Introduction

Stroke was defined according to WHO criteria as a syndrome of rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin. It is subdivided into ischaemic stroke (caused by vascular occlusion or stenosis) and haemorrhagic stroke (caused by vascular rupture, resulting in intra-parenchymal and/or subarachnoid haemorrhage). Ischaemic stroke accounts for about 85% of cases and haemorrhagic stroke about 15% ***(Thom et al., 2006).***

Stroke is considered to be one of the important global health problems as 15 million people worldwide suffer a stroke annually. Of these, 5 million die and another 5 million are left permanently disabled, placing a burden on family and community. Nowadays, it ranks the second most common cause of mortality in the world, and remains the most common cause of long-term disability in adults .Although the incidence of stroke is declining in many developed countries, largely as a result of better control of high blood pressure, and reduced levels of smoking, the absolute number of strokes continues to increase because of the ageing population ***(Taher et al., 2010).***

Based on the data collected by ***Zhang et al. (2012)***, the incidence of stroke in five European countries and the USA

ranges from 114 cases per 100,000 persons per year in France for first-ever stroke to 350 cases per 100,000 persons per year in Germany for all strokes; prevalence estimates ranged from 1.5% in Italy to 3% in the UK and USA. A systematic review recorded by ***Kulshreshtha et al. (2012)*** recorded that population-based studies from South Asia have stroke prevalence in the range of 45–471 per 100,000.

There are two community-based studies from Arabic countries: in Tunisia prevalence was 42 per 100,000 population; in Saudi Arabia the reported prevalence was 186 per 100,000 population ***(Attia et al., 1993).***

Because there have been no epidemiological studies of stroke in Egypt, a community-based three-phase door-to-door study survey was conducted in the Assiut Governorate to estimate the prevalence and risk factors of stroke in our community giving a crude prevalence rate of 963/100,000 ***(Khedr et al., 2013).***

In Egypt disability-adjusted life-years DALYS (the sum of life-years lost as a result of premature death and years lived with disability adjusted for severity) lost per 1000 population due to stroke is 8 in 2003. It is recorded that deaths from cerebrovascular diseases accounted for 42% of all deaths in 2002 ***(Taher et al., 2010).***

There are various classification systems for acute ischemic stroke. **The Oxford Community Stroke Project classification** (OCSP), also known as the Bamford or Oxford classification) relies primarily on the initial symptoms; based on the extent of the symptoms, the stroke episode is classified as total anterior circulation infarct (TACI), partial anterior circulation infarct (PACI), lacunar infarct (LACI) or posterior circulation infarct (POCI). These four entities predict the extent of the stroke, the area of the brain affected, the underlying cause, and the prognosis ***(Bamford et al., 1991).***

The TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification is based on clinical symptoms as well as results of further investigations; on this basis, a stroke is classified as being due to (1) thrombosis or embolism due to atherosclerosis of a large artery, (2) embolism of cardiac origin, (3) occlusion of a small blood vessel, (4) other determined cause, (5) undetermined cause (two possible causes, no cause identified, or incomplete investigation) ***(Adams et al., 1993).***

The **Causative classification of stroke (CCS)** is a web-based validated classification algorithm which subtypes ischaemic stroke according to pathophysiological mechanism to (1) Large artery atherosclerosis, (2) Cardio-aortic embolism, (3) Small artery occlusion, (4) Other causes, (5) Indeterminate causes. Each sub-type except for the indeterminate group is

sub-divided based on the weight of evidence as: Evident, Probable and Possible ***(Ay et al., 2007).***

The term ‘small vessel disease’ or ‘SVD’ has been used to reflect clinical, radiological, or pathological phenomena attributed to disease of small perforating arteries and arterioles supplying deep brain structures. More recently, the roles of venules and capillaries are also beginning to be emphasized. During life, phenotypes of SVD may be identified clinically, radiologically, or using both approaches ***(Pantoni, 2010).***

As SVD is difficult to directly visualize, we rely predominantly on radiological phenotypes as surrogate markers of disease. The advent of newer imaging techniques has contributed significantly to our understanding of these phenotypes, in particular, their effects on brain function and underlying risk factors. However, such recent descriptions also need to be carefully considered in the context of clinicopathological studies prior to the advent of brain imaging. The principal SVD phenotypes of clinical interest are small deep brain infarcts, cerebral white matter lesions (WMLs), deep brain haemorrhages, and cerebral microbleeds (CMBs) ***(Moran et al., 2012).***

Aim of the Work

- Detect the prevalence of cerebral microbleeds in ischemic stroke patients, through a study in Ain Shams University Hospitals.
- Evaluate the possible risk factors or "determinants" of microbleeds in patients with ischemic stroke and the correlation with functional outcome.

Chapter I: Cerebral Microbleeds (CMBs): Definition and Pathophysiology

The past decade has witnessed increasing interest in cerebral microbleeds (CMBs), reflected by increased publications about them. As magnetic resonance imaging (MRI) techniques become more sophisticated, CMBs are increasingly detected in various patient populations (including all types of stroke, Alzheimer's disease and vascular cognitive impairment) and healthy community-dwelling older people ***(Charidimou and Werring, 2011).***

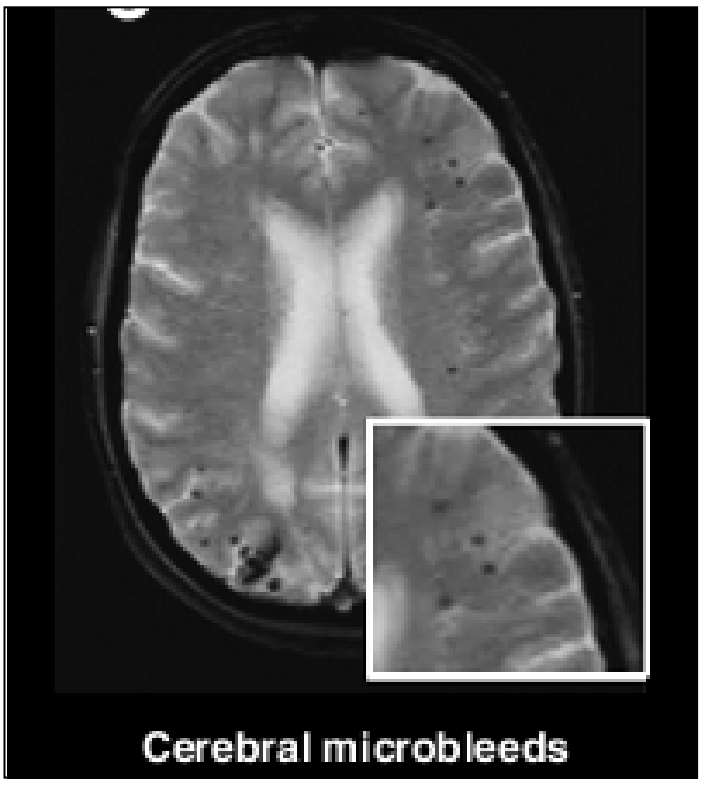

Fig. (1): Multiple cortical-subcortical CMBs (dark, rounded lesions) detected by axial T2*-GRE ***(Charidimou and Werring, 2012).***

Scharf* and colleagues *(1994) were the first to report on small, intracerebral black dots of signal loss on T2-weighted spin-echo MRI in patients with hypertensive cerebrovascular disease and intracerebral hemorrhage (ICH) associated with ischemic white matter disease and lacunar infarcts. They called these lesions 'hemorrhagic lacunes', and their further characterization using T2*- gradient recalled echo (GRE) MRI sequences led to the current radiologic definition of 'microbleeds', a term coined by ***Offenbacher and colleagues*** in 1996.

CMBs are defined radiologically as small, rounded, homogeneous, blooming, hypointense lesions on T2*-GRE and related MRI sequences that are sensitive to magnetic susceptibility ***(Greenberg et al., 2009)*** (Fig. 1).

There has so far been general agreement on a CMB cut-off size of 5–10 mm in diameter on standard GRE T2* MRI sequences, although in some studies, the minimum diameter used was 2 mm ***(Cordonnier et al., 2007).*** However, it should be appreciated that the measurement used for a radiological lesion is not a true reflection of the actual size of the CMB; because of the "blooming" effect of the MRI signal at the lesion border. The actual tissue lesion size is usually considerably

smaller and generally significantly less than approximately 5 mm ***(Schrag et al., 2011).***

The first studies on prevalence of CMBs in normal individuals indicated that the prevalence was quite low, for example 6.4% in the Austrian Stroke Prevention Study (ASPS) ***(Roob et al., 1999),*** and 4.7% in the Framingham Study ***(Jeerakathil et al., 2004).*** However, one major reason for these relatively low proportions was the quite young age groups included. Later population-based studies have shown a higher prevalence in higher age groups; 11.1% in the the Age Gene / Environment Susceptibility (AGES)-Reykjavik study (AGES-R) study ***(Sveinbjornsdottir et al., 2008)*** with a mean age of 76 years. Almost twice as high values were reported from the Rotterdam Study, which most likely reflects the MRI characteristics used ***(Vernooij et al., 2008a) (table 1)***.

Table (1): The principal features and findings in CMBs studies ***(Norrving, 2011):***

Cohort	No.	Mean age (years)	Prevalence of CMB (No.[%])	Associations with risk factors and other conditions
Population-based studies				
Austrian Stoke Prevention Study	280	60	18 (6.4)	Association with age and chronic hypertension
Framingham Study	472	64.4	22 (4.7)	Strong association with age, male sex
AGES-Reykjavik Study	1962	76	218 (11.1)	Association with age, sex, APOE ε4
Rotterdam Scan Study	1062	69.6	250 (23.5)	Associations with several risk factors, APOE, genotype and localization of CMBs

The prevalence of CMBs in ischemic stroke is approximately 20–30%, substantially higher than in the general population. Additionally when CMBs are present in these patients, they are more likely to be multiple (Figure 2). Among patients with ischemic stroke, CMBs are more common in lacunar stroke (35–60%) than in stroke caused by large artery atherosclerosis (12–26%) or cardioembolic stroke (4–30%) ***(Kato et al., 2002).*** The prevalence of CMBs in patients with ICH is even higher, at 50–70% ***(Lim & Kim, 2009).***

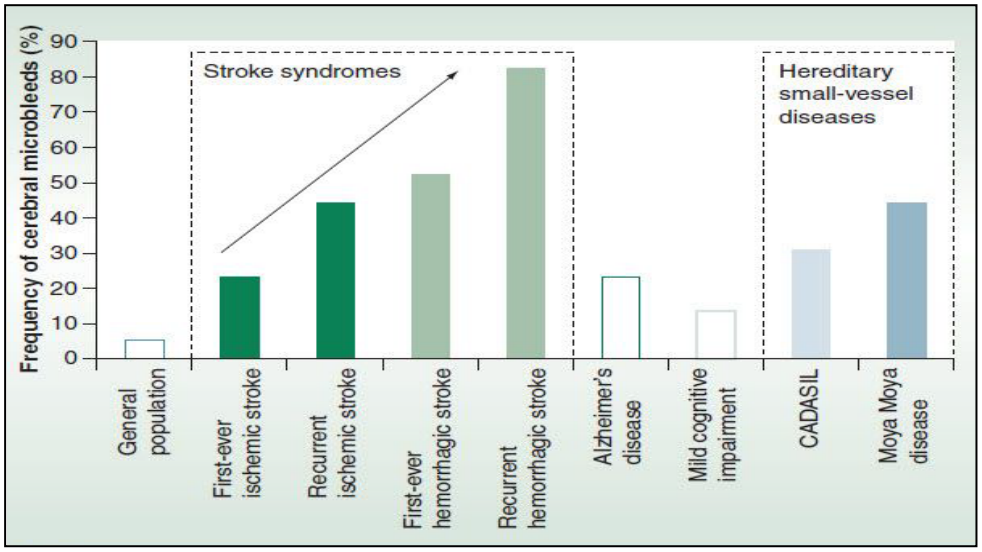

Fig. 2: Frequency of CMBs in Different Populations and Disease States ***(Charidimou & Werring, 2011).***

Pathophysiology of CMBs:

Histopathological correlation has shown that radiologically-defined CMBs are quite specific for small collections of blood-breakdown products (in particular,

haemosiderin contained within perivascular macrophages), adjacent to abnormal small vessels mainly affected by hypertensive arteriopathy or cerebral amyloid angiopathy (CAA) ***(Fazekas et al., 1999).*** Consequently, CMBs are unique among current MRI manifestations of small vessel disease, in that they seem to provide direct evidence of microvascular blood leakage by contrast to white matter lesions, which lack pathological specificity ***(Charidimou & Werring, 2011).***

Rarer causes of CMBs include: cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL); and moyamoya disease ***(Brandner, 2011) (table 2).***

Table (2): Common vasculopathies in CMBs ***(Brandner, 2011).***

Characteristics	Atherosclerosis	Hypertensive angiopathy with arteriosclerosis	CAA	CADASIL	Moyamoya
Vessels and distribution	Large extracranial and intracranial vessels; decreases in distal vessels (down to 2 mm)	Large extracranial and intracranial vessels; extends the range to more distal vessels (<2 mm down to 100 mm) Small vessel disease: (90–400 μm) (Fig. 6.1)	Type 1: arterioles in cortex and meninges and cortical capillaries Type 2: arterioles in cortex and meninges (Fig. 6.2)	Small and medium-sized arteries	Distal portions of the internal carotid arteries and proximal parts of the ACA and MCA; vessels branching off the posterior parts of the circle of Willis
Location	Subcortical, deep gray matter	Superficial perforating vessels (pial branches of ACA, MCA and PCA, supplying gray (short) and white matter (long) and basal areas) Deep perforating vessels: base of brain, PCA and lenticulostriatal (Fig. 6.5)	Meningeal and cortical, particularly occipital (Fig. 6.5)	White matter of frontal, parietal and occipital lobes; basal ganglia and thalamus, mesencephalon and pons (longitudinal tracts)	Effects of bilateral stenosis of distal carotid artery/MCA and MCA; hemorrhages in basal ganglia, thalamus and lateral ventricle wall
Pathogenesis	Dysfunction of endothelium; accumulation of low density lipoprotein in the intima; disruption of endothelial barrier function	Breakthrough of autoregulation; aggravation of arteriosclerotic effects; causes arteriosclerosis to extend more distally; focal disruption of blood–brain barrier	Deposition of $A\beta_{40}$ in the vessel wall	*NOTCH3* mutation causative but pathogenesis not known	Not known; gene association (linkage) with chromosome 3p24 and 8q23
Pathological findings	Collagenization; lipohyalinosis; atheroma; proliferation of smooth muscle cells; monocyte and macrophage immigration; formation of fibrous plaques	Collagenization; lipohyalinosis; atheroma; deposition of brightly eosinophilic "fibrinoid" in vessel walls; reduplication of basal lamina under endothelial cells	Amyloid deposition; thickening of the media; splitting of vessel wall (double barrel)	Thickening and fibrosis of arterial walls with PAS-positive deposits in the tunica media; granular osmiophilic deposits in the smooth muscle cells of degenerating vessels	Excessive fibrous thickening of intima; duplication of elastica

CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CAA, cerebral amyloid angiopathy; ACA, MCA and PCA, anterior, middle and posterior cerebral arteries, respectively; PAS, periodic acid–Schiff stain.

Small vessel disease

Small vessel disease refers to a group of pathological processes which affect the small arteries, arterioles and capillaries of the brain ***(Pantoni, 2010).***

The vessels affected by small vessel disease are:

- *Superficial perforating vessels*: pial branches of the anterior, middle and posterior cerebral arteries, which supply gray matter with short branches, reaching cortical layer III, layer V and the gray–white matter junction and the depth of the subcortical white matter with longer branches.

- *Basal perforating vessels*: basal(deep)perforating vessels branch off the first segments of the anterior and middle cerebral arteries and form the lenticulostriatal arteries to supply the basal ganglia; there are also deep perforating branches from the posterior cerebral artery to supply the thalamus ***(Brander, 2011).***

The small vessels of the brain can mainly be affected by two types of pathologic abnormalities: arteriolosclerosis and/or cerebral amyloid angiopathy. Arteriolosclerosis typically affects small vessels originating from deep arterial perforators that penetrate the white matter and deep gray nuclei, whereas CAA preferentially affects the small arteries and arterioles of the

cerebral cortex and gray–white matter junction by the deposition of amyloid-β in the vessel walls ***(Charidimou et al., 2012).***

Since small vessels cannot be visualized *in vivo*, the brain parenchymal lesions (detected on MRI) thought to be caused by the vessel changes described earlier have been adopted as a marker of the underlying cerebral small vessel diseases. These brain parenchymal lesions include WMLs, lacunar infarcts and CMBs (Fig. 3) ***(Charidimou & Werring, 2011).***

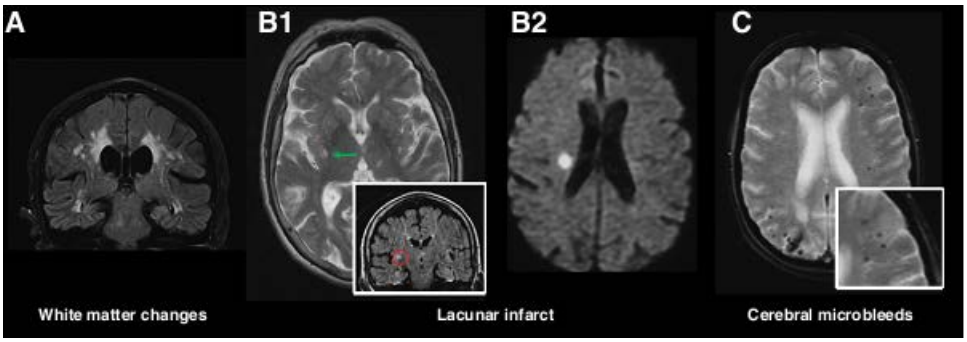

Fig. (3): MRI manifestations of cerebral small vessel disease ***(Charidimou & Werring, 2012).***

There may be interactions between the two pathologic abnormalities, since both CAA and hypertensive arteriopathy may coexist in elderly people ***(Cordonnier & van der Flier, 2011).***

In the setting of small-vessel disease, the vascular endothelium of small arterioles and capillaries seems to become permeable to elements such as red blood cells, inflammatory cells and plasma proteins, which are normally excluded by the blood brain barrier (BBB) ***(Cullen et al., 2005).*** Thus, it seems

highly plausible that endothelial/BBB derangement could play a key role in CMBs formation (Figure 4) ***(Wardlaw, 2010).***

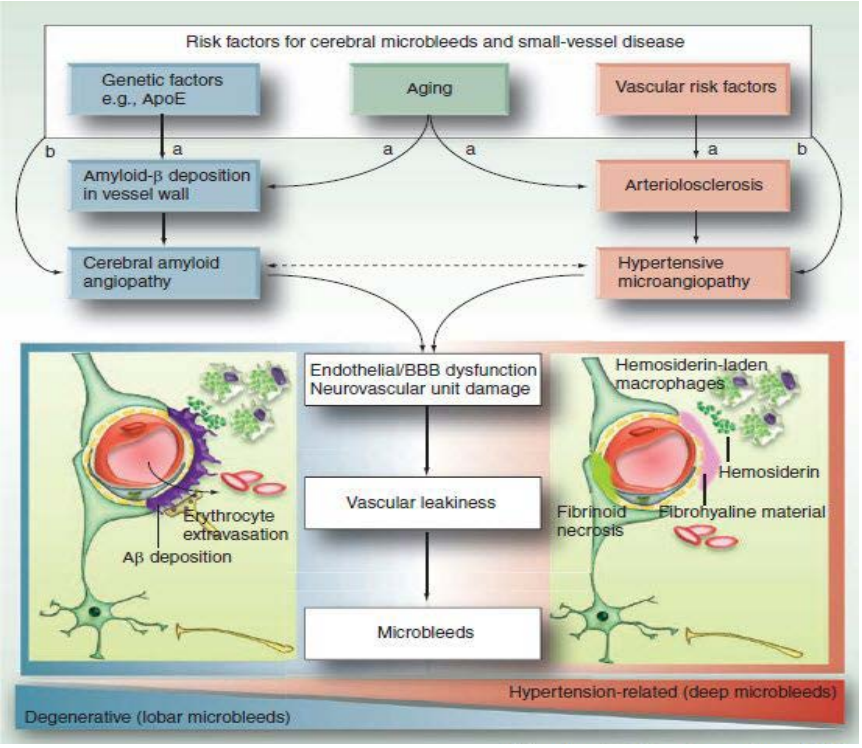

Fig. 4: Pathophysiolocal pathways that can give rise to CMBs ***(Charidimou & Werring, 2011).***

Hypertensive arteriopathy:

Chronic exposure to increased blood pressure leads to reactive changes in the vascular wall, termed remodeling. This remodeling is ultimately accompanied by endothelial dysfunction, changes in smooth muscle cell contractility and loss of vascular integrity ***(Bund & Lee, 2003).***

This leads to leakage of serum, serum proteins or red blood cells into the perivascular space. Increased expression of matrix metalloproteinases and elastase may promote helpful adaptive changes in early hypertension but could play a role in disruption of the basement membrane in more long-standing hypertension ***(Yasmin et al., 2005).***

Cerebral amyloid angiopathy (CAA):

It's a type of small vessel disease that occurs commonly in the elderly population. It results in thickening of the vessel wall, primarily in small arteries and arterioles of the leptomeninges and cerebral cortex. It can also affect cerebellar vessels. The primary constituent of the vascular amyloid deposits is the beta-amyloid peptide (Aβ), also the main component of the senile plaques observed in Alzheimer's disease. The earliest detectable vascular Aβ deposits typically occur between the smooth muscle cells of the media and the connective tissue of the adventitia. As the disease progresses, amyloid replaces the media with loss of smooth muscle cells ***(Vinters, 1987).*** Autopsy studies indicate that CAA is a common pathology of older individuals, with 10–40% prevalence in the general population and at least 80%among individuals with Alzheimer's disease ***(Jellinger, 2002).***

Although the precise origin of the vascular amyloid has not been definitively established, the predominant source