Original Research Article

Visual Ratings of Medial Temporal Lobe Atrophy Correlate with CSF Tau Indices in Clinical Variants of Early-Onset Alzheimer Disease

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Keywords

Biomarkers · Cerebrospinal fluid · Early-onset Alzheimer disease · Magnetic resonance imaging · Tau

Abstract

Background/Aims: Prior studies of late-onset Alzheimer disease (AD) have reported that cerebrospinal fluid (CSF) tau levels correlate with hippocampal/medial temporal lobe atrophy. These findings suggest that CSF tau indices in AD may reflect tau-related neurodegeneration in the medial temporal lobe. However, it remains uncertain whether elevated CSF tau levels in the clinically heterogeneous subtypes of early-onset AD (EOAD; amnestic, posterior cortical atrophy [PCA], and logopenic progressive aphasia [LPA]) are attributable to similar underlying mechanisms. **Methods:** We identified 41 EOAD patients (18 amnestic, 14 with LPA, and 9 with PCA) with CSF and brain MRI data. Semiquantitative ratings were used to assess medial temporal lobe atrophy and PCA, which were compared to CSF biomarker indices. **Results:** Lower CSF tau levels were seen in PCA relative to amnestic EOAD and LPA, but similar ratings for medial temporal lobe atrophy and PCA were seen across the groups. After adjustments for demographics and cognitive performance, both total ($p = 0.004$) and hyperphosphorylated ($p = 0.026$) tau levels correlated with medial temporal lobe atrophy across this EOAD cohort. **Conclusions:** These results replicate prior findings in late-onset AD and support the hypothesis that CSF tau levels primarily reflect tau-related neurodegenerative changes in the hippocampus/medial temporal lobe across the clinical subtypes of EOAD.

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Introduction

Sporadic early-onset Alzheimer disease (EOAD; age ≤ 65 years) has been categorized into three primary subtypes based on the predominant domain of initial cognitive symptomatology: (1) amnestic (memory); (2) logopenic progressive aphasia (LPA; language); and (3) posterior cortical atrophy (PCA; visuospatial) [1]. While these EOAD subtypes are primarily defined by their clinical features, prior work has indicated that they can also be distinguished by their regional patterns of underlying Alzheimer disease (AD) neuropathology [2–4], cortical atrophy on MRI [5–11], and hypometabolism on FDG-PET [7, 11–15]. Despite these differences, all three subtypes have shown similar profiles for β -amyloid ($A\beta$) biomarker indices, including indistinguishable patterns of increased $A\beta$ deposition on PET imaging [12, 13, 15, 16] and consistently low levels of $A\beta_{42}$ in the cerebrospinal fluid (CSF) [11, 16–27].

What remains less certain is whether CSF tau indices differ between these clinical EOAD subtypes. While several studies have suggested similar elevations in CSF total tau (t-tau) and phosphorylated tau (p-tau) across subtypes [11, 16–18, 20–22, 26, 27], others have raised the possibility that CSF t-tau and/or p-tau levels may be significantly lower in PCA relative to amnestic or LPA variants of EOAD [19, 24, 25]. These divergent findings have generated multiple hypotheses regarding the mechanistic implications of elevations in CSF tau indices in EOAD [24].

Amongst individuals at different stages of late-onset AD, many [28–34] (though not all [35, 36]) previous studies have demonstrated significant correlations between CSF tau indices and hippocampal/medial temporal lobe atrophy. In classification analyses of AD patients, these CSF and imaging biomarker abnormalities are often (though not always) seen in conjunction [37, 38]. On the basis of these findings, it has been postulated that elevations in CSF tau indices in AD reflect regional neurodegeneration [31] attributable to the deposition of neurofibrillary tangles (NFTs) [32], particularly in the hippocampus [30]. Such conclusions are consistent with other work suggesting that CSF biomarkers for AD may most closely reflect neuropathology in periventricular regions [39].

Investigations into the relationship between CSF tau indices and regional atrophy in EOAD subtypes may further clarify this relationship, given the more diverse patterns of NFT deposition across this patient population [2–4]. However, previous work investigating CSF biomarker indices and cerebral atrophy in EOAD subtypes using voxel-based morphometry (VBM) somewhat surprisingly failed to show significant correlations between CSF tau measures and regional cerebral volumetric measurements [27]. In the work presented below, we used another approach for measuring regional brain atrophy on MRI, semiquantitative visual ratings [40, 41], to determine whether prior reports of correlations between medial temporal lobe atrophy and CSF tau indices at different stages of late-onset AD are similarly applicable across EOAD variants.

Subjects and Methods

Participants

We performed a retrospective chart review of patients seen in the UCLA Neurobehavior Clinic, which focuses on the diagnosis and management of early-onset dementias, between 2002 and 2015. We identified 41 patients with an initial symptom onset before the age of 65 years who fulfilled the diagnostic criteria for probable amnestic EOAD ($n = 18$) [42], LPA ($n = 14$) [43], or PCA ($n = 9$) [2, 44] and had both CSF biomarker and brain MRI data available for review. The CSF indices for 24 of these patients had been included in a previous analysis [24]. All patients underwent assessments that included clinical history taking, the Mini-Mental State Examination (MMSE) [45], and neurological and neurobehavioral examinations. CSF biomarker levels and brain MRI images were either obtained at UCLA or available from prior medical evaluations. This retrospective review of patient records was approved by the UCLA Institutional Review Board.

CSF Analyses

The CSF samples were analyzed by Athena Diagnostics (Worcester, MA, USA) for $A\beta_{42}$, t-tau, and p-tau using commercially available ELISA kits (INNOTEST β -Amyloid(1–42), INNOTEST hTau Ag, and INNOTEST Phospho-Tau(181P); Innogenetics, Ghent, Belgium). p-tau measurements were not available for 2 patients in the LPA group and 1 patient in the amnestic group.

Visual Rating Assessments of MRI

Two trained and independent raters blinded to the patients' clinical data (E.G. and P.P.) performed semi-quantitative visual ratings of both medial temporal lobe atrophy [40] and PCA [41]. Such ratings can be performed and compared across images obtained from multiple different scanners.

Visual assessments of medial temporal lobe atrophy were performed on coronal images [40]. Non-contrast T1-weighted sequences were preferentially used for these analyses, but for a subset of patients, only T2-weighted and/or post-contrast T1-weighted sequences were available. The medial temporal lobe atrophy scores ranged from 0 (no atrophy) to 4 (severe atrophy). Visual assessments of PCA were based on the examination of axial sequences in conjunction with coronal and/or sagittal sequences [41]. The PCA scores ranged from 0 (no atrophy) to 3 (severe atrophy). When scores for specific patients from an individual rater differed by orientation, the highest score was used. For each rater, the right and left medial temporal lobes and the right and left posterior cortical regions were rated separately prior to being averaged together to derive a composite score for each region. Visual atrophy ratings for the medial temporal lobe for 1 patient in the amnestic EOAD group and for the posterior cortex for 1 patient in the PCA group were not performed due to missing MRI sequences.

Data Analyses

Statistical analyses were performed using SPSS 23 for Mac (IBM, Armonk, NY, USA). Demographic data were compared between the diagnostic groups using one-way ANOVA for continuous variables and Kruskal-Wallis tests for categorical variables. CSF biomarker data and MRI visual atrophy ratings were compared between the diagnostic groups using Kruskal-Wallis tests. Post hoc analyses were Bonferroni corrected for multiple comparisons where appropriate. The degree of agreement between the independent visual MRI raters was assessed using intraclass correlation coefficients (ICCs). ICC values <0.4 denote poor agreement, values between 0.4 and 0.59 denote fair agreement, values between 0.6 and 0.74 denote good agreement, and values >0.74 denote excellent agreement [46]. Associations between MRI atrophy ratings and CSF biomarker data were assessed with Spearman's rank correlation coefficients for unadjusted analyses and multiple linear regression for adjusted analyses.

Results

The demographic data for the patients with amnestic EOAD, LPA, and PCA with valid CSF and MRI data available for analysis are shown in Table 1. The three EOAD groups were similar in gender distribution, age at symptom onset, age at lumbar puncture (LP), symptom duration at LP, MMSE score at LP, and interval between MRI and LP (p values <0.05).

The box plots for the CSF indices in the three EOAD groups are shown in Figure 1. Similar $A\beta_{42}$ levels were seen across all three groups (Fig. 1a; $\chi^2(2, 41) = 0.06$, $p = 0.97$). However, significant group differences were seen in t-tau (Fig. 1b; $\chi^2(2, 41) = 9.12$, $p = 0.010$) and p-tau (Fig. 1c; $\chi^2(2, 38) = 7.76$, $p = 0.021$) levels. Bonferroni-corrected post hoc Mann-Whitney U comparisons (critical $p < 0.017$) revealed significantly higher t-tau ($Z(27) = -2.98$, $p = 0.003$) and p-tau ($Z(26) = -2.61$, $p = 0.009$) levels in amnestic EOAD relative to PCA. Marginally higher t-tau ($Z(23) = -2.39$, $p = 0.017$) and p-tau ($Z(21) = -2.27$, $p = 0.023$) levels were seen in LPA relative to PCA.

The ICC analyses of the consistency of the visual atrophy scores between the two blinded raters indicated excellent agreement for the left (ICC = 0.82) and right (ICC = 0.79) medial temporal lobes and for the left (ICC = 0.84) and right (ICC = 0.86) posterior cortical regions, comparable to that reported by other groups [47]. Wilcoxon signed-rank tests indicated

Fig. 1. Box plots for cerebrospinal fluid levels of Aβ₄₂ (a), total tau (t-tau) (b), and phosphorylated tau (p-tau) (c) in the amnestic early-onset Alzheimer disease (AMN), logopenic progressive aphasia (LPA), and posterior cortical atrophy (PCA) groups. * $p < 0.017$ versus PCA group.

Table 1. Demographic data

	Amnestic	LPA	PCA	$F(2, 38)/c^2(2, 41)$
Subjects, <i>n</i>	18	14	9	
Male, %	61	43	33	2.15
Age at symptom onset, years	53.2 (4.9)	55.8 (4.6)	54.0 (5.3)	1.09
Age at LP, years	56.3 (4.1)	59.0 (5.3)	57.2 (5.6)	1.20
Symptom duration at LP, years	3.1 (1.8)	3.2 (2.4)	3.2 (1.8)	0.01
MMSE score at LP	22.1 (6.3)	17.2 (8.1)	20.3 (4.4)	2.09 ^a
LP-to-MRI interval, months	8.9 (12.9)	14.9 (19.4)	5.8 (5.2)	1.23

Values in parentheses denote standard deviations. LPA, logopenic progressive aphasia; PCA, posterior cortical atrophy; LP, lumbar puncture. ^a $df = 2, 37$ due to missing data for 1 patient in the amnestic group.

similar atrophy ratings for the left and right medial temporal lobes and left and right posterior cortical regions for each rater (all p values >0.05). Therefore, for each rater and region, the atrophy scores were averaged across the hemispheres to generate regional composite scores, which were then averaged across the raters for subsequent analyses. The visual atrophy ratings for the medial temporal and posterior cortical regions in the three EOAD groups are shown in Figure 2. Similar regional atrophy scores were seen across the groups in both the medial temporal lobe (Fig. 2a; $\chi^2(2, 40) = 0.19$, $p = 0.91$) and the posterior cortex (Fig. 2b; $\chi^2(2, 40) = 2.02$, $p = 0.36$).

We subsequently sought to determine whether regional visual atrophy scores correlated with CSF biomarker indices. Unadjusted analyses indicated that medial temporal lobe atrophy ratings were significantly correlated with CSF t-tau levels (Fig. 3a; $r_s(40) = 0.38$, $p = 0.015$) and marginally correlated with CSF p-tau levels (Fig. 3b; $r_s(37) = 0.28$, $p = 0.098$) but were not correlated with CSF Aβ₄₂ levels ($r_s(40) = 0.03$, $p = 0.85$). PCA ratings did not correlate with

Fig. 2. Box plots for visual atrophy ratings of the medial temporal (a) and posterior cortical (b) regions in the amnesic early-onset Alzheimer disease (AMN), logopenic progressive aphasia (LPA), and posterior cortical atrophy (PCA) groups.

Fig. 3. Unadjusted correlations between cerebrospinal fluid total tau (t-tau) (a) and phosphorylated tau (p-tau) (b) levels and visual ratings of medial temporal lobe (MTL) atrophy across the amnesic early-onset Alzheimer disease (AMN), logopenic progressive aphasia (LPA), and posterior cortical atrophy (PCA) groups.

CSF t-tau ($r_s(40) = 0.13$, $p = 0.42$), p-tau ($r_s(37) = -0.13$, $p = 0.46$), or $A\beta_{42}$ ($r_s(40) = 0.10$, $p = 0.55$) levels.

Although there are conflicting reports in the literature regarding the association between demographic factors and CSF AD biomarkers, a subset of studies have suggested that age [48, 49], sex [50], and MMSE scores [49, 51] may modulate CSF tau indices. Therefore, we performed additional multiple regression analyses of CSF t-tau and p-tau versus visual atrophy ratings to adjust for these potentially confounding variables (Table 2). The adjusted analyses indicated that ratings of medial temporal lobe atrophy were significantly associated with both t-tau ($p = 0.004$) and p-tau ($p = 0.026$) across the entire EOAD cohort. However, the adjusted analyses failed to show any significant associations between ratings of PCA and CSF tau indices (data not shown).

Table 2. Multiple regression analysis of CSF t-tau and p-tau levels across the amnestic EOAD, LPA, and PCA groups

	t-tau			p-tau		
	β	<i>t</i>	<i>p</i>	β	<i>t</i>	<i>p</i>
Sex	0.32	2.44	0.020	0.20	1.32	0.198
Age	–0.44	–3.37	0.002	–0.35	–2.23	0.033
MMSE score	–0.06	–0.47	0.640	0.07	0.45	0.658
Medial temporal lobe atrophy	0.41	3.09	0.004	0.37	2.33	0.026
		<i>r</i> = 0.64			<i>r</i> = 0.50	

The reference condition for sex is male. CSF, cerebrospinal fluid; t-tau, total tau; p-tau, phosphorylated tau; EOAD, early-onset Alzheimer disease; LPA, logopenic progressive aphasia; PCA, posterior cortical atrophy.

Discussion

Our analyses of CSF AD biomarkers and semiquantitative MRI regional atrophy ratings across the clinical subtypes of EOAD demonstrate significant associations between CSF tau indices and atrophy in the medial temporal lobes but not in the posterior cortical regions. These findings are consistent with prior work in cohorts with participants in the prodromal and dementia stages of late-onset AD indicating that volumetric measurements of hippocampal atrophy correlate with CSF t-tau and/or p-tau levels [28–34], and they provide additional support for the hypothesis that elevated CSF tau indices in AD primarily reflect NFT-driven neurodegenerative changes in the hippocampus and medial temporal lobes [30–32].

Similar to our prior report (which included 24 of the patients studied here) [24], CSF t-tau and p-tau levels were lower in PCA than in amnestic EOAD or LPA. The literature regarding CSF tau indices in PCA remains inconsistent; a few studies have reported lower tau levels in PCA relative to other EOAD subtypes [19, 24, 25], but others have not [11, 16–18, 20–22, 27]. While the diagnostic criteria for PCA are well established [2, 44], subtle differences in their operationalization across research groups may have resulted in the inclusion of different subsets of PCA patients across studies.

We used regional visual atrophy ratings as a proxy for severity of neurodegeneration and NFT deposition. Somewhat unexpectedly, all three EOAD subgroups had similar overall atrophy ratings for the medial temporal and posterior cortical regions. Previous studies comparing AD subtypes have reported greater medial temporal and hippocampal atrophy in typical or amnestic AD [5–7, 9, 10], greater parietal/occipital atrophy in PCA [5, 6, 10], and greater left temporal/parietal atrophy in LPA [7, 8]. The absence of group differences in our visual atrophy rating indices may be related to the smaller sample sizes for our analyses or the potentially poorer precision of visual ratings relative to volumetric analyses. Additionally, since the CSF studies were conducted for clinical purposes, our cohort may have been enriched by patients with more atypical presentations [24]. Alternatively, our findings may reflect the partially overlapping networks of neurodegeneration that are seen across EOAD subtypes, particularly with disease progression [52].

The associations between medial temporal lobe atrophy and CSF tau indices seen in our EOAD patients mirror prior work in late-onset AD [29–34], despite the different overall patterns of atrophy between these AD subtypes [53]. One interpretation of these results is that CSF t-tau and p-tau levels, much like CSF A β ₄₂ levels [39], correlate most strongly with periventricular AD pathology. Recent work examining tau PET imaging with AV-1451 in late-

onset AD has shown a significantly elevated uptake in the medial temporal lobes [54]. Likewise, a significantly higher medial temporal lobe AV-1451 uptake is seen in amnesic EOAD, LPA, and PCA patients relative to controls [15], suggesting that elevations in CSF tau levels in EOAD may also be largely due to medial temporal lobe tau deposition. A definitive exploration of this hypothesis in EOAD awaits further studies of correlations between CSF tau indices and regional tau PET tracer uptake, particularly since CSF tau indices appear to correlate with tau PET signals in individuals with late-onset cognitive impairment across a number of regions, including the medial temporal lobes [54].

The results presented here differ from those of Ossenkoppele et al. [27], who demonstrated similar CSF t-tau and p-tau levels across amnesic EOAD, LPA, and PCA groups and failed to show significant correlations between these indices and cerebral volumetric measurements using VBM. These discrepant results could have arisen from our use of semi-quantitative ratings of regional visual atrophy (which were not adjusted for the degree of global cerebral atrophy) rather than volumetric measurements. However, the Scheltens medial temporal lobe rating scale [40] correlates closely with VBM [47], tensor-based morphometry [55], and other volumetric approaches to measuring hippocampal size [56, 57]. Nevertheless, it is perhaps notable that a prior study examining visual ratings of medial temporal lobe atrophy in mild cognitive impairment failed to find a correlation with CSF t-tau levels [36]. Alternatively, there may be inherent differences in EOAD cohort composition, as the participants in the study by Ossenkoppele et al. [27] were significantly older and had higher CSF A β ₄₂ levels than those included in our analyses.

A number of factors may limit the interpretation of our findings. The data were retrospectively gathered via chart review, and only a small proportion of the EOAD patients seen in the UCLA Neurobehavior Clinic had both CSF and MRI data available for review. This subgroup may not be entirely representative of our patient population. All patients received a clinical diagnosis of EOAD from a single rater (M.F.M.), but we did not have neuropathological confirmation of an underlying AD pathology. Prior postmortem studies have suggested that some PCA [2, 58, 59] and LPA [3, 4] patients may have a non-AD neuropathology. However, all of our EOAD patients had CSF A β ₄₂ levels <500 pg/mL, which has previously been used as a threshold suggestive of AD [18, 20]. The associations between medial temporal lobe atrophy ratings and CSF tau indices were relatively modest in magnitude, suggesting that other factors, including NFT deposition in other periventricular regions, are also likely to contribute to CSF tau levels in AD. MR images were obtained with multiple scanners, and the specific sequences available for review differed between the patients. However, the visual atrophy rating scales used in this study are likely to produce results that are robust across scanners and sequences [40, 41]. The CSF samples and MR images were not collected on the same day, which may have attenuated the association between these AD biomarkers. Nevertheless, the intervals between these measures amongst our participants are comparable to those in prior studies that demonstrated significant correlations between CSF tau indices and hippocampal atrophy [30] or regional tau PET tracer uptake [54] in late-onset AD.

Our results showing significant correlations between medial temporal atrophy and CSF tau indices across EOAD subtypes are concordant with the hypothesis that CSF tau levels in EOAD may be predominantly driven by hippocampal and/or medial temporal lobe NFT deposition, as has previously been postulated for late-onset AD [30–32]. However, these findings do not exclude other potential explanations for the diversity of CSF tau levels across EOAD subtypes [24], which include the possibility of greater etiologic heterogeneity in some cohorts [19] and/or different rates of disease progression between EOAD variants. Future studies that directly examine the relationship between CSF tau indices and regional tau PET tracer uptake in EOAD may be needed to confirm our conclusions.

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Disclosure Statement

There are no conflicts of interest or other disclosures to report.

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