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Imaging markers of cerebrovascular pathologies: Pathophysiology, clinical presentation, and risk factors

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Abstract Cerebrovascular pathologies (CVPs) are common pathologies associated with age-related cognitive decline along with Alzheimer disease pathologies. The impact of CVP on the prevalence of dementia is increasingly being recognized. The goal of this review is to improve our understanding of the pathophysiological underpinnings and the multimodal MRI and PET imaging changes that are associated with the hallmarks of CVP. This knowledge will facilitate the development of early detection, intervention, and prevention strategies that may contribute to lowering the risk of dementia. In this review, we will first discuss currently known risk factors of CVPs including cardiovascular, lifestyle, genetic, sex differences, and head injury. Next, we will focus on the pathophysiology of CVPs and their impact on neurodegeneration and downstream cognitive impairment. Specifically, we will discuss three of the most common cerebrovascular lesions seen on MRI: white-matter hyperintensity, microbleeds, and infarcts. Finally, we will discuss the unanswered open questions in this field.

Keywords: Cerebrovascular; Pathophysiology; Imaging; Aging

1. Introduction

Cerebrovascular pathologies (CVPs) are one of the most prevalent pathologies in older adults [1,2]. There is a monotonic age-related increase in the prevalence of cases with CVP, and it has been noted that there is detectable pathological evidence of CVP in 75%–90% of persons over age of 90 years [3]. The three main vessel disorders frequently underlying CVP are atherosclerosis (degenerative disorder of large- and medium-sized arteries), cerebral small-vessel disease, and cerebral amyloid angiopathy (CAA) [4]. All three disorders are related to cerebral infarction and hemorrhage. The pathological hallmarks of CVP are the presence of microvascular changes (white-matter hyperintensities [WMHs], microbleeds, and microinfarcts) and macrovascular changes (subcortical and cortical macroinfarcts) in the brain. With the advent of sophisticated MR and PET imaging methodologies, many previously invisible cerebrovascular changes can now be detected using multimodal imaging techniques.

Recently, there has been renewed interest in the field of CVP research because it contributes significantly to the risk of dementia by lowering the threshold of dementia detection [5] and is one of the more preventable pathologies associated with cognitive impairment [6]. Increased interdisciplinary research efforts are currently being undertaken to improve our understanding of vascular contributions to cognitive impairment and mechanisms through which CVP can be targeted and prevented. In this review, we describe currently known risk factors and pathophysiology of CVPs and their impact on neurodegeneration and downstream cognitive impairment. Specifically, we will discuss three of the most common cerebrovascular lesions seen on MRI: WMH, microbleeds, and infarcts.

2. Risk factors for cerebrovascular pathologies

Based on neuropathology studies, about 30% of nondemented elderly subjects have CVP [7–9]. Although the

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strongest risk factor for the occurrence of CVP is age [10–15], there are several other risk factors discussed in the following sections that are associated with increased risk of CVP.

2.1. Cardiovascular and lifestyle risk factors

Common cardiovascular risk factors such as hypertension, diabetes, dyslipidemia, atrial fibrillation, and smoking are associated with greater WMH burden [16], infarcts [17], and microbleeds [11], particularly when they occur in midlife [18]. It has been shown that subjects with metabolic syndrome have twice the probability of presenting with WMH [19]. These common risk factors contribute to cerebrovascular changes through build-up of atherosclerotic plaque, lipohyalinosis, arteriolosclerosis, and fibrinoid necrosis [20,21]. Healthy lifestyle behaviors specifically healthy diets and physical activity that are associated with lower cardiovascular disease have been associated with lower risk of CVP [22,23].

2.2. Genetic risk

Studies investigating genetic risk factors for CVP aim to identify genes that effect risk of disease, influence outcome after a cerebrovascular event, and interact with various therapeutics [24]. Genome-wide association studies (GWASs) have yielded possible genetic associations with different cerebrovascular lesions. The odds of having ischemic stroke are increased patients with genetic variations in *HDAC9* (related to large-vessel disease) and *PITX2* and *ZFHX3* (related to cardioembolism) [25]. The most common genetic risk factors for lobar microbleeds are APOE ε2 [26] and APOE ε4 [10] allele carrier status [13,27]. Mutations associated with familial conditions including cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy [28], Dutch-type or Iowa-type CAA and APP and presenilin mutations in familial AD are also associated with microbleeds [29]. WMH is likely associated with many different genes as it has heterogeneous etiologies [24]. APOE genotype is a well-known genetic indicator of risk for Alzheimer disease and is also shown to be associated with cardiovascular risk factors [30]. Many other gene candidates have presented themselves as links to CVP through GWAS investigations of cerebrovascular lesions as endophenotypes. However, the diversity of pathologies contributing to these various imaging hallmarks of CVP makes it difficult to firmly identify genetic underpinnings to pathology [17].

2.3. Sex differences

Risks and effects of cardiovascular disease differ greatly between males and females. Premenopausal women appear to have fewer strokes than age-matched men; however, rate and severity of strokes in postmenopausal women surpasses those of age-matched men [28]. There is evidence that the regional distribution and contributing risk factors to WMH differs among older men and women and that WMH is more common in women [31]. The impact of sex on risks and effects of cardiovascular disease might be attributed to sex-specific conditions, for example, pregnancy or menopause; a disproportionate effect of a disease or condition on one sex; and distinct causes, manifestations, outcomes, or treatments that are sex dependent [32].

2.4. Head injury

Acute and chronic traumatic encephalopathies (CTEs) as a result of one or more incidents of traumatic brain injury are gaining public and scientific notice as significant contributors to cognitive impairment and dementia [33]. Following an acute insult, there can be severe vascular pathology including contusions, intracerebral hemorrhage, and vasoconstriction in response to blood products. Even in "closed head" injuries in which the skull remains intact or mild head trauma without readily apparent brain damage, there is injury to the vasculature and meninges due to the strain exerted on them by the impact [33]. The study of pathologies ensuing from head injuries is evolving; current and future work will attempt to characterize the epidemiology, in vivo biomarkers, and pathologies of various types of traumatic brain injuries [33,34]. Although criteria for staging of CTE are still in progress, CTE pathology is being recognized largely as accumulation of tau pathology at the depths of the sulci and perivascularly, suggesting a connection between insult to vasculature and subsequent tauopathy [35]. Work has also begun to investigate possible therapeutic targets in the secondary immune reactions following vascular injury to ameliorate symptoms and progression of pathology [36].

3. Imaging hallmarks of cerebrovascular pathologies

Alzheimer disease has imaging biomarkers that are available for assessing the accumulation of amyloid β and tau pathologies; similarly several different cerebrovascular changes can be observed on imaging (Fig. 1). Although CT has been most commonly used clinically for assessing stroke, MRI is valuable in noncritical clinical assessments and research studies because it provides a more sensitive and detailed visualization of CVP damage to the brain. Fluid Attenuated Inversion Recovery (FLAIR) MRI and T2* MRI are the most common imaging sequences used to visualize ischemic cerebrovascular disease. In this section, we will describe the imaging hallmarks of CVP that are observed on MRI.

3.1. White-matter hyperintensities

3.1.1. Imaging

WMHs, also termed leukoaraiosis, white-matter lesions, or leukoencephalopathy, are areas of bilateral hyperintense signal in brain white matter on T2-weighted or FLAIR MRI (Fig. 2A). They occur in subcortical and periventricular white matter. These lesions are associated with pathologies in multiple disease contexts including vascular disease, multiple sclerosis, and leukodystrophies [21]. In addition to