

Stroke Subtypes and Evidence Basis of Thrombolysis

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Abstract: Understanding the mechanism of disturbance of blood flow in different stroke subtypes, their aetiopathogenic process and accurate anatomical localization are concepts essential for proper management and prognostication in stroke. As effective as thrombolysis might be in restoring blood flow after an ischaemic ictus, its application in haemorrhagic stroke can be disastrous. This review examines the current literature on the pathogenesis of the different types of stroke and the evidence basis for the use of intravenous thrombolysis as a primary treatment modality that has the possibility of restoring blood supply to the ischaemic brain.

I. Introduction

There are very few concepts and diagnoses as interesting and intriguing as stroke is because of its multiple types, subtypes, forms and diverse puzzling clinical presentations and indeed myriads of mimics. To the non-specialist, very few issues are this confounding. Despite the effectiveness of stroke scales none can accurately predict the outcome after a vascular event. Stroke indeed is a serious disease, which has been aptly described as “a life-changing event that affects not only stroke patients themselves but their family members and caregivers as well”[1].

The suddenness of stroke occurrence explains why the Greeks had referred to it as “apoplexy”. Apoplexy suggesting that one was violently struck down suddenly [2]. Its synonyms such as brain attack and cerebrovascular accident all support its definition as any sudden onset of neurologic loss that last longer than a day or leading to death, with the origin being vascular, and its presentation focal or global [3]. Stroke must be differentiated from transient ischaemic attack (TIA) which is “a neurological deficit caused by interruption in blood supply to brain (or retina), with symptoms resolving within 24 hours” [4]. Key to the proper enunciation of the characteristics of stroke is a focus on aspects like mechanism of disturbance of blood flow, aetiopathogenic process and accurate anatomical localization. These concepts are essential for proper understanding of its pathophysiology, management and prognosis.

Stroke is a major public health problem being the 3rd leading cause of mortality after myocardial infarction and cancer in many countries [1] [5]. Despite efforts at reducing the prevalence of stroke, the incidence will continue to rise due to the aging proportion of populations in most countries of the world. In the US, about 750,000 people have stroke each year with half of its sufferers left dependent on caregivers [1] [6]. The incidence in other regions of the world is 254/100,000 in the United Kingdom, 244/100,000 in rural South Africa and 330/100,000 in Taiwan [7, 8]. Though it affects people across all age group, one-quarter of those affected are over 65 years [5]. Stroke places a lot of burden on individual and national income, with about \$73 billion estimated to be the directly or indirectly cost of stroke care in 2010 [9]. Its prevalence is increasing in low and middle-income countries, with a recent Nigerian-review reporting stroke as being responsible for 4.5% of medical admission and 1.3% of total hospital admission [15].

The risk factors for stroke are traditionally divided into modifiable and non-modifiable risk factors [1]. Demographic and inherited tendencies like age, sex, race or ethnicity, and genetic make-up are the non-modifiable ones, while diabetes mellitus, hypertension, smoking (passive or active), heart disease like atrial fibrillation, hormonal replacement therapy at menopause, hormonal contraceptive pills, physical inactivity, obesity, drug abuse, excessive alcohol use and connective tissue disorders are the modifiable risk factors. Wahab et al [15] reported hypertension (85.2%), diabetes mellitus (23.8%), and tobacco smoking (22.8%) as common identifiable risk factors for stroke in a cohort of Nigerians admitted with stroke over a three-year period at a tertiary hospital in Western Nigeria.

II. Normal Cerebral Blood Flow

The brain uses 20% of cardiac output principally as source of oxygen and glucose for energy production at a rate of 500ml of oxygen and 100mg of glucose per milliliter of blood per minute. The average cerebral blood flow (CBF) is about 50ml per 100g per minute in adults, which is determined by the cerebral perfusion pressure (CPP) and cerebrovascular resistance [11]. Energy in the brain is produced mostly aerobically, which is why the brain is very sensitive to any changes in blood flow. Nature has instituted an auto-regulatory mechanism that maintains the Mean Arterial Pressure (MAP) within a safe limit of 50-150mmHg irrespective of changes in systemic blood pressure. Drop in CBF causes impaired CPP, which could result in cessation of

cellular metabolism and subsequently irreversible infarct if CPP is not restored to within safe limits. In people with chronic hypertension due to the maladjustment of the auto-regulatory process, a sudden reduction systemic blood pressure to within normal range can result in cerebral ischaemia [12]. At 20ml/100mg/minute of CBF the brain ability to extract oxygen drops; at 10ml/100mg/minute of CBF metabolic function at the cellular level is severely affected; but below 5ml/100mg/minute cell death either as apoptosis or necrosis occurs within minutes [5]. Normally at 20ml/100g/minute of CBF, metabolic demand of the brain can not be achieved despite increase oxygen extraction resulting in cerebral ischaemia [11,12,13]. Haemorrhagic and bland infarct are the two types of infarct that have been recognized. If there are vascular structures within or surrounding the area, upon reperfusion of the necrotic area erythrocytes move across the damaged arteriolar and capillary membrane resulting in a haemorrhagic infarct, but when there is no leakage of blood cell into the infarcted area it presents as a bland infarct [14].

III. Pathophysiology Of Ischaemic Stroke

Stroke is broadly divided into two major types based on the underlying mechanism of occurrence. The first being haemorrhagic stroke which accounts for only 15-20% of all strokes; it causes disruption of blood supply to a particular part of the brain following the rupture of a blood vessel. This is opposed to ischaemic stroke (about 80-85% of all strokes) where there is an obstruction to blood flow due to occlusion of the vessel by a thrombus or embolus. It could also occur as a result of hypoperfusion. Embolic stroke could be artery to artery (30-40%) or cardioembolic (30-40%). The third possible source of embolic strokes is from a deep venous thrombosis commonly of the leg veins, which only occurs when there is a communication in the heart allowing for right-to-left shunt usually in the form of an atrial septal defect (ASD) or ventricular septal defect (VSD). In addition to the pathophysiologic classification, stroke can also be grouped into anterior or posterior circulation strokes based on the broad division of arterial supply disrupted. Anterior circulation stroke involves areas supplied by the branches of the carotid artery while posterior circulation stroke involve areas supplied by the basilar or vertebral arteries [4].

Ischaemic stroke is further classified into lacunar infarct, border-zone infarct or wedge infarct. Lacuna infarcts are infarcts measuring less than 15mm on CT scan, while border-zone infarct occurs between arterial territories supplying the brain [5]. The wedge-infarct could involve any of the major cerebral artery territories including; anterior, middle or posterior cerebral artery territories. Based on the type of blood vessel involved infarct could be arterial (99%) or venous (1%), particularly cerebral venous thrombosis.

Mechanism of neuronal injury in ischaemic stroke:

Persistent ischaemia following thrombosis, embolism or haemodynamic failure as occurs in severe haemorrhage; cardiac arrest or bypass surgery, metabolic changes occurs including: intracellular influx of calcium ions resulting in mitochondrial dysfunction; anaerobic breakdown of glucose with production of lactic acid; increase release of excitatory neurotransmitters such as glutamate which mediates further calcium and sodium influx. These all contribute to cellular electrical failure and ultimately cell death through necrosis or apoptosis. The other postulated mechanism leading to apoptosis in ischaemia is the disruption and loss of membrane ionic pump, which is responsible for sodium-potassium exchange across the cell membrane [15]. The malfunctioning of the membrane pump results in impaired ionic gradient, which leads to loss of Potassium exchange for Sodium, Chloride and Calcium. Sodium and chloride influx into the cell is associated with passive diffusion of water resulting in cellular oedema (cytotoxic oedema). Cell death in ischaemia is either by necrosis (immediate cell death) or apoptosis (programmed cell death).

Concept of umbra and penumbra:

When there is an infarct, the presence of collateral circulation results in the delineation of three layers of tissue. The first is the innermost core with blood flow between 10-25% of normal; this is functionally (electrical failure) and structurally (neuronal and glial) dead (necrotic area). While the immediate area surrounding this is only functionally dead but morphologically alive hence remains salvageable by relieving the obstruction to blood flow. This can be achieved by clot lysing pharmacologically (thrombolysis) or mechanically (clot extraction). Ischaemia in the penumbra initiates the process leading to the release of oxygen free radicals, which causes damage to vascular endothelium, and also initiate the apoptotic pathway [16]. The third layers of tissues are those within normal MAP of 50-150mmHg hence functionally and morphologically alive. The cells within the umbra die by necrosis, while those within the ischaemic penumbra die by apoptosis if measures are not put in place to restore tissue perfusion [5].

Cerebral oedema:

The occurrence of morphological death in the ischaemic tissue results in two types of oedema which are either cytotoxic and vasogenic oedema. In cytotoxic oedema water moves into the cell and is restricted to a

particular vascular territory and forms the basis of computerized tomography scans diagnosis in early ischaemic stroke. In vasogenic oedema, there is extracellular accumulation of fluid due to endothelial cell injury. This fluid movement is along the lines of white matter tract [5]. Cytotoxic or cellular oedema involves all cell types including neurons, glial and endothelial cells. It occurs within minutes to hours of ischaemia and is reversible, unlike vasogenic oedema, which occurs over hours to days and is irreversible [16].

IV. Pathophysiology Of Haemorrhagic Stroke

Haemorrhagic stroke commonly occur around the thalamus and the basal ganglia. It is reported that 60% occur in the putamen and adjacent internal capsule; 20% in the pons; 10% in the cerebellum and others are found in temporal, frontal, parietal or occipital lobes [17]. The thalamoganglionic haemorrhage is strongly associated with hypertension as a major risk factor [18, 19, 20]. Chronic hypertension results in hyperplasia and proliferation of smooth muscles of the artery resulting hyperplastic arteriosclerosis and ultimately microaneurysms. Rupture of these Charcot-Bouchard aneurysms is responsible for intracerebral haemorrhage [21]. Lobar bleed is the second form of haemorrhagic stroke; it is associated with cerebral amyloid angiopathy in the elderly or arteriovenous malformation (AVM) in the young patients. Amyloid angiopathy has been seen in 20% of cases in patients who are 70 years and above [22]. Deposition of β -amyloid in the tunica media and adventitia of cortical and meningeal vessels results in fibrinoid changes, necrosis, segmental dilation, and aneurysm formation. These vessels will subsequently ruptures resulting in bleeding into the brain substance [23]. Another common risk factor for haemorrhagic stroke is anticoagulant use. About 0.3 to 0.6% of patients on chronic anticoagulation using warfarin have intracerebral haemorrhage annually [24]. The risk of bleeding in patients undergoing anticoagulation increases with higher intensity of anticoagulation, advancing age, history of hypertension, simultaneous use of antiplatelet agents, cortical amyloid angiopathy, and the presence of leukoariosis on neuroimaging [25,26]. Although the direct relationship between Intracerebral haemorrhage and antiplatelet use is not well established, it is associated with a larger haematoma size and ICH mortality rate [27,28,29]. Patients with acute ischaemic stroke treated with recombinant tissue plasminogen activator (rt-PA) have a 6% risk of having ICH [30]. The haematoma volume may expand thus increasing the depression of consciousness level. Haematoma expansion occurs within the first day of an haemorrhagic stroke in about 30% of patients [31,32]. The haematoma volume and expansion are useful in predicting the functional outcome and mortality 30 days following acute haemorrhagic stroke[31,33,34]. Subarachnoid haemorrhage (SAH) occurs when there is a bleed into the subarachnoid space, which is commonly associated with ruptured berry's aneurysm, but could also be associated with trauma or AVM. Intracerebral bleeding can extend into the subarachnoid space or commonly into the intraventricular space thus presenting with features of meningeal irritation, a presentation that might be difficult to differentiate from a straightforward SAH.

Mechanism of injury in haemorrhagic stroke:

The first major work exploring the basis for haemorrhagic stroke was that of Johann Wepfer in 1658. In his publication titled "Apoplexia", the vertebral and carotid arteries were observed to be the major source of blood to the brain. He also postulated that patient who died from apoplexy had bleed into the brain [2]. Haemorrhagic stroke occupies an important place in vascular neurology owing to the high mortality rate, which varies between 25 to 60%. The higher prevalence and impact of ICH reported among blacks and Hispanics populations is thought to be due to lack of proper medical care for hypertension and a genetic predisposition particularly Apo lipoprotein E [35]. Neurological impairment following haemorrhagic stroke occurs as a result of direct tissue destruction by toxic effect of blood or indirectly as a result of compression of neurological tissues by blood and associated mass effect displacing nearby tissues. The later depends on the rate of accumulation and volume of haematoma [5]. The third mechanism of injury follows the disruption of blood supply with consequent cerebral ischaemia. The cerebral injury due to mass effect is usually considered as the primary injury, while the injury from inflammation and cerebral oedema is seen as secondary injury [36]. Extension of the extravasated blood into the ventricular system can result in hydrocephalus which could be communicating or non-communicating. The non-communicating or obstructive form is due to obstruction of the flow of cerebrospinal fluid by haematoma within the ventricular system; the non-obstructive or communicating form is due to obstruction of the arachnoid villi by blood and debris. Dilatation of the third and fourth ventricles is indicative of a poorer prognosis [37,38]. Three stages of cerebral oedema have been documented in AIH. The first stage is due to the extrusion of substances with osmotic properties into intact brain tissue following the retraction of clots in the haematoma within hours of a bleed [39,40]. The second stage involves inflammation characterized by the activation of the coagulation cascade, complement system and white blood cells that release inflammatory mediators resulting in disruption of blood brain barrier leading to cerebral oedema. This occurs within the first two days of AIH [41,43]. Lysis of red blood cell with resultant haemoglobin induced neuronal toxicity accounts for the third stage of cerebral oedema. It occurs two to three weeks after the acute event

[42,43,44].The final postulated mechanism of cerebral injury in AIH is the ischaemia in the periphery of the clot resulting from the compression of microvascular structures and increased resistance due to mass effect. To overcome this resistance and maintain adequate regional CBF there is a need to increase the MAP [13,45,46,47,48].Cell death in acute intracerebral haemorrhage involves both apoptosis and necrosis. Haematoma formation exerts mechanical force which in combination with chemical toxicity of blood on brain cells results in both necrosis and apoptosis of the adjacent brain tissues [51, 52].

V. Evidence Base Underlying Thrombolysis

The cornerstone of treatment for acute ischaemic stroke is thrombolysis. The main aim of thrombolysis is to achieve reperfusion of ischaemic neurones and mitigate the impact of ischaemia on neuronal cell metabolism. This is very important as ischaemic stroke accounts for majority of all strokes. The first agent ever tried for this purpose in the 1980's was streptokinase, but it was associated with severe symptomatic intracranial haemorrhage as a complication [5]. Streptokinase was subsequently replaced by the now licensed drug rt-PA. Other agents that have been used in trials for thrombolysis includes: urokinase, recombinant pro-kinase and desmoteplase [53]. Recent studies suggest that a combining advanced neuroimaging techniques with tenecteplase is more beneficial than using alteplase, and that using Desmoteplase has potential benefit in a subgroup of patients with large artery occlusion in an extended time window [54].It has been established that admission into stroke unit which provides an organized stroke care and rehabilitation saves lives and ultimately reduces disability, but addition of thrombolytic therapy and neuroprotection offers additional benefit to patients with acute ischaemic stroke [55].“The first major randomized controlled trial (RCT) to show a positive benefit for any thrombolytic agent in terms of improved clinical outcomes was conducted by the National Institute of Neurological Disorders and Stroke (NINDS) study group: this is the paper that has been one of the most significant in changing my clinical practice” [56]. Indeed so important was this NINDS (1995) work on thrombolysis that several scholars have confessed to its impact on their clinical practice. The NINDS group of investigators using 624 patients were able to demonstrate that when patients with ischaemic stroke are given the standard dose of intravenous rt-PA of 0.9mg/kg within 3 hours of stroke onset, there was significant neurological improvement in one-third of them when assessed at three months, even though outcome measures did not improve within 24 hours. Although about 7% of the subjects had symptomatic intracranial bleed when compared to 0.6% of those given placebo, but the mortality was not significantly worse [57]. This study formed the bases for thrombolysis in acute ischaemic stroke.

The guidelines for intravenous rt-PA use in acute ischaemic stroke has both eligibility and exclusion criteria [5] [58] [59].While the Europeans license the use of rt-PA within four and a half hours, in the United States it is mostly used within three hours [60]. Eligibility criteria includes: age between 18 and 80 years; clinical diagnosis of acute ischaemic stroke; measurable neurological deficit; Glasgow Coma Scale score greater than 8; timing of symptom onset well established to be less than 3 hours; availability of imaging and blood results and CT/MRI consistent with diagnosis. The exclusion criteria includes: patient waking up from sleep with symptoms; minor symptoms that may be rapidly improving; haemorrhage on CT or MRI scan; possibility of a SAH; active bleeding from any site including gastrointestinal or urogenital tract; blood work-up showing a platelet count less than 100×10^9 per litre; any recent use of heparin or activated partial thromboplastin time (APTT) above normal values; recent use of warfarin or international normalized ratio (INR) greater than 1.4; a history of recent surgery or traumatic brain injury in the last two weeks; established history of intracranial aneurysm, AVM or intracranial haemorrhage; arterial puncture in a non-compressible site or lumbar puncture in the recent past; Blood pressure persistently greater than 185/110 mmHg; epileptic seizure at the time of symptom onset; confirmed or suspected pregnancy and acute pancreatitis. It may be given with caution in people aged ≥ 80 years; presence of severe neurological deficit as shown by National institute of health scale score (NIHSS) > 22 ; patients with diabetic retinopathy; if pre-treatment CT scan shows a large infarct involving greater than one-third of the middle cerebral artery (MCA) territory and in patient with evolving infarct up to 4.5 hours after the ictus. In these patients, the clinician has to weigh the risk of complications against the benefit the patient will derive from the treatment. The presence of aphasia may makes obtaining consent difficult but it is not an exclusion criteria.

The Third International Stroke Trial (IST-3) collaborative group [61,62], sort to determine the benefit of administering rt-PA (Alteplase) on long-term functional outcome and health related quality of life in both young and patient older than 80 years. This was a multicenter international randomized, blind end-point study that involved patients within six hours of developing symptoms and brain imaging to exclude ICH. They used rt-PA at a dose of 0.9mg/kg (maximum of 90mg). The study concluded that; use of alteplase for thrombolysis in acute ischaemic stroke results in significantly higher self-assessed health related quality of life and functional outcome after stroke, but does not impact on survival compared to placebo. In an earlier report [63], the group had focused on evaluating the benefit of given thrombolysis to patient in acute ischaemic stroke outside the traditional 3 hours therapeutic window. Even though the National Institute of Health and Clinical Excellence

(NICE) guideline still restrict the use of alteplase for ischaemic stroke to 3 hour after stroke onset [64], other national guidelines including that of American Stroke Association (ASA), European Stroke Organization (ESO), and the National Stroke Foundation of Australia (NSFA) have extended the therapeutic window to 4.5 hours [65]. The major study, which has substantiated the benefit of thrombolysis between the 3 to 4.5 hour time ranges, is the European Cooperative Acute Stroke Study (ECASS)-3 [66]. Meta-analysis of available data has shown that although there is an increase rate of intracranial haemorrhage if thrombolysis is given in the 6-hour window compared to 3-hour time window, there is an additional benefit of this therapy to the patients who ordinarily would have been excluded [67]. The benefit of thrombolysis in acute ischaemic stroke decreases within the elderly patients' age group [68]. The major problem with thrombolytic therapy using rt-PA is symptomatic intracranial haemorrhage, which can be fatal in about 30% of patients. Management of this haemorrhage is very difficult hence it is best prevented by proper patient selection [69]. The recent review by Wardlaw et al in 2014 [52] included all randomized trials of any thrombolytic agent versus control that were not treated with such agents in the setting of definitive diagnosis of acute ischaemic stroke. There were 27 trials that met their inclusion criteria involving 10,187 participants. The studies reviewed used drugs such as Urokinase, Streptokinase, rt-PA and recombinant pro-kinase and Desmokinase. They observed that thrombolytic therapy mostly administered up to 6 hours for AIS significantly reduce the death rate and dependence at three to six months but increased the risk of symptomatic ICH and early death. They also observed that participants who are older than 80 years benefitted equally with younger ones especially when treated with 3 hours of stroke. They therefore concluded that if thrombolytic therapy is administered within up to 6 hours the proportion of stroke patients that will be dead or dependent after stroke will definitely reduced. But they added that treatment within 3 hours confers more benefit to recipients. These benefit were observed despite an increase in incidence of symptomatic ICH, death at one week and death at final follow-up.

Low rate of thrombolysis:

Despite the established benefit of thrombolysis in acute stroke treatment, very few patients with ischaemic stroke are thrombolysed. The rate of thrombolysis in ischaemic stroke is reported to be about 3% [70]. The reasons documented to be responsible for most people do not accessing treatment with thrombolysis includes: patients and witnesses not recognizing symptoms as that of stroke; incorrect diagnosis and selection of patient by health workers; delays associated with brain scanning; difficulties obtaining consent; and doctors not being familiar with the use of rt-PA for thrombolysis in stroke [71]. Rather than seek for medical care early at presentation, patients occasionally opt to wait and see what will become of their "problem". Other reasons for inability to access stroke treatment include: patients not seeking urgent medical help; patients and relatives calling their GP instead of the ambulance service for assistance; inefficiency in hospital response to patients in emergency and delays in accessing neuroimaging services [55]. To overcome these challenges, it has been advocated that patients' education should be improved, the training of paramedical staffs should be reorganized to improve accuracy of stroke diagnosis, and re-organization of acute stroke systems to improve access to acute stroke care [55].

VI. Conclusion

Stroke is a major public health problem with half of its sufferers dependent on caregivers. A good history, examination and investigation are essential to proper diagnosis and patient selection for thrombolysis. Thrombolysis for eligible patients offers the possibility of a good immediate or long-term outcome. However, early patient presentation is very important, and evidence support the extension of the window for thrombolysis up to 6 hours particularly in well selected younger patients.

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