Brain Science Advances

Volume 4 | Number 1 Article 6

2018

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Yuanhan Yang
Department of Neurology, Kaohsiung Municipal Ta-Tung Hospital, Taiwan, China Department of Neurology, Kaohsiung Medical University Hospital, Kaohsiung 80708, Taiwan, China Department of and Master's Program in Neurology, Faculty of Medicine, Kaohsiung Medical University, Kaohsiung City 80708, Taiwan, China

Jongling Fuh
Faculty of Medicine, National Yang-Ming University School of Medicine, Taipei, Taiwan, China Department of Neurology, Neurological Institute, Taipei Veterans General Hospital, Taipei, Taiwan, China

Vincent C. T. Mok
Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong, China

Brain Science Advances 2018, 4(1): 39–48
https://doi.org/10.26599/BSA.2018.9050001
ISSN 2096-5958
CN 10-1534/R
REVIEW ARTICLE

Vascular contribution to cognition in stroke and Alzheimer's disease

Yuanhan Yang[1,2,3] (✉), Jongling Fuh[4,5], Vincent C. T. Mok[6]

[1] *Department of Neurology, Kaohsiung Municipal Ta-Tung Hospital, Taiwan, China*
[2] *Department of Neurology, Kaohsiung Medical University Hospital, Kaohsiung 80708, Taiwan, China*
[3] *Department of and Master's Program in Neurology, Faculty of Medicine, Kaohsiung Medical University, Kaohsiung City 80708, Taiwan, China*
[4] *Faculty of Medicine, National Yang- Ming University School of Medicine, Taipei, Taiwan, China*
[5] *Department of Neurology, Neurological Institute, Taipei Veterans General Hospital, Taipei, Taiwan, China*
[6] *Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong, China*

ARTICLE INFO

Received: 01 March 2018
Revised: 15 April 2018
Accepted: 08 May 2018

KEYWORDS

Alzheimer's disease, vascular cognitive impairment, post stroke dementia, white matter hyperintensity, diabetic mellitus, hypertension

ABSTRACT

Vascular factors to cognitive impairment in degenerative on non-degenerative diseases have been reported, examined, and debated for several decades. The various definitions of cognitive impairment due to vascular origins will make these results diverse. During this review, we are going to report currently update information of vascular contributions to cognitive function, in clinical or neuro-imaging findings. Risks factors and their managements also will be discussed and reported to have a comprehensive review.

1 Introduction

Those recognized contribution of vascular factors to cognitive impairment in degenerative on non-degenerative diseases have been reported and examined during the last century. In the early 20th century, progressive loss of cognitive function in late life was attributed to the narrowing and stiffness of the arteries accompanied with intracranial hypo-perfusion, and so-called arteriosclerotic dementia.

Among early-onset and late-onset dementia, Alzheimer disease (AD) pathologically with neurofibrillary tangles and senile plaques is still

Address correspondence to Yuan-Han Yang, endless@kmu.edu.tw

the most prevalent dementia [1]. In the 1990s, epidemiologic studies reported associations between stroke risk factors and cognitive impairment, including dementia, and led to the still-unproven but existed notion that vascular factors might promote Alzheimer disease. These complicated and complex associations are not easy to be clarified. The pathological and clinical studies have indicated that the vascular contribution to AD is still under-estimated because patients having stroke and dementia were sometimes considered as vascular dementia but actually they were AD with cerebral vascular disease or stroke [2]. Recently, the frequent co-occurrence of vascular and AD conditions (15% between ages 65 and 89; 30% after age 90 years), suggested that a multifactorial, rather than dichotomous, approach to diagnosis and treatment of AD with vascular lesion may better reflect the realities of cognitive impairment in elderly population.

Owing to that the diagnostic landscape has shifted from the clinical history and physically neurological examination to the advent of structural imaging, magnetic resonance imaging (MRI), some studies have reported asymptomatic white matter hyperintensities (WMH) and silent brain infarcts (SBI) were discovered on brain MRI in 20% to 30% of nondemented, community dwelling, elderly subjects [3]. In other words, the varied definition of vascular lesion, by clinical presentation, neuroimaging findings, or pathological examination, make vascular contributions to cognition blurred and puzzled.

2 Vascular cognitive impairment (VCI)

VCI is a syndrome, clinical status, or phenotype, not a definite disease. At its simplest, VCI embodies the concept that cognitive impairment is caused by vascular origins. The pathways leading from risk factors to cerebrovascular disease (CVD) to VCI are widely heterogeneous. Common sporadic forms of CVD include atherosclerosis, arteriolosclerosis, cerebral ischemic or hemorrhage infarction, toxic, inflammatory, and oxidative stress [4].

Moreover, recent consensus committee has reported the Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration in which six categories have reported. Recent small subcortical infarct, lacune of presumed vascular origin, white matter hyperintensity (WMH) of presumed vascular origin, perivascular space, cerebral microbleed, and brain atrophy are the main imaging features that contribute to degenerative disease [5].

Epidemiology

From a public health perspective, VCI is the second most common cause of cognitive impairment in late life after AD. The definitions of vascular dementia (VaD) or VCI so far are not consistent that the prevalence studies have various reports according to the definition of VCI or VaD they used. Some studies have reported 1of 3 persons meets criteria for dementia after their first stroke [6]. The prevalence of post-stroke dementia in the first year after stroke ranges from 7% in population-based studies of first-ever stroke excluding pre-stroke dementia to 41% in hospital-based studies including recurrent stroke and pre-stroke dementia [7].

Persons with stroke who are not initially demented are twice as likely as normal controls to subsequently have dementia over the next 10 years [8]. The risk of post-stroke dementia was found to be highest in the first months after stroke, which might partially be due to unrecognized cognitive impairment before stroke [9]. In other words, stroke may increase or accelerate the presentation of possibly underlying degenerated cognitive impairment.

After the initial post-stroke incidence of dementia, the cumulative incidence increases linearly at a rate of 3% and 1.7% per year in hospital-based and population-based studies, respectively [7]. Few studies used long-term outcomes: the longest observational period was 25 years in a population-based study finding a cumulative incidence of post-stroke dementia of 48% at year 25 [10]. The incidence of vascular dementia increases exponentially after 65 years of age, ranging from 3 to 19 per 1000 persons per year at age 80 years [11–13], approximately half the rate of AD.

Clinical presentation of vascular contribution to cognitions

VCI has been categorized in many ways including location (strategic location), clinical presentation (post stroke cognitive change), or MRI findings (e.g., small vessels disease).

3 Post stroke dementia (PSD)

In hospital- and community-based series, history of first stroke doubles the risk of subsequent dementia [6]. Reported risk factors for dementia at the time of stroke include lower educational level, older age, having diabetes mellitus, having atrial fibrillation, and recurrent stroke [14]. Stroke locations associated with higher likelihood of cognitive impairment include left, dominant, hemisphere, anterior and posterior cerebral artery distribution, multiple infarcts, and other strategic infarcts [6]. Neuroimaging variables associated with post-stroke dementia (PSD) include silent SBI, WMH, global and medial temporal atrophy, and others [5, 6]. Concomitant AD is also a major risk factor for PSD. A recent study has reported in their cohort, 41 in 72 subjects with cognitive impairment after stroke/transient ischemic attack found that those originally with positive amyloid-beta deposition detected by Carbon-11-labeled Pittsburgh compound B Positron Emission Tomography (C_{11}-PiB PET) after the index event experienced a more severe and rapid cognitive decline on the Mini Mental State Examination (MMSE) and the memory domain of the Montreal Cognitive Assessment (MoCA) during a 3-year follow-up compared with those with negative amyloid PET scans [15]. About 15% to 30% of persons with PSD have a history of dementia before stroke [16, 17], and approximately one-third have significant medial temporal atrophy [18].

Hypothesized paths for post stroke cognitive decline

Recent consensus committees have hypothesized the possible 4 clinical paths related to the cognitive change after stroke in relation to the original amyloid burden and neuro-inflammatory status after stroke. Possible trajectories of post-stroke cognitive decline:

Trajectory A: In the absence of brain parenchymal β-amyloid deposition, an ischemic infarct may cause a transient decline in cognitive function, but full or partial recovery is possible without further deterioration of cognitive status. The inflammatory could be transient.

Trajectory B: Similarly, in the absence of brain parenchymal β-amyloid deposition if vascular and inflammatory processes trigger ongoing secondary neuro-degeneration persistently, the post-stroke cognitive decline occurs.

Trajectory C: In the presence of intra-cranial amyloid deposition, there is slowly decline in his cognitive natural although the stroke and its accompanied transient inflammatory will worsen the cognition after the stroke. The transient progressed cognitive course will note but eventually the course is progressing.

Trajectory D: In the presence of deposition of cerebral amyloid, the ischemic lesion causes a

loss of cognitive reserve preventing cognitive recovery, and cognitive decline may even be accelerated if secondary degeneration is triggered by persistently inflammatory processes [19].

The hypotheses have been examined in a 3 years longitudinal VCI study at Hong Kong. Comparing cognitive changes between patients with and without original beta-amyloid deposition examined by C-PiB PET, using linear mixed models and analysis of covariance adjusted for age and education, those originally with beta-amyloid deposition experienced a more severe and rapid cognitive decline over 3 years after stroke/transient ischemic attack. Beta-amyloid was associated with changes in multiple cognitive domains [15].

4 White matter hyperintensity in AD

White matter hyperintensity in the brain, also called leukoaraiosis, is frequently observed on the brain images of older adults. The presence of WMH has been reported as a useful predictor of cognitive outcome of AD [20, 21].

Several factors have been examined and reported to be associated with WMH, in which peripheral blood inflammatory status, having hypertension, and age were considered to be associated with its severity [22]. From genetic view, evidences from familial and twin studies supports the hypothesis that genetic factors contribute to the WMH pathogenesis [23] although no consistent genetic polymorphisms have yet shown a convincing association with WMH in these studies [24]. The angiotensin-converting enzyme (ACE) gene locates on chromosome 17q23 [25] and the ACE gene insertion/deletion (I/D) polymorphism have been reported to be associated with ACE protein levels [26]. The ACE protein can degrade amyloid-β (Aβ) [27] and ACE activity has a significant influence on hypertension and inflammatory status [28]. These results suggest that the ACE I/D polymorphism, the gene involved in the degradation of Aβ and the regulation of blood pressure and inflammatory status, might play a vital role in the pathogenesis of WMH and the clinical course of AD.

In our study, we have examined 403 patients clinically diagnosed with AD and we have found that I allele was associated with a significantly lower total age-related white matter changes scale score (ARWMC) compared with the D allele (4.83 vs 5.93, $P = 0.013$). The total ARWMC score was significantly lower for patients with I/I genotype than those with I/D (4.37 vs 5.87, $P = 0.009$) and I/D+D/D genotypes (4.37 vs 5.91, $P = 0.006$), after adjustment for age and hypertension. In other words, AD Patients with ACE I/I genotype are less likely to have WMH, and such findings are particular prominent in female [29]. The AD patients having ACE I/I genotypes also will have the more rapidly cognitive worsening than those with other ACE genotype [29]. These findings have importantly signified that the contribution of ACE gene to the cognitive decline of AD is not relied on only WMH. Importantly and interestingly in our longitudinal study, we have found that the WMH will lead to the cognitive change only more prominent in AD patients having hypertension, not in all AD. The ACE gene contribute to the cognitive course of AD would be pleiotropic [29].

5 Identification and treatment of vascular factors

The beneficial effects of treating atherosclerotic risk factors (e.g., hypertension, diabetes mellitus, and dyslipidemia) for stroke risk reduction are well established [30]. It has been estimated that an 8% reduction of vascular risk factors over 10 years would significantly reduce the incidence of dementia [31].

5.1 Hypertension: Angiotensin converting enzyme inhibitor and angiotensin receptor blocker

Midlife hypertension is recognized as the risk factor to develop late-life AD, but not late-life hypertension [32]. These possible mechanisms for hypertension to develop dementia are heterogeneous. In a meta-analysis of several placebo-controlled trials, treatments of hypertension were significantly associated with reduction in the combined risk ratio of dementia [33]. The Syst-Eur trial [34, 35] suggested that treatment of 1000 patients for 5 years could prevent 20 cases of dementia. In progress, a secondary prevention trial among persons with previous stroke or transient ischemic attack [36], treatment with perindopril and indapamide showed a 19% relative risk reduction in cognitive decline and WMH progression compared to others who did not [37]. Retrospective, observational studies have suggested the possibility that specific classes of antihypertensive medications may have differential effects on cognitive outcome. For example, several studies have reported angiotensin-converting enzyme inhibitors and angiotensin receptor blockers were associated with fewer AD condition [38] and less longitudinal cognitive decline [39].

5.2 Ischemic stroke: Cilostazole

Recently, we have studied and published some new information for cilostazole in the add-on treatment in AD patients to show the secondary benefits of cilostazole preventing cognitive decline apart from its primary stroke prevention [40]. Basically cilostazol is an antiplatelet drug that inhibits the activity of cyclic adenosine monophosphate (cAMP) phosphodiesterase type 3 and is prescribed clinically for the prevention of cerebral ischemia [41, 42]. It reportedly exerts a protective effect on endothelium and sustains blood flow via endothelium independent vasodilatation [43, 44]. In cell line and animal study, cilostazol has been shown to decrease accumulation of Aβ and protect against Aβ-induced cognitive deficits [45]. In our case- control study, cilostazole 50 mg twice a day was added in case group: AD patients with peripheral artery occlusion disease (PAOD) together with their original medicine, donepezil 5 mg per day. The control group was AD patients without PAOD treated donepezil 5 mg only. After one year following up, the decline of MMSE score was significantly slow in case group after control other variables, age, sex, educational level, and apolipoprotein E genotype [40].

Another large scale 5 years longitudinally observation study also conducted by our team and has shown that patients initiating cilostazol therapy without the prior history of dementia will have the lower prevalence and incidence of having dementia and clinically diagnosed AD. The samples were identified from "Taiwan's National Health Insurance database" where a total of 9148 participants 40 years of age or older and free of dementia at baseline were analyzed. Patients using cilostazol (n = 2287) had a significantly decreased risk of incident dementia compared with patients not using that (n = 6861; adjusted HR (aHR) 0.75; 95% confidence interval (CI) 0.61–0.92). Moreover, cilostazol use was found to have a significant dose-dependent association with reduced rate of dementia emergence (p for trend = 0.001). Subgroup analysis identified a decline of dementia in cilostazol users with diagnosed cerebral vascular disease (aHR 0.34, 95% CI 0.21–0.54). These observations suggest that cilostazol use may reduce the risk to develop dementia, and a high cumulative dose further decreases the risk of dementia [46].

5.3 Type 2 diabetes mellitus (DM): Thiazolidinediones

Epidemiological studies have suggested that patients with type 2 diabetes are at an increased risk of dementia [47], including Alzheimer disease (AD) and vascular dementia [48]. Many drugs have been used extensively to treat DM with some secondarily therapeutic benefits.

Thiazolidinediones, agonists of nuclear receptor peroxisome proliferator-activated receptor gamma (PPAR-γ), can decrease insulin resistance and are approved medications for type 2 diabetes treatment. Secondary benefits apart from glucose control have been examined. Thiazolidinediones exert potent anti-inflammatory effects in the central nervous system and seem to exert neuroprotective effects *in vitro* [49]. Thiazolidinediones inhibit Aβ-stimulated proinflammatory responses and neurotoxicity [50].

In our retrospective study using claims data from "Taiwan's National Health Insurance Research Database", we have included 6401 patients with type 2 DM treated with pioglitazone and 12,802 age- and sex-matched patients with type 2 DM too but never treated with pioglitazone from 2004 to 2009. Meanwhile, both of these two groups did not have the diagnoses of dementia at their entrances of the study. After 5 years from 2004, 113 (1.8%) and 323 (2.5%) patients in receiving and not receiving the pioglitazone-treated cohorts have developed dementia, respectively. The relative risk of dementia decreased by 23% in the pioglitazone-treated cohort compared with that in the comparison cohort after adjustment for age, sex, hypertension, and stroke (adjusted hazard ratio (HR), 0.77; 95% confidence interval (CI) = 0.62–0.96). In addition, the adjusted HRs (95% CIs) for dementia were 0.50 (0.34–0.75, $P = 0.001$) in high-cumulative dose users, 0.53 (0.36–0.77, $P = 0.001$) in long-term users, and 0.66 (0.49–0.90, $P = 0.009$) in high-mean daily dose users. Our study has provided a promising finding that using pioglitazone could be decreased risk of having dementia in type 2 DM. The decreased risk also could be dose-dependent [51].

6 Conclusion

So far, cerebral vascular disease is the second leading cause of cognitive impairment in late life. The manifestations of vascular cognitive impairment are heterogeneous in clinical pictures, severity, pathophysiology, and also in neuroimaging and biomarkers.

MRI might reveal some evidence of vascular contribution to cognition such as those small vessels diseases including WMH, which were mainly associated with impairment in executive function. One-third of patients will have post-stroke dementia after cerebral stroke and, if not initially affected, stroke patients are at twice the risk of subsequent cognitive impairment over the coming10 years.

Many risk factors for VCI, such as hypertension, diabetes mellitus, or dyslipidemia are modifiable, although currently double-blind, placebo-controlled trials are often inconclusive because these intervention modifying these risks are often initiated too late, the therapeutic duration is not enough, or the weakness of study design to provide the possible benefits, if any.

By and large, the means for early detection and prevention of VCI are still to be determined for those heterogeneously unknown and known factors. The prevention and treatment of VCI could be individualized. The major rescues of vascular contribution to cognition remain those of diligent clinical practice, extensive researches, and public health implementation.

Conflict of interests

All contributing authors have no conflict of interests.

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Yuanhan Yang was a research fellow at the Alzheimer's Disease Research Center, Washington University in St Louis, St. Louis, MO, USA. He was awarded the First Place of Research Award by the Taiwan Dementia Society in 2010. He was listed in Marquis Who's Who in The World in 2014 and 2015, and was honored for 2017 Albert Nelson Marquis Lifetime Achievement Award. He has published over 100 dementia-related papers, some of which were featured in The Innovation and Impaction Papers: 2013 World Biomedical Frontiers. He was invited to join the Asian Society Against Dementia Collaborative Study for his work with AD8-Asia for screening early dementia and the Registration of Alzheimer's Disease in Asian Countries (ReAD-Asia) to foster collaboration in Asia. He has served as the Editor of *Frontiers in Bioscience*, Associate Editor of *Journal of Alzheimer's Disease*, Associate Editor-in-Chief of *Brain Science Advanses*, Lead Guest Editor of *The Scientific World Journal*, Lead Guest Editor of *Parkinson's Disease*, and as other editorial board members of many Journals.