EDITORIAL

Aspects of Stroke Imaging

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"If you cannot see, it's not your eyes, but your mind that is out of focus."

Mark Twain

This is an exciting time for stroke researchers and neurologists with an interest in stroke. Although the clinical presentation of cerebral vascular disease has taught the art of localization 'stroke by stroke' to generations of neurology residents, in the absence of imaging, it has been impossible to differentiate haemorrhagic stroke from stroke caused by cerebral ischemia. The advent of computerized tomographic (CT) imaging of the brain, highly sensitive for the detection of intracerebral haemorrhage, was the first (and obligatory) step in developing thrombolysis as an acute treatment for stroke. Detecting early ischemic change on CT has been harder but the paper by Silver et al,[1] in this issue of the Journal, is another step forward.

Trials of thrombolysis in the 1990s have shown that, in ischemic stroke patients treated within the first several hours following the onset of cerebral ischemia, benefit will accrue despite the increased risk of haemorrhage.[2-4] Initially the role of CT scanning was to exclude patients with haemorrhage and to audit the risk of haemorrhage following treatment. Most of our efforts have been focused on the risk of symptomatic haemorrhage following thrombolysis for stroke. For those who adhere to carefully developed protocols and who are treated with tPA within the first three to six hours the risks of a symptomatic bleed are relatively low; ie between 4% and 8%. Nevertheless it is this fear of symptomatic and fatal intracranial haemorrhage that has inhibited the development of thrombolysis as a widely available treatment for acute stroke. Much of the data collected from Phase Four studies[5] have focused on this risk and have concluded that increasing age, the more severe the stroke, increased baseline blood pressure, hyperglycemia[6] and early CT changes, suggestive of completed infarction,[7] all pose a higher risk. Concern therefore arose about the reliable detection of early ischemic change on the CT scan and its significance in relation to treatment-induced symptomatic haemorrhage (sICH).[7] The European Co-operative Acute Stroke Study (ECASS) trials have highlighted the importance of early CT ischemic changes and have suggested that patients with more than one-third of the middle cerebral artery (MCA) territory exhibiting ischemic changes, are far more likely to suffer intracranial haemorrhage.[4] As a result, much attention is now being paid to the accurate detection of early ischemia.[8-11] Attempts are now being made to use the integrity of the scan to predict not only those who are at a lower risk of haemorrhage but also to select patients who are more likely to benefit from the intervention.[11]

The paper by Silver et al[1] in this issue of the Journal is helpful as it builds on one of the earlier selection criteria defined by the ECASS trials namely the one-third MCA rule.[4] The National Institute of Neurological Diseases and Stroke (NINDS) trial had no such exclusion criteria in the under three hour patients.[2] The ECASS investigators in designing ECASS II defined pre-specified imaging criteria and patients were only eligible if the CT ischemic change involved less than one-third of the distribution territory of the MCA. Applying the one-third rule has proven difficult and inconsistent with poor specificity and sensitivity.[9,11] The London group devised a protocol which included specific criteria to determine whether or not one-third of the MCAterritory was involved, this method which bears the acronym ICE is a much needed method for improving the sensitivity and specificity of applying the one-third MCA rule. The ICE method involves idealizing (I) the MCA territory and then co-registers areas of ischemia, closes (C), and then estimates (E) the proportion of these two geometric areas. It is conceptually similar to the rule devised by the ATLANTIS investigators.[12] This method was shown to have excellent inter-observer reliability (K=0.8) which was similar to the ASPECT score[11] but in direct contrast to the ECASS one-third MCArule.[4] Its development adds further evidence that a systematic quantitative approach to the acute stroke CTscan is both reliable and provides prognostic and pathophysiologic information.[1]

The ICE method allowed the clinicians in London to select patients for whom they recommended treatment with improved safety. In two years, 30 patients were treated in London, Ontario. There were no instances of intra-cranial haemorrhage. Only two of the subsequently re-reviewed scans demonstrated more than one-third of the MCA territory involvement. While this paper may suggest improved safety, because the 95% confidence intervals (sICH rate = 0% (95%CI 0-11.6%)) includes sICH rates demonstrated in the randomized trials, much larger numbers will be needed to confirm this claim. What is perhaps more important is their observation that their patients appear to have done better than expected.

In the NINDS study with no equivalent CT selection there was an 11% absolute risk reduction for those treated: 20% of placebo patients made a full neurological recovery while 31% of those treated achieved an NIH score of 0 to 1.[2] In the London cohort, 37% achieved an excellent outcome suggesting, (although not statistically different from the treated group in the NINDS tPA Stroke Trial), that the selection criteria on CT scan may have not only reduced the risk of haemorrhage but also improved the likelihood of a full neurological recovery.[1]

The CT scan is the unquestioned "cardiogram of the brain" and is readily available in most urban communities. There is a growing appreciation and recognition of the signs of early brain ischemia. While MRI diffusion weighted imaging may have

superiority over CT in research centres,[13] it is quite clear that for most physicians treating stroke in the community, CT will be the imaging modality of choice. A systematic, quantitative approach to evaluating early CT ischemia will allow for the reduction in risk of haemorrhage and will allow the clinician insight into who is most likely to benefit. Facilitating the detection of reversible ischemia will allow future randomized trials to break out of the so called "NINDS box". The NINDS study, as well as others, have established safety and demonstrated efficacy using selection criteria that are very restrictive. For instance, these criteria apply only to those patients fitting an under three hour "time window". Although in well-developed Canadian centres approximately 5% of acute stroke patients are now being treated, many patients who are likely to benefit from thrombolysis are being excluded because they do not fit the rigid criteria (the inclusion/exclusion criteria) of the NINDS study.[14] We predict that by using CT selection criteria it will be possible to extrapolate low risks of haemorrhage and afford benefit to patients who go well beyond three hours such as those patients in the three to six hour category, those who wake up with a deficit, those who are found down without any time of onset and those who cannot communicate when the stroke occurred because of aphasia. By using CT criteria it will be possible to define "tissue windows" or "ASPECT windows" for future randomized trials for both thrombolysis and neuroprotection, ie. patients will be randomized on the basis of pathophysiology rather than arbitrary time criteria.[15]

Stroke is very heterogenous and while in an ideal world it should be possible to select people on the basis of a perfusion/diffusion mismatch using MRI,[13] in the real world of clinical medicine, we will likely have only clinical assessment and CT.

At the end of the day improved reliability in differentiating salvageable from already injured brain (early CT change) will make it safe to treat a lot more patients. This paper is another step in the development of increasing the proportion of patients who could be safely and effectively given thrombolysis for stroke.

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