Brain Imaging and Blood Biomarker Abnormalities in Children With Autosomal Dominant Alzheimer Disease: A Cross-Sectional Study

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**IMPORTANCE** Brain imaging and fluid biomarkers are characterized in children at risk for autosomal dominant Alzheimer disease (ADAD).

**OBJECTIVE** To characterize and compare structural magnetic resonance imaging (MRI), resting-state and task-dependent functional MRI, and plasma amyloid-β (Aβ) measurements in presenilin 1 (PSEN1) E280A mutation–carrying and noncarrying children with ADAD.

**DESIGN, SETTING, AND PARTICIPANTS** Cross-sectional measures of structural and functional MRI and plasma Aβ assays were assessed in 18 PSEN1 E280A carriers and 19 noncarriers aged 9 to 17 years from a Colombian kindred with ADAD. Recruitment and data collection for this study were conducted at the University of Antioquia and the Hospital Pablo Tobon Uribe in Medellin, Colombia, between August 2011 and June 2012.

**MAIN OUTCOMES AND MEASURES** All participants had blood sampling, structural MRI, and functional MRI during associative memory encoding and resting-state and cognitive assessments. Outcome measures included plasma Aβ1-42 concentrations and Aβ1-42:Aβ1-40 ratios, memory encoding-dependent activation changes, resting-state connectivity, and regional gray matter volumes. Structural and functional MRI data were compared using automated brain mapping algorithms and search regions related to AD.

**RESULTS** Similar to findings in adult mutation carriers, in the later preclinical and clinical stages of ADAD, mutation-carrying children were distinguished from control individuals by significantly higher plasma Aβ1-42 levels (mean [SD]; carriers, 18.8 [5.1] pg/mL and noncarriers, 13.1 [3.2] pg/mL; P < .001) and Aβ1-42:Aβ1-40 ratios (mean [SD]; carriers, 0.32 [0.06] and noncarriers, 0.21 [0.03]; P < .001), as well as less memory encoding task–related deactivation in parietal regions (eg, mean [SD] parameter estimates for the right precuneus were −0.590 [0.50] for noncarriers and −0.087 [0.38] for carriers; P < .005 uncorrected). Unlike carriers in the later stages, mutation-carrying children demonstrated increased functional connectivity of the posterior cingulate cortex with medial temporal lobe regions (mean [SD] parameter estimates were 0.038 [0.07] for noncarriers and 0.190 [0.057] for carriers), as well as greater gray matter volumes in temporal regions (eg, left parahippocampus; P < .049, corrected for multiple comparisons).

**CONCLUSIONS AND RELEVANCE** Children at genetic risk for ADAD have functional and structural brain changes and abnormal levels of plasma Aβ1-42. The extent to which the underlying brain changes are either neurodegenerative or developmental remains to be determined. This study provides additional information about the earliest known biomarker changes associated with ADAD.

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Autosomal Dominant Alzheimer Disease in Children

Original Investigation Research

Methods

Study Design and Participants

Between August 2011 and June 2012, cross-sectional structural MRI, resting-state and task-dependent functional MRI, and plasma Aβ measurements were assessed in children and adolescents with and without the PSEN1 E280A mutation from the world’s largest known ADAD kindred. Thirty-seven volunteers were recruited from the Colombian Alzheimer Prevention Initiative registry, which currently includes more than 3900 living members of the PSEN1 E280A kindred. The mutation carriers and noncarriers who were 9 to 17 years of age, had no history of learning or intellectual disabilities, and descended from a common ancestor were invited to participate in the study. Nineteen participants were PSEN1 mutation E280A carriers (mean [SD] age, 13.7 [2.6] years) and 18 were PSEN1 mutation noncarriers from the same kindred, who were matched to the carriers by age, sex, and education and who served as control individuals (mean [SD] age, 13.6 [2.6] years). Potential participants were screened in advance for the presence of neurological and psychiatric disorders, drug use, and MRI scanner compatibility. Imaging with positron emission tomography and lumbar punctures were not performed because of the participants’ young age.

Clinical history and neurological examination were performed by a neurologist or a physician trained in assessment of neurodegenerative disorders. Cognitive testing was conducted by neuropsychologists and psychologists trained in neuropsychology. Clinical data were recorded on the Systematized Information System for the Neuroscience Group of Antioquia. All participants’ parents provided written informed consent. The ethics committee of the University of Antioquia (Colombia) approved this study.

Procedures

All participants had clinical and neuropsychological evaluations, family history, neurological examination, PSEN1 and apolipoprotein E (APOE) genotyping, functional MRI during resting-state and face-name associative encoding task, and structural MRI assessment.

Clinical and neuropsychological assessments were undertaken at the University of Antioquia, Medellin, Colombia. Testing was done using a Spanish version of the Wechsler Intelligence for Children Scale, 3rd edition.

Plasma samples were also taken at the University of Antioquia. Venipunctures for blood collection were performed in the morning after an overnight fast. Plasma samples were processed, stored in polypropylene tubes, frozen at −80°C, and shipped on dry ice to Washington University (St Louis, Missouri) for biomarker analysis. Plasma Aβ40 and Aβ42 concentrations were quantified by INNO-BIA Plasma Aβ Forms Multiplex Assay (Innogenetics) by the Knight Alzheimer Disease Research Center Biomarker Core at Washington University. For genetic analyses, genomic DNA was extracted from blood by standard protocols, and PSEN1 E280A and APOE characterization was done as previously described.

In the present study, to characterize some of the earliest brain changes in preclinical ADAD, we sought to extend our findings of elevated plasma Aβ and structural and functional MRI abnormalities to children with the PSEN1 E280A mutation.
Every participant had structural and functional MRI done at the Hospital Pablo Tobon Uribe, Medellín, Colombia. Functional and structural MRI pulse sequences were acquired on a 1.5-T Siemens Avanto scanner. Functional MRI data were acquired using a T2*-weighted gradient echoplanar blood oxygen level–dependent pulse sequence (repetition time, 2 seconds; echo time, 40 milliseconds; flip angle, 90°; field of view, 200 × 200) during a face-name associative memory encoding task involving 3 conditions: novel face-name pairs, a control task involving repeated face-name pairs, and visual fixation, as previously described. Following the scanning session, recognition memory was assessed in response to previously viewed and new pairs using a discrimination index (percentage of hits–percentage of false alarms) and the median reaction time to correctly recognized pairs. Functional MRI (fMRI) data were also acquired during resting state (1 run of 8 minutes with eyes open). Structural data were acquired using two 3-dimensional T1-weighted MRI images (T1 free-flow electrophoresis; repetition time, 2530 milliseconds, echo time, 3.39 milliseconds; flip angle, 7°; field of view, 256 × 256; 1.0 × 1.0 × 1.0 mm; 176 slices).

Plasma samples were analyzed independently from the analysis of brain images. Researchers were blinded to the genetic status of the participants during data collection and all data analyses and preprocessing prior to the statistical analysis.

Statistical Analysis

Both task-related activation and resting-state fMRI data were preprocessed with SPM8 software (Wellcome Department of Cognitive Neurology, London, England). Each run was slice-time corrected, realigned to the first volume within a run using INRIAlign toolbox to correct for variance due to susceptibility-by-movement interactions, spatially normalized into standard Montreal Neurological Institute space, and spatially smoothed using a 6-mm full-width at half maximum gaussian filter.

For resting-state functional connectivity analysis of the default-mode network (DMN), we used seed regions taken from a prior report and included seed regions in the (1) right lateral temporal cortex, (2) left lateral temporal cortex, (3) medial prefrontal cortex, (4) posterior cingulate cortex, (5) left inferior parietal lobule, and (6) right inferior parietal lobule. Connectivity measurements were made by computing the pairwise correlations between these seeds and then compared between mutation carrier and noncarrier groups. To further explore whole-brain changes in DMN-associated functional connectivity with respect to genetic status, we computed whole-brain seed maps using the posterior cingulate cortex seed for each individual.

For the analysis of task-dependent changes in regional fMRI measurements (ie, regional changes in brain activity during a face-name memory encoding paradigm), a block design was used, such that each epoch of trials is modeled using a boxcar function convolved with a hemodynamic response function. Individual participant contrasts generated from the first-level models were then carried forward to group-level analyses. The main contrast of interest was novel face-name pairs vs repeated face-name pairs.

We used SPM8 with voxel-based morphometry, the DARTEL protocol, Jacobian modulation, and an 8-mm full-width at half maximum gaussian filter to generate segmented gray matter maps for all participants in the Montreal Neurological Institute brain atlas coordinate space and compare regional gray matter volumes in PSEN1 carriers and noncarriers.

Results

Table 1 shows the demographic characteristics, clinical ratings, and Wechsler Intelligence for Children Scale, 3rd edition test scores for participants. PSEN1 mutation carriers and noncarriers.
noncarriers did not differ significantly in their age, sex, education, neuropsychological performance, or proportion of APOE ε4 carriers. Figure 1 shows plasma measurements from mutation carriers and noncarriers. As predicted, mutation carriers had significantly higher plasma Aβ1-42 levels (mean [SD], 18.8 [5.1] pg/mL) than noncarriers (mean [SD], 13.1 [3.2] pg/mL) (P < .001), as well as significantly higher plasma Aβ1-42:Aβ1-40 ratios (mean [SD]: carriers, 0.32 [0.06] and noncarriers, 0.21 [0.03]; P < .001). The groups did not differ significantly in their plasma Aβ1-40 levels (P = .31).

Table 2. Location and Magnitude of the Most Significant Functional and Structural Brain Measures in PSEN1 E280A Mutation Carriers Compared With Noncarriers

<table>
<thead>
<tr>
<th>Brain Region</th>
<th>Hemisphere</th>
<th>Atlas Coordinates, mm*</th>
<th>P Valueb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Locations with less deactivation during associative memory encoding</td>
<td></td>
<td>x          y          z</td>
<td></td>
</tr>
<tr>
<td>Precuneus</td>
<td>Right</td>
<td>6          −49        71</td>
<td>3.6e-05</td>
</tr>
<tr>
<td>Precuneus</td>
<td>Right</td>
<td>3          −73        50</td>
<td>6.9e-04</td>
</tr>
<tr>
<td>Superior parietal</td>
<td>Left</td>
<td>−21        −79        50</td>
<td>5.7e-05</td>
</tr>
<tr>
<td>Superior parietal</td>
<td>Left</td>
<td>−9         −79        50</td>
<td>1.3e-03</td>
</tr>
<tr>
<td>Cuneus</td>
<td>Left</td>
<td>−12        −82        29</td>
<td>1.0e-05</td>
</tr>
<tr>
<td>Cuneus</td>
<td>Right</td>
<td>12         −76        41</td>
<td>1.6e-04</td>
</tr>
<tr>
<td>Cuneus</td>
<td>Right</td>
<td>18         −82        44</td>
<td>4.0e-04</td>
</tr>
<tr>
<td>Locations with greater gray matter volume</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Precuneus</td>
<td>Left</td>
<td>−4         −51        62</td>
<td>1.4e-04</td>
</tr>
<tr>
<td>Posterior cingulate</td>
<td>Right</td>
<td>2          −42        13</td>
<td>8.5e-05</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>Left</td>
<td>−32        −27        −5</td>
<td>5.5e-04</td>
</tr>
<tr>
<td>Parahippocampal*</td>
<td>Left</td>
<td>−22        3          −27</td>
<td>1.1e-03</td>
</tr>
<tr>
<td>Temporal pole*</td>
<td>Right</td>
<td>40         11         −21</td>
<td>5.1e-05</td>
</tr>
</tbody>
</table>

Abbreviation: PSEN1, presenilin 1.

* Atlas coordinates were obtained from Talairach and Tournoux. X is the distance to the right (+) or left (−) of the midline, y is the distance anterior (+) or posterior (−) to the anterior commissure, and z is the distance superior (+) or inferior (−) to a horizontal plane through the anterior and posterior commissures.

b Listed locations correspond to the magnitude of the t score for that given location: P < .005, uncorrected for multiple comparisons.

c Remained significant after correcting for multiple comparisons in the postulated search regions (parahippocampal, 0.049; temporal pole, 0.014).

Figure 1 shows plasma measurements from mutation carriers and noncarriers. As predicted, mutation carriers had significantly higher plasma Aβ1-42 levels (mean [SD], 18.8 [5.1] pg/mL) than noncarriers (mean [SD], 13.1 [3.2] pg/mL) (P < .001), as well as significantly higher plasma Aβ1-42:Aβ1-40 ratios (mean [SD]: carriers, 0.32 [0.06] and noncarriers, 0.21 [0.03]; P < .001). The groups did not differ significantly in their plasma Aβ1-40 levels (P = .31).

Figure 1. Plasma Amyloid-β Concentrations in Presenilin 1 (PSEN1) E280A Mutation Carriers and Noncarriers

Figure 2. Functional Connectivity in PSEN1 E280A Mutation Carriers and Noncarriers

As expected, highly significant resting-state functional connectivity was observed within the DMN in both the mutation carriers and noncarriers. There were no differences between groups in functional connectivity in the whole network metric (6 predefined nodes). However, PSEN1 mutation carriers showed paradoxically greater functional connectivity be-
between the posterior cingulate cortex and bilateral MTL regions \((P = .005\), uncorrected, \(P\) value was not significant after correcting for multiple regional comparisons\) \(\text{Figure 2C}\). The mean (SD) parameter estimates were 0.038 (0.070) for noncarriers and 0.190 (0.057) for carriers \(\text{Figure 2D}\). Mutation carriers did not show reduced functional connectivity when compared with noncarriers, as previously reportedin the later preclinical and clinical stages of AD.21-23

Table 2 and \textbf{Figure 3} show significant differences between mutation carriers and noncarriers in MRI measurements of regional gray matter volume. Mutation carriers had paradoxically greater gray matter volumes in the hippocampus, parahippocampus, and parietal and temporal lobe regions \((P = .005\), uncorrected for multiple regional comparisons\). Greater volumes in the parahippocampal gyrus and temporal pole remained significant after correcting for multiple comparisons in the postulated search regions \((P = .049\) and \(P = .01\), respectively\). \textit{PSEN1} mutation carriers did not show any reductions in brain regions when compared with noncarriers, as previously reported in the later preclinical and clinical stages of AD.

\textbf{Discussion}

This study describes some of the earliest brain changes associated with the predisposition to ADAD. As observed in the later preclinical and clinical stages of ADAD and in our previous study of young adults from the same kindred, 9- to 17-year-old \textit{PSEN1} E280A mutation carriers were distinguished from noncarriers by plasma biomarker evidence of A\(\beta\)1-42 overproduction and by reduced posterior parietal deactivation during a memory encoding task. In contrast to findings in the later preclinical and clinical stages of AD, the carriers were also distinguished from noncarriers by greater brain volumes and resting-state functional connectivity in some of the brain regions that are preferentially affected by AD.

As we previously reported in young adult \textit{PSEN1} E280A mutation carriers, 9- to 17-year-old mutation carriers were distinguished from noncarriers by significantly higher plasma A\(\beta\)1-42 levels and A\(\beta\)1-42:A\(\beta\)1-40 ratios and by less fMRI deactivation of posterior parietal regions during a memory encoding task. Findings were noted at a younger age than the ear-
liest evidence of fibrillar Aβ deposition (i.e., florbetapir standard uptake value ratio increases beginning at the mean age of 28 years and CSF Aβ1-42 declines beginning at the mean age of 24 years) in this kindred.1,24 With regard to brain changes, our results should be interpreted with caution given that not all of the tests survived correction for multiple comparisons. Notwithstanding this limitation, less fMRI deactivation of parietal regions, seen in the absence of MTL alterations, support the hypothesis that functional abnormalities in key regions of the DMN (e.g., parietal regions) may precede MTL changes in early disease.

Findings of greater gray matter volume in temporal and parietal regions are partly consistent with abnormalities that have been reported in APOE4 infant carriers. APOE4 infant carriers showed thicker cortex in frontal regions2 and greater gray matter volumes in posterior parietal, frontal, and occipital cortices.25 These common findings between PSEN1 and APOE4 carriers are consistent with the notion of a common mechanism. Unlike the infant studies, we did not find any significant reductions in brain volume in regions preferentially affected by AD, although we cannot exclude the possibility that the negative finding is attributable to limited statistical power in our smaller sample. Our findings are also partly consistent with an independent study done with older PSEN1 mutation carriers.26 They studied 11 52- to 55-year-old carriers and reported that they had greater cortical thickness in the caudate, precuneus, and parietotemporal regions when compared with noncarriers. The pathological mechanisms underlying these morphometric differences within AD-related regions remain to be defined. However, our data and those of others suggest that presenilin 1 function is altered in mutation carriers at a very early age, resulting in gray matter developmental changes. Presenilin 1 function is known to be essential for both neural and vascular development in animal models.27–29

Additional studies are needed to clarify the role of PSEN1 in neuronal and synaptic development and whether and how it may be related to differential pruning, compensation, or other developmental changes. Whether these neurodevelopmental processes may be relevant for the progressive pathological changes that begin to occur in young adult mutation carriers with AD and whether these processes are affected by any of the other genetic risk factors for AD (e.g., APOE) remain to be established.

The strengths of the present study were the use of brain imaging and blood biomarkers in members from a large homogeneous ADAD kindred, with a single-gene mutation, characterized ages at the onset of MCI (mean [SD], 44 [5] years) and dementia (mean [SD], 49 [5] years) and characterized associations between brain imaging and CSF biomarker measurements in adulthood.1,4,20,24 Studies of PSEN1 mutation carriers allow us to examine cognitively normal individuals who will go on to develop AD in the future with virtual certainty. Our findings add to the growing evidence that suggests brain MRIs, in combination with molecular markers, have the po...
tential to identify presymptomatic changes in individuals at a higher risk for developing sporadic AD.

Studies have not yet resolved whether there are changes in cognitive functioning associated with genetic risk for AD. In our study, we only used a measure of intellectual functioning and did not find differences between mutation-carrying children and age-matched control individuals. Our findings underscore the need for larger cross-sectional and longitudinal studies to characterize and compare performance across cognitive domains, with a special focus on learning skills and executive functioning.

This study also had several limitations including relatively small sample sizes, reduced statistical power for imaging findings, and uncertainty in the extent to which our findings may be generalizable to other AD-causing mutations as well as LOAD. While the present results are based on a relatively small sample size compared with studies of MCI or sporadic AD, the present sample represents one of the largest of its kind. While our findings are limited to PSEN1 E280A carriers, we have sought to harmonize our biomarker measurements and perform biological fluid assays in the same laboratory used in the study of many other ADAD mutation carriers and noncarriers from the Dominantly Inherited Alzheimer Network, thus providing complementary data and converging evidence in the preclinical study of ADAD. Most of our imaging findings did not survive correction for multiple comparisons and need to be considered as exploratory; however, the pattern of the gray matter and fMRI changes, their bilateral nature, the convergence of findings using different MRI measurements, and other studies suggesting few type I errors at \( P < .05 \) reduce the chance of type I errors. Finally, we could not rule out the possibility that some of the biomarker changes occurred in the presence of fibrillar plaques or potentially neurotoxic soluble Aβ effects that were not detected in the previous CSF and positron emission tomographic studies.

Conclusions

PSEN1 E280A mutation–carrying children have functional and structural MRI changes, along with plasma biomarker findings consistent with Aβ1-42 overproduction. This study demonstrates some of the earliest known brain changes in ADAD, it suggests that these changes may begin before biomarker evidence of Aβ plaque deposition, and it underscores the need for studies to clarify the earliest brain changes associated with the predisposition to AD. Further research is needed to determine the meaning and relevance of these changes for early detection of the disease and to evaluate them as reliable preclinical markers of AD. Longitudinal studies of this kindred may provide answers about progression and prevention of the disease. Further research is also needed to determine how the presenilin variants might modify brain development and how these neurodevelopmental changes may or may not be related to present or future pathophysiological changes associated with the predisposition to AD.

ARTICLE INFORMATION

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Author Contributions: Dr Quiroz had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data as analyzed.

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Acquisition, analysis, or interpretation of data: Quiroz, Schultz, Chen, Protas, Brickhouse, Fleisher, Langbaum, Thiyyagura, Fagan, Shah, Muniz, Arboleda-Velasquez, Munoz, Garcia, Acosta-Baena, Giraldo, Tirado, Ramírez, Dickerson, Sperling, Reiman.

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Study supervision: Quiroz, Lopera, Reiman.

Conflict of Interest Disclosures: Dr Quiroz has served as a consultant for MedAvante. Dr Fleisher has served as a consultant for Eli Lilly, Avid, Merck, Grifols, Quintiles, and Biogen. Dr Fleisher has been an invited speaker for Quintiles, Avid, and Lilly CME grant programs. Dr Fleisher has data and safety monitoring board membership with the National Institute on Aging (NIA), Merck, and Pfizer; grant funding from NIA and Eli Lilly, and has had studies sponsored by Merck, Roche, Genentech, Pfizer, Avanir, Takeda, Lilly, Bristol-Myers Squibb, Baxter, Neuroptix, and Wyeth. Dr Fleisher is a full-time employee of Eli Lilly as of April 2014. Dr Fagan is a member of the scientific advisory boards of IBL International and Roche, as well as a consultant for AbbVie. Dr Tariot has received consulting fees from Abbott Laboratories, AC Immune, Adamas, Allergan, Avanir, Boehringer-Ingelheim, Chase Pharmaceuticals, Chiesi, Elsi Inc, Elan, MedAvante, Merz Pharma, Neuroptix, Novartis, Otsuka, sanofi, Schering-Plough, and Worldwide Clinical Trials. Dr Tariot has also received consulting fees and research support from AstraZeneca, Avid, Bristol-Myers Squibb, Genentech, GlaxoSmithKline, Janssen, Eli Lilly, Medivation, Merck and Company, Pfizer Inc, Roche, Toyama, and Wyeth Laboratories, as well as research support from Baxter Healthcare Corp, Functional Neuromodulation (f[nm]), GE, and Targetcept. Dr Tariot has stock options in MedAvante and Adamas and holds patents related to biomarkers of Alzheimer disease. Dr Sperling has received consulting fees from Genentech, Roche, and Janssen, as well as research support from Eli Lilly, Avid, Janssen, and Elsi. Dr Reiman has received research funding from Avid and has a paid consultation role for Eli Lilly. No other disclosures were reported.

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