COGNITIVE DYSFUNCTION IN SMALL VESSEL DISEASE

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CERTIFICATE

This is to certify that the Dissertation entitled, **"COGNITIVE DYSFUNCTION IN SMALL VESSEL"** is the bonafide record work done by Dr.T.Muthu, under our guidance and supervision in the Institute of Neurology, Rajiv Gandhi Government General Hospital, Madras Medical College, Chennai, submitted as partial fulfilment for the requirements of D.M. Degree examination Branch I NEUROLOGY, AUGUST 2012, under The Dr.M.G.R. Medical University, Chennai.

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I solemnly declare that this dissertation titled "**COGNITIVE DYSFUNCTION IN SMALL VESSEL DISEASE"** is done by me in the Institute of Neurology, Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai under the guidance and supervision of Prof. Dr.R.Lakshmi Narasimhan, M.D.,D.M., Professor of Neurology, Institute of Neurology, Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai. This dissertation is submitted to the Tamil Nadu Dr.M.G.R Medical University, Chennai in partial fulfilment of the university requirements for the award of the degree of D.M. Neurology.

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CONTENTS

LIST OF ABBREVIATIONS

WML	-	white matter lesion
CNS	-	Central nervous system
CT	-	Computerized Tomogram
MRI	-	Magnetic Resonance Imaging
EEG	-	Electro Encephalogram
CAA	-	Cerebral amyloid angiopathy
CSF	-	Cerebrospinal Fluid
HIV	-	Human immunodeficiency virus
CADASIL	-	Cerebral autosomal dominant arteriopathy with subcortical ischaemic strokes and leukoencephalopathy
MELAS	-	Mitochondrial encephalopathy, lactic acidosis ans stroke like events
GRE	-	Gradient echo sequence
DWI	-	Diffusion weighted image

COGNITIVE DYSFUNCTION IN SMALL VESSEL DISEASE

Abstract

Introduction – cerebral small vessel disease is an important risk factor for stroke and cognitive dysfunction in the elderly population. Most often small vessel disease are asymptomatic, presenting as white matter hyperintensities. Detailed clinical evaluation may reveal cognitive dysfunction. Vascular risk factors may predispose to the occurence of small vessel disease , as these white matter changes are believed to be of ischemic in origin.

Aim and objective – To study the clinical cognitive dysfunction in asymptomatic patients, presenting with white matter hyperintensities. To study the correlation between the extent of white matter changes,as assessed by Fazekas visual rating scale and degree of cognitive dysfunction.

Materials and methods – Patients aged more than 40yrs, presenting with white matter hyperintensity without higher mental function disturbance were included. Those with MMSE<9, terminal illness, fulfilling criteria for Alzheimers's disease and psychiatric illnes were excluded. Toatl of 38 patients were studied.White matter changes were rated as mild, moderate and severe by Fasekas visual rating scale. Detailed higher mental function and individual lobar functions were evaluated and correlation assessed. Various risk factors were analysed.

Results - Age is found to be the most important risk factor, and white matter changes increase with age. Hypertension and smoking were also strong risk factors. On clinical evaluation, psychomotor slowing was observed in 55% of patients with small vessel disease. Higher cognitive function like social judgement, abstract thinking were affected in 47% of patients. Executive dysfunction and impairment in alternate sequence was noted in 39% of subjects. Attention was impaired in 37% cases. Memory was involved in 21% of pateints. On evaluating the MRI changes by visual rating scale, moderate degree of white matter changes were observed in most of the patients52%. Strong correlation existed between the severity of white matter changes and psychomotor slowing and higher cognitive involvement but statistical significance could not be obtained due to small cohart.

Conclusion – asymptomatic, subclinical involement of cognitive function was obserevd in patients with cerebral small vessel disease. Psychomotor slowing and higher cognitive function impairment were most commonly observed. As small vessel disease may cause significant impairment in activities of daily living, primary prevention by attending to the vascular risk factors is the best way to prevent morbidity in elderly population.

Keywords – cerebral small vessel disease, white matter hyperintensity, psychomotor slowing, higher cognitive function.

INTRODUCTION

Cerebral white matter disease, also known as cerebral small vessel disease[1] includes a group of pathological conditions of varied etiology that affect small arteries, arterioles, venules and capillaries of the brain. Age-related, hypertension-related and cerebral amyloid angiopathy are the most common forms of cerebral small vessel disease. The consequences of small vessel disease on the brain parenchyma are mainly lesions located in the subcortical structures such as lacunar infarcts, white matter lesions and microbleeds. Unlike large vessels, small vessels cannot be currently visualised. Therefore, the parenchymal lesions that are thought to be caused by these vessel changes have been adopted as the marker of small vessel disease. Small vessel disease has an important role in cerebrovascular disease and is a leading cause of cognitive decline and functional loss in the elderly.

It was for a long time, that small vessel diseases were regarded as an incidental finding with no therapeutic consequences, but now there is increasing evidence that it is associated with cognitive decline and a higher risk of stroke and death [2] . Given this clinical relevance, recent years have shown a growing interest in small vessel disease, it's pathology, epidemiology, risk factors and treatment options. Changes in subcortical

white matter are common incidental findings on computed tomography and magnetic resonance imaging (MRI) in healthy elderly subjects[3,4].

In some individuals, MRI white matter hyperintensity represent small infarcts; in others, there is accumulation of fluid adjacent to hypertensive vessels, while in still others only white matter pallor is detected.[5-7] Hachinski et al[8] have coined the term leukoaraiosis (thinning of cerebal white matter) to describe these white-matter abnormalities. The clinical significance of these WMLs remains unclear, with some studies reporting that, they are associated with neuropsychological deficits[9,10] and with others failing to document any relationship between the presence and severity of white-matter changes and cognitive abnormalities.[11-14] Some studies have shown that white matter lesions are not only associated with cognitive disorders but also with gait[15-17], mood disturbances,[18,19] and urinary problems.[20]

Thus small vessel disease presenting as WML are the cause of about a quarter of all acute ischaemic strokes. [21,22] Overall, strokes caused by small vessel disease are less severe, but, the long-term outcome of these patients cannot be thought of as benign in terms of mortality and functional impairment.[23] No specific treatment for strokes caused by small vessel disease in the acute phase has yet been proposed.

Hence, the study small vessel disease and its correlation with cognitive dysfunction is useful for future development of new therapeutic options and search for its risk factors.

Therefore, it is useful to study white matter lesions on MRI, their severity and clinical correlation with cognitive dysfunction.

AIM AND OBJECTIVES

To analyze the cognitive dysfunction in patients with small vessel disease who manifest as white matter hyperintensities on MRI. To assess the severity of white matter lesions on MRI by visual rating scale and to study whether correlation exists between white matter lesion load and clinical cognitive dysfunction.

REVIEW OF LITERATURE

Small vessel diseases are the most frequent pathological neurological processes[24], playing a crucial role in at least three conditions: stroke, dementia, and ageing. Pathological processes that affect the small vessels of the brain such as small arteries and arterioles, capillaries and small veins are included under small vessel disease. But most often, small vessel disease is used to refer only to the arterial vessels.

Cerebral arterial small vessels have two origins: superficially, they stem from the subarachnoid circulation as terminal vessels of medium-sized arteries that originate from larger arteries. Secondly, deeper system at the base of the brain that stem directly from the large vessels as perforators. These two systems converge towards each other. After having passed the cortical layers and the deep grey structures respectively, they tend to merge in the deepest areas of the subcortical white matter where there is a watershed area.[25] Since the small vessels can not be visualisded, MRI periventricular hyperintensities are adopted as marker of small vessel disease.

CLASSIFICATION

Small vessel diseases are systemic disorders that affect various organs of the body. In some cases, the brain may be the main target of

these diseases, and the lesions and effects of the disease may be confined to the brain. In other cases, brain may not be affected at all.

There are different types of small vessel diseases and a simplified aetiopathogenic classification is as follows:

Classification of small vessel disease[1]

Type 1: Arteriolosclerosis (or age-related and vascular risk-factor-related small vessel diseases)

Fibrinoid necrosis

Lipohyalinosis

Microatheroma

Microaneurysms (saccular, lipohyalinotic, asymmetric fusiform)

Segmental arterial disorganisation

Type 2: Sporadic and hereditary cerebral amyloid angiopathy

Type 3: Inherited or genetic small vessel diseases

Example - CADASIL, CARASIL, MELAS, Fabry's disease, hereditary cerebroretinal vasculopathy, small vessel diseases caused by COL4A1 mutations

Type 4: Inflammatory and immunologically mediated small vessel diseases

Example- Churg-Strauss syndrome, Wegener's granulomatosis, Microscopic polyangiitis, cryoglobulinaemic vasculitis, Henoch-Schönlein purpura, Primary angiitis of the CNS, Sneddon's syndrome, Nervous system vasculitis secondary to infections, nervous system vasculitis associated with connective tissue disorders such as systemic lupus erythematosus, Sjogren's syndrome, rheumatoid vasculitis.

Type 5: venous collagenosis

Type 6: other small vessel diseases

Example - Post-radiation angiopathy and Non-amyloid microvessel degeneration in Alzheimer's disease

Among these, type 1, arteriolosclerosis, and type 2, sporadic and hereditary cerebral amyloid angiopathy are the most prevalent forms. Recent reports show that inherited small vessel diseases are in increase.[26] Of these diseases, CADASIL (cerebral autosomal dominant arteriopathy with subcortical ischaemic strokes and leukoencephalopathy) and Fabry's disease are among the most prominent.[27-29] Inflammatory and immunologically mediated small vessel diseases are a heterogeneous group of diseases that are rare and characterised by the presence of inflammatory cells in the vessel walls (vasculitis). They usually present as part of a systemic disease[30]. Venous collagenosis is pathological appearance of

venules and veins that are closely located to the lateral ventricles.[31] These vessels have increased thickness of the walls due to collagen that results in narrowing of the lumen and even occlusion.

The application of CT in the seventies and the subsequent application of MRI to image the brain have revealed an unexpected number of changes in the cerebral white matter in both asymptomatic and cognitively impaired individuals.

The pathogenesis and the clinical significance of these white matter alterations and its pathological substrate are not completely understood. The optimal term to designate these changes are also controversial. Some authors assume that the cerebral white matter changes (demonstrated by CT or MRI) are synonymous with "Binswanger's disease", while others use the term leukoaraiosis to refer to all white matter changes visible on neuroimaging studies.

HISTORICAL OVERVIEW

In 1894, Otto Binswanger described the case of syphillis in a man, who developed a progressive decline in mental functions characterized by speech, memory disorder, depression and personality changes with diminished motor power in the lower limbs and slight hand tremor.[32,33] In 1902 Alzheimer,[34,35] attributed the clinical and pathological changes in

Binswanger's case was due to white matter changes caused by arteriosclerosis of the long penetrating vessels. In 1962 J.Olszewski, [36] reviewing Binswanger's original report, proposed the term subcortical arteriosclerosis in which vessels of the white matter and subcortical grey matter are affected predominantly. As on date, the diagnosis of Binswanger's disease had acquired new popularity after the introduction of CT and MRI. But, it soon became apparent that alterations in the white matter detected by either CT or MRI were common in both symptomatic and asymptomatic subjects.

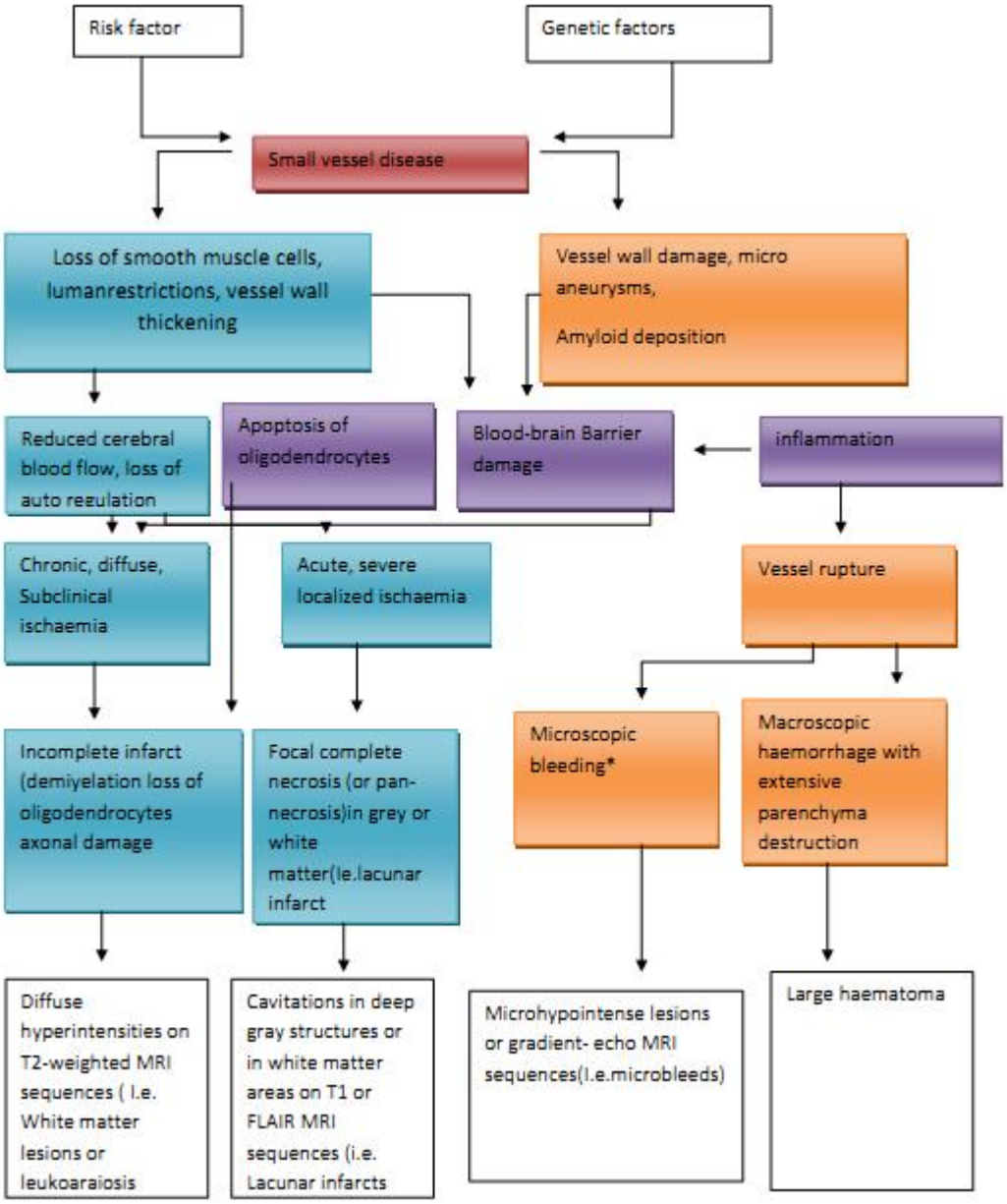
PATHOPHYSIOLOGY OF LEUKOARAIOSIS

Cerebral white matter disease, also called as cerebral small vessel disease, is reported frequently on neuroimaging, especially in older patients. It was regarded for a long time as an incidental finding, but with no therapeutic consequences. But now there is increasing evidence that it is associated with cognitive dysfuction as well as higher risk of stroke and death.

Cerebral small vessel disease is one of the common degenerative vessel disorders in the ageing human brain, along with cerebral atherosclerosis and cerebral amyloid angiopathy.[37] Its pathophysiology is still not completely understood. Endothelial dysfunction is proposed to

play an important role and is one of the first steps in the development of small vessel ischaemia. However, a recent review by stevenson et al., concluded that endothelial dysfunction may play a role in the development of small vessel disease but it is unlikely to be specific to small vessel diseases and also occurs in other types of cerebrovascular disease. Several factors may cause endothelial damage including mechanical factors like hypertension. Endothelial damage allows plasma proteins to leak into the vessel wall. This makes the vessel wall swell and may subsequently cause hyaline degeneration and fibrosis. This in turn leads to thickening of the wall, narrowing of the vessel lumen, reduced blood flow and cerebral perfusion and finally to ischaemia of the tissues supplied by these vessels.

Tissue injury caused by chronic ischaemia is one of the possible pathogenetic mechanism involved in the development of white matter lesions. In addition, endothelial damage leads to breakdown of the bloodbrain barrier. Plasma components which normally do not permeate through the bloodbrain barrier can now enter into the interstitial space and



brain parenchyma and cause damage to neurons and glial cells. These areas of damage in the brain may appear as white matter lesions on neuroimaging and on histopathological studies. White matter disease may hence be a consequence of varied pathological processes such as chronic ischaemia, breakdown of bloodbrain barrier and leakage of potentially

neurotoxic substances into the brain or of combination of any of these mechanisms.

The brains of patients with periventricular leukoaraiosis frequently show other pathological and imaging changes as well. For example, leukoaraiosis and lacunar infarcts often coexist.[38] Lacunar infarcts are caused by occlusion of small perforating vessels and are considered as another manifestation of small vessel disease even though their pathophysiology is different from that of leukoaraiosis. The co-existence of leukoaraiosis and occlusion of small perforating vessels leading on to lacunar infarct are associated with higher risk of major stroke in patients with leukoaraiosis. Enlarged perivascular spaces also known as VirchoweRobin spaces are another common finding in small vessel disease and is usually formed around the diseased vessel.[39] On CT brain images, these enlarged perivascular spaces may be misdiagnosed as lacunar infarcts, but can be clearly distinguished on MRImaging. The clinical significance of enlarged VirchoweRobin space is uncertain. Cerebral microbleeds are small haemorrhages involving the perivascular spaces. Pathologically, they represent the leakage of blood and its components through the vessel wall rather than frank haemorrhage. They are frequently seen in association with leukoaraiosis. They are most commonly found in cases of cerebral amyloid angiopathy, but can also

occur in patients whose hypertension is poorly controlled.[40] The clinical importance of microbleeds is on increase. Microbleeds may indicate an increased risk for cerebral haemorrhage, particularly in patients who are on anticoagulation therapy. Some clinicians even regard cerebral microbleed as a relative contraindication to anticoagulation therapy. But, data are not clear on the extent to which cerebral microbleeds increase the risk of cerebral haemorrhage. Further studies in this area are going on.

Finally, leukoaraiosis may also be associated with brain atrophy.[41,42] With increasing severity of white matter disease, there is often associated corresponding decrease in grey and white matter volume and an increase in the size of ventricles.[43] Grey matter atrophy may be caused by deafferentation due to loss of cortical-subcortical connections. Consequently,the ventricles may enlarge due to loss of subcortical white matter.[42]

PREVALENCE

The prevalence of leukoaraiosis varies widely between different studies. The prevalence rates vary from 5.3% [43] to more than 95%.[44] This high variability may be explained by the methodological differences between various studies, for example different ways for assessing leukoaraiosis in neuroimaging and differences in the risk factors and

comorbidities included in the study populations. With such varied estimates of the prevalence of leukoaraiosis, it is difficult to assess whether its prevalence has changed over time. However, the data so far available do not show any significant temporal changes in the prevalence of white matter disease.

This is surprising, because the better quality and more sensitive brain imaging available today might have led to a higher rate of diagnosis in ageing population. This may have led to a real increase in the prevalence of small vessel disease. But, today the awareness of risk factors are on the high and control of hypertension has certainly improved. Hence, an apparent increase in the prevalence of leukoaraiosis because of better imaging may have been offset by a real decrease due to aggressive blood pressure control. However, neuroimaging has only been easily and widely available since 1980s, and three decades may be too short a time to show significant changes in the leukoaraiosis prevalence.

RISK FACTORS

Risk factors associated with leukoaraiosis have been studied extensively and study findings are conflicting probably due to differences in study methodology adopted. Risk factors may be non-modifiable or

acquired and treatable. Hypertension is the strongest modifiable risk factor for leukoaraiosis. Most widely studied risk factors are discussed below.

Age

Increasing age is probably the most important risk factor associated with the development of leukoaraiosis,[44,45]Hence it is often referred as 'age-related white matter disease'. Though leukoaraiosis is a pathological phenomenon, it may to some extent be a part of the normal physiological ageing process. But, it is unclear at what age exactly white matter disease starts developing. Precise data on the extent of disease that can be considered as 'normal' at a particular age do not exist. Most of the studies suggest that at least some white matter lesions exist after the age of 50-65 years. It is clear that leukoaraiosis is a common finding in the elderly and it becomes more prevalent and more severe as age increases.

Sex

Studies analysing the association between the prevalence of leukoaraiosis and gender shows conflicting results. Some studies found that higher prevalence of leukoaraiosis was found in women,[46] while some showed a trend that men are at higher risk.[45] Such results may be partly explained by differences in the characteristics of the study population and by various confounding factors. There have been differences in the age or

the prevalence of hypertension between women and men suggesting an apparent sex difference in the white matter disease prevalence. But a recent systematic review did not find any such gender differences.

RACE

White matter disease occurs more frequently in Afro-Caribbean than Caucasian populations and this may be because of a higher prevalence of hypertension in the Afro-Caribbean.[47] And often hypertension is more severe and blood pressure control is poorly controlled in afro-caribeans. Genetic factors may also play a role in such gender difference.

GENETIC FACTORS

Genetic disorders like cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), are associated with prominent lesions in the white matter. But, CADASIL contributes only for a very small number of cases with white matter disease.[53] Several studies have shown that the presence of white matter lesions and polymorphisms in a number of genes, such as Apolipoprotein(a) or ACE are associated.[60] Such genetic disorders may not be directly associated with white matter disease but may predispose an individual to develop risk factors for small vessel disease, as well as their susceptiblity to develop end-organ damage due to the risk factors. For

instance, the development of hypertension to certain extent is determined genetically, and soforth, the tendency to develop small vessel disease as a result of hypertension might also be influenced by such genetic factors.

HYPERTENSION

Hypertension is one factor that is strongly associated with white matter disease and is the most important modifiable risk factor so far.[25] Studies indicate that elevation of both systolic and diastolic blood pressure are relevant in increasing the risk for leukoaraiosis. Threshold value above which the disease starts is not apparent, and the association is found to be a continuum. Apart from the absolute values, diurnal variation in blood pressure may also contribute to white matter disease.

DIABETES MELLITUS

The effect of diabetes mellitus on development of leukoaraiosis has shown conflicting results. Some studies show a positive association [48] in particular with periventricular lesions. Impaired fasting glucose (IFG) was found to be associated with the development white matter disease. A recent review comparing diabetics with and without leukoaraiosis found that higher insulin levels are present in those with white matter disease. All these data suggest that insulin resistance is a definite risk factor to cause white matter disease. However, the strength of association is not clear and

pathophysiology is uncertain. A few studies have failed to find any association.[49]

DYSLIPIDEMIA

Dyslipidemia is an important risk factor associated with large vessel disease. It is unclear whether abnormalities in lipid metabolism are also a risk factor for white matter disease. Few studies have shown that low high-density lipoprotein and hypertriglyceridaemia may increase the risk for developing small vessel disease.[50] However, other studies did not find any association between dyslipidaemia and small vessel disease.[51]

SMOKING

It is not clear whether smoking influences the development of small vessel disease. Some studies found that they are associated[45] whereas others found no differences in the prevalence of white matter changes between smokers and non-smokers.[49,51] Smoking predisposes to large vessel atherosclerosis. But the underlying pathology in leukoaraiosis is proposed to be disease of the small vessels and hence large vessel atheroma and leukoariosis may not necessarily be associated. Few studies have found an association between atherosclerotic disease and white matter lesions.

This can be explained by two different mechanisms. First, stenosis caused by atherosclerosis allows less blood into the brain and lesser perfusion that increases the risk for chronic ischaemia and hence the risk of developing white matter lesions. Second, small vessel disease and atherosclerotic disease have some risk factors in common which may occur concurrently.

HOMOCYSTEINE AND VITAMIN B12

Several studies have supported the association between low serum vitamin B12 levels and small vessel disease, especially those with periventricular lesions.[52] However, though there is some evidence that hyperhomocysteinaemia, which may be caused by deficiency of vitamin B12 and low vitamin B12 levels are associated with white matter lesions, there is yet no data showing that vitamin B12 substitution or lowering homocysteine improves leukoaraiosis or slows its progression.

To summarise, hypertension and increasing age are the only well accepted risk factors for white matter disease. The association between small vessel disease and other risk factors might be due to confounding by hypertension. For instance, Afro-Caribbean population who are more likely to be hypertensive have higher prevalence of white matter disease. The association of leukoaraiosis and other factors is less certain. This

includes diabetes mellitus which is widely believed to increase the risk of developing small vessel disease. Differences in study methodology can explain some of the conflicting results. But a recent systematic review of so far available data confirmed age and hypertension are the only consistent risk factors for white matter disease and no clear association exists with any other risk factor.

CLINICAL PRESENTATION

White matter lesions often remain asymptomatic until they affect a significant quantity of brain tissue.[54] Symptoms due to leukoaraiosis emerge slowly over time, and is often not possible exactly to determine their onset. Moreover, the symptoms due to white matter disease are non-specific and may also be attributed by other pathological conditions that are also common in ageing population. Frequently, such pathological conditions may often coexist. For instance, patients may be diagnosed as 'mixed dementia' because of having both vascular dementia and Alzheimer 's disease. It is henceforth, difficult to say at which stage white matter lesions become symptomatic and which are the specific symptoms it causes.

There is general agreement that leukoaraiosis is associated with

- Cognitive decline[54,55]

- Gait disturbance and falls[56,57]

- Depression[56]

- Increased stroke risk.

Among these, decline in cognitive function is the widely recognised clinical presentation. It may present with poor performance in a gross range of cognitive tests. Psychomotor slowing, executive dysfunction and attention impairment are predominantly affected by white matter lesions.[2,54] Additionally, leukoaraiosis is also associated with deterioration in gait and thus leading to an increased risk of falls.

Given the association of white matter lesions with cognitive dysfunction and gait disturbance, it is not unusual that in elderly patients,those with larger white matter lesions performed worse in their activities of daily living than those controls without significant leukoaraiosis.[58]

THE ASSOCIATION OF LEUKOARAIOSIS AND STROKE

White matter lesions and stroke are very closely associated. Previous history of stroke is associated with higher prevalence of white

matter lesions,[43] and leukoaraiosis is found to be a risk factor for the first ever and also for recurrent stroke.[2] This association may be explained by shared risk factors like increasing age, diabetes and hypertension. Moreover, leukoaraiosis is thought to be due chronic low-level ischaemia. Chronic ischaemia of brain tissue predisposes to higher risk of development of infarction if exposed to further insult in the form of ischaemia. There also exists a close association between white matter lesions and lacunar stroke. Both are found to be manifestations of cerebral small vessel disease and may occur together. Few authors believe that leukoaraiosis represents chronic ischemic changes whereas lacunar infarcts are due to an acute insult. Some authors have shown that the risk factors for these two conditions are different and hence suggest they may represent different pathologies.

IMAGING IN SMALL VESSEL DISEASE

With advent of newer brain imaging, particularly MRI and its various sequences, a multitude of focal, patchy or diffuse signal changes in the cerebral white matter are demonstrated.[59] The MRI changes may be hyperintense compared with the normal white matter on T2 or FLAIR sequences, with or without corresponding hypointensity on T1-weighted images.[60] Inspite of extensive research, pathogenic mechanism, clinical

significance and structural substrate of these changes are still incompletely understood.[61]

Various studies have shown that on MRI, the frequency of white matter hyperintensities increases with advancing age.[62,63] Risk factors associated with such white matter changes are hypertension, cardiac disorders, diabetes mellitus, smoking and cerebrovascular disorders. Such white matter lesions may present with clinical features like cognitive dysfunction, gait abnormality or mood disorder. But the results are conflicting. Some nonspecific white matter changes may exist in clinically normal healthy individuals.[63,64] The distinction between normal white matter changes and pathological white matter changes may be difficult.

Source of controversy in the previous studies could be due to different rating scales used to assess the white matter changes. There are about 13 commonly used MRI rating scales.

White matter changes may involve periventricular region and/or deep white matter region. Various visual rating scales have used various parameters to assess the white matter lesion load. Periventricular hyperintensities were rated by The Gerard and Weisberg scale and The Shimada scale. Periventricular and deep white matter hyperintensities were rated by scales like The Erkinjuntti scale, The Fazekas scale, The

Mirsen scale, The Scheltens scale, The Ylikoski scale, wahlud scale and the schimdt scale. Deep white matter hyperintensity scales include The Herholz scale, The Hunt scale, The van Swieten scale. Mantyala et al65 compared the 13 scales and states that international harmonization of white matter changes is needed.

SUBCORTICAL DEMENTIA

Subcortical ischemic vascular dementia is subtype of vascular dementia that inculcates small-vessel disease as the main pathological process with ischaemic white-matter lesions and lacunar infarct as the predominant brain lesions. The location of lesions is primarily subcortical and subcortical syndrome is the clinical manifestation. Subcortical dementia is quoted by overlapping clinical entities like Binswanger's disease, small vessel disease and the lacunar stroke.[66,67] Clinical identification of subcortical dementia may be based on a modified criteria of National Institute of Neurological Disorders and Stroke and the Association Internationale Recherche en Neurosciences (NINDS-AIREN) for vascular dementia.[68] Vascular dementia criteria require that onset of dementia is related to cerebrovascular disease. In subcortical dementia, the onset is more insidious and gradually progressive. Temporal relationship between neuroimaging, cognitive dysfunction, and evidence for

cerebrovascular disease is not always clear. Hence, the temporal relation association was omitted from research criteria for subcortical dementia. The neuroimaging criteria includes patients with predominant whitematter lesions (Binswanger type) and those with lacunar infarcts (lacunar state type).[68] The classification of subcortical dementia due to white matter lesions caused by small vessel disease identifies a homogenous group of patients with predictable clinical features, natural history of evolution, clinical outcomes and treatment responses. Yet, further research to define the syndrome, its clinical stages and validation of neuroimaging, Identification of mild and early subcortical dementia will enable new therapeutic options.

SMALL VESSEL DISEASE WITHOUT DEMENTIA

Small vessel disease without dementia mostly presents as white-matter lesions on MR imaging of brain. Such lesions of white matter hyperintensity may occur as early as thirties, but their prevalence increases strikingly with age and by 70 years of age almost 70% of the population has such lesions. Frequently, white matter lesions are associated with vascular risk factors. But oxidative stress is found to be a poorly recognised risk factor for white-matter lesions. White-matter lesions are implicated in causing important cognitive dysfunction even in the absence of dementia.[43,69,70] Some important non-cognitive and motor consequences

include depression, gait disorder, imbalance, urinary frequency that often impairs quality of dailyliving.[71]

SMALL VESSEL DISEASE AND ALZHEIMER'S DISEASE

Mixed dementia encompassing Alzheimer's disease(AD) with small vessel disease is a difficult concept. Although common, this coexistence is not well recognised by current diagnostic methods. Degenerative and vascular pathologies interact and manifest as cognitive impairment.[72] AD and small vessel disease share some common pathogenetic mechanisms.[73]

VASCULAR FACTORS IN ALZHEIMER'S DISEASE

The evidence for cerebrovascular pathology in AD, including small-vessel disease and microinfarction is considerable. This suggests a substantial overlap between vascular dementia and AD. Amyloid angiopathy is the most common pathologic vascular lesion in AD, present in almost all AD cases. Apolipoprotein E4 is a strong factor associated with the development of AD. It may cause cognitive dysfunction independent of plaque load and tangle pathology. Yet, its exact role in non-cognitive and cognitive features requires further clarification. Vascular risk factors such as diabetes mellitus, hypertension, atherosclerosis, ischaemic heart disease, smoking and raised homocysteine are also risk factors commonly associated with AD and biomarkers of systemic vascular

disease like hypercholesterolaemia are also associated with the aetiopathogenesis of AD. These vascular pathologies may result in localised or global cerebral hypoperfusion brain that may inturn lead to white-matter lesions, AD pathology or both. Genetic factors like apolipoprotein E can modify the progression of AD in the presence of cerebrovascular disease. And hence, the prevention or treatment of vascular risk factors may reduce occurrence of AD and mixed dementias. None current criteria distinguishes alzheimer's and mixed dementia. For the most part, none of these criteria have been satisfactorily validated by prospective study. Structural neuroimaging, especially MRI is the imaging tool of choice to assess cerebrovascular disease, but functional brain imaging is the potential instrument useful to differentiate AD with small vessel disease from vascular dementia.

HEREDITARY DISORDERS WITH VASCULAR COGNITIVE DYSFUNCTION

The genetic contribution to vascular dementia and stroke is important. The genetic defects for numerous monogenic disorders are identified. CADASIL is a monogenic cause of small-vessel disease manifesting as white matter disorder and stroke in young individuals. Clinical presentation may be transient ischaemic attacks and strokes (80%), migraine with aura (40%), cognitive deficits (50%), epilepsy (10%)

and psychiatric disorders (30%).[74] Mean age of disease onset is in thirties and neuroimaging may reveal small lacunar infarct and diffuse white-matter lesions.[75] The underlying pathovascular lesion is non-amyloid angiopathy of small arteries and capillaries primarily involving the brain, but also other organs. Diagnosis hence may be made by skin biopsy. Microscopic examination shows granular osmiophilic deposits in the vascular basal membrane. The disease is due to mutations in the NOTCH3 gene, that codes for a transmembrane receptor. CADASIL mutations involves a highly conserved cysteine residues in the epidermal-growth-factor repeat domains. Expression of NOTCH3 is always restricted to vascular smooth-muscle cells. The cerebral amyloid angiopathies are characterised by deposition of amyloid in the walls of leptomeningeal and cortical blood vessels. Clinical manifestation includes multiple and recurrent lobar haemorrhages resulting in cognitive deterioration and strokes. MRI often displays focal lesions that may be ischaemic or haemorrhagic as well as diffuse white-matter abnormalities. Blood vessels show amyloid deposition, microaneurysm formation and fibrinoid necrosis. Rupture of such structurally weakened vessels result in cerebral haemorrhage, especially in the cortex (lobar haemorrhage) rather than the subcortical regions like basal ganglia, thalamus that typical occur in hypertensive haemorrhage.

COGNITIVE AND PSYCHIATRIC SYMPTOMS

Vascular cognitive impairment includes many diverse syndromes of varied causes, with marked differences in clinical presentation and course. Single strategic infarcts may produce cognitive and other deficits which entirely depend on the location and size of the infarct. But, the characteristic neuropsychological profile of small vessel disease is early impairment of attention , executive dysfunction, slowing of motor performance and information processing.[76,77] Episodic memory is relatively spared compared with AD. Other cognitive functions are also affected variably, depending on the pathological substrate involved in individual cases. The concept of amnestic cognitive impairment is probably very limited because of early executive, attentional and motor disabilty in patients with early vascular disease.

The psychiatric profile of vascular cognitive impairment is not well established but there exists a strong relation between small vessel disease with white-matter lesions and depression. Another important factor is the site of the ischaemic lesions that involve the thalamocortical projections that may predispose to depression. In vascular cognitive impairment, the neurobiological substrates for the cognitive and psychiatric symptoms is yet to be established. Attentional impairments, executive dysfunction, slowed mentation and depression are probably due to disruption of

frontosubcortical circuits. Small-vessel disease causing lacunae and white-matter changes is likely to be the important pathological process resulting in cognitive dysfunction. The relationship between the symptoms and specific location of the lesion remains to be established. This information is essential for the rational conceptualisation of these vascular disorders and for developing targeted treatment. The variability of symptoms relate to the site and extent of specific lesions.

The contribution of white-matter changes as seen on MRI to the clinical progression of disease is of great importance but it remains to be established. In particular, progression of lesions is not yet clearly correlated with worsening of cognitive function. [78] With current available methods, more than 1 year follow-up is required to detect the progression of white-matter changes and for selection of those patients at high risk of disease progression.

PRIMARY PREVENTION

Knowledge of pathophysiological mechanisms of the disease process is essential to formulate any primary preventive measures. Since small vessel disease of the brain may result from various pathological processes, strategies for preventive measures vary accordingly. Small vessel disease is only one of the manifestations of systemic processes that

affect the blood vessels throughout the body. The pathophysiology in a given individual that result in small vessel disease of the brain but not in other organs is not well understood. Treatment of the primary risk factors is essential, so that secondary changes and clinical disease can be prevented. For instance, it is always better to prevent the occurance of stroke by early and aggressive treatment of systemic hypertension than by detecting and removing an established carotid atheroma. Early intervention is important because the risk factors cause vascular injury in early life, probably before the fourth decade. But it is difficult to intervene at this stage because the early stages of vascular injury may remain clinically silent.

For primary prevention to be successful, these strategies must be based on accurate identification of the pathological process that result in vascular injury. Further, the pathophysiological mechanisms, by which small vessel disease of brain cause cognitive dysfunction is to be explored. But current strategies insist on early detection and adequate treatment of known vascular risk factors.

SECONDARY PREVENTION

Treatment of acute vascular event has attained major advances especially with thrombolytic agents and antiplatelet drugs for ischaemic

stroke. But the studies on the role of neuroprotective agents are disappointing.[79] Treatment for recurrent episodes of stroke is now well studied and guidelines established[82] that include antiplatelet agents, warfarin for atrial fibrillation, carotid endarterectomy for atherosclerotic disease of carotids and adequate blood-pressure lowering. Eventhough the data are limited, trials on recurrent stroke prevention tends to offer the opportunity to investigate stroke-associated cognitive dysfunction and dementia.

SYMPTOMATIC TREATMENT

Several large, randomised, double-blind, controlled trials have already been done. Initial studies of varied drugs including nootropics, vasodilators and antioxidants in the treatment of vascular dementia are disappointing.[80] Adequate evidence is available with other agents like propentofylline and memantine in symptomatic treatment of vascular cognitive impairment.[81] The calcium channel antagonist and vasodilator nimodipine has been extensively studied. Studies have shown no overall evidence of efficacy of nimodipine invascular AD but beneficial effects are seen in patients with subcortical vascular dementia[82] and further studies in this area are continuing. Studies suggest evidence of efficacy for cholinesterase inhibitors in vascular cognitive impairment. In a double-blind, placebo-controlled trial with possible and probable vascular

dementia, by NINDS-AIREN criteria, donepezil, a cholineesterase inhibitor significantly improved cognitive function when compared with placebo.83 A study in patients with vascular cognitive dysfunction or AD with cerebrovascular disease, 24 mg galantamine improved cognition significantly when compared with placebo. Results from other trials are awaited. But evidence so far suggests that cholinesterase inhibitors may be of immense benefit in treating vascular dementia.

Thus various literature has shown that hypertension and ageing are the important risk factors for small vessel disease and understanding of its pathogenesis is essential for devising newer therapeutic modalities and drugs.

MATERIALS AND METHODS

STUDY GROUP

The study was conducted on inpatients and out patients of Institute of Neurology, Rajiv Gandhi Government General Hospital Chennai. Approval from the hospital ethical committee was obtained. The study was observational, cross sectional study in nature designed to analyse the patients in age group of 40 years and above , who presented with MRI showing white matter changes in the periventricular or deep white matter region.

The sample size was 38 and the study period was from January 2010 to December 2012.

Inclusion criteria

1. Subjects symptomatic or asymptomatic with age more than 40yrs
2. MRI showing white matter changes in the periventricular or deep white matter region

Exclusion criteria

1. Subjects with mini-mental score less than 9

2. Subjects meeting DSM-IV or Alzheimers disease and related disorders criteria for Alzheimers disease

3. Terminal illness

4. Major psychiatric illness

All subjects underwent a comprehensive higher mental function evaluation including detailed lobar function. Attention was assessed by Digit repition test- both digit forward and digit backward were tested and sustained attention assessed by “A” Random letter test. Comprehension, repitition and spontaneous speech were assessed. Verbal Fluency was tested by Animal-naming test and FAS test. Memory was tested by applying Wechsler memory scale. Executive function was tested by trail-making test. Cognitive function was tested by fund of knowledge, Calculation, Problem solving, Social awareness and Judgement and Abstract thinking by Proverb interpretation .

MRI white matter changes were assessed by Fazekas visual rating scale.

Fazeka visual rating scale

Scoring for Periventricular hyperintensities (PVH)

Absence - 0

Caps or pencil-thin lining -1

Smooth "halo" -2

Irregular PVH extending into the deep white matter -3

Deep white matter hyperintense signals (DWMH)

Absence -0

Punctate foci -1

Early confluence of foci -2

Large confluent areas -3

A total score of 0 to 2 was taken as mild, score of 3 and 4 taken as moderate and score of 5 and 6 is taken as severe. All patients underwent a thorough clinical examination and assessed for focal neurological deficit. Obtained data were tabulated statistical analysis done by IBM-SPSS statistical software.

RESULTS AND ANALYSIS

Cognitive dysfunction in patients with small vessel disease as manifested on MRI as white matter changes was studied. MRI changes were rated by Fazekas scale. Various cognitive domains were assessed by clinical methods and whether cognitive dysfunction correlated with severity of MRI white matter changes was studied. The results are as follows.

EPIDEMIOLOGY

Total number of subjects studied with MRI white matter changes was 38.

Table -1- Age Distribution

	Cases	
	No	**Percentage**
40-50	7	19
50-60	8	21
60-70	19	47
>70	3	13

In the present study, patients age ranges from 40-77 years. Most of the patients were in the age group of 60-70, which was about 47% of the total number of cases.

Table -2 Sex Distribution

Sex	Cases	
	No	**Percentage**
Male	26	68%
Female	12	32%

Out of the 38 patients studied, 68% were male and 32% were female.

Table -3 Risk factor profile

	Male Total-26	**Percentage**	**Female Total - 12**	**Percentage**	**Total percentage**
Hypertension	17	65	5	42	57
Diabetes	14	54	6	50	53
Smoker	20	77	0	0	53
Dyslipidemia	9	35	3	25	32

Hypertension, Diabetes, smoking and dyslipidemias were found in significant number of patients. Among the non-modifiable risk factors, hypertension(57%) was the most prevalent risk factor found in patients with white matter changes. Smoking was the modifiable risk factor present in 53% of the study population who were all men.

Table-4 EEG Profile

	Number of Patient	**Percentage**
Normal	29	76
Focal slowing	1	3
Diffuse slowing	8	21

Among the patients with white matter changes, twenty nine (76%) had normal EEG. Eight patients(21%) had diffuse slowing on EEG.

MRI white matter changes were scored by Fazekas scale and the number of patients with different scores are as follows.

Out of the 38 subjects studied, 8% had a score of 1, 24% had a score of 2, 32% had a score of 3, 21% had a score of 4, 10% had a score of 5, 5% had a score of 6. Most of the subjects had a score of 3.

Table -5 Fazeka Score Profile

Fazekas score	Number of patients	Percentage
1	3	8
2	9	24
3	12	32
4	8	21
5	4	10
6	2	5

Table- 6 Severity Grading – Fazekas Scale

Severity grade	Number	Percentage
Mild	12	32
Moderate	20	52
severe	6	16

Out of 38, 52% of patients, came in the category of moderate score of Fazeka rating scale.

Table- 7 Cognitive Dysfunction In Various Domain

Domain	Number of patients	Percentage
Executive Dysfunction	15	39
Attention	14	37
Alternate Sequence	15	39
Fluency	13	34
Psychomotor slowing	21	55
Memory	8	21
Higher Cognition	18	47

Among the 38 patients with white matter changes, 14 (37%) had normal function in all cognitive domains, whereas 24(63%) patients had dysfunction in one or more cognitive domains. Out of the thirty-eight patients with white matter changes, most common higher mental function disturbance was psychomotor slowing(55%). Memory was the least affected parameter(21%). Higher cognitive function was also significantly affected(47%). Attention (37%), Alternate sequence(39%) were also significantly affected.

Table - 8 Attention and MRI grading

MRI changes	Attention deficit	
	Number of patients	Percentage
Mild	3	21
Moderate	6	43
severe	5	36
Total	14	37%

Attention assessed by Digit Repetition Test and Random ‘A’ Letter Test was affected in fourteen(37%). Among them 43% had moderate white matter changes, 36% had severe white matter changes and 21% had mild white matter changes.

Table -9 Executive Dysfunction and MRI grading

MRI changes	Executive Dysfunction	
	Number of patients	**Percentage**
Mild	4	27
Moderate	5	33
severe	6	40
Total	15	39%

Executive dysfunction as tested by trail making test was impaired in 39% of subjects. Among them 40% had severe white matter changes, 33% had moderate white matter changes and 27% had mild white matter changes.

Table -10 Alternate Sequence and MRI Grading

MRI changes	Alternate sequence	
	Number of patients	**Percentage**
Mild	1	7
Moderate	9	60
severe	5	33
Total	15	39%

Out of the 38 subjects investigated, 39% had impairment in alternate sequencing. Among them 60% had moderate white matter changes, 7% and 33% had mild and severe white matter changes respectively.

Table – 12 Fluency and MRI Grading

MRI changes	Fluency Impairment	
	Number of patients	**Percentage**
Mild	1	8
Moderate	7	54
severe	5	38
Total	13	34%

Fluency tested by Animal naming test and FAS test was impaired in 34% of subjects. Among them, 54% had moderate white matter changes, 38% had severe white matter changes and 8% had mild white matter changes.

Table – 13 Psychomotor Slowing and MRI grading

MRI changes	Psychomotor slowing	
	Number of patients	**Percentage**
Mild	3	14
Moderate	12	57
severe	6	29
Total	21	55%

Out of the 38 subjects investigated, 55% had impairment in alternate sequencing. Among them 57% had moderate white matter changes, 29% and 14% had severe and mild white matter changes respectively.

Table -14 Memory Impairment and MRI grading

MRI changes	Memory Impairment	
	Number of patients	**Percentage**
Mild	0	0
Moderate	2	25
severe	6	75
Total	8	21%

Memory was tested Weschler memory scale and was impaired in 21% of patients. Among them, 75% had moderate white matter changes, 25% had moderate white matter changes.

Table – 15 Higher Cognition and MRI grading

MRI changes	Higher cognitive impairment	
	Number of patients	Percentage
Mild	2	11
Moderate	12	67
severe	4	22
Total	18	47%

Higher Cognitive function was tested by Fund of knowledge, Calculation, Problem solving, Social awareness and Judgement and Abstract thinking by Proverb interpretation. In the study population, 18(47%) had higher cognition impairment, of which 11% had mild, 67% had moderate and 22% had severe MRI white matter changes.

DISCUSSION

RajivGandhi Government General Hospital and Research Centre, Chennai is a premier institute and referral centre of southern India. Patients refered for various reasons, with MRI showing white matter hyperintensities were studied for cognitive dysfunction and correlation between severity of white matter changes and cognitive deterioration was analysed. Total of 38 patients were studied. This is a cross sectional study done between

Population Characteristics and Risk Profile

Analysing the age group in this study, maximum white matter changes were seen in the age group of 60-70 years(47%). The prevalence of white matter lesions increased with age, rising from 19% among 40 to 50year-old subjects to 47% among 60- to 70-year-old subjects. This higher prevalence rate compared to the younger age groups show, age is an important risk factor for white matter disease. Though the prevalence in age group > 70years was lesser, it could be due to higher morbidity associated with increasing age, as sick patients with lesser MMSE and bedridden patients were excluded from the study. Breteler et al's [84] study has shown that increasing age is an important risk factor for cerebral white

matter disease. Similar results were obtained in study by Awad et al[5] and Kertesz et al[85]

In our study 68% of the patients were male which shows significant male preponderance of white matter disease in male. This is in contrast with the study by sullivan et al [86] which shows higher prevalence in female(60%). Reinhold schmidt's study[87] also shows slight preponderance in female(female:male = 51:49)

Table – 16 comparison of sex distribution

Sex	Our study	Sullivan et al	Schmidt et al
Male	68%	40%	49%
Female	32%	60%	51%

Analysing the risk factors associated with white matter changes, Hypertension was the most common modifiable risk factor. Smoking was the most common non-modifiable risk factor and it had the strongest positive association with small vessel disease causing white matter lesions. Schmidt et al case control study with [89] patients, also confirmed previous results demonstrating a higher rate and extent of areas of WMH in hypertensive subjects compared with controls.[5,87,88]

Diabetes mellitus was presesent in more than 50 percent of patients in both male amd female. Study by Breteler[43] found no evidence for a relation between diabetes mellitus and white matter lesions.

In our study, dyslipidemia was present in significant number of patients(31%). Bretelers[43] study showed that total cholesterol and HDL cholesterol levels were not significantly associated with the presence of white matter lesions among all subjects combined. However, for subjects of elderly age group of 65 to 74 years of age, higher levels of total cholesterol tended to be associated with white matter lesions.

Analysis MRI white matter lesions

White matter changes in MRI were scored from 1-to 6 by Fazekas scale. In our study, score of 3 was found in most number of parients32%. Score of 2 and 4 was seen in 24% and 21% respectively. White matter lesions were sub classified as mild, moderate and severe. Moderate score was the most prevalent sub-group among the patients(52%). In comparison to our study, Zimmerman et al showed score of 1(43%) and 2(29.9%) were the most common patterns.

Van Den Heuvel on behalf of PROSPER study group, analysed the reliablity of visual scoring system in comparison with volumetric methods. He concluded that, reliablity of visual scoring system was good but

volumetric analysis in more sensitve and objective method to study longitudinal white matter changes.

Analysis of cognitive profile

In our study 28 patients(74%) had cognitive dysfunction in various domains and 10 patients(26%) had normal cognitive function. Among the asymptomatic patients, mild score on MRI was the most prevalent(64%). In symptomatic patients with impaired cognition, moderate scored lesions were most prevalent(62.5%)

Normal cognition = 10(26%)			**Cognitive impairment =28(74%)**		
Mild	8	80%	Mild	4	14%
Moderate	2	20%	Moderate	18	64%
Severe	0		Severe	6	22%

Specific Cognitve Dysfunction

Psychomotor slowing was the most prevalent cognitive domain affected in symptomatic patients. It was observed in 55% of patients. Executive dysfunction and impairment in alternate sequence was found to be abnormal in 39% each. Higher cognition was impaired in 47% of

patients. Memory was least affected, seen in 21% of patients. Multiple cognitive domain impairment was seen commonly in patients with small vessel disease presenting as white matter changes because the fronto-subcortical fibres for multiple cognitive function are present clustered in the periventricular region.

In our study, psychomotor slowing and executive dysfunction were the two most affected domains.

Amberla et al[89] study of small vessel disease in genetically mediated conditions like CADASIL showed early impairment of Executive fuction and later deficits in mental speed and set-shifting abilities.

Case - control study by Cohen et al[90] showed that executive dysfunctions and attention impairment were strongly associated to the presence and extension of Subcortical hyperintensities.

Kramer et al's[91] study also showed executive dysfunction as the earliest and most common domain affected.

In concordance with our study, Prins et al[92] in a population based study, concluded that measures of small vessel disease by MRI associated with cognitive decline in executive functions and processing speed.

Skoog et al[93] in his case control study concluded that white matter lesions correlated with general and specific cognitive domains like visuospacial orientation and processing speed.

In another study, Wen et al[94] inferred that white matter lesions but not lacunar infarcts correlated with impaired executive tests.

On analysing the severity of MRI changes with cognitive dysfunction, positive correlation existed between the two. Of the subjects with severe white matter changes, all of them had cognitive dysfunction in one or other domains. Of all the domains analysed, Psychomotor slowing and Higher Cognition were the two domains severely involved and their involvement correlated with severity of MRI white matter changes. Other domains like attention, alternate sequence, fluency also had positive correlation with MRI changes. Memory was the domain least involved in the our study population and it did not have positive correlation with MRI changes.

In concordance with our study, Cohen et al's[90] study has shown that executive dysfunction correlated with sub-cortical hyperintensity volume.

De groot et al's[95] population based study showed positive correlation between periventricular white matter hyperintensity and decline in cognitive function. Kramer et al[91] and Logan et al studies also shown that

extent white matter hyperintensity correlated with severity of cognitive dysfunction.

In contrast, De mendonca et al[96] and sabri et al[97] study have shown that white matter lesions were not correlated with cognitive dysfunction.

CONCLUSION

1. Asymptomatic subclinical cognitive dysfunction occur in cerebral small vessel disease manifesting as white matter hyperintensity.

2. Age is strong risk factor for small vessel disease and increasing age is associated with severe white matter changes and higher decline in cognitive function.

3. Psychomotor slowing was observed most commonly in patients with small vessel disease. Reaction time, paradigms to be done for further confirmation.

4. Impairment of Higher cognition like judgement, abstract thinking were observed in patients with small vessel disease.

5. Frontal lobe battery revealed Attention, alternate sequence, executive function and verbal fluency were also significantly impaired in small vessel disease.

6. Memory was least affected cognitive domain in small vessel disease.

7. Psychomotor slowing and higher cognitive dysfunction correlated the best with MRI white matter changes, though statistical significance could not be established in view of small cohart.

Thus, MRI white matter changes are considered as surrogate marker of cerebral small vessel disease. Patients with white matter changes had asymptomatic cognitive dysfunction involving various domains which is found to increase with increasing age. Progressive cognitive dysfunction leads to impairment of activities of daily living and moreover, small vessel disease is also risk factor for cerebrovascular accidents. Hence, the conditions that predispose to cerebral small vessel disease has to be checked to prevent cognitive dysfunction. Active treatment options are not available as on date for small vessel disease, hence preventive measures are essential. More studies are needed in small vessel disease to further understand its pathophysiology and to device new treatment modalities.

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INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI -3

Telephone No : 044 25305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr. T. Muthu
PG in DM Neurology
Madras Medical College, Chennai -3

Dear Dr. T. Muthu

The Institutional Ethics committee of Madras Medical College, reviewed and discussed your application for approval of the proposal entitled " Cognitive dysfunction in small vessel disease" No.39012012.

The following members of Ethics Committee were present in the meeting held on 27.01.2012 conducted at Madras Medical College, Chennai -3.

1.	Prof. S.K. Rajan. MD	-- Chairperson
2	Prof. Pregna B. Dolia MD Vice Principal, Madras Medical College, Chennai -3 (Director , Institute of Biochemistry, MMC, Ch-3)	-- Member Secretary
3.	Prof. B. Kalaiselvi. MD Prof of Pharmacology ,MMC, Ch-3	-- Member
4.	Prof. Shruti Kamal MS Prof of Surgery, Madras Medical College , Ch-3	-- Member
5.	Thiru. S. Govindsamy. BA BL	-- Lawyer

We approve the proposal to be conducted in its presented form.

Sd/ Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, and SAE occurring in the course of the study, any changes in the protocol and patients information / informed consent and asks to be provided a copy of the final report.

Member Secretary, Ethics Committee

FIG-1 AGE DISTRIBUTION

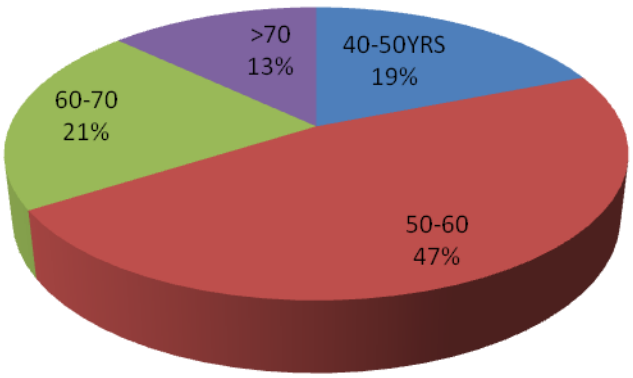
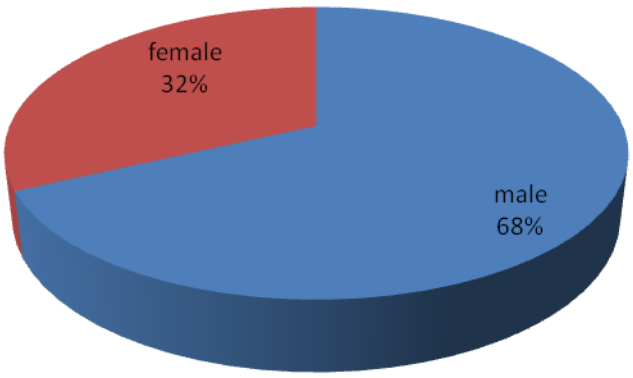


FIG-2 SEX DISTRIBUTION



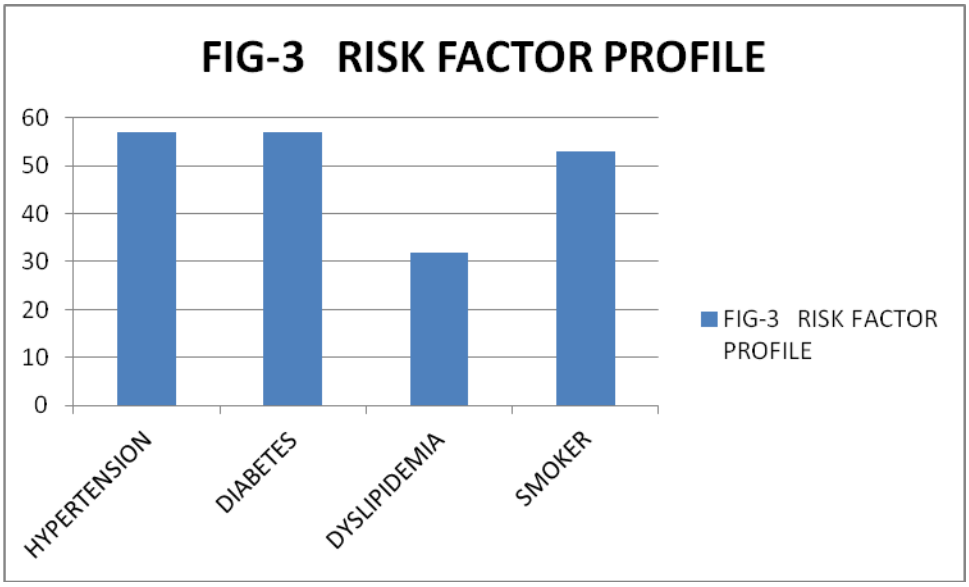
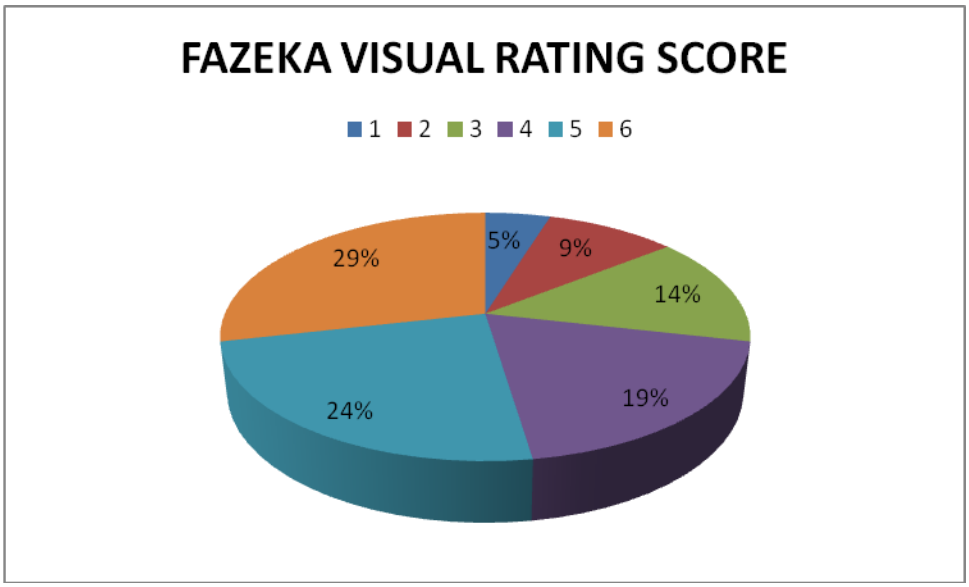


FIG-3 RISK FACTOR PROFILE
60
50
40
30
20
10
0
HYPERTENSION
DIABETES
DYSLIPIDEMIA
SMOKER
FIG-3 RISK FACTOR PROFILE


FAZEKA VISUAL RATING SCORE
1
2
3
4
5
6
5%
9%
14%
19%
24%
29%

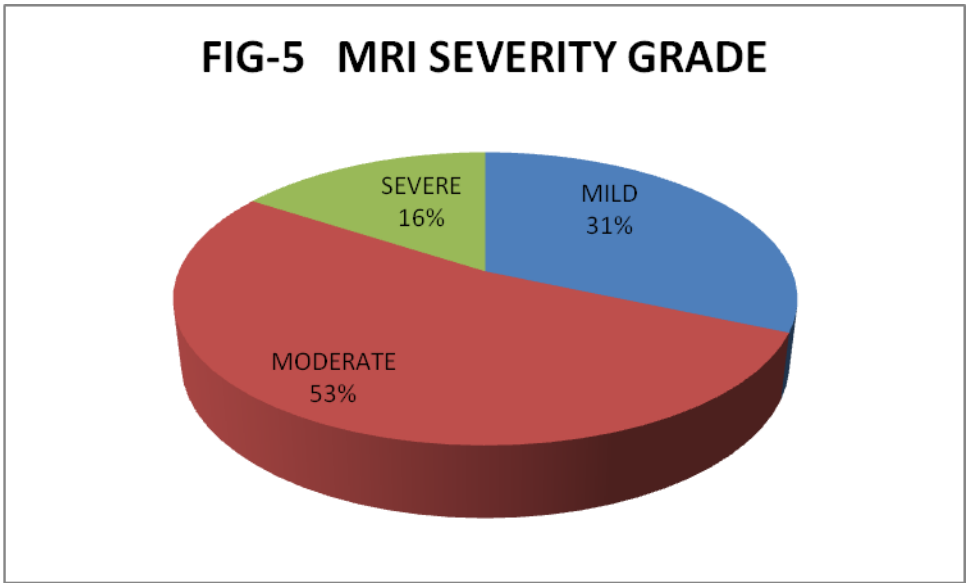


FIG-5 MRI SEVERITY GRADE
SEVERE
16%
MILD
31%
MODERATE
53%

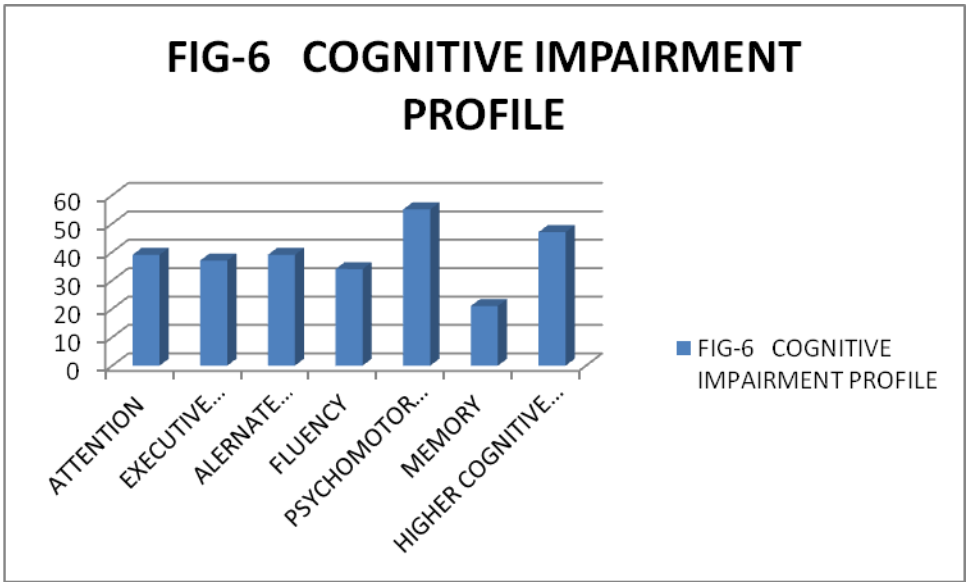
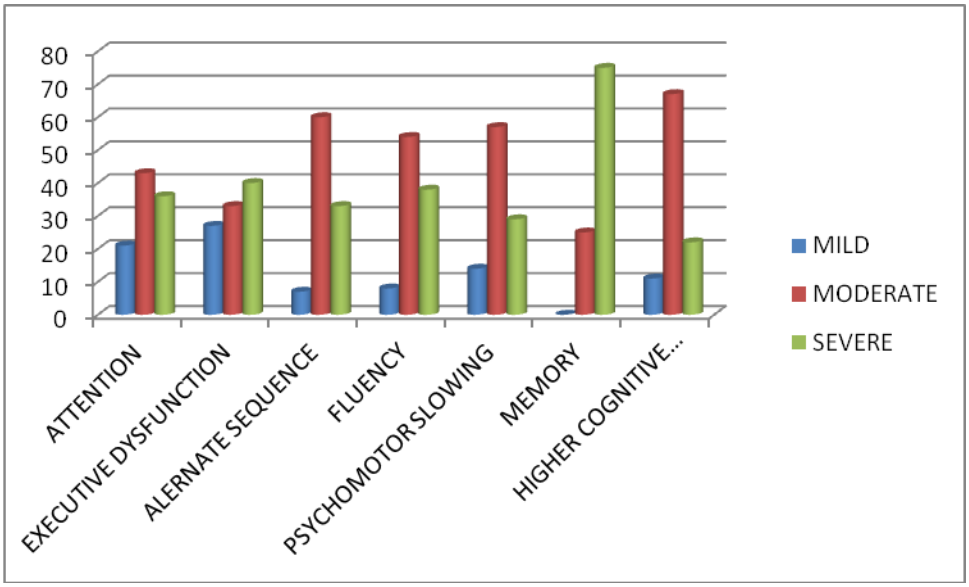


FIG-6 COGNITIVE IMPAIRMENT PROFILE
60
50
40
30
20
10
0
ATTENTION
EXECUTIVE...
ALERNATE...
FLUENCY
PSYCHOMOTOR...
MEMORY
HIGHER COGNITIVE...
FIG-6 COGNITIVE IMPAIRMENT PROFILE

FIG-7 COGNITIVE PROFILE IN RELATION TO MRI



PATIENT CONSENT FORM

STUDY TITLE : A STUDY ON ACUTE SYMPTOMATIC SEIZURES IN THE ELDERLY

Study Centre : Madras Institute of Neurology,

Madras Medical College, Chennai – 600 003

Patient's Name :

Patient's Age :

Identification Number : Patient may check (✓) these boxes

I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask the question and all my questions and doubts have been answered to my complete satisfaction. ☐

I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving any reason, without my legal rights being affected. ☐

I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethics committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the study. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study. ☐

I agree to take part in the above study and to comply with the instructions given during the study and to faithfully co-operate with the study team, and to immediately inform the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual symptoms. ☐

I hereby consent to participate in this Study on acute symptomatic seizures in the elderly ☐

I hereby give permission to undergo complete clinical examination and diagnostic tests including hematological, biochemical, radiological and urine examination. ☐

Signature / Thumb Impression _____ Place _____ Date _____

Patient's Name and Address: _____

Signature of the Investigator : _____ Place _____ Date _____

Study Investigator's Name : _____

PROFORMA

Cognitive Dysfunction In Patients With Small Vessel Disease

1. Patients name
2. Age
3. Sex
4. Phone number
5. Education
6. Occupation
7. Family h/o stroke
8. Hypertension
9. Diabetes mellitus
10. Dyslipidemia
11. Alcoholic
12. Smoker
13. Symptoms
14. Headcahe nausea/vomiting
15. CN symptoms
16. Limb weakness
17. Seizures
18. Altered consciousness
19. Amotivation
20. Self care
21. Memory disturbance

22. Way-finding difficulty

23. Hallucinations

Weight

BP

Peripheral disease

Renal disease

Cardiac disease

Cranial nerves

Limb weakness

MMSE

Digit span

3-7

7-4-9

8-5-2-7

2-9-6-8-3

5-7-2-9-4-6

8-1-5-9-3-6-2

3-9-8-2-5-1-4-7

Random letter test

L T P E A O A I C T D A L A A

A N I A B F S A M R Z E O A D

P A K L A U C J T O E A B A A

Z Y F M U S A H E V A A R A T

Verbal fluency

FAS test

Animal naming

Wechsler memory scale

Constuctional ability

Alternate visual pattern completion test

Alternating motor pattern test

Addenbrooks cognitive scale

Lobar function test

Investigations

Hemoglobin

FBS/PPBS

Urea

Creatine

Complete lipid profile

CXR

ECG

EEG

MR Imaging

Fazekas visual rating scale

KEY TO MASTER CHART

SEX

M-male , F-female

Diabetes mellitis : 1- present, 2- absent

Systemic hypertension: 1- present, 2- absent

Smoker : 1- yes, 2- no

Dyslipidemia : 1- present, 2- absent

Attention : 1 – Impaired, 2- normal

Executive dysfunction : 1 – Impaired, 2- normal

Alternating sequence : 1 – Impaired, 2- normal

Memory : 1 – Impaired, 2- normal

Fluency : 1 – Impaired, 2- normal

Psychomotor slowing : 1 – Impaired, 2- normal

MRI BRAIN – fazekas visual rating scale

1-mild, 2 – moderate, 3- severe.

s.no	Age	Sex	DM	HT	Dyslipidemia	Alcohol	Smoker	EEG
1	46	2	1	2	1	2	2	1
2	53	1	1	1	2	1	1	1
3	48	1	2	1	1	2	2	1
4	66	1	1	1	2	2	1	1
5	71	1	1	1	2	2	1	2
6	52	2	2	1	2	2	2	1
7	59	2	1	1	2	2	2	1
8	68	1	2	2	2	2	2	3
9	76	2	2	2	1	2	2	1
10	43	1	2	1	2	1	1	1
11	57	1	1	1	2	2	2	3
12	63	2	1	1	2	2	2	1
13	59	1	1	1	1	1	1	1
14	47	1	1	2	2	2	2	1
15	67	1	2	1	1	2	1	3
16	54	1	1	1	2	2	1	1
17	49	2	2	1	1	2	2	1
18	56	2	1	1	2	2	2	3
19	74	1	2	1	2	2	2	1
20	58	2	2	2	2	2	2	1
21	46	1	1	2	1	1	1	1
22	61	1	2	1	2	2	2	1
23	54	2	1	2	2	2	2	3
24	55	1	1	1	1	1	1	1
25	54	1	1	2	2	2	1	1
26	75	1	2	2	2	2	1	1
27	56	1	1	1	1	2	1	1
28	47	2	2	2	2	2	2	3
29	51	1	2	1	2	1	1	1
30	67	1	2	2	2	2	1	1
31	58	1	1	1	2	2	1	1
32	54	2	2	2	2	2	2	1
33	66	1	1	1	1	1	1	3
34	58	2	2	2	2	2	2	1
35	72	1	1	2	1	1	1	1
36	55	1	2	2	2	2	1	1
37	63	1	2	1	2	1	1	3
38	56	1	1	2	1	1	1	1

Attention	cutive funct	lt sequenc	Fluency	omotor slc	Memory	gher Cogniti	MRI score
2	2	2	2	1	2	2	2
1	1	1	2	1	2	2	1
2	2	2	2	2	2	2	2
2	1	2	2	1	1	1	3
2	2	2	2	2	2	2	1
2	2	1	1	2	1	2	2
2	2	1	2	2	2	2	2
1	1	2	1	1	2	1	1
2	2	1	1	2	2	1	2
2	2	2	2	2	2	2	1
2	2	2	2	2	2	2	2
1	1	1	1	1	1	1	3
2	2	2	2	2	2	2	1
2	2	1	2	1	2	1	2
2	2	2	1	2	2	1	2
1	1	1	1	1	1	1	3
2	2	2	2	2	2	2	1
1	1	1	2	1	2	1	2
2	2	2	2	1	2	1	2
1	1	1	1	1	1	2	3
2	2	2	2	2	2	2	1
2	2	2	2	1	2	1	2
1	1	1	1	1	2	1	2
2	2	2	2	2	2	2	1
1	1	1	1	1	1	2	3
1	1	2	2	1	2	2	1
2	2	2	2	2	2	2	1
2	2	2	2	2	2	2	2
2	1	2	2	2	2	1	1
1	1	1	1	1	1	1	3
2	2	2	2	2	2	2	1
2	2	2	2	1	2	1	2
1	1	1	1	1	2	2	2
1	2	2	2	2	2	1	2
2	1	1	1	1	2	2	2
2	2	2	2	1	2	1	2
1	1	1	1	1	1	1	2
1	2	2	2	1	2	1	2