Published in final edited form as:
J Alzheimers Dis. 2011 January ; 24(4): 767–774. doi:10.3233/JAD-2011-101995.

Analysis of Postmortem Ventricular Cerebrospinal Fluid from Patients with and without Dementia Indicates Association of Vitamin E with Neuritic Plaques and Specific Measures of Cognitive Performance

Kenneth Hensley[a], **Lisa L. Barnes**[b], **Alexandar Christov**[a], **Christy Tangney**[c], **William G. Honer**[d], **Julie A. Schneider**[e], **David A. Bennett**[f], and **Martha Clare Morris**[g,*]

[a]Department of Pathology and Department of Neuroscience, University of Toledo Medical Center, Toledo, OH, USA

[b]Departments of Neurological Sciences and Behavioral Sciences, and Rush Alzheimer's Disease Center, Rush University Medical Center, Chicago, IL, USA

[c]Department of Clinical Nutrition, Rush University Medical Center, Chicago, IL, USA

[d]Department of Psychiatry, University of British Columbia, Vancouver, BC, Canada

[e]Departments of Pathology and Neurological Sciences, and Rush Alzheimer's Disease Center, Rush University Medical Center, Chicago, IL, USA

[f]Department of Neurological Sciences and Rush Alzheimer's Disease Center, Chicago, IL, USA

[g]Section on Nutrition and Nutritional Epidemiology, Department of Internal Medicine, Rush University Medical Center, Chicago, IL, USA

Abstract

Ventricular cerebrospinal fluid (vCSF) obtained at autopsy from 230 participants in the Religious Orders Study was analyzed for alpha tocopherol (αT, vitamin E) and gamma tocopherol (γT) in relation to brain tissue neuropathological diagnoses (NIA-Reagan criteria); neuritic plaque density and neurofibrillary tangle state (Braak stage); and cognitive function proximate to death. Neither vCSF αT nor γT was related to the pathological diagnosis of Alzheimer's disease, but vCSF αT concentration was inversely related to neuritic plaque density ($\beta = -0.21$, SE = 0.105, $p = 0.04$) in regression models adjusted for age, gender, education, and APOE-4. Ventricular CSF αT concentration was positively associated with perceptual speed ($\beta = 0.27$, SE = 0.116, $p = 0.02$) whereas the γT/αT ratio was negatively associated with episodic memory ($\beta = -0.037$, SE = 0.017, $p = 0.04$). Only vCSF αT, but not γT, was correlated with postmortem interval (PMI). Adjustment for PMI had no effect on significance of associations between αT and perceptual speed or γT/αT and episodic memory, but after this adjustment the αT concentration was no longer significantly associated with neuritic plaques. These data suggest that vCSF αT, but not γT, is weakly associated with less Alzheimer's disease neuropathology, specifically neuritic plaques, and correlates with better performance on tests of perceptual speed.

*Correspondence to: Martha Clare Morris, Martha C, Morris@rush.edu.

Authors' disclosures available online (http://www.j-alz.com/disclosures/view.php?id=736).

Keywords

Alzheimer's disease; cerebrospinal fluid; Religious Orders Study; tocopherol; vitamin E

INTRODUCTION

Tocopherols are plant-derived antioxidants that protect plasma membranes against oxidative damage and may buffer inflammatory reactions by affecting arachidonate metabolism [1]. Although gamma tocopherol (γT) is the major tocopherol form in the U.S. diet [1, 2], tocopherol in tissue is mostly the alpha tocopherol (αT or vitamin E) form because αT is preferentially packaged into low-density lipoproteins (LDL) by a hepatic tocopherol transporter [3]. In recent years some debate has arisen regarding the optimum amount and type of tocopherols that should be consumed to maximize health of the aging cardiovascular and central nervous systems. Prospective epidemiologic studies have found that higher dietary and plasma levels of vitamin E are associated with decreased Alzheimer's disease (AD) risk [4–7]. In a randomized controlled trial by Sano et al., supplemental αT slowed progression of AD as evidenced by quality-of-life assessments and a delayed institutionalization [8]. However, other intervention trials do not show a protective benefit of high dose αT in patients at risk for, or suffering from AD [9, 10]. Some researchers have speculated that negative findings of vitamin E supplementation trials may arise in part from unintended depletion of γT that occurs when high dose αT supplements are taken [1, 11]. Because γT is more potent than αT as an inhibitor of prostaglandin synthesis [12, 13] and also more effectively scavenges reactive nitrogen species (RNS) in some model systems [14], the possible contribution of dietary γT to neurological health should not be discounted.

Several research groups have measured tocopherols in blood of AD patients (e.g., [15, 16]), whereas there are fewer studies that report tocopherol concentrations in cerebrospinal fluid or brain parenchyma. At least one of these studies reported significant diminution of αT in cerebrospinal fluid of AD patients [17]. In another study in which both αT and γT were assayed in human brain parenchyma, γT rather than αT was decreased in affected regions of AD brain relative to brains from neurological disease-free subjects, concomitant with an increase in the nitration product 5-nitro-gamma tocopherol ($5NO_2\gamma T$) [18].

In the present study we examined the association of CSF tocopherols to neuropathology and cognition in subjects from the Religious Orders Study (ROS) [19]. Postmortem-collected ventricular cerebrospinal fluid (vCSF) was analyzed for αT and γT by high performance liquid chromatography with electrochemical array detection (HPLC-ECD). Tocopherol concentrations in vCSF were related to performance in a number of different cognitive domains, and with indices of AD neuropathology, including AD pathologic diagnosis, neuritic plaques and neurofibrillary tangles.

MATERIALS AND METHODS

Subject population and sample collection

Clinical and postmortem data were derived from participants in the ROS, an ongoing longitudinal clinical pathological study of aging and AD in older Catholic nuns, priests, and brothers from religious orders at 40 sites across the U.S. [19, 20]. The study was approved by the Rush Institutional Review Board. All participants were without dementia at baseline, and agreed to annual clinical evaluations and brain donation at the time of death. Since January 1994, 1150 persons have enrolled in ROS: the overall follow-up rate exceeds 95% of survivors. As of August 2010, a total of 523 participants have died and 492 (94%) have

undergone brain autopsy. CSF was available on 268 persons who came to autopsy, 230 of which had complete data on all covariates for analysis.

Clinical evaluation

Each participant had a uniform evaluation that included the procedures recommended by the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) [21] as previously described [19, 20, 22]. Briefly, the evaluation included a medical history, neurological and neuropsychological evaluations, and medication inspection. Follow-up evaluations, identical in all essential details, were performed annually by examiners blinded to previously collected data. Identification of AD and dementia was based on the Joint Working Group of the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association [23] and determined by a board-certified or board eligible neurologist or geriatrician after review of all available data from that year.

Apolipoprotein E genotyping was performed by Agencourt Bioscience Corporation (Beverly, MA) using high throughput sequencing at codon 112 (position 3937) and codon 158 (position 4075) of exon 4 of the *APOE* gene on chromosome 19, as previously described [24]. Direct visual inspection of all prescription and over-the-counter medications was documented at each annual evaluation, and medications were coded using the Medi-Span database system [25].

Cognitive performance testing

A battery of 19 cognitive function tests was used to assess functions commonly affected by aging and AD [26, 27]. We computed a global cognitive measure based on all 19 tests and separate summary measures of five specific cognitive abilities including: episodic memory (7 tests); semantic memory (4 tests); working memory (4 tests); perceptual speed (2 tests); and visuospatial ability (2 tests). The use of composite measures minimizes floor and ceiling effects and other sources of measurement error [27]. Raw scores on each test were converted to *z* scores by using the baseline mean and standard deviation, and the *z* scores were averaged to form the composite measures [26].

Brain collection and histopathology

Brain autopsies were performed at Rush and 11 pre-determined sites across the United States [20]. Postmortem ventricular CSF samples were collected at autopsy, prior to brain removal. Postmortem interval (PMI) was 7.2 ± 7.0 h (median 5.1 h). Briefly, after the calvarium was removed, a needle was inserted into the occipital horn of the lateral ventricle and approximately 20 mL of vCSF was removed, centrifuged, and stored in cryogenic tubes at −80°C. The brain was then removed, weighed, and slabs from one hemisphere frozen. Slabs from the contralateral hemisphere were fixed in 4% paraformaldehyde. Blocks from specific regions were dissected, processed, embedded in paraffin, cut into 6 μm sections, and mounted on glass slides. Bielschowsky silver stain was used to visualize plaques and tangles [20]. Neuritic plaque density was characterized by a semi-quantitative measure including none, mild, moderate or severe plaque density. Neurofibrillary tangle stages ranged from 0 (no pathology) to 6 (most severe) as recommended by Braak staging [28, 29]. The pathological diagnosis of AD followed recommendations by the National Institute on Aging (NIA)-Reagan criteria [30]. For analyses a diagnosis was made of high or intermediate likelihood of AD versus low or no likelihood as previously described [20].

Examination for cerebral infarcts documented gross appearance (acute, subacute, chronic), size, and location of all infarcts visible to the naked eye on fixed slabs [31]. All grossly visualized and suspected macroscopic infarcts were dissected for histological confirmation.

For the current analysis, chronic macroscopic infarcts were defined as present (≥1) or absent [31]. Lewy body pathology was identified in 6 μm sections of cortex (midfrontal, middle temporal, inferior parietal, anterior cingulate, and entorhinal cortices) and substantia nigra using α-synuclein immunochemistry [32] and dichotomized as present (if detected in any region) or absent.

Tocopherol analyses

Tocopherol analyses were conducted similar to previous reports [18]. Amounts of 500 μl of 100% ethanol and 30 μl of 100 μM delta tocopherol (δT) dissolved in methanol (internal control for extraction efficiency) were added to 1 ml vCSF samples, followed by sonication for 20 s. Tocopherols were then extracted with 6 mL per sample HPLC-grade hexane. Hexane fractions were evaporated to dryness under high-purity nitrogen gas and reconstituted in 500 μl of HPLC-grade methanol. Samples were filtered through a 0.2 μm × 13 mm polyvinylidene difluoride (PVDF) syringe filter and analyzed by HPLC-ECD. Chromatography was conducted using a TOSOH Bioscience, LLC (Montgomeryville, PA) ODS-80, reverse-phase C18 column (5 μm particle size, 4.6 × 250 mm). The isocratic mobile phase contained 83% acetonitrile, 12% methanol, 0.2% acetic acid, and 30 mM lithium acetate. Using an ESA Model 582 Solvent Delivery Module, 60 μL of each sample were injected at a flow rate of 2 mL/min from an ESA Model 542 autosampler. The 12 consecutive electrochemical cells, connected to a 12-channel coulometric electrode detector (ESA, Chelmsford, MA) were operated in the oxidizing mode and were assigned the following potentials: 200, 300, 400, 525, 600, 625, 650, 675, 700, 750, 825, and 900 mV. Analyte concentrations were determined using a 5-point external calibration curve. During automated analyses, standards were interspersed regularly among samples. vCSF αT and γT were adjusted for recovery efficiency based on the internal δT spike recovery efficiency prior to statistical analyses.

Data analysis

We first examined simple correlations of the different tocopherol measures (αT, γT) with basic demographics, PMI, pathologic diagnosis, and composite measures of cognition. Next, multiple linear regression models were used to test the extent to which the different tocopherol forms were related to level of global cognitive function assessed proximate to death. To determine whether tocopherols were related to some cognitive abilities but not others, an examination was made of their associations with separate summary measures of five different cognitive abilities. All models were reassessed using γT/αT ratios to account for possible reciprocal relationships of the two forms [1]. All models were adjusted for the potentially confounding effects of age, gender, education, and APOE-4 allele status. Finally, to determine whether tocopherols were associated with measures of pathology in brain, separate logistic regression models were constructed to examine the association of tocopherols with a pathologic diagnosis of AD, macroscopic infarcts, or Lewy body disease. Linear regression models were used to examine the association of vCSF tocopherols with neuritic plaque density and neurofibrillary tangle stage. Because the post-mortem interval may affect measurement of tocopherols in CSF, we repeated each of these models and included a term for PMI. Analyses were carried out in SAS® and models were validated graphically and analytically.

RESULTS

The average age at death was 87.2 years (Table 1). The cohort was 61% female, 98% white, and participants had a mean education level of 18 years. Upon final examination proximate to death, 31.2% of the study population had no cognitive impairment, 20.8% had mild cognitive impairment, 34.9% had probable AD, 10.0% had possible AD, and 3.4% had

dementia due to other conditions. Approximately 60% of the cohort had a pathologic diagnosis of AD. Approximately 22% of the cohort had severe neurofibrillary tangle pathology (Braak stages V–VI, Table 1). Macroscopic infarcts were present in 35.7% of persons and 21% had Lewy bodies.

The mean αT concentration in vCSF was approximately twice that of γT (mean ± SD, 220 ± 630 nM for αT and 110 ± 120 nM for γT, respectively; Table 2). Tocopherol concentrations did not vary significantly by age, gender, or education. There were no significant associations between vCSF αT or γT concentrations, or the γT/αT ratio and a pathologic diagnosis of AD, Lewy bodies or cerebral infarcts in logistic regression models adjusted for age at death, gender, education and APOE-4 (Table 2). Higher vCSF αT was associated with a lower neuritic plaque density (Table 3). Neither vCSF γT nor the γT/αT ratio was significantly associated with plaques or tangles though there was a tendency of the γT/αT measure to be associated with higher AD pathology ($p = 0.06$ and $p = 0.07$, respectively). The metabolite $5NO_2$-γT was not detected in vCSF within the detection limits of the assay (approximately 20 nM).

Ventricular CSF αT and γT concentrations were not significantly related to global cognitive scores, although αT concentrations tended to be higher in persons with higher scores (β = 0.21, SE = 0.122, $p = 0.09$; Table 4) and the γT/αT ratio tended to be lower (β = −0.24, SE = −0.014, $p = 0.09$; Table 4). Analysis of individual cognitive subdomains indicated that vCSF αT was positively and significantly associated with perceptual speed (PS; β = 0.27, SE = 0.12, $p = 0.02$ for αT; Table 4). The only other significant, yet inverse relationship was between vCSF γT/αT and episodic memory (EM; β = −0.037, SE = 0.02, $p = 0.04$; Table 4).

Pearson correlation coefficients were calculated to evaluate the relationships between each tocopherol level and PMI. The results indicated a positive association of αT to PMI ($r = 0.41$, $p < 0.001$), but no association of γT to PMI ($r = 0.11$, $p = 0.11$). Thus, in secondary models, we repeated the regression and logistic models to adjust for the potentially confounding effect of PMI. In these models, the associations of αT and γT with the cognitive function and pathology measures were largely unchanged, except for the association of αT and CERAD, which became slightly weaker in magnitude and was no longer significant (β = −0.19, SE = 0.12, $p = 0.13$ for αT).

DISCUSSION

In this large clinical-pathological study of a community cohort initially free of dementia at enrollment, postmortem vCSF tocopherol concentrations were assessed in relationship both to AD pathology and to neuropsychological performance testing proximate to death. Specifically, higher vCSF αT (vitamin E) was associated with a lower density of neuritic plaques (based on CERAD guidelines), but only in statistical models that excluded PMI effects on measured vCSF αT concentration. Higher vCSF αT was associated with higher performance on tests of perceptual speed regardless of whether PMI corrections were incorporated into the statistical analysis. Ventricular CSF αT was not related to infarcts, Lewy bodies or other cognitive performance measures. Ventricular CSF γT concentration was not associated with any of these neuropathologies, or cognitive performance tests.

Several previous studies have reported associations of plasma or serum tocopherols with AD or dementia risk. For instance, a study of Swedish octogenarians found that high plasma tocopherol levels were associated with lower risk of incident AD [33]. Few studies have examined cerebrospinal fluid for evidence of tocopherol relationships to dementia, though there is ample reason to suspect that this compartment may better index brain tissue status than does circulating blood. Final concentrations of the vCSF tocopherols are a product of

complex equilibria at the blood-brain barrier, and of transport processes from the gut to the periphery. Relatively little information is available regarding CSF tocopherol concentrations, and with the exception of Vatassery's group [34, 35], there are virtually no data for γT in CSF. Thus, analysis of ventricular cerebrospinal fluid tocopherols in relationship to AD fills a significant gap in the field.

The vCSF αT concentrations observed in our study (0.22 ± 0.63 μM) are higher than previously reported; double that reported by Pappert et al. [36] in a small group of Parkinson's disease patients (0.11 ± 0.08 μM), and ten-fold higher than three other studies of AD patients and controls [17, 37, 38]. One possible explanation for the different concentrations amongst studies is the site of CSF acquisition. Our study and that of Pappert et al. analyzed ventricular CSF whereas that analyzed in the other studies was acquired from the lumbar spinal column [17, 37, 38]. Differences in the subject population may also account for differences in observed tocopherol concentrations. For example, in the present report, vCSF was acquired from over 200 adults with and without dementia. Ventricular CSF tocopherol concentrations reported by Pappert and coworkers [36] were from a small number of individuals ($n = 5$), they were not postmortem samples, and they were acquired from subjects with moderate to severe Parkinson's disease with Ommaya shunts. The positive association that we observed between vCSF αT and PMI suggests that the relatively high tocopherol concentrations in our study may be due, at least in part, to postmortem accumulation of tocopherols in the vCSF. Future studies of vCSF analytes should incorporate PMI into statistical analysis of the data.

Our findings that higher concentrations of vCSF αT are associated with better performance in perceptual speed have not been previously reported, although three previous studies [17, 37, 38] found slightly but significantly lower tocopherol concentrations among AD patients as compared to controls. Two of the studies [17, 37] examined the relationship of αT in lumbar CSF to the Mini Mental State examination score, but none was observed.

Another prior study measured γT and αT in AD brain parenchyma [18] and found that γT was significantly depleted in AD brain in a region-specific fashion, concomitant with formation of substantial nitration product, whereas αT was less affected. Limitations in our current knowledge as to how tocopherol concentrations in the brain relate to concentrations in the vCSF make comparisons between this prior study of brain tissue tocopherols and our present findings of vCSF tocopherols difficult.

This report lends support to a large body of animal, laboratory, and epidemiological literature on the preventive roles of tocopherols in dementia. Replication of these novel findings by other clinical-pathologic studies is necessary to confirm the results. Future studies as to how tocopherol levels in the brain relate to CSF and plasma, and to dietary intake, would be required to more fully understand the roles of tocopherols in brain health and in AD etiology.

Acknowledgments

This work was funded in part by the National Institutes of Health (R01 AG31553, R01 AG15819, and P30 AG10161). The authors thank the nuns, priests and brothers from the following groups who participated in the Religious Orders Study: Archdiocesan priests of Chicago IL, Dubuque IA, and Milwaukee WI; Benedictine Monks, Lisle IL, Collegeville MN, and St. Meinrad IN; Benedictine Sisters of Erie, Erie PA; Benedictine Sisters of the Sacred Heart, Lisle IL; Capuchins, Appleton WI; Christian Brothers, Chicago IL and Memphis TN; Diocesan priests of Gary, Gary IN; Dominicans, River Forest IL; Felician Sisters, Chicago IL; Franciscan Handmaids of Mary, New York NY; Franciscans, Chicago IL; Holy Spirit Missionary Sisters, Techny IL; Maryknolls, Los Altos CA and Ossining, NY; Norbertines, DePere WI; Oblate Sisters of Providence, Baltimore MD; Passionists, Chicago IL; Presentation Sisters, B.V.M., Dubuque IA; Servites, Chicago IL; Sinsinawa Dominican Sisters, Chicago IL and Sinsinawa WI; Sisters of Charity, B.V.M., Chicago IL and Dubuque IA; Sisters of the Holy Family, New Orleans

LA; Sisters of the Holy Family of Nazareth, Des Plaines IL; Sisters of Mercy of the Americas, Chicago IL, Aurora IL and Erie PA; Sisters of St. Benedict, St. Cloud and St. Joseph MN; Sisters of St. Casimir, Chicago IL; Sisters of St. Francis of Mary Immaculate, Joliet IL; Sisters of St. Joseph of LaGrange, LaGrange Park IL; Society of Divine Word, Techny IL; Trappists, Gethsemani KY and Peosta IA; Wheaton Franciscan Sisters, Wheaton IL.

The authors thank Traci Colvin, MPH and George Hoganson for Religious Orders Study Coordination; Hong Li, MS for analytic programming; Greg Klein for data management; and the staff and faculty of the Rush Alzheimer's Disease Center.

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Table 1

Characteristics of the Religious Order Study participants from whom ventricular CSF vitamin E determinations were made (N = 230; mean ± SD)

Proportion female (%)	61.3
Proportion black (%)	1.7
Age at death (y)	87.2 ± 6.9
Education (y)	18.1 ± 3.6
Global cognitive score at last visit[1]	−1.11 ± 1.26
Proportion with a pathological diagnosis of AD (%)[2]	60.0
Proportion with Braak stage V–VI (%)	22.0
Proportion with cerebral infarcts (%)[3]	35.7
Proportion with Lewy bodies (%)	21.0
Ventricular CSF alpha tocopherol (μmol/L)	0.22 ± 0.63
Ventricular CSF gamma tocopherol (μmol/L)	0.11 ± 0.12
Ventricular CSF ratio of gamma/alpha tocopherol	1.01 ± 0.90

[1] *Z*-score based on baseline scores of all participants.

[2] NIA-Reagan criteria 1 and 2 (see text).

Table 2

Adjusted odds ratio (95% confidence intervals) for a pathological diagnosis of Alzheimer's disease, Lewy body disease, and the presence of cerebral infarctions by tocopherol concentrations in ventricular cerebrospinal fluid of 230 Religious Order Study participants[1]

Ventricular CSF tocopherol measure	Pathologic diagnosis of AD[2] OR (95% CI)	Lewy body disease OR (95% CI)	Cerebral infarcts OR (95% CI)
αT (μmol/L)	0.69 (0.39, 1.23)	1.09 (0.67, 1.78)	0.90 (0.56, 1.44)
γT (μmol/L)	2.30 (0.12, 4.56)	0.27 (0.006, 2.31)	0.23 (0.008, 6.26)
γT/αT ratio	1.051 (0.95, 1.16)	0.92 (0.81, 1.05)	0.97 (0.089, 1.05)

[1] Logistic regression models included age at death, gender, education (y), and APOE-4 allele (present vs. none).

[2] NIA-Reagan criteria (see text).

Table 3

Adjusted β-coefficients (standard error, *p*-value) of associations between neurofibrillary tangle pathology (Braak stage) or density of neuritic plaques (CERAD quantitative measure), and tocopherol concentrations in ventricular cerebrospinal fluid of 230 Religious Order Study Participants[1,2]

Ventricular CSF tocopherol measure	Neurofibrillary tangle pathology β (SE, *p*-value)	Density of neuritic plaques β (SE, *p*-value)
αT (μmol/L)	−0.17 (0.118, 0.16)	−0.21 (0.105, 0.04)
γT (μmol/L)	0.46 (0.627, 0.46)	−0.29 (0.561, 0.60)
γT/αT	0.026 (0.014, 0.06)	−0.02 (0.012, 0.07)

[1] Linear regression models adjusted for age at death, gender, education (y), and APOE-4 allele (present vs. none).

[2] Braak staging was scored 0 to 6; CERAD was scored from 4 (no neuritic plaques) to 1 (frequent neuritic plaques).

Table 4

Linear regression models for the associations between global cognitive performance and five individual cognitive domains with tocopherol concentrations in ventricular cerebrospinal fluid (CSF) of 230 Religious Order Study participants[1,2]

Ventricular CSF tocopherol measure	Global Cognitive Score (GCS)	Episodic memory	Semantic memory	Working memory	Perceptual organization or visuospatial	Perceptual speed
αT (μmol/L)	0.21 (0.122, 0.09)	0.23 (0.151, 0.14)	0.13 (0.139, 0.36)	0.17 (0.099, 0.09)	0.14 (1.000, 0.15)	0.27 (0.116, 0.02)
γT (μmol/L)	0.24 (0.649, 0.71)	−0.311 (0.802, 0.70)	0.372 (0.735, 0.61)	0.456 (0.527, 0.38)	−0.140 (0.531, 0.79)	0.043 (0.619, 0.94)
γT/αT	−0.024 (0.014, 0.09)	−0.037 (0.017, 0.04)	−0.013 (0.016, 0.43)	−0.015 (0.011, 0.21)	−0.017 (0.012, 0.15)	−0.020 (0.013, 0.15)

[1] Cognitive testing before at the last visit before death; vCSF obtained at the time of death.

[2] Linear regression models reflect the β estimate (SE, *p*-value) after adjusting for age at death, gender, education (y), and presence or absence of an APOE-4 allele.