



Differences of Clinical Characteristics of Ischemic Stroke in Patients with and without Renal Impairment

Thesis

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LIST OF ABBREVIATIONS

ACR	: Albumin Creatinine ratio
ASUSH	: Ain Shams University Specialized Hospital
AT	: Atherosclerosis
ATP	: Adenosine Triphosphatase
BUN	: Blood Urea Nitrogen
CABG	: Coronary Artery Bypass Grafting
CBF	: Cerebral Blood Flow
CBV	: Cerebral Blood Volume
CKD	: Chronic Kidney Disease
CVD	: Cardiovascular Disease
Echo	: Echocardiography
EF	: Ejection Fraction
eGFR	: estimated Glomerular Filtration Rate
ESR	: Erythrocyte Sedimentation rate
FBS	: Fasting Blood Sugar
FMD	: Flow Mediated Dilatation
HB	: Hemoglobin
IBD	: Inflammatory Bowel Disease
ICP	: Increased Intracranial Pressure
IL-1	: Interleukin 1

iNOS	: inducible Nitric Oxide Synthase
LVH	: Left Ventricular Hypertrophy
LVD	: Large Vessel Disease
MDRD	: Modification of Diet in Renal Disease
mRS	: modified Rankin Scale.
NHANES	: National Health and Nutritional Examination Survey
NIHSS	: National Institute of Health Stroke Scale
NINDS	: National Institute of Neurological Disorders and Strokes
OCSP	: Oxford shire Community Stroke Project
SAD	: Small Artery Disease
SD	: Standered Deviation
SVD	: Small Vessel Disease
SUD	: Stroke of undetermined etiology.
TNF	: Tumor Necrosis Factor
TOAST	: Trial of Org in Acute Stroke Treatment
UAE	: Urinary Albumin Excreation

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INTRODUCTION & AIM OF THE WORK

Renal dysfunction is now an accepted risk factor for cardiovascular diseases (*Matsushita et al., 2010*) including stroke (*Nickolas et al., 2008*) peripheral arterial disease (*O'Hare et al., 2004*) and silent brain infarction (*Kobayashi et al., 2009*). Several reports have indicated that renal dysfunction is associated with a high prevalence of stroke (*Wannamethee et al., 1997; Go et al., 2004; Ninomiya et al., 2005(A); Weiner et al., 2006(A); Nakayama et al., 2007; Abramson et al., 2003*).

In 2002, the Kidney Disease Outcomes Quality Initiative (K/DOQITM) proposed a definition and classification (staging) for chronic kidney disease (CKD), outlining the treatments required to prevent end-stage renal disease (*K/DOQI clinical practice guidelines, 2002*) and many reports have indicated that end-stage renal disease, including conditions requiring haemodialysis, is associated with a higher incidence of stroke (*Seliger et al., 2003; Toyoda et al., 2005*), especially cerebral haemorrhage, (*Iseki et al., 1993*) and with greater severity of stroke.

Even moderate renal dysfunction is thought to be a risk factor for cardiovascular disease (*Weiner et al., 2009(B)*).

In a study of coronary heart disease and renal dysfunction, patients with hypertension and a moderately reduced glomerular filtration rate (GFR) were more likely to develop coronary heart disease than end-stage renal disease (**Rahman et al., 2006**). However, studies on the clinical features of stroke patients with moderate renal dysfunction but not end-stage disease are limited (**Haruhiko et al., 2012**).

Mounting evidence indicates that even relatively minor impairments in chronic renal function, are common in the setting of cardiovascular disease, and predictive of vascular events including stroke (**Weiner et al., 2004**). Indeed, the independent association between chronic kidney disease (CKD) and stroke occurrence has now been reported in several studies (**Koren-Morag et al., 2006; Ovbiagele 2008**).

However, beyond the link between baseline renal dysfunction and incident vascular disease, mild to moderate CKD, has been related to generally poorer clinical outcomes following an index vascular event (**Anavekar et al., 2004**).

Yet, several studies in a variety of clinical settings reflect poor surveillance for, and management of, renal disease in these at-risk patients (**Baumelou et al., 2005**).

Early identification of undiagnosed CKD may facilitate initiation of therapy aimed at limiting further renal function deterioration or optimizing vascular risk reduction, thereby

boosting clinical outcomes among persons with established cerebrovascular disease (*Brosius 3rd et al., 2006*).

Advanced renal dysfunction is often associated with cardiovascular diseases or stroke. Indeed, recent investigations have indicated that even microalbuminuria or mildly decreased glomerular filtration rate (GFR) may be a predictor of cardiovascular disease or stroke (*Sarnak et al., 2003; Ninomiya 2008(B); Go et al., 2004; Koren-Morag et al., 2006; Nakayama et al., 2007; Bos et al., 2007*).

The estimated prevalence of chronic kidney disease (CKD), defined as GFR, 60 mL/min/1.73 m², is 5% among adults in the United States (*Kidney Disease Outcome Quality Initiative (2002)*) and as high as 10% in adults in Japan (*Imai et al., 2009*).

But although CKD may be a risk factor for stroke, the prevalence of renal dysfunction among patients with cerebrovascular events has not been well documented (*Yuuko et al., 2011*).

AIM OF WORK:

To assess the effect of renal dysfunction on clinical features ,severity and prognosis of acute ischemic stroke ,in order to identify the patients at high risk for poor outcome who may benefit from earlier and specialized management.

PATHOGENESIS OF STROKE

Stroke is a clinical syndrome characterized by the rapid onset of focal neurological signs, lasting more than 24 hours or leading to death, with a presumed vascular cause. This definition includes stroke due to both infarction and hemorrhage (*Hugh , 2012*).

Stroke is the leading cause of disability worldwide, the second most common cause of dementia and the third leading cause of death (*Bakhai, 2004*). It has enormous clinical, social, and economic implications and demands a significant effort from both basic scientists and clinicians in the quest for understanding the underlying pathogenetic mechanisms, and thereby adopting suitable preventive measures and successful therapies, beyond thrombolysis, which is but available to <5% of all patients (*Heuschmann et al.,2003*).

Owing to its high prevalence, high burden of illness and economic cost, well-defined modifiable risk factors, and effective preventive measures, stroke is well suited for prevention. However, unfavorable trends in stroke risk factor profile as lack of awareness among public and medical fraternity, misapplication or underutilization of stroke preventative programmes and lack of emphasis on preventive training in medical school and postgraduate programmes throughout the world, have precipitated

high stroke rates and culminated into widening the stroke prevention gap (*Gorelick et al.,2002*).

Stroke Subtypes:

Approximately 87% of strokes are ischemic (*Rosamond et al., 2008*), with subtypes based largely on pathophysiology. Various schemes have been developed to classify subtypes, including the Trial of Org 10172 in Acute Stroke Treatment (TOAST), the National Institute of Neurological Disorders and Strokes (NINDS), the Oxford shire Community Stroke Project (OCSP), and those based on brain imaging (*Jackson et al., 2005*).

Although these systems differ in terms of nomenclature, weight placed on risk factors, clinical features, and brain imaging techniques, they all differentiate between strokes of large vessel (cortical), small vessel (lacunar), cardioembolic, other determined cause, and cryptogenic origin (*Howard ,2009*).

The prevalence of stroke subtypes varies among races and ethnicities (*Shin et al. ,2005; Kitamura et al. ,2006*). Compared with Caucasians, Asians are more likely to present with small vessel disease (SVD), while Hispanics and Blacks have a higher prevalence of all stroke subtypes, particularly SVD (*Ohira et al. ,2006*). A possible explanation is that patients with SVD strokes have milder impairments and better outcomes than patients with large vessel disease (LVD) strokes (*Grau et al., 2001; Petty et*

al.,2000) thus, they may be more likely to meet study eligibility criteria (*Howard ,2009*).

Approximately 60–70% of first recurrent strokes have the same mechanism as the incident stroke (*Shin et al., 2004; Petty et al. ,2000*). Patients with LVD are more likely to experience a recurrent event, especially within the first 3 months, than those with SVD or cardio-embolic stroke (*Grau et al.,2001; Lovett et al.,2004*) perhaps owing to cerebral micro-embolism from plaque ulceration (*Moroney et al.,1998*) or procedure-related cerebral ischemia (*Grau et al.,2001; Petty et al.,2000*).

Also, there is the modified TOAST system which classifies stroke etiology into 5 different categories: atherosclerosis (AT), small-artery disease (SAD), cardio embolism, stroke of other determined etiology (SOD), and stroke of undetermined etiology (SUD). In addition, SUDs are further divided into the subcategories SUDm (two etiologies are identified), SUDu (no likely etiology was found despite extensive evaluations), and SUDi (the etiology of stroke cannot be determined due to incomplete evaluation) (*Han et al.,2005*).

The modified TOAST criteria differ from that of the TOAST in that a relevant artery stenosis <50% with an unstable plaque is placed in the AT category. In addition, a single ischemic lesion occurring in a single perforating arterial territory without relevant large artery stenosis (determined by angiographic evaluation) is considered due to SAD. A patient with a small brain

lesion (<2 cm) is classified as AT if a relevant and systemic arterial stenosis or occlusion is identified on angiography (**Wan et al., 2011**).

Pathophysiology of stroke:

Ischemic stroke:

Ischemic stroke, which account for 85% of all strokes, (**Beal, 2010**) may manifest in the form of thrombotic stroke (large vessel and small vessel types), embolic stroke (with/without known cardiac and /or arterial factor), systemic hypoperfusion (Watershed or Border Zone stroke), or venous thrombosis. Embolisms cause approximately 75% of all cerebral vessel occlusions, and are the most frequent cause of focally-obstructed blood flow within the brain (**Mergenthaler et al, 2004**).

Irrespective of the cause, compromised vascular supply to the brain is the primary event in majority (85–90%) of acute strokes. Low respiratory reserve and complete dependence on aerobic metabolism make brain tissue particularly vulnerable to effects of ischemia. Regions suffering the most severe degrees of hypoperfusion rapidly progress to irreversible damage, representing the 'ischaemic core'. This tissue exhibits very low cerebral blood flow (CBF), cerebral blood volume (CBV) and metabolic rates of oxygen and glucose (**Marchal et al, 1999**).

The remaining hypoperfused tissue exhibits impairment of the normal blood flow autoregulatory mechanisms and is pathophysiologically divided relative to a well-defined perfusion threshold into two compartments, namely, the 'penumbra' and 'oligaemia'. In the penumbra, oxygen metabolism is preserved relative to CBF **(Baron et al, 1995)**.

Tissue within the penumbra is potentially salvageable, yet its extent decreases over time by gradual recruitment into the core and as such, represents a key target for therapeutic intervention **(Baron et al, 1995)**.

This course of events varies from patient to patient, but most exhibit substantial volumes of penumbra for many hours **(Baron, 1999)** or exceptionally, days after stroke onset **(Perez et al, 2006)**.

The oligoemic compartment, on the other hand, suffers a milder degree of hypoperfusion with normal oxygen consumption and elevated CBV, and is not normally at risk of infarction. If the occlusion persists, however, secondary events such as systemic hypotension, intracranial hypertension or hyperglycemia may topple this delicate balance and force the oligoemia into a penumbral state and eventually recruitment into the necrotic core. **(Baron et al, 1995)**.

Small vessel disease:

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 (***Pantoni , 2010***).

There are different types of small vessel diseases and a simplified aetiopathogenic classification is proposed in the figure 1. The frequency of these types is very different .Type1, arteriolosclerosis, type 2, sporadic and hereditary cerebral amyloid angiopathy, are the most prevalent forms (**Leonardo et al.,2010**)..