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CASE REPORT

Ginkgo biloba Extract Containing Plasmalogen May Improve Long COVID and Brain Fog: A Case Report

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ABSTRACT

Other than pneumonia, Long COVID is currently cited as a problem with COVID-19. Among them, brain fog is a particular problem. Brain fog, as the name suggests, refers to a state in which the brain is foggy, and it is thought that there is a communication abnormality in the central nervous system, including fatigue. It has been pointed out that this may be caused by a cytokine storm, and since it lowers QOL (Quality of Life), countermeasures are urgently needed. In this study, we used plasmalogen containing *Ginkgo biloba* extract and found improvement in patients complaining of brain fog. As a result, we were able to confirm a case of excellent efficacy, which we report here.

Introduction

Although COVID-19, which has seen a global pandemic, seems to have calmed down somewhat, it has been repeatedly increasing and decreasing, so it cannot be said that it has converged yet [1]. Currently, although the number of people infected with COVID-19 itself has stabilized in Japan, there are many patients who are worried about the sequelae caused after infection, especially brain fog [2]. According to the WHO (World Health Organization), "in people with COVID-19, persisting for at least two months, and unexplained as a symptom of another disease (usually three months after the onset of COVID-19. It can also be seen after a month.)" and defines sequelae (post COVID-19 condition) [3]. Brain fog, as the name suggests, is a state in which the brain continues to be foggy [4], concentration is lost [5], a state of constant fatigue [6], and voice comes in even when spoken to a decline in cognitive function such as the inability to understand the content [7]. These are not medically defined diseases but are defined only as symptoms [1]. Since it is quite possible that Quality of Life (QOL) deteriorates in this symptom, countermeasures are urgently needed [8]. SARS-CoV-2, the cause of COVID-19, infects the epithelial cells of the upper respiratory tract, but if the infection ends there and inflammation occurs, the symptoms will be relatively mild [9]. However, when SARS-CoV-2 reaches the alveoli, it is known to cause fatal symptoms due to pneumonia and Acute Respiratory Distress Syndrome (ARDS) [10]. As mentioned above, the aftereffects of COVID-19 are a problem, and two factors are thought to be the causes. The first is thought to be caused by cytokine storm, which is the excessive release of cytokines after infection with COVID-19 [11]. Second, the virus itself destroys the Blood Brain Barrier (B.B.B),

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invades the brain, and presents the CNS [12]. It is believed that this is caused by suppressing the release of neurotransmitters in the brain [13]. At present, TMS (repetitive transcranial magnetic stimulation) treatment is available as a treatment method [14], but at this stage it can only be performed at specific medical institutions. In addition, the current situation is that it has not spread to the general public at this stage, such as cases where it is necessary to go to the hospital. Therefore, there is an urgent need to search for a method that can be treated with pharmaceuticals and functional foods.

Brain fog is characterized by the following symptoms [15].

1. Persistent fatigue.
2. Malaise.
3. Cognitive decline.
4. Difficulty returning to work.
5. Perceived stress.

It is thought that these are characteristically caused by insufficient neurotransmission in the brain. In other words, it is thought that information processing in the brain cannot catch up due to insufficient secretion and action of neurotransmitters such as acetylcholine, resulting in these symptoms [16,17].

Although there are still many unknowns about the treatment of brain fog, one hypothesis is that by addressing these two points, insufficient blood flow to the brain and stimulation of the brain, it is predicted that brain fog will be improved [18,19]. Therefore, this time, we used *Ginkgo biloba* extract [20] as a substance that improves blood flow in the brain and plasmalogen [21,22], which is said to stimulate the brain itself. I tried an approach to brain fog. If the hypothesis is proved in this research, we can approach the elucidation of the mechanism of brain fog in the future, and furthermore, plasmalogen containing *Ginkgo biloba* extract is effective for Alzheimer's dementia, which is considered to be an extension of this research [23].

Case Report

With the approval of the Ethics Committee of the Hino Kosei Clinic (HKC_N10032022), the questionnaire was collected anonymously via the Internet. Since it is assumed that you have contracted COVID-19, we compiled a questionnaire on the following items ($n = 87$). In addition, the questionnaire items were created based on the details examined by the Brain Fog Study Group.

Question	Answer
1. Have you ever tested positive for COVID-19?	YES: 53 (60.9%) NO: 34 (39.1%)
2. Have you ever had COVID-19?	YES: 53 (60.9%) Maybe yes: 10 (11.5%) NO: 24 (27.6%)
3. Have you taken any psychiatric drugs such as sleeping pills or antidepressants for 10 or more consecutive days in the last 3 months?	YES: 14 (16.1%) NO: 73 (83.9%)
4. Do you feel stressed out every day?	YES (Short time): 34 (39.1%) YES (Long time): 40 (46.0%) NO: 13 (14.9%)
5. Do you feel like you have a fog in your head?	Occasionally experience: 27 (31.0%) Now experiencing: 54 (62.1%) NO: 6 (6.9%)
6. Do you feel like you are dreaming even though you are awake?	YES: 46 (52.9%) NO: 41 (47.1%)
7. Do you have sudden lethargy?	YES: 72 (82.8%) NO: 15 (17.2%)
8. Do you feel more irritable lately?	YES: 52 (59.8%) NO: 35 (40.2%)
9. Do you have a habit of using negative words such as troublesome?	YES: 59 (67.8%) NO: 28 (32.2%)
10. Do you feel like you've suddenly become more forgetful lately?	YES: 71 (81.6%) NO: 16 (18.4%)
11. Do you feel sluggish?	YES: 80 (92.0%) NO: 7 (8.0%)
12. Is it becoming more and more difficult to do housework these days?	YES: 64 (73.6%) NO: 23 (26.4%)
13. Tired of going out?	YES: 72 (82.8%) NO: 15 (17.2%)

14. Have you noticed a change in how long it takes you to wake up in the morning and take action?	YES (since 2-3 years ago): 21 (24.4%) YES (recently): 40 (46.5%) NO: 25 (29.1%)
15. Have you been trying to do something but have been finding it difficult to take action recently?	YES: 74 (85.1%) NO: 13 (14.9%)
16. "Free description" What kind of symptoms do you have? Have you been in the past?	Irritability, nightmares, heart palpitations, nervousness, headaches, a feeling of hollowness in the head, a feeling that blood is not flowing throughout the brain, and difficulty in speaking and writing.
17. Free description (Excerpt representative examples)	<ul style="list-style-type: none"> • I contracted COVID-19 in April. After that brain fog continues • My forgetfulness has gotten worse recently. • The content that I was trying to talk about just before is completely lost. • When I went out to eat with a friend on a day when I had a combination of lack of sleep and mental and physical fatigue, I felt like my body was awake, but my brain was asleep. What she wanted to say came to her mind, but she couldn't say it, and she couldn't respond well. I can only return reactions that seem appropriate. • -sleepiness. • I can't think of anything. • It feels like the inside of your head is foggy rather than foggy. • It feels like there are many invisible walls between the real world and the real world. • My head is empty and I can't think of anything. • -I do not want to do anything. • I feel very tired. • It was difficult to have a conversation because I couldn't understand the conversation and it was all I could hear. • Frequently misspelled words in conversations. • I forgot what I was asked to do the moment I left the room. • It is difficult to live with only oblivion, such as forgetting even if you put it in the microwave. • Difficult to recall. • I can't do anything, and I have no choice but to lie down and rest quietly and wait for recovery. • I can't read books or long sentences. • Simple calculations are difficult. • Decreased ability to concentrate Decreased ability to think Lack of short-term memory. • I feel like my brain gets tired quickly. • - Poor concentration. • -Difficulty remembering conversations. • I can't speak fluently. • Forgetting what you feel or think. • I don't always have a clear head. • Immediately after giving the pet water, forgetting to give it. Obviously funny. • Numerical analysis and analysis work in the work content was easy until now, but it is not progressing. • I can't read and understand the manual correctly. • Extreme fatigue and drowsiness after just a few minutes of mental work. • Unable to sit still. • I can't understand the words of the person I'm talking to face to face. • Even though you know what you want to say in your head, it doesn't come out easily. • Even though I do it all the time, I can't do it unless I think a little and remember the procedure. • Even if I like to do something, I can no longer concentrate. • During work, when my boss is speaking, I try to understand and listen, but when the conversation is over, I find myself unable to understand the main points. • Dangerous to drive. • I can't read the characters. • I can't hear the words. • Sometimes it's hard to explain because it's hard to say. • Feeling that the head is light. • I can't keep up with the conversations around me. • I can't remember the past. • It's difficult to read the atmosphere because you can't turn your head. • Thoughts are very shallow. • For that reason, I am at a loss as to how to react in everyday conversation. • Being very stressed and feeling depressed as a result. • It is especially stressful at work. I have a strange self-awareness, but when I see it from the surroundings, I can't see it. • There are times when I think I would be better off dead if this continues. • I'm wondering if I should take a leave of absence from work. • I can't concentrate for a long time, and I can read for hours, but I can only read for about 10 minutes. • I can't remember the sentences. Even short words and numbers that I intended to memorize are quickly forgotten. • Even if I listen to people talk, it doesn't stay in my head. • I'm not good at expressing what I'm thinking in words. • I can't remember or say the names of people close to me. • I forget where to put things. Now I don't know where I put things. • Even if you read the document, you do not understand the meaning or content.

[Ages]
 10's: 2
 20's: 12
 30's: 20
 40's: 32
 50's: 12
 Over 60: 9
 [Sex]
 Men: 30
 Women: 57

As mentioned above, men and women of all ages responded equally to the questionnaire, confirming that this symptom can occur to anyone regardless of gender or age differences. In addition, there was a significantly higher proportion of items complaining about symptoms of brain fog in the content of the questions. (Chi-square test, $p < 0.05$).

Results

Looking at the questionnaire, the number of people infected with COVID-19 was 60.9%, and it is thought that the majority of those who have confirmed these symptoms are Long COVID. In addition, since it is predicted that QOL will decline in such symptoms, improvement cases were confirmed when plasmalogen containing *Ginkgo biloba* extract (Dialethea®) was used. In the most improved cases, there was an opinion that fatigue disappeared, thinking was organized, and cognitive function improved. As for other items, plasmalogen containing *Ginkgo biloba* extract (Dialethea®) will continue to be used, and will be reported in the second report. In addition, although we should normally exclude cases of using sleeping pills, we do not know what kind of psychoactive drug is being used this time, and brain fog in benzodiazepine anxiolytic drugs. This time, it was included in the case without excluding it.

Discussion

In this study, among Long COVID, we focused on brain fog and confirmed its improvement. I'm still taking it, so it's still unknown, but I can expect to see a lot of improvements. As the name suggests, plasmalogen containing *Ginkgo biloba* extract is a combination of *Ginkgo biloba* extract and plasmalogen. Plasmalogen is generally said to help improve cognitive function [21,22]. In this study, the intake of plasmalogen extracted from chicken breast was set to 1500 µg per day. In addition, *Ginkgo biloba* extract [20], which is said to contribute to the improvement of cerebral blood flow, is added to it, and it is thought that it is a combination that improves cerebral blood flow and improves cognitive function, that is, it has a positive effect on the brain be done.

Ginkgo biloba extract

Ginkgo biloba leaves originally contain flavonoids, which

are said to promote the removal of active oxygen [24,25]. Since the generation of active oxygen in inflammation is thought to be one of the causes of brain fog, it is thought that this active oxygen can be removed in the first stage [26]. *Ginkgo biloba* extract also contains terpene lactones, which reduce blood viscosity and increase blood flow, resulting in improved cerebral blood flow [27]. It is predicted that brain fog will be partially improved by removing reactive oxygen species and improving cerebral blood flow in this way [26,28]. In addition to brain fog, cerebral blood flow decreases as blood vessels harden with age, which may lead to cognitive decline [29]. Under such circumstances, it is considered appropriate to use the *Ginkgo biloba* extract.

Plasmalogen

Plasmalogen is a type of phospholipid present in the nervous system, heart, and skeletal muscle of the human body [30]. It is said that 90% of the nervous system is in the brain [22]. In particular, this study focuses on brain fog, that is, the central nervous system, and plasmalogens account for 30% of glycerophospholipids in the brain and up to 70% of ethanolamine glycerophospholipids in the myelin sheath [31]. The brain is a collection of nerve cells. There are various types of nerve cells, but among them, the axons of myelinated nerve cells have a myelin sheath, which is composed of the ethanolamine glycerophospholipid mentioned above [32]. The area between these myelin sheaths is called the ring of Ranvier, and nerve transmission is carried out using this [33]. When this myelin sheath becomes dysfunctional (lack of plasmalogen), neurotransmission becomes impossible, and as a result, it is possible that cognitive function declines [34]. Therefore, it is considered necessary to ingest plasmalogen, which decreases with age [35].

This is the first time in the world that the combination of *Ginkgo biloba* extract and plasmalogen has been used to improve brain fog. It is thought that brain fog could be improved by a multi-faceted approach that includes the antioxidant action and improvement of cerebral blood flow by *Ginkgo biloba* extract, activation of brain cells (repair of myelin sheath) by plasmalogen, and improvement of cognitive function. Future tasks include further increasing the number of its effects on cases and elucidating molecular pharmacological effects. This suggests the possibility of pharmacologically elucidating not only brain fog but also improvement of dementia.

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Ethical Considerations

This study was conducted after obtaining approval from the ethics committee of Hinokosei Clinic. (HKC_N10032022)

Conflict of Interest

There are no conflicts of interest in this study.

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