INTRODUCTION

Leukoaraiosis (LA), a radiological term introduced by Hachinski in 1987, refers to a disorder of white matter disturbances induced by various causes, and is commonly observed in the elderly through Magnetic Resonance Imaging ***(Hachinski, 1987).***

Leukoaraiosis (LA), is revealed as hyperintensities in T2 sequences and fluid-attenuated inversion recovery (FLAIR) in magnetic resonance imaging (MRI) or hypodensity with ill-defined margins in computed tomography (CT) in the areas of cerebral white matter ***(Pantoni et al., 2002).***

Leukoaraiosis is associated with cognitive impairment, gait abnormalities, falls, and late-onset depression ***(Ovbiagele, 2006; O'Sullivan, 2008).*** Moreover, LA also represents an independent risk factor to predict future stroke. Leukoaraiosis is frequently observed in patients with acute stroke, ischemic as well as hemorrhagic. Stroke and leukoaraiosis are likely two related diseases, LA is an ischemic disease, as is ischemic stroke. Also, intra cerebral hemorrhage (ICH) and LA share a common cause, that of arterial hypertension ***(Mijajlovic et al., 2011).***

Stroke outcome in patients with LA is poor ***(Kissela et al., 2009).*** Few studies had focused on the association

between leukoaraiosis and the prognosis of cerebral infarction in elderly patients. One of the most recent studies revealed that patients with leukoaraiosis had a higher rate of self –care incapability than patients without leukoaraiosis and there is associations between the degree of brain white matter hyperintensity (WMH) and clinical prognosis, neurological function recovery and self care capability in elderly with acute cerebral infarction .In addition patients with severe leukoaraiosis often also have cognitive dysfunction, which may affect functional recovery so severe leukoaraiosis in elderly patients with acute cerebral infarction is associated with poor prognosis and poor recovery of neurological functions ***(Huang et al., 2014).***

The major pathology of LA is myelin pallor, enlargement of perivascular spaces, gliosis, and axonal loss**.** It has been considered to be a consequence from cerebral small vessel disease ***(Patel, 2011).***

Leukoaraiosis is probably caused by chronic cerebral ischemia ***(Pantoni, 1997).*** It has been strongly linked to lacunar infarction ***(Rost et al., 2010).*** Studies suggests that LA and lacunar infarction are two manifestations of a shared underlying etiology, most commonly, this is likely to be due to small vessel changes associated with hypertension and increasing age. Metabolic syndrome is significantly associated with the incidence of leukoaraiosis

(Park et al., 2007).

Impact of large-artery disease on LA is not yet clear. Large-artery atherosclerosis, especially carotid atherosclerosis, has been demonstrated to be closely related with ischemic stroke. In fact, insufficient cerebral perfusion due to large vessel atherosclerosis may affect the severity of LA and an increased frequency of LA has been reported in patients with carotid atherosclerosis ***(Fazekas et al., 1988; Kobari 1990).*** Moreover, LA could be partially reversible in patients with carotid artery stenosis ***(Yamada, 2010).***

Recently, increasing evidence indicate a relationship between carotid atherosclerosis and LA, although this remains controversial ***(Chutinet, 2012).*** Some studies considered LA and carotid atherosclerosis as two separate entities, whereas another recent study considered leukoaraiosis as ‘a chronic atherosclerotic disease’, accordingly there is association between leukoaraiosis and carotid artery atherosclerosis ***(Ben-Assayag, 2012).***

Multiple studies reported that white matter hyperintensity were related to atherosclerosis, as this was associated with increased common carotid intima-media thickness and carotid plaques ***(Breteler et al., 1994; Manolio et al., 1999; Leeuw et al., 2000; Pico et al., 2002)***, however more several recent studies suggested that

LA has more tendency of association with carotid plaques than with carotid stenosis ***(Liao et al., 2014).***

However, there are also other disease processes that cause leukoaraiosis and lacunars infarcts ***(Smith, 2010)*** such as cerebral myeloid angiopathy and CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukencephalopathy). It is also related to acceleration of the progress of Alzheimer's disease, which in turn has been attributed to increase in frequency of mild cognitive impairments and parkinsonism ***(Price et al., 2012).***

Atherosclerosis is a pathologic phenomena which is characterized by the stiffness and enlargement of the arterial walls due to the deposit of lipid carbohydrates, blood products and calcium into the sub endothelial space. The risk factors of arterial diseases make their impact in all arteries of the human body. It is clear to know that the composition of the plaque is the major determinant for its risk of rupture and for its logic consequence, thrombosis. Following plaque rupture, lipidic core and its high content of factors, gives a powerful substrate for the activation of the coagulation cascade ***(Esper, 2004).***

The normal intima-medial thickness of common carotid artery as evaluated by B-mode ultrasound imaging was 0.74±0.14 mm ***(Mohan, 2000).*** Some studies also

indicated that Carotid artery intima-media thickness CAIMT <0.8 mm is associated with normal healthy individuals, and a value of CAIMT at or above 1 mm is associated with atherosclerosis so Carotid artery intima-media thickness (CAIMT) is increasingly used as a surrogate marker of early atherosclerosis ***(Paul, 2012).*** Many studies observed that (CAIMT) of healthy controls were 0.73mm ***(Howard et al., 1992; Kumar, 2009).***

There are no effective treatment for leukoaraiosis has been reported yet, thus performing certain methods of intervention to slow down its progression is important to delay its adverse outcome ***(Liao et al., 2014).***

Several studies demonstrated greater prevalence of leukoaraiosis in intra-cranial rather than extra-cranial atherosclerotic disease of the cerebral vessels ***(Lee et al., 2008; Lee, 2010).***

Therefore to date, association of leukoaraiosis and carotid atherosclerosis in population-based studies remains controversial. A relationship between them may help in controlling its progress in the future, thus potentially improving the quality of life of patients with leukoaraiosis.

Aim of the Work

The aim of the study

1. To investigate whether there is a significant relationship between carotid artery atherosclerosis with the development of leukoaraiosis.
2. To study the impact of leukoaraiosis on neurological recovery in acute ischemic stroke patients.

Chapter (1): Pathophysiology of Leukoaraiosis

Leukoaraiosis is a neuroimaging term for periventricular and subcortical white matter changes (WMCs). It is frequently observed on computed tomography (CT) and magnetic resonance imaging (MRI) brain scans of elderly individuals. These changes are seen on CT as bilateral patchy or diffuse areas of hypodensity with ill-defined margins. Also seen as hyperintensities on T2-weighted and fluid attenuated inversion recovery (FLAIR) images on magnetic resonance imaging (MRI) scans ***(O'sullivian, 2008).*** (Figure 1).

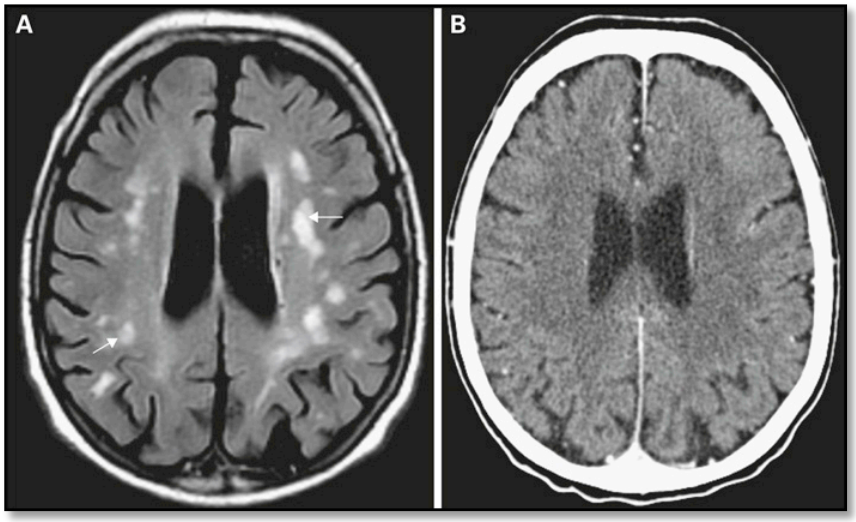

Fig. (1): Leukoaraiosis on (flair) images and CT scan brain ***(Jean et al., 2011)*** (MRI, axial Flair-weighted images (**A**). Presence of multiple signal abnormalities in the deep white matter (white arrows) corresponding to leukoaraiosis. CT scan of the same patient **(B)**: the lesions are much less well demonstrated).

The most common cause of white matter changes (WMCs) is ischemic leukoaraiosis (ILA), which is diagnosed after the exclusion of other possible causes of WMCs that appear radiologically similar as (demyelinization, vasculitis, Fabry's diseases, etc.). The prevalence of ILA increases with age ***(Leeuw et al., 2001).*** Leukoaraiosis are often found incidentally on MRI scans of clinically asymptomatic individuals ***(Vernooj et al., 2007).*** However, in its advanced form, (Figure 2) ILA is associated with cognitive decline, functional loss, psychiatric disorders and gait disturbance ***(O'Sullivan 2008; Pantoni 2010; Poggesi, 2011).***

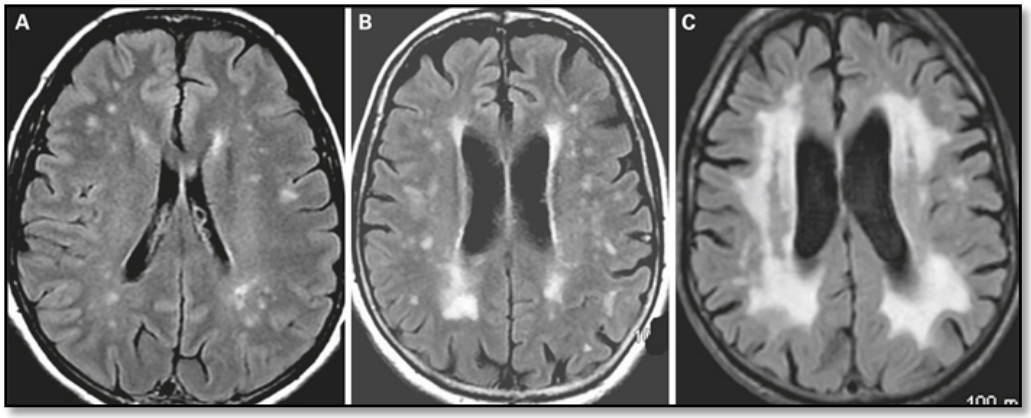

Fig. (2): Classification of the severity of lesions in Leukoaraiosis 3 grades according to Fazekas scale ***(Jean et al., 2011)*** Appendix II

Pathophysiology of leukoaraiosis

The pathophysiologic mechanisms causing ILA are not well known ***(O'Sullivan, 2008; Pantoni, 2010; Poggesi, 2011)*** ILA is today recognized as one of the manifestations of cerebral small-vessel disease ***(Pantoni, 2010).*** This is supported by strong pathological and clinical

associations with the other major manifestation of small vessel disease, lacunar stroke. The pathogenesis of cerebral small vessels disease is still a matter of investigation but both clinical and pathological studies support the most popular hypothesis that acute disruption of blood supply in one arterial territory results in lacunar infarction while a more chronic and widespread reduction in perfusion causes leukoaraiosis. This is consistent with the spatial pattern and distribution of leukoaraiosis, which arises first in those areas furthest from the origin of the arterioles in the periventricular and deep white matter regions ***(Pantoni, 2002; Hassan et al., 2003; Birns and Kalra, 2008).***

One of the recently discussed possible mechanisms is ischemic microvascular injury associated with atherosclerosis of large arteries ***(Mitchell et al., 2011; Poels et al., 2012; Webb et al., 2012; Brisset et al., 2013).*** It is well known that aging and vascular risk factors contribute to the stiffening of the large elastic arteries ***(Lee and Oh, 2010).*** Increased large artery stiffness exposes the small vessels in the brain to abnormal flow pulsations and, as such, may contribute to the pathogenesis of ILA ***(O'Rourke and Safar, 2005; Poels et al., 2012).*** Aortic arterial stiffness has already been reported to correlate with development, progression and degree of ILA ***(Henskens et al., 2008; Ohmine et al., 2008; Kearney-Schwartz et al., 2009; Kuo et al., 2010; van Elderen et al., 2010; Mitchell et al., 2011; Hatanaka et al., 2011; Poels et al., 2012; Webb et al., 2012).*** However, it is still not known if carotid

stiffness is also related to ILA. Recently new study revealed that carotid stiffness parameters were increased in patients with ILA ***(Turk, 2015).***

Also it is unclear whether the mechanisms are the same for large and small punctuate foci and for extensive diffuse leukoaraiosis. It has been assumed that the ischemic insult, responsible for LA, results from the vulnerable nature of the long penetrating end-arteries that feed the deep white matter. The deep brain structures (white matter and deep gray nuclei) are supplied by perforating arteries that are end-arteries with no collateral supply. These penetrating arteries do not arborise but give off perpendicularly oriented short branches that irrigate the white matter, each of which provides the blood supply to a cylindrically shaped metabolic unit. In the region between the cortical and ventricular surfaces, centripetal and centrifugal penetrating arteries from an internal watershed area lacking anastomoses is particularly susceptible to being injured as a result of systemic or focal decreases in cerebral blood flow ***(Birns and Kalra, 2008).***

Supporting the role of ischemia in the pathogenesis of leukoaraiosis, the results of a study showed a statistically significant correlation between the presence and severity of leukoaraiosis and degree of carotid stenosis. A trend toward increased risk of development of leukoaraiosis in carotids with fatty plaques also was observed. The data confirmed that the development of leukoaraiosis is strongly correlated with age ***(Saba, 2009).*** A further study showed a

statistically significant correlation between increased carotid artery wall thickness and LA and its severity ***(Saba et al., 2011).***

Endothelial dysfunction-blood-brain barrier abnormalities

Histopathological evidence of endothelial cells activation and retraction with increased vascular permeability, increased circulating levels of leukocyte adhesion molecules such as intercellular adhesion molecule-1 (ICAM1) and a rise in the markers of coagulation activation (including thrombin antithrombin complex and prothrombin fragments 1+2) have been reported in patients with leukoaraiosis compared with controls ***(Hassan et al., 2003).***

In addition, serum concentration of Thrombomodulin and Von Willebrand factor, which are both molecular markers of endothelial cell damage, have been shown to correlate with MRI evidence of leukoaraiosis ***(Birns and Kalra, 2008).***

A number of studies have shown that chronic hypertension predisposed to impaired blood brain barrier function, with endothelial cell retraction, increased vascular permeability and greater susceptibility to white matter injury for relatively small insults ***(Pantoni, 2002).***

Disturbances in cerebro-spinal fluid circulation

The disturbances in cerebro-spinal fluid circulation may play a role in the pathogenesis of leukoaraiosis ***(Murata, 1981).*** Also increased accumulation of cerebro-spinal fluid in the ventricules raises the interstitial pressure in the periventricular parenchyma, thus causing ischemia to the white matter ***(Birns and Kalra, 2008).***

Plasma viscosity

Plasma viscosity was elevated in patients with leukoaraiosis and lacunar infarction and considered that it may alter cerebro-spinal fluid properties and favor chronic ischemic white matter damage ***(Schneider, 1997).***

Platelet hyperaggregability and other coagulation abnormalities:

One of the studies demonstrated a significantly increased incidence of platelet hyperaggregability in 73 patients with leukoaraiosis compared with 102 controls. Twenty one patients with leukoaraiosis and uncorrected platelet hyper-aggregability were compared with 21 controls matched for age, grade of leukoaraiosis and observation period whose platelet hyper-aggregability was corrected. The results of their study showed that the progress of leukoaraiosis is significantly inhibited by long-term correction of platelet hyperaggregability, suggesting platelet hyper-aggregability as a risk factor for leukoaraiosis ***(Fujita, 2005).***

Another study investigated whether there is a direct correlation between plasma fibrinogen levels and the amount of leukoaraiosis in 28 patients with symptomatic small-vessel disease. They found a significant correlation between plasma fibrinogen levels and the amount of leukoaraiosis in patients with symptomatic cerebral small-vessel disease. This result suggests that fibrinogen may be involved in the pathophysiology of leukoaraiosis in these patients ***(Marti-Fàbregas, 2002).***

Cerebral venous circulation impairment:

Some authors found an age-related gradual increase in the thickness of the walls of veins and venules near the lateral ventricles and a striking degree of vessels wall thickening, resulting in narrowed lumina and even occlusion, in patients with leukoaraiosis. The thickened vascular walls stained strongly for collagens I and III. In the studied cases, the degree of venous collagenosis statistically correlated with the severity of leukoaraiosis. The authors questioned whether increased resistance to venous blood flow resulting from the venous stenosis, might induce chronic ischaemia and/or oedema in the deep white matter, perhaps somehow leading to leukoaraiosis, or indeed whether the collagenosis itself occurs as a result of ischaemia ***(Brown, 2002).***

More recently, there is a hypothesis that chronic cerebral hypoperfusion associated with vasogenic edema, microbleeding or/and endothelial dysfunction found in leukoaraiosis favors venous ischemia, instead of arterial ischemia, as its pathogenesis ***(Chung and Hu, 2010).***

Given that the involved regions in leukoaraiosis (periventricular and subcortical regions) are the drainage territory of deep cerebral venous system and the watershed region between the superficial and deep cerebral venous system respectively, and adding the facts that periventricular venule collagenosis, and retinal and intraparenchymal venules dilatation are related to the severity of leukoaraiosis ***(Chung and Hu, 2010).***

The authors suggested that cerebral venous hypertension caused by downstream venous outflow impairment might play a major role in the pathogenesis of leukoaraiosis. Jugular venous reflux is therefore suggested to play a key role in the pathogenesis of leukoaraiosis through a sustained or long-term repetitive retrograde-transmitted cerebral venous pressure and venous outflow insufficiency, which might lead to chronic cerebral venous hypertensions, abnormal cerebral venules structural changes, decreased cerebral blood flow, endothelial dysfunction, and vasogenic edema in cerebral white matters ***(Chung and Hu, 2010).***

Others hypothesis:

It has been also demonstrated that homocysteine (which is toxic to the endothelium) to be a strong risk factor for small-vessel disease on 90 patients with leukoaraiosis and lacunar infarction compared to 52 patients with isolated lacunar infarction after controlling for both conventional risk factors and age ***(Hassan at al., 2003; Birns and Kalra, 2008).***

Genetic factors

RNA expression was assessed in the blood of individuals with and without extensive white matter hyperintensities (WMH) to search for evidence of oxidative stress, inflammation, and other abnormalities described in WMH lesions in brain. Cluster and principal components analyses showed that the expression profiles for almost 300 genes distinguished patient with WMH from Patients without WMH. Function analyses suggested that WMH specific genes were associated with oxidative stress, inflammation, detoxification, and hormone signaling, and included genes associated with oligodendrocyte proliferation, axon repair, long-term potentiation, and neurotransmission ***(Xu H et al., 2010).***

Another study analyze 212 single nucleotide polymorphisms (SNPs) in 142 patients with ischemic stroke, generating a total of 30104 genotypes. Seventy-nine subjects (55.6%) presented leukoaraiosis measured by the Fazekas scale and 69 (48.6%) by age related white matter changes (ARWMC) scale. This study revealed that the genes associated with leukoaraiosis were involved in blood-brain barrier (BBB) homeostasis ***(Fernandez-Cadenas et al., 2010).***

Sites of white matter changes

WMHs can be divided into the subcortical and periventricular region. There is evidence that periventricular WMHs are especially related to cognitive