Ageing Research Reviews 47 (2018) 41–48

Contents lists available at ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Cerebral small vessel disease and the risk of Alzheimer's disease: A systematic review

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ARTICLE INFO

Keywords:
Small vessel disease
Alzheimer's disease
White matter lesions
Aβ pathology
Cerebral microbleeds

ABSTRACT

Background: Cerebral small vessel disease (CSVD) comprises a variety of disorders affecting small arteries and microvessels of the brain, manifesting as white matter hyperintensities (WMHs), cerebral microbleeds (CMBs), and deep brain infarcts. In addition to its contribution to vascular dementia (VaD), it has also been suggested to contribute to the pathogenesis of Alzheimer's disease (AD).

Method: A systematic review of the literature available on Medline, Embase and Pubmed was undertaken, whereby CSVD was divided into WMHs, CMBs and deep brain infarcts. Biomarkers of AD pathology in the cerebrospinal fluid or plasma, or positron emission tomographic imaging for amyloid and/or tau deposition were used for AD pathology.

Results: A total of 4117 articles were identified and 41 articles met criteria for inclusion. These consisted of 17 articles on vascular risk factors for clinical AD, 21 articles on Aβ pathology and 15 articles on tau pathology, permitting ten meta-analyses. CMBs or lobar CMBs were associated with pooled relative risk (RR) of AD at 1.546, (95%CI 0.842–2.838, z = 1.41 p = 0.160) and 1.526(95%CI 0.760–3.063, z = 1.19, p = 0.235) respectively, both non-significant. Microinfarcts were associated with significantly increased AD risk, with pooled odds ratio OR at 1.203(95%CI 1.014–1.428, 2.12 p = 0.034). Aβ pathology was significantly associated with WMHs in AD patients but not in normal age-matched controls. The pooled β (linear regression) for total WMHs with CSF Aβ42 in AD patients was -0.19(95%CI -0.26–0.11, z = 4.83 p = 0.000) and the pooled r (correlation coefficient) for WMHs and PiB in the normal population was -0.10 (95%CI -0.11–0.30, 0.93 p = 0.351). CMBs were significantly associated with Aβ pathology in AD patients. The pooled standardized mean difference (SMD) was -0.453, 95%CI -0.697– -0.208, z = 3.63 p = 0.000. There was no significant relationship between the incidence of lacunes and levels of CSFAβ, with a pooled β of 0.057 (95%CI -0.050–0.163, z = 1.05 p = 0.295). No significant relationship was found between CMBs and the levels of CSFt-tau/CSFp-tau in AD patients (-0.014, 95%CI -0.556–0.529, z = 0.05 p = 0.960; -0.058, 95%CI -0.630–0.515, z = 0.20 p = 0.844) and cortical CMBs and CSF p-tau in the normal population (0.000, 95%CI -0.706–0.706, z = 0.00 p = 0.999).

Conclusions: Some CSVD markers were significantly associated with clinical AD pathology and may be associated with Aβ/tau pathology. WMHs and microinfarcts were associated with increased risk of AD. It remains unclear whether they precede or follow AD pathology.

1. Introduction

Alzheimer's disease (AD) is the most prevalent cause of dementia, accounting for about 60% of all cases. The pathological hallmarks of AD include but are not limited to extracellular amyloid plaques containing abnormal aggregates of amyloid-beta (Aβ) protein, intracellular neuronal fibrillary tangles (NFTs) composed of hyperphosphorylated tau protein, synapsis loss, neuronal death, mitochondrial dysfunction, oxidative stress and metabolic disorders neuroinflammation, and loss of cholinergic neurons. However, the molecular basis of AD remains controversial, and effective treatments are still not available (Ryan et al., 2015). In the last three decades, the interaction(s) between cerebrovascular disease (CVD) and AD have attracted much interest. Mixed AD/CVD pathology is commonly seen in patients with clinically

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https://doi.org/10.1016/j.arr.2018.06.002
Received 8 March 2018; Received in revised form 10 May 2018; Accepted 5 June 2018

diagnosed AD (Toledo et al., 2013), and this trend increases with age. Combined vascular and AD pathology is the leading cause of dementia in the very old (Schneider et al., 2007), with a debate on whether this is due to an additive effect of both pathologies on cognitive impairment, or it additionally represents an interaction between the pathologies.

Epidemiological studies have shown that AD and CVD share a series of common risk factors including age, hypertension in midlife, diabetes, smoking, hypercholesterolemia, hyperhomocysteinemia, and *APOE4* isoforms (Gorelick et al., 2011; Casserly and Topol, 2004; Jellinger and Attems, 2008). Cardiovascular risk factors such as atrial fibrillation have also been associated with the pathogenesis of AD (Toledo et al., 2012).The findings in animals are consistent with those of humans. High-fat/glucose induced diabetes II can result in insulin resistance and aggregate Aβ pathology in APP transgenic animal models (Ho et al., 2004; Yang et al., 2013; Mehla et al., 2014) and can be reversed by insulin (Vandal et al., 2014). It is also observed that type 2 diabetes mellitus(T2D can induce hyperphosphorylation of tau by altering glycogen synthase kinase 3β(GSK3β) (Ho et al., 2004; Ke et al., 2009) and protein phosphatase 2 A(PP2 A) (Papon et al., 2013).Chronic hypertension has been shown to accelerate amyloid deposition, blood-brain barrier (BBB) dysfunction, microglial cells activation and subsequent neuronal loss and cognitive impairment in AD transgenic models (Kruyer et al., 2015).Cholesterol and homocysteine levels were also found to affect AD pathogenesis in rodents (Maulik et al., 2013; Li et al., 2014).

There are pathobiological mechanisms that are shared by AD and vascular dementia (VaD), including oxidative stress, inflammation, mitochondrial disruption and metabolic dysfunction. However, the role of combined cerebrovascular pathology and AD in causing dementia is still under discussion, and data obtained from epidemiological and clinical-pathological studies regarding their relationship remain controversial. The molecular mechanisms linking CVD to AD are not fully understood. A possible reason is that there are limited animal models to accurately study reproducible vascular lesions and AD pathology. Most conclusions on the interaction of these two pathologies stems from clinical studies and AD models with vascular risk factors.

This systematic review examines all relevant clinical studies of defined AD risk and AD pathology, including Aβ and tau pathology, in individuals with WMHs, CMBs or deep brain infarcts, to explore the interactive effect of CVD on the development of AD.

2. Methods

2.1. Search strategy

We identified studies through searches of Medline and Embase (1996 to present) databases. The search terms used were: CSVD, including WMHs “(White matter hyperintensities) OR (white matter lesion) OR (white matter disease) OR (white matter change) OR (leukoaraiosis)”; CMBs “(microbleed) OR (microhemorrhage) OR (microhaemorrhage) OR ((“dot-like”) AND (susceptible* OR hemoside*)” and deep brain infarcts “Lacunes OR deep infarct OR subcortical infarct OR deep stroke OR subcortical stroke OR silent stroke OR silent brain infarct OR small vessel infarct or small vessel stroke OR lacunar stroke OR microinfarct or microscopic infarct OR etat crible”. The search strategy for CSVD referred to “Literature search methods and terms” concluded by Wardlaw (Wardlaw et al., 2013). The AD terms and AD pathology terms used included “Alzheimer’s disease, “amyloid beta-protein”, “Aβ”. “β-amyloid protein”. “PiB”. and “tau”. We identified relevant studies by reviewing titles and abstracts of identified articles and supplemented these by reviewing references to included articles.

2.2. Inclusion criteria

A study was selected from the initial search if it met the following criteria: (i) it described at least one cerebral vessel disease; (ii) it was a full length article published in a peer reviewed English language journal; (iii) the study design was either a longitudinal or cross-sectional study; (iv) the sample population was defined as normal, MCI, subjective cognitive impairment (SCI) or AD; and v)Clinical AD risk or Aβ/tau pathology were measured as dependent variables, and SVD as an independent variable.

2.3. Meta-analysis

Meta-analyses were conducted to include at least 2 independent published studies. The pooled ORs/RRs and 95% CIs were estimated for dichotomous study. For studies reporting continuous data, the standardized mean difference (SMD) was used, and the pooled SD was calculated as $\sqrt{\frac{(Ne-1)SDe^2+(Nc-1)SDc^2}{Ne+Nc-2}}$ (Where N_E and N_C are the sample sizes in the experimental and control groups, respectively, and SD_E and SD_C are their standard deviations.). When the SD_E was not shown in articles, we assumed SD_E was same as SD_C, with the formula of 95% CIs being SMD $\pm \sqrt{\frac{Ne+Nc}{Ne\times Nc}+\frac{SMD^2}{2(Ne+Nc)}}$. For meta-analyses for studies that used correlation coefficient as the ES, the r was transformed into Fisher’s z. Heterogeneity between studies was tested using the Q-statistic test ($p < 0.1$ indicates significant heterogeneity), and the degree of inconsistency across studies was quantified using the I2 statistic. We used random effects models considering the variability between study samples. Funnel plots were obtained to detect publication bias. All statistical analyses were conducted using Stata 12.0, and $p < 0.05$ was considered statistically significant.

3. Results

3.1. Search results

The search result has been summarized in Fig. 1. A total of 80 studies that met the inclusion criteria were included following review of title and abstracts. Of these, 40 articles were included; 40 articles were excluded due to: (i) all cause dementia was the outcome variable; (ii) AD risk or Aβ was an independent variable; (iii) the diagnosis was either vascular dementia or CAA; (iv) the article was a duplicate; and (v) the article was a review. We chose the more recent or comprehensive article when more than one article was found for the same population. There were few longitudinal studies on the effect of CSVD on AD. Additionally, 12 articles met our criteria for WMHs and AD risk, 15 articles for WMH and Aβ pathology, 8 articles for WMH and tau pathology, 3 articles for CMBs and AD, 9 articles for CMBs and Aβ pathology, 8 articles for CMBs and tau pathology,6 articles for deep brain infarcts and AD, 4 articles for deep brain infarcts and Aβ pathology, and 1 article for deep brain infarcts and tau pathology

3.2. WMHs and the risk of clinical AD

We identified 5 studies which investigated the relationship between WMHs and AD in the general population (Kuller, 2003; Meguro et al., 2007; Rosano et al., 2007; Brickman et al., 2015a; Miwa et al., 2016). Another 7 studies were conducted in MCI populations (Tapiola et al., 2008; Staekenborg et al., 2009; Hertze et al., 2013; Eckerstrom et al., 2015; Kim et al., 2015; Nolze-Charron et al., 2015; Tosto et al., 2015). 10 studies applied the National Institute of Neurological and Communicative Diseases and Stroke-AD and Related Disorders Association (NINCDS-ADRDA) diagnostic criteria (McKhann et al., 1984). The methods used for the quantitation of WMHs were various in these studies, including the age-related white matter changes (ARWMC) scale (Wahlund et al., 2001), Fazekas scale (Fazekas et al., 1987), Scheltens scale (Scheltens et al., 1993), CREDOS WMH visual rating scale (Noh et al., 2014), the Atlas scale (Yue et al., 1997) and WMH volumes (Schwarz et al., 2009). In 3,375 participants of the Cardiovascular