Seung-Hoon Lee
Jae-Sung Lim
Editors

Stroke Revisited:
Vascular Cognitive Impairment

Springer

Stroke Revisited

This authoritative book series presents state of the art knowledge on the pathophysiology, prevention, diagnosis, and treatment of stroke, highlighting the many very important advances that have been achieved in recent years. Current issues in management are addressed in detail, equipping readers with an understanding of the rationale for particular approaches in different settings and with a sound knowledge of the role of modern imaging methods, surgical techniques, and medical treatments. The inclusion of numerous high-quality illustrations facilitates understanding of practical aspects and rapid retrieval of fundamental information. The series will be of value for stroke physicians, surgeons, other practitioners who care for patients with stroke, and students.

More information about this series at http://www.springer.com/series/15338

Seung-Hoon Lee • Jae-Sung Lim
Editors

Stroke Revisited: Vascular Cognitive Impairment

Springer

Editors
Seung-Hoon Lee
Department of Neurology
Seoul National University Hospital
Seoul
South Korea

Jae-Sung Lim
Department of Neurology
Hallym University Sacred Heart
Hospital, Hallym Neurological Institute
Hallym University College of Medicine
Anyang-si, Gyeonggi-do
South Korea

ISSN 2522-5588 ISSN 2522-5596 (electronic)
Stroke Revisited
ISBN 978-981-10-1432-1 ISBN 978-981-10-1433-8 (eBook)
https://doi.org/10.1007/978-981-10-1433-8

This Springer imprint is published by the registered company Springer Nature Singapore Pte Ltd.
The registered company address is: 152 Beach Road, #21-01/04 Gateway East, Singapore 189721, Singapore

Preface

Dementia is one of the biggest challenges facing the aging society. However, clinical trials related to the development of therapeutic agents for Alzheimer's disease have failed in succession and have frustrated not only researchers but also major pharmaceutical companies and patient groups. Lessons from the failure of Alzheimer's drug trials have redirected attention to other therapeutic targets besides the amyloid cascade. One of these targets is "vascular contributions to cognitive impairment and dementia."

The Framingham heart study reported a reduction in the incidence of dementia at each study epoch, mainly due to a reduction in the incidence of vascular dementia rather than Alzheimer's disease. In addition, the population attributable risk of common modifiable risk factors was reported to be comparable to that caused by APOE genotypes, which is the most well-known risk factor for Alzheimer's disease.

We can reach a deeper understanding of the functional localization of human cognition by understanding various vascular disorders accompanied by focal lesions, just as we have accumulated knowledge of localization of brain functions through discovery of "lesion-symptom" mapping in the late nineteenth to early twentieth century.

Thus, vascular cognitive impairment has attracted attention as a disease that can be prevented through comprehensive cardiovascular risk factor control, and as a disease model that can explain the pathogenesis of cognitive dysfunction through interaction between vascular lesions and neurodegenerative changes.

This book presents the recent developments as clearly as possible for beginners in this field. It also looks at the changes in the diagnostic criteria that have been made recently and their conceptual background. This book discusses the clinical characteristics of post-stroke dementia and subcortical vascular dementia, two major axes of vascular cognitive impairment. It also deals with gait disturbances and behavioral and psychological symptoms of dementia that are relatively unrecognized. The interactions of neurodegenerative changes and vascular factors are now being investigated due to recent advances in imaging technology, and the results of recent studies are summarized. In addition, recent updates involving brain imaging studies, including the STRIVE protocol for unified research, are reviewed. Finally, the results of previous studies on therapeutic agents are summarized.

Vascular cognitive impairment is an area where its pathophysiology is not clearly defined yet. We hope that this book will give you a chance to keep up with the accumulated knowledge and to learn the latest concepts. We would like to thank all the authors for their willingness to contribute to this book.

Anyang-si, Gyeonggi-do, South Korea — Jae-Sung Lim
Seoul, South Korea — Seung-Hoon Lee

Contents

Contributors

Sandra E. Black Hurvitz Brain Sciences Program, Sunnybrook Research Institute, Toronto, ON, Canada

Canadian Partnership for Stroke Recovery, Sunnybrook Research Institute, Toronto, ON, Canada

LC Campbell Cognitive Neurology Unit, Sunnybrook Research Institute, Toronto, ON, Canada

University Health Network Toronto Rehabilitation Institute, Toronto, ON, Canada

Neurology Division, Department of Medicine, University of Toronto, Toronto, ON, Canada

Philip B. Gorelick Davee Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Department of Translational Neuroscience, Michigan State University College of Human Medicine, Grand Rapids, MI, USA

Il-Woo Han Department of Neurology, Hyoja Geriatric Hospital, Yongin-si, Gyeonggi-do, South Korea

Jihye Hwang Department of Neurology, Keimyung University Daegu Dongsan Hospital, Daegu, South Korea

Jee Hyang Jeong Department of Neurology, Ewha Womans University Mokdong Hospital, Ewha Womans University College of Medicine, Seoul, South Korea

Geon Ha Kim Department of Neurology, Ewha Womans University Mokdong Hospital, Ewha Womans University College of Medicine, Seoul, South Korea

Yeo Jin Kim Department of Neurology, Chuncheon Sacred Heart Hospital, Hallym University College of Medicine, Chuncheon-si, Gangwon-do, South Korea

Ho Ko Department of Medicine and Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong, SAR, China

Li Ka Shing Institute of Health Sciences, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong, SAR, China

Chow Yuk Ho Technology Center for Innovative Medicine, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong, SAR, China

Therese Pei Fong Chow Research Centre for Prevention of Dementia, Gerald Choa Neuroscience Centre, Lui Che Woo Institute of Innovative Medicine, Margaret K. L. Cheung Research Centre for Management of Parkinsonism, The Chinese University of Hong Kong, Hong Kong, SAR, China

Bonnie Yin Ka Lam Department of Medicine and Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong, SAR, China

Therese Pei Fong Chow Research Centre for Prevention of Dementia, Gerald Choa Neuroscience Centre, Lui Che Woo Institute of Innovative Medicine, Margaret K. L. Cheung Research Centre for Management of Parkinsonism, The Chinese University of Hong Kong, Hong Kong, SAR, China

Seung-Hoon Lee Department of Neurology, Seoul National University Hospital, Seoul, South Korea

Si-Hyun Lee Korean Cerebrovascular Research Institute, Seoul, South Korea

Jae-Sung Lim Department of Neurology, Hallym University Sacred Heart Hospital, Hallym Neurological Institute, Hallym University College of Medicine, Anyang-si, Gyeonggi-do, South Korea

Vincent Chung Tong Mok Department of Medicine and Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong, SAR, China

Therese Pei Fong Chow Research Centre for Prevention of Dementia, Gerald Choa Neuroscience Centre, Lui Che Woo Institute of Innovative Medicine, Margaret K. L. Cheung Research Centre for Management of Parkinsonism, The Chinese University of Hong Kong, Hong Kong, SAR, China

Eun-Sun Park Seoul National University Hospital and Korean Cerebrovascular Research Institute, Seoul, South Korea

Walter Swardfager Hurvitz Brain Sciences Program, Sunnybrook Research Institute, Toronto, ON, Canada

Department of Pharmacology & Toxicology, University of Toronto, Toronto, ON, Canada

Canadian Partnership for Stroke Recovery, Sunnybrook Research Institute, Toronto, ON, Canada

LC Campbell Cognitive Neurology Unit, Sunnybrook Research Institute, Toronto, ON, Canada

University Health Network Toronto Rehabilitation Institute, Toronto, ON, Canada

Fernando D. Testai Department of Neurology and Rehabilitation, University of Illinois at Chicago, Chicago, IL, USA

Cindy W. Yoon Department of Neurology, Inha University School of Medicine, Incheon, South Korea

Di Yu Hurvitz Brain Sciences Program, Sunnybrook Research Institute, Toronto, ON, Canada

Department of Pharmacology & Toxicology, University of Toronto, Toronto, ON, Canada

Canadian Partnership for Stroke Recovery, Sunnybrook Research Institute, Toronto, ON, Canada

LC Campbell Cognitive Neurology Unit, Sunnybrook Research Institute, Toronto, ON, Canada

1 Definition and Concept of Vascular Cognitive Impairment

Fernando D. Testai and Philip B. Gorelick

1.1 Epidemiology and Global Impact of Dementia

Dementias constitute one of the largest public health challenges. A systematic review including 147 epidemiological studies showed that approximately 35.6 million people worldwide carried the diagnosis of dementia in 2010. The highest prevalence was noted in Western Europe (7.0 million) followed by East Asia (5.5 million), South Asia (4.5 million), and North America (4.4 million). When organized by country, the largest prevalence of dementia was in China (5.4 million) followed by the United States (3.9 million) and India (3.7 million). The number of people with dementia is projected to double every 20 years resulting in a total number of cases of 65.7 million in 2030 and 115.4 million in 2050 [1]. Current trends indicate that the increase in prevalence will be particularly steeper in low- and middle-income countries (LMIC). It was determined that 58% of the dementia cases in 2010 occurred in LMIC; however, this proportion is expected to increase to 63% in 2030 and 68% in 2050 [2].

Every year, 7.7 million new cases of dementia are diagnosed worldwide which results in a new case every 4 s. The incidence of dementia doubles every 5.9 years of age and increases exponentially from 3.1 per 1000 person-years for subjects aged 60–64 to 175 person-years for older than 95 years [1]. Interestingly, the incidence of dementia is lower in LMIC than in high-income countries. Methodological factors, exposure to environmental and acquired risk factors, and region-specific patterns of survival may account, at least in part, for the apparent lack of correlation between prevalence and incidence.

Dementias shorten life expectancy and are associated with an approximately two-and-a-half-fold increased risk of death. The mortality attributable to dementias is 10% in men and 15% in women above the age of 65 years; these estimates increase steadily with age and reach 18% for men and 23% for women 85–89 years old. Life expectancy differs among different dementia subtypes. The median survival for individuals with Alzheimer disease (AD) is 7.1 years and for vascular dementia (VaD) 3.9 years. Dementias are the leading cause of dependency and disability in both LMIC and high-income countries. The economic burden of this condition at the personal

F. D. Testai (✉)
Department of Neurology and Rehabilitation, University of Illinois at Chicago, Chicago, IL, USA
e-mail: Testai@uic.edu

P. B. Gorelick
Davee Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Department of Translational Neuroscience, Michigan State University College of Human Medicine, Grand Rapids, MI, USA
e-mail: pgorelic@mercyhealth.com

S.-H. Lee, J.-S. Lim (eds.), *Stroke Revisited: Vascular Cognitive Impairment*, Stroke Revisited,
https://doi.org/10.1007/978-981-10-1433-8_1

and societal levels is considerable. Worldwide, the total costs of dementia were $604 billion in 2010. This was unevenly distributed with aggregated costs of approximately $29 billion in LMIC and US$ 537 in high-income countries [1]. Projections that incorporate variables such as aging population, increasing costs of medical care, and annual inflation estimated that the global cost of dementia will continue to increase steadily in the subsequent years and likely cross the threshold $1 trillion in 2018 [2].

The annual cost of care for an individual with dementia ranges from $868 in low-income countries to $56,218 in high-income countries [2]. An elevated proportion of dementia patients become physically, mentally, financially, and legally vulnerable requiring continuous supervision and assistance of a caregiver to perform their basic (e.g., eating, bathing, etc.) and/or instrumental activities of daily living (e.g., shopping, managing personal finances, etc.). It was estimated that in 2016, more than 15 million of unpaid Americans, including friends and family members, provided approximately 18 billion hours of care to patients with dementia resulting in an estimated monetary cost of $221 billion [3]. Finally, dementias have a relentless and progressive course. The increasing disability and dependence take a toll on the resilience and productivity of family members, friends, and other unpaid caregivers. Observational studies have shown that caregivers of dementia patients have higher rates of psychologic stress, represented by anxiety and depression, and poorer health, including higher inflammatory burden, than noncaregivers [4].

1.2 Current Diagnostic Criteria and Consensus of Vascular Cognitive Impairment (NINDS-AIREN, DSM-V, AHA-ASA Statement, VasCog Statement, VICCCS)

Historically, terms such as “hardening of the arteries” and “arteriosclerotic psychosis” have been used to denote underlying vascular causes of cognitive impairment and failure of cerebral function in patients with vascular cognitive impairment (VCI) [5]. In the 1950s, Roth described arteriosclerotic psychosis in those with focal signs and symptoms of cerebral vascular disease, fluctuating or remitting course which might include emotional incontinence, preservation of insight, and epileptiform seizures [6]. Later, the criteria were refined by Mayer-Gross, Slater, and Roth to portray a condition with age of onset in the 60–70 year range, presence of hypertension, conspicuous symptoms following a stroke such as memory disturbance, restlessness, wandering at night and emotionality, somatic complaints, maintenance of creative and intellectual powers, cooling of emotions, diminished drive and initiative, but preservation of judgment and personality [7]. The term was subsequently replaced by multi-infarct dementia (MID), a categorization coined by Hachinski and colleagues referring to progressive loss of cognitive function with impairment of social skills that appeared with abrupt onset, stepwise deterioration, fluctuating course, and focal neurological signs associated with cerebral infarcts [8]. This definition led to the Hachinski Ischemic Score, a tool used to differentiate dementia associated with cerebral infarcts from neurodegenerative dementia such as AD. It was C. Miller Fisher who remarked that cognitive impairment associated with stroke was a matter of strokes large and small [5].

Over time, the terminology used to refer to cognitive impairment associated with stroke has changed. In more recent epochs, the term VaD has evolved as a broader term than MID and one that takes into account any dementia related to underlying disease of the cerebral blood vessels [9]. Thus, VaD represents a heterogeneous entity that may be classified according to the location of stroke and underlying stroke subtype or mechanism [5]. For example, superficial or deep brain infarcts responsible for cognitive impairment might emanate from large or smaller brain blood vessels and any of many underlying stroke mechanisms. VaD included not only brain infarcts but also brain hemorrhage and the consequent vascular mechanism responsible for the hemorrhage. Therefore, use of VaD to define or categorize cognitive impairment associated with stroke led

to an emphasis on an understanding of the underlying vascular mechanism underlying cognitive impairment.

Cerebral small vessel disease responsible for subcortical brain changes (e.g., white matter disease, small subcortical infarcts, and cerebral micro-hemorrhages) is considered to be the most common type of cognitive impairment associated with stroke [10]. There seems to be a common mechanistic theme underlying cognitive impairment associated with cerebral small vessel disease that includes hypoxic hypoperfusion, lacunar infarction, oxidative stress, and inflammation with disruption of the blood-brain barrier resulting in damage to deep brain myelin [10]. The neurovascular unit (NVU) comes under attack by oxidative stress and inflammation with resultant neurovascular dysfunction, brain injury, and VCI. An upstream mechanistic approach to reduce vascular risks has been advocated to identify and prevent the cascade of events in the at-risk brain stage before subcortical brain injury progresses [11].

Contemporarily, we now use terms such as VCI and vascular cognitive disorder (VCD) to refer to cognitive impairment associated with stroke. We now review diagnostic criteria for cognitive impairment associated with stroke that has evolved since the 1990s.

1.2.1 National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement in Neurosciences (NINDS-AIREN) Research Diagnostic Criteria

NINDS-AIREN diagnostic criteria for VaD included acknowledgment of the heterogeneity of vascular dementia syndromes and underlying neuropathologic subtypes, the importance of linking a temporal relationship between stroke and occurrence of dementia, clinical features, and variability of clinical course (e.g., the classic stepwise cognitive deterioration expected with stroke might not be the case, and a static, remitting, or progressive time course could occur) [12]. Specific clinical features early in the course of the disorder might include gait dysfunction, urinary incontinence, and mood or personality changes. The criteria also emphasized the value of neuroimaging, formal neuropsychological testing of multiple cognitive domains, and correlative neuropathologic-clinical-neuropsychologic evaluation to establish a proper diagnosis. NINDS-AIREN criteria were devised to classify cases according to the following probabilistic categories: possible, probable, and definite.

NINDS-AIREN VaD research diagnostic criteria may be simply broken down into the following components: (1) presence of dementia; (2) cerebral vascular disease according to neurological history, clinical exam, or brain imaging; and (3) a reasonable linkage between the temporal occurrence of stroke and dementia [12]. A diagnosis of dementia was met if there was impairment of memory, loss of cognitive abilities sufficient to cause impairment of activities of daily living (ADLs), and deficits in at least two other major cognitive domains. Whereas NINDS-AIREN criteria have been the most widely used ones in clinical trials of VaD, the inclusion of memory loss as a necessary criterion to establish a diagnosis of VaD has been a point of contention. Controversy exists as memory impairment could serve as a criterion whereby AD cases or mixed vascular and neurodegenerative cases could be present as opposed to the occurrence of pure VaD [13].

1.2.2 State of California Alzheimer Disease Diagnostic and Treatment Centers (ADDTC) Criteria for Ischemic Vascular Dementia (IVD)

ADDTC research diagnostic criteria draw a distinction between IVD and VaD [14]. The ADDTC criteria also served to emphasize a broader concept of VaD, the value of neuroimaging to help establish a diagnosis, the need for validation of the criteria, and research gaps in the field of study. Dementia was operationalized as deterioration in

cognition from a prior known level of intellectual function sufficient to result in loss of one's ability to carry out customary affairs of life independent of level of consciousness and verified by bedside mental status assessment or, preferably, formal neuropsychological testing.

Diagnostic criteria were scored according to a probabilistic scheme, whereby there was probable, possible, and definite IVD [14]. Probable IVD was characterized by the presence of dementia, evidence of one or more strokes by neurological history, examination, and/or neuroimaging, or the occurrence of a single stroke with a clear temporal association with dementia. According to this criterion, at least one brain infarct was required to be outside the cerebellum. Suggestive features to establish a diagnosis of IVD were multiple brain infarcts in brain regions known to be associated with cognitive impairment, history of transient ischemic attack (TIA), and other features [14]. There were also supportive features (e.g., abnormal gait early in the course of the disorder) and "neutral" features (e.g., slowly progressive time course). The key characteristics of possible IVD were presence of dementia and single stroke or Binswanger's disease. Definite IVD included the presence of dementia and multiple brain infarcts on neuropathologic exam with some infarcts being found outside the cerebellum [14]. ADDTC criteria included the possibility of mixed dementia if AD neuropathology was present.

1.2.3 Consensus Statement for Diagnosis of Subcortical Small Vessel Disease (SSVD)

This statement is an expert consensus piece to establish diagnostic criteria for SSVD that emphasizes a mechanistic approach [15]. SSVD was defined as subcortical gray and white matter lesions appearing as lacunar infarcts and white matter hyperintensities on MRI brain study. Neuropathologic or mechanistic linkages included lipohyalinosis and fibrinoid change for lacunar infarcts and, for example, blood-brain barrier leakage of substances toxic to myelin as a possible explanation for damage to the white matter, respectively [15]. Subtypes of SSVD were defined such as Binswanger's disease (gait and executive dysfunction, active deep tendon reflexes, apathy, and depression) and cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) secondary to the notch 3 gene mutation with white matter changes and lacunar infarcts. Mixed dementias were also defined. The work of this group is being used to help develop clinical trials for SSVD based on biomarker-enabled studies.

1.2.4 American Heart Association/ American Stroke Association (AHA/ASA) Diagnostic Criteria for VCI

As part of an initiative to characterize vascular contributions to cognitive impairment, AHA/ASA convened an expert panel that included addressing the definition of VCI [16]. VCI, distinct from VaD, represents a continuum of cognitive impairment associated with stroke taking into account the at-risk brain stage to slight to moderate to severe cognitive impairment or VaD. Thus, VCI not only takes into consideration the severity of cognitive impairment and the continuum of such, but it also emphasizes the importance of mechanism and prevention or delay in cognitive impairment.

Basic to the definition of VCI is a linkage between cognitive impairment and vascular disease, cognitive dysfunction according to neuropsychological test criteria, and a history of stroke or evidence of cerebral brain injury or disease associated with some form of stroke [16]. In contradistinction to the definition of VaD [12], VCI criteria do not require a diagnosis of memory loss and specify that the occurrence of white matter lesions in the elderly may be of less diagnostic value than in younger patients. In addition, dementia is specifically defined as a decline in cognitive function from a prior higher level involving two or more cognitive domains