Cerebral Microbleeds and Cognition in Patients with Symptomatic Small Vessel Disease

Thesis

Submitted for Partial Fulfillment of the Master Degree in Neurology and Psychiatry

Presented By

Kholoud Mahmoud Abdullah
M.B.B.CH

Under Supervision of

Prof. Dr. Hany Mahmoud Zakieldine
Professor of Neurology and Psychiatry
Faculty of Medicine - Ain Shams University

Dr. Iman Mohamed Bayomy
Consultant of Neurology and Psychiatry
Faculty of Medicine - Ain Shams University

Dr. Mona Mokhtar Wahideldin
Lecturer of Neurology and Psychiatry
Faculty of Medicine - Ain Shams University

Faculty of Medicine
Ain Shams University
2018

سورة البقرة الآية: ٣٢

Acknowledgment

First and foremost, I feel always indebted to **ALLAH,** *the Most Kind and Most Merciful.*

I'd like to express my respectful thanks and profound gratitude to **Prof. Dr. Hany Mahmoud Zakieldine,** *Professor of Neurology and Psychiatry, Faculty of Medicine- Ain Shams University for his keen guidance, kind supervision, valuable advice and continuous encouragement, which made possible the completion of this work.*

I am also delighted to express my deepest gratitude and thanks to **Dr. Iman Mohamed Bayomy,** *Consultant of Neurology and Psychiatry, Faculty of Medicine, Ain Shams University, for her kind care, continuous supervision, valuable instructions, constant help and great assistance throughout this work.*

I am deeply thankful to **Dr. Mona Mokhtar Wahideldin,** *Lecturer of Neurology and Psychiatry, Faculty of Medicine, Ain Shams University, for her great help, active participation and guidance.*

I could not forget while writing these words the effort and support that was provided by **Dr. Mareyse Youseff Awadallah,** *Asisstant Professor of Radiology, Faculty of Medicine, Cairo University,* **and Youseff Awadallah Radiology Centre.** *They made a great example for encouraging medical research and providing better chances for scientific work.*

Finally, i would like to express my gratitude to everyone who helped me in this work. My great parents, who always gave me love and support. My husband, who has always been my backbone, supporting me in the hardest of times and handling my absence with love. My two lovely kids, "Eyad and Omar" who gave me hope and courage in every day battle. Thanks all for making it possible when I thought it wasn't.

Kholoud Mahmoud Abdullah

List of Contents

List of Tables

List of Tables (Cont...)

List of Tables (Cont...)

List of Figures

List of Figures (Cont...)

List of Abbreviations

Abb.	Full term
AD	*Alzheimer disease*
ADC	*Apparent diffusion coefficient*
ApoE	*Apolipoprotein E*
Aβ	*Amyloid β-peptide*
BG	*Basal Ganglion*
CAA	*Cerebral amyloid angiopathy*
CADASIL	*Cerebral autosomal dominant arteriopathy with subcortical ischemic strokes and leukoencephalopathy*
CARASIL	*Cerebral autosomal recessive arteriopathy with subcortical ischemic strokes and leukoencephalopathy*
CMBs	*Cerebral microbleeds*
cSVD	*Cerebral small vessel disease*
CT	*Computed tomography*
DPWM	*Deep / periventricular WM*
ERPs	*Event-related potentials*
FLAIR	*Fluid-attenuated inversion recovery*
*GRE T2 **	*Gradient Echo T2**
HV	*hypertensive vasculopathy*
ICH	*Intracerebral hemorrhage*
MARS	*Microbleed Anatomical Rating Scale*
MCI	*Mild cognitive impairment*
MELAS	*Mitochondrial encephalopathy with lactic acidosis and stroke-like episode*
MMSE	*Mini Mental State Examination*
MoCA test	*Montreal Cognitive Assessment tests*
MRI	*Magnetic Resonance Imaging*
PET	*positron emission tomography*
PiB	*Pittsburgh compound B*

List of Abbreviations (Cont...)

Abb.	Full term
SVD	*Small vessel disease*
SWI	*Susceptibility weighted imaging*
TFNEs	*Transient focal neurological episodes*
TIA	*Transient ischemic attack*
VCI	*Vascular cognitive impairment*
VaD	*Vascular Dementia*
WMLs	*White matter lesions*

ABSTRACT

Background: as life expectancy is increasing worldwide, cognitive impairment and dementia are becoming a major public health challenge facing all societies. Accumulating evidence is suggesting that cerebral small vessel disease (cSVD) is a leading cause for cognitive deterioration. Cerebral microbleeds (CMBs) are common in (cSVD) with less consistent results concerning their relation to cognition.

Aim of the Study: determine whether CMBs correlate with cognition in patients with symptomatic small vessel disease (SVD). If cognitive impairment is detected, determine whether this association remained after controlling for other MRI markers of SVD. Also to study the relation between different locations of CMBs and their effect on domains of cognition according to Montreal cognitive assessment (MoCA) test.

Subjects and Methods: this cross sectional study included eighty five Egyptian patients with symptomatic SVD, from the neuropsychiatry clinic of the Main Suez Hospital in Suez city, in the period between February 2017 and February 2018. Subjects were classified according to CMBs presence into CMB positive and negative groups .Both groups are assessed using MRI imaging and MoCA test for cognitive function.

Results: In our study, CMBs recorded a high prevalence rate of SVD patients. Subjects with MBs were mainly males and significantly older, with higher white matter lesion volume and more lacunar infarcts. MoCA test detected significant impairment in in visuospatial/ executive function, attention and total scores in CMB positive group. Both Frontal and Parietal MBs showed independent association with visuospatial/executive impairment. Deep MBs in Basal ganglia was proved to be independent risk factor for attention affection.

Conclusion: Presence and Location of MBs proved to be important in determining cognitive consequences. The relations with cognitive performance were mainly driven by frontal, parietal, and deep located MBs in basal ganglia. Memory affection in frontal MBs was dependent to severe white matter intensities and lacunes.

Keywords: *Cerebral Microbleeds – Cognition – Small Vessel Disease*

INTRODUCTION

Small vessel disease is a term used with various meanings and in different contexts (i.e., pathological, clinical, and neuroimaging aspects). These diseases are thought to be the most frequent pathological neurological processes and prevalent brain conditions that have a crucial role in at least three fields: stroke, dementia, and ageing ***(Ding et al., 2017).*** Cerebral small vessel disease (cSVD) is described as a predictor of cognitive decline and a major cause of vascular cognitive impairment (VCI) ***(Lawrence et al., 2015; Pantoni, 2010; Romero et al., 2017).***

Unlike large vessels, small vessels cannot be currently visualised in vivo; therefore, the parenchyma lesions that are thought to be caused by these vessel changes have been adopted as a marker of small vessel disease.

Lacunar infarcts and white matter lesions (WMLs) have been recognized for years as characteristic MRI manifestations of SVD. In addition, cerebral microbleeds (CMBs) are recently recognized as an important new manifestation and diagnostic marker of small vessel pathology ***(Charidimou & Werring, 2011).***

WMLs and lacunar infarcts have been well established through studies to be associated with cognitive impairment ***(Yan et al., 2015).*** However, CMBs clinical impact on cognition remains an active field of research ***(Shoamanesh et al., 2018).***

CMBs are detected in about 5% of healthy individuals with no neurological disorder with a prevalence increasing with age to reach about 40% in those over 80 years old ***(Vernooij et al. , 2008)***. CMBs are commonly found in patients with cerebrovascular diseases, including ischaemic or haemorrhagic stroke, Alzheimer disease (AD) and vascular dementia (VaD) ***(Cordonnier et al., 2007; Kester et al., 2014).***

Most studies were conducted on such groups of patients. They examined the association of CMBs with increased risk of stroke recurrence and intracerebral hemorrhage ***(Imaizumi et al., 2015),*** haemorrhagic transformation after ischaemic stroke and impairment of cognitive function ***(Hashimoto et al., 2004) (Gregoire et al., 2013).*** Investigation of their presence in relation to poorer microstructural integrity of brain white matter was conducted for explanation of such cognitive impairment ***(Akoudad et al., 2013).***

There is a strong correlation between CMBs presence and the presence of other cerebral SVDs. Subjects with CMBs had significantly higher number of lacunar infarcts and more severe WMLs ***(Chung et al., 2016)***. This made the studying of CMBs relation with cognitive performance important in patients with SVD, which may give more explanations for different vascular pathology and mechanisms of cognitive impairment in SVDs.

Aim of the Study

Determine whether CMBs correlate with cognition in patients with symptomatic SVD. Also studying the relation between different locations of CMBs and their effect on various domains of cognition. Determine whether these associations were independent of coexisting WMLs and lacunar infarcts.