imbalance between the production and clearance of amyloid β (amyloid cascade hypothesis[6]). Imaging studies that focused on amyloid deposition in sporadic Alzheimer's disease,[7] and a neuropathological study of cognitively intact people and those with MCI,[8] remind us of the work of Braak and Braak,[9] who suggested that amyloid deposition has a predilection for isocortical association areas whereas the hippocampus remains relatively devoid of amyloid deposition during the early stages of Alzheimer's disease.

As we have learned from animal studies,[10,11] atrophy progression, as assessed in the study by Ridha and colleagues, could feasibly be the result of increased neuronal vulnerability, at least for those individuals with a mutation of presenilin 1. We should also be open to the notion that early in the course of the disease at least some portion of the atrophy in the medial temporal lobe and, in particular, in the hippocampus is secondary to causes occurring upstream in the association cortices (eg, inferior parietal lobule and supramarginal gyrus), which are so vital for providing the input to the hippocampus.

More work is clearly needed from the basic science, clinical, pathological, and pharmacological specialties before we can say that we understand the mystery that is Alzheimer's disease. Open and collegiate collaborations, such as the various Alzheimer's Disease Neuroimaging Initiative projects being developed around the world, help to foster the environment needed to defeat this disorder. Studies such as that presented by Ridha and co-workers give us a chance to reflect upon the hypotheses we are pursuing and to explore how the results of mechanistic changes either fit or conflict with what we thought we understood.

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1 Ridha BH, Barnes J, Bartlett JW, et al. Tracking atrophy progression in familial Alzheimer's disease: a serial MRI study. *Lancet Neurol* 2006; **5:** 828–34.
2 Blennow K, de Leon, MJ, Zetterberg H. Alzheimer's disease. *Lancet* 2006; **368:** 387–403.
3 Atiya M, Hyman BT, Albert M, Killiany RJ. Structural magnetic resonance imaging in established and prodromal Alzheimer disease: a review. *Alzheimer Dis Assoc Disord* 2003; **17:** 177–95.
4 Gregory GC, Macdonald V, Schofield PR, Kril JJ, Halliday GM. Differences in regional brain atrophy in genetic forms of Alzheimer's disease. *Neurobiol Aging* 2006; **27:** 387–93.
5 Hardy J. Amyloid, the presenilins and Alzheimer's disease. *Trends Neurosci* 1997; **20:** 154–59.
6 Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *Science* 2002; **297:** 353–56.
7 Buckner RL, Snyder AZ, Shannon BJ, et al. Molecular, structural and functional characterization of Alzheimer's disease: evidence for a relationship between default activity, amyloid and memory. *J Neurosci* 2005; **25:** 7709–17.
8 McKee AC, Au R, Cabral HJ, et al. Visual association pathology in preclinical Alzheimer's disease. *J Neuropathol Exp Neurol* 2006; **65:** 621–30.
9 Braak H, Braak E. Alzheimer neuropathology and limbic circuits. In: Vogt BA, Gabriel M, eds. Neurobiology of cingulate cortex and limbic thalamusa: a comprehensive handbook. Boston, USA: Birkhauser, 1993: 606–26.
10 Terro F, Czech C, Esclaire F, et al. Neurons overexpressing mutant presenilin-1 are more sensitive to apoptosis induced by endoplasmic reticulum-Golgi stress. *J Neurosci Res* 2002; **69:** 530–39.
11 Lazarov O, Peterson LD, Peterson DA, Sisodia SS. Expression of a familial Alzheimer's disease-linked presenilin-1 variant enhances perforant pathway lesion-induced neuronal loss in the entorhinal cortex. *J Neurosci* 2006; **11:** 429–34.

Ultra-early doppler sonography for stroke

See **Articles** page 835

Stroke is the third most common cause of death and the leading cause of disability in the UK and is predicted to become the most common cause of death worldwide by 2020.[1] Several large multicentre, randomised, placebo-controlled trials have shown benefit for early treatment with alteplase (recombinant tissue plasminogen activator) in acute ischaemic stroke, despite a risk of early haemorrhage.[2–4] Thrombolytic treatment needs to be started within 3–6 h of onset of symptoms and this timely delivery has required substantial reorganisation of conventional stroke services. The extent to which this reorganisation has actually occurred varies between stroke units and between countries.

The standard assessment of patients who present with an acute stroke includes medical history, clinical examination, and early CT of the brain. Unfortunately, this approach gives no clear indication as to whether the patient is likely to benefit from potentially harmful thrombolytic treatment. Although perfusion imaging can be of assistance, the procedure is not widely available. However, several small studies have indicated that identification of occlusion of the middle-cerebral artery (MCA) by use of transcranial doppler ultrasound is a good predictor of poor outcome.[5,6]

In a large prospective multicentre study published in this issue, the Neurosonology in Acute Ischemic Stroke

(NAIS) Study Group showed that ultra-early doppler sonography provides additional functional prognostic information in the hyperacute phase of anterior circulation strokes.[7]

In addition to the standard work up, patients also underwent an ultrasound examination of the cerebral circulation, including duplex examination of the extracranial circulation (common, external, and internal carotid arteries) and transcranial doppler ultrasound examination of the intracranial circulation (intracranial internal-carotid artery, middle-cerebral artery, anterior-cerebral artery, and posterior-cerebral artery). Where necessary, intravenous echogenic contrast media was used to improve resolution. Patients with occlusion of the MCA at 6 h were more likely to have an adverse clinical outcome at 3 months than were those with a patent MCA. The ultrasound diagnosis remained an independent predictor after adjustment for age, severity of the neurological deficit on admission, CT findings on admission, and risk factors.

This is the first large study to show that occlusion of the middle-cerebral artery is associated with subsequent high rates of death or dependency. If these findings are confirmed, then ultra-early transcranial doppler should reduce the need for thrombolysis in those patients whose symptoms are already resolving. The procedure should also identify those patients who might benefit from additional interventions, such as ultrasound enhanced thrombolysis[8] or intra-arterial thrombolytic treatments.[9]

The Article raises important issues. Although best practice suggests that thrombolysis should be widely available, in reality this is not always the case. To offer best care for patients with acute stroke there has to be a substantial change in the way in which acute-stroke care is managed.

In those units that already provide acute thrombolytic services, further stratification of a patient's predicted clinical outcome seems to be possible on the basis of the patency status of the MCA on admission. Transcranial doppler is often perceived as a complex investigation that can only be done in major units and usually only within office hours. However, the equipment is modestly priced compared with that for MRI, CT, or PET scanning. The techniques are sufficiently straightforward so there is no good reason why transcranial doppler should not be widely available in any hospital that admits patients with acute strokes.[10] The absence of a suitable temporal bone window for examination by transcranial doppler was an exclusion criteria in the NAIS study and so cannot be assessed from these findings, but it usually occurs in 10–20% of individuals.

Widespread adoption of ultra-early transcranial doppler assessment of MCA status requires 24 h availability of either a vascular technician or an appropriately skilled clinician. In this study, both clinical and ultrasound examinations were undertaken by the admitting clinician, which seems to be the most pragmatic and realistic solution. However, in many units this approach would have implications for training and manpower and, consequently, resources.

If the NAIS study findings are confirmed, it will allow better stratification of patients. Those with better prognoses need not be exposed to the high-risk treatments that should be reserved for those with poorer predicted outcomes. The need for perfusion imaging (where available) would be reduced. In patients undergoing ultrasound-accelerated thrombolyis, rapid and repeated reassessments of the efficacy of treatments can be made.

Improvement of outcome in acute ischaemic stroke needs a multifaceted approach. Stroke symptoms need to be recognised by the general public and affected patients need rapid transfer to a suitably staffed and equipped stroke unit where timely investigation and initiation of treatment can be undertaken. The NAIS study suggests that ultrasound techniques could be used to predict probable subsequent clinical outcome at a very early stage, thereby allowing therapeutic interventions to be appropriately and optimally modified to suit individual patients.

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1 Murray CJL, Lopez AD. Alternative projections of mortality and disability by cause 1990–2020: Global Burden of Disease Study. *Lancet* 1997; **349:** 1498–504.
2 The National Institute of Neurological Disorders and Stroke rt-PA Study Group. Tissue plasminogen activator for acute ischemic stroke. *New Engl J Med* 1995; **333:** 1581–87.

3 Hacke W, Kaste M, Fieschi C, et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke: the European Cooperative Acute Stroke Study (ECASS). *JAMA* 1995; **274:** 1017–25.

4 Hacke W, Kaste M, Fieschi C, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute iscaemic stroke (ECASS II). *Lancet* 1998; **352:** 1245–51.

5 Baracchini C, Manara R, Ermani M, Meneghetti G. The quest for early predictors of stroke evolution: can TCD be a guiding light? *Stroke* 2000; **31:** 2942–47.

6 Goertler M, Kross R, Baeumer M, et al. Diagnostic impact and prognostic relevance of early contrast enhanced trans cranial color coded Duplex sonography in acute stroke. *Stroke* 1998; **29:** 955–62.

7 Allendoerfer J, Goertler M, von Reutern G-M, Neurosonology for Acute Ischaemic Stroke (NAIS) Study Group. Prognostic relevance of ultra-early doppler sonography in acute ischaemic stroke: a prospective multicentre study. *Lancet Neurol* 2006; **5:** 835–40.

8 Alexandrov AV, Demchuk AM, Burgin WS, Robinson DJ, Grotta JC, CLOTBUST Investigators. Ultrasound-enhanced thrombolysis for acute ischemic stroke: findings of the CLOTBUST trial. *J Neuroimaging* 2004; **14:** 113–17.

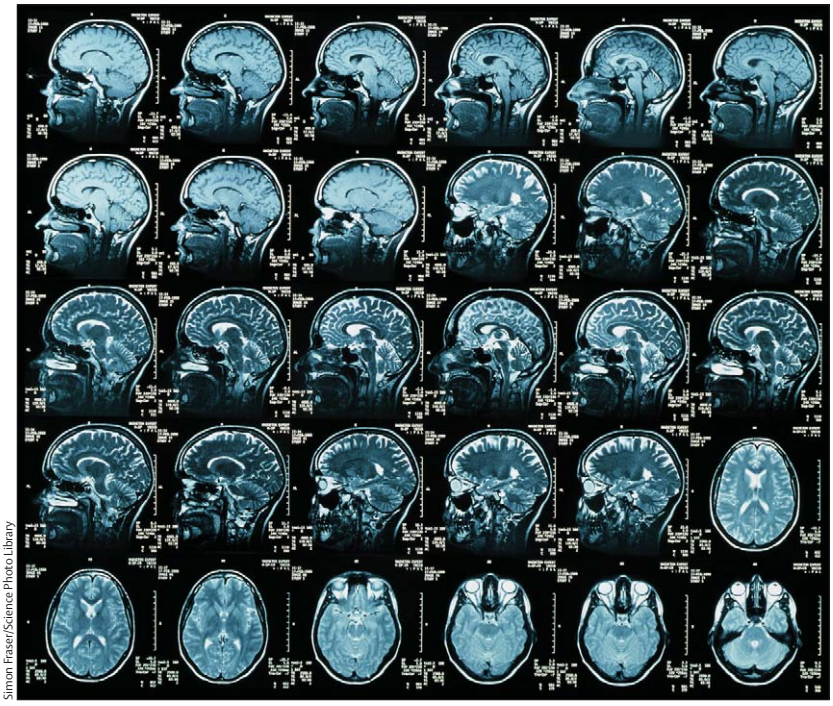
9 Furlan A, Higashida R, Weschler L, et al. Intra-arterial prourokinase for acute ischemic stroke. The PROACT II Study: a randomized controlled trial. Prolyse in Acute Cerebral Thromboembolism. *JAMA* 1999; **282:** 2003–11.

10 Imray CH, Tiivas CA. Are some strokes preventable? The potential role of transcranial doppler in transient ischaemic attacks of carotid origin. *Lancet Neurol* 2005; **4:** 580–86.

The use of MRI in the diagnosis of multiple sclerosis

See **Review** page 841

In this issue of *The Lancet Neurology*, Charil and colleagues[1] present the conclusions of an international consensus panel conference that was held in Amsterdam in 2005 with the goal of identifying and assessing so-called "MRI red flags" in the differential diagnosis of multiple sclerosis. These red flags are envisioned to represent certain MRI findings reported in disorders other than multiple sclerosis—such as systemic lupus erythematosus, sarcoidosis, or small-vessel ischaemic disease—that should lead clinicians to "extensively assess patients" for possible alternative diagnoses to multiple sclerosis. Charil and colleagues provide a broad review of an important topic, discuss alternative diagnoses to multiple sclerosis, and compare the MRI findings in these disorders with those in typical multiple sclerosis. There is much useful information about MRI features of these alternative diseases.



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Is MRI really useful after standard clinical tests for multiple sclerosis?

Unfortunately, however, this Review provides little information that can be directly applied to the diagnosis of multiple sclerosis in individual patients. The article lacks any real guidance to help clinicians decide which patients to assess more extensively (either with other laboratory investigations or invasively). The reasons for this are two-fold. First, contrary to what is asserted in the text, this review has not been developed in a true evidence-based format. Thus, the sensitivity and specificity of these red flags in specific clinical contexts, in general, is neither provided nor considered by the authors and without these, other values such as the positive and negative predictive values for each red flag cannot be calculated or even estimated. Second, the positive and negative predictive value for each red flag will be heavily affected by the pretest probabilities assigned to multiple sclerosis and the alternative disorders. These probabilities, in turn, must be estimated by the clinician based the medical history of the patient and examination of the patient. As with the issue of sensitivity and specificity, this feature of MRI has not been considered. These points are not made as a criticism of the consensus statement, which is actually quite thorough in its assessment of the MRI features of these various alternative disorders. Rather, they are