CHOROID PLEXUS: FUNCTIONAL AND STRUCTURAL CHANGES IN HEALTHY SUBJECTS IN RISK OF DEVELOPING ALZHEIMER’S DISEASE

Pablo Garcia-Polo1,2, Virginia Mata1,3, Gonzalo Pajares4,5, Daniel Garcia-Frank1, Norberto Malpica1, Ana Ramos5, Juan Alvarez-Linera1, Eva Carro5, and Juan Antonio Hernandez-Tamames6

1LAIMBIO-DTE, Universidad Rey Juan Carlos, Mostoles, Madrid, Spain; 2Center for Biomedical Technology U.P.M., Pozuelo de Alarcon, Madrid, Spain; 3Center for Alzheimer’s Disease Queen Sofia Foundation CIEN Foundation, Madrid, Spain; 4Center for Alzheimer’s Disease Queen Sofia Foundation CIEN Foundation, Madrid, Spain; 5IdiPAZ, Madrid, Spain; 6Radiología, Hospital 12 de Octubre, Madrid, Spain; 7Hospital Ruber Internacional, Madrid, Spain; 8Neurology-Neuropsychology, Hospital 12 de Octubre, Madrid, Spain

Target audience: Physicians, psychologists, radiologists and MR researchers.

Purpose: To find abnormal features based on MR imaging of the Choroid Plexus (CP), both structural and physiological, in order to obtain early biomarkers for probable Alzheimer’s disease (AD) development.

Introduction: Some previous works have reported functional alterations in the choroid plexus. In this work, we investigate the integrity of the CP as a biomarker, other than volume loss of hippocampi, entorhinal cortex and amygdala, in the research criteria of AD. The CP is a structure, consisting mainly of capillaries in the brain ventricles, where cerebrospinal fluid is produced. It works as a recycler and cleaner of metabolites and toxins in the CSF. Anatomical 3D T1 weighted images have been widely used to assess the volume and thickness of cortical and subcortical structures. Here we include the analysis of perfusion images through the Arterial Spin Labeling (ASL) technique and Diffusion Weighted Imaging (DWI) to evaluate additional physiological and micro structural changes in CP. ASL is a non-invasive MRI technique, which allows the quantification of regional cerebral blood flow (rCBF) without contrast agents by labeling a small bolus of blood at the level of the carotid arteries with a radiofrequency pulse. This technique has shown its validity in detecting changes in mild cognitive impairment (MCI) and AD patients. DWI, derived Fractional Anisotropy (FA) and Mean Diffusivity (MD) maps allow for studying the easiness of movement of free water in the brain. Our data comes from the Vallecas Project which is a longitudinal study that evaluates normal ageing in a cohort of more than 600 healthy elder people (ages between 70y and 85y). The prevalence (13%) of AD in people older than 65 years suggests that a certain number of those subjects will develop AD in the next years. We hypothesize that changes in the CP, that may occur in the very early stages of AD, simultaneously or prior to gray matter loss in hippocampi, entorhinal cortex and amygdala, are detectable with MR imaging.

Methods: 632 subjects underwent an MR scan on a 3T Sigma HDx MR scanner (GE Healthcare, Waukesha, WI) using an eight-channel phased array coil. The first sequence was a 3DT1w SPGR with a TR=10.024ms, TE=4.56ms, TI=600ms, NEX=1, acquisition matrix=288x288, full brain coverage, resolution=1x1x1mm, flip angle=12. The second sequence was a 3D pCASL pulse sequence with full brain coverage, matrix size= 128x128, resolution=1.875x1.875x4mm, flip angle = 155, transit time=2.025s, TR=4.733s and TE=9.812ms was used to generate the rCBF maps. The third sequence was a DWI consisting of one reference image (b=0 s/mm²) followed by 21 images measuring 21 directions (b = 800 s/mm²) isotropically distributed in space. Parameters of the DWI sequence were: TR=9200 ms, TE=86.7 s, resolution = 1.875x1.875x3mm, flip angle=90 and axial acquisition with full brain coverage. The FA and MD maps were calculated using Functool software (GE 4.3. Advantage Windows). All 3DT1w were processed with Freesurfer in order to obtain the cortical and subcortical volumes for each subject. The left and right hippocampi volumes (LHV, RHV) were normalised by the total grey matter volume (GM). This normalise measure allowed us to divide the sample into three groups: Control group (LHV, RHV)>mean hippocampus (MH)+1std., mean group (MH-2std.<LHV, RHV)<MH+1std.) and probable AD group (PAD) (LHV, RHV<MH-2std.). We performed subsequent analyses comparing an age and gender matched Control (25subjects) and PAD (25subjects) groups. The 50 selected 3DT1w images were processed with the standard SPM DARTEL pipeline and analysed with a General Linear Model (GLM) by means of a two sample t-test. The rCBF maps of the Control and PAD groups were processed with the ASL Toolbox to obtain smoothed (FWHM=4x4x4mm), Partial Volume Effect corrected and MNI normalised perfusion maps for each subject. Again, statistical maps, using a two sample t-test analysis within the GLM were obtained. DTI post-processing was performed using Statistical Parametric Mapping toolbox.

Results: Fig. 1 shows the results of gray matter changes between Control and PAD groups (p<0.05). As expected, there is LH and RH volume loss in the PAD group. No CSF changes or increase in ventricle volume are found. Fig. 2a shows volume loss (p<0.01) in the CP structure (classified as GM by SPM) for PAD. Fig. 2b shows hypoperfusion patterns (p<0.001) in CP for PAD. Fig. 2c and 2d show a decrease in FA (p<1e^-8) and an increase in MD (p<1e^-8) for PAD CP.

Discussion: A significant reduction in left and right hippocampus volume is found, supporting the idea that the PAD group is in risk of developing AD. Hypoperfusion and FA and MD changes in CP appear in those people in risk of developing AD. No increase in ventricle size or CSF volume is found, suggesting that the integrity of CP structure is affected both structurally and functionally in subjects in risk of developing AD.

Conclusion: We suggest that CP structure plays a major role in the development of AD and its study by MR imaging should be further included in the research for the early diagnosis of AD.

Acknowledgements: This work has been partially granted by the project TEC2012-39095-C03-01 of the Spanish Ministry of Economy and Competitiveness.

References:
[4] 2012 Alzheimer’s disease, facts and figures; Alzheimer’s Association; Alzheimer’s & Dementia; 2012; 8(2)