CHOLINERGIC SUBCORTICAL HYPERINTENSITIES: RELATIONSHIPS WITH COGNITIVE DYSFUNCTION AND HIPPOCAMPAL ATROPHY

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BACKGROUND

The presence of subcortical hyperintensities (SH) strategically located within the cholinergic pathways is believed to reflect cerebrovascular compromise of the cholinergic system in dementia [1, 2]. Hippocampal (HP) atrophy is a commonly used biomarker for Alzheimer’s disease (AD) and has been shown to be associated with cognition and memory dysfunction [3, 4, 5].

PURPOSE & HYPOTHESIS

To examine the relationships between vascular burden in the cholinergic pathways, HP atrophy, and cognition, in a sample of AD patients (n=234).

We hypothesized that:

• Severity of chSH volumes would be related to executive and memory functioning.

• Hippocampal atrophy would relate to this strategic vasculopathy.

METHODS

Statistical analyses were conducted to examine the relationships between chSH volumetric data, neuropsychological data and HP volumetric data.

Subjects were evenly divided into low (n=117) and high (n=117) chSH groups based on the median split, after head size correction.

MRI-derived volumetrics:

• The cholinergic mask and chSH volumes were obtained using SABRE [6] and a modified version of Lesion Explorer (LE) [7], see figure 2 & 3. This method was highly correlated with the Cholinergic Pathways Hyperintensities Scale (CHIPS) [1] (r=0.84, p<0.001), see figure 1.

• Automatic HP volumes were acquired using the SunnyBrook Hippocampal Volumetry (SBHV) Tool [8], an in house multi-atlas segmentation tool.

• The individualized cholinergic pathway mask encompassed the lateral cholinergic fibre projections through the white matter starting from the most inferior point of the external capsule, reaching superiority to the centre of the centrum semiovale, laterally to the insula and medially to the putamen, see figures 2 & 3.

Neuropsychological Assessment [9]:

EXECUTIVE:

• Verbal Fluency ‘FAS’ Test

• Wisconsin Card Sort Testing

VISUOSPATIAL:

• Benton Judgement of Line Orientation Test

• Rey-Osterrieth Complex Figure Copy Test

MEMORY:

• California Verbal Learning Test

• Visual Reproduction

• Dementia Rating Scale, Memory

RESULTS

A significant difference was found between low and high chSH group memory scores (p<0.05, d=0.22) independent of age, sex, YOE, BPF, DS score and Global SH, see figure 5.

DISCUSSION

This study presents a novel method that allows for volumetric quantification of SH within the cholinergic tracts. Strategic signs of SVD within the cholinergic projections may be associated with specific cognitive dysfunction in cases with high cholinergic SH load. This suggests a possible threshold effect [10, 11], where cognitive dysfunction is only detectable when a chSH threshold is exceeded. Damage to the cholinergic fibres, independent of global SH may be related to HP atrophy and memory dysfunction in AD. More research is needed to fully understand the etiology and impact of this damage in order to assess the efficacy of cholinergic therapies in AD with SVD.

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