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Cytokine-induced Neurogenesis for the Prevention and Treatment of Alzheimer's Disease

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ABSTRACT

Alzheimer's disease (AD) is a progressive neurodegenerative disease for which no curative treatment has been established. We administered cytokine-induced neurogenesis treatment combined with a ketogenic and elimination diet to a 66-year-old male AD patient carrying APOE ε4/ε4 alleles to regenerate residual neuronal stem cells. The treatment resulted in the successful regeneration of the atrophied hippocampus, which was associated with improved cognitive function and the resolution of electrophysiological abnormalities. We analyzed food allergies to identify the modifiers that influence AD progression. A food allergy analysis panel revealed that the specific IgG antibodies for casein, cow milk, and whey were positive, whereas the specific IgG antibody for gluten was negative; these allergies were improved by the ketogenic and elimination diet and associated with improved cognition.

Keywords: Alzheimer's Disease (AD), APOE, Cytokine, Neurogenesis, Food Allergy, Molecular Chaperone, Ketogenic Diet.

INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disease for which no curative treatment has been established [1,2]. Aducanumab and lecanemab were recently approved by the Food and Drug Administration (FDA) and have potential disease-modifying effects. However, the long-term efficacy and safety of these drugs need further validation [3]. Regenerative approaches to AD treatment have been extensively researched, but they are still in the early phase of preclinical trials [4]. However, a recent pathological study clearly revealed that neural precursor cells were detected in the hippocampi of 18 participants with a mean age of 90.6 years, including persons with AD, suggesting that hippocampal neurogenesis persists in aged and diseased human brains [5]. In a previous study, we explored the possibility that cytokines that induce the differentiation of residual neural precursor cells can regenerate atrophied brains in patients with AD and frontotemporal dementia (FTD) and reported that a particular combination of cytokines successfully regenerated the atrophied hippocampus of AD and FTD patients [6]. In subsequent studies, we reported evidence that cytokine-induced neurogenesis can reverse cognitive decline in AD patients who are apoprotein E (APOE) ε4/ε4 carriers [7] or have vascular dementia [8] or bipolar disorder [9]. Heuston and colleagues reported

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that diet and exercise play important roles as cognitive modulators in stress-induced susceptibility of adolescent hippocampal neurogenesis [10]. Among various therapeutic diets, ketogenic diet has a neuroprotective impact for neurodegenerative disorders like AD [11]. In the present study, we analyzed food allergies and introduced a ketogenic diet as a nutritional intervention for an AD patient carrying APOE ε4/ε4 alleles to determine whether a ketogenic and elimination diet may modulate the progression and clinical efficiency of cytokine-induced neurogenesis in AD patients. The results suggested that cytokine-induced neurogenesis combined with a ketogenic and elimination diet may be an option for the prevention and treatment of AD.

METHOD

The cytokine cocktail formulation used in this study was designed and developed by Luis Carlos Aguilar Cobos at the Livant Neurorecovery Center, Mexico, as described previously [7-11]. In this case study, 6 cytokine formulations were used. Our group has paid special attention to the cytokines that favor the clearance of amyloid beta, including some cytokines such as insulin-like growth factor-1 (IGF-1), insulin-like growth factor-2 (IGF-2), IRISIN and FGF21. Another cytokine included is progranulin that improves the neuroinflammation present in AD pathology. Exosomes derived from young adult porcine brains with a predominance of miR-124 are also included. Cytokine cocktail containing HPLC-purified GDNF, omega 3 and exosomes extracted from Salmon was also used in this case. Cytokine cocktail was administered sublingually 3 times per day.

CASE DESCRIPTION

A 66-year-old company manager developed gradually progressing memory dysfunction with well-preserved language comprehension, emotional control, and orientation to time and place. On the patient's first visit to the Ochanomizu Health and Longevity Clinic in Tokyo on April 11, 2022, the Mini-Mental State Examination (MMSE) score indicated normal cognitive function (MMSE 30/30) with complaints of mild memory impairment. Emotional control and language comprehension were well preserved. APOE genotype analysis revealed that the patient was a homozygous carrier of the APOE ε4 allele (genotype ε4/ε4). A cognitive function examination performed with Cognitrax on April 11, 2022, revealed normal motor speed, attention, cognitive flexibility, executive function, reasoning, and working memory with impaired verbal memory and reaction time (Figure 1). Although MMSE score was 30/30, Cognitrax test showed impaired verbal memory and reaction time, suggesting that Cognitrax is more sensitive for the assessment of detailed cognitive functions (Figure 1). Magnetic resonance imaging (MRI) data acquired on April 11, 2022, revealed moderate atrophy of the cerebral cortex in the parietal lobes and mild atrophy in the frontal and temporal lobes (Figure 2A). A cross-sectional cortical image revealed reduced volumes of both gray matter and white matter with enlarged sulci in the left parietal lobe (Figure 2C) and the frontal lobes (Figure 2E). In silico endoscopic images of the left hippocampus (Figure 3A) and right hippocampus (Figure 3B) revealed mild atrophy in the neck portions of both hippocampi (Figure 3A & 3B, indicated by red arrows). Electroencephalography (EEG) examination on April 11, 2022, revealed abnormal slow waves at the frontal, central, and parietal leads at rest (data not shown). P300 EEG data analyzed by Neuroscan Software (https://compumedicsneuroscan.com/) revealed that after a target stimulus of high-pitched sound, premature and asymmetric P300 responses were detected at the frontal, central, and parietal leads (Figure 4A, red lines). P300 responses at the right and left parietal leads were also premature and asymmetrical (Figure 4B, red lines). Coherence analysis of P300 revealed low fluctuations in the bilateral frontopolar, right frontal, right temporal, right parietal, and bilateral occipital leads (Figure 4C). Flash visual evoked potential analysis revealed moderate dissociation between the right and left frontal leads (F7 and F8, Figure 4D), suggesting disorganized neuronal circuits within the cerebral cortex in the frontal lobe. The emotional control test on April 11, 2022, revealed that the patient exhibited imbalanced hyperexcitable emotional reactions to happy, sad, angry, or expressionless faces presented on the screen (Figure 4E). We therefore diagnosed this patient with early-stage AD with an APOE ε4/ε4 genotype on the basis of clinical symptoms, morphological abnormalities, and electrophysiological abnormalities, which were compatible with neurodegenerative pathology in the cerebral cortex and hippocampus.

To induce neurogenesis, we therapeutically applied OST EM, Epatrof (H23 AZ), CAL, and Neurogen EP from April 11, 2022, to October 3, 2023, and Neurogen RN and Renotrof (23) SAL EM from February 7, 2023, to October 3, 2023 (Figure 1). On February 7, 2023, 10 months after cytokine cocktail treatment began, the patient's verbal memory function, which had been declining, with a Cognitrax score of 75 on February 7, 2023, had recovered to normal levels, with a Cognitrax score of 115 (Figure 1); this improvement was maintained on October 3, 2023, with a Cognitrax score of 112 (Figure 1).

We reevaluated the patient's EEG signals on Feb 7, 2023, which revealed a significant decrease in slow waves (data not shown). The asymmetrical P300 EEG response was significantly improved in the frontopolar, frontal, frontolateral, central, and parietal leads (Figure 4A, black lines), suggesting that inhibitory GABAergic interneurons

and excitatory glutamatergic pyramidal neurons were regenerated, causing symmetrical P300 responses evoked by a target stimulus of high-pitched sound. Higher magnification of P300 responses in the parietal leads clearly revealed that the P300 response voltage significantly increased to 17.50 μV^2 in the left and right parietal leads at 240 msec (Figure 4B, black lines). Coherence analysis of P300 signals recorded on April 4, 2022, revealed improvements in neural circuit connectivity at the right frontopolar, right frontal, right frontolateral, right central, right parietal, and bilateral occipital leads after treatment (Figure 4C). Flash visual evoked potential analysis revealed that dissociated evoked potentials between the right and left frontolateral leads (Figure 4D, left panel) were significantly improved on February 7, 2023, after treatment (Figure 4D, right panel), suggesting that cortical neuronal networks had regenerated with functionally relevant synaptic functions. The emotional control test results revealed balanced emotional neuronal responses, with a reaction peak of 3,000 μV^2 after treatment (Figure 4E).

On February 16, 2024, we performed MRI, which revealed no marked changes in the volume of the atrophied gyri in the parietal cortex (Figure 2B) or the frontal cortex (Figure 2F). The cut surface image revealed reorganized gray matter in the parietal cortex (Figure 2D), suggesting that structural alterations were induced by the cytokine treatment, as suggested previously [7]. In silico endoscopy revealed that the previously observed atrophy in the neck of the left hippocampus (Figure 3C) and right hippocampus (Figure 3D) was significantly reversed after treatment; this result is clinically compatible with the recovery of verbal memory observed on February 7, 2023 (Figure 1). In our clinic, three dimensional (3D) MRI was constructed in silico from 1mm sagittal sections of T1 weighted image so that the surface fine structure of hippocampus is more accurately observed than ordinary voxel-based morphometry (VBM) method.

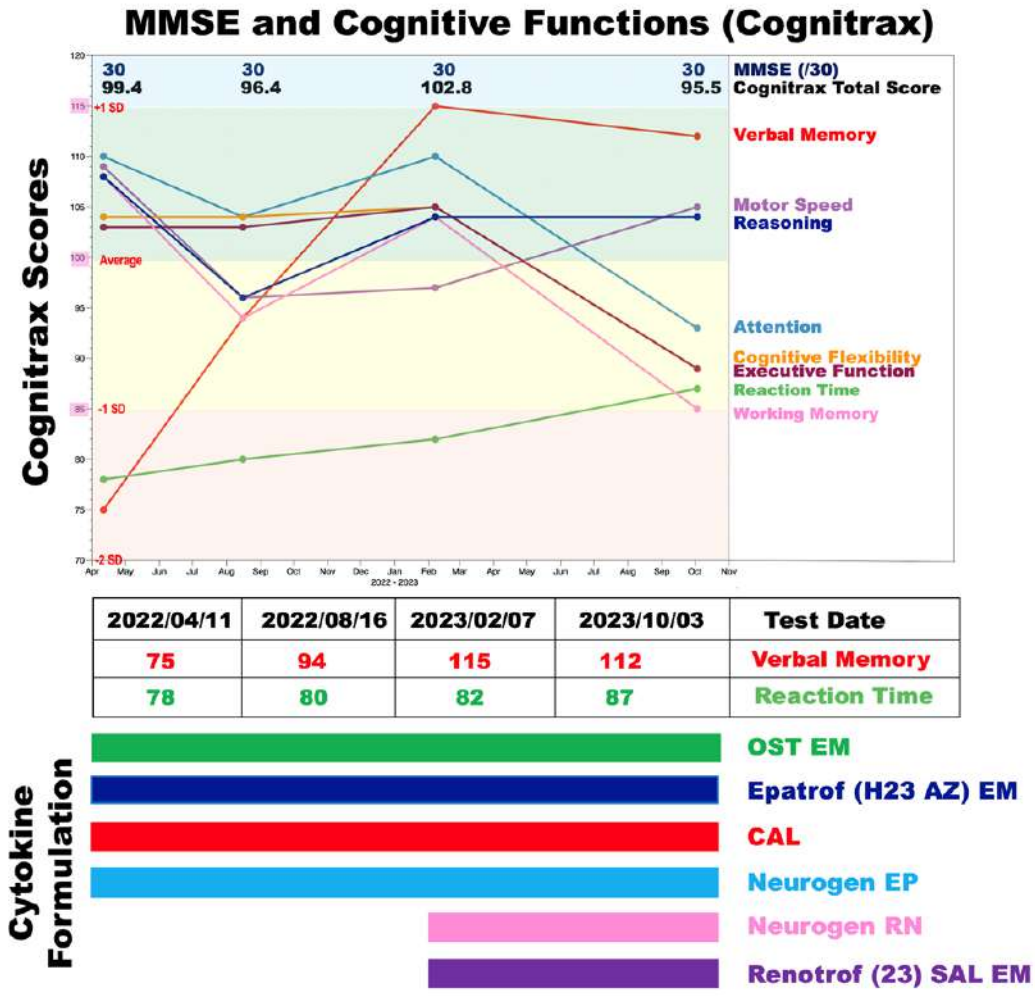

Figure 1. MMSE score and cognitive function before and after cytokine-induced neurogenesis.

Cognitive function was evaluated by CognitraxR and the Mini-Mental State Examination (MMSE) on April 11, 2022; August 16, 2022; February 7, 2023; and October 3, 2023. The MMSE scores are annotated in the upper part of the graph. Cognitrax scores for verbal memory (red), motor speed (plum), reasoning (dark blue), attention (light blue), executive function (brown), cognitive flexibility (yellow), reaction time (green), and working memory (magenta) are chronologically illustrated as line graphs. A Cognitrax score of 100 is the average score among the Japanese population of the same age. Green indicates the zone of scores ± 1 SD from the average, yellow indicates the zone of scores from 1 SD to 2 SDs less than the average, red indicates the zone of scores more than 3 SDs less than the average, and blue indicates the zone of scores 1 SD above the average. Verbal memory score and reaction time scores are summarized in the middle table. The administered cytokines and exosomes are shown under the graph.

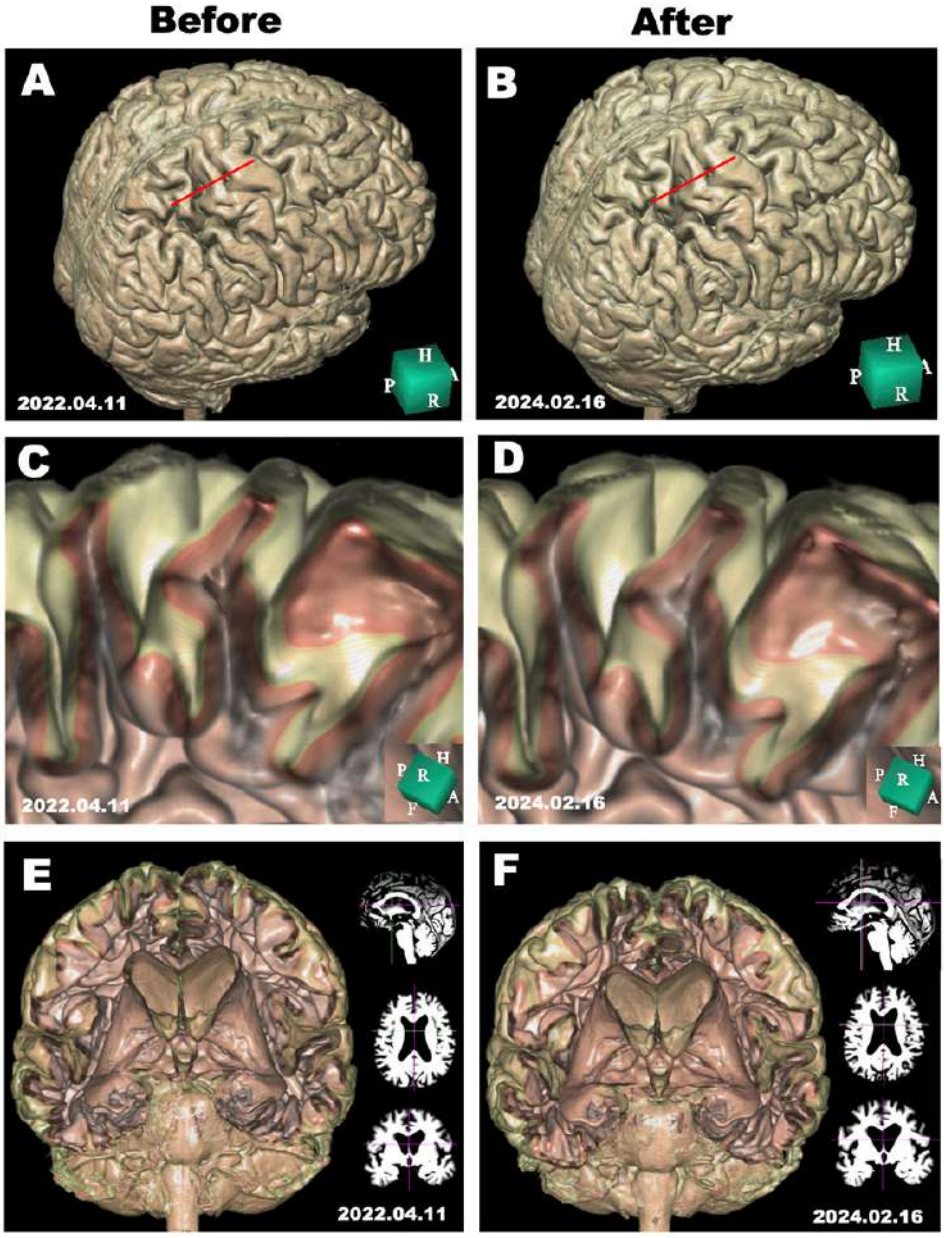

Figure 2. Morphological evaluations before and after cytokine-induced neurogenesis.

MRI scans collected on April 4, 2022, and February 16, 2024, before and after cytokine cocktail treatment. A, B. 3D structure of the cerebral cortex reconstructed in silico from T1-weighted MR images with 1 mm sagittal slices before and after cytokine cocktail treatment using Expert INTAGER software. C, D. Cut surface images of the parietal lobe as indicated by the red lines in A and B showing the regeneration of the atrophied cerebral cortex. E, F. Cut coronal images of the frontal lobe, as indicated by the green lines in the upper insets, showing regeneration of the atrophied cerebral cortex.

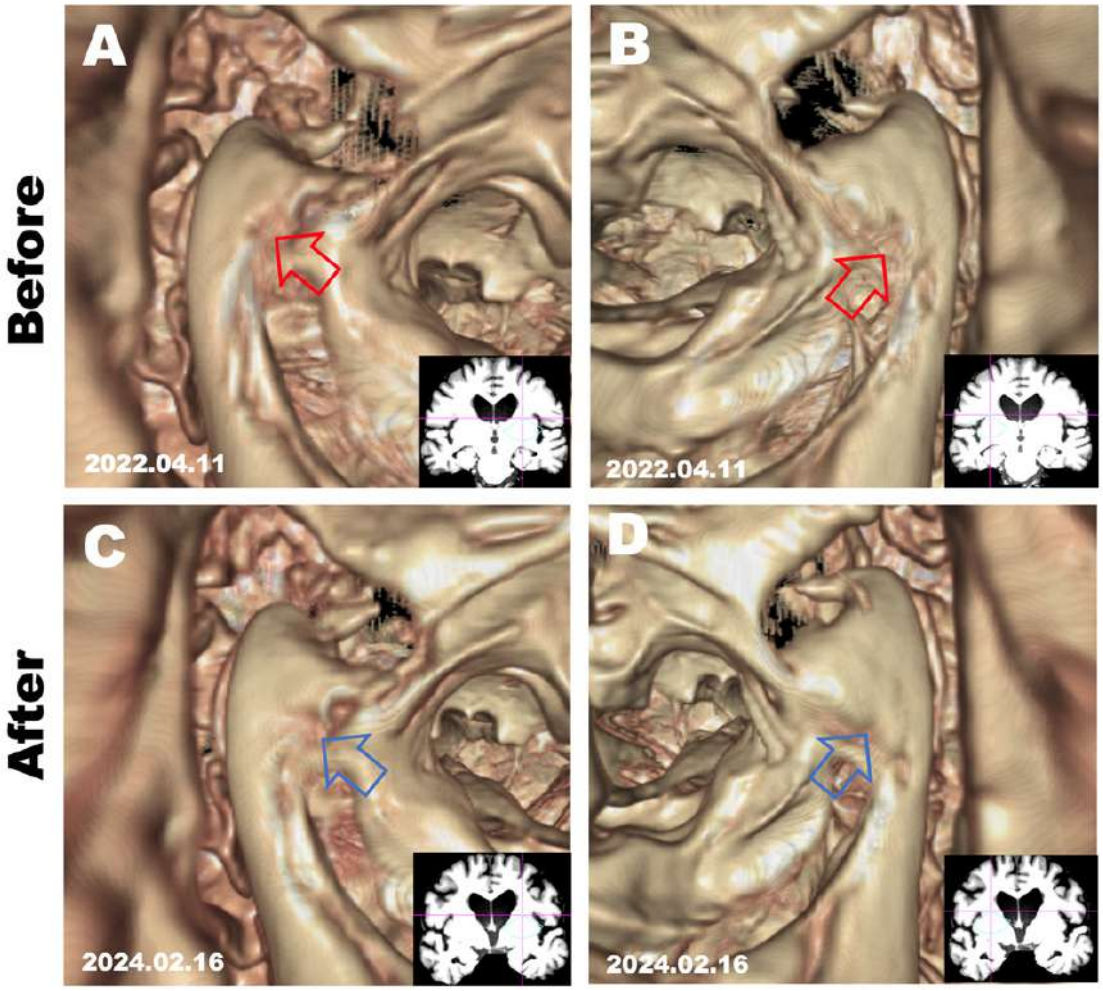

Figure 3. Morphological evaluations of the hippocampus before and after cytokine-induced neurogenesis. A, B. Endoscopic in silico views of the left hippocampus (A) and right hippocampus (B) showing atrophy at the neck portion of the hippocampus. C, D. Endoscopic in silico views of the left hippocampus (C) and right hippocampus (D) after cytokine treatment showing regeneration in the neck of the hippocampus.

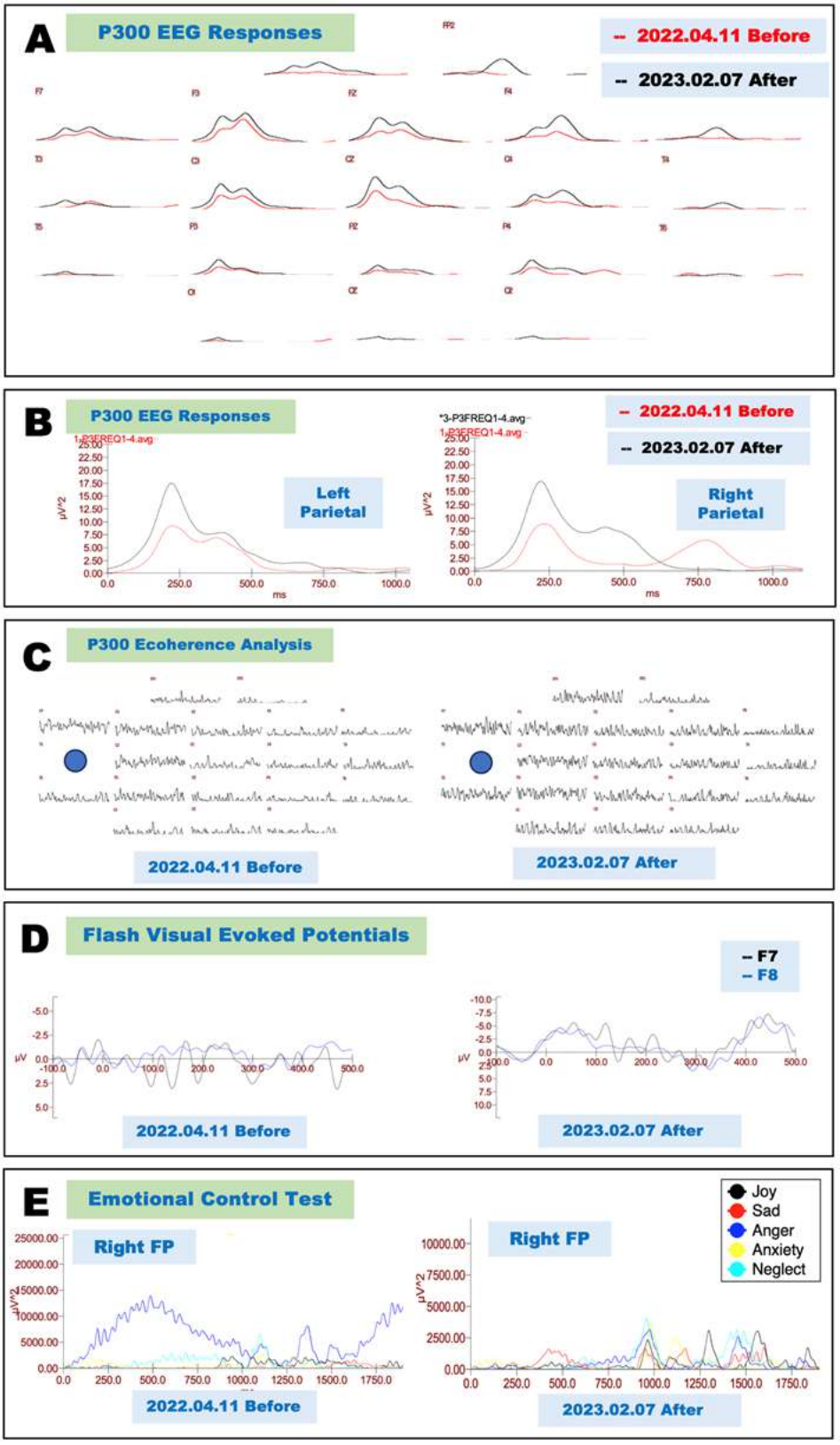

Figure 4. Neurophysiological evaluations before and after cytokine treatment.

A. Electrophysiological evaluation of P300 EEG responses before and after cytokine-induced neurogenesis. P300 EEG responses recorded on April 11, 2022, before treatment, are shown as red lines, and those recorded on February 7, 2023, after treatment, are shown as black lines.

B. Magnified recordings of the parietal leads in Fig. 4A show that the asymmetrical P300 component recorded on April 11, 2022 (red lines), significantly improved at both parietal leads recorded on February 7, 2023 (black lines; left, left parietal lead; right, right parietal lead).

C. Coherence analysis of P300 before and after cytokine-induced neurogenesis. Impaired neural network connections between the left temporal lead (T3, indicated by blue circles) and other leads of the cerebral cortex recorded on April 11, 2022, were significantly improved at the frontopolar, frontal, central, parietal and occipital leads on February 7, 2023.

D. Electrophysiological records of flash visual evoked potentials before and after cytokine treatment. Asymmetrical potentials were recorded on April 4, 2022, between F7 (left frontolateral lead, black line) and F8 (right frontolateral lead, blue line); these potentials improved on February 7, 2023 (right panel).

E. Emotional control analysis before and after cytokine-induced neurogenesis. EEG recordings at the right frontopolar electrode while viewing a happy face (black), sad face (red), angry face (blue), expressionless face (light blue), and worried face (yellow) recorded on April 11, 2022 (left panel), and February 7, 2023 (right panel).

To investigate the modifying factors that influence the progression of AD, the patient was tested with the food allergy panel for 96 food antigens (Figure 5). The patient was positive for casein, cow milk, whey, yogurt, almond, kelp, and rice but negative for gluten and other food antigens on April 11, 2022. After cytokine-induced neurogenesis treatment combined with a ketogenic and elimination diet, specific IgG titers for casein, cow milk, and whey protein significantly decreased, as measured on October 3, 2023. The patient had no allergic gastrointestinal or dermatological symptoms for these specific antigens.

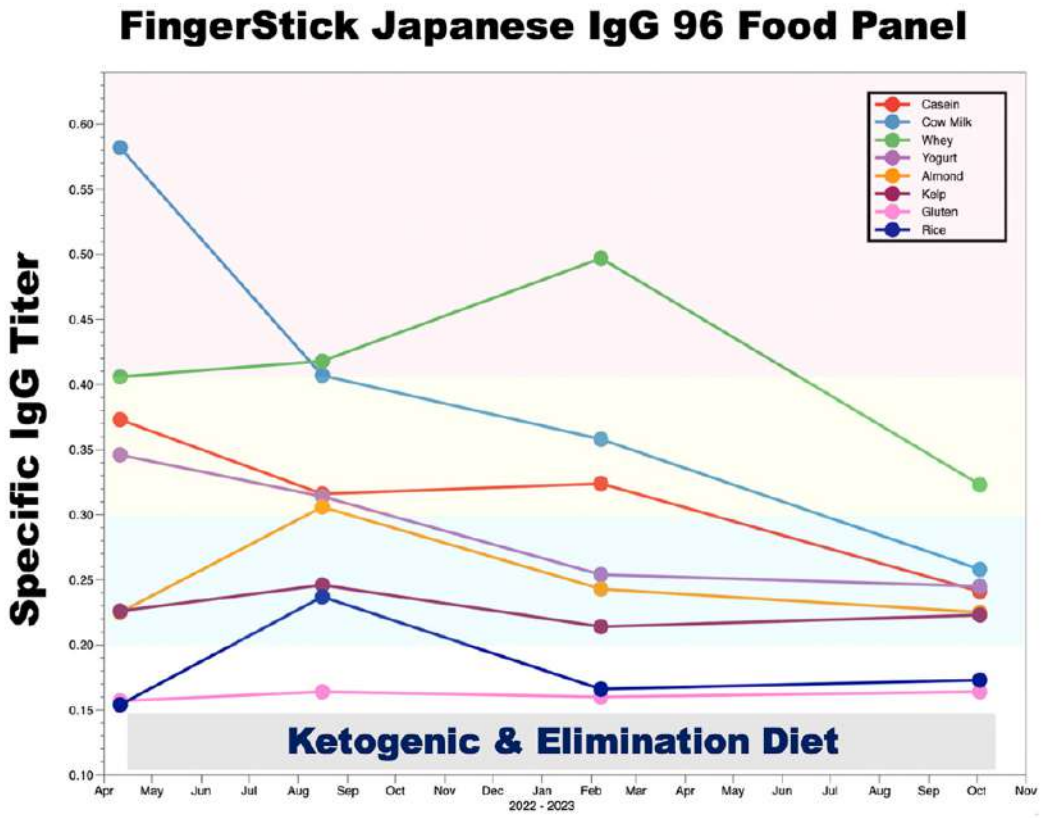

Figure 5. Clinical evaluation of food allergy before and after cytokine treatment combined with a ketogenic and elimination diet.

Specific IgGs for food antigens were evaluated by ALLETESS Medical Laboratory on April 11, 2022; August 16, 2022; February 7, 2023; and October 3, 2023. The patient was positive for casein (red), cow milk (light blue), whey (green), yogurt (violet), almond (orange), kelp (brown), and rice (blue) but negative for gluten (pink) and other food antigens on April 11, 2022. Specific IgG titers for casein, cow milk, and whey protein significantly decreased on October 3, 2023, in response to the ketogenic and elimination diet. The red background indicates high IgG titers, the yellow background indicates middle IgG titers, and the blue background indicates mild IgG titers.

DISCUSSION

In this case report, we showed that cytokine-induced neurogenesis regenerated the atrophied hippocampus of an AD patient who was an APOE ε4/ε4 carrier, concomitant with the reversal of cognitive declines in domains such as verbal memory and reaction time. As shown in Figure 4A, a neurophysiological examination revealed no typical premature P300 reactions, which are often observed in AD patients as described previously [6,7], suggesting that amyloid-beta (Aβ) deposition in the cerebral cortex is milder than that in symptomatic AD patients with the APOE ε4/ε4 genotype. In addition, P300 hyperexcitability was not clear in the entire cerebral cortex, indicating that the neuroinflammatory process was compromised in this patient. An MRI examination also revealed that the cortical and hippocampal architectures were only mildly damaged, whereas atrophy of the cerebral cortex in the parietal lobes was moderate (Figures 2, 3), suggesting that neurodegenerative pathology was progressing more slowly in this patient than it does in patients with aggressive AD with the APOE ε4/ε4 genotype. The APOE ε4 allele is the strongest genetic risk factor for sporadic AD, and recent evidence suggests that not only Aβ deposition but also tau neurofibrillary degeneration, microglia and astrocyte responses, and blood–brain barrier (BBB) disruption play important roles in the pathogenesis of AD, as shown in Figure 6 [12]. Emrani and colleagues also suggested that the heterogeneity among APOE carriers has a previously unappreciated degree of complexity that may make therapeutic treatment more difficult [13]. In addition to genetic factors, several other risk factors, such as age; head injuries; vascular diseases; infections; lifestyle factors, such as diet, exercise, and sleep; and environmental factors, play a role in the progression of AD [14]. Therefore, other modulating factors may slow the neurodegenerative pathology of AD, particularly the accumulation of Aβ or neuroinflammation, and thereby mitigate the clinical symptoms of AD.

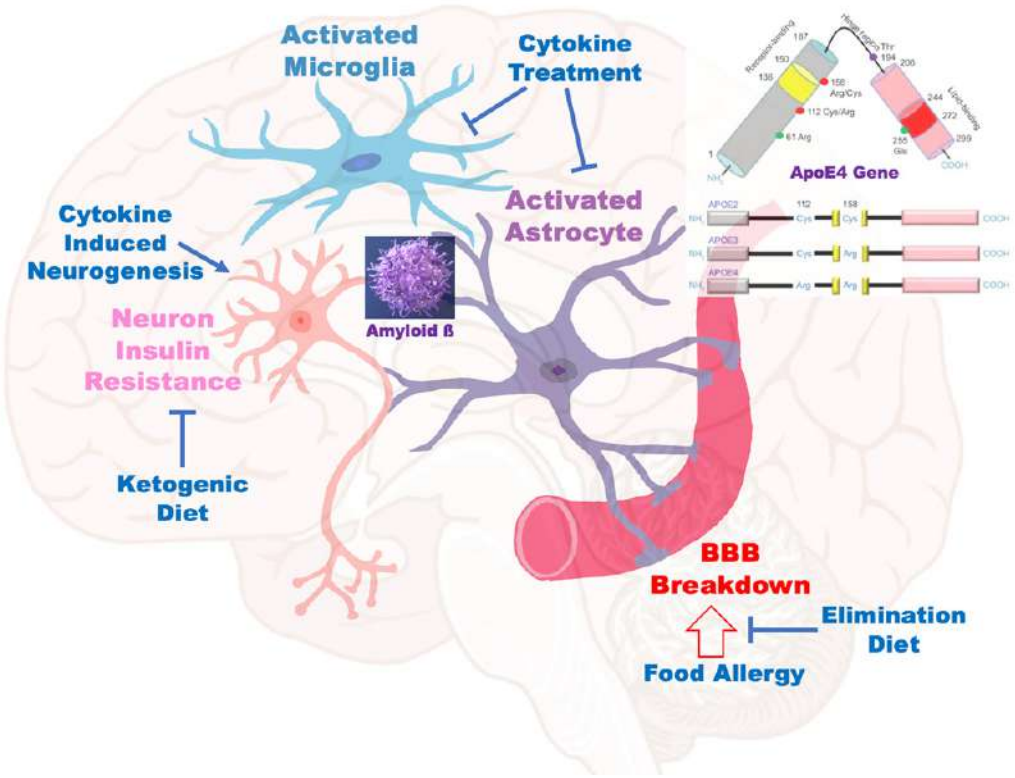

Figure 6. Pathogenic role of APOE in the progression of AD.

The structure of APOE isoforms is illustrated in the upper right inset. APOE is a soluble secreted protein with N-terminal and C-terminal domains linked by a central hinge region. The N-terminal domain (gray) contains the receptor-binding domain (yellow), and the C-terminal domain (pink) contains the lipid-binding region (red). Each isoform differs from the others at amino acid positions 112 and 158. The cysteine at position 158 (Cys158) in APOE2 is believed to cause a deficiency in receptor binding, whereas the arginine at position 112 (Arg112) in APOE4 changes the conformation of the entire domain. APOE4 enhances aggregation of the Aβ protein, breakdown of the blood–brain barrier (BBB), activation of astrocytes and microglia, and neuronal insulin resistance. A ketogenic diet improves neuronal insulin resistance, whereas an elimination diet ameliorates food allergies and BBB breakdown. Cytokine treatment suppresses the activation of astrocytes and microglia.

In this case, we used a cocktail enriched with 6 cytokines, namely, IGF-1 and IGF-2, IRISIN, FGF21, progranulin, and GDNF, as well as exosomes, as illustrated in Figure 1. Although these cytokines work synergistically to improve neurogenesis and cognitive function [6,8,15], the combination of progranulin and exosomes successfully improved cognitive functions such as verbal memory and reaction time in this patient (Figure 1). Interestingly, plasma level of FGF21 is decreased in AD while its level is highest in centenarians' offspring, suggesting that FGF21 emerges as a candidate biomarker of healthy aging [16]. Furthermore, plasma level of progranulin was 13% higher in AD and MCI patients compared the controls in the UCSF-MAC cohort [17], suggesting the possibility that plasma progranulin is another promising biomarker reflecting neurodegenerative pathology. We use both exosomes extracted from adult porcine brain (Neurogen EP as in Figure 1) as well as newborn porcine brain (Neurogen RN as in Figure 1), however, the potential to stimulate the adult neuronal stem cell is stronger with the exosome extracted from newborn porcine (Neurogen RN). That is the reason why we use both brain exosomes in the maintenance for the neurogenesis of AD with APOE ε4/ε4 carrier. We also used exosome extracted from Salmon since Salmon exosome contain miR-124 [18] that has the therapeutic potential for neurodegenerative disease [19]. We have already used the exosomes extracted from porcine, salmon, and oyster via sublingual administration for more than 200 patients since 2020 in our clinic and found no cross-species allergic reactions in our clinic. We also checked the specific IgG for porcine, salmon, and oyster and have not found any increase specific IgG.

Many modulators influence the pathophysiology of AD [20]. Among the environmental modulators, diet, lifestyle, alcohol, smoking and pollutants may influence the aggregation and degradation of Aβ accumulation [21]. Among dietary interventions, ketogenic diets (KDs) involve a high fat and low carbohydrate and medium-chain triglyceride (MCT) intake. KDs result in the production of ketone bodies to fuel the brain in the absence of glucose [22]. We guided the patient through a KD and found that the patient was ketogenic, with total ketone bodies of 3,378 μmol/L, acetoacetate of 414 μmol/L, and 3-hydroxybutyrate of 2.964 μmol/L, as measured on July 19, 2022. These ketogenic interventions are validated treatments for pharmacoresistant epilepsy, consequently leading to better intellectual development in epileptic children [23]. Additionally, in neurodegenerative diseases and cognitive decline, the potential benefits of a KD have been previously noted [24]. In AD patients, glucose hypometabolism in the brain is observed before the onset of symptoms [22]. Aβ accumulation, a main pathology of AD, is also related to impaired insulin action and glucose metabolism (Figure 6), whereas ketone metabolism is not affected. Therefore, the shift from glucose metabolism to ketone metabolism may be a reasonable pathway to achieve neuronal protection [25]. To promote ketone metabolism, MCT oil could be introduced as an alternative source of energy in the brains of AD patients [26]. We also recommended that the patient eliminate milk, casein, and whey protein and found that specific IgG antibodies for these antigens were significantly downregulated, as measured on October 3, 2023 (Figure 5). Casein or gluten can cause leaky gut syndrome, which can induce a neuroinflammatory reaction via breakdown of the BBB in AD patients (Figure 6) [27]. In this context, in our clinic, gluten-free or casein-free diets are recommended for AD patients who are positive for anti-gluten IgG or anti-casein IgG.

Among other modulators, we focused on 3 molecular chaperones, transthyretin, cystatin C, and ApoA1, that can inhibit the oligomerization of neurotoxic Aβ, as shown in Figure 7 [28,29]. The aggregation of the Aβ monomer and oligomer may be related to protein–protein interactions with molecular chaperones, as shown in Figure 7. Amyloid aggregates usually contain not only a single type of amyloid protein but also other types of proteins, and this phenomenon can be rationally explained by the processes of protein cross-seeding and co-assembly [29]. The interactions of Aβ peptides with other amyloids, which have been reported as either integrated parts of the Aβ neurotoxicity process or indicators of a preventive role in AD pathogenesis by directly binding to Aβ as chaperone molecules such as transthyretin, cystatin C and apolipoprotein A1, as shown in Figure 7. Interestingly, cytokines such as IGF-1 or phytochemicals such as curcumin can increase the expression of transthyretin [30,31]. Cystatin C binds soluble Aβ peptides and inhibits cerebral amyloid deposition in Aβ precursor protein (APP)-transgenic mice [32], suggesting that modulation of the cystatin C concentration may have therapeutic implications [32]. Interestingly, an association was found between a marked decrease in plasma apolipoprotein A1 (HDL) and late-onset non-familial AD in Japan [33]. Immunohistochemical studies revealed the presence of ApoA1 and HDL molecules in senile plaques, suggesting potential cross-interaction with the Aβ peptide [34]. Interestingly, the administration of Cuban policosanol attenuated abnormal oxidative stress and the inflammatory response via amyloid plaque reduction in 5xFAD mice [35], suggesting Cuban policosanol as another nutraceutical option for the prevention of AD (Figure 7).

The limitation of this study is the number of cases with which we applied cytokine-induced neurogenesis treatment combined with dietary intervention for 20 AD patients with

APOE ε4/ε4 alleles in our clinic since 2018. We successfully evaluated to able to stop the pathological progression of AD by electrophysiological evaluation and morphological evaluation with electrophysiological resolution and structural reconstruction of hippocampus and cerebral cortex except one case so far [6,36] [7,37]. However, taken together with the fact that AD risk of APOE ε4/ε4 allele is 15 times higher than APOE ε3/ε3 allele [13], the feasibility of this cytokine cocktail therapeutic approach is strong enough for the clinicians who are seeing AD patients with APOE ε4/ε4 allele. The most advanced case of AD with APOE ε4/ε4 allele in our clinic was 74-year-old female AD patient with APOE ε4/ε4 allele who had been initially diagnosed as juvenile onset of AD at age 63, visited our clinic in 2018 with MMSE 0/30. We applied cytokine-induced neurogenesis in 2018 and have continued cytokine-induced neurogenesis treatment for 6 years until recently, when she died of old age, not dementia at 82 at home, not at nursing home, surrounded by her family members with the dignity and humanity.

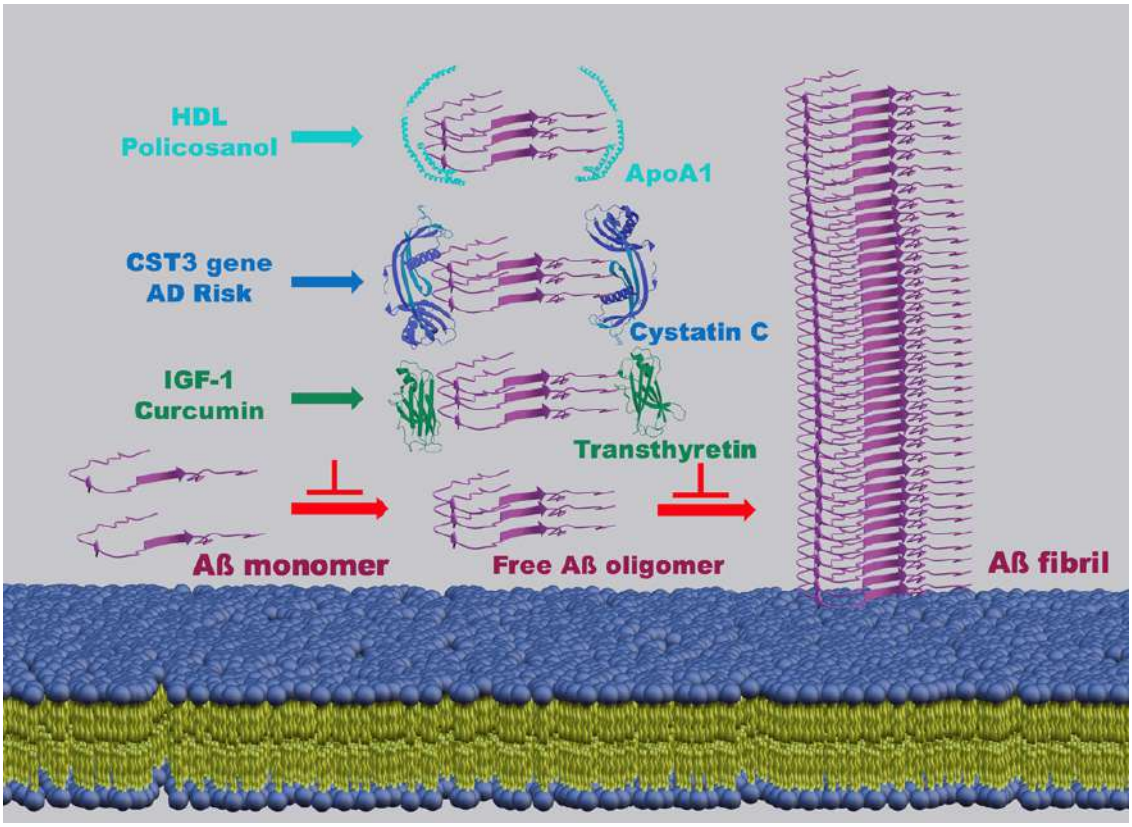

Figure 7. Molecular chaperones and dietary interventions that inhibit oligomerization and fibril formation of Aβ in the pathogenesis of AD.

Aβ monomers secreted outside neurons spontaneously form free Aβ oligomers. The Aβ oligomer then polymerizes and forms Aβ fibrils in the extracellular space of the cerebral cortex. Free Aβ oligomers are neurotoxic and play important roles in the pathogenesis of AD [28]. Oligomerization, polymerization, and fibril formation are suppressed by molecular chaperones such as transthyretin [38], cystatin C [32], and ApoA1 [29]. Increased HDL levels and policosanol administration increase levels of ApoA1 [39]. Administration of Cuban policosanol attenuates amyloid plaque deposition in AD model mice [35]. CST3 gene polymorphisms confer AD risk associated with the production of cystatin C. No dietary intervention has been reported. IGF-1 and curcumin increase the production of transthyretin [31].

CONCLUSION

AD is a progressive neurodegenerative disease for which no curative treatment has been established. In this study, we showed that cytokine-induced neurogenesis regenerated the hippocampus of an AD patient with an APOE ε4/ε4 genotype, concomitant with cognitive enhancement in domains such as memory and reaction time. We also investigated IgG-type food allergies to elucidate the modifying factors that influence the progression of AD. A food antigen panel revealed that the specific IgG for casein was positive but became negative with an elimination diet, which may modify the progression of AD pathology when combined with a KD. We applied the similar

cytokine cocktail combined with ketogenic and elimination diet therapeutic approach

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ETHICAL APPROVAL OF STUDIES AND INFORMED CONSENT

Written informed consent was obtained from the patient.

CONFLICT OF INTEREST

The authors have no conflicts of interest.

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