NEUROLOGY 2004

A Kelso, SpR Neurology, Western General Hospital, Edinburgh, Scotland

The neurology symposium held at the Royal College of Physicians of Edinburgh is an event of high quality attracting physicians from all specialties and levels of seniority.

In the first session, 'Infection and the Nervous System.' Dr Hadi Manji (Consultant Neurologist, National Hospital for Neurology and Neurosurgery, London, England), talked about 'Central nervous system (CNS) infection in the immunocompromised patient, and difficulties in diagnosis and treatment'. Human immunodeficiency virus (HIV) is now the commonest worldwide cause of acquired immunosuppression. There are three basic principles of immunocompromise in HIV: impaired humoral responses; impaired cell-mediated immunity; and the likelihood of multiple comorbid diagnoses. The CD4 count can be of value in predicting the type of secondary infection.

Dr Peter Newman (Consultant Neurologist, Middlesbrough General Hospital, Middlesbrough, England) followed with 'Tropical neurological infections and their reference to the UK neurologist'. Cerebral malaria (the most serious neurological complication of infection with the *plasmodium falciparum*) was described, as were the choices and suitability of prophylactic treatments. He also emphasised the morbidity of helminth infections such as schistomiasis, the commonest neurological manifestation being spinal cord compression secondary to granuloma formation. Cysticercosis is the commonest cause worldwide of acquired epilepsy, and the life cycle of the parasite, routes of transmission and options for treatment were presented.

The final speaker in this session was Dr David Wilks (Consultant in Infectious Diseases, Western General Hospital, Edinburgh, Scotland), who outlined and discussed the management guidelines for meningitis produced by the Meningitis Research Foundation (www.meningitis.org) in association with the British Infection Society (www.britishinfectionsociety.org). Time was devoted to antibiotics (the bottom line being lots, intravenous, now!), the methods of diagnosis and the current evidence on the use of steroids. Steroids should be targeted to those with severe pneumococcal meningitis, and given with the first dose of antibiotics.[1,2]

Session 2 on Stroke Imaging, featured Dr Andy Molyneux (Consultant Radiologist, Frenchay Hospital, Bristol, England) presenting the current evidence on the management of intracranial aneurysms. The International Study of Unruptured Intracranial Aneurysms (partly retrospective, partly prospective and observational) includes around 5,000 cases and shows that the risk of aneurysmal rupture increases with increasing size of the aneurysm together with a previous subarachnoid haemorrhage (SAH), and that the risk–benefit ratio favours treatment with increasing aneurysmal size.[3] Having a history of one first-degree relative with a ruptured aneurysm increases the absolute risk slightly, with a greater effect (between two and three times) if two first-degree relatives are affected.[4] The methods of screening were discussed: computed tomography angiography (CTA) and magnetic resonance angiography (MRA) both have 100% sensitivity in detecting aneurysms of 5 mm diameter or greater (i.e. at significant risk of rupture), and are the investigations of choice. The evidence on management of ruptured intracranial aneurysms was recently improved with the publication of the International Subarachnoid Aneurysm Trial, which compared (for aneurysms suitable for either approach) endovascular treatment with best surgical treatment. It found strongly in favour of the endovascular arm,[5] and practice has changed considerably in the UK since its publication.

The Lilly Lecture is an annual event and has featured many distinguished speakers since its inception. The College was proud to welcome Dr Christian Confavreux presenting 'Lessons from the natural history of multiple sclerosis'. He elegantly described his opinions on the relationship between two cardinal features of multiple sclerosis (MS): relapse and progression. The current view is that relapse (caused by inflammation) and progression (caused by degeneration) are causally linked. The degenerative process is diffuse, occurs early, and is chronic and progressive. In an autoimmune model, the inflammatory reactions are directly related to degeneration – indeed they are considered to be the main driver of this process. There is some support for this argument: in the Lyon Natural History of MS study,[6] 20% of the cohort had significant clinical sequelae following the first episode, and 30% of those with relapsing-remitting disease had sequelae. In the placebo arm of a randomised controlled trial published by Lublin,[7] 28% of cases had a rise in the expanded disability status scale (EDSS) of at least 1 point, and 42% had a rise of 0·5 points 64 days after a relapse. The conclusions from this work are that the

degree of recovery time to the second episode, and number and frequency of relapses, are predictive of the rate of progression. However, there are arguments that inflammation may be beneficial. For instance, relapses are generally followed by clinical remission, and protective growth factors have been identified in acute MS lesions *ex vivo*. Nine per cent of the MS population have only primary progressive or progressive relapsing disease, with no initial relapsing-remitting stage, and the rate of progression in this group is the same as in those with other forms of the disease. When the evidence described above is re-examined, it seems that, although there are changes in the EDSS at three months, they are not sustained at two years.[8] There is work looking at the time between symptom onset and progression to significant disability (disability status scale (DSS) 4, 6 and 7), and it becomes clear that although patients with relapsing-remitting MS take longer to get to DSS 4 than those with primary progressive disease, the two groups then progress at the same rate. Also, there is no difference in the progression rate in the group who experienced relapses during progression.[9] In secondary progressive MS, there is no difference in progression, regardless of the presence or absence of relapses. If the initial relapses in relapsing-remitting MS are infrequent, the time from onset to DSS 4 is longer, but once progression is established, there is again no difference between this group and those with frequent initial relapses.[9] It is also known that the cerebral atrophy seen on magnetic resonance imaging (MRI) is present at an early stage of the disease, advances at a steady rate during the disease, and is independent of the presence or absence of focal lesions. This is consistent with the β-interferon trials where relapse rate was reduced with a corresponding reduction in MRI activity, but the effects on disease progression and disability are less convincing. Similarly, in the CAMPATH-1A trial, there is a large reduction in the relapse rate, but 50% of patients continued to progress with a 1 point drop in their EDSS.[10] Two new hypotheses can be generated: either MS is an autoimmune disease, where inflammation initiates degeneration that then becomes self-sustaining, or it is a primary neurodegenerative disease, with inflammatory events occurring as a secondary phenomenon. Although more questions than answers are generated, it seems plausible that MS is relapse dissociated and amnesic of early relapses. There is still a role for standard and novel anti-inflammatory treatments, but future developments should also target neuroprotection and neuro-repair.

Session 3, 'Managing neurodegenerative diseases,' considered motor neurone diseases and the dementias. Dr Kevin Talbot (Consultant Neurologist, Radcliffe Infirmary, Oxford, England) discussed the possible aetiologies, clinical features, epidemiology and management of the motor neurone diseases, and talked about the current work on understanding the pathogenesis of amyotrophic lateral sclerosis. The mutation in the superoxide dismutase-1 gene, at one time thought to exert its deleterious effect through an excitotoxic mechanism, is now believed to cause abnormal protein folding, triggering apoptosis and disruption of neurofilaments by a dominant negative effect. Spinal muscular atrophy can be caused by a mutation in the survival motor neurone protein, levels of which are decreased in this disease.[11] This protein appears to be important in the production of β-axin protein, which is involved in axonal development. Motor neurones are particularly sensitive to disruption of RNA metabolism, as they rely on RNA transport (an unusual intracellular phenomenon) to generate proteins at their site of function, up to one metre distant from the nucleus of the cell. Animal studies have identified multiple agents that promised initial benefit in slowing the symptoms of motor neurone disease, but none of them (except for riluzole) have translated to a human model. Perhaps the clinical phenomenology of the disease reflects downstream neuronal injury more accurately than the initial neuronal insult or susceptibility? Professor Martin Rossor (Professor of Clinical Neurology, St Mary's Hospital, London, England) summarised the presentation of (and treatments for) Alzheimer's disease, dementia with lewy bodies and fronto-temporal lobar degeneration. The trial of immunisation in Alzheimer's disease has been discontinued early because of severe adverse complications (including meningoencephalitis), but not before generating some questions and indications to guide further investigations.

The (now traditional) debate proposed 'Copying out-patient letters to patients: Scotland should follow England and Wales'. Arguing for the motion were Dr Phil Smith (Consultant Neurologist, University Hospital of Wales, Cardiff, Wales) and Professor Michael Sharpe (Professor of Liaison Psychiatry, University of Edinburgh, Edinburgh, Scotland) and arguing against, Professor David Bates (Professor of Clinical Neurology, Royal Victoria Infirmary, Newcastle, England) and Dr Richard Knight (Consultant Neurologist, Western General Hospital, Edinburgh, Scotland). The vote was evenly split pre-debate (40·7% for and 42·6% against), and after a lively and playful contest, the audience had swung against the motion (20·8% for and 77·4% against). The losers claimed foul play, asserting that a late change in the motion (a matter of subtle linguistic interpretation) accounted for their poor performance!

This symposium is always of a high quality, and was well attended, but there did seem to be fewer generalists, general practitioners and medical students present than in previous years. Perhaps there was less in the programme to interest the non-neurologist, but a meeting for neurologists and those with a special interest in neurology was equally welcome.

REFERENCES

1 de Gans J, van de Beek D. Dexamethasone in adults with bacterial meningitis. *New Engl J Med* 2002; **347(20):**1549–56.
2 Heyderman RS, Lambert HP, O'Sullivan I *et al.* Early management of suspected bacterial meningitis and meningococcal septicaemia in adults. *J Infect* 2003; **46(2):**75–7.
3 The International Study of Unruptured Intracranial Aneurysms Investigators. Unruptured intracranial aneurysms – risk of rupture and risks of surgical intervention. *N Engl J Med* 1998; **339(24):**1725–33.
4 Wardlaw JM, White PM. The detection and management of unruptured intracranial aneurysms. *Brain* 2000; **123(2):**205–21.
5 Molyneux A, Kerr R, Stratton I *et al.* International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2,143 patients with ruptured intracranial aneurysms: a randomised trial. *Lancet* 2002; **360(9342):**1267–74.
6 Confavreux C, Vukusic S, Adeleine P. Early clinical predictors and progression of irreversible disability in multiple sclerosis: an amnesic process. *Brain* 2003; **126(4):**770–82.
7 Lublin FDM, Baier MP, Cutter GP. Effect of relapses on development of residual deficit in multiple sclerosis. *Neurology* 2003; **61(11):**1528–32.
8 Liu C, Blumhardt LD. Disability outcome measures in therapeutic trials of relapsing-remitting multiple sclerosis: effects of heterogeneity of disease course in placebo cohorts. *J Neurol Neurosurg Psychiatry* 2000; **68(4):**450–7.
9 Confavreux C, Vukusic S, Moreau T *et al.* Relapses and progression of disability in multiple sclerosis. *New Engl J Med* 2000; **343(20):**1430–8.
10 Coles AJ, Wing MG, Molyneux P *et al.* Monoclonal antibody treatment exposes three mechanisms underlying the clinical course of multiple sclerosis. *Ann Neurol* 1999; **46:**296–304.
11 Lefebvre S, Burglen L, Reboullet S *et al.* Identification and characterization of a spinal muscular atrophy-determining gene. *Cell* 1995; **80(1):**155–65.