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Cerebrospinal fluid ferritin levels predict brain hypometabolism in people with underlying β-amyloid pathology

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ABSTRACT

β-Amyloid pathology is elevated in ~30% of cognitively normal people over 65, and is associated with accelerated neurodegeneration in the pre-clinical stages of Alzheimer's disease. Recent findings reveal that brain iron might also act to propel neurodegeneration in people with underlying amyloid pathology. Here, repeated PET scans of fluorodeoxyglucose (FDG) were used as a biomarker for brain hypometabolism and a downstream biomarker of neurodegeneration to investigate whether levels of ferritin in the cerebrospinal fluid (CSF; a reporter of brain iron load) are associated with prodromal disease progression of people with high β-amyloid pathology determined by established cut-off values in CSF t-tau/$A\beta_{42}$ ratio. Nineteen cognitively normal participants with low t-tau/$A\beta_{42}$, and 71 participants with high t-tau/$A\beta_{42}$ who were cognitively normal or had mild cognitive impairment were included as participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI) study. These subjects had repeated FDG-PET scans at 6-month intervals for 2 years, and yearly intervals for up to a further 3 years. In mixed-effects linear models of FDG signal, baseline CSF ferritin was associated with an accelerated decline in FDG PET in high t-tau/$A\beta_{42}$ participants (β[SE] = −0.066 [0.017]; P = .0002), but not in people with low t-tau/$A\beta_{42}$ (−0.029 [0.049]; P = .554). These data implicate iron as a contributing factor to neurodegeneration associated with β-amyloid pathology, and highlight CSF ferritin as a complementary prognostic biomarker to the t-tau/$A\beta_{42}$ ratio that predicts near-term risk for disease progression.

1. Introduction

Insidious neurodegeneration in the pre-clinical stages of Alzheimer's disease immediately precedes cognitive decline and progresses throughout the disease (Jack Jr. et al., 2013; Karow et al., 2010). Fluorodeoxyglucose (^{18}F-FDG) is a PET imaging tracer that measures cerebral glucose metabolism in neuronal and glial cells and is used to investigate brain hypometabolism and as downstream biomarker for neurodegeneration in AD (Rice & Bisdas, 2017). Reduced signal of FDG in the prodromal stages of the disease is associated with increased risk of future cognitive decline (Cabral et al., 2015; Herholz et al., 2011).

Deposition of β-amyloid, confirmed using PET or CSF biomarkers, occurs in the decades prior to neurodegeneration in the temporal staging of AD (Jack Jr. et al., 2013), but the variance in the rate of deterioration between individuals precludes the use of β-amyloid alone as a prognostic biomarker of imminent decline. We have recently shown that brain iron content, as measured by either quantitative susceptibility mapping (QSM)-MRI is associated with longitudinal cognitive decline (Ayton et al., 2017a).

Brain iron load may also be assessed by measuring ferritin in CSF. Ferritin is the major iron storage protein, and the expression and secretion of ferritin is increased by elevated iron[9,1011]. Ferritin levels in

Abbreviations: Aβ, beta amyloid; AD, Alzheimer's disease; ADNI, Alzheimer's Disease Neuroimaging Initiative; CSF, cerebrospinal fluid; FDG-PET, fluorodeoxyglucose positron emission tomography; MCI, mild cognitive impairment

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CSF likely reflect iron levels in the brain since, for example, Restless Legs Syndrome, a disorder of low brain iron that is treated with iron supplementation, is characterised by low CSF ferritin[12]. We have previously shown in the Alzheimer's disease Neuroimaging Infinitive (ADNI) cohort that CSF ferritin is associated with longitudinal cognitive decline and β-amyloid accumulation (Ayton et al., 2015a; 2017b; 2018). Here, we combine CSF biomarkers of Aβ pathology (t-tau/$A\beta_{42}$) and iron (ferritin) to determine whether iron is associated with accelerated loss of FDG PET signal, and whether CSF ferritin might offer added value in predicting near-term risk of brain hypometabolism and neurodegeneration in those with underlying proteinopathy.

2. Methods

2.1. Study design and participants

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu) on 30/7/2018. The data files include ADNIMERGE and "Biomarkers Consortium ADNI CSF Multiplex Raw". The ADNI study has been previously described in detail (Weiner et al., 2012). The ADNI study was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial MRI PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. For up-to-date information, see www.adni-info.org.

2.2. CSF biomarkers

CSF was collected on a sample of the ADNI cohort at baseline. Ferritin and apolipoprotein E levels were measured with the RBM multiplex platform, while levels of CSF $A\beta_{1-42}$ and total tau (t-tau) were measured with the multiplex xMAP Luminex platform (Ayton et al., 2015b).

2.3. FDG-PET

As previously described (Popuri et al., 2018), the ADNI FDG-PET images used in this study were pre-processed using a series of steps to mitigate inter-scanner variability and obtain FDG-PET data with a uniform spatial resolution and intensity range for further analysis (http://adni.loni.usc.edu/methods/PET-analysis). Briefly, the original raw FDG-PET frames of the baseline scan were co-registered and averaged to obtain a single FDG-PET image, which was then mapped from its native space to a standard $160 \times 160 \times 96$ grid with $1.5 \times 1.5 \times 1.5\,mm^3$ voxels. This image then serves as a reference image for performing only one co-registering across all the PET frames (including baseline and the follow-up) on that subject. This will reduce the amount of interpolation. After this spatial normalization, a subject-specific mask of pons region based on a T1-weighted template was generated. The intensity range of each FDG-PET image was normalized using the mean of the top 50% of FDG voxels within the pons mask. The intensity normalized images were then filtered using scanner-specific filter functions to obtain FDG-PET data at a uniform smoothing level of isotropic 8 mm full width at half maximum (FWHM) Gaussian kernel. This leads to a resulting image which is adjusted for inter-scanner or inter-site variability.

Based on the established relationship between regional glucose metabolism and cognitive decline (Landau et al., 2011; Landau et al., 2010), the average signal of the combined angular, temporal, and posterior cingulate cortices were considered for this study (available in ADNIMEGE data file). In particular, Left Angular Gyrus, Right Angular Gyrus, Bilateral Posterior Cingular, Left Inferior Temporal Gyrus, Right Inferior Temporal Gyrus were included.

2.4. Statistical analysis

Baseline demographics of participants included in this study were described overall and in strata of Aβ pathology, based on previously published CSF t-tau/$A\beta_{42}$ ratio threshold: t-tau/$A\beta_{42}$ ratio < 0.27 for low pathology and ≥ 0.27 for high pathology (Shaw et al., 2018). Factors associated with baseline ferritin were analysed in a linear regression model of ferritin as dependant variable including age, gender, *APOE* ε4 genotype, diagnosis (NC, MCI), apolipoprotein E levels, baseline FDG and the ratio t-tau/Aβ as independent variables. To assess associations between longitudinal changes in FDG PET and ferritin (as a continuous variable), participants were stratified by CSF t-tau/$A\beta_{42}$ ratio. Data were modelled with mixed linear models including age, sex, diagnosis, *APOE* ε4, apolipoprotein E levels, t-tau/$A\beta_{42}$ and ferritin as covariates. Models was performed with R (version 3.5.0) and tested for multicollinearity and normal distribution of residuals.

3. Results

We identified 133 ADNI subjects with complete data for biomarkers (CSF values of ferritin, tau, $A\beta_{42}$ and apolipoprotein E) and demographic variables (age, sex, *APOE* ε4 allele, diagnosis) and follow-up data for FDG PET. The cohort was stratified according to the absence or presence of Aβ brain pathology based on a previously established t-tau/$A\beta_{42}$ ratio cut-off (Shaw et al., 2018). We excluded MCI subjects who had CSF t-tau/$A\beta_{42}$ below the cutoff for Aβ brain pathology, because numbers were low (n = 11) and these participants were unlikely to be developing AD. FDG PET has been used to stratify dementia type (Vaidyanathan et al., 2015), and could possibly be used to determine the underlying cause of memory impairment in these 11 cases, but considering there may be several causes of memory impairment (e.g. vascular, Lewy Body, frontotemporal) we considered this group to be too small and heterogenous to analyse. We also excluded AD subjects because of < 2 years of follow-up were available.

Among the included 90 participants selected for this study, 19 cognitively normal (CN) subjects (cognitive score mean [S.E.]; MMSE: 29.1 [1.1]; CDR-SB: 0.08 [0.2]; ADAS-cog: 10.8 [3.5]) were below the Aβ brain pathology cutoff by t-tau/$A\beta_{42}$ ratio, 71 subjects had t-tau/$A\beta_{1-42}$ ratios above the Aβ brain pathology cutoff, including 13 clinically characterised as CN (cognitive score mean [S.E.]; MMSE: 29.1 [1.1]; CDR-SB: 0.08 [0.2]; ADAS-cog: 10.2 [3.45]) and 58 who were diagnosed as MCI (cognitive score mean [S.E.]; MMSE: 26.9 [1.7]; CDR-SB: 1.6 [0.9]; ADAS-cog: 19.3 [6.2]).

The demographic variables were similar between groups, except for the frequency of the *APOE* ε4 allele, which increased in the high t-tau/$A\beta_{42}$ (63%) compared to the low t-tau/$A\beta_{42}$ group (16%), as expected (Table 1). The cohort was mostly of white/Caucasian ethnicity: in the low t-tau/$A\beta_{42}$ group 18 were of white ethnicity and one was black; in the high t-tau/$A\beta_{42}$ group 67 were white and 4 were black. The numbers of participants at each time point who had an FDG PET scan are reported in Table 2.

Table 1
Participant baseline demographics in strata of Alzheimer's disease diagnosis and β-amyloid pathology.

	Low t-tau/$A\beta_{42}$	High t-tau/$A\beta_{42}$
n	19	71
Age (years): mean (S.D.)	75.18 (6.46)	74.90 (6.72)
Female gender: n (%)	6 (31.6)	23 (31.90)
MCI diagnosis	–	58 (81.69)
APOE ε4 genotype: n (%)	3 (15.8)	45 (63.4)
Baseline FDG-PET: mean (S.D)	1.3 (0.15)	1.21 (1.15)
CSF t-tau/$A\beta_{42}$: mean (S.D.)	0.15 (0.04)	0.56 (0.24)
CSF ferritin: mean (S.D.)	6.23 (1.83)	6.72 (2.41)
CSF apolipoprotein E: mean (S.D.)	7.26 (2.25)	6.98 (2.29)

Table 2
Number of subjects scanned using FDG PET for each time point.

	Baseline	6 months	12 months	18 months	24 months	36 months	48 months	60 months
Low t-tau/$A\beta_{42}$	18	19	16	0	19	19	8	5
High t-tau/$A\beta_{42}$	71	71	71	56	63	47	12	9

Table 3
Association between CSF ferritin and clinical variables. Data are from multiple regression models of CSF ferritin in subjects with low and high CSF t-tau/$A\beta_{42}$ ratio. The table displays the association between CSF ferritin and each of the covariates (Italicised values indicate significant associations). Female and Cognitively Normal subjects were assigned as the reference, the β values for the sex and diagnosis variables describe the association with FDG-PET signal due to being male and having MCI. The β coefficients assigned to the continuous variables (age, CSF apolipoprotein E, t-tau/$A\beta_{42}$ and baseline FDG-PET) represent change in CSF ferritin units (ng/ml) according to unit change of these variables.

	Low t-tau/$A\beta_{42}$			High t-tau/$A\beta_{42}$		
	β	SE	P	β	SE	P
Age (years)	0.004	0.006	0.512	0.001	0.002	0.709
Sex (male)	0.024	0.066	0.722	0.007	0.033	0.841
MCI diagnosis				−0.037	0.044	0.403
APOE ε4	−0.020	0.101	0.846	0.081	0.033	*0.018*
CSF apolipoprotein E	0.389	0.274	0.185	0.662	0.116	3.7×10^{-7}
CSF t-tau/$A\beta_{42}$	−0.669	1.01	0.523	0.019	0.073	0.793
Baseline FDG-PET	−0.126	0.284	0.574	−0.076	0.109	0.487

Table 4
Association between ferritin and change in FDG. Data are from mixed models of longitudinal change in FDG including the covariates: time, age, sex and *APOE* ε4, diagnosis, and CSF levels of apolipoprotein E, t-tau/$A\beta_{42}$ and ferritin. The table displays the interaction between time and the other included covariates (Italicised values indicate significant associations). Female and Cognitively Normal subjects were assigned as the reference, the β values for the sex and diagnosis variables describe the association with change in FDG-PET signal due to being male and having MCI. The β coefficients assigned to the continuous variables (age, CSF apolipoprotein E, t-tau/$A\beta_{42}$ and ferritin) represent change in FDG-PET signal according to unit change of these variables.

	Low t-tau/$A\beta_{1-42}$			High t-tau/$A\beta_{1-42}$		
	β	SE	P	β	SE	P
Age (years)	0.001	0.001	0.490	0.001	0.0003	*0.006*
Sex (male)	0.014	0.010	0.152	0.013	0.005	*0.008*
MCI diagnosis				−0.015	0.006	*0.009*
APOE ε4	0.019	0.014	0.184	0.003	0.005	0.543
CSF apolipoprotein E	0.026	0.043	0.546	0.040	0.023	0.080
CSF t-tau/$A\beta_{42}$	−0.043	0.134	0.751	0.020	0.011	0.060
CSF Ferritin	−0.029	0.049	0.554	−0.066	0.017	*0.0002*

In cross sectional analysis (multiple regression; Table 3), CSF ferritin was not associated with baseline FDG-PET signal, but was associated with APOE ε4 genotype (β[SE]: 0.081 [0.03], P = .018), and apolipoprotein E levels (β[SE]: 0.66[0.11], P = 3.70×10^{-7}), as we have previously shown (Ayton et al., 2015b).

In longitudinal modeling of FDG signal, baseline CSF ferritin was associated with an accelerated decline of FDG uptake over 5 years in the high t-tau/$A\beta_{42}$ subjects (β[SE] = −0.066 [0.017]; P = .0002). This association was robust to loss of patient follow-up since the CSF ferritin predicted accelerated loss of FDG uptake when the model was restricted to follow-up of 4 years (β[SE] = −0.063 [0.047]; P = .002), 3 years (β[SE] = −0.069 [0.021]; P = .002) and 2 years (β[SE] = −0.068 [0.061]; P = .023). Being of male sex was associated with slower decline in FDG signal (β[SE] = 0.013 [0.005]; P = .008) in this group, as was, perhaps unexpectedly, being of higher age (β[SE] = 0.001 [0.0003]; P = .006), where as having a diagnosis of MCI was associated with accelerated loss of FDG signal, as expected (β[SE] = −0.015 [0.044]; P = .009).

In longitudinal modeling of FDG signal in the low t-tau/ $A\beta_{42}$ subjects there was no association between baseline CSF ferritin and change in FDG PET signal over 5 years of follow up (β[SE]: 0.029 [0.049]; P = .554, Table 4) or when the models were restricted to any shorter follow up (data not shown). Fig. 1 illustrates the association of CSF ferritin with longitudinal changes in FDG PET in strata of Aβ pathology and ferritin (median dichotomisation).

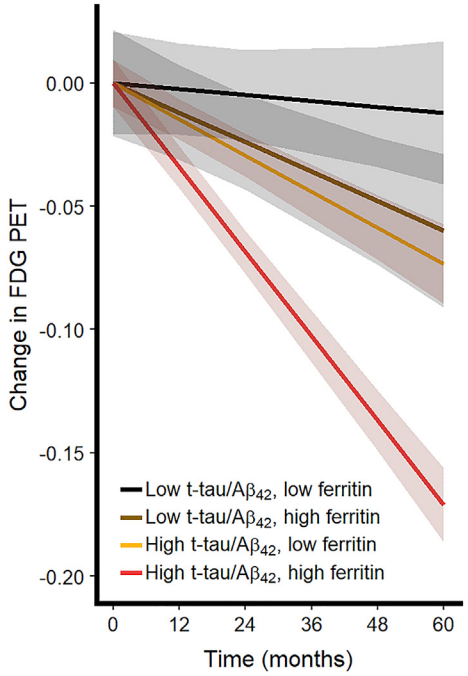

Fig. 1. Ferritin in the cerebrospinal fluid is associated with a decline in FDG-PET in people with high t-tau/$A\beta_{42}$. The figure represents mean change in FDG PET (+/−standard error). High and low ferritin groups were defined using the median ferritin value. β-amyloid pathology group was defined with t-tau/$A\beta_{42}$ ratio < 0.27 for low pathology and ≥0.27 for high pathology. Standard error of the mean is represented in grey shading for low t-tau/$A\beta_{42}$ ratio group, and red shading for high t-tau/$A\beta_{42}$ ratio. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

4. Discussion

Here we report that CSF ferritin levels predict decline in FDG PET over 5-years of follow-up among ADNI participants with underlying Aβ pathology. While we did not find evidence that CSF ferritin levels are elevated during the course of the disease, and they were also not associated with cross-sectional FDG signal, those people with evidence of AD pathology and who also had comparatively high CSF ferritin levels (but still within the normal range) were at higher risk of brain hypometabolism. These findings accord with previous reports on brain iron, measured by QSM or CSF ferritin (in the same cohort as the present

study), which also predicted future cognitive decline and brain atrophy (Ayton et al., 2017a; Daugherty et al., 2015). Results from this study in combination with previously reported findings reveals the utility of CSF ferritin levels in predicting decline in FDG signal and demonstrates the robust performance of CSF ferritin as a prognostic biomarker for several outcome measures in the AD prodrome. This study also adds evidence to the growing literature demonstrating iron as a risk factor in the pathogenesis of AD.

The association of CSF ferritin levels with change in FDG signal over time was only observed in people with high CSF t-tau/$A\beta_{42}$ ratio, which may indicate that iron becomes toxic in the brain when Aβ pathology is present. Iron may propel neurodegeneration in the presence of AD proteopathy by catalysing oxidative stress through the Fenton reaction (Winterbourn, 1995), or induce cell death by ferroptosis (Dixon et al., 2012).

A limitation in the interpretation of our results is that CSF ferritin is not a direct measure of iron levels in the brain. Ferritin may become elevated with inflammation, but we previously showed that other markers of neuroinflammation are poorly correlated with ferritin in the ADNI cohort (Ayton et al., 2015b). Even if inflammation is a feature of AD pathogenesis, it seems that this is not reflected by changes in CSF ferritin levels because CSF ferritin levels are not increased with either the AD proteopathy or by clinical diagnosis. FDG PET has also been used as a marker of inflammation (Vaidyanathan et al., 2015), however in this case the FDG uptake is increased in inflamed cells, whereas the FDG signal declines during the natural history of AD. We also found that CSF ferritin levels were not associated with baseline FDG PET signal, therefore it is unlikely that CSF ferritin levels report inflammatory changes reflected by FDG PET.

Therefore, it is likely that brain iron level underlies the signal of CSF ferritin and, if so, the present study provides further evidence for a role of iron in AD, and supports the therapeutic strategies of targeting iron and ferroptosis pathways to slow disease progression. But regardless of what underlies the ferritin signal, this study demonstrates the potential utility of CSF ferritin as a predictive biomarker of disease progression in the prodromal stages of AD. The need for prognostic biomarkers which add value to biomarkers for β-amyloid (CSF t-tau/$A\beta_{1-42}$, or PET) is made obvious by the fact that 30% of cognitively normal people over the age of 65 have high plaque burden (Rowe et al., 2013), yet exhibit variable rates of decline over the near term (Lim et al., 2014). In the present study, CSF ferritin levels were able to stratify risk of future hypometabolism in people with high pathology. Brain hypometabolism reflects reduced synaptic function and glucose utilisation of neurons and glia in the brain, and is a downstream marker of neurodegeneration that has been shown to be associated with increased risk of future cognitive decline (Cabral et al., 2015; Herholz et al., 2011). Thus, iron may act to drive disease progression in the prodromal stages of AD, and CSF ferritin may be an accessible biomarker to investigate this chemistry and, in clinical settings, prognosticate risk for AD.

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Author disclosures

Dr. Bush is a shareholder in Prana Biotechnology Pty Ltd., Cogstate Pty Ltd., Eucalyptus Pty Ltd., Mesoblast Pty Ltd., Brighton Biotech LLC, Nextvet Ltd., Grunbiotics Pty Ltd., Collaborative Medicinal Development LLC, and a paid consultant for Collaborative Medicinal Development. Drs. Ayton, Diouf, and Bush, have a filed a provisional patent that contains data from this manuscript. Drs Ayton and Bush have received funding relevant to this study from the NHMRC, Alzheimer's Association, Alzheimer's Research UK, The Michael J. Fox Foundation for Parkinson's Research, and Weston Brain Institute.

Author contribution

Diouf- Data modeling, preparation of figures and tables. Fazlollahi-FDG data and methods, wrote manuscript. Bush- Supervised analysis, edited manuscript. Ayton- Scientific concept, wrote manuscript, data modeling.

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