What is New in Stroke?

Literature on Stroke has been considerable over the past 5 years. Large clinical trials right from the introduction of rt-PA to the latest ones and the development of $^{133}$Xe to measure cerebral perfusion to the novel technique of Laser Speckle-Flowmetry, have led to the development of new therapeutic and investigational modalities, many of which have a very strong bearing on the management as well as understanding of the pathophysiology of stroke, related therewith.

Let us have a bird’s eye view of such new aspects regarding stroke with an effort to touch the researches in totality as feasible as it can be, in the form of developments in pathophysiology, with an overview of genetic linkages, neuro-imaging and therapeutics (treatment per se/ preventive strategies/ predictive analysis)

Developments in the Field of Pathophysiology and Genetics

Recently, it has been shown that in ammatory and immune reactions may play an important role in the pathogenesis of stroke.$^{1,2}$ A significant increase in the median percentage of CD4+ CD28- cells in patients of stroke was seen especially those with poor outcome, as adjudged by the Barthel Index.$^1$ Clonal expansion of the T cells expressing specific T Cell Receptor VB region has been seen in the carotid atherosclerotic plaque, suggesting the influence on the T cell populations by specific antigens (immune stimulation), the nature of which is presently unknown. The role of Herpes virus, Adenovirus, Human Immunodeficiency Virus, etc. has been speculated to exemplify the clonal expansion of T cell populations and studies to consolidate this aspect are coming up. First report of Herpes Simplex Virus mediated bcl-2 transfection leading to blockade of Apoptosis Inducing Factor and improved striatal neuron survival following experimental stroke has already been put forward. Adding to the list of clues is the Northern Manhattan Study, predicting the risk of ischemic stroke on the basis of elevated leukocyte count, possibly as a result of inflammation.$^1$ An increase in leukocyte counts, especially neutrophils, over baseline levels has also been shown to herald a period lasting about one week, of elevated risk of recurrent stroke. This has been substantiated by the finding of decreased risk of hemorrhagic transformation by neutrophil depletion by neutrophils-depletion antibodies.$^1$ Leukoaraiosis similarly has been linked with anticoagulant associated recurrent hemorrhage and as an independent risk factor for stroke.$^1,3$
The mitochondrial cell death pathway plays an important role in the execution of neuronal cell death after transient cerebral ischemia. The bcl-2 family member proteins are critical to the integration of this pathway. BAD, a protein of proapoptotic bcl-2 family, has been shown to translocate to the mitochondria and interact with 14-3-3 and bcl-xL. This has been substantiated for the first time that BAD translocated to the mitochondria after dissociation from 14-3-3, and dimerized with bcl-xL after focal cerebral ischemia. The BAD expression was found to play a key role in cell survival and death. It was suggested that BAD pathway played an instigator or reinforcement role in neuronal cell death after transient focal cerebral ischemia.¹

The Stroke Prevention in Young Women Study has showed that promoter variants in the eNOS gene are associated with susceptibility to early-onset ischemic stroke in African-American women. The -922 G/A and -786 T/C Single Nucleotide Polymorphisms were in very strong linkage disequilibrium.¹ It has also been demonstrated that Nitric Oxide enhances angiogenesis in ischemic brain via increases in vascular endothelial derived growth factors and cyclic GMP. In the latter study Sildenafil significantly increased the numbers of newly generated vessels in the boundary of the ischemic regions, as a part of its mechanism of action of inhibition of cGMP and phosphodiesterase 5.¹

The G-protein α3 (GNB3) 825T allele was previously shown to be associated with hypertension, diabetes and obesity. It has also been identified as an independent risk factor for the occurrence of non-cardioembolic ischemic stroke. The marking point is this that it infers protection against atrial fibrillation and has special association with male subjects.¹ KRIT 1 mutations have been studied in patients with cerebral cavernous malformations and incomplete penetration or spontaneous mutations have been shown apart from familial cases.¹ Mutations within exons 3, 4, 5, 6 of the Notch 3 gene associated with CADASIL (cerebral autosomal dominant arteriopathy subcortical infarcts and leukoencephalopathy) have been readdressed and screening modalities have come up to detect such cases beforehand.¹

Several studies have addressed the issue of post-thrombolysis hemorrhagic complications. It has been shown that recombinant tissue plasminogen activator (rt-PA) triggers Matrix Metalloproteinase-9 (MMP-9) upregulation after cerebral ischemia.¹,4,5 MMP-2 has been similarly implicated. Of note is the fact that blood brain barrier (BBB) breakdown after ischemic stroke is caused in part by activation of pro-inflammatory factors viz. MMPs (gelatinases). MMP-7 (matrilysin) contributes to the final size of the infarct, and may participate in the mediation of BBB breakdown following transient stroke. MMP-7, perhaps an upstream activator of MMP-9 and MMP-2, also recognizes and cleaves a variety of substrates, including fibronectin, type IV collagen, and other MMP precursors. The counter balance is maintained by the increased production of Interleukin-6 (IL-6) and MMP inhibitors such as α2-macroglobulin.¹

Activated Protein C and increased Peroxisome Proliferator Activated Receptor γ (PPARγ) expression have been shown to have Neuroprotective effects and may serve as good therapeutic substrates.¹

Developments in Neuro-imaging
Supposedly this has been the most sought advancement in the field of stroke. Be it pathophysiology, treatment protocol analysis or assessment of risk, neuro-imaging is indispensible. Also, immense amount of work has been seen in this field. Latest guidelines and recommendations of the Stroke Council of the American Heart Association have come up to spearhead the complexities of stroke and dilute the ambiguities. Ever since the introduction of ¹³⁳Xenon in early seventies, the developments have come a long way. Xenon-Enhanced Computed Tomography (XeCT) can be used to acquire quantitative data, especially absolute values of cerebral blood ow (CBF), and may be helpful in determining the risks and benefits of revascularization of the acute stroke patient, including post-thrombolysis hemorrhage (grade A). XeCT perfusion imaging with an acetazolamide challenge test can be used to define a group of patients...
with chronic ischemic who are at significant risk for infarction (grade A).

Single Photon Emission CT (SPECT) CBF studies can be used to determine the relative risks of hemorrhage following thrombolysis in acute stroke patients, whatever the time after onset of symptoms (grade A). Because both the quantitative (XeCT) and semiquantitative (SPECT) methods provide class I data regarding the risks of hemorrhage following thrombolysis, and both may be helpful in identifying patients at greater risk of hemorrhage after thrombolysis, comparative studies are required to determine the relative merits of the 2 methodologies.

Perfusion-weighted (PW) and Diffusion-weighted (DW) Magnetic Resonance Imaging (MRI) have the ability to image not only cerebral perfusion, but also the status of the tissue, the patency of the vasculature, and the anatomical substrate during the same imaging session. PWI & DWI has been recommended as techniques that have been proven capable of demonstrating severely ischemic tissue in acute stroke patients. These techniques are probably useful at differentiating between reversibly and irreversibly ischemic tissues (grade B), although the issue of reversibility of a diffusion abnormality, especially in the early stages of ischemia, requires more study. Mean Transit Time on PWI is said to predict more accurately the infarcted tissue and response to reperfusion than cerebral blood flow or cerebral blood volume. It has been hypothesized that HARM (Hyperintense Acute Reperfusion Marker-Gadolinium enhancement of intrasulcal space) on FLAIR MRI is associated with reperfusion and hemorrhagic transformation. Echo-Planer Gradient-Echo MRI has been shown to be more effective for detection of thromboembolic occlusion of the Middle Cerebral Artery (MCA) than CT, especially when the embolus is located in MCA branches.

Although the concept of perfusion CT (CTP) is not new, the ability to measure these perfusion parameters with accuracy has been made possible with the development of high-speed helical/spiral CT scanners having solid-state detectors and a gantry design to contain the very high gravitational forces generated by high-speed rotation of the x-ray tube. Software development has been a crucial part of this development, allowing rapid electronic transfer of data from the detector arrays and rapid image reconstruction for perfusion analysis. Quantitative CTP may possibly be useful to differentiate between reversibly and irreversibly ischemic tissues in the acute stroke patient (grade C). Large prospective and appropriately blinded studies will be necessary to determine the value of this technique. There are no data regarding the ability of this technique to predict the potential for hemorrhage following thrombolysis, as there is for the diffusible tracer techniques. Qualitative mapping of CBV with the slow-infusion method, in combination with the acquisition of CTA, may possibly be of value to determine emergent forms of therapy for the acute stroke patient (grade C). Again, larger prospective studies are needed.

This is the first time that evidence of existence of ischemic penumbra in white matter of humans with acute ischemic stroke has been presented using penumbral marker $^{18}$F-Misonidazole ($^{18}$FMISO) with Positron Emission Tomography (PET). The first objective quantitative characterization of the spatial and temporal evolution of the ischemic penumbra following stroke in humans has similarly been forwarded.

A novel technique of Laser Speckle-Flowmetry has been shown to be more effective than Laser Doppler-Flowmetry to image different arterial territories bilaterally and simultaneously, and to differentially assess ow changes in the cerebral vasculature.

**Developments in Therapeutics:**

**Treatment Modalities**

The publication of the National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Study and subsequent approval of thrombolytic treatment by the USFDA in 1996 marked the
beginning of a new era in the field of invasive and prospective treatment of stroke. As of now intra-
venous rt-PA within 3 hours of onset of ischemic stroke in the only grade A recommendation of the
Stroke Council\textsuperscript{9}, in the thrombolytic category. Intra-arterial thrombolysis in selected patients with major
stroke of < 6 hours duration due to large vessel occlusions of the middle cerebral artery is still a grade B
recommendation. A lot of trials are addressing the issue of thrombolysis, both intra-venous and
intra-arterial, in order to improve the strategies regarding the increase in the window period and better
thrombolytic drugs viz. Teneckteplase\textsuperscript{1}, along with more evidence based patient selection.

Now it has been shown that a resistance to rt-PA, produced by several endogenous fibrinolysis
inhibitors, might decrease the benefit obtained after thrombolysis-induced recanalization in a certain
subset of patients. Thrombin-activable fibrinolysis inhibitor (TAFI) is a recently identified fibrinolysis
inhibitor. After blocking several residues from fibrin, plasminogen binding sites are eliminated and
fibrinolysis is inhibited, consuming plasma TAFI levels i.e. low TAFI levels predict rt-PA-induced
recanalization resistance. In the future, TAFI related drugs might increase the efficacy of thrombolysis
for stroke.\textsuperscript{1,10} Circadian fluctuations of endogenous fibrinolysis may play a role in the success of
thrombolytic therapy. Recanalizations have been said to be more frequent in the afternoon whereas
most reocclusions in the morning hours. This however is more pronounced in patients with cardio-
embolic stroke.\textsuperscript{1}

In contrast to rt-PA, the vampire bat salivary protease, Desmodus rotundus Salivary Plasminogen
Activator (DSPA-Desmoteplase) has been shown not to promote kainate or NMDA-mediated
neurotoxicity in vivo. These results provide significant impetus to evaluate DSPA in patients with
ischemic stroke.\textsuperscript{11} SolCD39, a soluble form of recombinant human ecto-ADPase (NTPDase1) – a new
class of anti-thrombotic agents, has been therapeutically exploited prior to MCA occlusion and also
three hours after occlusion.\textsuperscript{12}

As detailed above, MMP inhibitors may be a target for pharmacologic intervention in stroke. BB-94
is one such inhibitor and has been shown to reduce the mortality significantly in experimental stroke
and preventing the opening of BBB. It may also prolong the therapeutic window with rt-PA treatment.\textsuperscript{1}
The GSK (Glycogen Synthase Kinase) 3β inhibitor Chir98025 has proved to be effective in reducing
infarct size after induced ischemic stroke by way of modulating apoptosis.\textsuperscript{1} NXY-059, a nitrate-based
free radical trapping agent, has substantial beneficial functional effects when administered immediately
after the onset of ischemia in a primate model of stroke.\textsuperscript{1,13} Hyperbaric Oxygen along with Edavarone
(a free radical scavenger) has also been evaluated in a study with favorable results.\textsuperscript{1}

Unique therapeutic modalities in the form of intravenous transplantation of Neural Stem Cells,\textsuperscript{14}
intracisternal transplantation of Adult Subventricular progenitor cells\textsuperscript{1} and intravenous transplantation
of Endothelial progenitor cells\textsuperscript{1} are being extensively studied to improve functional recovery in
experimental stroke, and the preliminary results are promising

Preventive Strategies
Administration of aspirin within 24 to 48 hrs of stroke but not after thrombolysis within 24 hrs is a
grade A recommendation of Stroke Council.\textsuperscript{9} Aspirin, combination of aspirin with extended-release
dipyridamole or clopidogrel are among the grade A recommendation for secondary prevention. The
combination of aspirin with extended-release dipyridamole only has been discredited shown to be more
effective than other drugs. Few studies have shown the lack of antiplatelet effect of aspirin in a subset
of patients and have advocated the use of PFA 100 in routine for care of the patient.\textsuperscript{15}

As far as anticoagulants are concerned the INR goal has been set at 2.5 (2.0-3.0) for stroke prevention. Ximelagatran is a novel oral direct thrombin inhibitor under investigation as an alternative anticoagulant
to warfarin for prevention of thromboembolism in patients with nonvalvular atrial fibrillation.\textsuperscript{1}
Argatroban is a similar counterpart, inhibiting the action of both free and clot bound thrombin.\textsuperscript{1}
In a randomized trial (LIFE study), angiotensin II receptor antagonist, losartan, reduced the rate of stroke by 25% as compared to other antihypertensives in spite of the same degrees of antihypertensive effects, suggesting that losartan may exert cerebral protective effect.\(^1\) PROGRESS\(^{16,17}\) and HOPE\(^{18}\) trials have already shown the beneficial effects of Perindopril and Ramipril in the prevention of stroke.

A novel permanent arterial filtration diversion device (The Diverter)\(^1\) and Percutaneous Left Atrial Appendage Transcatheter Occlusion (PLAATO)\(^1\) are the upcoming modalities to prevent the embolic phenomenon.

Predictive Analysis
Predictive analysis deals with the state of the patient prior to a specific treatment modality and consequences thereafter. This is a very important concept in selection of patients and evaluation of outcome.

An innovative CT Angiography (CTA) scale has been developed as a simple scale to provide reliable and potentially valuable information regarding the proximal and LM collateral circulation.\(^1\) The Alberta Stroke Program Early CT Score (ASPECTS) scoring allows for a strong and conclusive estimation of the presence of 1/3 MCA territory involvement\(^19\). In a retrospective assessment of stroke severity, the modified National Institute of Health Stroke Scale (mNIHSS) has been shown to perform better than the standard NIHSS and may be easier to use since it has fewer and simpler items.\(^20\) It has also been shown that the NIHSS could not only reliably quantify initial lesion volume in intracranial hemorrhage (ICH), originally being used for ischemic stroke, but also could become a more sensitive marker of disease progression/response to treatment than the Glasgow Coma Scale (GCS).\(^1\) MOST is a combined three-item scale of NIHSS, ASPECTS and TCD (Transcranial Doppler) that allows a better prediction of functional outcome and risk of ICH than clinical, CT, and TCD factors taken alone. This prediction can be made ultra-early, i.e. during or shortly after completion of TPA infusion.\(^1\)

Neurochemical monitoring by microdialysis for the identification of patients threatened by malignant MCA infarction has revealed higher levels of Glutamate, Aspartate, GABA and purine catabolites viz. adenosine, hypoxanthine, inosine, and xanthine in prone patients.\(^21\) Serum cardiac troponin I\(^1\), homocysteine\(^22\), lipoprotein (a) \(^1\), mean platelet volume\(^1\), C-reactive protein\(^23\) and glucose levels\(^24\) all have stated for outcome analysis of patients of stroke.

Conclusion
The future of treatment of stroke is very bright. Gone are the days when one was left with supportive treatment with simply no idea as to how the conditions would turn out to be. Emerging strategies targeting at genetic counseling and the development of anti-sense oligonucleotides are no more abstract. The only important thing, how these researches are extrapolated to the general population in the form of guidelines, remains to be seen.

References


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