Myo-inositol changes precede amyloid pathology and relate to APOE genotype in Alzheimer disease

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ARTICLES

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OBJECTIVE: We aimed to test whether in vivo levels of magnetic resonance spectroscopy (MRS) metabolites myo-inositol (mI), N-acetylaspartate (NAA), and choline are abnormal already during preclinical Alzheimer disease (AD), relating these changes to amyloid or tau pathology, and functional connectivity.

METHODS: In this cross-sectional multicenter study (a subset of the prospective Swedish BioFINDER study), we included 4 groups, representing the different stages of predementia AD: (1) cognitively healthy elderly with normal CSF Aβ-amyloid 42 (Aβ42), (2) cognitively healthy elderly with abnormal CSF Aβ42, (3) patients with subjective cognitive decline and abnormal CSF Aβ42, and (4) patients with mild cognitive decline and abnormal CSF Aβ42 (Ntotal = 352). Spectroscopic markers measured in the posterior cingulate/precuneus were considered alongside known disease biomarkers: CSF Aβ42, phosphorylated tau, total tau, [18F]-flutemetamol PET, fMRI, and the genetic risk factor APOE.

RESULTS: Amyloid-positive cognitively healthy participants showed a significant increase in mI/creatinine and mI/NAA levels compared to amyloid-negative healthy elderly (p < 0.05). In amyloid-positive healthy elderly, mI/creatinine and mI/NAA correlated with cortical retention of [18F] flutemetamol tracer (β = 0.44, p = 0.02 and β = 0.51, p = 0.01, respectively). Healthy elderly APOE ε4 carriers with normal CSF Aβ42 levels had significantly higher mI/creatinine levels (p < 0.001) than ε4 noncarriers. Finally, elevated mI/creatinine was associated with decreased functional connectivity within the default mode network (rpearson = −0.16, p = 0.02), independently of amyloid pathology.

CONCLUSIONS: mI levels are elevated already at asymptomatic stages of AD. Moreover, mI/creatinine concentrations were increased in healthy APOE ε4 carriers with normal CSF Aβ42 levels, suggesting that mI levels may reveal regional brain consequences of APOE ε4 before detectable amyloid pathology. Neurology 2016;86:1754-1761

GLOSSARY

AD = Alzheimer disease; Cho = choline; Cr = creatinine; DMN = default mode network; fMRI = functional MRI; GLM = general linear model; MCI = mild cognitive impairment; mI = myo-inositol; MMSE = Mini-Mental State Examination; MRS = magnetic resonance spectroscopy; NAA = N-acetylaspartate; PCC = posterior cingulate cortex; SCD = subjective cognitive decline; t-tau = total tau; VOI = volume of interest.

Potential biomarkers for predicting onset and progression of Alzheimer disease (AD) can be detected by proton magnetic resonance spectroscopy (MRS)—a noninvasive imaging technique that allows in vivo assessment of brain biochemistry. Decreased levels of neural marker N-acetylaspartate (NAA) and increased concentrations of myo-inositol (mI) belong to the more consistent MRS findings in patients with AD dementia.1-4

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To understand the underlying causes of the observed abnormalities in the MRS neurochemical profile in AD, it is important to study their association with known pathologic processes in individuals at different disease stages. We hypothesized that at the early predementia stages, incipient AD pathology is responsible for MRS metabolite abnormalities.

We aimed to evaluate the relationship between MRS-detected brain metabolites and known AD biomarkers in the following 4 predementia groups: healthy controls with no evidence of amyloid pathology, healthy controls with abnormal levels of CSF Aβ42, patients with subjective cognitive decline (SCD) with abnormal Aβ42 levels, and patients with mild cognitive impairment (MCI) with abnormal Aβ42 levels.

In these groups, we studied the relationship among metabolites NAA, mI, and choline (Cho) in the posterior cingulate cortex (PCC)/precuneus and Aβ deposition measured by [18F]-flutemetamol PET or CSF Aβ42 as well as the CSF neurodegenerative markers total tau (t-tau) and phosphorylated tau. In addition, we evaluated MRS metabolites in relation to (1) carriership of the APOE ε4 allele—the main known genetic risk factor for AD—and (2) functional connectivity in the PCC/precuneus measured using functional MRI (fMRI), due to the default mode network (DMN) involvement in predementia AD.

METHODS Standard protocol approvals, registrations, and patient consents. All participants gave written consent to participate in the study. Ethical approval was given by the ethical committee of Lund University, Sweden. [18F]-flutemetamol PET imaging approval was obtained from the Swedish Medicines and Products Agency and the local Radiation Safety Committee at Skåne University Hospital, Sweden.

Participants. The study population stemmed from the prospective and longitudinal Swedish BioFinder study (more information available at www.biofinder.se and the coinvestigator list on the Neurology® Web site at Neurology.org). Among others, the BioFinder consecutively enrolls (1) cognitively healthy elderly participants and (2) patients without dementia with mild cognitive symptoms. Individuals from these 2 cohorts were selected for the present study. Data were collected between 2009 and 2014 in accordance with a standardized protocol.

The first cohort consisted of cognitively normal elderly participants who were eligible for inclusion if they (1) were aged ≥60 years old, (2) scored 28–30 points on Mini-Mental State Examination (MMSE) at the screening visit, (3) did not have any subjective cognitive impairment, and (4) were fluent in Swedish. Exclusion criteria included presence of significant neurologic disease (e.g., stroke, Parkinson disease, multiple sclerosis), severe psychiatric disease (e.g., severe depression or psychotic syndromes), dementia, or MCI.

The second cohort contained patients who were enrolled consecutively at 3 memory outpatient clinics in Sweden. They were referred for assessment of cognitive complaints and assessed by physicians with special interest in dementia disorders. The inclusion criteria were as follows: (1) referred to the memory clinics because of cognitive impairment; (2) not fulfilling the criteria for dementia; (3) MMSE score of 24–30 points; (4) age 60–80 years; and (5) fluent in Swedish. The exclusion criteria were (1) cognitive impairment without doubt explained by another condition (other than prodromal dementia); (2) severe somatic disease; and (3) refusing lumbar puncture or neuropsychological investigation. Further, patients were classified into MCI and SCD based on a neuropsychological battery assessing the cognitive domains of verbal ability, visuospatial construction, episodic memory, and executive functions and the clinical assessment of a senior neuropsychologist.

For the current study, only participants with CSF analysis and a high-quality MRS spectrum were eligible (see figure e-1 for flowchart). This resulted in the following 4 groups: from cohort 1, (1) healthy controls with normal (negative) CSF Aβ42 (n = 156) and (2) healthy controls with abnormal (positive) CSF Aβ42 (n = 59); from cohort 2, (3) patients with SCD with abnormal (positive) CSF Aβ42 (n = 49); and (4) patients with MCI with abnormal (positive) CSF Aβ42 (n = 88).

CSF Aβ42 levels at and below 530 ng/L were considered abnormal.

MRS acquisition. Single-voxel MRS was performed at 3T on a Siemens TrioTim scanner; the point-resolved spectroscopy sequence was applied at echo time of 30 ms and repetition time of 2,000 ms. The 2 × 2 × 2 cm³ voxel was placed mid sagittally in the PCC/precuneus area (figure 1). This region demonstrates histopathologic changes, cortical thinning, and decreased glucose metabolism early in the disease course. The PCC/precuneus area has previously been selected for MRS voxel placement in large-scale spectroscopy studies and was recommended for MRS studies in AD by the MRS consensus group.

For details on structural MRI and resting-state fMRI, see appendix e-1.

MRS analysis. Metabolite quantification was carried out using the LCModel software relative total creatine (Cr) concentration (a resonance peak, composed of the metabolites creatine and phosphocreatine). This means of internal referencing is often used in clinical spectroscopy due to the relative stability of the Cr peak. All processed spectra were visually inspected for quality and artefacts. Only spectra with full width at half maximum ≤11 Hz were considered. For complete quality control procedures, see appendix e-1. Examples of spectra can be found in figure 1.

Resting-state fMRI analysis. Initial preprocessing of resting-state fMRI data was performed with an FSL-based pipeline. A 15-mm-diameter sphere centered in the MRS region of interest was used as a seed. Correlation maps were obtained between the seeds’ average and all gray matter voxels’ processed blood oxygenation level-dependent time series. A normal connectivity mask was defined by averaging the maps of all Aβ42-negative controls and applying a correlation threshold of approximately 0.2 (corresponding to r < 0.01). Participant-specific functional connectivity summary statistic was extracted as the sum of all seed...
correlation values within the normal connectivity mask. For detailed description of fMRI procedures, see appendix e-1.

PET acquisition and analysis. The cerebral Aβ burden of the patients was visualized using [18F]-flutemetamol PET. Images were analyzed using the software NeuroMarQ provided by GE Healthcare. A volume of interest (VOI) template for different cortical and subcortical regions was applied. The following 9 bilateral regions were used in the study: prefrontal, parietal, lateral temporal, medial temporal, sensorimotor, occipital, anterior cingulate, PCC/precuneus, and a global neocortical composite region. The standardized uptake value ratio was defined as the regional tracer uptake in a VOI, normalized for the mean uptake in the cerebellar cortex. For details on PET procedures, see appendix e-1.

CSF collection and analysis. The procedure and analysis of the CSF followed the Alzheimer’s Association Flow Chart for CSF biomarkers. Lumbar CSF samples were collected at 3 centers, stored in polypropylene tubes at −80°C, and analyzed at the same time using 2 different ELISAs. CSF Aβ42 and tau phosphorylated at Thr181 were analyzed by INNOTEST ELISAs (Fujirebio Europe, Ghent, Belgium). CSF t-tau was analyzed by EUROIMMUN ELISA (EUROIMMUN AG, Lübeck, Germany).

Statistical procedures. Statistical analyses were performed within the general linear model (GLM) framework. Associations between MRS metabolites and other variables were assessed using multiple stepwise linear regression with backward elimination. Thus, age and sex were included in the model and their partial effects accounted for only when these variables were demonstrated to be significant predictors.

Between-group differences were tested using independent-samples t test or using analysis of variance followed by Tukey honestly significant difference test for post hoc comparisons. Significance levels: *p < 0.05, **p < 0.01, ***p < 0.001. CTL Aβ42− = controls with CSF Aβ42 > 530 ng/L; CTL Aβ42+ = controls with CSF Aβ42 ≤ 530 ng/L; SCD Aβ42+ = patients with subjective cognitive decline with CSF Aβ42 ≤ 530 ng/L; MCI Aβ42+ = patients with MCI with CSF Aβ42 ≤ 530 ng/L.

RESULTS Sample characteristics. Demographic details of the diagnostic groups are provided in table 1 (additional cognitive tests in table e-1). MRS, MRI, and CSF data were available for all participants, whereas PET and fMRI data were available for a subset (NPET = 166, NfMRI = 206). An overview of modalities per diagnostic group is available in table e-2.
MRS in different stages of predementia AD. MRS outcome variables mI/Cr, NAA/Cr, and Cho/Cr measured in the PCC/precuneus were assessed across the 4 diagnostic groups. For a summary of metabolite concentrations and an account of group differences, see figure 1 and table e-3.

All spectroscopic measures were significantly different between the CSF Aβ42-negative controls and the CSF Aβ42-positive MCI group: mI/Cr was elevated ($p < 0.001$, $d$ [Cohen] = 0.64), Cho/Cr was elevated ($p < 0.01$, $d = 0.44$), and NAA/Cr was reduced ($p < 0.001$, $d = 0.35$) in the CSF Aβ42-positive MCI group.

More importantly, mI/Cr was significantly increased in CSF Aβ42-positive healthy controls compared to CSF Aβ42-negative healthy controls ($p < 0.05$, $d = 0.46$), revealing that mI/Cr levels are already changed in PCC/precuneus of asymptomatic individuals at risk for developing AD.

MRS and CSF biomarkers. In the entire cohort, we found that decreased CSF Aβ42 was associated with increased mI/Cr ($\beta = -0.23$, $p < 0.001$) as well as decreased NAA/Cr ($\beta = 0.11$, $p = 0.05$). Further, elevated CSF tau levels correlated with decreased NAA/Cr levels ($\beta = -0.14$, $p = 0.01$).

In the cognitively healthy group, we found that increased mI/Cr correlated with decreased CSF Aβ42 ($\beta = -0.21$, $p = 0.002$), confirming that mI levels are associated with amyloid pathology already during asymptomatic stages.

Finally, in the CSF Aβ42-positive MCI group, we detected a significant association between NAA/Cr and CSF t-tau. Both measures are known correlates of the extent of neuronal injury and degradation—a process ongoing in patients with MCI.

See table e-4 for a complete account of significant associations between MRS and CSF markers.

MRS and [18F]-flutemetamol PET. CSF Aβ42 and amyloid PET reflect somewhat different aspects of Aβ pathology. Therefore, we explored whether MRS metabolites were associated with cortical retention of the amyloid PET ligand [18F]-flutemetamol in predementia AD.

We found that increased level of mI/Cr was linked to higher [18F]-flutemetamol retention in the PCC/precuneus region in healthy elderly individuals. Further, this association was only present in the CSF Aβ42-positive group, $p < 0.05$.

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Table 2: Significant associations between brain metabolites measured by magnetic resonance spectroscopy and [18F]-flutemetamol uptake in the posterior cingulate cortex/precuneus in healthy controls

<table>
<thead>
<tr>
<th>Predictor PET Aβ parameters</th>
<th>Standardized beta β</th>
<th>T</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All healthy controls</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ml/Cr</td>
<td>0.32</td>
<td>3.45</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CSF Aβ42-positive controls</td>
<td>0.44</td>
<td>2.62</td>
<td>0.02</td>
</tr>
<tr>
<td>Amyloid PET-positive controls</td>
<td>0.48</td>
<td>2.76</td>
<td>0.01</td>
</tr>
<tr>
<td>Cho/Cr</td>
<td>0.44</td>
<td>2.52</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Abbreviations: Cho = choline; Cr = creatine; ml = myo-inositol.

MRS and functional MRI. Next we studied whether MRS metabolites in precuneus/PCC were associated with functional connectivity between precuneus/PCC and other regions within the DMN. We found that increasing levels of ml/Cr, but not NAA/Cr, were associated with reduced DMN connectivity across all groups (r = –0.16, p = 0.02) (figure 2).

We further investigated whether the association between ml/Cr levels and DMN connectivity was driven by Aβ pathology. Entering CSF Aβ42 as a covariate in a GLM yielded t = −2.08 (p = 0.04) for ml/Cr and t = 0.63 (p = 0.53) for CSF Aβ42, suggesting that the relationship between functional connectivity and ml/Cr may be Aβ-independent. Using [18F]-flutemetamol retention in the PCC/precuneus as a proxy of Aβ pathology gave analogous results (appendix e-2).

MRS and APOE genotype. Finally, we aimed to study the relationship between APOE and MRS metabolites in different stages of predementia AD. GLM analysis revealed that healthy APOE e4 carriers with still normal CSF Aβ42 levels had significantly higher ml/Cr concentrations than APOE e4 noncarriers (t = −3.61, d = 0.47, p < 0.001). APOE e4 carriership did not influence ml/Cr levels in the remaining diagnostic groups—those where CSF Aβ42 levels were already abnormal (figure 3).

DISCUSSION The present study aims to describe changes in the MRS neurochemical profile across 4 well-characterized groups that follow the hypothetical course of predementia AD.22 Biomarker-negative participants with no evidence of subtle cognitive decline are plausible true controls unlikely to be at risk for AD. At-risk individuals include those with no cognitive symptoms but with abnormal CSF Aβ42 levels, as well as patients with SCD and MCI with evidence of abnormal CSF Aβ42.

In this study, stratification of participants into groups was based in part on CSF Aβ42 cutoff values. A cutoff might in some cases mask subclinical effects—those that take place below the set threshold. We also used classification cutoffs based on mixture modeling for [18F]-flutemetamol PET data. Although this method has been extensively used previously to establish unbiased thresholds,23 such a cutoff is nevertheless study-specific.

Elevated ml/Cr and decreased NAA/Cr belong to the more reproducible MRS findings in AD, with abnormal ml/Cr appearing earlier and decreased NAA/Cr later in the disease course.24 As expected, we detected that NAA/Cr and ml/Cr ratios were significantly different between biomarker-negative controls and biomarker-positive patients with MCI—the 2 groups on the opposite ends of the predementia spectrum. More intriguingly, we detected that abnormal elevation of ml/Cr in the PCC/precuneus region occurs already in the asymptomatic at-risk individuals.

We found that early changes in ml/Cr were temporally associated with the initial decline in CSF Aβ42 levels, as the increase in ml/Cr was linked to a decrease in CSF Aβ42 in controls, but not in symptomatic individuals. CSF Aβ42 levels are already fully decreased 10–20 years before dementia onset25,26; brain ml/Cr is increased already at predementia stages in individuals with Down syndrome27 and familial dementias.28 Although the mechanistic linkage between CSF Aβ42 and ml/Cr cannot be established directly from our study, their contemporaneous changes may be related to the same pathologic process, one that predicts cognitive decline.

Abnormally low levels of CSF Aβ42 are accurate in revealing disturbed Aβ metabolism. Although CSF Aβ42 predicts conversion to dementia, levels do not correlate well with rate of disease progression. In contrast, the amount of cortical retention of amyloid PET ligands is more directly related to the accumulation of Aβ fibrils in the neocortex, increasing continuously throughout the prodromal stages of AD.29 In the largest study linking changes in MRS measures to in vivo Aβ deposition,11 cognitively normal elderly participants demonstrated significant positive association between ml/Cr measured in the PCC and cortical retention of Pittsburgh compound B. We detected an analogous association between ml and plaque load in healthy controls as ml/Cr concentrations were shown to correlate with [18F]-flutemetamol uptake. Moreover, we detected that this association was driven by the subgroup harboring amyloid burden, and was absent in amyloid-free participants.
Regarding MRS measures and CSF neurodegenerative markers, we detected that an increase in NAA/Cr was linked to a decrease in CSF t-tau in the CSF Aβ42-positive MCI group. Both measures are markers of neuronal damage; an association between the 2 in prodromal MCI only is consistent with the fact that neuronal injury takes place at a later time point in the predementia continuum. Loss of NAA/Cr in the PCC/precuneus at the symptomatic stage preceding AD is in line with this region’s involvement in attention and memory. The significance of the changes in Cho/Cr in AD is not well-understood. We detected elevated Cho/Cr levels in CSF Aβ42-positive MCI compared to CSF Aβ42-negative controls—a finding often attributed to an upsurge in membrane turnover due to neurodegeneration, or possibly underlying cholinergic dysfunction in the MCI group.

Carriership of the APOE ε4 is the main genetic risk factor for AD. APOE ε4 enhances AD pathology, and is thought to trigger the initiation and acceleration of Aβ deposition in the brain, without having any primary effect on Aβ production. APOE ε4 also contributes to AD pathogenesis by being implicated in the process of neuroinflammation. Regarding the relationship between APOE genotype and MRS measures, elevated mI/Cr has previously been detected in the PCC/precuneus of older ε4 carriers compared to noncarriers in a healthy aging population. However, whether this was a consequence of underlying Aβ pathology in ε4 carriers has not been investigated previously. We show that in cognitively healthy amyloid-free elderly, mI/Cr levels were significantly elevated in the ε4 carriers compared to the noncarriers. In the remaining subgroups—those with evidence of Aβ pathology—mI/Cr levels were no longer modified by APOE carriership. It seems that mI/Cr has the potential to detect manifestations of the APOE genetic effect, which precede cognitive decline and may antedate or be independent of amyloid pathology, perhaps even detecting the more pronounced proinflammatory state associated with ε4 carriership.

The PCC/precuneus region plays a key role within the DMN, operating as a node for structural and functional connections. Regions involved in the DMN are affected by amyloid deposition early in the course of AD. We observed a hitherto unreported association between elevated mI/Cr levels and reduced DMN connectivity. Furthermore, our findings suggest that the link between mI/Cr in the PCC/precuneus and functional connectivity in this region may not be a direct consequence of Aβ deposition.

Increasing attention is being paid to detailed characterization of the earliest stages of AD, warranting further research into cost-effective noninvasive early markers. Although the exact mechanisms behind early changes in the MRS profile cannot be inferred directly from the results of this study, our findings situates changes in the MRS profile within the context of existing clinical, pathologic, and functional information in individuals at risk for AD. We provide evidence of the involvement of brain mI at very early stages in AD progression; in particular our data show
that mI/Cr levels are elevated in APOE ε4 carriers with no evidence of amyloid pathology.

AUTHOR CONTRIBUTIONS
Study design and concept: O. Voevodskaya and Drs. Westman and Hansson. Acquisition, analysis, and interpretation of data: O. Voevodskaya and Drs. Sundgren, Strandberg, Zetterberg, and Hansson. Drafting of the manuscript: O. Voevodskaya and Drs. Westman and Hansson. Critical revision of the manuscript for important intellectual content: Drs. Sundgren, Strandberg, Zetterberg, Minthon, Blennow, and Wahlund. Statistical analysis: O. Voevodskaya and Dr. Strandberg. Obtained funding: Dr. Hansson. Administrative, technical, and material support: Drs. Sundgren, Strandberg, Zetterberg, Minthon, Blennow, and Wahlund. Study supervision: Drs. Westman and Hansson.

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DISCLOSURE
O. Voevodskaya, P. Sundgren, O. Strandberg, H. Zetterberg, and L. Minthon report no disclosures relevant to the manuscript. K. Blennow has served on advisory boards for Eli-Lilly, IBL International, Novartis, and Roche Diagnostics. L. Wahlund, E. Westman, and O. Hansson report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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