Can MRI screen for CSF biomarkers in neurodegenerative disease?

Corey T. McMillan, PhD
 Brian Avants, PhD
 David J. Irwin, MD
 Jon B. Toledo, MD
 David A. Wolk, MD
 Viviana M. Van Deerlin,
 MD, PhD
 Leslie M. Shaw, PhD
 John Q. Trojanowski,
 MD, PhD
 Murray Grossman, MD,
 EdD

Correspondence to
 Dr. McMillan:
mcmillan@mail.med.upenn.edu

ABSTRACT

Objective: Alzheimer disease (AD) and frontotemporal lobar degeneration (FTLD) may have overlapping clinical presentations despite distinct underlying neuropathologies, thus making in vivo diagnosis challenging. In this study, we evaluate the utility of MRI as a noninvasive screening procedure for the differential diagnosis of AD and FTLD.

Methods: We recruited 185 patients with a clinically diagnosed neurodegenerative disease consistent with AD or FTLD who had a lumbar puncture and a volumetric MRI. A subset of 32 patients had genetic or autopsy-confirmed AD or FTLD. We used singular value decomposition to decompose MRI volumes and linear regression and cross-validation to predict CSF total tau (tt) and β -amyloid ($A\beta_{1-42}$) ratio (tt/ $A\beta$) in patients with AD and patients with FTLD. We then evaluated accuracy of MRI-based predicted tt/ $A\beta$ using 4 converging sources including neuroanatomic visualization and categorization of a subset of patients with genetic or autopsy-confirmed AD or FTLD.

Results: Regression analyses showed that MRI-predicted tt/ $A\beta$ is highly related to actual CSF tt/ $A\beta$. In each group, both predicted and actual CSF tt/ $A\beta$ have extensively overlapping neuroanatomic correlates: low tt/ $A\beta$ consistent with FTLD is related to ventromedial prefrontal regions while high tt/ $A\beta$ consistent with AD is related to posterior cortical regions. MRI-predicted tt/ $A\beta$ is 75% accurate at identifying underlying diagnosis in patients with known pathology and in clinically diagnosed patients with known CSF tt/ $A\beta$ levels.

Conclusion: MRI may serve as a noninvasive procedure that can screen for AD and FTLD pathology as a surrogate for CSF biomarkers. *Neurology*® 2013;80:132-138

GLOSSARY

A β = β -amyloid; **AD** = Alzheimer disease; **FTLD** = frontotemporal lobar degeneration; **GM** = gray matter; **ROI** = region of interest; **SVD** = singular value decomposition; **tt** = total tau.

There is urgent need to improve in vivo diagnosis of neurodegenerative conditions like Alzheimer disease (AD) and frontotemporal lobar degeneration (FTLD) because of potential treatments targeting the underlying abnormal proteinopathies. Despite distinct biochemical abnormalities, AD and FTLD often share similar clinical features and thus clinical diagnosis alone is unreliable.¹ CSF biomarkers based on a ratio of total tau (tt) and β -amyloid ($A\beta_{1-42}$) (tt/ $A\beta$) provide a highly sensitive and specific in vivo diagnostic tool for discriminating between AD and FTLD.²⁻⁴ In our autopsy series, tt/ $A\beta$ yields 90% sensitivity and 97% specificity.⁴ Despite reasonable diagnostic accuracy, a lumbar puncture is often viewed by patients as invasive. In the setting of a clinical trial where repeated monitoring of endpoints such as CSF biomarkers may be important, an alternative biomarker that provides equivalent diagnostic accuracy, but is more appealing to patients, would be ideal. Volumetric MRI may serve this role since patients with autopsy- or CSF-defined AD and FTLD have relatively distinct neuroanatomic profiles of gray matter (GM) neurodegeneration.⁵⁻⁷

We present a novel screening method for discriminating between AD and FTLD based on MRI-predicted tt/ $A\beta$ CSF values in individuals. This approach yields a single, biologically

Editorial, page 126

Supplemental data at
www.neurology.org

Supplemental Data

From the Department of Neurology (C.T.M., D.J.I., D.A.W., M.G.), Center for Neurodegenerative Disease Research (D.J.I., J.B.T., V.M.V.D., L.M.S., J.Q.T.), Department of Radiology (B.A.), Penn Memory Center (D.A.W.), and Department of Pathology & Laboratory Medicine (V.M. V.D., L.M.S., J.Q.T.), University of Pennsylvania, Philadelphia.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

meaningful value that can screen individuals with a noninvasive MRI and identify borderline cases that would benefit from a more invasive CSF follow-up analysis. Additionally, our approach, in contrast to radioligand PET imaging, is widely available and considerably less expensive. Based on 4 converging analyses, our findings suggest that MRI can yield a noninvasive biomarker screening for neurodegenerative disease.

METHODS Protocol approval, registration, and patient consent. Patients were recruited from University of Pennsylvania Department of Neurology. Written informed consent was obtained using a University of Pennsylvania Institutional Review Board–approved protocol.

Participants. We investigated 185 patients clinically diagnosed with a neurodegenerative disease, who had a CSF profile (see below) consistent with AD ($n = 88$) or non-AD ($n = 97$). Based on their phenotypic characteristics, we inferred that non-AD is consistent with FTLT. All patients were clinically diagnosed by a board-certified neurologist (M.G.), an expert in neurodegenerative diseases, using published criteria.^{8–13} Demographic information is summarized in table 1. Clinical phenotypes included in the cohort are detailed in table e-1 on the *Neurology*[®] Web site at www.neurology.org. All participants had a lumbar puncture and volumetric MRI, acquired on average 4.9 months ($SEM = 1.4$) apart, and 58.9% were acquired the same day. Patients with AD and patients with FTLT only had mild dementia and were matched for disease severity using the Mini-Mental State Examination [$t(177) = 1.81$; $p = 0.07$], age at MRI [$t(183) = 0.22$; $p > 0.1$], and education [$t(183) = 1.05$; $p > 0.1$]. Patients with AD and patients with FTLT were also matched for disease duration ($U = 3756$; $p > 0.1$). Patient groups differed in gender ($\chi^2 = 7.98$; $p = 0.005$), but an analysis of variance comparing linear regression models (see below) that did not include gender and that included gender as a nuisance covariate revealed no significant difference ($F = 2.63$; $p > 0.1$).

Validation cohort. A subset of patients ($n = 32$) additionally had either a pathogenic genetic mutation consistent with AD (*PSEN1*) or FTLT (*GRN*, *C9orf72*) or a detailed neuropathologic

investigation, as described in appendix e-1. This includes 11 with AD and 21 with FTLT.

CSF analysis. CSF analytes of tt and $A\beta_{1-42}$ were obtained using previously reported procedures and evaluated with either a sandwich ELISA (INNOTEST, Innogenetics, Ghent, Belgium)² or a LUMINEX xMAP platform (INNO-BIA AlzBio3, Innogenetics).¹⁴ $tt/A\beta$ values were combined across platforms using an autopsy-validated conversion factor.⁴

Structural MRI methods. A detailed description of MRI methods is provided in appendix e-1, A–G, and figure e-1. Briefly, all participants underwent a high-resolution structural T1-weighted magnetization-prepared rapid gradient echo MRI acquired using a 3.0 T Siemens Trio scanner (appendix e-1A). MRI images were registered into a common stereotactic space and segmented into GM cortical density maps (appendix e-1B). To manage the large number of voxels within each GM volume, we employed a dimensionality reduction technique that identifies spatial patterns that account for the variance within a dataset. Specifically, we used singular value decomposition (SVD) to decompose the images into eigenvectors and eigenvalues that account for the variance in the data (appendix e-1C). SVD is a data-driven region-of-interest (ROI) method that is similar to a traditional principal components statistical approach. This identifies sets of voxels that are correlated with one another, and reduces dimensionality from thousands of voxels to a smaller number of eigenvectors or intercorrelated clusters that capture the variance across a given dataset.

To identify the optimal number of eigenvalues, we first used a k -folds cross-validation procedure that involved randomly dividing the entire cohort of MRI images into 20 folds, each comprised of 9–10 images. Cross-validation was used in an effort to not only identify significant relationships, but to evaluate the predictive role of this algorithm for application in novel datasets. To do this we performed linear regressions using 19 folds for training, tested on the remaining fold, and then repeated this process a total of 20 times until each fold was tested. For each of 20 splits of the data, we used the training set to identify an optimal linear model by iteratively increasing the number of eigenvectors in the model ($tt/A\beta \sim 1 + EIG_1$; $tt/A\beta \sim 1 + EIG_1 + EIG_2 + \dots + EIG_{N-1}$). We selected the model with the lowest mean prediction residual, and found that the first 15 eigenvectors most accurately predicted $tt/A\beta$ (appendix e-1D). We then applied the training model to the test set to identify prediction error on the held out data. We repeated the procedure across each of 20 folds such that $tt/A\beta$ was predicted for each individual patient (appendix e-1E). Finally, since our SVD procedure does not yield neuroanatomic regions, we performed whole-brain voxelwise regressions in SPM8 (<http://www.fil.ion.ucl.ac.uk/spm/>) to relate actual and predicted $tt/A\beta$ values to the anatomic distribution of MRI cortical density (appendix e-1F).

Classification evaluation. To evaluate the classification accuracy of our MRI-based prediction algorithm, we first generated a receiver operating characteristic curve using actual CSF $tt/A\beta$ values to determine sensitivity and specificity in our validation cohort with known AD and FTLT. We selected the cutoff that mutually maximized sensitivity and specificity (appendix e-1G).

RESULTS $tt/A\beta$ prediction results. We computed a linear regression to examine the relationship between MRI-predicted $tt/A\beta$ values on the basis of GM atrophy and actual $tt/A\beta$ values measured in CSF. This was accomplished by entering the 15 optimal eigenvectors identified during cross-validation and feature selection as independent factors and the actual CSF $tt/A\beta$ values as a

Table 1 Mean (SEM) demographic characteristics of CSF-defined Alzheimer disease and frontotemporal lobar degeneration cohort

Demographic/clinical measure	AD ($n = 88$)	FTLT ($n = 97$)
Age, y	62.1 (1.0)	62.4 (0.8)
Education, y	16.3 (1.0)	15.3 (0.3)
M/F	38/50	62/35
MMSE (out of 30) ^a	21.0 (0.8)	22.9 (0.7)
Disease duration, y	3.1 (0.2)	3.9 (0.3)
$tt/A\beta$	0.67 (0.05)	0.13 (0.01)

Abbreviations: $A\beta$ = β -amyloid; AD = Alzheimer disease; FTLT = frontotemporal lobar degeneration; MMSE = Mini-Mental State Examination; tt = total tau.

^aMMSE was only available for 83 patients with AD and 95 patients with FTLT.

dependent variable. This revealed a highly significant fit between MRI-predicted $\text{tt}/\text{A}\beta$ values and actual CSF $\text{tt}/\text{A}\beta$ values ($F_{15,169} = 9.61$; $p < 0.0001$). The mean (SEM) prediction error for this regression was 0.61 (0.04). This suggests that MRI can be used to predict $\text{tt}/\text{A}\beta$ obtained from CSF using a noninvasive procedure.

Neuroanatomic visualization. To illustrate the neuroanatomic regions related to CSF- and MRI-predicted $\text{tt}/\text{A}\beta$ values, we performed 2 voxelwise whole-brain regressions. First, the regression relating CSF $\text{tt}/\text{A}\beta$ to GM revealed that lower actual $\text{tt}/\text{A}\beta$ values, which are associated with FTLN (see below), were related to reduced GM density in ventromedial prefrontal cortex, orbital frontal cortex, insula, thalamus, and anterior temporal cortex (figure 1A, yellow and green). Higher $\text{tt}/\text{A}\beta$ values associated with AD were related to reduced GM density in posterior regions including superior parietal cortex, precuneus, and occipital association cortex (figure 1B, yellow and green).

A regression revealed a very similar distribution of reduced GM density associated with $\text{tt}/\text{A}\beta$ levels

predicted by MRI. Lower predicted $\text{tt}/\text{A}\beta$ values, consistent with FTLN, were related to reduced GM density in frontal regions including ventromedial prefrontal cortex, orbital frontal cortex, insula, caudate, and anterior temporal cortex (figure 1A, blue and green). By comparison, higher predicted $\text{tt}/\text{A}\beta$ values, consistent with AD, were related to reduced density in posterior GM regions, including superior parietal cortex, precuneus, angular gyrus, and occipital cortex (figure 1B, blue and green).

In figure 1, overlapping regions identified in the regression analyses relating both predicted and actual $\text{tt}/\text{A}\beta$ to GM density are illustrated in green. We found considerable overlap between neuroanatomic regions associated with $\text{tt}/\text{A}\beta$. The anatomic peaks of all clusters observed in the neuroanatomic validation analyses are summarized in table 2.

Measured and MRI-predicted CSF $\text{tt}/\text{A}\beta$ classification in patients with known pathology.

To determine how well actual CSF $\text{tt}/\text{A}\beta$ classified individual patients as having AD or FTLN in our genetic and autopsy validation cohort, we computed a receiver operating characteristic curve. Actual CSF $\text{tt}/\text{A}\beta$ values provided a strong classifier of neuropathologic diagnosis (area under the curve = 0.92; $p < 0.001$). Using a cutoff of -1.38 , we obtained 91% sensitivity and 81% specificity for correctly classifying AD, with an overall classification accuracy of 84%. Seventeen of 21 patients were classified as having FTLN, and 10 out of 11 patients were correctly classified as having AD.

Using CSF $\text{tt}/\text{A}\beta$ predicted from MRI and the -1.38 cutoff identified in the actual CSF analysis, we found 75.0% overall classification accuracy. In patients with genetic or autopsy-confirmed FTLN, 17 out of 21 (81%) were accurately predicted as having FTLN using CSF $\text{tt}/\text{A}\beta$ predicted from MRI. The 4 misclassified cases were identified using genetic mutations (2 *C9orf72*; 2 *GRN*) as a proxy for underlying neuropathology and it is possible that these patients have comorbid AD in addition to FTLN.¹ Alternatively, recent neuroimaging evidence suggests that patients with *C9orf72* expansion and *GRN* mutations may have a more posterior distribution of disease,¹⁵ which can partially overlap with the distribution of disease observed in AD and therefore lead to misclassification. For patients with genetic or autopsy-confirmed AD, 7 out of 11 (64%) were accurately classified as having AD using MRI-predicted CSF $\text{tt}/\text{A}\beta$. A χ^2 analysis confirmed significantly accurate classification of AD and FTLN in this validation cohort on the basis of predicted $\text{tt}/\text{A}\beta$ ($\chi^2 = 6.36$; $p < 0.05$). Overall classification accuracy based on MRI-predicted $\text{tt}/\text{A}\beta$ and actual CSF values did not statistically differ ($\chi^2 = 0.36$; $p > 0.1$).

To evaluate whether misclassification was consistent across CSF and MRI modalities, we evaluated the underlying pathology for each misclassified case, and these are

Figure 1 Univariate regression results relating actual $\text{tt}/\text{A}\beta$ and predicted $\text{tt}/\text{A}\beta$ to GM density in MRI

(A) Decreasing $\text{tt}/\text{A}\beta$ is related to decreased density in anterior GM regions consistent with frontotemporal lobar degeneration. (B) Increasing $\text{tt}/\text{A}\beta$ is related to decreased density in posterior GM regions consistent with Alzheimer disease. Green reflects overlap of both actual and predicted $\text{tt}/\text{A}\beta$, yellow reflects only actual $\text{tt}/\text{A}\beta$, blue reflects only predicted $\text{tt}/\text{A}\beta$. Markers are y-axis of coronal slices in Montreal Neurological Institute coordinate space. $\text{A}\beta = \beta$ -amyloid; GM = gray matter; tt = total tau.

Table 2 Neuroanatomic regions with reduced cortical density related to actual tt/A β and predicted tt/A β

Contrast and neuroanatomic region (Brodmann area)	L/R	Peak coordinate			t Score
		x	y	z	
Lower actual tt/A β associated with reduced cortical density					
Subgenual cingulate (25)	L	-13	15	-17	4.38
Ventromedial prefrontal (11)	R	25	33	-19	4.31
Anterior temporal (38)	R	20	13	-42	4.15
Insula (12)	L	-34	23	-3	4.15
Thalamus	R	11	16	-17	4.08
Ventromedial prefrontal (11)	M	3	36	-10	3.99
Nucleus accumbens	L	-27	-1	-25	3.90
Orbital frontal (47)	L	-23	27	-18	3.81
Higher actual tt/A β associated with reduced cortical density					
Occipito-parietal junction (19/7)	L	-37	-69	42	7.78
Precuneus (7)	L	-9	-37	47	6.44
Middle occipital (18)	L	-10	-94	20	6.04
Lower predicted tt/A β associated with reduced cortical density					
Ventromedial prefrontal (11)	R	8	23	-25	6.16
Orbital frontal (47)	L	-23	26	-19	5.36
Subgenual cingulate (25)	M	-4	26	-11	5.25
Anterior temporal (36/28)	L	-22	-3	-33	5.24
Ventromedial prefrontal (11)	R	28	44	-13	5.10
Inferior frontal (44)	R	42	13	9	4.90
Insula (12)	L	-37	22	-3	4.89
Caudate	L	-14	23	2	4.58
Higher predicted tt/A β associated with reduced cortical density					
Middle occipital (19)	L	-31	-72	31	11.81
Angular gyrus (39)	L	-49	-56	16	10.74

Abbreviations: A β = β -amyloid; tt = total tau.

summarized in figure e-2. One case of autopsy-confirmed FTLD had CSF and MRI consistent with AD. Three cases of autopsy-confirmed FTLD had CSF consistent with FTLD but were predicted on the basis of MRI as AD. Four additional cases had autopsy-confirmed AD with CSF consistent with AD, but were classified on the basis of MRI as FTLD.

Measured and MRI-predicted CSF tt/A β classification in clinical patients with CSF. To evaluate the overall accuracy of MRI for screening clinical patients for underlying pathology, we compared the accuracy of predicted tt/A β relative to actual tt/A β for the entire cohort of patients included in our study. A χ^2 analysis confirmed significant screening accuracy ($\chi^2 = 46.65$; $p < 0.001$) and a comparison of the distribution of patients classified as

having AD or FTLD using actual CSF tt/A β does not differ statistically from classification using MRI-predicted tt/A β ($\chi^2 = 0.02$; $p > 0.1$). Of 97 patients with a CSF tt/A β profile consistent with FTLD, 73 also demonstrated a predicted tt/A β consistent with FTLD (75.3% accuracy). Of 88 patients with a CSF tt/A β profile consistent with AD, 66 also achieved a predicted tt/A β consistent with FTLD. Together, we achieved 75.1% overall classification accuracy based on MRI-predicted CSF tt/A β relative to actual tt/A β levels (see figure 2).

Since our cohort was clinically heterogeneous, we evaluated whether MRI classification accuracy differed across clinical phenotypes. A χ^2 analysis confirmed that classification was equally accurate across clinical phenotypes ($\chi^2 = 3.36$; $p > 0.1$) (see table e-1).

DISCUSSION GM density measured noninvasively with MRI can be used to predict tt/A β values that distinguish between AD and FTLD with reasonable accuracy. Specifically, MRI-predicted and actual CSF tt/A β values are highly correlated, predicted tt/A β accurately defines the anatomic distribution of atrophy in AD and FTLD, and predicted tt/A β values are reasonably accurate at classifying individual patients as having AD or FTLD pathology. This study establishes empirical evidence that an MRI-based technique can predict a single, biologically valid level of CSF tt/A β . This may contribute to diagnosis and treatment trials of neurodegenerative conditions by screening for individuals requiring a more invasive diagnostic lumbar puncture. In comparison to nonspecific MRI approaches, this MRI-based technique also potentially minimizes power demands of studies by reducing multifocal regions associated with neurodegenerative disease to a single value and thus provides a candidate marker to monitor in clinical treatment trials.

Structural MRI has been proposed to contribute to clinically relevant studies such as meeting inclusion criteria and ascertaining response during treatment trials.¹⁶ This is valuable in neurodegenerative conditions like AD and FTLD, where clinical criteria are less than optimal markers of disease. In some work, the anatomic distribution of GM atrophy using MRI has been suggested to help identify patients meeting diagnostic criteria for entry into a trial. This is more straightforward in AD, where a single region—the hippocampus—is often the focus of anatomic diagnosis.^{17–19} However, potential difficulties include hippocampal sparing in some clinical variants of AD.²⁰ In FTLD, there may be several different anatomic foci of atrophy,⁵ or lobar atrophy may not be observable.^{21,22} With 75% overall diagnostic accuracy, MRI-based classification using predicted CSF is intended to serve as a screen to identify individuals requiring additional diagnostic studies. This algorithm may reduce the number of more invasive diagnostic procedures such as lumbar punctures.

Figure 2 Scatterplot illustrating actual CSF $\text{tt}/\text{A}\beta$ relative to predicted $\text{tt}/\text{A}\beta$ derived from MRI screening procedure

Dotted lines represent CSF-defined total tau (tt)/ β -amyloid ($\text{A}\beta$) cutoff values identified in receiver operating characteristic curve analysis of autopsy and genetic validation cohort. Blue indicates patients with actual CSF $\text{tt}/\text{A}\beta$ consistent with frontotemporal lobar degeneration (FTLD) and red indicates patients with actual CSF $\text{tt}/\text{A}\beta$ consistent with Alzheimer disease (AD).

Likewise, the advantages of using predicted CSF $\text{tt}/\text{A}\beta$ values derived from individual MRI are immense when considering MRI as an outcome measure in a treatment trial.¹⁶ Nonspecific MRI markers such as analyses of whole brain and ventricular volumes have been proposed to minimize missing longitudinal changes in a heterogeneous group of patients with different anatomic distributions of focal atrophy. This approach is associated with a large cost because of reduced sensitivity and limited power—anatomic ascertainment is nonspecific in order to minimize the error to detect change that can occur in several different brain regions. The SVD-mediated analysis of MRI GM atrophy used in the present study does not depend on a multiplicity of anatomic locations and instead integrates brain-wide atrophic voxels into a single biologically meaningful cluster. Since the outcome measure reflects the actual CSF $\text{tt}/\text{A}\beta$ value in individual subjects with reasonable accuracy, this approach additionally provides an opportunity to measure direct molecular effects of intervention trials designed to target tau or $\text{A}\beta_{1-42}$.²³⁻²⁵

Comparative studies are very important because of the frequent difficulty distinguishing clinically similar phenotypes with distinct underlying histopathologic features. Inappropriate patients may be entered into etiologically specific trials based on sensitive data that identify members of a group relative to healthy controls, but

these data are not specific. Beyond the obvious biological problems, there are increased power demands associated with diagnostic inaccuracy. Previous automated MRI-based classification studies for discriminating between AD and FTLD have yielded relatively high accuracy, but these studies were restricted to clinically diagnosed patients, and patient groups were not defined on the basis of CSF or autopsy studies,^{26,27} and thus it is difficult to infer true accuracy. One additional comparative MRI classification study has been conducted to discriminate between neuropathology-confirmed AD and FTLD, and this yielded high sensitivity (94.7%) and specificity (83.3%) for diagnosis.²⁸ However, the report was restricted to smaller cohorts with many different scanners and relied on a highly complex support vector machine approach. A major advantage of the SVD approach is that the only parameter is the amount of variance that should be retained for the model (the number of eigenvectors), and this single parameter may easily be set by cross-validation. Our approach provides information on individual patients as well.

To implement this screening procedure for individual patients, the current eigenvalues and corresponding regression weights would require application to each individual's MRI volume. Since optimal eigenvalues were defined using 20-fold cross-validation, they should be reproducible in an independent cohort. More recent SVD methods may facilitate extending this procedure to individuals by implementing a "sparseness" parameter that constrains eigenvalues to clusters of voxels that exceed an a priori extent threshold and thus can support a more traditional ROI-based approach.²⁹ This is consistent with research suggesting that "signature regions" are useful for evaluating neurodegenerative disease.³⁰

In the current study, we used whole-brain voxelwise regression analyses to visualize GM regions associated with increased or decreased $\text{tt}/\text{A}\beta$ ratios. Few previous studies have evaluated the direct relationship between CSF biomarkers and MRI.^{3,31-33} In one study, a relationship was observed between $\text{A}\beta_{1-42}$ and whole brain volume in healthy adults, and between tt and whole brain volume in patients with AD.³¹ However, these relationships involved only nonspecific global brain volume. In a study of a clinically defined cohort of patients with frontotemporal dementia, reduced tt levels correlated with insula, anterior cingulate, ventromedial and orbital frontal, and superior temporal cortical density.³ In the present study, we observed that higher predicted $\text{tt}/\text{A}\beta$ values are related to reduced GM density in posterior cortical regions, consistent with imaging studies of AD; lower predicted $\text{tt}/\text{A}\beta$ values were related to reduced GM density in anterior cortical regions, consistent with imaging studies of FTLD.⁵⁻⁷ We restricted our analysis to the ratio of $\text{tt}/\text{A}\beta$ since this combination of analytes is most sensitive and specific for the diagnosis of FTLD and AD.^{2,3,34} Future studies independently evaluating

the relationship between other CSF biomarkers and MRI may help elucidate the complex relationship between CSF analytes and cortical atrophy.

One caveat to consider in using MRI as a CSF screening procedure is related to the trajectory of disease. While we demonstrate that the distribution of GM atrophy in AD and FTLN is highly related to a distinct range of CSF $\tau/A\beta$ values, these biological changes may occur at different stages in the disease course.³⁵ Empirical data regarding longitudinal changes in CSF analyte values is scant, and results have been controversial.^{36,37} In this context, one reason for the paucity of longitudinal CSF studies is patients' perception of invasiveness and their unwillingness to undergo multiple lumbar punctures. The lack of longitudinal CSF studies highlights the importance of establishing an alternative, less invasive screening procedure such as MRI.

Our results suggest that MRI provides a reasonably accurate screening tool discriminating between AD and FTLN. MRI-based screening yields an acceptable anatomic distribution of disease and predicted CSF values that are similar to actual CSF values from a procedure that is perceived as less invasive and more easily repeated. Since this method yields a single biological value, it is possible to use MRI to screen patients for inclusion in clinical trials in a cost-effective manner and to provide a biologically plausible outcome measure that optimizes power in drug treatment trials.

AUTHOR CONTRIBUTIONS

Corey T. McMillan and Brian Avants drafted/revised manuscript for content, contributed to study concept/design, performed analysis/interpretation of the data, and performed statistical analysis. David Irwin, Jon Toledo, David Wolk, and Viviana Van Deerlin contributed to analysis/interpretation of the data and acquisition of the data. Leslie Shaw, John Trojanowski, and Murray Grossman drafted/revised manuscript for content, contributed to study concept/design, performed analysis/interpretation of the data, obtained funding, and provided supervision.

STUDY FUNDING

Supported by the Wyncote Foundation and the NIH (HD060406 to C.T.M., NS44266 to M.G., AG17586 to M.G., J.Q.T., and V.V., AG15116 to M.G., AG32953 to M.G. and J.Q.T., NS53488 to M.G., J.Q.T., and V.V., and AG10124 to J.Q.T. and V.V.). D.J.I. is supported by the NIH T32-AG000255. J.B.T. was supported by a grant of the Alfonso Martín Escudero Foundation.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

Received May 17, 2012. Accepted in final form August 14, 2012.

REFERENCES

- Toledo JB, Brettschneider J, Grossman M, et al. CSF biomarkers cutoffs: the importance of coincident neuropathological diseases. *Acta Neuropathol* 2012;124:23–35.
- Bian H, van Swieten JC, Leight S, et al. CSF biomarkers in frontotemporal lobar degeneration with known pathology. *Neurology* 2008;70:1827–1835.

- Grossman M, Farmer J, Leight S, et al. Cerebrospinal fluid profile in frontotemporal dementia and Alzheimer's disease. *Ann Neurol* 2005;57:721–729.
- Irwin DJ, McMillan CT, Toledo JB, et al. Comparison of cerebrospinal fluid levels of tau and $A\beta_{1-42}$ in Alzheimer's disease and frontotemporal degeneration using two analytical platforms. *Arch Neurol* 2012;69:1018–1025.
- Avants BB, Cook PA, Ungar L, Gee JC, Grossman M. Dementia induces correlated reductions in white matter integrity and cortical thickness: a multivariate neuroimaging study with sparse canonical correlation analysis. *NeuroImage* 2010;50:1004–1016.
- Rabinovici GD, Seeley WW, Kim EJ, et al. Distinct MRI atrophy patterns in autopsy-proven Alzheimer's disease and frontotemporal lobar degeneration. *Am J Alzheimers Dis Other Dement* 2007;22:474–488.
- Whitwell JL, Josephs KA, Murray ME, et al. MRI correlates of neurofibrillary tangle pathology at autopsy: a voxel-based morphometry study. *Neurology* 2008;71:743–749.
- Gorno-Tempini ML, Hillis AE, Weintraub S, et al. Classification of primary progressive aphasia and its variants. *Neurology* 2011;76:1006–1014.
- Rascovsky K, Hodges JR, Knopman D, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain* 2011;134:2456–2477.
- Murray R, Neumann M, Forman MS, et al. Cognitive and motor assessment in autopsy-proven corticobasal degeneration. *Neurology* 2007;68:1274–1283.
- Golbe LI, Ohman-Strickland PA. A clinical rating scale for progressive supranuclear palsy. *Brain* 2007;130:1552–1565.
- Strong MJ, Grace GM, Freedman M, et al. Consensus criteria for the diagnosis of frontotemporal cognitive and behavioural syndromes in amyotrophic lateral sclerosis. *Amyotroph Lateral Scler* 2009;10:131–146.
- McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging–Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011;7:263–269.
- Shaw LM, Vanderstichele H, Knapik-Czajka M, et al. Cerebrospinal fluid biomarker signature in Alzheimer's Disease Neuroimaging Initiative subjects. *Ann Neurol* 2009;65:403–413.
- Whitwell JL, Weigand SD, Boeve BF, et al. Neuroimaging signatures of frontotemporal dementia genetics: C9ORF72, tau, progranulin and sporadics. *Brain* 2012;135:794–806.
- Knopman DS, Jack CR, Kramer JH, et al. Brain and ventricular volumetric changes in frontotemporal lobar degeneration over 1 year. *Neurology* 2009;72:1843–1849.
- Costafreda SG, Dinov ID, Tu Z, et al. Automated hippocampal shape analysis predicts the onset of dementia in mild cognitive impairment. *NeuroImage* 2011;56:212–219.
- Gerardin E, Chételat G, Chupin M, et al. Multidimensional classification of hippocampal shape features discriminates Alzheimer's disease and mild cognitive impairment from normal aging. *NeuroImage* 2009;47:1476–1486.
- Morra JH, Tu Z, Apostolova LG, et al. Automated 3D mapping of hippocampal atrophy and its clinical correlates in 400 subjects with Alzheimer's disease, mild cognitive impairment, and elderly controls. *Hum Brain Mapp* 2009;30:2766–2788.
- Murray ME, Graff-Radford NR, Ross OA, Petersen RC, Duara R, Dickson DW. Neuropathologically defined subtypes of Alzheimer's disease with distinct clinical characteristics: a retrospective study. *Lancet Neurol* 2011;10:785–796.

21. Josephs KA, Whitwell JL, Jack CR, Parisi JE, Dickson DW. Frontotemporal lobar degeneration without lobar atrophy. *Arch Neurol* 2006;63:1632–1638.
22. Koedam ELGE, Van der Flier WM, Barkhof F, Koene T, Scheltens P, Pijnenburg YAL. Clinical characteristics of patients with frontotemporal dementia with and without lobar atrophy on MRI. *Alzheimer Dis Assoc Disord* 2010;24:242–247.
23. Lee VM-Y, Brunden KR, Hutton M, Trojanowski JQ. Developing therapeutic approaches to tau, selected kinases, and related neuronal protein targets. *Cold Spring Harb Perspect Med* 2011;1:a006437.
24. Brunden KR, Ballatore C, Crowe A, Smith AB, Lee VM-Y, Trojanowski JQ. Tau-directed drug discovery for Alzheimer's disease and related tauopathies: a focus on tau assembly inhibitors. *Exp Neurol* 2010;223:304–310.
25. Herrmann N, Chau SA, Kircanski I, Lanctôt KL. Current and emerging drug treatment options for Alzheimer's disease: a systematic review. *Drugs* 2011;71:2031–2065.
26. Good CD, Scallan RI, Fox NC, et al. Automatic differentiation of anatomical patterns in the human brain: validation with studies of degenerative dementias. *NeuroImage* 2002;17:29–46.
27. Zhang Y, Schuff N, Ching C, et al. Joint assessment of structural, perfusion, and diffusion MRI in Alzheimer's disease and frontotemporal dementia. *Int J Alzheimers Dis* 2011;2011:546871.
28. Klöppel S, Stonnington CM, Chu C, et al. Automatic classification of MR scans in Alzheimer's disease. *Brain* 2008;131:681–689.
29. Avants B, Dhillon P, Kandel BM, et al. Eigenanatomy improves detection power for longitudinal cortical change. Presented at the 15th International Conference on Medical Image Computing and Computer Assisted Intervention; October 4, 2012; Nice, France.
30. Dickerson BC, Wolk DA, on behalf of the Alzheimer's Disease Neuroimaging Initiative. MRI cortical thickness biomarker predicts AD-like CSF and cognitive decline in normal adults. *Neurology* 2012;78:84–90.
31. Fagan AM, Head D, Shah AR, et al. Decreased cerebrospinal fluid Abeta(42) correlates with brain atrophy in cognitively normal elderly. *Ann Neurol* 2009;65:176–183.
32. Apostolova LG, Hwang KS, Andrawis JP, et al. 3D PiB and CSF biomarker associations with hippocampal atrophy in ADNI subjects. *Neurobiol Aging* 2010;31:1284–1303.
33. Walhovd KB, Fjell AM, Brewer J, et al. Combining MR imaging, positron-emission tomography, and CSF biomarkers in the diagnosis and prognosis of Alzheimer disease. *AJNR Am J Neuroradiol* 2010;31:347–354.
34. Irwin DJ, McMillan CT, Toledo JB, et al. Comparison of cerebrospinal fluid levels of tau and Aβ 1-42 in Alzheimer disease and frontotemporal degeneration using 2 analytical platforms. *Arch Neurol* 2012;69:1018–1025.
35. Jack CR, Knopman DS, Jagust WJ, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurol* 2010;9:119–128.
36. Wahlund L-O, Blennow K. Cerebrospinal fluid biomarkers for disease stage and intensity in cognitively impaired patients. *Neurosci Lett* 2003;339:99–102.
37. Mattsson N, Portelius E, Rolstad S, et al. Longitudinal cerebrospinal fluid biomarkers over four years in mild cognitive impairment. *J Alzheimers Dis* 2012;30:767–778.

New FREE NeuroSAE[®]: Annual Meeting Edition Now Available—AAN Member Exclusive!

Need to earn CME credits? Planning to attend the 2013 AAN Annual Meeting in San Diego and overwhelmed by choices? Take the new NeuroSAE[®]: Annual Meeting Edition, the AAN's latest self-assessment examination, for your chance to earn 10 self-assessment CME credits towards your ABPN-mandated maintenance of certification requirements while receiving personalized recommendations on the best courses of study from which to build your ideal Annual Meeting learning plan.

FREE to AAN members only, the new online NeuroSAE: Annual Meeting Edition is easy and convenient to use:

1. Take the convenient online pre-test by March 15, 2013
2. Build your CME learning plan based on your pre-test score report, peer comparison, and recommendations for further courses of study at the 2013 Annual Meeting
3. Register for the Annual Meeting, or adjust your Annual Meeting course schedule as needed
4. After attending the 2013 Annual Meeting, complete the convenient online post-test exam by June 25, 2013, to gauge your improvement
5. Earn a score of 70% or higher and receive 10 **FREE** self-assessment CME credits

Learn more at www.aan.com/view/NeuroSAEAM