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Hypothesis: Intravenous administration of mesenchymal stem cells is effective in the treatment of Alzheimer's disease

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ABSTRACT

We propose the intravenous administration of autologous adipose-derived stem cells as a new treatment for Alzheimer's disease. We hypothesize that the stem cells will secrete neprilysin in the brain to break down and remove amyloid deposits in the Alzheimer's brain. We have shown a case of skin amyloid deposition that disappeared after stem cell administration and confirmed that the stem cells administered had neprilysin activity. In addition to neprilysin secretion, other mechanisms of action of stem cells include nerve regeneration, nerve repair, growth factor secretion, anti-inflammatory effects, and angiogenesis. The harvesting of adipose-derived stem cells is minimally invasive, and intravenous administration can be safely repeated. We hope that the efficacy of this new treatment will be verified and that it will bring a ray of hope to patients suffering from this incurable disease.

Introduction

Alzheimer's disease is the leading cause of dementia, one of the most important issues facing the world. The cause of Alzheimer's disease is still unknown, but amyloid deposition in the brain is a strong candidate for the cause. If we can remove amyloid deposits, we may be able to treat Alzheimer's disease. There have been attempts to create antibodies against amyloid and administer them to treat the disease [1], as well as to inhibit the formation of amyloid [2], but these have yet to yield satisfactory results. On the other hand, mesenchymal stem cells are expected to be an effective treatment for several intractable diseases [3]. We have focused on the ability of stem cells to degrade abnormal proteins. In the case of amyloid, one of its degrading enzymes is neprilysin. Mesenchymal stem cells secrete neprilysin [4,5]. So we thought that mesenchymal stem cell administration might be an effective treatment for Alzheimer's disease.

The Hypothesis: Intravenous administration of mesenchymal stem cells is effective in the treatment of Alzheimer's disease.

Rationale for the hypothesis

Regarding amyloid

Amyloid is defined as a substance that stains orange on Congo red staining, exhibits green polarization on polarized light microscopy, and exhibits a fiber structure of 7–15 nm under electron microscopy [6]. The term amyloidosis is used to refer to any disease in which amyloid is deposited in the interstitium. In most cases, the precursor protein, amyloid precursor protein (APP), polymerizes due to folding disorder, and accumulates and aggregates as insoluble fibrils rich in beta-sheet structure. It is characterized by the organs in which the amyloid is deposited and is broadly classified into systemic amyloidosis and localized amyloidosis. Among localized amyloidosis, the condition in which amyloid is deposited in the brain is called cerebral amyloidosis, and Alzheimer's disease is one of its representative diseases.

Neprilysin

Neprilysin generally acts on peptides of 5 kDa or less and cleaves

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peptide bonds at the amino-terminal side of hydrophobic amino acid residues in the peptide. It is a major enzyme in the brain involved in the degradation of amyloid-β, which is expected to play a central role in the development of Alzheimer's disease [7]. It is thought to be the only peptidase capable of degrading not only monomeric amyloid-β but also the more neurotoxic oligomeric amyloid-β [8].

Alzheimer's disease

Alzheimer's disease is thought to be an amyloid deposition disease in the brain. Neprilysin regulates amyloid-β peptide levels [9]. Neprilysin activity is reduced in the brains of Alzheimer's patients, especially in areas where amyloid is deposited [10]. Mesenchymal stem cells administered intravenously through a drip can be used to regenerate the brain. Stem cells secrete neprilysin at amyloid deposition sites in the brain and may eliminate amyloid deposits [11,12].

Literature review and our experience in support of the hypothesis.

1 It is known that mesenchymal stem cells secrete neprilysin [4], and we have also confirmed neprilysin activity in stem cells cultured by us.
2 The safety of intravenous administration of autologous mesenchymal stem cells has been established [13,14]. Collection of autologous adipose-derived stem cells is minimally invasive, and their intravenous administration is repeatable.
3 Skin amyloid deposits disappeared in patients treated with autologous mesenchymal stem cells. This strongly supports the idea that stem cell derived neprilysin can work in the body to break down amyloid. We present this case as follows.

The case that led us to come up with the hypothesis.

An 84-year-old man with COPD was treated with autologous adipose-derived stem cells (ADSCs) by intravenous transfusions for 3 times: August, October, and November 2018. Numbers of ADSCs infused at each time were 8.4×10^7, 8.1×10^7, and 9.0×10^7, respectively.

His symptoms included shortness of breath while walking, dyspnea at rest, and sputum at night. On September 2017, the low attenuation area (LAA) of his chest CT was 748.2 cm^2 (17.4%). Forced expiratory volume in one second (FEV1.0%) was 67.98%.

FEV1.0% improved to 68.19% and 71.15% 2 months after the 1st administration of ADSCs and after 2 months after the 2nd administration, respectively. Forced expiratory volume in one second volume (FEV1) and forced vital capacity (FVC)) were 2.23 L and 3.48 L on September 2017, 2.08 L and 3.35 L 2 months after the 1st administration of ADSCs, and 2.22 L and 3.31 L 2 months after the 2nd administration, respectively (Table 1).

FEV1: forced expiratory volume in one second volume
FVC: forced vital capacity
FEV1.0%: forced expiratory volume in one second

Subjective symptoms improved after the first dose and then more so after the second dose.

Unexpectedly, he noticed and informed us that his amyloid deposition on his lower limbs decreased soon after the first ADSCs administration (Fig. 1A). Subsequently, we followed up his skin amyloid after that. Skin pigmentation kept fading (Fig. 1B), and the deposition became inconspicuous at 2 years after the first administration of ADSCs (Fig. 1C). During this observation period, no treatment was administered for amyloidosis. Until then, skin amyloid deposition gradually became darker over the years.

ADSCs administered to the patient were positive for CD10 (Positive CD10 indicates that neprilysin is expressed.), CD73, CD90, and CD105, and negative for CD31, CD34, CD45, and HLA-DR.

The stem cell therapy was performed according to the guideline of the quality management concerning clinical research of human ADSCs from the Ministry of Health, Labour and Welfare, and was approved by this ministry. Written informed consent from the patient was obtained.

Table 1
Results of respiratory function tests before and after the administration of stem cells.

	Before the administration of ADSCs	2 months after the 1st administration of ADSCs	2 months after the 1st administration of ADSCs
FEV1	2.23 L	2.08 L	2.22 L
FVC	3.48 L	3.35 L	3.31 L
FEV1.0%	67.98%	68.19%	71.15%

Mechanism of action other than neprilysin of mesenchymal stem cells as a potential treatment for Alzheimer's disease.

1 Inflammation occurs in the brain in Alzheimer's disease. Stem cells have an anti-inflammatory effect [15,16].
2 Stem cells secrete a number of growth factors [17], such as acidic fibroblast growth factor, basic fibroblast growth factor [18], insulin like growth factor, hepatocyte growth factor [19], granulocyte-colony stimulating factor, vascular endothelial growth factor, glial cell line-derived neurotrophic factor, and brain-derived neurotrophic factor [20], etc. Stroma cell derived factor-α(SDF-1α) has been shown to have angiogenic and neuroprotective effects [21,22]. They may contribute to neuronal repair [23].
3 Stem cells promote angiogenesis and improve blood flow [24]. As a result, brain function can be improved.
4 Stem cells can differentiate into neurons [25,26]. They may function as substitutes for damaged or dead nerve cells.
5 Stem cells may degrade and eliminate tau, another hallmark of Alzheimer's disease lesions [27]. However, it is not yet known whether the stem cells have the enzymatic activity to break it down.
6 Intravenously administered stem cells have a tendency to collect at the site of injury or lesion, known as homing [28].

Feasibility of hypothesis testing

1 Amyloid in the brain can be examined by amyloid PET scan [29].
2 Amyloid changes in the brain can be estimated by spinal fluid [30] and blood tests [31].
3 Assessment of cognitive function in Alzheimer's disease can be done with several established cognitive function tests, such as MoCA [32], and by examining the patient and interviewing caregivers.
4 Since there is currently no fundamental cure for Alzheimer's disease, we believe that safe, repeatable autologous stem cell therapy research is ethically permissible and worthwhile.

A

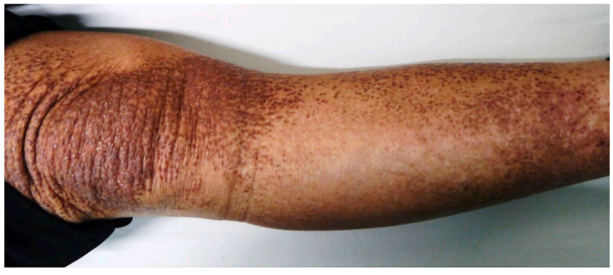

Fig. 1A. Amyloid deposition on the right leg 2 months after the 1st administration of ADSCs.

B

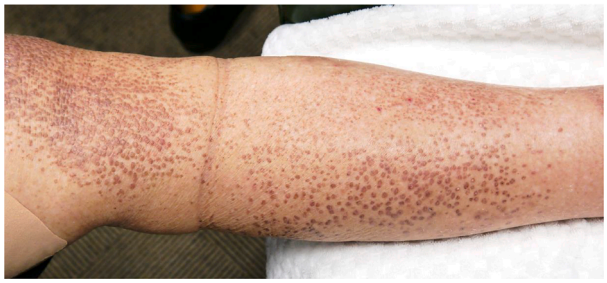

Fig. 1B. Amyloid deposition on the right leg 4 months after the 1st administration of ADSCs.

C

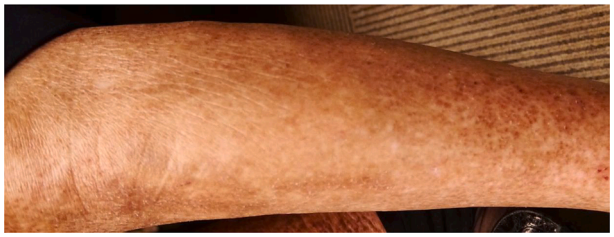

Fig. 1C. Amyloid deposition on the right leg 23 months after the 1st administration of ADSCs.

Conclusion

We proposed the hypothesis that autologous adipose-derived stem cells may be useful as a new treatment for Alzheimer's disease, for which there is currently no fundamental cure. Stem cells secrete neprilysin, which can break down amyloid deposits in the brain and promote nerve repair and regeneration.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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