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Research Article

Changes in Brain Tissue Following Administration of Adipose-Derived Stem Cells

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Abstract

Introduction It is estimated that the number of dementia (Alzheimer's disease) patients worldwide will reach 16.2 million by 2050, and urgent measures are required. Prevention of dementia must continue from childhood to old age, and behavioral changes in lifestyle are important.

At present, there is no effective method for all stages of Alzheimer's disease from the pre-MCI stage to all stages of Alzheimer's disease. In this study, we focused on autologous tissue regeneration of adipocyte-derived stem cells to investigate an effective method for all stages of Alzheimer's disease from the pre-MCI stage.

Adipocyte-derived stem cells have the ability to differentiate into various cell types and are expected to be applied to tissue regenerative medicine.

Therefore, we investigated whether adipocyte-derived stem cells are effective for all brain atrophy.

Methods 5-10 g of subcutaneous adipose tissue was collected from the abdomen of the subjects, and mesenchymal stem cells were isolated and cultured from the adipose tissue. The cultured autologous adipocyte-derived stem cells were administered intravenously to the subjects and evaluated by VSRAD until 1, 2, 3, 4, and 5 months after administration.

Results Both subjects (n=2) showed a trend toward maintenance or improvement as analyzed by VSRAD.

Conclusion In this study, except for the administration of adipocyte-derived stem cells, the subjects were only instructed to maintain their previous lifestyle, and the number of subjects was small, so it is not possible to determine the effect of the treatment.

However, the fact that improvement in brain atrophy was observed is a new finding.

Keywords: Alzheimer's disease; mild cognitive impairment; VSRAD; Autologous adipocyte-derived stem cells; regenerative medicine

Abbreviations

Quality of life (QOL), Mild cognitive impairment (MCI), Voxel-based specific regional analysis system for Alzheimer's disease, age-related cognitive decline (ARCD).

Introduction

In 2015, there were 47 million people with dementia (Alzheimer's) worldwide, and it is estimated that the number of people with dementia will increase by one person every three seconds, reaching 106.2 million by 2050 [11].

It is estimated that if the onset of dementia could be delayed by one year worldwide, the number of patients could be reduced to 9 million by 2050. Among the risk factors for dementia, there are factors that cannot be modified (e.g., the genetic risk factor APOE-ε4) and factors that can be modified (e.g., lifestyle, such as smoking) [7].

Moreover, even modifiable lifestyle-related factors may not be feasible for everyone.

Nevertheless, it is believed that if lifestyle modifications, or behavioral changes in daily life, can be implemented at the appropriate time in each lifetime, more people will now be able to reach the end of life before they develop dementia.

Even if not everyone can achieve the same effect, simply lengthening the time to dementia by a few years could reduce the number of people with dementia in the population as a whole.

If lifestyle-related diseases and lifestyle changes are addressed to the nine risk factors for dementia, the risk of dementia could be reduced by 35% [9].

Nine Dementia Risk Factors

1. education in childhood.
2. high blood pressure in middle age [6, 8].
3. obesity in middle age [3].
4. Hearing loss in middle age.
5. Diabetes mellitus in old age.
6. Smoking in old age.
7. Depression in old age [2].
8. Lack of exercise in old age.
9. Social isolation in old age.

In other words, prevention of dementia must continue from childhood through old age, and behavioral changes in lifestyle are important.

It should be noted, however, that there are numerous risk and protective factors for dementia, including sleep, dietary factors, alcohol consumption, and olfactory and head trauma (4.5,10).

For those who have already developed dementia, the key point is to reduce the severity of the disease and to improve the quality of life (QOL) of the patient and his/her family by minimizing the mental and behavioral disorders associated with dementia by providing appropriate nursing care and fully exploiting remaining cognitive functions through pharmacotherapy and non-drug therapy.

To this end, it is necessary to create a society that can always consider interventions not only for dementia patients but also for their families who care for them. The increase in the number of dementia patients is a critical and important issue worldwide in terms of the decline in QOL at the individual level, the burden on caregivers, the impact on society, and the pressure on social security costs.

Three interventions currently recommended for the prevention and improvement of dementia are cognitive training, hypertension control, and increased physical activity, although there is no conclusive evidence for these interventions [1].

Cholinesterase inhibitors, a treatment for Alzheimer's disease, are thought to be effective in all stages of Alzheimer's disease, but even if taken in mild cognitive impairment (MCI), the stage before dementia, they are not thought to prevent the transition from MCI to dementia.

In other words, at present, there is no effective method from the pre-MCI stage to all stages of Alzheimer's disease.

Therefore, in this study, we focused on autologous tissue regeneration of adipocyte-derived stem cells to investigate an effective method for all stages of Alzheimer's disease from the pre-MCI stage to all stages of Alzheimer's disease.

We believe that autologous tissue regeneration is essentially at the root of healing, and we conducted an intervention investigation using adipose tissue-derived mesenchymal stem cells based on basic physiological research and clinical research on stem cells that have been conducted in Japan and overseas as cell therapy.

Stem cells are cells that can differentiate into various cells and tissues and are present at specific locations in the body. They have the ability to generate cells to replace those cells when tissue is damaged, for example.

Adipocyte-derived stem cells also have the ability to differentiate into cells that form bone, cartilage, cardiac muscle cells, blood vessels, etc. Since they are expected to be used in regenerative medicine for various tissues, we investigated whether they might be effective for brain cell atrophy in all conditions.

In this study, the Voxel-based specific regional analysis system for Alzheimer's disease (VSRAD) for Alzheimer's disease was used for objective evaluation.

Materials and Methods

5-10 g of subcutaneous adipose tissue was harvested from the subject's abdomen. Local anesthesia was administered during the procedure. Mesenchymal stem cells were isolated from the collected adipose tissue and cultured. One hundred million cultured autologous adipocyte-derived stem cells were injected intravenously into the patient's left brachial artery puncture site over approximately 1 hour.

The adipocyte-derived stem cells were cultured at a cell culture processing facility (Japan Cell Culture Co., Ltd.) and administered by a physician at Kurume Central Hospital.

A 24-hour contact system was in place for the first week after administration, in consideration of possible side effects. In addition, checkups were conducted on the third and seventh days after administration to confirm the condition of the whole body as well as the site of administration.

Considering scientific compromises such as regenerative medicine, patients who received this treatment were given checkups at least five times a year to check their progress.

Patients who were unable to receive checkups on the scheduled checkup dates were contacted by phone or letter for follow-up.

Subjects were instructed to follow the same lifestyle (diet, sleep, weight maintenance) as before for 5 months before and after the study, and were cautioned not to add any special exercise, cognitive training, or pharmacotherapy.

VSRAD (Voxel-based specific regional analysis system for Alzheimer's disease)

VSRAD is an image statistical analysis method for computerized analysis of brain volumes obtained by MRI in voxel units, and is a system for analyzing and converting morphological image information of medial temporal atrophy unique to early Alzheimer's disease into diagnostic support information.

Using VSRAD, the degree of hippocampal and parahippocampal atrophy can be easily evaluated numerically using the voxel-based morphometry (VBM) method.

VOI (volume of interest) refers to the hippocampus and its surrounding area, which is responsible for memory and cognition. By comparing the atrophy of VOI with that of the entire brain, it is possible to confirm the degree of progression of brain atrophy related to memory and cognition.

VOI atrophy is a numerical value that compares the atrophy of the VOI with that of the brain as a whole, and a value of 1 or higher indicates that the person is in a state of more than age-related atrophy and is at high risk of developing dementia.

Although the results of VSRAD cannot be used to diagnose Alzheimer's disease, this study used the Z-score, which provides a numerical evaluation of the degree of atrophy in the hippocampus and parahippocampal gyrus, for evaluation.

The evaluation items were Severity of VOI atrophy, Extent of GM atrophy, Extent of VOI atrophy, and Ratio of VOI to whole brain atrophy (Ratio of VOI / GM atrophy), The VSRAD was defined as the ratio of the maximum value in VOI (Max in VOI) to the percentage of whole brain atrophy (Extent of WM atrophy).

VSRAD was evaluated at 1, 2, 3, 4, and 5 months after the administration of adipocyte-derived stem cells.

Results and Discussion

The pre-treatment condition (pre) and results up to 1, 2, 3, 4, and 5 months post-treatment are shown in Table 1.

subject		pre	One month after administration	After 2 months	After 3 months	After 4 months	After 5 months
SY	Severity of VOI atrophy	0.79	0.68	0.66	0.67	0.71	0.61
	Extent of GM atrophy	3.89	4.12	4.32	4.03	4.01	4.28
	Extent of VOI atrophy	1.16	0.61	0.43	0.67	0.24	0.24
	Ratio of VOI / GM atrophy	0.3	0.15	0.1	0.1	0.06	0.06
	Max in VOI	2.36	2.39	2.38	2.39	2.11	2.17
	Extent of WM atrophy	3.42	3.05	3.13	3.02	3.16	2.82
NY	Severity of VOI atrophy	1.5	1.49	1.48	1.39	1.35	1.34
	Extent of GM atrophy	3.29	3.32	4.66	3.43	3.36	2.83
	Extent of VOI atrophy	29.19	27.72	26.32	24.05	19.77	17.93
	Ratio of VOI / GM atrophy	8.86	7.92	5.95	7.01	5.89	6.33
	Max in VOI	3.21	3.43	3.05	3.21	3.46	3.04
	Extent of WM atrophy	2.41	2.2	2.75	2.36	2.1	2.04

Table 1: Pretreatment (PRE) status and results up to 1, 2, 3, 4, and 5 months post-treatment.

There was no change in body weight between pre and post study for either subject.

In both subjects, Severity of VOI atrophy, Extent of GM atrophy, Extent of VOI atrophy, Ratio of VOI / GM atrophy, Max in VOI and Extent of WM atrophy, compared to pre, tended to be maintained or improved as a result of VSRAD The results of the analysis using VSRAD showed a trend toward maintenance or improvement.

In particular, Extent of VOI atrophy showed improvement in both subjects, and a representative example is shown in Figure (Figure 1).

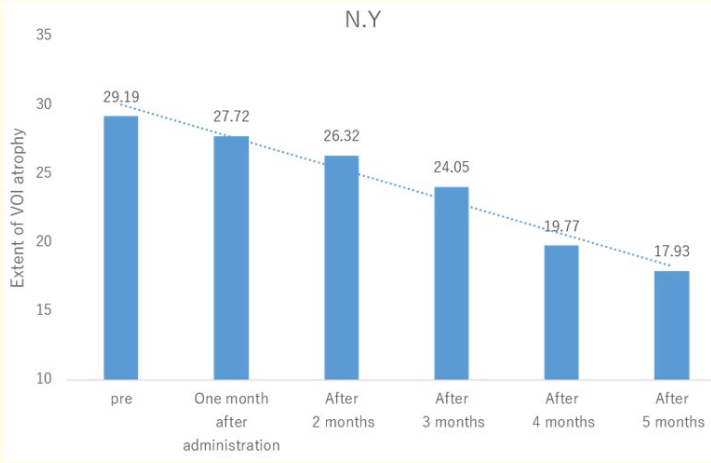

Figure 1: Typical example of Extent of VOI atrophy. The pre-treatment condition (pre) and results up to 1, 2, 3, 4, and 5 months post-treatment.

Conclusion

Currently, there is no clear distinction between delaying age-related cognitive decline (ARCD), preventing or delaying the development of MCI as a heterogeneous group, and preventing or delaying dementia when a dementia disease such as Alzheimer's disease causes a progression from prodromal phase - MCI - to dementia.

The three are quite different but not clearly differentiated: preventing or delaying the progression of dementia from the prodromal stage - MCI - to dementia due to a dementia disease such as Alzheimer's disease.

It has also been reported that lifestyle-related disease prevention/correction and lifestyle modification may reduce the risk of dementia by 35% for 9 risk factors for dementia [5], but these are not clearly distinguished from ARCD delay, MCI prevention/delay and Alzheimer's disease prevention/delay, because lifestyle from childhood to old age is important.

However, there is still no effective way to delay ARCD, prevent or delay MCI, or prevent or delay Alzheimer's disease [5].

In this study, we focused on adipocyte-derived stem cells, which are expected to be used in regenerative medicine for various tissues, and conducted an investigation in the hope of finding an improvement in brain atrophy in all conditions by administration of adipocyte-derived stem cells.

As a result, both subjects showed improvement in VSRAD evaluation.

The subjects in this study were two normal-weight, nonsmoking women (mean age 57.2 years, mean BMI 24.6).

Although the pre-study VSRAD evaluation did not indicate progressive brain atrophy, more improvement was seen with the administration of adipocyte-derived stem cells.

In this study, except for the administration of adipocyte-derived stem cells, it is not possible to determine the effectiveness of the treatment, because the patients were only instructed to maintain their previous lifestyle and there were only two subjects in the study.

However, the improvement in brain atrophy is a new finding and may be effective for all brain atrophy.

In addition to the nine risk factors, there may be a variety of other influences such as obesity, hearing loss, blood pressure, exercise, antidepressants, diet, alcohol consumption, smoking, diabetes and sleep disorders, which require further investigation, but the administration of adipocyte-derived stem cells in this study showed improvement rather than maintenance or delay.

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