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Neurology symposium

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INTRODUCTION

The specialty of neurology is better known for an 'ivory tower' approach rather than involvement in acute care, but neuroscience units around the UK are changing, with greater emphasis on prompt early neurology review to provide early diagnosis and correctly targeted investigations. This theme was reflected in the symposium with overviews of disorders related to pregnancy, critical care, vascular neurology and a presentation on liaison neurology in the acute medical unit. In addition updates on multiple sclerosis (MS) therapeutics, neuromyelitis optica, and the clinical approach to an efficient cognitive assessment provided the varied audience with an engaging and informative programme.

SESSION 1: NEUROINFLAMMATION AND COGNITIVE NEUROLOGY

Dr Martin Duddy (Royal Victoria Infirmary, Newcastle) began the session describing how, over the last 20 years, the treatment landscape for disease modifying therapy in relapsing remitting multiple sclerosis (RRMS) has expanded with eight regimens currently available. These comprise the traditional injectables (interferon beta and glatiramer acetate), newer oral agents (fingolimod, teriflunamide and dimethyl fumarate), pegylated interferon and two NICE-approved monoclonal antibodies (natalizumab and alemtuzumab).[1] Dr Duddy emphasised the difficulty of predicting the long-term outcomes of these treatments using evidence from trials lasting 2–3 years. However, the outcome of the UK Department of Health Risk-sharing Scheme for traditional disease modifying therapies modelling natural history data has shown modest benefit in disability scores at six years follow-up.

Appraisals of RRMS therapies are based on outcome measures combining annual clinical relapse rate, disability scores and inflammatory and neurodegenerative lesion load on magnetic resonance imaging (MRI). Using these outcome measures the efficacy of the various treatments in short-term clinical trials are: traditional injectables (reduction in annual relapse rate and short-term disability of 30% and 12–37%, respectively); fingolimod and dimethyl fumarate (approximately 50% and 30%, respectively); natalizumab and alemtuzumab (approximately 70% and 50%, respectively). Debate continues as to how well these outcome measures predict later disease. However, clinical experience indicates that the two monoclonal therapies offer significantly better short- and long-term health outcomes compared to the established therapies but come with increased risk and thus more intense monitoring. With natalizumab, the principal risk is of progressive multifocal leucoencephalopathy. This is associated with reactivation of neurotropic JC virus that remains latent in carriers, and confers 60% mortality rate and 20% severe disability. Risk stratification of patients is based on JC virus antibody status and titres, history of previous immunosuppression and duration of therapy, with surveillance in all patients including 3-monthly liver function tests and annual review and consent. In lower risk JC negative patients, 6-monthly JCV antibody testing to detect seroconversion and annual MRI brain is advocated and, after two years of therapy, JC positive patients require 6-monthy imaging surveliance. In addition JC low titre positive patients should have serology tested every six months and natalizumab non-responders checked for neutralising antibodies. Alemtuzumab offers best efficacy and with its short-term treatment regimen of a single infusion for five days and then three days the following year (+/- 'top up' doses as required) is very attractive for patients; however it is associated with a high risk of secondary autoimmunity including thyroiditis, haemolytic anaemia,

idiopathic thrombocytopaenic purpura, and glomerulonephritis. These potential complications necessitate a risk management protocol including predose varicella zoster virus, HIV, hepatitis B and C, tuberculosis serology and cervical screening, oral aciclovir for the first month following therapy, monthly FBCs, U&Es and TFTs for five years and annual MRI brain scans to determine efficacy. In summary, first line therapy includes interferons or teriflunamide for active RRMS (two relapses in two years) and natalizumab for rapidly evolving MS (two relapses in one year and active MRI lesions). Alemtuzumab could be considered in rapidly evolving MS in JC positive patients or natalizumab failure (+/- neutralising antibodies).

Other monoclonal antibodies are on the horizon with daclizumab recently reporting a positive phase 3 trial, and the anti-CD20 agents' ocrelizumab and ofatumumab have ongoing studies. In addition, natalizumab has an ongoing phase 3 trial in secondary progressive MS. In conclusion, patient selection and provision of informed treatment options is a challenging area for the MS specialist.

Dr Anu Jacob (The Walton Centre, Liverpool) reviewed the immune-mediated CNS astrocytopathy neuromyeltis optica, mediated by the anti-aquaporin-4 antibody. However, 20% of NMO patient are seronegative. Aquaporin-4 is highly expressed in the spinal cord, optic nerve, brainstem, periventricular and fourth ventricular regions. The core clinical criteria for the condition include longitudinal extensive transverse myelitis, optic neuritis, area postrema syndrome (nausea, vomiting and intractable hiccoughs) and brainstem syndromes. Additional clinical features include endocrinopathy, dysautonomia and narcolepsy. It is seen more commonly in Asians, but is increasingly diagnosed in Caucasians. The severe nature of attacks with permanent disability occurring early on warrants early disease modifying treatment. Indeed, 50% of seropositive cases relapse within one year. Acute attacks are managed with high dose intravenous methylprednisolone followed by a slow oral taper of prednisolone over 3–6 months, with plasma exchange in steroid non-responders. Disease modifying therapy used in RRMS such as interferon beta, natalizumab and fingolimod appear to worsen neuromyeltis optica. Immunomodulatory treatment options include azathioprine and mycophenolate mofetil which reduce relapse rate to <0.5/year, with rituximab reserved for intractable cases.[2]

Dr Chris Butler (University of Oxford) outlined the cognitive domains that are assessed using the Addenbrooke's Cognitive Exam (ACE-III) and the various lobar dementia syndromes using illustrative video cases. The recall and recognition aspect of memory function in medial temporal lobe pathology are both impaired whereas in frontal pathology the latter is relatively preserved which can help in the diagnosis of Alzheimer's disease. The 'head turning sign' is thought to be a sensitive sign for an organic brain disorder.

Fronto-temporal lobar degenerations are common in patients under 65 and the second most common dementia in this age group after Alzheimer's. Patients present with behavioural changes (e.g. inappropriate social interaction), dysexecutive syndrome (problems with motivation, planning and sequencing tasks) and language deficits. This categorises patients broadly into behavioural variant fronto-temporal dementia (with early self-neglect, loss of social awareness, obsessive traits, aggression and perseveration); sematic dementia (a fluent aphasia with loss of word meaning characterised by phonemic paraphrasia (substitution of a word with a nonword that preserves at least half of the segments and/or number of syllables of the intended word); sematic paraphrasia (the replacement of one word by another real word that is related to that of the intended word, e.g. brother for sister) that progresses to logorrhoea (abundant, unfocused speech); and progressive non-fluent aphasia with predominant anomic dysphasia localising pathology to the left inferior frontal lobe.

A case study of posterior cortical atrophy illustrated how this has an early predilection for the occipital-parietal dorsal stream visual pathways needed for visual perception and attention. The occipital-temporal ventral stream for visual identification is unaffected early in the course of this dementia. In summary, an efficient diagnostic appraisal of cognitive function includes a witness account, patient observation, and elucidation of the temporal evolution of cognitive domains affected in combination with the ACE-III profile.

SESSION 2: CRITICAL CARE AND COMA

Dr Max Damian (Addenbrooke's Hospital, Cambridge) opened the second session with an overview of UK neurocritical care services. Two-thirds of patients on ICU with encephalopathy without focal signs have a metabolic disorder. He presented cases of hyperammonaemic encephalopathy (despite normal liver function tests), antifreeze poisioning (with raised anion gap acidosis) and reversible iatrogenic encephalopathies caused by cytotoxic or immune therapies. The management of non-convulsive status epilepticus was reviewed and in hyper-refractory (> 48hrs despite conventional treatment) cryptogenic cases plasma exchange should be considered to treat unknown autoimmune aetiologies. Serial examinations using The Four Score which also includes oculomotor assessment and respiratory pattern can be more informative than the Glasgow Coma Scale in monitoring patients on the ICU.[3]

Prognostication guidelines in coma post-cardiac arrest have changed since the use of therapeutic hypothermia and neurological assessment should be undertaken after three days of normothermia.[4] Clinical circumstances surrounding cardiac arrest such as time to return of spontaneous circulation have no prognostic use but absence of cortical evoked potentials can indicate poor outcome.

Dr Damian concluded that dedicated neurocritical care can improve mortality in neurosurgical patients and outlined a proposal of an interactive telemedicine link between district general hospitals and tertiary units to improve management of neurological patients on the ICU.

The Sydney Watson Smith Lecture was given by Professor Adrian Owen (Western University, Ontario, Canada) on using neuroimaging to detect conscious awareness in the vegetative state. His lecture demonstrated that using functional MRI (fMRI), a clear subset of patients in the vegetative state (VS) did not conform to the traditional definition of wakefulness without awareness. Using fMRI to detect the presence of neural activity in response to verbal commands such as 'imagine you're playing a game of tennis' or 'moving around the house' can reliably categorise patients into VS-responders and VS-non-responders, and predict coma recovery up to six months post-brain injury. VS-responders may represent a subgroup of patients (1 in 5) who are in a minimally conscious state not detected by standard clinical assessment and who may have more favourable longer term outcomes. Proof of concept using language stimuli and fMRI as a method of communication in VS-responders was demonstrated with associations between imagery patterns and yes/no answers to simple questions. The cognitively demanding nature of the tennis/spatial imagery tasks prompted alternative methods using fMRI to detect residual consciousness including displaying simple movies to patients and analysing the fMRI signatures relating to plot interpretation, auditory and visual stimuli.

On a practical level, the use of EEG and brain-computer interface technology may be used in future to utilise these scientific advances in order to communicate with patients in various disorders of consciousness.

SESSION 3: ACUTE NEUROLOGY

Dr Edward Dunn (Leeds General Infirmary) outlined the implementation and impact of running an acute neurological liaison service resulting in reduced length of stay in hospital (median two days as compared with eight pre-implementation) and appropriate prompt investigation and treatment. The case mix presented highlighted some important points including having a working knowledge of clinical cord syndromes, not to easily dismiss first ever presentation of migraine with aura, normal cerebrospinal fluid analysis in early encephalitis and atypical acute presentations such as acute bulbar symptomatology in myasthenia gravis and motor neurone disease and acute akinetic-rigid syndrome in catatonia.

The success of this service informed the joint Association of British Neurologists/Royal College of Physicians report on local adult neurology services for the next decade.[5]

Dr Marc Randall (Leeds Teaching Hospitals) addressed the importance of transient ischaemic attack (TIA) triage. The risk of stroke after TIA is 5% at seven days and 10–15% at 90 days.[6] Clinically based risk prediction models such as the six point Age, Blood pressure, clinical features, TIA duration and presence of diabetes score (ABCD2)[7] allow patients with recovered symptoms to be targeted for rapid clinic review based on their likely recurrence risk. However, the ABCD2 score was originally designed in secondary care for risk stratification. ; clinicians should be aware that it is not a diagnostic tool, as one-third of patients with a high score have TIA mimics and it does not take into account high risk crescendo TIAs. The take home message was that TIA remains a clinical diagnosis, and that MRI diffusion weighted imaging is negative in 50% of TIAs and should not be used to decide on appropriate secondary prevention such as antiplatelet drugs, blood pressure control and cholesterol lowering agents.

SESSION 4: NEUROLOGY AND PREGNANCY

Dr Dougall McCorry (Queen Elizabeth Hospital, Birmingham) reviewed epilepsy management in pregnancy using case examples. Half of all pregnancies are unplanned which should influence prescribing decisions in woman of childbearing age. Pre-conceptual decision making includes both maternal risks (mortality, seizure control and impact on driving and employment) and neonatal teratogenic risks (major congenital malformations, minor congenital malformations and neurodevelopmental impact). Sodium valproate carries a dose-related 6.7–9% risk of major congenital malformation and a reduction in 7–10 IQ points, with a higher risk associated with doses > 1000mg/day compared with other monotherapy. In addition a higher risk of neurodevelopmental disorders, including autistic spectrum disorders, is attributed to sodium valproate therapy. Carbamazepine and lamotrigine monotherapy are associated with a 2.6–3% risk of major congenital malformations. Importantly, 5mg folic acid daily has a protective effect and should be advised during preconception counselling.

Epilepsy antenatal clinics also provide an opportunity for diagnostic re-appraisal, capture non-attenders and instigate appropriate post-delivery care plans and follow-

up. It is important to check adherence by measuring serum levels of antiepileptic drugs in patients who appear not to be responding and be aware that serum levels of lamotrigine decline in pregnancy with increased clearance necessitating dose escalation and possibly routine monthly monitoring. The ongoing EMPIRE study endeavours to determine if therapeutic drug level monitoring in pregnancy correlates with seizure control and outcomes. In summary, an attempt should be made to conceive on antiepileptic drug monotherapy at lowest effective dose to produce seizure control with folic acid supplementation. Sodium valproate should be avoided, when possible.

Dr McCorry also delivered Dr Dominic Heaney's (National Hospital for Neurology and Neurosurgery, London) talk on the joint obstetric neurology clinic. This highlighted that the Confidential Enquiry into Maternal Deaths (2006–2008) showed that 36/88 were neurological diagnoses and that 14/36 were epilepsy-related. Management of common neurological conditions in pregnancy such as migraine and MS were briefly discussed.

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