translate as increased MD. These findings likely reflect retrograde degeneration of the thalamo-cortical neurones secondary to fibre damage, known to translate in its early stage as hypometabolism and microglial activation in positron emission tomography (PET) studies using the tracers ^{18}FDG and ^{11}C-PK11195, respectively,[3 4] and in its late stage as reduced thalamic volume on structural imaging (also observed by Hervé *et al*).

Fractional anisotropy—the degree to which diffusion is anisotropic—reflects the parallel arrangement of fibres, so is used as an index of integrity for any particular bundle. However, this method is limited because to obtain quantitative values for a given fibre tract, a region of interest must be positioned within the bundle based on *a priori* knowledge. A sophisticated application of DTI referred to as tractography applies mathematical modelling to three dimensional anisotropy data to map the trajectory of a fibre in both directions from a chosen ''seed'' point in the bundle. Among the various tractography techniques, one particularly promising approach takes into account all possible directions rather than just the main eigenvector, which in turn allows the probabilistic mapping of connections between gray matter areas, including cortical to deep nuclei and vice versa.[5] Exquisite mapping of the thalamo-cortical connection systems has been obtained using this method; the application to stroke is eagerly awaited.

But what purposes will the mapping of fibre and cell degeneration after stroke serve? Whilst studies such as these are just the beginnings, several potential uses of this new approach are emerging. Quantifying with FA the degree of damage to a single well identified tract such as the pyramidal may, in conjunction with functional imaging such as fMRI, help to understand the pathophysiological mechanisms underlying recovery. For instance, knowing this quantitative index of damage could allow one to derive in quantitative terms the amount of recovery that can be ascribed to adaptive plasticity.[6] Also, estimating the number of fibres connecting two or more cortical centres may help to determine the occurrence of functional versus anatomical disconnection. However, because the effects measured with DTI only reflect secondary effects of stroke that develop as patients recover, no obvious direct clinical implication of these studies has emerged thus far, and accordingly Hervé *et al*[2] found no significant correlation between the changes they measured in the ipsilateral thalamus and concomitant clinical scores or changes thereof. Although these remote degeneration effects might therefore be epiphenomenal, one may envisage that they may impede or slow down recovery if they were to impact on intact but inter-connected structures for example. Whilst arguably a long shot, one could in turn wonder whether arresting or even preventing secondary degeneration could be worthwhile – although by doing so one might perhaps worsen rather than enhance outcome if the degeneration served to re-set the local excitatory/inhibitory balance.[7] More work is obviously needed to address these issues but we now at last have a tool at our disposal to quantify secondary degeneration after stroke and to monitor any effect of intervention in parallel with clinical function.

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Retinal artery thrombolysis

Thrombolysis for central retinal artery occlusion

G T Plant, K Landau

Results of a controlled trial are needed before recommending this treatment

Central retinal artery occlusion is an uncommon cause of unilateral visual loss and a rare cause of blindness. In this issue (*see pp 196–9*), Arnold *et al*[1] describe a retrospective analysis of intra-arterial thrombolysis (IAT) of central retinal artery occlusion within six hours of symptom onset in 37 patients. The visual outcome was compared with 19 control patients. Before treatment, cranial computed tomography was carried out (to exclude intracranial haemorrhage), along with four vessel angiography. The cases are divided into those with local thrombotic causes (73%), cardioembolism (24%), and carotid stenosis (3%). The classification was based on the TOAST criteria,[2] which were developed for the evaluation of cerebral strokes where there is no possibility of observing the embolus. One third of patients seen within six hours could not be treated because no neuroradiologist was available. Periprocedural adverse events occurred in two patients who experienced transient ischaemic attacks and in one patient who suffered brain infarction. No haemorrhagic complications were seen. The outcome measure was visual acuity.

Thrombolysis in central retinal artery occlusion is not new[3] but it is Deiter Schmidt and Martin Schumacher in Freiburg, Germany, who have championed the technique,[4] treating over 60 cases[5] and compelling us to examine our practice. IAT to treat ischaemic stroke is a goal of stroke units; however, the time interval between event and intervention is critical. Sudden visual loss tends to present to eye casualty departments. In cases of acute blindness a competent ophthalmic examination is essential but will increase the ''time to treat'', especially where the eye hospital is a stand-alone unit.

Who is doing it? In the United Kingdom a few anecdotal cases are

described at meetings but only over coffee. In the USA the procedure is being done, but no systematic information is available (Miller N and Aldrich E, personal communication). In contrast IAT for central retinal artery occlusion is commonplace in Germany, Switzerland, and Austria. In Zurich, for example, 88 consecutive patients with central retinal artery occlusion have been treated between 1995 and 2002: IAT was undertaken in 23 patients while 65 were managed conservatively (unpublished data). A trend for a better visual acuity outcome was observed in the thrombolysis group, which became statistically significant for younger patients who had slightly better initial visual acuities. A small subgroup of patients profited significantly from IAT, all of whom were treated within six hours. Unknown factors other than the time to thrombolysis contribute to the outcome.

It is not our opinion that the results presented by Arnold *et al* should encourage centres to begin using this treatment in advance of a randomised study. Such a study is under way in Europe (no UK centre is involved but the acronym is English: EAGLE, European assessment group for lysis in the eye).

Our reasons for this view are as follows. First, central retinal artery occlusion is usually a monocular disorder and therefore (apart from the risk of pre-existing or subsequent pathology in the fellow eye) the likelihood of significant disability is less than with cerebral arterial occlusions.

Second, the logistic problems associated with setting up a protocol for IAT in central retinal artery occlusion are substantial. In our experience patients often do not notice monocular visual loss for some time or may ''wait for it to clear'' before seeking medical advice. Furthermore the additional review by an ophthalmologist mentioned above adds time compared with the journey of a patient with a hemisphere stroke. Furthermore, many patients wake with loss of vision, so how can we know when the event occurred?

Third, there is no information in this study on the extent of visual field loss as an outcome measure. This is significant for disability and may not correlate well with visual acuity because acuity may be preserved where a cilioretinal artery is present and with residual retinal branch artery based defects.

Fourth, there was a low level of statistical significance in the study under review.

Finally, Arnold *et al* defined a subclass of patients with central retinal artery occlusion who would have a greater chance of benefiting from IAT. In the light of a trend in their own data, existing animal studies, and recommendations for thrombolysis in cerebral ischaemic stroke, they suggest that treatment within *three* hours might be the goal.

The following analysis should be carried out in a large city:

- The incidence of unilateral central retinal artery occlusion needs to be established.
- A logistic study should be undertaken of the likelihood of such patients presenting to an interventional neuroradiological unit within three hours having undergone an ophthalmological examination, a medical/neurological examination, brain neuroimaging to exclude haemorrhage (but is this necessary in central retinal artery occlusion as opposed to hemisphere strokes?), sufficient blood tests *with laboratory results available* to exclude vasculitis and blood dyscrasias, and four-vessel interventional angiography to ensure adequate access to the ophthalmic artery.
- The additional cost to eye departments and stroke units of maintaining a 24 hour referral and treatment service for central retinal artery occlusion should be estimated, as should the geographical density required for such units, taking into account the results of the first two investigations above.
- A meta-analysis of existing studies should be done, including those employing intravenous treatment and other thrombolytic agents.
- The number of cases required should be determined, given the statistical significance in the existing retrospective studies, to permit not only a definitive overall result but also stratification of the cases according to time to thrombolysis, age, and other clinical features such as the type of embolus where visible.
- Perimetry should be evaluated as an outcome measure.
- Evaluation of visible emboli is required: can thrombolysis be effective in a patient with a calcific embolus sitting at the bifurcation of the central retinal artery as opposed to a local thrombosis?
- An evaluation should be made of the presence or absence of a macular cilio-retinal artery, which will influence preservation of central acuity but not necessarily disability (patients with a macular cilio-retinal artery are often left with 6/9 acuity but a tiny central island of vision of little practical use).

As neuro-ophthalmologists our aim is to preserve vision wherever possible. There are times when the task of obtaining the evidence we need seems *im*possible. However, we should remember the words of Louis XVI's finance minister, Charles Alexandre de Calonne: ''Madame, si c'est possible, c'est fait; impossible? Cela se fera''—better known as the US Army paraphrase ''The difficult we do immediately; the impossible takes a little longer.'' As Calonne discovered, it sometimes takes a little too long.

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