INTRODUCTION

Cerebrovascular Stroke is a costly disease from human, family and societal perspectives. It is a leading cause of death and disability. As a consequence, stroke ranks as the second cause of death in the world population after ischemic heart disease (the third only if neoplastic diseases are considered as a group) ***(Di Carlo et al., 2000).*** Annually, about 16 million first ever strokes occur in world, causing a total of 5.7 million deaths ***(Strong et al., 2007).*** About 85% of all stroke deaths are registered in low- and middle-income countries, which also account for 87% of total losses due to stroke in terms of disability-adjusted life years, calculated worldwide, in 72 million per year ***(Lopez et al., 2006).***

Given the immense burden that ischemic stroke exerts, the need to develop more precise estimates of prognosis remains an important goal. The prediction of outcome after ischemic stroke is important for clinicians, patients, and researchers ***(Kristian et al., 1998).***

Early predictors of functional outcome after stroke are necessary for better planning of treatment and care ***(Chamorro et al., 1995).***

Unfortunately, prognostic models have not gained much acceptance in clinical practice due to doubts about

their predictive accuracy because of issues such as observation bias, problems with generalization of results, and the complexity of algorithms that hamper practical implementation ***(Counsell et al., 2001).*** Emphasis is given to improve prognostic research by developing guidelines for the reporting of prognostic studies in health care ***(Stroup et al., 2008)***.

Aim of the Study

This study aims to determine the characteristics of the patients who initially present with acute ischemic stroke and to identify the predictors of early (7 days) outcome after one week from the onset of ischemic stroke.

Chapter (I): Clinical Picture, Investigations, and Complications of Ischemic Stroke

Acute ischemic stroke is characterized by the sudden loss of blood circulation to an area of the brain, typically in a vascular territory, resulting in a corresponding loss of neurologic function. Stroke is a nonspecific state of brain injury with neuronal dysfunction that has several pathophysiologic causes. Strokes can be either hemorrhagic or ischemic ***(Mozaffarian et al., 2015)***.

Pathophysiology

Cell membrane and cell depolarization. Influx of sodium and calcium ions and passive inflow of water into the cell lead to cytotoxic edema ***(Dirnagl et al., 1999; Yuan and Yankner, 2000 and Donnan et al., 2008).***

An acute vascular occlusion produces heterogeneous regions of ischemia in the affected vascular territory. Local blood flow is limited to any residual flow in the major arterial source plus the collateral supply. Affected regions with cerebral blood flow of lower than 10 mL/100 g of tissue/min are referred to collectively as the core. These cells are presumed to die within minutes of stroke onset ***(Latchaw et al., 2003).***

Zones of decreased or marginal perfusion (cerebral blood flow < 25 mL/100g of tissue/min) are collectively called the ischemic penumbra. Tissue in the penumbra can remain viable for several hours because of marginal tissue perfusion ***(Latchaw et al., 2003).***

On the cellular level, the ischemic neuron becomes depolarized as ATP is depleted and membrane ion-transport systems fail. Disruption of cellular metabolism also impairs normal sodium-potassium plasma membrane pumps, producing an intracellular increase in sodium, which in turns increases intracellular water content. This cellular swelling is referred to as cytotoxic edema and occurs very early in cerebral ischemia. Cerebral ischemia impairs the normal sodium-calcium exchange protein also found on cell plasma membranes. The resulting influx of calcium leads to the release of a number of neurotransmitters, including large quantities of glutamate, which in turn activates N-methyl-D-aspartate (NMDA) and other excitatory receptors on other neurons. These neurons then become depolarized, causing further calcium influx, further glutamate release, and local amplification of the initial ischemic insult. This massive calcium influx also activates various degradative enzymes, leading to the destruction of the cell membrane and other essential neuronal structures ***(Kasner and Grotta, 1997).***

Free radicals, arachidonic acid, and nitric oxide are generated by this process, which leads to further neuronal damage. Ischemia also directly results in dysfunction of the cerebral vasculature, with breakdown of the blood-brain barrier occurring within 4-6 hours after infarction. Following the barrier's breakdown, proteins and water flood into the extracellular space, leading to vasogenic edema. This produces greater levels of brain swelling and mass effect that peak at 3-5 days and resolve over the next several weeks with resorption of water and proteins ***(Gotoh et al., 1985)***.

Within hours to days after a stroke, specific genes are activated, leading to the formation of cytokines and other factors that, in turn, cause further inflammation and microcirculatory compromise Ultimately, the ischemic penumbra is consumed by these progressive insults, coalescing with the infarcted core, often within hours of the onset of the stroke ***(Kasner and Grotta, 1997).***

Infarction results in the death of astrocytes, as well as the supporting oligodendroglial and microglial cells. The infarcted tissue eventually undergoes liquefaction necrosis and is removed by macrophages, with the development of parenchymal volume loss. A well-circumscribed region of cerebrospinal fluid–like low density, resulting from encephalomalacia and cystic change, is eventually seen. The evolution of these chronic changes may be seen in the weeks to months following the infarction ***(Thompson, 1996 and Kopito and Jeff, 2001).***

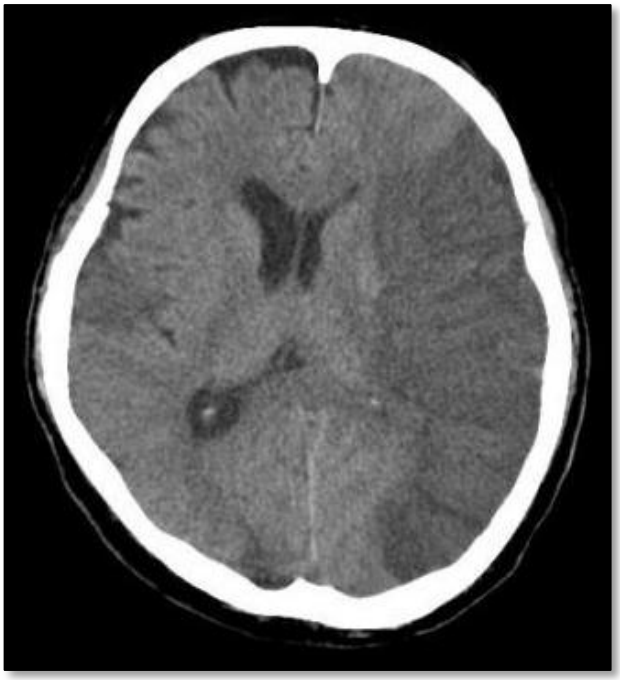

Figure (1): Vascular distributions: Middle cerebral artery (MCA) infarction. Noncontrast computed tomography (CT) scanning demonstrates a large acute infarction in the MCA territory involving the lateral surfaces of the left frontal, parietal, and temporal lobes, as well as the left insular and subinsular regions, with mass effect and rightward midline shift. There is sparing of the caudate head and at least part of the lentiform nucleus and internal capsule, which receive blood supply from the lateral lenticulostriate branches of the M1 segment of the MCA. Note the lack of involvement of the medial frontal lobe (anterior cerebral artery [ACA] territory), thalami, and paramedian occipital lobe (posterior cerebral artery [PCA] territory) ***(Ashrafian, 2010).***

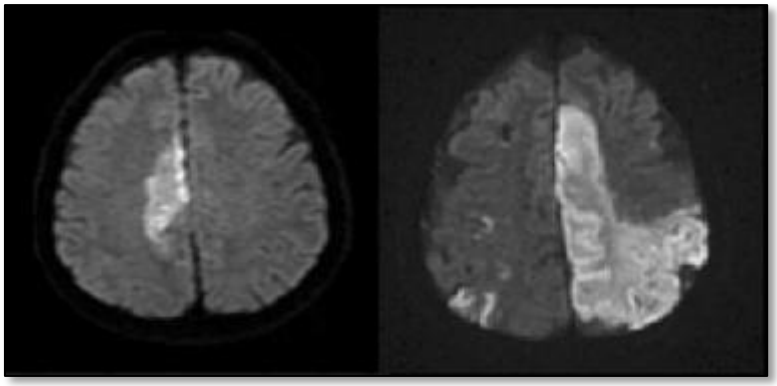

Figure (2): Vascular distributions: Anterior cerebral artery (ACA) infarction. Diffusion-weighted image on the left demonstrates high signal in the paramedian frontal and high parietal regions. The opposite diffusion-weighted image in a different patient demonstrates restricted diffusion in a larger ACA infarction involving the left paramedian frontal and posterior parietal regions. There is also infarction of the lateral temporoparietal regions bilaterally (both middle cerebral artery [MCA] distributions), greater on the left indicating multivessel involvement and suggesting emboli ***(Ovbiagele et al., 2013).***

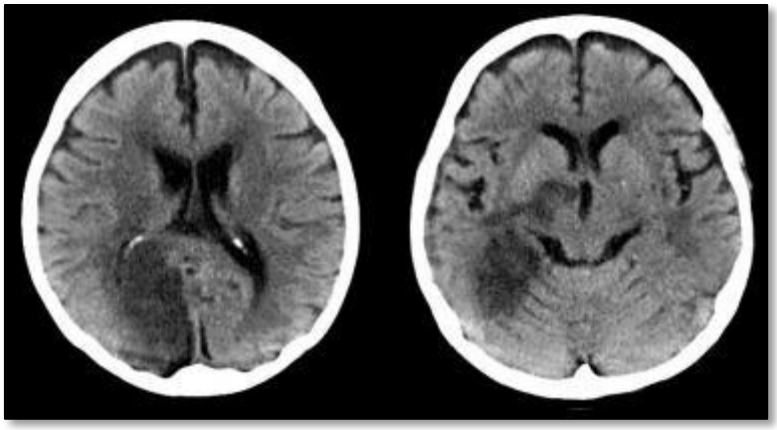

Figure (3): Vascular distributions: Posterior cerebral artery (PCA) infarction. The noncontrast computed tomography (CT) images demonstrate PCA distribution infarction involving the right occipital and inferomedial temporal lobes. The image on the right demonstrates additional involvement of the thalamus, also part of the PCA territory ***(Thompson, 1996).***

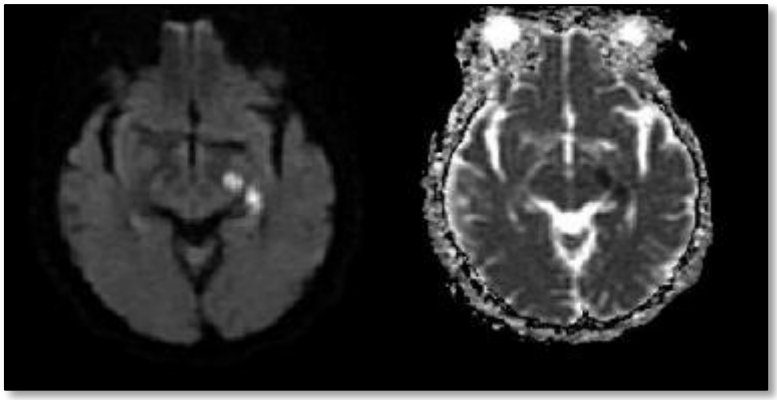

Figure (4): Vascular distributions: Anterior choroidal artery infarction. The diffusion-weighted image (left) demonstrates high signal with associated signal dropout on the apparent diffusion coefficient (ADC) map involving the posterior limb of the internal capsule. This is the typical distribution of the anterior choroidal artery, the last branch of the internal carotid artery (ICA) before bifurcating into the anterior and middle cerebral arteries. The anterior choroidal artery may also arise from the middle cerebral artery (MCA) ***(Lehman et al., 2016).***

Hemorrhagic transformation represents the conversion of an ischemic infarction into an area of hemorrhage. This is estimated to occur in 5% of uncomplicated ischemic strokes, in the absence of fibrinolytic treatment. Hemorrhagic transformation is not always associated with neurologic decline, with the conversion ranging from the development of small petechial hemorrhages to the formation of hematomas that produce neurologic decline and may necessitate surgical evacuation or decompressive hemicraniectomy. Proposed mechanisms for hemorrhagic transformation include reperfusion of ischemically injured tissue, either from recanalization of an occluded vessel or from collateral

blood supply to the ischemic territory or disruption of the blood-brain barrier. With disruption of the blood-brain barrier, red blood cells extravasate from the weakened capillary bed, producing petechial hemorrhage or more frank intraparenchymal hematoma ***(Mullins, 2005 and Donnan et al., 2008).***

Hemorrhagic transformation of an ischemic infarct occurs within 2-14 days after onset, usually within the first week. It is more commonly seen following cardioembolic strokes and is more likely to occur with larger infarct volumes ***(Nighoghossian et al., 2002 and Donnan et al., 2008).*** Hemorrhagic transformation is also more likely following administration of rt-PA in patients whose computerized tomography scans demonstrate areas of hypodensity ***(Dubey et al., 2001; Albers et al., 2004 and González, 2006).*** Cerebral edema and herniation are the most common causes of early death in patients with hemispheric stroke ***(Adams et al., 2007)***.

Epidemiology

The epidemiology of stroke is changing over time as a result of a number of factors, including an aging population and advances in the prevention and treatment of stroke. Given the observed changes in the epidemiology of stroke over time, it is important to obtain a good overview of the most recent data ***(Dragutin et al., 2012).***

Epidemiological trials usually include hospital material, but population trials provide the most accurate epidemiological data. Whereas population trials are important for stating morbidity (incidence and prevalence), mortality, long-term outcome and life quality after stroke, clinical epidemiological trials enable estimation of case fatality and short-term outcome of the disease ***(Dragutin et al., 2012).***

Subtypes of acute stroke

There are different approaches to classification of acute stroke. International classification of diseases and problems made by the WHO regarding health (tenth audit-ICD 10) includes diseases and signs, symptoms, abnormal test results, complaints, social circumstances and external causes of injuries and illnesses. This classification classifies stroke under codes from 160 to 169 into following subgroups: subarachnoidal hemorrhage, intracerebral hemorrhage, other non-traumatic hemorrhages, cerebral infarct caused by extracerebral or intracerebral occlusion, as well as non-specific stroke ***(Caplan, 2013).***

Classification of Oxford Community Stroke project is primarily based on initial symptoms; episodes of ischemic stroke are classified based on development of symptoms such as total anterior circulation syndrome,

partial anterior circulation syndrome, lacunar circulation syndrome and posterior circulation syndrome. These five entities anticipate the development of stroke, part of brain which was compromised, the main cause behind the incident and disease prognosis ***(Bamford, 2000).***

Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification of ischemic stroke is very practical and is based on clinical symptoms, as well as on results of further research. Based on that, stroke is classified as a consequence of: thrombosis or embolism due to atherosclerosis of large blood vessels; embolism which started in the heart; occlusion of small blood vessels; other stated causes; undetermined causes. The TOAST is an evidence-based classification algorithm for acute ischemic stroke designed to determine the most likely etiology in the presence of multiple competing mechanisms ***(Adams et al., 1993 and Hakan et al., 2007).***

The subtypes according to TOAST classification include large vessel disease (LVD), small vessel disease (SVD), cardioembolic (CE) stroke, stroke of other determined etiology, undetermined stroke and cryptogenic stroke. The large vessel disease constitutes about 15-20% of all strokes, but the proportion varies by age, sex and ethnicity. The pathogenesis is atherosclerotic disease in large and medium sized precerebral and cerebral arteries. The

atherosclerotic plaques typically develop near branching points and places of confluence. In white populations the atherosclerotic plaques are more frequent in the extracranial arteries whereas intracranial atherosclerosis is more prevalent among the Asian, Hispanic and black populations. The reason for the different distribution is unknown. Cerebral ischemia by atherosclerosis may be caused by distal artery to artery embolization from an atherosclerotic lesion (considered the most common mechanism) or by hemodynamic mechanisms ***(Kirshner, 2009).***

The small vessel disease (SVD) accounts for one quarter of all ischemic strokes. According to the lacunar hypothesis ***(Fisher, 1982)***, a lacunar infarction is the result of an occlusion of a single deep perforating end-artery arising from the circle of Willis or from the basilar artery. The most common locations are the deep white matter, the internal capsule, the thalamus and the paramedian and lateral regions of the brainstem. The infarcts are usually small (0.2-15mm). The pathology is not clear but microatheroma, intimal thickening and hyalinization and wall fibrosis in the small penetrating vessels have been described ***(Bailey et al., 2012)***.

The clinical manifestations of a lacunar syndrome include pure motor hemiparesis, pure sensory stroke, sensorimotor stroke, ataxic hemiparesis and dysarthria-

clumsy hand syndrome and atypical lacunar syndromes ***(Fisher, 1982).*** However, in up to 20% of cases, a lacunar syndrome may also be caused by for example an embolic occlusion of cardiac or arterial origin or by vasculitis. Therefore, a thorough diagnostic work-up should be done, to exclude other causes than SVD ***(Arboix and Marti-Vilalta, 2009).***

The cardioembolic (CE) stroke is considered to cause approximately 25% of all ischemic strokes, but in elderly patients it is the most common subtype ***(Arboixand Marti-Vilalta, 2009).*** Embolism from the heart to the brain leads to a vessel occlusion and the most common underlying etiology is atrial fibrillation (AF). Recent myocardial infarction (MI), mechanical prosthetic valve, dilated myocardiopathy, mitral rheumatic stenosis, atrial myxoma, and endocarditis are also considered as high-risk sources of cardioembolism. Studies show that CE strokes are often severe, have a dramatic onset of symptoms and have a high early recurrence rate. Another characteristic of CE stroke is the high proportion of hemorrhagic transformation compared with non CE strokes ***(Ferro, 2003)***. In contrast to other stroke subtypes, anticoagulation with vitamin K antagonists (VKA) is effective as preventive medication after most CE stroke. Recently, new direct oral anticoagulants such as dabigatran, rivaroxaban, apixaban have also received approval for stroke prevention in nonvalvular AF ***(Mani and Lindhoff-Last, 2014).***

The cryptogenic stroke accounts for 25-30% of all ischemic strokes and is more prevalent among young stroke sufferers. An ischemic stroke is classified as cryptogenic if the etiology cannot be identified despite an extensive work-up. In most studies, cryptogenic stroke has not been defined as a separate subtype, but included in the undetermined stroke category ***(Grau et al., 2001)***. It has been suggested that the proportion of cryptogenic stroke could be reduced by putting more effort on the diagnostic work-up ***(Guercini et al., 2008).*** Many studies in recent years have focused on revealing potential etiologies that may have escaped detection in the initial work-up, for example with prolonged ambulatory electrocardiogram (ECG) and insertable cardiac monitoring, AF was found in 9-16% of patients with cryptogenic stroke ***(Sanna et al.,2014).***

In about 5% of all ischemic stroke cases the cause is of other determined etiology and this proportion is higher the younger the population is (up to16% in patients less than 50 years). The most common cause in this category is arterial dissection. Other more rare causes include hematological disorders, vasculitis, monogenic syndromes, and migraine stroke ***(Rutten-Jacobs et al., 2013)***.

The cases where multiple etiologies are identified and where the work-up is incomplete are classified as undetermined. Consequently, the proportion for this category varies depending on how much effort is spent on diagnostic evaluation ***(Nam et al., 2012).***