarding the medicinal use of cannabis derivatives in the treatment of migraine occurred as early as the 19th century and pointed to the efficacy of their use for both prophylactic and abortive treatment of this condition. Over the years, pre-clinical studies were developed to understand the mechanism of action of cannabinoids and their influence on the pathophysiology of migraine.[2]

The endocannabinoid system (ECS) is composed of endocannabinoid substances, enzymes that degrade them, and cannabinoid receptors, mostly CB1 and CB2. The CB1 receptor is widely expressed in pain pathways, both in the central and peripheral nervous system, and its activation inhibits the release of neurotransmitters such as glutamate, serotonin, GABA, and dopamine. The CB2 receptor, in turn, more abundant in peripheral tissues and immune system cells, exerts anti-inflammatory and immunosuppressive action, by regulating the release of cytokines and cell migration, which are exacerbated in severe and chronic forms of migraine, besides promoting analgesic effect through the modulation of dopamine release.[3,5]

Several mechanisms have been proposed to explain the relationship between ECS and the pathophysiology of migraine and the consequent action of cannabinoids in the treatment of this pathology. Such mechanisms involve systemic, neurological, and vascular pathways. The inhibition of glutamate release from activation of CB1 receptors in the microglia by endogenous or exogenous agonists promotes suppression of cortical spreading depression, the neurobiological event that originates migraine aura. Studies have revealed that platelets of individuals with migraine have low levels of endocannabinoids and that migraine may result, in part, from the release of serotonin from activated platelets, contributing to cerebral vasodilation. Thus, cannabinoids would be able to stabilize platelets, preventing the release of serotonin.[2,6-10]

Endocannabinoids also exert modulation on afferent nociceptive signals, since activation of the CB1 receptor in the periaqueductal gray matter modulates nociceptive transmission through the trigeminocervical complex. The endocannabinoid anandamide was shown to inhibit dural vasodilation caused by nitric oxide, CGRP, and capsaicin, which promote hyperactivation of the nociceptive response of the trigeminovascular system, resulting in neurogenic inflammation.[11,12]

Patients with migraine, in episodic and chronic forms, present low levels of endocannabinoids, which generates an imbalance in the functioning of the ECS, culminating in a hyperalgesic response triggered by the periaqueductal gray matter, a structure deeply related to the genesis of migraine.[8,13]

The main pharmacological components present in Cannabis sp. are CBD and THC, capable of mimicking the action of endocannabinoids on CB1 and CB2 receptors, with different degrees of affinity. Given the analgesic and anti-inflammatory properties of these components, their use in both prophylactic and acute treatment of migraine began to be tested over the years, resulting in the publication of several papers.

Conclusion

Literature still lacks clinical studies with a high level of evidence that robustly demonstrate the efficacy of migraine treatment with phytocannabinoids. However, this report presented the case of a migraine patient who responded very satisfactorily and long-term to the use of broad-spectrum CBD oil, corroborating the pathophysiological hypothesis of previously published studies, and demonstrating the value of phytocannabinoids as a therapeutic option in migraine refractory to several pharmacological treatments.

Authors' contribution: LMMR, conceptualization of the work, acquisition of data, literature survey, writing of the article; MRAS, conceptualization of the work, acquisition of data, intellectual review of the content. Both authors approved the final version of the article.

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