New year, new editorial team
M N Rossor, M G Hanna

The New Year brings a change of editorship; after seven years of exceptional custodianship the journal says goodbye to Professor Chris Kennard. During his tenure he has maintained the key role of the journal as a premier European clinical neuroscience publication and witnessed an increase in submissions from about 1200 to over 2000 per annum. He has established online submissions via Bench>Press and established the website. He has overseen the introduction of Neurology in Practice, edited by Ian Bone and Geraint Fuller, which will continue in this series until 2005. A number of new features have been introduced, such as editorial commentaries. All of these provide added value to the quality of the submitted articles. It is this added value which is of such importance during the time of the information explosion and online publishing opportunities. These opportunities are indeed substantial, both to increase the amount of information available but also to distribute journals to a wider audience at ever lower marginal cost. The danger, however, is that as quantity increases quality falls. Chris Kennard has met these challenges and hands over the journal in excellent shape.

THE FUTURE
What of the future? JNNP was first published in 1938 (under the title of Journal of Neurology and Psychiatry) and the custodianship of such a journal is both an exciting challenge and a heavy responsibility. We reaffirm the aim of publishing the very best articles of clinical relevance in neurology, neurosurgery, and psychiatry. There are few clinical neuroscience journals that are as broadly based and it would be easy to focus just on neurology. However, we believe that this multidisciplinary nature is its strength, and indeed we hope to foster increased submissions in neurosurgery and psychiatry.

Alzheimer’s disease

Contribution of cerebral amyloid angiopathy to Alzheimer’s disease
S Love

In patients with Alzheimer’s disease (AD), focal and diffuse ischaemic abnormalities of the cerebral white matter can be demonstrated neuropathologically and neuroradiologically. The focal lesions have been shown to contribute to motor and neuropsychiatric manifestations of AD, and the more widespread or diffuse abnormalities to impaired cognition. In some series, ischaemic cerebral lesions in AD have been more frequent in patients homozygous or heterozygous for the epsilon 4 (e4) allele of the apolipoprotein E gene (APOE), but other studies have found no such association. Studies of the relation between white matter damage in patients with AD or probable AD, and the systemic manifestations of arteriosclerotic vascular disease, have yielded inconsistent findings.

Several observations implicate cerebral amyloid angiopathy (CAA) as the probable cause of much of the white matter damage in AD. The vascular deposition of amyloid β protein (Aβ) is much more frequent and tends to be much more severe in patients with AD than in age-matched controls. Furthermore, CAA is a well documented risk factor for cerebral infarction and for focal and diffuse white matter ischaemic lesions. The mechanisms whereby CAA may cause ischaemic damage to the white matter probably include a combination of luminal stenosis, endothelial damage, basement membrane thickening, thrombosis, loss of autoregulation, and vasospasm. Because evidence of the involvement of CAA in AD is largely based on post-mortem studies, which are by their nature skewed towards end stage disease, it could be argued that any contribution of CAA may be confined to the terminal stages of disease. If this were true, it might be expected that an inverse relationship between the severity of CAA at autopsy and the duration of AD would be found. That this is not the case suggests that CAA may exacerbate AD even at an early stage.

The occurrence of CAA in AD is strongly associated with possession of the e4 allele of APOE. Indeed, possession of the e4 allele of APOE is much more strongly correlated with vascular than parenchymal deposition.
This may reflect on the pathogenesis of neurodegeneration in AD in patients with e4. AD patients with severe CAA, almost all of whom possess at least one e4 allele, have significantly less parenchymal Aβ than do patients with lesser degrees of CAA. This further evidence against the argument that CAA is simply a late manifestation of AD, and raises the possibility that CAA and parenchymal Aβ have additive effects on the progression of clinical disease. Although the Aβ within vessel walls could, in theory, also cause local neurotoxicity in the cerebral cortex, we have found no evidence of any associated reduction in the density of immunostaining of synaptophysin, a sensitive marker of presynaptic integrity.

Observations of Weller and colleagues suggest that the involvement of CAA in AD may go beyond a contribution of ischaemia to the clinical and pathological manifestations of the disease, and that CAA may be involved in the development of plaques and tangles. Support for this comes from the occasional finding of tau immunopositive neurites clustered around larger arteries with dyshoric amyloid angiopathy (angiopathy in which amyloid extends from the affected blood vessels into the surrounding brain parenchyma) (fig 1). Although the flow of interstitial fluid within the perivascular space occurs in the opposite direction to that of the arterial blood flow, it may be enhanced by the pulsatile arterial dis-tension. A failure of this propulsive mechanism has been proposed to explain the association of capillary CAA with thrombosis of overlying cortical arteries.

However, several other observations indicate that the relationship between CAA, plaques, and tangles is more complicated than would be predicted by a simple model of obstruction to drainage. These include the mutually exclusive topographical relationship between capillary CAA and extensive diffuse plaques, and the inverse correlation between overall severity of amyloid angiopathy and parenchymal amyloid load in patients with moderate to severe CAA. Further evidence suggests that soluble Aβ within the brain is largely cleared by lipoprotein receptor related protein-1 mediated transcytosis across the endothelial cells of the blood–brain barrier. Impaired clearance of Aβ across the blood–brain barrier is probably central to the development of CAA in hereditary cerebrovascular amyloidosis with Dutch type haemorrhage caused by a G→C transition at codon 693 of the β amyloid precursor protein gene.

Studies by Wyss-Coray et al. identify transforming growth factor β (TGFβ) as a key influence on the relationship between parenchymal and vascular Aβ in AD. TGFβ1 levels are significantly increased in patients with...
AD, not only in the cerebral cortex, but also in the serum and CSF. Chao et al observed a significant in vivo correlation between the level of TGFβ1 in the serum and the severity of dementia. On the face of it, this might seem paradoxical, as TGFβ1 has been shown to promote the clearance of Aβ from the parenchyma of transgenic mice expressing human β amyloid precursor protein. However, in contrast to the beneficial effects of TGFβ1 on clearance of parenchymal amyloid, expression of TGFβ1 by astrocytes in transgenic mice actually induces deposition of amyloid in cerebral blood vessels, this being accelerated by co-expression of human β amyloid precursor protein. A parallel can be drawn between the latter finding and the detection of severe CAA in regions of brain with markedly reduced parenchymal Aβ in a patient with AD who was immunized with Aβ (peptide fragment AN-1792). The relevance of the observations of Wyss-Coray et al to AD was strengthened by the authors’ demonstration of a strong correlation between TGFβ1 mRNA levels and the severity of CAA in post-mortem brain tissue from 15 patients with AD and 7 controls. However, while these post-mortem findings are of interest, it should be noted that the number of cases studied was small.

Many questions remain as to the relation between CAA and AD. Apart from e4, the putative genetic risk factors for CAA show relatively little overlap with those for AD, and despite the fact that e4 is a major risk factor for CAA in AD and in patients presenting with cerebral haemorrhage, CAA is probably not associated with the APOE genotype if these conditions are excluded. Although CAA is present in over 90% of patients with AD, it is not present in all cases and is therefore clearly not necessary for the development of the disease. Indeed, it is becoming increasingly clear that what we refer to as AD is really a spectrum of disorders with different genetic (and possibly environmental) risk factors but having overlapping pathological and clinical phenotypes. For example, e4 associated AD tends to be a disease with moderate to severe CAA, AD caused by some presenilin mutations is characterized by cotton wool plaques and pyramidal tract degeneration, and AD in patients with an ε2 APOE allele and CAA carries an increased risk of parenchymal brain haemorrhage.

The accurate diagnosis of CAA is likely to become increasingly important as we evaluate and implement treatments such as immunization, which are aimed at clearing parenchymal Aβ in AD, particularly if these carry a risk of promoting vascular deposition of Aβ. However, the antemortem diagnosis of CAA in AD remains a challenge. Measurement of plasma levels of Aβ and TGFβ2 was found to be unhelpful in predicting CAA. For the time being, except in the relatively few patients who manifest with lobar cerebral haemorrhage or have a brain biopsy, we will have to continue to rely on examination of the brain at autopsy to make a confident diagnosis of CAA.

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Reference

Depression and cognitive decline

Depressive symptoms and cognitive decline—disentangling the effect of affect

R Stewart

Time to take depression seriously?

Is depression a risk factor for cognitive decline? Dementia, a potential consequence of cognitive decline, is a devastating disorder. If depression is a risk factor, it is important because it is common. Therefore, even a weak risk–outcome association might represent a substantial population level impact and “account for” a large number of dementia cases. It is not surprising that a growing body of observational research has sought to address this question, including the analysis by Wilson et al in this issue (pp 126–9). However, unfortunately we are still a long way from establishing causation and measurements of exposure leave a lot to be desired.

Several prospective studies have shown that depressive symptoms are associated with an increased risk of developing dementia. It is possible that depression may actually initiate or accelerate neurodegenerative processes. This is obviously of particular interest given the implied possibility of preventing cognitive decline and dementia. However, there are other potential explanations. Depression may simply be a reaction to a perceived deterioration in cognitive function. Alternatively, cognitive function may be impaired during a depressive episode because of reduced attention and motivation, so that someone may present with apparent clinical dementia at a relatively early stage of neurodegeneration. These two explanations are addressed in the analysis carried out by Wilson et al and are not supported by their findings because increased baseline depressive symptoms predicted cognitive decline independently of baseline cognitive function. A third explanation is that depression is a prodromal symptom of dementia rather than a risk factor. This hypothesis is less easy to test. It would predict a greater level of neurodegenerative pathology associated with depressive symptoms in people without clinical dementia in life. However, population-based pathological data are hard to come by. Wilson et al cite a report in press at the time of submission which may shed light on this issue but further research is likely to be required.

So where do we go from here? A disappointing feature of most research in this area has been the simplistic approach to depression as an exposure. Some studies focus on categories such as major depression, which poorly characterise late life affective disorder. Most, including that by Wilson et al, do not investigate depression but depressive symptoms. But can a person’s mood state be adequately reflected by summing up a short list of symptoms? What about the perverseness of individual symptoms themselves, their nature (such as the type of sleep disturbance) or underlying clustering (for example, motivation and affect)? Levels of affective disturbance fluctuate throughout the life course and are likely to have complex, interdependent relations with other aspects of health, such as cognitive function and somatic states (for example, vascular disease). Secondary analyses of high quality longitudinal datasets have undoubtedly made substantial contributions to this research field, but are invariably limited by measurements that have to cover a large number of objectives. Dysphoric symptoms predict a wide variety of adverse outcomes but are rarely measured in any detail. Perhaps it is time to take depression seriously.

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