β-Amyloid Dynamics in Human Plasma

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**Objectives:** To investigate dynamic changes in human plasma β-amyloid (Aβ) concentrations, evaluate the effects of aging and amyloidosis on these dynamics, and determine their correlation with cerebrospinal fluid (CSF) Aβ concentrations.

**Design:** A repeated plasma and CSF sampling study.

**Setting:** The Washington University School of Medicine in St Louis, Missouri.

**Participants:** Older adults with amyloid deposition (Amyloid+), age-matched controls without amyloid deposition (Amyloid−), and younger normal controls (YNCs) were enrolled for the study.

**Main Outcome Measures:** Hourly measurements of plasma Aβ were compared between groups by age and amyloidosis. Plasma Aβ and CSF Aβ concentrations were compared for correlation, linear increase, and circadian patterns.

**Results:** Circadian patterns were observed in plasma Aβ, with diminished amplitudes with aging. Linear increase of Aβ was only observed for CSF Aβ in the YNC and Amyloid− groups, but not in the Amyloid+ group. No linear increase was observed for plasma Aβ. No significant correlations were found between plasma and CSF Aβ concentrations.

**Conclusions:** Plasma Aβ, like CSF, demonstrates a circadian pattern that is reduced in amplitude with increasing age but is unaffected by amyloid deposition. However, we found no evidence that plasma and CSF Aβ concentrations were related on an hourly or individual basis.


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Dementia is one of the most prevalent diseases among older populations. As people continue to live longer and the aging population increases, so will the number of individuals with Alzheimer disease (AD), the most common form of dementia. β-Amyloid (Aβ) plaques are a hallmark of AD pathology. The amyloid hypothesis suggests that an imbalance between Aβ production and clearance is responsible for the amyloid plaque buildup found in brains of patients with AD.

Prior studies have shown that cerebrospinal fluid (CSF) concentrations of Aβ42, the most amyloidogenic species of Aβ, were decreased by approximately half in individuals with AD compared with age-matched controls. Various factors, including differences in study designs and choices of laboratory assays, may have contributed to the inconsistency in these reports. Our recent study on the dynamics of CSF Aβ concentrations further elucidated that CSF Aβ concentrations were not static but demonstrated an intrinsic circadian rhythm that diminished with aging and a pattern of linear increase over time during the study, which was lost in individuals with AD. Disrupted circadian rhythms in sleep and activities have also been associated with AD in prior studies, and certain circadian characteristics were correlated with cognitive performance in an older population. These findings highlight the importance of both concentrations and circadian patterns of CSF Aβ as diagnostic and predictive markers for AD and amyloidosis.

Plasma is a more accessible and less invasive source than CSF for estimating Aβ concentrations in circulation. However, results from different studies using plasma Aβ concentrations as diagnostic markers are conflicting. Various factors, including differences in study designs and choices of laboratory assays, may have contributed to the inconsistency in these reports. Our recent study on CSF Aβ dynamics also underlined the importance of sampling time in determining Aβ concentrations, since Aβ concentrations fluctuated by up to 40% from peak to trough, and this fluctuation followed a circadian rhythm.
pattern. However, it is unclear whether plasma Aβ concentrations also have dynamic patterns and whether plasma Aβ concentrations correlate with CSF concentrations.

In this study, plasma and CSF Aβ40 and Aβ42 concentrations over time were measured in study participants using a highly sensitive and standardized Lumines xMAP bead-based method. The aims of our study were to explore how plasma Aβ concentrations change over time, whether Aβ dynamics differ with aging and amyloidosis, and if there is a correlation between plasma and CSF Aβ concentrations and dynamics.

**METHODS**

**STUDY DESIGN**

This was a repeated plasma and CSF sampling study conducted at the Washington University School of Medicine in St Louis, Missouri. Participants of this study were from 2 age groups: a group of older participants (n = 20), consisting of both patients with AD and cognitively normal older controls, and a younger normal control (YNC) group (n = 10). The group of older participants was drawn from individuals 60 years and older who were enrolled in longitudinal studies of aging and dementia conducted by the Knight Alzheimer’s Disease Research Center at Washington University. Participants in this group were analyzed for ApoE genotypes and assessed clinically for cognitive performance. Individuals were deemed to be cognitively normal with a Clinical Dementia Rating of 0 or to have very mild dementia with a Clinical Dementia Rating of 0.5 or mild dementia with a Clinical Dementia Rating of 1. Younger controls were recruited from the community and were between the ages of 18 and 60 years. All participants were in good general health and had no neurological illnesses other than dementia for patients with AD. Individuals with active infections or bleeding disorders or those who were treated with anticoagulants were excluded from this study. None of the participants were involved in anti-Aβ trials at the time when they participated in our study. All human study protocols were approved by the Washington University Human Studies Committee and the General Clinical Research Center Advisory Committee. Informed consent was obtained from all participants.

**ESTIMATING STATUS OF AMYLOID DEPOSITION IN OLDER PARTICIPANTS**

For older participants (n = 20), we determined the status of brain amyloid deposition either by Pittsburgh compound B positron emission tomography (PiB PET) scan or by CSF Aβ42 to Aβ40 ratios based on the high inverse correlation between CSF Aβ42 concentrations and PiB PET values. Pittsburgh compound B binds to fibrillar amyloid cerebral deposits, and the binding potential of the prefrontal, precuneous, lateral temporal, and gyrus rectus were averaged to yield the mean cortical binding potential for each participant. A mean cortical binding potential of 0.18 or greater was considered amyloid plaque positive (Amyloid+), and a mean cortical binding potential of less than 0.18 was considered amyloid plaque negative (Amyloid−). The PiB PET scans were obtained for 12 participants to determine the presence of amyloid plaques in the brain. For the remaining 8 older participants without PiB PET scan data, we used the CSF Aβ42 to Aβ40 ratio to predict their amyloid deposition status. A separate data set of combined PiB PET and CSF Aβ42 to Aβ40 ratio was modeled to determine the optimal cutoff value of the CSF Aβ42 to Aβ40 ratio for prediction of amyloidosis. This additional second data set was composed of 26 participants with both PiB PET measures and CSF Aβ concentrations as measured by the enzyme-linked immunosorbent assay (ELISA) and the 8 older participants who only had ELISA data for CSF Aβ concentrations. Data of the 26 participants with both PiB PET and ELISA measurements were used as the training set to estimate the sensitivity and specificity of the CSF Aβ42 to Aβ40 ratio as compared with the gold standard of the PiB PET scan in determining amyloid deposition status. The receiver operating characteristic was constructed with an area under the curve of 0.95 (eFigure 1, http://www.archneurol.com). Based on the receiver operating characteristic analysis, a CSF Aβ42 to Aβ40 ratio of less than 7% was chosen as the cutoff value for positive amyloid deposition, with a sensitivity of 100% and specificity of 72%. The status of amyloid deposition was assigned for the 8 participants who did not have a PiB PET scan, based on this cutoff value and their respective CSF ELISA measurements.

**SAMPLE COLLECTION**

An intrathecal lumbar catheter and an intravenous catheter were placed between 7:30 AM and 9 AM and sample collection started between 8 AM and 9:30 AM in all participants. Six milliliters of CSF were obtained each hour for 36 hours; likewise, 6 mL of blood plasma were obtained hourly for the first 15 hours, decreasing to only odd hours for the remainder of the study. The CSF and plasma aliquots were frozen at −80°C immediately after collection in 1.7-mL Oxygen maximum-recovery polypropylene tubes. Participants were encouraged to stay in bed and were allowed free choice of when to sleep, read, watch television, use their laptops, or talk throughout the study. Participants had meals served at 9 AM, 1 PM, and 6 PM and snacks, at 11 AM, 3 PM, and 8 PM.

**CSF AND PLASMA ANALYSES**

Cerebrospinal fluid and plasma were thawed and analyzed for concentrations of Aβ40 and Aβ42 using Lumines xMAP bead-based methods (INNO-BIA plasma Aβ forms; Innogenetics). Each sample was assessed in duplicate. All samples from each participant were measured together on the same xMAP plate to avoid interplate variation. The means of the intrasample coefficients of variation for duplicates were 3.8% for Aβ40 and 3.8% for Aβ42.

**COSINOR ANALYSIS**

Cosinor analysis was performed as previously described in Huang et al. Briefly, single cosinor analysis was used to analyze the patterns of 36-hour CSF and plasma Aβ40 and Aβ42 concentrations in each participant. A cosine transformation was applied to the time variable using 24 hours as the default circadian cycle, and the PROC NLIN procedure in SAS (SAS Institute Inc) was used to estimate the parameters of the circadian patterns for Aβ fluctuations. The mesor (midline of the Aβ oscillation), amplitude (distance between the peak and mesor), and acrophase (the time corresponding to the peak of the curve) were calculated for each participant and averaged within each group. For the group-averaged data, linear increase of Aβ concentrations over time was estimated using the PROC REG procedure in SAS. Cosinor analysis was applied to data after linear trend subtraction from the raw Aβ values.
STATISTICAL ANALYSES

All analyses were performed using SAS version 9.2. Graphs were plotted in GraphPad Prism version 4.03 for Windows (GraphPad Software). The relationship of CSF to plasma was explored in this study. Circadian rhythms of Aβ fluctuation over time were examined in this study as previously described.

RESULTS

DEMOGRAPHICS OF STUDY PARTICIPANTS

The study population consisted of 60% women and 40% men. The demographic summary of participants is given in Table 1. There was no statistical difference in age between the Amyloid+ and Amyloid− groups (P = .61). There was a statistical difference in genotype distribution between the Amyloid− and Amyloid+ groups (P < .05).

INCREASED PLasma Aβ40 AND Aβ42 WITH AGING

Plasma concentrations of Aβ40 and Aβ42 were significantly higher for both older groups compared with the YNC group (>30% higher; P < .01) (Table 2) and were not different between the Amyloid+ and Amyloid− groups (P > .05), suggesting that plasma Aβ concentrations increase with aging. The correlation coefficients were 0.71 between age and plasma Aβ40 concentration (P = .03) and 0.40 between age and plasma Aβ42 concentration (P = .03).

Variability of plasma Aβ concentration in each participant was calculated as the standard deviation of serial Aβ measurements over time, and the 36-hour mean Aβ concentration was averaged by group (YNC, Amyloid+, and Amyloid−) as shown in Table 2. Despite increased plasma Aβ concentrations in the 2 older groups, Aβ variability over time decreased by about 30% for Aβ42 (P = .06) and 20% for Aβ40 (P = .09) compared with the YNC group. Taken together, plasma Aβ concentrations increased, but Aβ variability decreased with age.

Concentrations and variability were also investigated for CSF Aβ peptides (Table 3). The CSF Aβ42 concentrations decreased by 17% in the Amyloid+ group (P = .08) and by 44% in the Amyloid− group (P < .01) compared with the YNC group. The CSF Aβ42 variability decreased by 36% in the Amyloid+ group (P = .07) and by 65% in the Amyloid− group (P < .01) when compared with the YNC group. Changes in individual CSF and plasma Aβ concentrations are presented in eFigure 2.

These results suggest that CSF Aβ42 concentrations and variability declined with amyloidosis and, to a lesser extent, with age. No difference was found in mean Aβ40 concentration or mean Aβ40 variability (P > .05) between the YNC, Amyloid+, and Amyloid− groups.

LINEAR INCREASE IN CSF BUT NOT IN PLASMA Aβ

Linear increase of CSF Aβ40 concentration (Figure 1A) was observed in both the YNC (18%/24 h) and Amyloid− groups (27%/24 h) but diminished in the Amyloid+ group (12%/24 h). Similarly, linear increase of CSF Aβ42 concentration (Figure 1B) was observed in both the YNC (15%/24 h) and Amyloid− group (19%/24 h) but dramatically reduced in the Amyloid+ group (3%/24 h). When examining plasma Aβ40 and Aβ42 concentrations, no linear increase was observed in any of the 3 groups (all <4%/24 h) (Figure 1).

DECREASED PLASMA Aβ CIRCADIAN AMPLITUDES WITH AGING

Cosinor analysis was used to assess the circadian patterns of plasma Aβ40 (Figure 2A) and Aβ42 (Figure 2B) dynamics in the Amyloid+, Amyloid−, and YNC groups using the mean-adjusted group average. Amplitudes of diurnal pattern were increased 2-fold in YNC group compared with the 2 older groups.

Cosinor analysis was also used to assess the circadian patterns of CSF Aβ dynamics in the Amyloid+, Amyloid−, and YNC groups using the mean-adjusted group average data after the linear trend was subtracted (Figure 2C and D). Similar to the plasma data, amplitudes of diurnal CSF Aβ fluctuation in the YNC group were 40% to 70% higher than the 2 older groups. Goodness of fit for these cosinor models (R2) was between 0.29 and 0.64 (eTable 1).

Cosinor analysis was used to assess the circadian patterns of CSF and plasma Aβ dynamics in each individual participant. Cosinor parameters, including the mesor, amplitude, and amplitude to mesor ratio, were calculated for each participant and averaged for the 3 groups (eTable 2 and eTable 3). The cosinor goodness of fit for each participant was highly correlated for plasma Aβ40 and Aβ42 (r = 0.92; P < .001) in the YNC group and less so for the Amyloid+ (r = 0.6; P = .04) and Amyloid− (r = 0.7; P = .05) groups (eTable 4).

Correlations between age and cosinor amplitudes for mean-adjusted CSF and plasma Aβ peptides were calculated (eFigure 3). Significant negative correlations with

Table 1. Characteristics of Study Participants

<table>
<thead>
<tr>
<th>Group</th>
<th>YNC</th>
<th>Amyloid−</th>
<th>Amyloid+</th>
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</thead>
<tbody>
<tr>
<td>Age, y, mean (SD)</td>
<td>35.6 (12.9)</td>
<td>72.0 (6.9)</td>
<td>73.6 (6.9)</td>
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<td>CDR</td>
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<td>6</td>
<td>3</td>
</tr>
<tr>
<td>0.5</td>
<td>NA</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>1</td>
<td>NA</td>
<td>1</td>
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<td>ApoE genotype</td>
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<td>E3/E3</td>
<td>NA</td>
<td>6</td>
<td>7b</td>
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<tr>
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<td>NA</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>E3/E4</td>
<td>NA</td>
<td>0</td>
<td>5</td>
</tr>
</tbody>
</table>

Abbreviations: Amyloid−, age-matched control without amyloid deposition; Amyloid+, older adult with amyloid deposition; CDR, Clinical Dementia Rating; NA, not applicable; YNC, younger normal control.

bStatistically different distribution of ApoE genotypes between the Amyloid+ and Amyloid− groups (P < .05).
age were found for CSF Aβ40, CSF Aβ42, and plasma Aβ40 (P < .05). Negative but nonsignificant correlation was found between age and plasma Aβ42 (P = .16).

In summary, diurnal patterns were observed in both CSF and plasma Aβ concentrations, with the highest amplitudes in both fluids occurring in the YNC group. For the group average data, the acrophases of the cosinor curves differed between CSF and plasma Aβ concentrations. The peaks for CSF Aβ concentrations occurred around 9 hours after the start of the study (corresponding to 6 PM), and the peaks for plasma Aβ concentrations occurred around 15 hours after the start of the study (corresponding to 12 AM); thus, there was approximately a 6-hour time difference between the plasma and CSF peaks for Aβ concentrations. However, individual cosinor models were highly variable in terms of their acrophase (mean [SD] plasma Aβ40 acrophase, 4.7 [2.7] hours; mean [SD] plasma Aβ42 acrophase, 0.05 [7.8] hours).

Table 2. 36-Hour Mean Concentrations for Plasma Aβ42 and Aβ40 in 3 Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Plasma Aβ42</th>
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<tbody>
<tr>
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<td>36-h Mean</td>
<td>36-h Mean</td>
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<td></td>
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</tr>
<tr>
<td></td>
<td>Concentration (SD), pM</td>
<td>Variability (SD), pM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>YNC (n = 10)</td>
<td>6.9 (1.8)</td>
<td>1.0 (0.7)</td>
<td></td>
<td>39.1 (8.7)</td>
<td>4.7 (2.7)</td>
</tr>
<tr>
<td>Amyloid− (n = 8)</td>
<td>8.8 (2.4)b</td>
<td>0.6 (0.3)</td>
<td></td>
<td>55.0 (10.2)b</td>
<td>4.0 (1.4)</td>
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<td>Amyloid+ (n = 12)</td>
<td>9.9 (2.6)b</td>
<td>0.7 (0.3)</td>
<td></td>
<td>55.5 (9.0)b</td>
<td>3.8 (1.3)</td>
</tr>
</tbody>
</table>

Abbreviations: Aβ, β-amyloid; Amyloid−, age-matched control without amyloid deposition; Amyloid+, older adult with amyloid deposition; YNC, younger normal control.

The YNC group had lower concentrations of plasma Aβ42 and Aβ40 compared with the other 2 groups. The YNC group was set as the reference group for statistical comparisons.

Table 3. 36-Hour Mean Concentrations for CSF Aβ42 and Aβ40 in 3 Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>CSF Aβ42</th>
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<tbody>
<tr>
<td></td>
<td>36-h Mean</td>
<td>36-h Mean</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Concentration (SD), pM</td>
<td>Variability (SD), pM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>YNC (n = 10)</td>
<td>374.1 (148.7)</td>
<td>75.9 (36.0)</td>
<td></td>
<td>2365.0 (566.7)</td>
<td>487.4 (176.7)</td>
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<tr>
<td>Amyloid− (n = 8)</td>
<td>311.6 (153.3)</td>
<td>48.4 (26.8)</td>
<td></td>
<td>2984.6 (1686.5)</td>
<td>635.5 (490.7)</td>
</tr>
<tr>
<td>Amyloid+ (n = 12)</td>
<td>208.0 (97.7)b</td>
<td>26.7 (17.6)b</td>
<td></td>
<td>2484.7 (813.2)</td>
<td>414.9 (174.7)</td>
</tr>
</tbody>
</table>

Abbreviations: Aβ, β-amyloid; Amyloid−, age-matched control without amyloid deposition; Amyloid+, older adult with amyloid deposition; CSF, cerebrospinal fluid; YNC, younger normal control.

The Amyloid+ group had lower concentrations of CSF Aβ42 compared with the other 2 groups. The YNC group was set as the reference group for statistical comparisons.

Figures 1. Cerebrospinal (CSF) β-amyloid 40 (Aβ40) (A) and Aβ42 (B) concentrations linearly increase in the younger normal control (YNC) and age-matched control without amyloid deposition (Amyloid−) groups. However, in the older adult with amyloid deposition (Amyloid+) group, the linear increase of CSF Aβ42 was absent and the linear increase of CSF Aβ40 was diminished. In contrast, plasma Aβ40 (A) and Aβ42 (B) concentrations did not have a linear rise in any of the 3 groups.
hours), and the group 6-hour lag in peak plasma Aβ concentration was not observed.

**LACK OF CORRELATION BETWEEN CSF AND PLASMA Aβ CONCENTRATIONS**

Average CSF and plasma Aβ concentrations of each participant over time were calculated (36-hour mean) and correlations between these 2 sets of values were estimated. Correlation coefficients between average CSF and plasma Aβ42 concentrations were −0.14 (P = .46) for all participants, 0.52 (P = .16) for the Amyloid− group, −0.27 (P = .42) for the Amyloid+ group, and −0.01 (P = .97) for the YNC group. Correlation coefficients between average CSF and plasma Aβ40 concentrations were −0.19 for all participants, −0.48 (P = .18) for the Amyloid− group, −0.51 (P = .11) for the Amyloid+ group, and −0.01 (P = .97) for the YNC group. Furthermore, to test CSF and plasma Aβ association on individual concentrations, hourly CSF Aβ40 and Aβ42 measurements were

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**Figure 2.** β-Amyloid (Aβ) diurnal patterns diminish with increased age. The diurnal amplitude of plasma Aβ40 (A), plasma Aβ42 (B), cerebrospinal (CSF) Aβ40 (C), and CSF Aβ42 (D) was decreased by approximately half in the older groups (age-matched control without amyloid deposition [Amyloid−] and older adult with amyloid deposition [Amyloid+]) compared with the younger group, regardless of amyloid deposition. Data are group averaged mean-adjusted Aβ concentrations over time. YNC indicates younger normal control.
correlated with plasma Aβ concentrations for each participant. The average correlation coefficient for Aβ40 was 0.03 (SD: 0.32; minimum: −0.62; and maximum: 0.48) and for Aβ42 was 0.08 (SD: 0.38; minimum: −0.57; and maximum: 0.73). Since changes in plasma Aβ may lag those in CSF, the correlations between CSF Aβ concentrations at a specific time and plasma Aβ concentrations 6 hours later were also investigated. The average correlation coefficient for Aβ40 was 0.03 (SD: −0.20; minimum: −0.92; and maximum: 0.50) and for Aβ42 was 0.08 (SD: −0.13; minimum: −0.90; and maximum: 0.51) after the time effect was taken into consideration.

**CORRELATION BETWEEN PLASMA Aβ40 AND Aβ42**

For each study participant, hourly plasma Aβ40 and Aβ42 concentrations were highly correlated (average r = 0.79) (eTable 5). No statistical differences in the mean correlation coefficients were found among the Amyloid⁺, Amyloid⁻, and YNC groups (P > .05). In addition to the strong hourly Aβ40 and Aβ42 correlation in each individual, statistically significant correlations were observed between the 36-hour average Aβ40 and Aβ42 concentrations combining the 3 groups (P < .01) (eFigure 4).

We found a significant linear rise in CSF Aβ for the YNC and Amyloid⁺ groups with decreased Aβ40 concentration and absent Aβ42 linear rise in the Amyloid⁻ group. We found no evidence for a linear rise in plasma Aβ for any group. Together, these findings suggest that the Aβ linear rise in CSF is a specific central effect of increasing CSF Aβ concentrations in the lumbar space. We postulate that the procedure of repeated sampling of lumbar CSF may cause increased subarachnoid CSF closer to the brain to be sampled in the lumbar space. If correct, an Aβ rostral-caudal gradient may exist in healthy controls, but not in the presence of amyloidosis. Alternative explanations include increased central Aβ production due to decreased contiguous sleep or increased stress or decreased clearance from the central compartment.

To our knowledge, this is the first report of a plasma Aβ circadian pattern over time. The plasma Aβ circadian amplitudes decrease with aging independent of amyloidosis, similar to findings in the CSF. The amplitude of the plasma Aβ42 circadian pattern is similar to CSF, while the relative amplitude of plasma Aβ40 is half that of CSF. The average acrophase of plasma Aβ is 6 hours later compared with the CSF Aβ40 acrophase. Although a 6-hour delay in plasma acrophase could be due to the time it takes for lumbar CSF to be resorbed into the bloodstream, this is not supported by the lack of correlation between hourly CSF and plasma Aβ values because CSF Aβ concentrations are highly dynamic hour to hour, while plasma changes relatively little over a few hours. This suggests that other factors contribute to dynamic changes in CSF Aβ outside of circadian regulation. These other factors may include neuronal activity, secretase activity, amyloid precursor protein production, or transport and clearance mechanisms.

Further, the age-associated increase in plasma Aβ was not mirrored by a similar increase in CSF and several other studies have shown no difference in plasma Aβ concentrations between controls and individuals with AD, despite the marked reduction in CSF Aβ42 concentrations in individuals with AD. Therefore, plasma Aβ may be largely influenced by peripheral mechanisms of production (eg, platelets or other cells) and clearance (eg, within the liver) that are different from CSF Aβ. Thus, circadian processes may influence both the peripheral and central production and clearance of Aβ.

These findings provide useful results for both plasma and CSF Aβ diagnostic and therapeutic biomarker studies. For example, time of collection for both blood and CSF should be controlled. Further, this study suggests that Aβ peptides in both the central and peripheral compartments are regulated in a circadian pattern that is part of the normal dynamic physiologic control of Aβ concentrations. This study also indicates that peripheral Aβ concentrations are not useful as direct surrogates for central Aβ concentrations.

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