P4-362

BRAIN GLUCOSE METABOLISM IN PATIENTS WITH MILD TO MODERATE ALZHEIMER'S DISEASE BEFORE AND AFTER SIX MONTHS TREATMENT WITH INTRAVENOUS IMMUNOGLOBULIN (OCTAGAM 10%): A PHASE II DOUBLE BLIND, PLACEBO-CONTROLLED MULTI-CENTER STUDY

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Background: Octagam® 10% is a human immunoglobulin solution for intravenous administration (IVIG) first developed for treating immune deficiency. We now assess the effect of six months treatment with IVIG versus placebo on cerebral glucose metabolism in patients with mild to moderate Alzheimer's disease (AD). **Methods:** 58 patients with mild to moderate AD were included, of whom 55 patients received a baseline [18F]FDG PET and MRI scan. This was followed by treatment with Octagam® 10% over 24 weeks, consisting of either (1) six infusions at 4-week intervals of low, medium or high dose (0.2, 0.5, or 0.8 g/kg) or (2) 12 infusions at 2-week intervals (0.1, 0.25, or 0.4 g/kg) (3) or corresponding placebo at 2- or 4-week intervals. After six months, 44 patients had a follow-up [18F]FDG PET scan. After coregistration of the FDG-PET scans to the individual MRI, spatial normalization and uptake scaling using global mean normalization, both automated region of interest analyses and statistical parametric mapping using SPM5 were performed. **Results:** Voxel-wise analyses ($p < 0.001$, uncorr.) revealed a relative decrease of glucose metabolism in bilateral hippocampal / temporomesial brain regions at six months in patients receiving placebo by 4.3 ± 1.8%. In the same cluster, brain glucose metabolism was unaltered in patients receiving low (0.4 ± 3.5%) or medium dose (-0.9 ± 2.9%), and decreased by 1.8 ± 5.0% in patients receiving high dose IVIG at the follow-up scan. Therefore all treatment patients showed significantly less decrease of glucose metabolism in this brain region during follow-up compared to placebo patients ($p < 0.01$). Furthermore IVIG-treated patients displayed significantly increased glucose metabolism in widespread parietal and frontal brain regions at follow-up relative to baseline ($p < 0.05$, FDR-corrected). **Conclusions:** Treatment of mild to moderate AD patients with Octagam® 10% for six months significantly attenuated the decline in cerebral glucose metabolism typically seen in the hippocampal / temporomesial brain region, in affected AD patients. Furthermore the IVIG group showed a significant increase in FDG-uptake in the parietofrontal cortex, which in part is usually a preserved brain region in AD patients and might be related to compensatory mechanisms. These results corroborate earlier findings with IVIG in AD and encourage further longer studies with IVIG in larger patient cohorts.

P4-363

APOE e4 STATUS MODULATES THE ASSOCIATION OF PLASMA AND CORTICAL Aβ: RELATION OF PLASMA Aβ AND [11C]PIB PET IN THE ADNI COHORT

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Background: Plasma levels of beta-amyloid (Aß) are potential biomarkers for Alzheimer's disease (AD). Measuring plasma Aß levels is a minimally invasive and relatively inexpensive procedure. However, to date only one study has investigated the relationship of plasma Aß with brain Aß as measured by [11C] Pittsburgh Compound-B (PiB), a positron emission tomography (PET) ligand [1]. We performed a whole-brain voxel-wise analysis to determine the association of plasma Aß with brain Aß as measured by PiB uptake using participants in the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort. **Methods:** Ninety-six ADNI participants with initial PiB-PET scans [2] and plasma measurements of Aß1-40 and Aß1-42 at the time of scan were used in this study. Correlations between plasma Aß1-40, Aß1-42 and their ratio (Aß1-40/Aß1-42) with PiB uptake were obtained on a whole-brain voxel-level using a multiple regression approach in SPM5. An interaction term was included in the model to determine significant interactions of plasma Aß with APOE status (e4 positive vs. e4 negative groups). A voxel-level threshold of $p < 0.005$ (uncorrected) and a cluster size threshold of $k = 50$ contiguous voxels were used to determine significance. **Results:** Analysis of the plasma Aß1-40/Aß1-42 by APOE status interaction yielded a cluster in the left inferior frontal gyrus (MNI peak value coordinates: $x = -40$, $y = 18$, $z = -6$; $k = 6152$ voxels; cluster-level pcorrected<0.001) (Figure 1(a)). Mean PiB uptake value for this cluster was extracted for each participant. A positive relationship between plasma Aß1-40/Aß1-42 and mean PiB uptake was observed in the e4 negative group (Slope = 0.250, $p = 0.001$); but not in the e4 positive group (Slope = -0.050, $p = 0.378$) (Figure 1(b)). APOE status alone explained 13% of the variation in mean PiB uptake. Inclusion of plasma Aß1-40/Aß1-42 and the interaction term in the model increased the variance explained to 23%. **Conclusions:** Plasma and brain Aß are associated but this relationship is modulated by APOE e4 status. These results support the utility of plasma Aß as a potential AD biomarker but underscore the importance of genetic context in interpretation of plasma levels. 1. Lui et al. J Alzheimers Disease 20(2010);1233-1242. 2. Jagust et al. Alzheimer's Dement 6(2010);221-229.

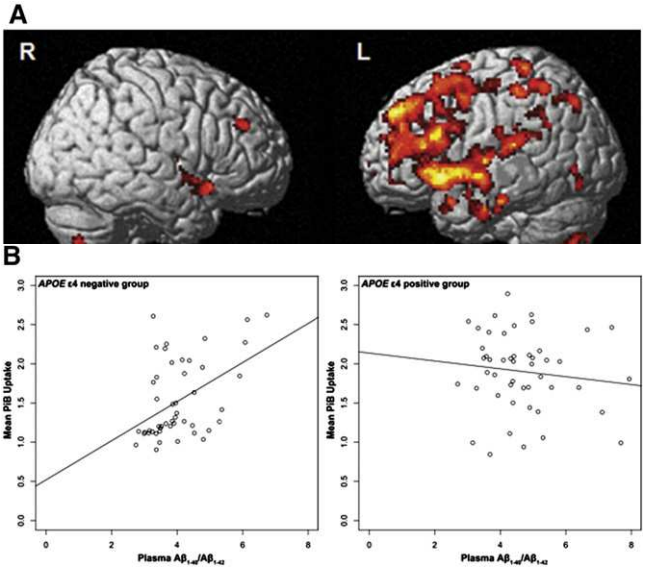

Figure 1. (a). Visualization of the interaction term results from the Statistical Parametric Mapping analysis. The regions with significant (uncorrected $p<0.005$, cluster size$\geq$50 voxels) PiB uptake are shown in the color. The red-to-yellow scale depicts increasing magnitude of the depth-weighted interaction t-statistics. (b). Scatterplot of mean PiB uptake from the significant cluster identified in the whole-brain voxel-wise analysis vs. plasma $A\beta_{1\text{-}40}/A\beta_{1\text{-}42}$ in the *APOE* ε4 negative group (Left) and *APOE* ε4 positive group (Right).

P4-364

CHARACTERISTICS OF SENILE COGNITIVE FUNCTION ON MULTICHANNEL NIRS: COMPARISON WITH DEMENTIA PATIENTS

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Background: Early discovery and treatment of dementia are important. Our facility performs a 'forgetfulness checkup' 6 times a year for elderly persons