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RESEARCH HIGHLIGHT

Plasma Replacement Therapy for Alzheimer's Disease

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Alzheimer's disease (AD) is the most common neurodegenerative disease that affects memory, thinking, behavior, and the ability to perform everyday activities. It has been estimated that more than 35 million people worldwide suffered from AD in 2018 [1], and this figure continues to grow. Unfortunately, no cure or treatment that slows the progression of the disease has been discovered despite extensive efforts from academics and the pharmaceutical industry. Most drug trials for AD have targeted the β-amyloid protein [2], which accumulates in this disease, and the failure of amyloid-based drugs to impact on cognition in people with AD has led to re-questioning of the amyloid hypothesis of AD, and has provided a fresh impetus to explore alternative therapeutic strategies.

Recently, Sha and colleagues [3] performed a randomized clinical trial to test the safety, tolerability, and feasibility of weekly administration of young fresh-frozen plasma (yFFP) to treat patients with mild to moderate AD. The same research group had previously shown that young mouse plasma treatment enhances learning and memory in aged mice [4] and that aged immunodeficient mice treated with human cord plasma have impaired memory [5]. Based on the hypothesis that anti-aging agents in the young blood can provide therapeutic benefits for AD patients, the authors have now translated these mouse studies into an early clinical trial of 18 patients who were divided into two groups matched for age, sex, baseline Mini-Mental State Examination score, and the apolipoprotein E4 genotype. The first group served as an open-label cohort which included 9 patients, and the patients were informed that treatment with 250 mL yFFP once a week for four weeks was applied. The second group, which also contained 9 patients, participated in a double-blind crossover protocol. Four of the 9 patients in the second group received yFFP once a week for four weeks, followed by a 6-week washout, and then saline was infused once a week for four weeks until the conclusion of the trial. The remaining 5 patients received saline first, followed by washout and yFFP infusion. In baseline and post-yFFP assessments, there were no related serious adverse events and no statistically significant differences were found in the outcomes, including cognitive, functional, and magnetic resonance imaging analyses.

Almost at the same time, Grifols, the largest plasma production company in Europe, also performed a clinical trial for AD using plasma exchange therapy under a different working hypothesis. Grifols had discovered previously that albumin can modify the levels of cerebrospinal fluid (CSF) and plasma amyloid (Aβ) 1–42 [6] and that the post-translational nitro-glycated modification state [7] as well as the oxidation state of albumin [8] are significantly increased in AD. They hypothesized that albumin binds to circulating Aβ in plasma and CSF, and this could mobilize Aβ from the brain to the plasma. Therefore, Grifols combined plasmapheresis with albumin, and evaluated the efficacy of plasma exchange using different replacement volumes. They also examined various concentrations of albumin. In a cohort of moderate AD patients, the authors demonstrated a statistically significant

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reduction of 61% in disease progression from baseline across both primary efficacy endpoints as measured by the AD Assessment Scale—Cognitive and the AD Cooperative Study—Activities of Daily Living scales. These data therefore highlight the potential of plasma exchange as a potential therapeutic strategy for AD.

However, the mechanism underlying how plasma exchange therapy benefits AD patients remains unknown. Tissue inhibitor of metalloproteinases 2 (TIMP2) has been shown by the same group to be a key factor in plasma that reverses senility in aged mice [5]. They showed that systemic injection and shuttling of TIMP2 from the blood into the brain mediates increased synaptic plasticity in the normally-functioning hippocampus, and induces significant improvements in behavior, long-term potentiation, and memory performance in aged mice; however AD mouse models have yet to be investigated. Others have used parabiosis and shown that peripheral Aβ can enter in the brain to increase the amyloid plaque burden [9], and removal of Aβ from the blood can reduce brain Aβ levels in mice [10], which may provide mechanistic insights. Nevertheless, aging is the most critical risk factor for AD [11], and the molecular mechanisms of aging can be clearly distinguished from the pathogenesis of AD [12]. The fact that plasma exchange therapy works in both aging alone, and AD, suggests that it may not be specific strategy for the disease.

Meanwhile, plasma replacement therapy is currently applied to rare, chronic diseases like alpha-1 antitrypsin deficiency, primary immune deficiency diseases, von Willebrand disease, and hemophilia; these patients generally require regular infusions or injections throughout their lives. According to the WHO Global Plasma Status Report, the plasma resource gap exceeds 10,000 tons (The 2016 global status report on blood safety and availability. World Health Organization 2017. http://www.who.int/iris/handle/10665/254987). The World Federation of Hemophilia estimates that 70% of patients with hemophilia worldwide are still unable to access any treatment. In this case, if plasma replacement is approved as a therapy for AD, it will face the same challenge as the fetal disorders to allocate the source of blood, and the dilemma of which disease the limited resource should supply.

Overall, the work by Sha and colleagues has added an important avenue to our efforts to cure AD. Further studies and discussions are needed to identify the mechanism of plasma exchange therapy, to investigate its specificity, and to address the ethical concerns related to the low worldwide supply of this human product.

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Conflict of interest The authors declare no conflict of interests.

References

1. Patterson, C. World Alzheimer Report 2018. The state of the art of dementia research: new frontiers. An analysis of prevalence, incidence, cost and trends. Alzheimer's Disease International 2018.
2. Sun BL, Li WW, Zhu C, Jin WS, Zeng F, Liu YH, *et al.* Clinical research on Alzheimer's disease: progress and perspectives. Neurosci Bull 2018, 34: 1111–1118.
3. Sha SJ, Deutsch GK, Tian L, Richardson K, Coburn M, Gaudioso JL, *et al.* Safety, Tolerability, and feasibility of young plasma infusion in the plasma for Alzheimer symptom amelioration study: a randomized clinical trial. JAMA Neurol 2019, 76: 35–40.
4. Villeda SA, Plambeck KE, Middeldorp J, Castellano JM, Mosher KI, Luo J, *et al.* Young blood reverses age-related impairments in cognitive function and synaptic plasticity in mice. Nat Med 2014, 20: 659–663.
5. Castellano JM, Mosher KI, Abbey RJ, McBride AA, James ML, Berdnik D, *et al.* Human umbilical cord plasma proteins revitalize hippocampal function in aged mice. Nature 2017, 544: 488–492.
6. Boada M, Anaya F, Ortiz P, Olazaran J, Shua-Haim JR, Obisesan TO, *et al.* Efficacy and safety of plasma exchange with 5% albumin to modify cerebrospinal fluid and plasma amyloid-beta concentrations and cognition outcomes in Alzheimer's disease patients: a multicenter, randomized, controlled clinical trial. J Alzheimers Dis 2017, 56: 129–143.
7. Ramos-Fernandez E, Tajes M, Palomer E, Ill-Raga G, Bosch-Morato M, Guivernau B, *et al.* Posttranslational nitro-glycative modifications of albumin in Alzheimer's disease: implications in cytotoxicity and amyloid-beta peptide aggregation. J Alzheimers Dis 2014, 40: 643–657.
8. Costa M, Horrillo R, Ortiz AM, Perez A, Mestre A, Ruiz A, *et al.* Increased Albumin oxidation in cerebrospinal fluid and plasma from Alzheimer's disease patients. J Alzheimers Dis 2018, 63: 1395–1404.
9. Bu XL, Xiang Y, Jin WS, Wang J, Shen LL, Huang ZL, *et al.* Blood-derived amyloid-beta protein induces Alzheimer's disease pathologies. Mol Psychiatry 2018, 23: 1948–1956.
10. Jin WS, Shen LL, Bu XL, Zhang WW, Chen SH, Huang ZL, *et al.* Peritoneal dialysis reduces amyloid-beta plasma levels in humans and attenuates Alzheimer-associated phenotypes in an APP/PS1 mouse model. Acta Neuropathol 2017, 134: 207–220.
11. Yu Q, Zhong C. Membrane aging as the real culprit of Alzheimer's disease: modification of a hypothesis. Neurosci Bull 2018, 34: 369–381.
12. Fjell AM, McEvoy L, Holland D, Dale AM, Walhovd KB. What is normal in normal aging? Effects of aging, amyloid and Alzheimer's disease on the cerebral cortex and the hippocampus. Prog Neurobiol 2014, 117: 20–40.