Neurobiology of Aging 70 (2018) 10–17

Contents lists available at ScienceDirect

Neurobiology of Aging

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

Watershed microinfarct pathology and cognition in older persons

Alifiya Kapasi [a,b,*], Sue E. Leurgans [a,c], Bryan D. James [a,d], Patricia A. Boyle [a,d], Zoe Arvanitakis [a,c], Sukriti Nag [a,b], David A. Bennett [a,c], Aron S. Buchman [a,c], Julie A. Schneider [a,b,c]

[a] Rush Alzheimer's Disease Center, Rush University Medical Center, Chicago, IL, USA
[b] Department of Pathology (Neuropathology), Rush University Medical Center, Chicago, IL, USA
[c] Department of Neurological Sciences, Rush University Medical Center, Chicago, IL, USA
[d] Department of Behavioral Sciences, Rush University Medical Center, Chicago, IL, USA

ARTICLE INFO

Article history:
Received 8 March 2018
Received in revised form 22 May 2018
Accepted 22 May 2018
Available online 30 May 2018

Keywords:
Brain watershed regions
Microinfarcts
Vascular pathology
Cognition

ABSTRACT

Brain microinfarcts are common in aging and are associated with cognitive impairment. Anterior and posterior watershed border zones lie at the territories of the anterior, middle, and posterior cerebral arteries, and are more vulnerable to hypoperfusion than brain regions outside the watershed areas. However, little is known about microinfarcts in these regions and how they relate to cognition in aging. Participants from the Rush Memory and Aging Project, a community-based clinical-pathologic study of aging, underwent detailed annual cognitive evaluations. We examined 356 consecutive autopsy cases (mean age-at-death, 91 years [SD = 6.16]; 28% men) for microinfarcts from 3 watershed brain regions (2 anterior and 1 posterior) and 8 brain regions outside the watershed regions. Linear regression models were used to examine the association of cortical watershed microinfarcts with cognition, including global cognition and 5 cognitive domains. Microinfarcts in any region were present in 133 (37%) participants, of which 50 had microinfarcts in watershed regions. Persons with multiple microinfarcts in cortical watershed regions had lower global cognition (estimate = −0.56, standard error (SE) = 0.26, $p = 0.03$) and lower cognitive function in the specific domains of working memory (estimate = −0.58, SE = 0.27, $p = 0.03$) and visuospatial abilities (estimate = −0.57, SE = 0.27, $p = 0.03$), even after controlling for microinfarcts in other brain regions, demographics, and age-related pathologies. Neither the presence nor multiplicity of microinfarcts in brain regions outside the cortical watershed regions were related to global cognition or any of the 5 cognitive domains. These findings suggest that multiple microinfarcts in watershed regions contribute to age-related cognitive impairment.

1. Introduction

Microinfarcts are focal areas of necrosis of ischemic origin that are not observed on gross examination, and are commonly found in the aging brain (Smith et al., 2012). While advances in neuroimaging modalities contribute to the detection of microinfarcts (van Veluw et al., 2015a; 2015b), the full spectrum, especially the smallest of microinfarcts, is most accurately identified by neuropathological examination. It is becoming increasingly recognized that microinfarcts, above and beyond, macroscopic infarcts, are important contributors to neurologic dysfunction, including cognitive impairment. Multiple large community-based studies show a higher frequency of microinfarcts in persons with dementia, with their presence being relatively independently associated with dementia or cognitive impairment (Brundel et al., 2012; Kovari et al., 2004; Sonnen et al., 2007; Troncoso et al., 2008; White et al., 2002), and previous studies by our group and others indicate persons with multiple microinfarcts have the most cognitive impairment (Arvanitakis et al., 2011; Sonnen et al., 2007). However, despite these latter studies which took account of common neuropathologies of aging and dementia, the clinical impact of microinfarcts, especially in the context of Alzheimer's disease (AD) pathology, has also been challenged (Lee et al., 2000).

Precise mechanisms for microinfarct pathogenesis and their contribution to cognitive dysfunction are still largely unclear. Multiple underlying causes may contribute to microinfarct pathology including small vessel disease, hypoperfusion, and microemboli (van Veluw et al., 2017). In addition, some studies suggest that the etiology of microinfarct pathology differs depending on the

* Corresponding author at: Rush Alzheimer's Disease Center, Rush University Medical Center, Jelke Building, 1750 West Harrison Street, Chicago, IL 60612, USA. Tel.: +1 312 563 3559; fax: +1 312 563 3745.
E-mail address: Alifiya_Kapasi@rush.edu (A. Kapasi).

0197-4580/$ – see front matter © 2018 Elsevier Inc. All rights reserved.
https://doi.org/10.1016/j.neurobiolaging.2018.05.027

location of microinfarct burden (Arvanitakis et al., 2011; Kovari et al., 2004). Microinfarcts can be found in all brain regions, particularly in regions more vulnerable to hypoxic ischemia. The cerebral hemisphere is supplied by the anterior, middle, and posterior cerebral arteries. The brain watershed regions are supplied by the distal arterial branches of 2 or more major arteries, and located the furthest from arterial supply, making them making more vulnerable to hypoxic ischemic events than any other brain region (Miklossy, 2003; Suter et al., 2002). Based on their cortical location in the brain, watershed regions are often specified as either anterior watershed regions, located between the cortical territories of the anterior and middle cerebral arteries, or posterior watershed regions, located between the anterior-middle and posterior-middle cerebral arteries. In addition to cortical watershed regions, deep subcortical watershed regions have also been described, which overlie the territories of the deep arterial lenticulostriate and white matter perforators arising from the middle cerebral artery, and cerebellum watershed regions, bordered by the major cerebellar arteries (Lee et al., 2005; Mangla et al., 2011).

Owing to their increased susceptibility to ischemia and hypoperfusion, watershed regions are interesting areas to investigate microvascular pathologies. In addition, older persons may be particularly vulnerable, because cerebral vessel disease pathology including atherosclerosis and arteriolosclerosis is common (Arvanitakis et al., 2017). There are limited data on the frequency of microvascular pathologies in watershed regions, and the role of watershed microinfarcts in cognitive impairment in older persons is yet to be explored. To address this gap in our knowledge, we collected data from 356 Rush Memory and Aging Project (MAP) participants to document the presence of microinfarcts (single vs. multiple) in cortical (anterior and posterior) watershed regions, and the association with cognitive impairment. Controlling for demographics and neuropathological factors, we investigated whether there was an independent association of cortical watershed microinfarcts, above and beyond the presence of microinfarcts in other brain regions, with global cognition and 5 different cognitive domains proximate to death.

2. Methods

2.1. Study design

Brain specimens were obtained from a consecutive subset of deceased and autopsied participants of the Rush MAP, effective from January 1, 2013, as this was when watershed regions were added to the MAP study for neuropathological evaluation. Rush MAP is an ongoing epidemiologic clinical-pathological cohort study of aging, which began in 1997, and approved by the Institutional Review Board of the Rush University Medical Center (Chicago, IL, USA). We used demographic, neuropathological, and clinical data. Participants are enrolled without known dementia, give informed consent to the study, and agree to brain donation at the time of death. Follow-up and autopsy rates exceed 80%.

2.2. Clinical data

Structured and uniform baseline and clinical assessments were conducted annually, and included a medical history, neuropsychological testing, and a physical examination with a focus on the neurologic examination. A standard battery of neuropsychological tests was administered at baseline and each follow-up evaluation. All neuropsychological data were reviewed by clinicians blinded to previous data collected. In addition to the Mini-Mental State Examination, which was used for clinical descriptive purposes only, an additional 17 individual cognition tests were administered to create composite summary indices for global cognition and 5 cognitive domains. Seven tests of episodic memory, 3 of semantic memory, 3 of working memory, 2 of perceptual speed, and 2 of visuospatial ability, were administrated as previously described (Bennett et al., 2006; Wilson et al., 2002). Raw individual scores of all tests were converted to z scores and averaged to obtain a measure of global cognitive function score. Summary scores for each cognitive domain were derived by averaging the z scores of the neuropsychological tests specific to that particular cognitive domain.

2.3. Neuropathological data

Brain autopsies were performed at the Rush University Medical Center (Bennett et al., 2012; 2013) with an average postmortem interval of 8.4 hours (SD = 5.67). All neuropathologic data were collected at the Rush AD Center laboratory. After an external examination, 1 hemisphere was fixed for at least 48–72 hours in 4% paraformaldehyde in 0.1 M phosphate buffer. Paraformaldehyde-fixed cerebral and cerebellar hemispheres were cut into 1 cm coronal slabs, and a standard set of 11 regions were blocked, including 3 cortical watershed regions (2 from the anterior and 1 from the posterior watershed areas), 4 cortical regions outside the watershed regions (middle temporal, entorhinal, inferior parietal, and anterior cingulate cortices), 2 subcortical regions (basal ganglia and thalamus), hippocampus, and midbrain. In addition, blocks were taken for any macroscopic infarcts observed during gross examination. All blocks were dehydrated, embedded in paraffin wax, and sections (6 μm) stained with hematoxylin-eosin were assessed for microscopic pathologies (AD pathology and microscopic infarcts) (Fig. 1B).

2.3.1. Anatomic location of cortical watershed regions

The focus of this study was to investigate microvascular pathologies in the cortical watershed regions, bordered by the large cerebral arteries. The anatomic location of the anterior watershed is located between the border zones of the anterior and middle cerebral arterial territories. For the purpose of this study, 2 anterior watershed regions were taken; the midfrontal gyrus (Brodmann area 9/46) and anterior white matter taken deep to the midfrontal cortex. We specify the 2 regions as midfrontal anterior watershed and white matter anterior watershed. The posterior watershed lies within the border zone of the middle-posterior and middle-anterior cerebral arterial territories. The posterior watershed region was taken medial to the posterior parietal cortex (Brodmann area 7), and included the parieto-occipital cortex with underlying white matter (Fig. 2).

2.3.2. Postmortem assessment of AD pathology

AD pathology was assessed in the midfrontal watershed, middle temporal, entorhinal, and inferior parietal cortices, and in the hippocampus. Paraffin-embedded blocks were sectioned into 6-μm sections and stained with a modified Bielschowski stain. Manual counts of neuritic and diffuse plaques, and neurofibrillary tangles from all 5 regions were averaged across regions and divided by the SD to create a summary measure of the AD pathology score across the 5 regions in each case, as previously described (Schneider et al., 2004).

2.3.3. Postmortem assessment of macroscopic and microscopic infarcts

Location, age, and size of macroscopic infarcts visible on gross examination were documented. Subsequently, the age of infarct was confirmed by microscopy and documented as acute, subacute, or chronic. Paraffin-embedded blocks for the standard set of 11 regions were sectioned into 6-μm sections, stained with hematoxylin and eosin, and assessed for microinfarcts. Age (acute, subacute, and chronic) and location for all microinfarcts was documented as previously described (Arvanitakis et al., 2011).