Vascular Pathology and Hippocampal Atrophy in Alzheimer's Disease: Insights from the National Alzheimer's Coordinating Centre Database

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1. BACKGROUND

- Alzheimer's Disease (AD) is a global health challenge, with social and economic consequences. Developing effective therapy regimen relies on critical understanding of the pathogenesis.
- The classic plaques and tangles theory have dominated the AD research field, however, many clinical trials targeting these hallmarks have failed to progress. The heterogeneity of AD also suggests that other mechanisms are involved.
- Vascular pathologies are believed to play a major role in the development and progression of AD, with two-way interactions existing between vascular dysfunction and AD neuropathology.[1,2]

2. AIM AND OBJECTIVES

The **aim** of this study is to analyse the association between various vascular pathologies and degree of hippocampal atrophy (HA) in AD patients.

Objectives:

- To investigate the association between large and small vessel disease and HA in AD
- To explore the potential link between vascular disease risk factors and HA in AD
- To analyse whether MRI can be used to predict the severity of HA in AD

3. METHODS

- A data request was submitted to and approved by the National Alzheimer's Coordinating Centre (NACC)
- The data utilised were UDS (demographics), neuropathology (NP), biomarker and imaging data sets.
- The data was filtered according to the criteria (see Figure 1 below)
- Participants are said to be pathologically confirmed with AD when the Braak stage is V or VI (B3)

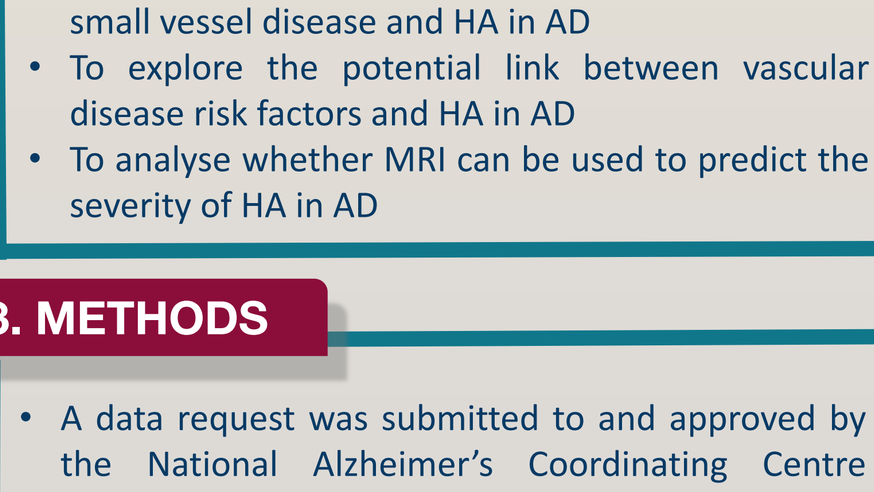

Figure 1: Participant Selection

- Descriptive statistics and univariate analyses were performed for all variables
- Chi-square and Cramer's V for categorical variables
- ANOVA or Kruskal-Wallis for continuous variables
- Simple and Multivariate regression analyses for variables associated with severity of HA

4. RESULTS

Of the vascular pathologies, severity of HA was most strongly associated with the following:

1. **Cerebral amyloid angiopathy** (CAA), p<0.001
2. **Atherosclerosis of the Circle of Willis,** p=0.002
3. **Arteriolosclerosis**, p=0.000
4. **White matter rarefaction** (WMR), p<0.001

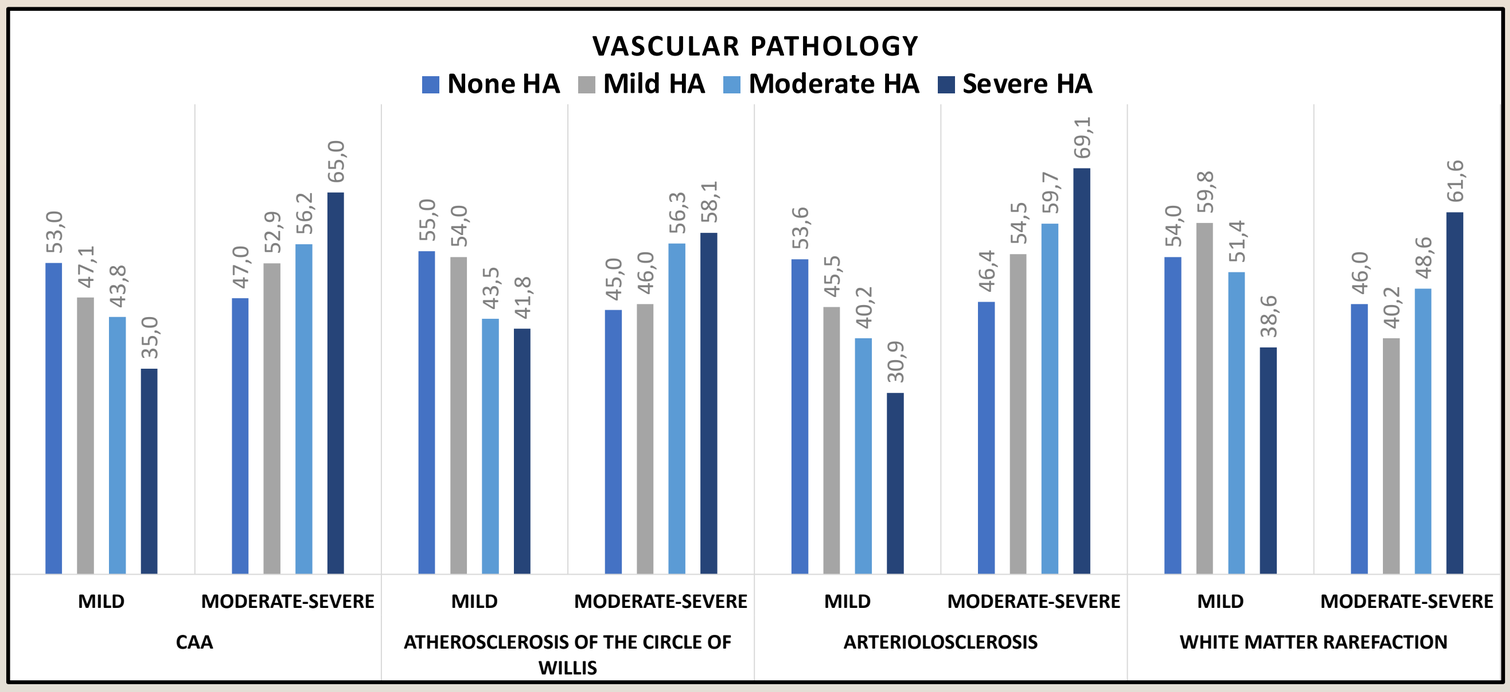

Figure 2: Vascular Pathologies across 4 Levels of HA

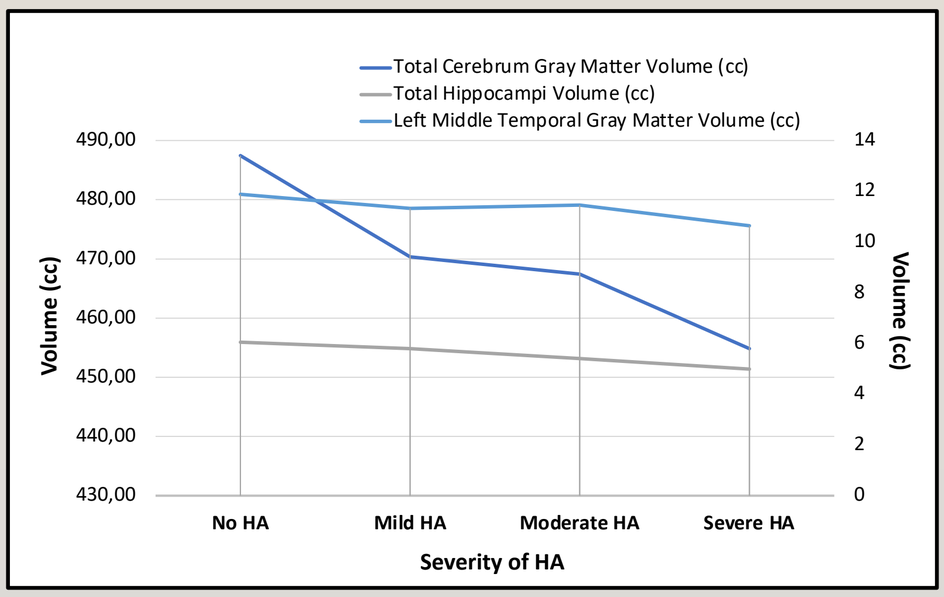

Figure 3: Brain Regional Volumes across 4 Levels of HA

Brain volumes in MRI associated with severity of HA:

1. Total cerebrum gray matter, p=0.039
2. **Total hippocampi volume**, p<0.001
3. Left middle temporal gray matter, p=0.009

Furthermore, it was observed that white matter hyperintensity is increased in patients with any degree of HA in comparison to no HA

Table 1: Simple Regression of Individual Variables

Univariate analysis of predictors of HA	*F*	*P*	*R-squared (adjusted)*
Vascular Pathology			
CAA	18,06	p=0.000	1.38%
Atherosclerosis of CoW	**13,65**	**p=0.000**	**1.70%**
Arteriolosclerosis	**28,36**	**p=0.000**	**2.28%**
WMR	17,01	p=0.000	1.88%
Imaging (volume)			
Cerebrum gray matter	8,01	p=0.005	3.69%
Total hippocampus	**27,5**	**p=0.000**	**12.65%**
Left middle temporal lobe	8,78	p=0.003	4.08%
General Pathology			
Cortical Atrophy	**161,47**	**p=0.000**	**25.56%**
Lobar Atrophy	4,5	p=0.034	0.24%
Hippocampal Sclerosis	**63,98**	**p=0.000**	**4.13%**
Risk Factors			
APOE e4 allele	**6,27**	**p=0.002**	**0.82%**
Atrial Fibrillation	**4,46**	**p=0.001**	**0.93%**

Significant univariate predictors and model from multivariate regressions are shown here, with **cortical atrophy, hippocampal sclerosis and atherosclerosis of CoW** as predictors.

Table 2: Multiple Regression

Multivariate model of predictors of HA	
Model Summary	
n	505
R^2	32.39%
Adjusted R^2	31.59%
Significant F change	40.33
Coefficients, B (95% CI for B)	
Cortical atrophy	2.26 (2.01-2.52)
Hippocampal Sclerosis	0.74 (0.42-1.06)
Atherosclerosis of CoW	0.73 (0.48-0.98)

5. CONCLUSION

Cerebral amyloid angiopathy, atherosclerosis in the Circle of Willis, arteriolosclerosis and white matter rarefaction are the vascular pathologies associated with the severity of HA. Also associated with the severity of HA are cortical atrophy and hippocampal sclerosis, along with APOE e4 genotype and atrial fibrillation as risk factors.

6. FUTURE WORKS

Future research can look into the particular molecular mechanisms of the pathophysiology of vascular dysfunction in AD and other neurodegenerative diseases.

7. REFERENCES

1. Scheltens P, De Strooper B, Kivipelto M, Holstege H, Chételat G, Teunissen CE, et al. Alzheimer's disease. The Lancet: Elsevier B.V.; 2021. p. 1577-90.
2. Rius-Pérez S, Tormos AM, Pérez S, Taléns-Visconti R. Vascular pathology: Cause or effect in Alzheimer disease? Neurología (English Edition). 2018;33(2):112-20.