

Removal of blood amyloid- β with hemodialysis reduced brain amyloid- β , confirmed by brain imaging: a case report

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Abstract: The accumulation of amyloid- β protein (A β) in the brain signifies a major pathological change of Alzheimer's disease (AD). Extracorporeal blood A β removal system (E-BARS) has been under development as a tool for enhancing the clearance of A β from the brain. Previously, we revealed that dialyzers remove blood A β s effectively, evoking substantial A β influx into the blood during hemodialysis sessions as one form of blood A β removal by E-BARS, and that postmortem brains of hemodialysis patients exhibited lower A β accumulation. Here, we present a case report of a 77-year-old male patient with end-stage renal failure whose A β accumulation in the brain declined by initiating and continuing hemodialysis for 6 months. This report suggests that blood A β removal by E-BARS could be an effective therapeutic method for AD.

Keywords: amyloid- β , A β , PiB/PET, blood purification, blood A β removal, Alzheimer's disease, E-BARS, extracorporeal blood A β removal system

Introduction

The deposition of amyloid- β protein (A β) is one of the major hallmarks in the brain of Alzheimer's disease (AD).¹ Of several A β species present in the brain and plasma, 40-amino acid A β_{1-40} and 42-amino acid A β_{1-42} are the most prevalent. A β_{1-42} aggregates more readily to form neurotoxic A β oligomers. Recent findings suggested that the decreased clearance of A β from the brain could be a mechanism for the increase of brain A β , especially in sporadic AD cases.^{1,2}

As a tool for enhancing the clearance of A β from the brain, we proposed extracorporeal blood A β removal system (E-BARS) based on our hypothesis that the rapid removal of blood A β could facilitate peripheral A β drainage from the brain.³ As shown in Figure 1, blood A β s are extracorporeally removed using A β removal devices, decreasing the concentrations of blood A β s, which might accelerate A β transport from the brain into the blood. There are several effective A β removal devices. We found that the most efficient materials are hexadecyl-alkylated cellulose beads⁴ and hollow fibers in dialyzers made of hydrophobic materials such as polysulfone and polymethylmethacrylate.^{5,6} These materials exhibit A β removal efficiencies as high as ~100% for both A β_{1-40} and A β_{1-42} in vitro, with enough contacting time with A β s,⁴⁻⁶ and 50% or more in extracorporeal circulation with a blood flow of 200 mL/min, such as in hemodialysis.^{7,8} Adsorption is the primary A β removal mechanism, even in dialyzers used for hemodialysis. An investigation of patients with end-stage renal failure revealed that a massive influx of A β from certain tissues into the blood occurred during hemodialysis sessions, which removed blood A β s as one form of blood A β

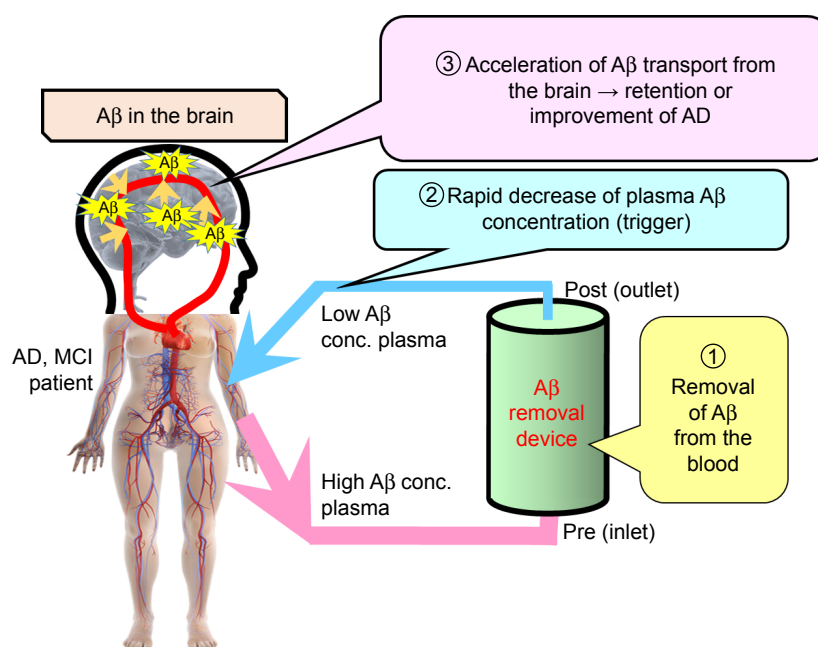


Figure 1 Schematic of extracorporeal blood A β removal system.

Note: Rapid removal of blood A β reduces A β concentrations in the blood, which might accelerate A β transport from the brain into the blood.

Abbreviations: A β , amyloid- β protein; AD, Alzheimer's disease; conc., concentration; MCI, mild cognitive impairment.

removal by E-BARSs.⁷⁻⁹ One of the origins of this large A β influx could be the brain, based on our histopathological studies reporting that the A β accumulation in the brains of patients undergoing hemodialysis was markedly lower than that in age-matched controls without hemodialysis.¹⁰ Furthermore, we revealed that cognitive functions of hemodialysis patients were maintained or marginally improved in a prospective study of 30 hemodialysis patients,⁹ and that a longer hemodialysis duration correlated with a lower dementia risk based on an analysis of over 200,000 hemodialysis patients in Japan.¹¹

As a different method from our study to remove blood A β s, plasma exchange therapy (discarding plasma containing A β s, followed by the administration of albumin that is an A β -binding substance) was also effective in improving cognitive functions in patients with AD.¹² In addition, peritoneal dialysis, which uses patients' peritonea as dialysis membranes, reduced plasma A β in humans and brain A β in mouse AD models.¹³ Thus, the therapeutic strategy of removing blood A β has gathered attention as the peripheral A β clearance for AD.¹⁴

However, seemingly, no direct evidence indicates that A β in the brain could be reduced by hemodialysis, which removes blood A β . The present study prospectively investigates the change in the brain A β caused by hemodialysis in a patient with renal failure whose A β accumulation in

the brain was confirmed at the hemodialysis initiation by positron emission tomography (PET) imaging with [C-11]-(2-[4-methyl-amino phenyl]-1,3-benzothiazol-6-ol) or Pittsburgh compound B (PiB) as a probe (PiB/PET). This prospective study was approved by the Institutional Review Board at Fujita Health University (latest approval number: HM16-266); the approval included permission to publish a case report. In addition, the patient provided written informed consent to participate in this study and to have the case details and any accompanying images published.

Case report

A 77-year-old male patient with end-stage renal failure was admitted to our hospital for hemodialysis initiation. He was nondiabetic and had a 60-year smoking history from age 16 to 76 years, and had no ApoE4 (ϵ 4 allele). His preexisting diseases were hypertension and hyperuricemia. On admission, initial investigation revealed high serum creatinine (Cr; 8.63 mg/dL) and blood urea nitrogen (87.8 g/dL) concentrations in the patient's blood. Other results were as follows: white blood cells, 5,900/ μ L; hemoglobin, 9.4 g/dL; platelets, 23.7 $\times$ 10⁴/ μ L; total protein, 5.7 g/dL; and albumin, 2.8 g/dL. Urinalysis revealed urinary protein (3+) and occult blood (1+). Ultrasonography showed atrophy of the kidneys. Although the reason for renal failure was unclear,

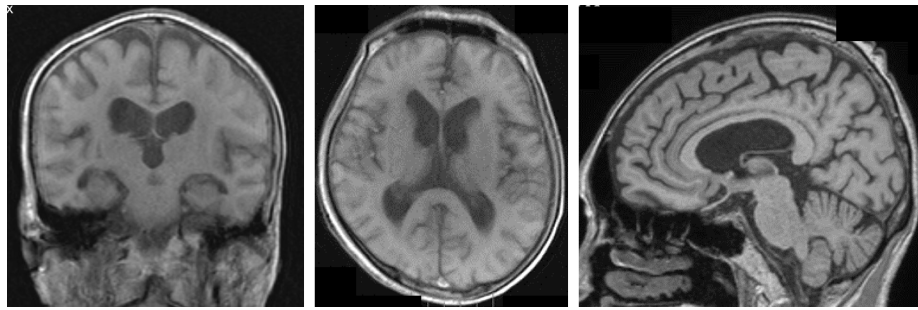


Figure 2 Images from the magnetic resonance imaging at the hemodialysis initiation.
Notes: Left, coronal; middle, axial; right, sagittal.

we considered it to be nephrosclerosis. On the basis of these data, the patient was started on hemodialysis.

At the hemodialysis initiation, the patient was diagnosed with mild cognitive impairment per the criteria of Petersen et al.¹⁵ Although he exhibited mild memory impairment, he experienced no trouble in his routine life. His Mini-Mental State Examination (MMSE) score was 23 points (disorientation to time, recall, and calculation). In addition, the score of Wechsler Memory Scale-Revised was 14/50 for Logical Memory I and 13/50 for Logical Memory II (the period of his education was within 9–12 years), suggesting a score near the low border of the normal range. His score on the short Japanese version of the Geriatric Depression Scale (GDS-S-J; published by Sugishita and Asada with the permission of the copyright holder¹⁶) was 6, indicating mild depressives. He exhibited no abnormality in the thyroid function, and vitamin B12 and serum calcium concentration levels. Furthermore, he displayed no signs and symptoms of any other psychological disorder.

The cranial magnetic resonance imaging (MRI; Figure 2) was performed 3 days before the hemodialysis initiation. The MRI revealed no apparent atrophy, and the patient's hippocampus seemed to be normal. Regarding white matter lesions, the periventricular hyperintensity was grade 2,

and deep white matter hyperintensity was grade 1, as evaluated using the scale of Fazekas et al.¹⁷ Furthermore, the Hachinski et al's ischemic score¹⁸ of the patient was 3, suggesting a low possibility of vascular dementia. Hence, his cerebrovascular impairment was concluded as very mild and seemed not to affect his clinical symptoms.

Regarding the A β accumulation in the brain, three-dimensional static PET imaging for 50–70 minute after the intravenous injection of PiB was conducted using a PET-computed tomography camera, Biograph True V (Siemens Healthineers, Erlangen, Germany), as reported previously.⁹ PiB images were visually rated as PiB-positive or PiB-negative, as described previously.¹⁹ The first PiB/PET was performed 14 days after the hemodialysis initiation (Figure 3, top), which showed a PiB-positive result. A quantitative analysis using the method of Australian Imaging, Biomarkers and Lifestyle (AIBL)²⁰ showed 1.91 as the global standard uptake value ratio with whole cerebellum as reference (SUV_{wCb}). After the patient received maintenance hemodialysis (4 h/day, 3 days/week) for 6 months (visit 2), PiB/PET was performed again. After 6-month hemodialysis, the A β accumulation in the brain was decreased (Figure 3, middle). The global SUV_{wCb} was 1.72, which was lower by “0.19” than that of visit 1. On visit 3, PiB/PET was performed

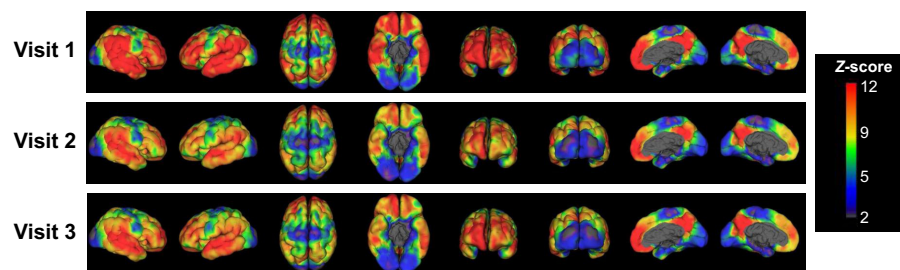


Figure 3 The SUV_{wCb} image from the surface projection of PiB/PET.

Notes: Top, visit 1 (at the hemodialysis initiation); middle, visit 2 (6 months after the hemodialysis initiation); bottom, visit 3 (12 months after the hemodialysis initiation).
Abbreviations: PiB/PET, positron emission tomography with Pittsburgh compound B as probe; SUV_{wCb} , standard uptake value ratio with whole cerebellum as reference.

Table 1 PiB/PET evaluations of visits 1–3

	Months after hemodialysis initiation		
	0	6	12
Visual rating	Positive	Positive	Positive
SUVR _{WCB}	1.91	1.72	1.78
Change in SUVR _{WCB} from hemodialysis initiation	–	–0.19	–0.13

Abbreviations: PiB/PET, positron emission tomography with Pittsburgh compound B as probe; SUVR_{WCB}, standard uptake value ratio with whole cerebellum as reference.

again after maintenance hemodialysis of 12 months (Figure 3, bottom). The global SUVR_{WCB} was 1.78, which was lower by “0.13” than that of visit 1. The change in SUVR_{WCB} is summarized in Table 1.

Regarding cognitive functions, MMSE scores were the lowest at 23 points at the hemodialysis initiation but gradually increased during 3 months of maintenance hemodialysis (Figure 4). Then, the scores marginally increased (improved) and were maintained at 26 points after 194 and 285 days of the hemodialysis initiation, and at 27 points after 355, 453, and 719 days (the last data are not shown in Figure 4).

We measured the concentrations of A β monomers and oligomers in the plasma, as described previously (Figure 4).⁹ At the hemodialysis initiation, both plasma A β_{1-40} and A β_{1-42} concentrations, measured with High Sensitive Human β Amyloid (1–40) and (1–42) ELISA Kit Wako II (WAKO Pure Chemical, Osaka, Japan), were as high as 971 and 73.7 pg/mL, respectively, because of renal failure. After the hemodialysis initiation, both plasma A β_{1-40} and A β_{1-42} concentrations decreased for around 6 months, but then increased and were maintained as 709–1,033 and 77.2–99.2 pg/mL, respectively. In addition, the ratios of A β_{1-40} to A β_{1-42} were 0.077 (Day 3; Figure 4) and 0.076 (Day 0) just before the hemodialysis initiation. However, the ratios increased up to 0.117 for 6 months after hemodialysis initiation, but then were maintained between 0.08 and 0.10 (Figure 4).

Contrary to A β monomers, the concentrations of A β oligomers in the plasma, measured with Human Amyloid β Oligomers (82E1-specific) Assay Kit (IBL, Fujioka, Japan), were below the detection limit (0; Figure 4) at the hemodialysis initiation and were maintained at 0 for 194 days after hemodialysis initiation. Then, plasma A β oligomer concentrations increased to 13.6–33.8 pmol/L after 285 days of the hemodialysis initiation (Figure 4).

Serum Cr and β 2-microglobulin (β 2MG) concentrations just before hemodialysis sessions are shown in Figure 4 (measured by clinical test companies such as SRL, Nagoya, Japan). The change in both Cr and β 2MG concentrations was small compared to A β monomers and oligomers.

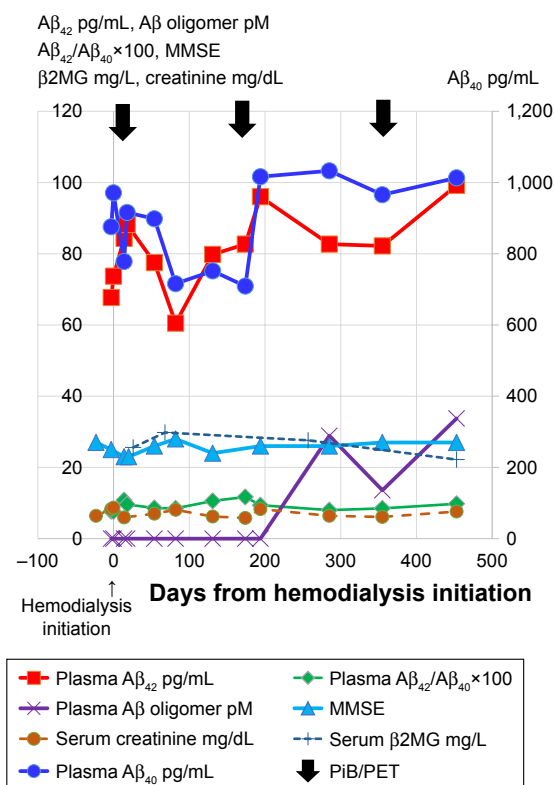


Figure 4 The concentration change of A β s in the blood and MMSE score after the hemodialysis initiation.

Notes: The left vertical axis represents A β_{1-42} (pg/mL), A β oligomers (pmol/L), A β_{1-42} :A β_{1-40} ratio ($\times 100$), MMSE scores, β 2MG (mg/L), and creatinine (mg/dL). The right vertical axis represents A β_{1-40} (pg/mL). Black arrows indicate the day of PiB/PET. The horizontal axis represents days from the hemodialysis initiation. The blood samples were collected just before the start of each hemodialysis session for the period after the hemodialysis initiation.

Abbreviations: A β , amyloid- β ; β 2MG, β 2-microglobulin; MMSE, Mini-Mental State Examination; PiB/PET, positron emission tomography with Pittsburgh compound B as probe.

Discussion

Although this study reports only one case, it is worth mentioning that 6-month hemodialysis decreased A β in the brain by “–0.19 SUVR” as measured by PiB/PET (Figure 3; Table 1). The reduction of “–0.19 SUVR” is comparable with that observed in a clinical study of aducanumab, where a decrease in SUVR of around 0.14 for 6 mg/kg and 0.21 for 10 mg/kg was noted after 26 weeks of administration.²¹

Our previous histochemical study reported that the A β accumulation in the postmortem brains of hemodialysis patients was markedly lower than those of age-matched controls.¹⁰ Although this histochemical study was cross-sectional, even 2-year hemodialysis seemed to decrease the A β accumulation in the brain;¹⁰ this finding is consistent with the finding of the present case report. Furthermore, the concentrations of both A β_{1-40} and A β_{1-42} in the cerebrospinal fluid decreased during the removal of blood A β s by extracorporeal circuits with an A β adsorbent, hexadecyl-alkylated

cellulose beads, in a study on rats;²² this finding also supports the decrease of the A β accumulation in the brain measured by PiB/PET in this study.

Clinical studies of anti-A β antibody therapy for AD revealed amyloid-related imaging abnormality (ARIA), such as microedema/microeffusion or hemosiderin deposition, as one of the adverse events to be considered.²³ Because E-BARS removes blood A β s, it may remove A β s deposited in cerebral blood vessels²⁴ as well as in brain parenchyma.¹⁰ Therefore, ARIA could occur in hemodialysis patients. Although we did not perform follow-up MRI for this patient, we have checked for the presence or absence of ARIA-like changes in a cross-sectional study of A β deposition in the brain slices of 17 hemodialysis patients. We did not find any ARIA-like changes, even in their brains, after 6–24 months of hemodialysis periods. Therefore, hemodialysis is less likely to cause ARIA-like changes.

Regarding the concentration change of A β s in the blood, a study showed that the concentrations of A β_{1-40} and A β_{1-42} in the blood of patients with renal failure increased along with a decline of renal functions.⁸ Thus, the blood concentrations of A β_{1-40} and A β_{1-42} of our patient were very high at the hemodialysis initiation (Figure 4). After the hemodialysis initiation, which removes blood A β effectively, both A β_{1-40} and A β_{1-42} decreased for about 6 months, but then increased and maintained (Figure 4); this tendency is consistent with the findings of a previous prospective study of 30 hemodialysis patients.⁹ The ratio of A β_{1-42} to A β_{1-40} increased just after the hemodialysis initiation from 0.077 to 0.108 and was sustained at around 0.10.

The MMSE scores of our patient increased and were almost maintained at 26–28 points after 1 year of hemodialysis initiation (Figure 4); this tendency of improvement or maintenance of cognitive functions by hemodialysis, which removes blood A β s, was also observed in our previous prospective study.⁹ As reported recently, higher concentrations of A β_{1-42} in the blood correlate with higher cognitive functions and larger hippocampal volume.²⁵ Furthermore, a larger ratio of A β_{1-42} to A β_{1-40} in the blood predicts less risk of development of AD and dementia.²⁶ Based on these reports, our finding of high concentrations of blood A β_{1-42} and a higher A β_{1-42} :A β_{1-40} ratio after 6 months of hemodialysis might correlate with high MMSE scores in the same period.

Uremic toxins also cause cognitive impairment.²⁷ Hemodialysis can remove uremic toxins from the blood and improve cognitive functions. Cognitive impairment caused by uremia is generally worst at initiation of hemodialysis and improves in a few weeks' time. In our previous prospective

study, MMSE scores were improved within just a few weeks after hemodialysis initiation.⁹ This short-term improvement may be attributed to removal of uremic toxins. In contrast, extracorporeal blood A β removal might contribute to the long-term effects of hemodialysis on cognitive improvement or maintenance, as shown in this study (Figure 4), in our prospective study of 30 hemodialysis patients during 18–36 months,⁹ and in our cross-sectional study of over 200,000 hemodialysis patients.¹¹

It is known that β 2MG deposition is observed in some hemodialysis patients resulting in dialysis-related amyloidosis, which causes carpal tunnel syndrome.²⁸ β 2MG is amyloidogenic but has a totally different amino acid sequence compared to A β s. Recently, hemodialyzers have been improved to enhance the efficiency of removal of blood β 2MG, resulting in fewer patients suffering from carpal tunnel syndrome. In our independent study, we found the removal efficiency of dialyzers (pre-/post-dialyzers) for β 2MG was ~50%, similar to that for A β_{1-42} during hemodialysis sessions.²⁹ The blood β 2MG concentrations in our patient showed a small change after hemodialysis initiation compared to A β s (Figure 4). This difference may be attributed to molecular weights (11.8 kDa for β 2MG vs ~4 kDa for A β monomers), origins (almost all nucleated cells vs neurons), influx pathway (absence vs presence of the blood–brain barrier), absolute concentrations (mg/L vs pg/mL), and other factors such as the amounts of insoluble deposition and production rates.

According to the findings of this case report, a patient's response to the hemodialysis initiation could be divided into two phases as follows. During the first phase – from 0 to 6 months during which a decrease in SUVR can be measured by PiB/PET – decrease in blood A β s and improvement in cognitive functions are observed; during this phase, not so tightly aggregated/deposited A β s might migrate into the blood. The influx of A β s into the blood may not be so large, resulting in marginally lower concentrations of blood A β s. The second phase – from 6 to 15 months during which no obvious change in SUVR can be shown by PiB/PET – increase in blood A β s, especially A β_{1-42} , and maintenance of cognitive functions can be observed. A β oligomers in the blood increase in this phase, may be because the influx of A β s from the brain into the blood is gradually increased. The influx of A β monomers into the blood may increase, because the concentrations of blood A β monomers are high in the second phase despite high A β removal efficiencies of dialyzers compared to the first phase. The production and clearance of A β s in the brain almost become balanced; however, this speculation should be evaluated with a larger sample size.

In conclusion, this case report suggests that E-BARS could be an effective therapeutic tool for AD.

Acknowledgments

The authors thank Dr Yoshiaki Inui for discussing the ischemic status, and Clinical Psychologist Ms Tomoko Kitayama, Clinical Engineer Mr Shojiro Kitagawa, and Ms Miwa Sakata for their assistance. The authors also thank Dr Kazuyoshi Sakai and Mr Hiroshi Kawachi for discussion about ARIA and β 2MG, respectively. This work was partly supported by KAKENHI (20509008, 23500531, 26282126), and the Smoking Research Foundation.

Author contributions

Nobuya Kitaguchi contributed to study design, steering the study, and measurements of blood A β monomers and oligomers. Takashi Kato, Kaori Iwata, and Kengo Ito contributed to performing PiB/PET, analyzing the data of PiB/PET and MRI, and single-photon emission computed tomography. Shinji Matsunaga and Hajime Takeuchi contributed to neurological diagnosis. Kyoko Hirano, Kiyoshi Fujita, Midori Hasegawa, and Yukio Yuzawa contributed to recruitment of the patient, diagnosis and treatment of renal failure, and initiation and maintenance of his hemodialysis. Kazunori Kawaguchi contributed to measurements of blood A β monomers and oligomers. All authors contributed toward data analysis, drafting and revising the paper, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

Dr Kitaguchi has patents issued to this work (JP5843345 and US 10,112,000). The authors report no other conflicts of interest in this work.

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