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Research Article

Long COVID, the Mysterious Disease: A Role for Cannabidiol?

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Abstract

Long COVID is a mysterious condition characterised by a plethora of symptoms lasting 3 months but usually longer after the onset of the acute infection. Although its cause and mechanisms are still incompletely understood, current hypotheses favour an immunopathological nature leading to a multi-inflammatory, multi-organ syndrome that can persist for months or even years. It seems to be fuelled by persisting and/or newly formed antigens that trigger inflammatory responses at the side of tissue attacks by antigens. An impressive number of patients complain symptoms related to the nervous system such as chronic fatigue, concentration/memory/cognitive deficit, anxiety, Post-Traumatic Stress Disorder (PTSD), depression, sleep abnormalities and the like. Cannabidiol (CBD) is a substance that easily crosses also the intact blood-brain barrier, has anti-inflammatory properties and demonstrated immunomodulating effects in various immunopathological conditions. Although human experiences in Long COVID are still missing, CBD seems to be a promising substance.

Keywords: Autoimmune disorder; Cannabidiol; CBD; Chronic fatigue; Long COVID; SARS-CoV-2

Introduction

Post-acute coronavirus disease 2019 (COVID-19, PACD), and particularly "Long COVID" (sometimes called post COVID-19 syndrome, protracted COVID-19, post COVID-19 condition or persistent COVID) is still a mysterious condition characterised by a plethora of symptoms lasting 3 months but usually longer after the onset of the acute infection. A recent WHO document on Long COVID /post COVID-19 condition defines Long COVID as follows: "occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19, with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis" [1]. Such sequelae following recovery from an acute infection are not uncommon, and are observed, e.g., after Epstein-Barr virus or Borrelia burgdorferi (Lyme disease) [2]. Except in immunocompromised subjects, the presence of the infectious agent itself cannot be demonstrated in Long COVID. Therefore it should not be misinterpreted or confused with persisting infection.

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Multisystem Inflammatory Syndrome is Neither Acute COVID nor Long COVID

In very rare cases, a hyper inflammatory, sepsis-like syndrome (multisystem inflammatory syndrome, MIS) leading to serious, life-threatening secondary multi-organ dysfunction has been observed post acute COVID-19 infection in children (MIS-C, Kawasaki-like syndrome) as well as in adults (MIS-A) [3,4]. With an incidence in the order of 0.5 to 30/100,000 it is uncommon but more frequent in children than in adults, whereas the mortality rate in adults is approximately seven times as high as that seen in children [5]. MIS-A presents approximately one month after initial diagnosis of acute COVID-19, twice as frequent in men then in women, in whom an overlap between the symptoms of acute COVID-19 and MIS-A has been observed in 60% of cases studied [6]. Distinguishing MIS from both, acute biphasic COVID-19 and post-acute sequelae of SARS-CoV-2 infection or Long COVID respectively, is often difficult. The main presenting symptoms of MIS-A are fever, increased coagulopathy and impairment of cardiac function as well as of other organs [7,8]. Intriguingly, in most patients the virus had already been cleared from the nose and upper airways whereas virus RNA can still be found in the stool. At present it is not known exactly what causes MIS and how it could be prevented.

Long COVID is a Condition with a Wide Range of Symptoms

As mentioned, Long COVID should not be confused with an acute or protracted infection nor with MIS. Symptoms post SARS-CoV-2 infection are numerous and extremely heterogeneous. An early study that included 3,762 participants found 205 symptoms related to Long COVID with a mean number of 55.9 ± 25.5 symptoms per patient [9]. Of those, 45.2% required a reduced work schedule and an additional 22.3% were not working at all due to illness. Symptoms can last at least up to 15 months after infection [10]. Estimating the prevalence of 55 long term effects from 47,910 patients it was found that the five most common symptoms were fatigue (58%), headache (44%), attention/cognitive disorder (27%), hair loss (25%), and dyspnoea (24%) [11]. Other studies came to similar conclusions with the most frequently reported symptoms being chronic fatigue, concentration/memory/cognitive deficit, anxiety, post-traumatic stress disorder (PTSD), depression, sleep abnormalities, dyspnoea, cardiac dysrhythmia/ palpitations, diffuse pain, hair loss, and impaired/loss of smell and/or taste [12,13]. Although much less prominent than in MIS, impaired function of organs other than the heart or lung (e.g.,

liver, kidney, intestinal tract) can occur as well. Many of these symptoms have a high prevalence in the normal population which makes the assessment of causality and reliable percentages related to Long COVID difficult. Taken together, symptoms indicating impairment of the central nervous system particularly of cognitive symptoms ranks among the most prevalent sequelae. The common denominator of Long COVID seems to be an inflammatory process.

It is still subject of research why some patients get Long COVID and others not. Long COVID affects persons of all ages, anywhere from about 5% to 30% of those infected by SARS-CoV-2 [14]. Considering the large number of subjects that have been infected since the beginning of the pandemic in 2019/2020, it is easy to anticipate the enormous threat Long COVID represents, also in terms of both health and economic burden. It is more common with increasing age, in female subjects slightly more than in males, and also more prevalent in patients with a severe course of primary SARS-CoV-2 infection as well as in patients with comorbidities such as diabetes, high body mass index (BMI) and pre-existing autoantibodies [15,16].

Long COVID also affects children but data are scant despite that the high spread of virus in this group especially since they are less often vaccinated than adults. Although a severe course of acute COVID is less frequent in children than adults, it is becoming increasingly apparent that children are experiencing long-term effects as well, basically similar to that in adults. A recent review estimates the prevalence between 4% and 66% [17]. with symptoms being more common in the group aged between 6 and 18 years than in younger subjects [18]. Median or mean age was mostly between 9 and 13 years. According to an Italian survey, 43% children aged between 6 and 16 years, suffered from one or more symptoms for longer than 4 months [19].

Long COVID can occur regardless of the initial severity of infection, i.e. after severe symptoms, after very mild acute disease but also after asymptomatic infection. Long COVID-like symptoms have also been reported as resulting occasionally from vaccination (LongCOVIDSOS vaccine report 2021; available at go.nature.com/3yfqem2).

After 3 months, roughly 10% to 20% of those testing positive for SARS-CoV-2 still remain symptomatic. According to recent studies, some patients affected by Long COVID have still not recovered even after 12 months or longer [10,20]. Although less likely, Long COVID can occur despite having been vaccinated. The incidence of Long COVID is however reduced by more than 50% after the second vaccine dose. According to the Office for National Statistics of the UK (ONS), Long COVID symptoms have been reported by 9.5% of double-vaccinated adult subjects compared with 14.6% in a similar but unvaccinated group 12 weeks or later after infection. Of those, 42% still suffered even 12 months after infection to [21].

An international survey of 900 people of which more than 70% had been experiencing symptoms for nine months or more showed that non-vaccinated persons with Long COVID may benefit from vaccination; 56.7% of people saw an overall improvement and 11.4% reported that all their symptoms had improved, while worsening of part of their symptoms or relapses was reported by 18.7%. Only 2.9% indicated that *all* their symptoms had deteriorated [22].

The results vary depending on the symptoms investigated and may be further influenced by the nature of the vaccine administered. At present, neither a universally applicable diagnostic biomarker is known for Long COVID nor a unanimously accepted treatment. Most of the common blood tests fail to supply specific results.

Long COVID Seems to be a form of Immune Dysfunction

As above, Long COVID is considered to be a multi-inflammatory, multi-organ syndrome that can persist for months or even years. Most interestingly, trained sniffer dogs correctly discriminate all PCR-positive cases (256 cases with or without symptoms, i.e. 100% sensitivity). Of 203 "control" cases that were PCR-negative *and* asymptomatic, dogs detected further 6.2% that were initially PCR negative but turned positive after a repeat PCR-test (93% specificity in asymptomatic patients; [23].

In Long COVID patients (also named "long haulers") it is very likely that the ongoing inflammation is fuelled by some antigen that persists [24-26]. Multiple hypotheses exist that attempt to explain the phenomenon of this ongoing, long-term immune-activation. Chronic infection or inflammation respectively may be caused by a "viral reservoir" resulting from incomplete elimination of the virus itself and/or of virus particles by the immune system of the host organism [27]. Intriguingly, olfactory mucosa samples from patients showing long-term persistence of COVID-19-associated anosmia revealed the presence of virus transcripts and of SARS-CoV-2-infected cells, together with protracted inflammation [28]. Moreover, the virus could hijack brain tissue via the nose and the olfactory nerve tract by crossing the neural-mucosal interface. However, in none of the nasopharyngeal swabs the presence of SARS-CoV-2 could be demonstrated so far and also not in stool samples [29]. Nonetheless, virus particles such as the S1 fragment of the spike protein as well as virus mRNA may persist. Both could act as immunogenic factors that trigger the symptoms of long-COVID, in particular neuroinflammation.

One of the primary immunogenic factors seems to be the spike protein. It shares antigenic epitopes with human molecular chaperons resulting in autoimmunity, activating toll-like receptors (TLRs), and leading to release of inflammatory cytokines [26]. In a subset of monocytes of Long COVID patients (non-classical monocytes CD14Lo, CD16+), S1 spike protein fragments were found even 16 months after the initial infection [30]. They easily cross the intact blood-brain barrier (in contrast to protective antibodies) and enter brain parenchyma and other organs inducing local inflammation [31-33]. To a lesser extent, S1 spike protein fragments cross the intestinal barrier cell layer. Whereas in one study SARS-CoV-2-specific RNA could not be detected in the brain of 8 patients analysed [34], in a separate case report viral RNA has been isolated from the CSF of a female, 42-year old subject, about 4 months after confirmed infection [35]. Conversely, nucleic acids were found in biopsies of the small bowel as late as 4 months after the onset of COVID-19, in 50% of even asymptomatic individuals [24].

In addition to spike proteins, newly formed antigens could also play a role in Long COVID, although their contribution is less clear. A possible mechanism may be that after initial formation of antibodies against the virus, later on these protective antibodies trigger a new antibody response to themselves (secondary antibodies, anti-idiotype antibodies). As these potentially mirror the original antigen (molecular mimicry), they can clear the initial protective antibodies after a while, and can trigger the same receptors as the virus before, sharing its detrimental effects [36]. This could explain, together with the well

established presence of ACE2 receptors in a wide range of different cell types, why many symptoms of Long COVID overlap with the symptoms of acute infection.

A persistent elevation of inflammatory cytokines such as IFNβ, IFNγ, IL-6, IFNλ2/3 and pentraxin 3, as found in about 80% of patients with long-COVID, suggests a delayed or defective resolution of inflammation. Hyperstimulation of the immune system eventually leading to the development of immune dysfunction/dysregulation with multiple types of autoantibodies and autoimmune diseases, is known to occur after many other virus infections such as coxsackie virus, cytomegalovirus or Epstein Barr Virus (EBV) [16,37-39].

A dramatic increase in autoimmune reactivities in the course of COVID-19 seems to be more common than originally thought according to a number of recent studies [40-43]. A recent review showed that COVID patients may develop over 15 separate types of autoantibodies and above 10 distinct autoimmune diseases [44].

Intriguingly, the probability of developing Long COVID symptoms is clearly higher in patients with a severe course of the primary disease, and with other comorbidities such as type 2 diabetes, COPD, asthma bronchiale, reactivation of EBV and circulating mRNA fragments of SARS-CoV-2 (RNAemia) at the beginning of the acute disease [15,16]. In consequence, it is likely that more than just one single, isolated process triggers the large number of Long COVID symptoms.

A Role for CBD?

It has been suggested that the use of cannabis might be a risk factor for COVID or its complications. Whereas the Institut Nationale de Santé Publique de Quebec [45] found that current data are insufficient to support such a risk, an Ecological Geospatial Study on interactions between cannabis and coronavirus infections concluded that cannabis use correlated with coronavirus infection rates and is an independent risk factor similar to tobacco [46]. If so, then this may be related to the wide variety of different cannabinoids and plant constituents found in cannabis and cannabis extracts. In consequence, it is preferable to start by exploring the potential of individual cannabinoids such as highly pure cannabidiol (CBD).

CBD Demonstrated Immunomodulating Properties in Models of Autoimmune Disorders

Recently it has been shown that pure CBD inhibits SARS-Cov-2 spike (S) protein-induced cytotoxicity and inflammation through downregulating PPARγ [47]. Furthermore, binding of CBD to the spike protein has recently been demonstrated *in silico* [48]. CBD was also effective at inhibiting SARS-CoV-2 spike protein expression in host cells even 2 hours after infection, and effectively eradicated viral RNA expression [49]. Given that widespread and persisting neurological or psychiatric symptoms are the primary reported sequelae of infection [50], it is important to note that CBD easily crosses also the intact blood-brain barrier and can - similar to other cannabinoids - downregulate the immune response and neuroinflammation. CBD decreased the T cell infiltration into the CNS, the number of Th1 and Th17 proinflammatory cells (known to be increased in inflammatory autoimmune pathologies) and the production of the proinflammatory cytokines such as interleukin (IL) IL-1b, IL-6, IL-12, IL-17A, interferon (IFN)-γ, and Tumour Necrosis Factor (TNF-α). Conversely, CBD has been shown to increase levels of anti-inflammatory cytokines such as IL-4, IL-10 and TGF-β [51]. In the following, a few animal models of autoimmune disorders that studied effects of CBD are described in more details.

Multiple Sclerosis (MS)

In more than 12 different preclinical rodent models CBD has demonstrated immunomodulating effects in a variety of autoimmune disorders such as in experimental autoimmune encephalitis (EAE), the canonical murine model for multiple sclerosis (MS). CBD (mostly 5mg i.p./kg/day up to 20mg/kg/day, beginning from immediately after EAE induction to up to 32–68 days) was consistently effective in reducing the severity of EAE; it delayed the onset of symptoms, attenuated clinical signs and reduced disease progression (reviewed by [52]. Such doses would correspond to relatively low daily doses of 0.4 to 1.6 mg/kg in man.

T Cell–Mediated Chronic Autoimmune Myocarditis

Myocarditis is often associated with autoimmune processes in which cardiac myosin is a major autoantigen. In a mouse model of experimental autoimmune myocarditis, CBD (10mg i.p./kg/day) attenuated T cell–mediated inflammation, associated oxidative stress markers (IL-1ß, IL-6, IFN-γ, MCP-1), and cardiomyocyte cell death. Furthermore, it protected against fibrotic remodelling of the myocardium and prevented from myocardial dysfunction [53].

Diabetes Mellitus Type 1 (DMT1)

DMT1 (insulin-dependent diabetes) is a chronic autoimmune disorder characterized by the destruction of pancreatic ß cells and autoantibodies against some pancreatic proteins, such as insulin, glutamate decarboxylase, islet antigen 2, zinc transporter 8, and tetraspanin-7. CBD (1-10-20 mg i.p. /kg /day, for 3 months) administered to mice at the onset of streptozotocin-induced diabetes, prior to identified pain, limited the development of later neuropathic pain and prevented increases in microglial density and the expression of phospho-P38 (p-p38) mitogen-activated protein kinase in the dorsal spinal cord [54].

Rheumatoid Arthritis (RA)

Articular cartilage degeneration in RA is mediated through matrix metalloproteinases (MMPs), particularly MMP-2, MMP-3, and MMP-13. CBD reduces in vitro nuclear factor-κB (NF-κB) activation and consequently the degradation of collagen and proteoglycans as well as the production of MMP by fibroblasts. Furthermore, CBD increases intracellular calcium levels, reduces cell viability and IL-6/IL-8/MMP-3 production of rheumatoid arthritis synovial fibroblasts [55]. Altogether, these effects contribute to reducing the extracellular matrix degradation in the articular cartilage. In murine collagen-induced arthritis, CBD, administered after onset of clinical symptoms, showed a dose dependent suppression of disease with an optimal effect at 5mg/kg per day i.p. or 25 mg/kg per day orally. Clinical improvement was associated with protection of the joints against severe damage [56].

In other inflammatory immune disorders such as Systemic Lupus Erythematosus (SLE) or ulcerative colitis no improvement could be demonstrated so far in animal models.

CBD has a Favourable Effect on Immunopathological Conditions also in Humans

Although clinical studies in immune-mediated disorders in humans are still scarce, favourable effects of CBD have been reported in various articles. These observations are briefly summarised below.

In a phase II study, CBD (300mg/day) was given orally to 48 patients undergoing allogeneic haematopoietic cell transplantation (alloHCT) starting 7 days before transplantation until day 30, together with a standard GVHD prophylaxis consisting of cyclosporine and a short course of methotrexate. None of the patients developed acute GVHD while consuming CBD. In comparison to historic controls, the median time to onset of acute GVHD was significantly longer in subjects receiving CBD compared with the control group (60 versus 20 days, $p = 0.001$); relapse mortality at 1 year after transplantation were also in favour for CBD (CBD 8.6%, controls 13.4%). Furthermore, patients treated with CBD had less often skin and gastrointestinal problems [57].

Low dose CBD may also improve "ASIA-syndrome" which seems to be related to a disturbed immune system after vaccination [58]. In an open study, pure CBD dissolved in hemp seed oil was administered to 12 young female patients (aged 12–24 years) with ASIA-syndrome (autoimmune/inflammatory adjuvant-induced syndrome) which is characterized mainly by headache, insomnia, chronic fatigue, cognitive problems, muscle weakness and neuropathic pain, symptoms similar to Long COVID. All had also high titers of autoantibodies such as anti-Epstein-Barr Virus (EBV), Anti-Nuclear Antibody (ANA), and HLA. The common feature of these clinical conditions is previous exposure to an external stimulus (including HPV-vaccines) that triggers an undefined immune mediated response. Treatment was started with 25mg CBD/5ml sublingually per day, increased by 25mg CBD/5ml every week up to 150mg CBD/30ml/day after 6 weeks. After the 7th week, the dose was slowly decreased, again in weekly steps of 25mg/5ml/d. Four patients dropped out. In the remaining 8 patients, quality of life assessment (SF-36) showed significant benefits in the physical component score, vitality, social role functioning and a significant reduction of pain after the 3-months treatment.

Rheumatoid arthritis is another autoimmune disorder, affecting joints. A patient with rheumatoid arthritis and treatment-resistant chronic pain since 10 years showed marked improvement after adding CBD (2x 200mg/day) to his treatment (aprednisolone, metamizol, hydromorphone, adalimumab, stable since 2 years). Pain scores (VAS) and pain medication except adalimumab was reduced by CBD by more than 50% [59].

CBD Improves Symptoms that are Common in Long COVID Patients

Apart from these examples of immunomodulating effects in man, CBD (about 300mg/day) positively affects a number of typical symptoms of Long COVID such as anxiety [60,61], sleep, post-traumatic stress disorder [62], cognitive impairment [63], and diffuse pain including neuropathic pain [64], whereas wakefulness was increased [65], In patients with Parkinson's disease, CBD (up to 300mg/day) improved complex sleep-related behaviours associated with Rapid Eye Movement (REM) sleep behaviour disorder [66]; REM sleep behaviour disorder may be associated with neurodegenerative conditions. Moreover, CBD (20mg/kg/day, 8 weeks) improved behaviour in intellectually disabled children in a small double-blind, randomised, placebo-controlled pilot study (4 received CBD, 4 placebo) [67].

Discussion and Conclusion

Studies of CBD in patients with Long COVID are still required. However, in a large case series that compared patients hospitalised for acute SARS-CoV-2 infection, it was demonstrated that CBD (up to 300mg/day) improved a number of laboratory parameters such as PCR results, lymphocyte counts, LDH, ferritin and CRP compared to a historic control group not receiving CBD but the same standard care [68].

Similarly, in acute SARS-CoV-2 infection stages, CBD (2x 10mg/d) plus melatonin (20mg/d) with or without angiotensin 1-7 supplementation (2x 0.5 mg/day orally) achieved a rapid disappearance of fever and myalgia in COVID19-infected patients, as well as a relief of asthenia compared to patients who received standard care only (paracetamol, expectorants, low dose dexamethasone). Hospitalisation for respiratory failure occurred only in the control group (5/30 i.e. 17%) [69]. Moreover, in a cross-sectional analysis of 93,000 patients tested for SARS-CoV-2, patients taking pure CBD had the lowest rate of testing positive (1.2%) compared with a matched group of the general population not taking CBD which had a 10 times higher infection risk [49]. It should be noted that in that analysis combination of CBD with THC (1:1) suppressed the efficacy of CBD. Moreover, the study's findings do not suggest that consuming commercially available products with CBD additives that vary in potency and quality ("CBD-oils") can prevent COVID-19. Only CBD was effective but not other closely related cannabinoids.

In summary, preliminary data suggest that CBD possibly has a favourable influence on the acute phase of the disease in hospitalised patients. Pure phyto-CBD is well tolerated and available for treatment in a number of countries. Moreover, a number of preclinical observations show that CBD has a positive influence on a dysregulated immune system, reduces inflammation and improves a number of symptoms commonly observed in patients with Long COVID.

Therefore one might speculate that CBD could be a treatment option in patients with Long COVID. This remains, however, to be demonstrated in appropriate clinical trials.

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