

How Could Cannabinoids Be Effective in Multiple Evanescent White Dot Syndrome? A Hypothesis

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ABSTRACT

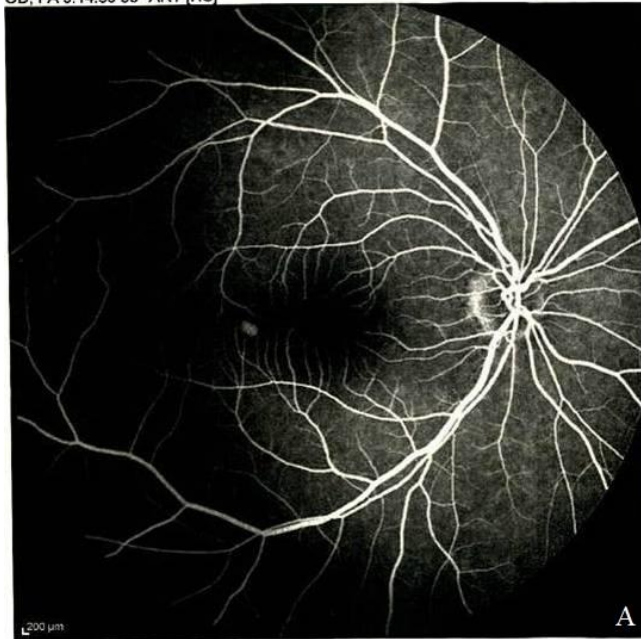
Multiple evanescent white dot syndrome (MEWDS) is an inflammatory eye disease which causes decreasing in visual acuity even to 20/400. So far, no molecular pathway has been suggested for MEWDS. Although no exact treatment is suggested for MEWDS, two major medications are being used for treatment already; anti-vascular endothelial growth factor (VEGF) monoclonal anti-bodies and methylprednisolone. Cannabinoids are known as active compounds of *Cannabina Sativa* with wide variety of biological activities. Methylprednisolone is able to inhibit inflammation through suppressing Interleukin-6 (IL-6), IL-8, and tumor necrosis factor- α (TNF- α). According to the data, cannabinoids are able to inhibit both angiogenesis and inflammation by targeting VEGF, IL-6, IL-8 and TNF- α and other related angiogenic and inflammatory cytokines. Thus herein authors of this study suggest cannabinoids for treatment of MEWDS since it covers both inhibition of angiogenesis and inflammation. However, feature complementary studies are necessary in the field.

Introduction

White dot syndromes are a group of rare ophthalmologic disorders also known as a type of chorioretinopathies. Multiple evanescent white dot syndrome (MEWDS) is a unilateral inflammatory eye disease which mostly occurs in young population (20-50 years old) especially in women. This phenomenon is associated with several symptoms such as decreased visual acuity (less than 20/400), blurred vision and photopsia with an acute onset [1]. Although the exact pathogenesis of MEWDS is still unclear, it has been showed to usually involve outer retina, retinal pigmented epithelial cells and choroid. Based on fluorescein angiography results of these patients, optic disk and nerve hyperemic status has also been reported (Fig 1). Beside of inflammation, choroidal neovascularization (CNV) is established to be a role player in this scenario too [2]. According to these facts so far several treatments are used in order to target inflammation or angiogenesis in MEWDS [3-4]. For anti-inflammatory therapy, methylprednisolone pulse therapy was used in order to decrease inflammatory reactions which successfully returned patients' VA. Also in some cases

Ranibizumab® and Bevacizumab®, two anti-vascular endothelial growth factor (VEGF) monoclonal anti-bodies, have been used for inhibition of neovascularization and also treating symptoms in these patients [4]. Although exact pathogenesis of MEWDS is not completely clear, according to the ability of methylprednisolone on the suppression of inflammatory cytokines such as Interleukin-6 (IL-6), IL-8, and Tumor necrosis factor- α (TNF- α) [5] and critical role of these factors in eye inflammation and neovascularization [6] they could have key roles in MEWDS pathogenesis. However, considering activity of the mentioned monoclonal anti-bodies, VEGF seems to be important too. Although MEWDS seems to be a self-limited disease, most cases require a treatment plan since the etiology of the disease depends on various factors like occupational positions and patients' stress. Cannabinoids (CBNs) are active compounds of *Cannabis Sativa* (Marijuana) which are known by their strong anti-inflammatory and anti-angiogenic activity [7]. CBNs mostly exert their effect through cannabinoid receptor-1 and 2 (CBR-1 and 2).

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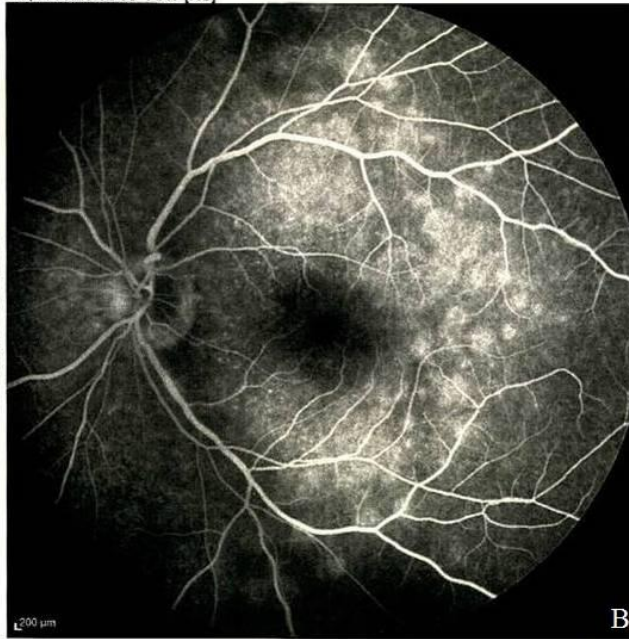


Fig 1. Fluorescein angiography in a patient suffering from MEWDS. A: Normal angiography in right eye. B: With dots are seen in the left eye due to the MEWDS (Patient was a young Iranian female).

Hypothesis

Authors of this study suggest CBNs for treatment of MEWDS due to their strong anti-angiogenic and anti-inflammatory activity. These compounds are able to inhibit and stop several inflammatory and angiogenic steps.

Evaluation of hypothesis

Regarding the data presented in introduction, it seems that VEGF, TNF- α , IL-6 and IL-8 play critical roles in MEWDS pathogenesis. As mentioned above, CBNs are categorized as anti-angiogenic and anti-inflammatory agents. Regarding the mentioned potentials, CBNs are also suggested for treatment of corneal neovascularization [7]. In angiogenesis profile, they can inhibit both migration and proliferation of endothelial cells (ECs) *in vivo*. So far, Ranibizumab® and Bevacizumab® have been used in order to treat MEWDS. These two strong anti-angiogenic monoclonal antibodies target VEGF [3-4] which is an angiogenic factor responsible for migration and proliferation of ECs and also an activator or inducer of other angiogenic cytokines such as matrix metallo proteinases (MMPs) [8-9]. On a molecular level, CBNs suppress expression and secretion of angiogenic factors such as VEGF-A, VEGF-B, VEGF receptor-2, hypoxia inducible factor-1 (a key element of angiogenesis), Ang-2 [10], MMP-2 and TNF- α [7].

They are able to reduce expression of TNF- α , IL-6 and IL-8 [9] and also alleviate inflammatory conditions such as uveoretinitis [11]. These cytokines also could be suppressed by methylprednisolone which has been used for treatment of MEWDS. Also CBNs are able to inhibit angiogenesis via decreasing endothelial cells proliferation and migration. Furthermore, CBNs are able to inhibit and suppress angiogenesis through different pathways such as suppressing PDGF, MMP-9 and endothelin-1 which may affect the molecular pathway of MEWDS [12]. Also CBNs are used in patients with recurrent glioblastoma multiforme with only a few minor side effects reported as hypothermia, bulimia and mild euphoria [13].

Conclusion

Considering the role of both neovascularization and inflammation and also different cytokines such as VEGF, TNF- α , IL-6 and IL-8 in possible molecular pathway interfere with MEWDS, it seems that suppressing any factor involved in mentioned pathways may be a treatment choice for MEWDS. It could be concluded that by aiming two targets of angiogenesis and inflammation with one shot, CBNs would be a reasonable choice of treatment for MEWDS. However, it is still of great necessity to do more investigations in the form of pre-clinical studies.

Acknowledgment

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Conflict of interest

There is no conflict of interest related to study from the authors.

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