Intoduction

Microcirculatory brain disease is a collective terminology that comprises vascular arteriolar pathology, metabolic endocrinal abnormalities and haemorheological abnormalities. Clinically it is characterized by the existence of cerebral ischemic events that have a peculiar tendency for recurrence and progression to multi infarct dementia. These ischaemic events are commonly associated with increased incidence of depression, parkinsonian manifestations, essential hypertension and blood hyperviscosity. The associates of the microvascular brain disease are collectively called the metabolic syndrome. However, misleadingly, the term small vessel disease is used to describe only the pathologic component of the ischemic process. Instead abroader view of small vessel disease should be kept in mind, particularily for therapeutic aspects, because patients of small vessel disease also have a risk of hemorrhage **(Metwally, 2001)**.

Pathology of ischemic cerebral parenchymal consequence of microvascular diseases includes central and cortical atrophy which is secondary to chronic global reduction of brain perfusion. Leukoaraiosis is an ischaemic demyelination of the immediate periventricular white matter with axonal loss,

astrogliosis and interstitial edema. Lacunar infarctions are secondary to the micro vascular thromboocclusive episodes. They are most numerous in the periventricular gray matter (thalamus and basal ganglia) and the immediate periventricular white matter. Spasm of the fine penetrating arterioles (secondary to increased vascular smooth muscles (VSMCs) sensitivity) can also result in lacunar infarctions. Initially lipohyalinosis was thought to be the predominant small vessel pathology of lacunes; however, microatheroma now is thought to be the most common mechanism of arterial occlusion or stenosis.Granular atrophy is defined pathologically as infarctions localized to the cerebral cortex and not extending to the subcortical white matter. Basal ganglionic calcifications are calcification of the the arteriolar wall of the microcirculation within the basal ganglia. Pathologic dilatation of Virchow-Robin spaces is most commonly associated with arteriolar abnormalities that arise due to aging, diabetes, hypercholesterolemia, smoking, and hypertension and other vascular risk factors. Cerebral microbleeds are small brain hemorrhages that are presumed to result from leakage of blood cells from damaged small vessel walls. Concerning the pathology of the haemorrhagic division of microvascular disease it's caused by arteriosclerosis secondary to hypertension this leads to formation of microaneuysms liable for rupture.

Cerebral amyloid angiopathy has significant role in lobar haemorrhage **(Ghatak et al., 1974; Fisher, 1982; Lang, 2001; Thomas et al., 2002)**.

Many risk factors are associated with microvascular disease of the brain. These risk factors include diabetes mellitus, hypertension, smoking, high low density lipoprotein. Hypertriglycridemia, hyperuricemia, type 2 diabetes, insulin resistance and truncal obesity (The metabolic syndrome**)** and hyperhomocystenemia. There is also genetic factors like cerebral autosomal dominant arteriopathy with subcortical infarction and leukoencephalopathy (CADASIL), cerebral autosomal recessive arteriopathy with subcortical infarction and leukoencephalopathy (CARASIL) and hereditary endotheliolopathy with retinopathy, nephropathy and stroke (HERNS). Heamrheology changes also plays an important role in microvascular disease of the brain due to Increased whole blood viscosity and hypercoagulability characterized by an increased plasminogen activator inhibitor-1 (PAI-1) level. Non modifiable risk factors like age, sex and race should also considered (**Metwally, 2001; khan et al., 2007; Richard et al., 2007**).

There seems to be a complex interrelationship between Alzheimer disease (AD) and cerebrovascular disease that extends beyond the coexistence of these 2 disease processes. Imaging features of small vessel disease are seen at higher frequency in Alzheimer's disease than in healthy controls. Cerebrovascular disease and Alzheimer disease often coexist, whereas stroke often exacerbates preexisting, sometimes previously subclinical disease. Furthermore, Alzheimer disease, Vascular dementia and microvascular brain disease share common risk factors, such as diabetes and hypertension, as well as genetic factors for brain tissue vulnerability (presenilins, amyloid precursor protein, APOE genes) **(Small et al., 2008)**.

Management of microvascular disease of the brain depends on early diagnosis clinically and on brain imaging. Clinical picture may be stroke, transient ischemic attacks (TIAs), multi-infarct dementia, depression or parkinsonism. The diagnosis of lacunar infarction relies upon finding clinical syndrome that is consistent with the location small noncortical infarct seen on computerized tomography (CT) or magnetic resonance imaging (MRI). CT brain has low sensitivity for lacunar infarction and leukoariosis but it is important for exclusion of cerebral haemorrhage.MRI Diffusion-weighted imaging help in rapid diagnosis and FLAIR differentiate

between acute and chronic lacunar infarction. However; several recent studies have shown that GRE MRI (T2*) sequences are accurate as CT for the detection of intraparenchymal haemorrhge and far superior to CT for the detection of chronic haemorrhage. MRI techniques have made a significant contribution to understanding of how structural alterations in small vessel disease contribute to cognitive deficits. The neuroanatomy of cognitive networks is complex and the spatial distribution of lesions is an important factor to consider to develop a richer understanding of the links between structure and cognitive function **(Kidwell, 2002; Fiebach, 2002; Chalela, 2007; O'Sullivan, 2010; Koch, 2011)**.

Treatment of small vessel disease of the brain must be directed to control risk factors like DM and hypertension and secondary prevention to avoid progression and recurrence. Some data on antiplatelet drugs in secondary prevention after stroke caused by small vessel disease can be drived from a few trials: trial of asprin plus dipyridamole versus placebo, trial of ticlopidine versus placebo and trial of aspirin versus placebo in early prevention after thirteen days. Results from all these studies suggested efficacy of the drug study in the subgroup of patients with stroke caused by small vessel disease but there was no evidence that one drug, or combination, was better than

another. More over there was no data about the risk of haemorrhage.Patients with microvascular disease also benefit from statin therapy **(Bousser et al., 1983; Gent et al., 1989; CAST, 1997)**.

Aim of the Work

To overview update in pathophysiology and new trends of prophylaxis and treatment of microvascular disease of the brain. And to provide clinicians with some concepts of the modern overview of micovascular disease of the brain to enable understanding of recent progress and future direction in this field.

Overview of Microvascular Diseases of the Brain

Definition of microvascular diseases of the brain:

The term small vessel disease encompasses all the pathological processes that affect the small vessels of the brain, including small arteries and arterioles but also capillaries and small veins. However, the definition of a small vessel is not uniform: the results from a survey showed that there was less than 50% agreement among leading neuropathological centres on its definition. Most often, small vessel disease is used to refer only to the arterial vessels and little attention has been paid to the venous compartment. This possible exclusive reference to the arterial part of the vascular tree must be kept in mind when dealing with small vessel disease **(Pantoni et al., 2006)**.

Microcirculatory brain disease is a collective terminology that comprises small arteries and arterioles vascular pathology but also capillaries and small veins, metabolic endocrinal abnormalities and haemorheological abnormalities. Clinically it is characterized by the existence of cerebral ischemic events that have a peculiar tendency for recurrence and progression to multi infarct dementia. These ischaemic events are commonly

associated with increased incidence of depression, parkinsonian manifestations, essential hypertension and blood hyperviscosity. The associates of the microvascular brain disease are collectively called the metabolic syndrome. However, misleadingly, the term small vessel disease is used to describe only the pathologic component of the ischemic process. Instead a broader view of small vessel disease should be kept in mind, particularily for therapeutic aspects, because patients of small vessel disease also have arisk of haemorhage **(Metwally, 2001)**.

Anatomy of microvascular circulation of the brain:

There are two systems of microvascular circulation of the brain The centrifugal subependymal system and centripetal pial system. The centrifugal subependymal system originates from the subependymal arteries which are terminal branches of choroidal arteries, then extends cetrifugally into periventricular white and grey matter especially basal ganglia and thalamus. The centripetal pial system originates from pial arteries then extends centripetally towards the ventricular system to supply the cortical grey matter and immediate subcortical white matter. Most lacunes occurs in the basal ganglia, pons and subcortical white matter (internalcapsule and corona radiata). These small branches originate directly from large arteries, making them particularly vulnerable to the effects of hypertension, probably explaining this peculiar distribution as shown in figure (1). A

study using fluorescent and radiopaque dye injection techniques has demonstrated that penetrating vessels supply distinct microvascular territories of the basal ganglia, with minimal overlap and sparse anastomoses between the penetrating vessels. The ultimately terminal rather than anastomotic nature of these vessels is another factor explaining the predisposition of this region to lacunar infarction **(Feekes, 2005)**.

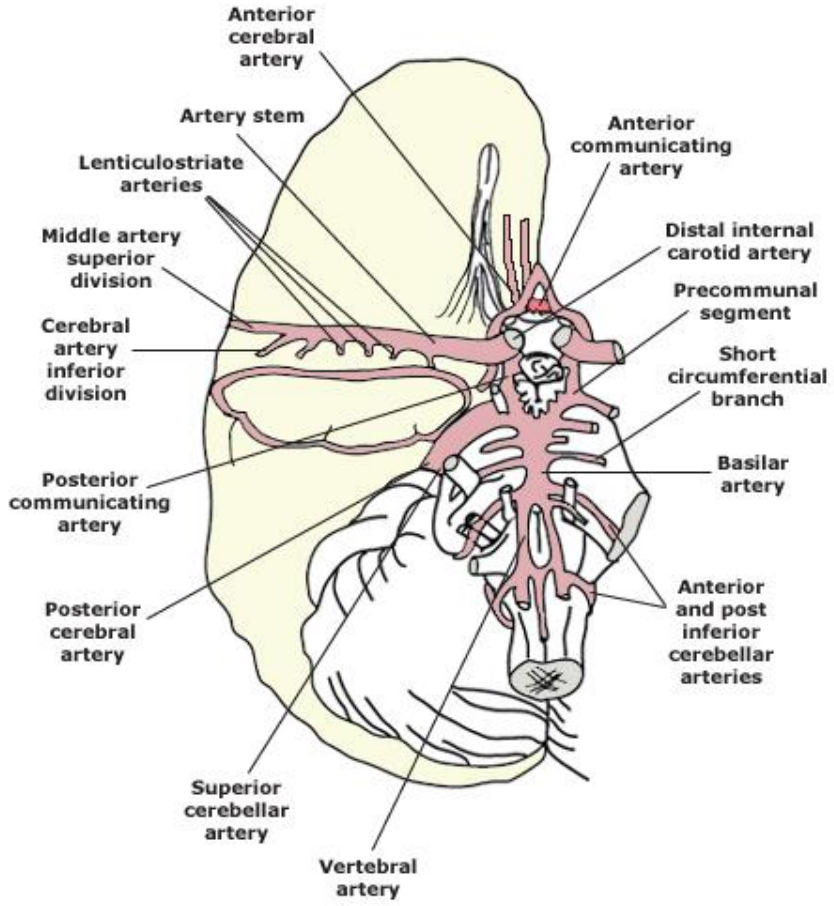

Figure (1): Anatomic location of lentriculostriate, thalamoperforant and paramedian pontine branches **(Kistler et al., 1994)**.

Pathogenesis of cerebral damage in small vessel disease:

The mechanisms that link small vessel disease with parenchyma damage are heterogeneous and not completely known. There is little knowledge because animal models that convincingly reflect the pathological changes in human small vessel disease are scarce **(Hainsworth and Marcus, 2008)**.

The hypothesised cascade of pathophysiological events leading from small vessel disease to brain damage is summarised in figure (2). Pathological changes in the small vessels can lead to both ischaemic and haemorrhagic consequences. The reason why some vessel ruptures lead to major haemorrhage while others lead to microhaemorrhage is unknown. In cerebral amyloid angiopathy, differences in thickness of vessel walls are thought to explain the differences in haemorrhage, with thicker walls associated with more microhaemorrhages **(Greenberg et al., 2009)**, the pathogenesis (and even the aetiology) of some ischaemic lesions such as white matter lesions is more hypothetical **(Pantoni et al., 2002)**.

In ischaemic lesions caused by small vessel disease, the vessel lumen restriction is thought to lead to a state of chronic hypoperfusion of the white matter, eventually resulting in degeneration of myelinated fibres as a consequence of repeated

selective oligodendrocyte death. This ischaemic mechanism has been demonstrated in animals **(Petito et al., 1998)**.

This kind of white matter damage is thought to be a form of incomplete infarct or selective necrosis similar to what has been described for neurons. Alternatively, acute occlusion of a small vessel is hypothesised to occur, leading to focal and acute ischaemia and complete tissue necrosis (pannecrosis): this is the putative mechanism of lacunar infarcts **(Garcia et al., 1997)**.

Other mechanisms such as blood–brain barrier damage **(Wardlaw et al., 2003),** local subclinical inflammation **(Rosenberg, 2009)**, and oligodendrocytes apoptosis could be involved in the so-called ischaemic forms of small vessel disease and contribute to the final pathological picture **(Brown et al., 2000)**.

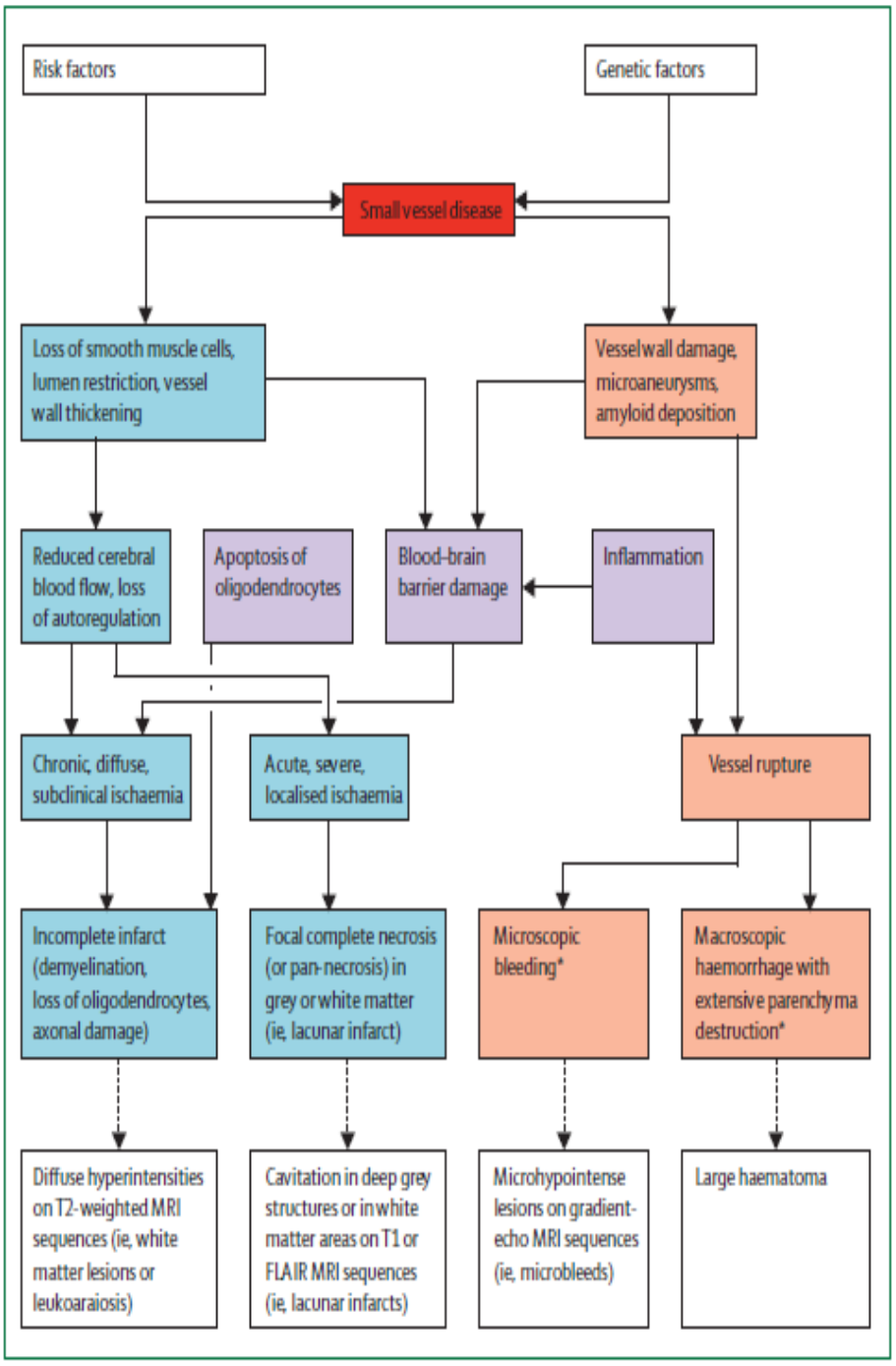

Figure (2): pathogenesis of cerebral damage as result of small vessel disease **(Pantoni, 2010)**.

CEREBRAL PARENCHYMAL CONSEQUENCES OF MICROVASCULAR BRAIN DISEASE

1- Leukoaraiosis:

Pathophysiology of leukoaraiosis:

Several pathophysiologic mechanisms have been proposed to explain the histology of leukoaraiosis. In addition to ependymitis granularis and Virchow-Robin space dilatation, more extensive regions of leukoaraiosis have been attributed to the ischemic effects of chronic oligemia and to perivascular edema and retrograde axonal degeneration **(Roman et al., 1987).**

A-Chronic hypoperfusion:

In the severe (Binswanger's disease) form of leukoaraiosis, chronic microvascular oligemia and intermittent thrombotic occlusion appear responsible for the observed pattern of multiple lacunar infarcts with interspersed areas of edema, demyelination, and gliosis. Unlike the richly collateralized cerebral cortex, the leukoaraiosis vulnerable white matter is perfused by long penetrating corticofugal endarteries with few side branches, a vascular architecture that provides little protection from the ischemic effects of microvascular stenosis **(Roman et al., 1987).**