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Co-medication with Cannabidiol May Slow Down the Progression of Motor Neuron Disease: A Case Report

Gerhard Nahler*

CIS Clinical Investigation Support GmbH, Wien, Austria

***Corresponding author:** Gerhard Nahler, CIS Clinical Investigation Support GmbH, Wien, Austria, Tel: +43-1-5234015; E-mail: cis-qa@aon.at

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Abstract

Amyotrophic lateral sclerosis (ALS, also called Charcot disease, Lou Gehrig disease), is a progressive, neurodegenerative disease caused by the degeneration of motor neurons in the brain and spinal cord. There is no cure. This report describes a case of motor neuron disease with typical weakness in one leg, one hand and the tongue. Despite of treatment with riluzole, symptoms progressed relatively fast. Therefore, the patient decided to take cannabidiol (CBD, 2 × 200 mg/day) as co-medication, which was started 8 weeks after riluzole, and increased to a daily dose of 2 × 300 mg. Within 6 weeks, the impaired function of the right hand and foot reversed almost completely and dysphagia partially. Improvement was maintained for about 10 weeks, when again a slow progression of dysarthria and dysphagia was observed. Eighteen months after onset, speech is almost completely lost, and dysphagia also progressed. However, symptoms of the limbs (weakness, fasciculation, atrophy) worsened much less. It is concluded, that Co-medication with CBD may be able to slow down the progression of some but not all symptoms of motor neuron disease.

Keywords: Amyotrophic lateral sclerosis; Cannabidiol; Cannabinoids; Motor neuron disease

Abbreviations ALS: Amyotrophic Lateral Sclerosis; CBD: Cannabidiol; CB1: Cannabinoid Receptor 1; CB2: Cannabinoid Receptor 2; COX: Cyclooxigenase; GPR: G-protein coupled Receptor; IL: Interleukine; MND: Motor Neuron Disease; PPARg: Peroxisome Proliferator Activated Receptor gamma; THC: Delta-9-tetrahydrocannabinol; TNF-α: Tumor Necrosis Factor Alpha

Introduction

Amyotrophic lateral sclerosis, also called maladie de Charcot/Charcot disease or Lou Gehrig disease, is a rare neurodegenerative disorder characterized by progressive degeneration of motor neurons in the brain and spinal cord with an incidence of about 1 to 3 cases/100,000 [1]. It affects most often middle aged adults, men slightly more often than women.

Although ALS is clinically a heterogeneous disease, the first sign of ALS is often weakness in one leg, one hand, the face, or the tongue. The weakness slowly spreads to both arms and both legs. Over time, problems with speaking, eating, walking, and breathing increase. There is no cure. Weight loss is nearly ubiquitous in ALS and has a negative, statistically significant impact on survival [2]. The most common causes of death are pneumonia, lung- or heart failure. Respiratory failure occurs within three to five years of the onset of symptoms, though about 10% of sufferers live for 10 or more years. Because of the variability in the speed of the progression, median survival varies widely between 676 days [3] and 67 to 71 months [4,5]. As ALS-phenotypes differ, each person's disease course is likely unique.

The cause of ALS is unknown; in about 5 to 10% of the cases there is a positive family history. Some of these cases seem to be associated with mutations in the gene for an enzyme called copper-zinc superoxide dismutase 1 (Cu-Zn SOD1) which destroys reactive oxygen species (ROS), but a dozen or more of other genetic mutations may also be linked to ALS. Among the primary hypotheses underlying motor neuron vulnerability are susceptibility to excitotoxicity and oxidative damage. ALS patients' spinal cord demonstrates motor neuron damages marked by cannabinoid receptor 2 (CB2) positive microglia/macrophages and cyclooxygenase-2 (COX-2) activity that fuel neuroinflammation [6,7]. Oxidative stress, mitochondrial dysfunction and excitotoxicity are thus general hallmarks.

Actual treatment options approved by the FDA are limited; two drugs received so far marketing approval, Riluzole (Rilutek™) and Edavarone (Radicava™). Whereas Riluzole can be administered orally, Edavarone must be given by IV route. Riluzole may increase survival in certain groups by about 3 to 24 months at the best [4]; no reversal of symptoms has been reported. Complementary and alternative medicine may increase survival [2]. Given the lack of medications with a more pronounced effect on disease progression and survival, it is not surprising that many patients try complementary or alternative therapies.

Case Description

About eighteen months ago, the patient, a general practitioner at the beginning of his sixties, observed a painless weakness and impaired function of his right hand. Within about 3 weeks, paresthesia, at the beginning only on the little finger, progressed to the other fingers of the same hand, and included the foot of the same side, with a similar spread from digit 5 to digit 3, suspecting a motor neuron disease. With a slight delay, dysarthria was also observed. At the time of neurological examination, about three weeks after the first symptoms, the impaired function of the right hand and right foot as well as a slurred speech had progressed. Examination demonstrated hyporeflexia, positive Hoffmann's reflex, as well as abnormal electromyography findings with almost normal nerve conduction, suspecting ALS. There were no

sensory abnormalities. Diagnose was made on clinical aspects only; neuroimaging was not done. No risk factor (e.g., positive family history, smoking) was identified.

Riluzole (Rilutek™, Aventis Pharma S.A., Antony, France), 2 × 50 mg/d, was started; an increase to 2 × 100 mg/d was not tolerated due to severe sedation. To this treatment, Sanopal™ (a dietary supplement consisting of alpha-ketoglutaric acid, potassium hydroxid, 5-hydroxy-methylfurfural, magnesium chloride, saccharose and water, manufacturer: C.Y.L. Pharmazeutika GmbH, Laßnitzhöhe, Austria) was added. However, condition worsened, with fasciculation, muscle cramps, increased weakness, dysarthria as well as dysphagia. Therefore, 8 weeks after starting with riluzole, the patient included 2 × 200 mg cannabidiol (CBD) per day to his treatment regimen. Crystalline CBD of herbal origin (purity>99.5%) is available in Austria as pharmacy preparation in form of capsules, solutions of 10% and 20% or as suppositories (manufacturer: BSPG, Sandwich, UK; import: Trigal Pharma GmbH, Vienna, Austria).

Within two weeks on Co-medicationwith CBD, the patient noticed improvement of his symptoms, with a further amelioration when the dose was increased to 2 × 300 mg CBD/day. Six weeks after starting CBD, complete reversal of paresthesia in the foot was observed and most of paresthesia in the right hand; only a slight weakness remained in digit 5 and 4. Dysphagia also improved, whereas dysarthria remained almost stable without significant changes. Improvement was maintained for the following 10 weeks after which a slight progression of dysarthria was observed again. A dose increase to 2 × 400 mg CBD had no additional effect. During the following 12 months (now about eighteen months after onset) dysphagia, dysarthria and fatigue progressed; speech is actually almost lost. However, other symptoms worsened much less; the patient can still use his right hand and ride his bicycle, although muscle weakness and atrophy has slightly progressed. Other functions are maintained with no significant changes.

Discussion and Conclusion

Despite of growing evidence for an implication of the endocannabinoid system in the pathophysiology of motor neuron disease including ALS, as well as of potential benefits from cannabinoids, this is, to the best of our knowledge, the first report with pure CBD for treating a motor neuron disease.

Preclinical studies suggest neuroprotective and antiapoptotic activities of cannabinoids in neurodegenerative processes whereby animal experiments using a transgenic ALS mouse model demonstrated a prolongation of survival with Delta-9-tetrahydrocannabinol [8]. Later, a combination of phytocannabinoids, THC and CBD in a ratio of about 1:1 (nabiximols/Sativex™), was tested in SOD1-G93A mice with moderately positive results [9]. In two anonymous surveys, each including over 100 ALS patients, 10% to 21% judged medical marijuana very effective, particularly in stimulating appetite (75%), aiding sleep (65%), relieving anxiety (80%), relieving depression (70%), and providing muscle relaxation (60%) [10,11]. Annecdotal community reports exist as well. Further on, a four weeks, randomized, double-blind, cross-over pilot study of 19 ALS patients, 2.5-10 mg of dronabinol (synthetic THC) per day was associated with improvements in sleep and appetite; however cramps or fasciculation did not improve. A dose of 10 mg THC is considered dose-limiting [12]. These few clinical studies with medical marijuana, extracts or dronabinol demonstrate alleviation of some ALS-related symptoms; however, control of disease progression or even reversal was not reported. As up to one half of the motor neurons innervating a muscle may be lost in ALS before clinical signs of weakness or atrophy are found [13], rapid diagnosis and early onset of treatment seems to be crucial to delay symptom development.

CBD, a non-psychotropic cannabinoid, is well known for its multi-target effects, with potent anti-inflammatory and neuro-protective properties in neurological preclinical models [14], although the anti-inflammatory mechanism is still incompletely understood. Experiments have demonstrated that low doses of CBD act as adenosine A2A receptor-and Peroxisome Proliferator Activated Receptor gamma (PPARg) agonist, and as G-protein coupled receptor 55 (GPR55) antagonist, decreasing the levels of inflammatory mediators such as TNF-alpha, IL-6 and IL-12, without acting directly on cyclooxygenase 1 or 2 (COX-1, COX-2 [15]. In addition, CBD is a very potent anti-oxidant, more protective than α-tocopherol or vitamin C [16]. On CB1 receptors, CBD acts as negative allosterical modulator, decreasing partially the activity of ligands [17]. On CB2 receptors, CBD can act as receptor-inverse agonist. This may explain, at least in part, its anti-inflammatory effects and its inhibition of the migration of macrophages, microglial cells and neutrophils [18]. CBD shares with Riluzole effects on ion channels that are responsible for repetitive firing and transmitter release [19]. As some cases seem to be associated with mutations in the gene for copper-zinc superoxide dismutase 1 (Cu-Zn SOD1), a powerful natural antioxidant, it is noteworthy that CBD alters the expression of a wide range of genes involved in zinc homeostasis, oxidative stress, mitochondrial dysfunction, excitotoxicity, glutathione deprivation and anti-inflammatory signalling pathways [20,21].

These mechanisms of CBD are interesting as they fit many of the current hypothetical requirements for a successful drug for motor neuron diseases. Further on, CBD seems to be well tolerated and safe in humans, even at high doses and with chronic use [22], and can easily be combined with existing treatment regimens. However, more observations and thorough investigations are needed for assessing the potential role of CBD in this deadly disease.

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