International Journal of Immunology Research
www.immunologyjournal.in
Online ISSN: 2664-8873, Print ISSN: 2664-8865
Received: 18-10-2021, Accepted: 04-11-2021, Published: 19-11-2021
Volume 3, Issue 1, 2021, Page No. 1-3
DOI: https://doi.org/10.33545/26648865.2021.v3.i1a.7

A therapeutic neuroimmune proposal with the pineal hormone melatonin, cannabidiol and angiotensin 1-7 in the treatment of post-covid19 syndrome

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Abstract
It has been shown that the link of Covid19 spike protein to ACE2 receptors does not allow only the entry of virus into the cells, but also a reduced ACE2 functions, with a following diminished production of its main product, Ang 1-7, which has appeared to play a fundamental anti-inflammatory role. In more detail, Ang 1-7 has been shown to inhibit the secretion of the main inflammatory cytokines, including IL-17, IL-6 and TNF-alpha, which are responsible for Covid19 infection-related respiratory distress and thromboembolic events. Ang 1-7 deficiency could explain at least in part the persistence of some cardiopulmonary and neurological disfunctions, which constitute the post-Covid19 syndrome. Other two fundamental neuroendocrine systems involved in the control of the inflammatory response are represented by brain endocannabinoid system and the pineal gland through its most studied hormone, melatonin (MLT). Because of the complete lack of therapeutic indications in the treatment of the post-Covid19 infection syndrome, on these bases a study was planned with Ang 1-7, MLT and cannabidiol (CBD) in patients with post-Covid19 persistent asthenia and other symptoms. The study included 14 patients. All drugs were orally administered. Ang 1-7 was given at 0.5 mg twice/day, MLT at 50 mg/once day in the night, and CBD at 10 mg twice/day. An evident relief was reached within the first week of therapy in 12/14 (86%). An improvement of dyspnoea was also obtained in 3/4 (75%) patients. Finally, myalgia, neuropathy, and mood also improved, while the diminished taste perception persisted for a longer time. This preliminary results would suggest that a neuroendocrine regimen carried out to correct possible Covid19 infection-induced Ang 1-7-pineal and cannabinoid deficiencies, may improve the symptomatology of post-Covid19 syndrome.

Keywords: angiotensin 1-7, cannabidiol, covid19 infection, melatonin, post-covid19 syndrome

Introduction

Covid19-induced death has appeared to be mainly depending on respiratory failure due to a clinical form of acute respiratory distress syndrome (ARDS), and on thromboembolic phenomena [1-3]. Both events have been proven to depend on an exaggerated inflammatory response following the abnormal release of inflammatory cytokines induced by the link of viral spike protein to ACE2 receptor on cell surface [4]. The main involved cytokine would be represented by IL-17 [5], which may stimulate the release of other inflammatory cytokines, including IL-6 and TNF-alpha [6], furtherly inhibit ACE2 expression [7], and induce endothelial alterations and enhanced capillary permeability [8, 9], with consequent ARDS and thrombotic events. The block of ACE2 activity induced by both viral link and enhanced IL-17 secretion allows a diminished production of its active product, angiotensin 1-7 (Ang 1-7), which is provided by anti-inflammatory activity and protective effect on the cardiovascular system and on lung functionless [10-12]. Then, the pathogenesis of Covid19 disease could simply consist of an acute and severe Ang 1-7 endogenous deficiency, with a consequent uncontrolled inflammatory response. Moreover, it has been shown that Covid19 infection is followed by the persistence of several symptoms, including respiratory dysfunction, autoimmune phenomena promoted by the exaggerated cytokine secretion, vasculitis, thrombotic predisposition, anti-phospholipid syndrome, myositis, myocarditis, central or peripheral neuropathy and cognitive decline, which constitute the post-Covid19 syndrome [13-15]. The block of the activity of ACE2-Ang 1-7 system induced by the interaction between viral spike protein and ACE2 receptor would require a long period of time to replace its functionless. Therefore, the symptomatology of post-Covid19 syndrome would be due at least in part to a persistent Ang 1-7 deficiency. In more detail, it has been shown that Ang 1-7 may inhibit TGF-beta secretion [16], which has appeared to be responsible for Covid19 infection-induced fibrotic processes [17]. The importance of the inhibitory action of Ang 1-7 on the fibrotic evolution of Covid19 infection is furtherly amplified by the evidence that asymptomatic infected patients may also present a fibrotic evolution, with the consequent disturbances of the function of lungs and other organs [15]. On the bases, the continuous administration of Ang 1-7 as a substitutive therapy could represent the main therapy of post-Covid19 syndrome [18]. Moreover, because of the existence of a neuroendocrine regulation of the cytokine network and of the inflammatory response [19], mainly mediated by the pineal gland [20] and the endogenous cannabinoid system [21], the pineal hormone melatonin (MLT) and cannabinoid agents, such as cannabidiol

(CBD), could also be effective in the treatment of Covid19 infection-induced chronic inflammatory status by inhibiting IL-17 secretion [21, 22]. Moreover, both MLT [23] and Ang 1-7 [16] have appeared to inhibit TGF-beta-induced fibrotic processes following the Covid19-induced exaggerated inflammatory status. At present, there is no clear specific indicated therapy for post-Covid19 syndrome other than the simple physiotherapy. On the contrary, since Covid19 physiopathology would essentially consist at least in part of a severe Ang 1-7 deficiency, the therapy of post-Covid19 syndrome could simply be represented by the exogenous replacement of Ang 1-7 defect. On these bases, the present preliminary study was performed to evaluate the efficacy of a neuroimmune regimen containing Ang 1-7, MLT and CBD in the treatment of post-Covid19 syndrome.

Patients and Methods

The study included 14 consecutive patients (M/F: 6/8; median age 63 years, range 48-83) with molecular diagnosis of Covid19 infection by RT-PCR assay, and important symptomatology, 5 of whom were demitted from the hospital after hospitalisation for initial or severe respiratory failure, which required mechanical ventilation, where the other 9 patients were followed by home therapy. Eligibility criteria were, as follows: previous molecular diagnosis of Covid19 infection by RT-PCR assay, symptomatic disease, negativity of molecular diagnosis, but with persistence of an important symptoms, consisting of asthenia in association with at least another symptom, including dyspnoea, loss of taste, neuropathic pain, myalgia, peripheral neuropathy, mood depression, and disturbances of consciousness. After the approval of the Ethical Committee, the experimental protocol was explained to each patient, and written consent was obtained. As far as the symptomatology is concerned, in addition to asthenia, which occurred in all patients, other symptoms consisted of moderate dyspnoea in 4/14 (29%) patients, myalgia in 3(21%), peripheral neuropathy and neuropathic pain in 2 (14%), low taste perception in 2, and mood depression in 2 patients. All drugs were orally administered. MLT was given at 50 mg/day in the dark period, CBD at 10 mg twice/day and Ang 1-7 at 0.5 mg twice/day. The treatment was continued without interruption for at least one consecutive month. The immune status was evaluated by detecting the lymphocyte-to-monocyte ratio (LMR). Normal values observed in our laboratory (95% confidence limits) was greater than 2.1, with lymphocyte number more than 1,500/mm3 and monocyte count below 500/mm3. Data were reported as mean +/- SE, and statistically analysed by the chi-square test and the Student's t test.

Results

Clinical characteristics of patients and their response to therapy is reported in Table 1. The treatment was well tolerated in all patients, and no side-effect occurred. Particularly, no important decline in blood pressure values was observed. On the contrary, most patients referred a relief of anxiety and an improvement in their quality of sleep. Moreover, a relief of asthenia occurred in 12/14 (86%), which was rapidly achieved within few days of treatment in 7 patients and more progressively in the remaining 5 patients. Significant differences in the relief of asthenia were seen neither between males and females (5/6 vs 7/8), nor between patients younger or older than 60 years (5/6 vs 7/8). Dyspnoea rapidly improved in 3/4 (75%) patients. On the same way, myalgia, neuropathic pain, and depression improved in all patients, while the low taste perception persisted for a longer time. Moreover, most patients also experienced a perception of a major integration between consciousness and biological body. In addition, most patients referred an increased diuresis. No therapy-related toxicity was observed. On the contrary, most patients experienced a relief of anxiety and an improvement in the quality of sleep. Finally, as far as the immune profile is concerned, a normalization of monocyte count occurred in all four patients with persistent monocytosis prior to therapy, and lymphocyte count increased, without, however, significant differences with respect to the pre-treatment values. Therefore, LMR mean values observed at the end of therapy were significantly higher than prior to therapy (2.9 +/- 0.2 vs 2.1 +/- 0.1, $P< 0.05$).

Discussion

The present preliminary results would suggest that a neuroendocrine regimen with Ang 1-7, the pineal hormone MLT and cannabinoid agents may improve the subjective and objective symptomatology of the post-Covid19 syndrome, which could be due to a persistence of an inflammatory status, and probably to a persistent Ang 1-7 deficiency induced by the same infection. The important anti-inflammatory action of MLT, CBD and Ang 1-7 would explain their ability to correct the persistence of an inflammatory condition, as reflected by the evidence of monocytosis in the same patients. The most evident therapeutic effect induced by the neuroimmune regimen in the present study was the relief of asthenia, and this evidence is important from a physio-pathological point of view, because of the mechanisms responsible for asthenia as a loss of forces need to be better investigated and defined. Recently, it has been demonstrated the existence of a ACE2-Ang 1-7 system also at brain level [4, 11], which could play cognitive functions, including the status of consciousness, the emotions, and the subjective perception of own forces. Then, Covid19 infection-induced Ang 1-7 deficiency could allow the symptomatology of asthenia. Before Covid19 dramatic planetary experience, the knowledge of the fundamental role of Ang 1-7 in modulating the biological immuno in flammatory response was only known to the experimental scientists [10-13], but now each clinician needs to taken into consideration the fundamental role of Ang 1-7 in the regulation of all biological functions, mainly host inflammatory response itself, and to be conscious that an acute deficiency of Ang 1-7 may be responsible for death due to ARDS or generalized thromboembolism, as well as that a possible chronic Ang 1-7 deficiency, as probably occurring in the post-Covid19 syndrome, may imply consciousness disturbances and cardiopulmonary disfunctions. In conclusion, with respect to the common guidelines, which has no specific therapy for the post-Covid19 syndrome other than physiotherapy, this preliminary study would suggest that a neuroendocrine approach carried out to correct possible Covid19 infection-induced deficiencies involving the pineal gland, brain cannabinoid system, and ACE2-Ang 1-7 system by an exogenous substitute therapy with the pineal MLT, cannabinoids and Ang 1-7 itself may contribute to resolve the symptomatology of post-Covid19 syndrome. The time required to treat the post-Covid19 syndrome would probably depend on

the entity of Covid19 infection-induced alterations of ACE2-Ang 1-7 system, as well as brain cannabinoid system, and the pineal gland. Therefore, these preliminary results justify further randomized studies to confirm the efficacy of a neuroendocrine regimen with MLT, cannabinoids and Ang 1-7 in the treatment of post-Covid19 infection syndrome.

Table 1: Characteristics of patients and their response to therapy with melatonin, cannabidiol and angiotensin 1-7.

Cases	Sex	Age	Hospitalisation	Symptomatology	Therapeutic Response
1	M	64	yes	Asthenia and neuropathic pain	Progressive complete resolution
2	F	65	no	Asthenia and loss of taste	Progressive resolution of asthenia
3	F	56	no	Asthenia and mood depression	Rapid resolution of mode depression
4	M	66	yes	Dyspnoea and asthenia	Slow resolution of both symptoms
5	F	52	no	Asthenia and loss of taste	Rapid resolution of asthenia
6	M	83	no	Dyspnoea and asthenia	Rapid resolution of dyspnoea
7	M	62	no	Asthenia and myalgia	Rapid resolution of both symptoms
8	F	48	no	Asthenia and myalgia	Rapid resolution of asthenia
9	M	53	no	Asthenia	Progressive resolution of asthenia
10	F	72	yes	Asthenia and myalgia	Rapid resolution of both symptoms
11	F	52	no	Asthenia and mood depression	Slow resolution of both symptoms
12	M	58	yes	Dyspnoea and asthenia	Slow resolution of both symptoms
13	F	72	no	Asthenia and neuropathic pain	Rapid resolution of both symptoms
14	F	63	yes	Asthenia and dyspnoea	Slow resolution of both symptoms

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