Acta Scientific Neurology (ISSN: 2582-1121)

Volume 4 Issue 10 October 2021

Case Report

Cannabinoid Efficacy in Vanishing White Matter Disease: A Case Report

Giulia Galli[1]*, Virgilio E[1,2], Naldi P[1], Fornara R[4], Baricich A[5], Vecchio D[1,3] and Cantello R[1,3]

[1]Neurology Unit, Department of Translational Medicine, University of Piemonte Orientale, Azienda Ospedaliera-Universitaria Maggiore della Carità, Novara, Italy

[2]Phd Program in Medical Sciences and Biotechnologies, Department of Translational Medicine, University of Piemonte Orientale, Novara, Italy

[3]Interdisciplinary Research Center of Autoimmune Diseases (IRCAD), Department of Health Sciences, University of Piemonte Orientale, Novara, Italy

[4]Neurosurgery Unit, Department of Translational Medicine, University of Piemonte Orientale, Azienda Ospedaliera-Universitaria Maggiore della Carità, Novara, Italy

[5]Physical Medicine and Rehabilitation, Department of Translational Medicine, University of Piemonte Orientale, San Giuliano Hospital, Novara, Italy

***Corresponding Author:** Giulia Galli, Neurology Unit, Department of Translational Medicine, University of Piemonte Orientale, Azienda Ospedaliera-Universitaria Maggiore della Carità, Novara, Italy.

Received: September 08, 2021

Published: September 29, 2021

Abstract

Background: An oromucosal spray formulation (Sativex®) containing delta-9-tetrahydrocannabinol and cannabidiol is indicated to treat unresponsive severe spasticity in Multiple Sclerosis. A lot of clinical trials are underway demonstrating a potential role as supplemental therapy in various neurological conditions, in particular addressing pain and spasticity in adults and children.

Case Report: We present a 30-year-old man who was diagnosed with Vanishing White Matter disease at the age of 9. VWMS is a rare autosomal recessive syndrome characterized by progressive white matter deterioration, due to mutations in either one of the five subunits of eukaryotic translation initiation factor eIF2B. The classic phenotype includes ataxia, spasticity, cognitive decline and seizures from early childhood. As young adult, our patient showed severe spastic tetraparesis with spasms and neck muscle stiffness with right laterocollis. Clonazepam, baclofen and botulinum injections were tried with poor results. THC-CBD spray at the dose of 4 sprays per day improved muscular pain, spasms and night sleep, reduced modestly spasticity and caused only mild drowsiness. To maximize the spasticity treatment, a baclofen intrathecal infusion pump was positioned, but Sativex® was continued after surgery for its positive effect on patient's quality of life.

Conclusion: To our knowledge, this is the first time that THC-CBD has been in an adult patient with VWM. The treatment was well-tolerated, act moderately on spasticity but muscular spasm and night sleep improved as well as quality of life.

Keywords: Vanishing White Matter Disease; Leukoencephalopathy; Spasticity Treatment; THC-CBD Spray; Cannabinoids

Abbreviations

THC-CBD: Delta-9-Tetrahydrocannabinol and Cannabidiol; VWM: Vanishing White Matter Disease; MoCA: Montreal Cognitive Assessment; WAIS: Wechsler Adult Intelligence; MAS: Modified Ashworth Scale; FLAIR: Fluid Attenuated Inversion Recovery; QoL: Quality of Life; VAS: Visual Analogue Scale; NPRS: Numeric Pain Rating Scale

Introduction

Vanishing White Matter disease is a rare autosomal recessive syndrome characterized by progressive white matter deterioration, due to mutations in either one of the five subunits of eukaryotic translation initiation factor eIF2B, a stress-responder protein complex. The classic phenotype includes cerebellar ataxia, spasticity, modest cognitive decline and seizures from early childhood. Patients are particularly susceptible to stressful events, including febrile illnesses, which can precipitate the neurological condition even to death [1]. Patients with an earlier age of onset have a more severe form with rapid decline, while juvenile and adult forms are slowly progressive, so that the time to death ranges from few months to 15 years.

Spasticity reduces mobility, is associated with painful muscular spasms and weakness, and predisposes to disability. Many drugs have been reported to have an anti-spasticity effect, such as baclofen, benzodiazepines, tizanidine and cannabinoids. An oromucosal spray formulation (Sativex®), containing 1:1 fixed ratio of tetrahydrocannabinol (THC) and cannabidiol (CBD) is indicated in severe spasticity in adults with Multiple Sclerosis who have not responded adequately to other medication [2].

We describe a 29-year-old man with VWM who was treated with Sativex® for severe spasticity with benefit in his quality of life.

Case Description

A 29-year-old man with a previous diagnosis of VWM came to our attention almost wheelchair-bound. His medical history started when he was 9, presenting progressive limb ataxia and right mild emiparesis. According to a severe leukoencephalopathy on imaging and excluding differential diagnosis, he underwent genetic testing and was diagnosed with VWM disease at the age of 9 due to a mutation in gene EIF2B5. He was able to walk independently until the age of 12, when he started to use a cane. In his twenties he was still able to practice one-hour cyclette four times a week and to stand up from the sitting position ("Time up and go" Test 28 seconds). At 27 years old he progressively lost walking ability and one year later he became wheelchair bound. His clinical course was complicated by generalized tonic-clonic epileptic crisis at the age of 17, treated with valproic acid (1000 mg/die), tapered and stop at 23 years old. Then, after a nocturnal tonic epileptic seizure, he started levetiracetam (1000 mg/die) with benefit. Regarding the cognitive status, he was able to complete half of the high school studies and then he was employed as office clerk for few hours a week. At that time cognitive evaluation showed moderate impairment: reduced verbal fluency, MoCA 25/30 (normal values > 26/30), WAIS Scale 81. When he came to our attention, he had severe spastic tetraparesis, neurologic bladder with moderate urine retention and consequents infections. Neurological examination also showed absence of trunk control, spastic hypertonia at four limbs with spasms, hyperreflexia, bilateral achilles clonus, Hoffman and Babinski signs, neck muscles stiffness with right laterocollis. According to MAS, spasticity was assessed as follow: shoulder 3/4 bilaterally, right elbow and wrist 3/4, left elbow and wrist 2/4, hip 3/4 bilaterally, right knee and ankle 3/4, left knee and ankle 2/4. Brain MRI showed diffuse cystic degeneration of the white matter with hight intensity signal in FLAIR sequences (Figure 1A-1C); cervical spine MRI showed spinal hypotrophy (Figure 1D).

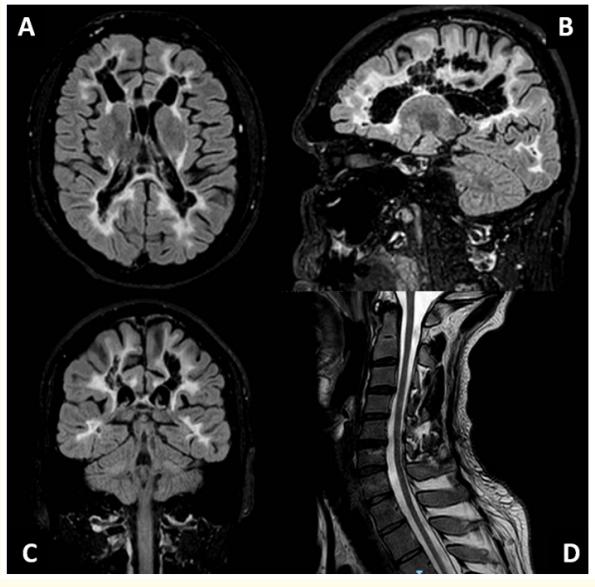

Figure 1: Brain MRI (A, B, C) shows diffuse symmetrical involvement of cerebral white matter with cystic degeneration. White matter presents with T2-FLAIR hyperintensity, extending from periventricular areas to the subcortical arcuate fibers, and over time it is replaced by CSF intensity fluid. Cervical spine MRI (D) shows prominent reduction of spinal diameters due to parenchymal hypotrophy.

First, a permanent suprapubic catheter was positioned to prevent further infections. Then, in order to treat spasticity, which was markedly disabling and painful, several medications were tried with limited effect: clonazepam (0.5 mg every 12 hours), well toler-

ated but ineffective; baclofen (25 mg every 12 hours), moderately effective but associated with drowsiness and cognitive-motor slowing; eperisone (300 mg/die), ineffective; botulin toxin injections (Dysport®) in right arm and leg muscles, useful at few courses. We subsequently tried oral THC-CBD spray (Sativex®). It was gradually titrated up to 8 sprays per day. In the following three months, we reported an improvement in muscular pain, spasm and night sleep, with a modest impact on spasticity (MAS reduced to 2-3/4 in right arm and leg). Compared to baclofen, drowsiness was minimal and did not interfere with daily activities. Finally, to maximize the spasticity treatment, a baclofen intrathecal infusion pump (Medtronic Syncromed II® 120 mcg/die) was positioned with limited side-effects and gradual, significant spasticity reduction (MAS reduced to 2/4 in the right limbs and 1+/4 in the left limbs). Sativex® was interrupted after surgery, but it was reintroduced 2 months later till 4 sprays per day for its benefits on patient's QoL, especially pain and sleep. After a six-month follow-up he stabilized at the condition described above. Despite symptom control, he became severely compromised in his daily life activities in about three years, as expected by the natural history of this disease, according to Health Utility Index Classification System (Table 1). Treatments were maintained as the caregiver reported a greater ease in transferring, passive mobilization and personal hygiene activities.

Grade	Description		
0	No increase in muscle tone		
1	Slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end of the ROM when the affected part(s) is moved in flextion or in extension.		
1+	Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the reminder (less than half) of the ROM.		
2	More marked increase in muscle tone throughout most of the ROM but affected part(s) easily moved.		
3	Considerable increase in muscle tone, passive movement is difficult.		
4	Affected part(s) rigid in flexion or extension.		
MAS	**Before THC-CBD spray**	**After THC-CBD spray**	**After baclofen infusion- pump**
Right arm			
• Shoulder	3	3	2
• Elbow	3	2/3	2
• Wrist	3	2/3	2
Left arm			
• Shoulder	3	3	2
• Elbow	2	2	1+
• Wrist	2	2	1+
Right leg			
• Hip	3	3	2
• Knee	3	2/3	2
• Ankle	3	2/3	2
Left leg			
• Hip	3	3	2
• Knee	2	2	1+
• Ankle	2	2	1+

Table 1: The modified Ashworth scale (Bohannon and Smith, 1987).

	2019	2021
Self-care	4: Requires the help of another person to eat, bath, dress or use the toilet.	4: Requires the help of another person to eat, bath, dress or use the toilet
Vision	2: Able to see well enough to read ordinary newsprint and recognize a friend on the other side of the street, but with glasses.	5: Unable to read ordinary newsprint and unable to recognize a friend on the other side of the street, even with glasses.
Hearing	1: Able to hear what is said in a group conversation with at least three other people, without hearing aid.	4: Able to hear what is said in a conversation with one other person in a quiet room, without hearing aid, but unable to hear what is said in a group conversation.
Speech	1: Able to be understood completely when speaking with strangers or friends.	4: Unable to be understood when speaking with strangers but able to be understood partially by people who know me well.
Ambulation	6: Cannot walk at all.	6: Cannot walk at all.
Dexterity	5: Limitations in use of hands or fingers, requires the help of another person for most tasks (not independent even with special tools).	6: Limitations in use of hands and fingers, requires the help of another person for all tasks.
Emotion	3: Somewhat unhappy.	2: Somewhat happy.
Cognition	2: Able to remember most things but have a little difficulty when trying to think and solve day to day problems.	5: Very forgetful and have great difficulty when trying to think or solve day to day problems.
Pain	2: Mild to moderate pain	3: Moderate pain that prevents some activities.
HUI3 Multi-Attribute Utility Function	0.009	- 0.259

Table 2: Health utility index classification system, as calculated during a 3-year follow up. As we can see Health-related quality of life (HRQL) significantly worsened as the disease progresses. The score is on a scale from 1.0 (perfect health) to 0.0 (death), but negative scores are possible (max -0.371) and indicates life conditions considered worse than death.

Discussion

To our knowledge this is the first time that THC-CBD is used in an adult patient with VWM. The treatment was well-tolerated compared to other medications (particularly baclofen) and caused only minimal drowsiness, that did not interfere with daily activities. Diffuse muscular pain, spasms and night sleep significantly improved, despite the effect on spasticity if scored only with MAS was limited.

Overall, our patient had an improvement in the QoL, as described in patients with chronic neuropathic pain [3]. Numerous trials demonstrated the efficacy of cannabinoids not only in Multiple Sclerosis, but in many other neurological conditions, such as amyotrophic lateral sclerosis, stroke, dystonia, neuropathic pain. In a study, 94% of patients obtained benefit from THC-CDB spray formulation, especially on muscle pain, night sleep and improvement in some daily activities, such as common objects manipulation and transferring. These impressions were largely confirmed by their caregivers [4]. However, the evaluation of QoL in neurological patients is complex and the use of evaluation scales only (ex. VAS or NPRS for pain, MAS for spasticity) provides an incomplete assessment, because they did not consider various aspects (ex. MAS only assets the difficulty in passively moving the limb of the patient and do not bear the relation to functional impairment or autonomy) [5]. For this reason, the effect of cannabinoids on spasticity, which was limited according to MAS, should be considered in a wider perspective.

Another important aspect is the synergic effect that different medications could have on the symptoms. In our patient the most effective pattern was obtained with the baclofen-infusion pump as-

sociated with Sativex®. The combination of different medications is probably the best approach in patients with neurodegenerative conditions, because provides a synergic action with lower doses of drugs, thus avoiding collateral effects.

Finally, our case remarks the importance of the off-label use of Sativex® in clinical practice. Although the effect of cannabinoids on spasticity could be modest, the smallest improvement in the quality of life of patients with neurodegenerative disorders should be valued.

Conclusion

To our knowledge, this is the first time that THC-CBD has been in an adult patient with VWM. The treatment was well-tolerated, act moderately on spasticity but muscular spasm and night sleep improved as well as quality of life.

Bibliography

1. Bugiani M., *et al*. "Vanishing white matter: a leukodystrophy due to astrocytic dysfunction". *Brain Pathology* 28.3 (2018): 408-421.

2. Cristino L., *et al*. "Cannabinoids and the expanded endocannabinoid system in neurological disorders". *Nature Reviews Neurology* 16.1 (2020): 9-29.

3. Cannabinoid Buccal Spray for Chronic Non-Cancer or Neuropathic Pain: A Review of Clinical Effectiveness, Safety, and Guidelines. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health (2016).

4. Notcutt WG. "A questionnaire survey of patients and carers of patients prescribed Sativex as an unlicensed medicine". *Primary Health Care Research and Development* 14.2 (2013): 192-199.

5. Shakespeare D., *et al*. "Anti-spasticity agents for multiple sclerosis (Review)". *The Cochrane Library* 1 (2009): CD001332.

Volume 4 Issue 10 October 2021