

COMMENTARY

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Diurnal oscillation of CSF A β and other AD biomarkers



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Abstract

To assess stages of Alzheimer's disease (AD) pathogenesis and the efficacy of drugs during clinical trials, there has been immense interest in the field to establish baseline cerebrospinal fluid (CSF) concentrations for potential AD biomarkers such as amyloid- β (A β) and tau. Significant within-person variations in CSF A β concentrations over time found that this variation followed the sleep-wake cycle. A recent paper in *Molecular Neurodegeneration* reported the absence of diurnal variations in multiple classical and candidate AD biomarkers, such as soluble APP, A β , tau, p-tau, YKL-40, VILIP-1, or apolipoprotein E. This commentary addresses these apparently discordant results regarding the diurnal variability of APP and A β compared with the literature. Despite our concerns, we appreciate the authors' interest in this important topic and contribution to improve our knowledge about the factors influencing A β diurnal variation.

Keywords: Alzheimer's disease, Amyloid- β , Biomarkers

Background

To assess stages of Alzheimer's disease (AD) pathogenesis and the efficacy of drugs during clinical trials, there has been immense interest in the field to establish baseline cerebrospinal fluid (CSF) concentrations for potential AD biomarkers such as amyloid- β (A β) and tau. For instance, lumbar punctures performed in individuals demonstrate low levels of A β 42 in individuals cerebral with amyloid deposition [1]. Large fluctuations in A β levels also were noted in individuals over years when sampled by lumbar puncture [2]. Indwelling lumbar catheters have also been used to obtain more frequent CSF sampling over 24–48 h to understand A β metabolism for pharmacological modeling during drug trials. These catheter studies found significant within-person variability in CSF A β concentrations over the sampled time [3].

After A β release was demonstrated to be driven by neuronal activity in vivo [4], further investigations in rodents and humans found that the central nervous system concentration of A β fluctuated with the sleep-wake cycle. The amplitude of A β oscillation was decreased by both amyloid deposition in the brains of AD

mouse models and humans, and in individuals with autosomal dominant AD mutations [5–7]. Soluble amyloid precursor protein (APP) and plasma A β also oscillate with sleep-wake activity [8, 9]. An analysis of serial A β concentrations from 178 participants who underwent CSF sampling via indwelling lumbar catheters in multiple academic and industry studies found an A β diurnal pattern in 16 of 17 studies [10]. The only study without a diurnal oscillation was confounded by a bacterial filter placed on the catheter during collection that removed A β from the CSF samples [11]. The A β diurnal pattern has also been replicated using different assays (enzyme-linked immunosorbent assay and mass spectrometry) [12].

Main text

Recently, Cicognola et al. [13] reported the absence of diurnal variations in multiple classical and candidate AD biomarkers, such as soluble APP, A β , tau, p-tau, YKL-40, VILIP-1, or apolipoprotein E. The authors sampled from 13 neurosurgical patients by either ventricular or lumbar CSF drainage at six time points over a 24-h period: 08:00, 12:00, 16:00, 20:00, 00:00, and 08:00. Four ml of CSF was collected at each time point.

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Several factors may have led to the apparently discordant results regarding the diurnal variability of APP and A β , compared with the literature, in the Cicognola et al. study. First, it is possible that neurosurgical patients may have disrupted sleep-wake cycles that might alter diurnal patterns, particularly if the patients were sampled while in intensive care units where sleep would be fragmented due to frequent interruptions for clinical care. Further, brain tumors, hydrocephalus, and other intracranial pathologies could independently disturb sleep-wake activity and CSF flow.

Second, a longer sampling period may be necessary to observe fluctuations of A β in this population. For example, sampling periods up to 168 h were required to correlate A β fluctuations with changes in neurological status in patients with brain injury [14].

Third, the authors collected CSF from two different types of drains. Presumably, CSF was collected during the patients' routine clinical care between the research sampling time points. Previous reports have found that more frequent sampling will increase the rate of linear

rise in A β [10, 15]. The authors do not record how much CSF was drained between these time points for clinical purposes to control for this effect.

Fourth, we expect that CSF sampling was not frequent enough to detect an A β oscillation over 24 h and that the study is underpowered to detect any oscillation that may be present in this patient population.

Fifth, a repeated measures ANOVA may not be the correct test to determine if there is a diurnal oscillation as we would predict A β concentrations to oscillate together over the 24 h day.

Conclusion

Understanding how A β concentrations change over short periods of time (e.g. hours) in the human central nervous system is critical to the design and implementation of anti-A β AD treatment trials. Despite our concerns, we appreciate the authors' interest in this important topic and contribution to improve our knowledge about the factors influencing A β diurnal variation.

Author's response: Is there an association of diurnal variation with cerebrospinal fluid biomarkers for Alzheimer's disease?

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We thank Lucey and co-workers [16] for their interest in our paper [13]. The authors point out some potential confounders that may influence sleep-wake cycles and variability of biomarkers for Alzheimer's disease pathophysiology, thereby affecting the possibility to identify diurnal patterns of variation in biomarker concentrations [16]. As acknowledged in the discussion section of our paper, these types of potential confounders may underlie the inconsistencies in outcomes between studies, as also recently reviewed [17]. For example, acute brain trauma [18] and other possible disease- or drug-related effects on brain functioning and A β metabolism in neurosurgical patients [13, 14], may give different results than

studies in healthy controls [10, 19]. Further, sampling procedures, e.g., the use of lumbar or ventricular catheters [10, 13, 19] or intracerebral microdialysis catheters [14], or even plasma [9], reflect different compartments that will impact the results.

Undoubtedly, we need to perform more studies using highly standardized protocols, controlling for clinical confounder as well possible artefacts due to variable sampling time-points and volume-related disturbances in CSF dynamics [15], to resolve whether A β and other biomarkers reflecting AD pathophysiology vary with the normal sleep-wake cycle, and show a true diurnal variation.

Abbreviations

AD: Alzheimer's disease; ANOVA: Analysis of variance; APP: Amyloid precursor protein; A β : Amyloid- β ; CSF: Cerebrospinal fluid

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Authors' contributions

BPL drafted this commentary. AMF, DMH, JCM, and RJB revised and edited this commentary. CC drafted the Author's response. DC, PE, UA, HV, HZ, LP and KB revised and edited the Author's response. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

Not applicable.

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