Patterns of Hypometabolism Can Suggest Frontotemporal Dementia in Clinically Diagnosed Alzheimer’s Disease Subjects Enrolled in the Alzheimer’s Disease Neuroimaging Initiative

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INTRODUCTION

The Alzheimer’s Disease (AD) Neuroimaging Initiative (ADNI) is a $60 million, 5-year public-private partnership with a primary goal of testing whether biomarkers such as serial magnetic resonance imaging (MRI), positron emission tomography (PET), and neuropsychological assessment can be used to measure the progression of mild cognitive impairment and AD.

A major challenge to initiatives such as ADNI is the complex nature of neurodegenerative diseases, many of which have overlapping presentations. These conditions have different prognoses and symptomatic treatments, but are often difficult for clinicians to differentiate.

The enrollment of these patients without AD into initiatives and clinical trials could be diluting treatment effects and producing inaccurate results. Consequently, it is essential that biomarkers are developed that can aid in the reliable distinction of different forms of neurodegenerative disease.

One method that has shown promise is measuring cerebral glucose metabolism using positron emission tomography with [18F] fluorodeoxyglucose (FDG-PET). This test can generate contrasting patterns of hypometabolism. In one study, the use of FDG-PET improved the accuracy of the clinical diagnosis of AD vs. FTD by 11% when FDG-PET with clinical scenario was used rather than the clinical scenario alone.

The purpose of this study was to determine the prevalence of subjects with a pattern of glucose metabolism highly consistent with FTD within the ADNI clinically diagnosed AD population. This examination is important to demonstrate that these subjects may not be reliably identified on a clinical basis alone.

HYPOTHESES

• Some subjects enrolled in ADNI who were clinically diagnosed as having AD have a pattern of hypometabolism consistent with FTD.
• Other data such as demographics, MRI structural information, and neuropsychological testing will help differentiate the two groups.

METHODS

Source Data: The data in this project was acquired through the Alzheimer’s Disease Neuroimaging Initiative (ADNI) database (wwwinformatics.ucsd.edu/ADNI). 97 Subjects from within the “mild Alzheimer’s Disease” category who had received an FDG-PET brain scan shortly after a standardized baseline clinical evaluation were selected. Raw FDG-PET image files were downloaded for all subjects. 3D-FDG-PET brain scan shortly after a standardized baseline clinical evaluation were performed.

Statistical analysis was performed to determine consistency among raters. Additional information such as demographics, MRI structural data, neuropsychological testing, and cerebral spinal fluid (CSF) measures were also downloaded from ADNI. Statistical differences between the two groups were compared by a student t-test (two tailed, equal variance).

RESULTS

After the first round of classification, the raters classified 88 of the 97 FDG-PET scans alike, giving an overall agreement rate of 0.918 (k = 0.727). After a consensus discussion 15 subjects were found to have a pattern of hypometabolism consistent with FTD (prevalence = 15.5%). The FTD-like group consisted of 10 males and 5 females and had an average age of 80.02 years. The non FTD-like group had 48 males and 34 females with an average age of 74.98 years. The age difference was significant (p = 0.014). Data from MRI structural information, neuropsychological testing and CSF can be seen on table 1 and table 2.

CONCLUSIONS

• Many subjects enrolled in ADNI who were clinically diagnosed as having AD show a pattern of hypometabolism consistent with FTD.
• Data such as demographics, MRI structural information and neuropsychological suggest that there are significant differences between the two groups.
• Impressive of whether or not subjects with a FTD pattern of hypometabolism are found to have AD pathology at autopsy, this group of subjects may represent a significant cause of subject heterogeneity that has a sizeable effect of outcomes.
• Additional research testing what effect the exclusion of those with a FTD pattern of hypometabolism has on outcome measures needs to be completed. If there is a significant benefit in excluding those with an FTD pattern of hypometabolism, alternative enrollment strategies using FTG-PET as a screening tool may be advantageous.

Future Directions

• Although the use of FTG-PET to distinguish AD from FTD has been shown to be highly accurate, a definitive diagnosis of these patients cannot be made without autopsy confirmation. It may be the case that AD is occasionally represented by a frontal predominant pattern of hypometabolism. Molecular imaging, such as Pittsburgh compound B (PiB) PET, looking for the presence of beta-amyloid deposits would be a useful tool in this regard and should highly compliment the use of FTG-PET as a screening tool.

ACKNOWLEDGEMENTS AND REFERENCES

This project was supported by: the Alzheimer’s Image Analysis Laboratory, the University of Utah Center for Alzheimer’s Care, Imaging, and Research, and the University of Utah Medical Student Summer Research Program. Special thanks to Richard King, Norman Foster, Angela Wang, Jeanette Berberich, Brandon Brown, David Brayford, and Andres Morgado.

Methods

Image Classification: Two neurologists (Dr. Norman Foster, Dr. Richard King) with experience in dementia care and FDG-PET imaging served as raters. To establish a consistent technique to interpretation, the raters completed a training session using criteria validated in a previous study. Once training was complete, a modified Delphi procedure was used to classify PET images as FTD-like or Non-FTD-like. An inter-rater reliability analysis using the Kappa statistic was performed to determine consistency among raters.

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