RESEARCH LETTER

Alzheimer Disease–Related Biomarkers in Patients on Maintenance Hemodialysis

To the Editor:

INTRODUCTION

Mild cognitive impairment (MCI) and dementia are common in patients with kidney failure requiring hemodialysis (HD) and occur at 7-fold higher incidence compared with age-matched controls without kidney disease.[1] Cerebrovascular disease has been identified as an important driver of cognitive impairment in this setting. However, other major causes of dementia, such as Alzheimer disease (AD), are suggested by the relatively younger age at which AD becomes evident among HD patients, the potential for AD risk to be augmented by disordered metabolism and recurrent cerebrovascular injury from blood pressure changes during HD, and emerging data consistent with AD-type patterns of decline on cognitive assessments and neuroimaging.[2-4] Circulating biomarkers are being increasingly recognized that correlate with the presence of AD-related pathology in the presence of clinical MCI and dementia. In this study, we assessed levels of AD biomarkers circulating in patients undergoing HD, linking their measurements to the time elapsed since the initiation of dialysis and comparing them with those of historical controls with preserved kidney function and normal cognitive function or with MCI.

METHODS

Between December 21, 2021 and January 18, 2023, consenting adults who underwent maintenance HD at 5 participating outpatient HD units in New York City were enrolled in 3 strata according to the following dialysis vintage: ≤6 months, >6 months-2 years, and >2 years. The project was approved by the New York University Grossman School of Medicine institutional review board (i20-01887). All participants provided written informed consent. Participants' medical history and HD charts were reviewed and a blood sample was collected immediately before HD. Albumin and C-reactive protein concentrations were measured in a Clinical Laboratory Improvement Amendments–certified clinical laboratory. Serum samples were incubated at room temperature for up to 1 hour, spun at the same temperature for 10 minutes at 1,300*g*, and stored in aliquots at −80 °C. Serum biomarker results were compared with those of plasma biomarkers from participants having normal cognition or MCI based on consensus and normal kidney function. These participants were recruited from the New York University Grossman School of Medicine Alzheimer's Disease Research Center (Item S1: Supplementary methods). Serum or plasma was processed using the SIMOA SR-X Analyzer (Quanterix Corporation) to quantify amyloid β-42 (Aβ42), Aβ40, total tau, phosphorylated tau181 (p-tau181), neurofilament light chain (NfL), glial fibrillary acidic protein (GFAP), and ubiquitin C-terminal hydrolase L1 (UCH-L1). We limited comparisons among HD, normal cognition, and MCI biomarker concentrations to those other than amyloid and total tau, given these may be inaccurately compared between serum and plasma, whereas the others are reportedly not significantly affected by source.[5,6]

Data are presented as mean ± standard deviation, median (interquartile range), or n (%) according to distribution. Spearman correlation coefficients were used to assess correlations, and biomarker concentrations were compared among the normal, cognitively impaired, and HD groups using t tests. Tests of linear trends were used to compare biomarkers according to HD vintage with $P < 0.05$ considered as significant.

RESULTS

Baseline characteristics of HD participants (N = 39) and biomarker concentrations based on vintage and those in the normal (N = 164) and MCI (N = 43) comparison groups are shown in Table 1 and Table S1. All patients were subjected to dialysis using high-flux membranes. Among HD patients, there were no significant correlations between AD biomarker concentrations and Kt/V, C-reactive protein, or serum albumin concentration (Table S2). HD participants showed an approximately 5-fold elevation in p-tau181, 10-fold increase in NfL, 4-fold elevation in UCH-L1, and 1.3-fold increment in GFAP versus normal controls (Fig 1A-D). A pathologic reduction in Aβ42/40 (ratio of AD-specific to nonspecific Aβ) and increases in p-tau181/total tau (ratio of AD-specific phosphorylated tau relative to total nonspecific tau), NfL, and GFAP were observed with higher dialysis vintage (Fig 1E-H).

DISCUSSION

In this study, several serum AD biomarkers in patients undergoing HD were found to be significantly elevated compared with those in participants with normal cognitive function or MCI. These data suggest several mechanisms that may contribute to AD and related dementias in this population, including AD-related cerebral amyloidosis and tauopathy (p-tau181), neurodegeneration (p-tau181 and NfL), subcortical axonal degeneration (NfL), inflammation (GFAP), and vascular/blood–brain–barrier disruption (UCH-L1).[7-9] Prior studies have compared a more limited set of peripheral markers among HD patients or versus normal, non-HD controls.[10] Our results build on previous studies by demonstrating abnormalities in HD patients compared with MCI participants not on HD, and expanding involved biomarkers of importance to include GFAP and UCH-L1.

There were several limitations to this study. We were underpowered to detect small-moderate changes in biomarker concentration with increasing dialysis vintage.

Table 1. Baseline Characteristics and Biomarker Concentrations According to Dialysis Vintage

Variable	≤6 mo (N = 5)	>6 mo-2 y (N = 12)	>2 y (N = 22)	Total (N = 39)
Demographics				
Age (y), mean ± SD	65.0 ± 9.1	61.2 ± 14.2	58.2 ± 13.1	60.0 ± 12.9
Female, n (%)	1 (20.0)	1 (8.3)	8 (36.4)	10 (25.6)
Race, n (%)				
White	2 (40.0)	2 (16.7)	3 (13.6)	7 (17.9)
Black	2 (40.0)	2 (16.7)	8 (36.4)	12 (30.8)
Other	1 (20.0)	8 (66.7)	11 (50.0)	20 (51.3)
Hispanic or Latino	3 (60.0)	9 (75.0)	13 (59.1)	25 (64.1)
Comorbid conditions, n (%)				
Diabetes	3 (60.0)	9 (75.0)	11 (50.0)	23 (59.0)
Coronary artery disease	1 (20.0)	2 (16.7)	8 (36.4)	11 (28.2)
Peripheral vascular disease	0 (0.0)	0 (0.0)	4 (18.2)	4 (10.3)
Congestive heart failure	1 (20.0)	2 (16.7)	4 (18.2)	7 (17.9)
Hypertension	5 (100.0)	7 (58.3)	17 (77.3)	29 (74.4)
Hyperlipidemia	1 (20.0)	2 (16.7)	8 (36.4)	11 (28.2)
Stroke	1 (20.0)	3 (25.0)	3 (13.6)	7 (17.9)
Dialysis vintage (mo), mean ± SD	1.6 ± 2.3	15.0 ± 3.9	88.9 ± 47.8	54.9 ± 53.0
Dialysis vintage (mo), median (IQR)	0.0 (0.0, 3.0)	15.0 (12.8, 18.2)	85.0 (62.2, 95.5)	27.0 (13.5, 90.0)
Laboratories, mean ± SD				
Kt/V[a]	1.34 ± 0.23	1.63 ± 0.26	1.93 ± 0.20	1.79 ± 0.29
C-reactive protein (mg/L)	10.7 ± 15.9	7.3 ± 6.3	6.2 ± 8.5	7.1 ± 9.0
Albumin (g/L)	3.4 ± 0.6	3.9 ± 0.4	3.8 ± 0.4	3.8 ± 0.4
Biomarker concentration, mean ± SD				
Aβ42 (pg/mL)[b]	38.4 ± 15.3	47.5 ± 11.8	44.2 ± 11.4	44.4 ± 12.1
Aβ40 (pg/mL)[b]	756.0 ± 293.9	1,174.8 ± 342.3	1,053.6 ± 293.7	1,049.3 ± 327.8
Aβ42/Aβ40[b]	0.05 ± 0.01	0.04 ± 0.01	0.04 ± 0.01	0.04 ± 0.01
Total tau[b] (pg/mL)	15.7 ± 10.0	9.6 ± 5.7	9.6 ± 3.9	10.4 ± 5.8
Total tau/Aβ42[b]	0.4 ± 0.2	0.2 ± 0.1	0.2 ± 0.1	0.3 ± 0.2
p-Tau181[c] (pg/mL)	11.7 ± 2.5	9.1 ± 4.4	10.9 ± 6.9	10.5 ± 5.9
p-Tau181/Aβ42[d]	0.4 ± 0.2	0.2 ± 0.1	0.3 ± 0.2	0.3 ± 0.2
p-Tau181/total[d] tau	1.0 ± 0.5	1.4 ± 0.9	1.3 ± 0.8	1.3 ± 0.8
GFAP[e]	145.7 ± 53.0	238.3 ± 87.5	217.5 ± 136.1	214.4 ± 117.4
NfL[e]	105.7 ± 37.1	208.3 ± 211.6	154.0 ± 85.3	163.2 ± 130.3
UCH-L1[e]	131.5 ± 32.9	215.2 ± 102.9	130.0 ± 49.9	154.2 ± 76.1

Abbreviations: GFAP, glial fibrillary acidic protein; IQR, interquartile range; NfL, neurofilament light chain; p-tau181, phosphorylated tau181; UCH-L1, ubiquitin carboxy-terminal hydrolase L1.
[a] $n = 37$.
[b] $n_{6\ mo\text{-}2\ y} = 11$, $n_{>2\ y} = 20$, and $n_{total} = 36$.
[c] $n_{6\ mo\text{-}2\ y} = 10$, $n_{>2\ y} = 21$, and $n_{total} = 35$.
[d] $n_{6\ mo\text{-}2\ y} = 9$, $n_{>2\ y} = 19$, and $n_{total} = 33$.
[e] $n_{<6\ mo} = 4$, $n_{6\ mo\text{-}2\ y} = 9$, $n_{>2\ y} = 19$, and $n_{total} = 32$.

Given the small sample size and multiple endpoints assessed, our findings should be considered hypothesis generating. Cognitive function of participants treated with dialysis was not evaluated. Our study design does not allow analysis of the effects of dialytic flux on the biomarkers, although a single study including 37 patients suggested that a single dialysis session reduced circulating Aβ40 and Aβ42 by 51% and 33%, respectively.[11] Similarly, we cannot distinguish between increased production and reduced kidney or dialytic clearance as the cause of observed elevations. However, elevations in circulating amyloid, tau, and UCH-L1, in particular, may cause pathology regardless of the underlying pathogenesis of elevation. Our analyses also represent a significant advance as a large proportion of HD patients may have MCI on dialysis initiation. Moreover, the pathophysiology of AD and related dementias may extend beyond amyloid, tau, and neurodegeneration. Our findings, although not statistically significant, additionally suggest that AD-related amyloidosis and tauopathy (ie, Aβ42/40 and p-tau181) and neurodegeneration and inflammation (ie, NfL and GFAP) may progress during the course of HD by mechanisms independent of systemic inflammation. In addition to providing potential insights into the underlying mechanisms of cognitive decline on HD, our data suggest the potential of using these biomarkers for early diagnosis of cognitive impairment, selection of HD patients at a high risk of cognitive decline for AD therapies, or following

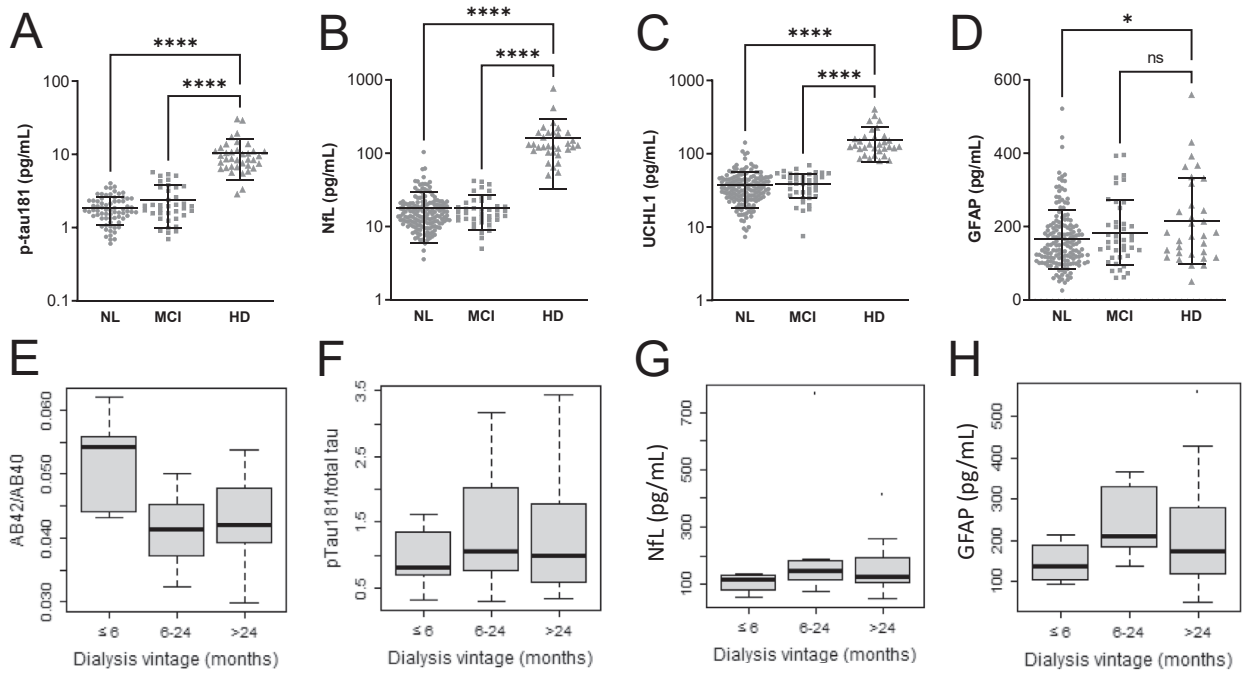

Figure 1. (A-D) Biomarkers in hemodialysis (HD) patient serum compared with those in the plasma from controls with normal cognition (NL) or mild cognitive impairment (MCI). (A) Phosphorylated tau181 (p-tau181) (n = 71 NL, 38 MCI, and 37 HD). (B) Neurofilament light chain (NfL: n = 162 NL, 41 MCI, and 32 HD). (C) Ubiquitin carboxy-terminal hydrolase L1 (UCH-L1: n = 159 NL, 40 MCI, and 32 HD). (D) Glial fibrillary acidic protein (GFAP: n = 162 NL, 41 MCI, and 32 HD); *P < 0.05, ****P < 0.0001. (E-H) Trends in biomarker concentration based on dialysis vintage (months on HD): reduction in plasma (E) amyloid β-42/40 (Aβ42/40) ratio (n = 36) and increase in (F) p-tau181/tau ratio (n = 33), (G) NfL (n = 32), and (H) GFAP (n = 32).

response to therapy. Further investigation is needed to better understand mechanisms contributing to cognitive impairment and dementia in patients on maintenance HD.

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SUPPLEMENTARY MATERIALS

Supplementary File (PDF)

Item S1: Supplementary methods.

Table S1: Baseline Characteristics of Historical Control Participants With Preserved Kidney Function and Normal Cognitive Function or Mild Cognitive Impairment.

Table S2: Associations With Biomarker Concentrations. Spearman Correlation Coefficients and *P* Values Are Shown.

Descriptive Text for Online Delivery

ARTICLE INFORMATION

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