NEUROLOGY 2002*

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INTRODUCTION

The Neurology Symposium at the Royal College attracted interest from primary care specialists, neurologists, general physicians and students, and provided information on both acute neurological conditions, and chronic diseases (myotonic dystrophy (MD) and Parkinson's disease (PD) in particular). The afternoon debate was punctuated with vigorous discussion.

SESSION 1

ACUTE NEUROLOGY

Chaiman: Dr Richard Roberts, Reader in Neurology, University of Dundee

Management of acute stroke

Dr Elizabeth Warburton, Addenbrooke's Hospital, Cambridge

Stroke is an acute neurological emergency for which there are three basic evidence-based recommendations:

1. Aspirin, given within 48 hours of stroke onset, reduces death and disability at six months.
2. Patients admitted to a stroke unit within one to four weeks of stroke onset have a better outcome.
3. Thrombolysis for ischaemic stroke appears to improve outcome, though it has been tried in only 5,000 patients, compared to 17,000 patients in myocardial infarction trials.

There is extensive clinical experience of aspirin in this context. A Cochrane Library review of anti-platelet therapy[1] showed that aspirin, if started in the first 48 hours, independently reduced death and dependency at six months, with no difference in the observed effect with dose (50–150mg). There was no difference in outcome (either for further stroke or death) in the subgroup of patients with intracranial haemorrhage.

A recent Cochrane Library collaboration[2] showed that admission to a stroke unit reduced both death and dependency (between one and four weeks post-stroke). These reductions were maintained beyond the stroke unit stay, and were relevant to all ages and stroke subtypes. This benefit is thought to be due partly to better 'brain protection' (acute treatment of hypo/hypertension, constant cardiac and oxygen saturation monitoring with oxygen therapy if required, treatment of fever, insulin administration if BM >15mmols/L), improved management of other medical complications, early mobilisation and rehabilitation, multidisciplinary teams and use of protocols (e.g. for oxygen, fluids and antipyretics).

The evidence for benefit of thrombolysis is less firm. The Cochrane collaboration[3] has conducted a systematic review of 17 randomised controlled trials (RCTs) (5,216 patients) looking at streptokinase, tissue plasminogen activator (tPA) and urokinase. There was an overall reduction in death and dependency at six months, but balanced against this were the early risks of fatal intracranial haemorrhage (adjusted risk increase (ARI) 4·4% in the first seven to ten days) and death by end of follow-up (ARI 3·3%). Many issues surrounding thrombolysis remain unresolved: timing (there seems to be benefit from thrombolysis given within four and a half hours), severity of stroke, subtypes, significance of early computerised tomography (CT) changes, and age. Intra-arterial thrombolysis looks promising but requires further study. Results from the open label tPA studies are awaited. The effect of giving thrombolysis in instances of carotid and vertebral artery dissection is unknown, but studies so far seem to show no change in overall outcome.

Patients who would benefit from thrombolysis may be better identified with imaging modalities other than CT. Positron emission tomography (PET) scanning does not generate images that correlate with the clinical scenario, but diffusion-weighted magnetic resonance imaging (DWI) and perfusion-weighted magnetic resonance imaging (PWI) are more promising. Diffusion-weighted magnetic resonance imaging measures changes in the diffusion of extra-cellular water, and in some models, changes measured early (less than two hours) reflected final outcome,[4] and could differentiate between salvageable and dead brain. Further research into these areas may determine a subgroup of patients in which thrombolysis is especially helpful.

Headache

Dr Richard Davenport, Western General Hospital, Edinburgh

Acute headache (AOH) is defined as a headache arising and reaching maximal intensity within seconds to minutes. It is common, accounting for 1–2% of Accident & Emergency work. The differential diagnosis for AOH

*This is the report of the lectures given at the Neurology Symposium held at the Royal College of Physicians on 22 November 2002.

TABLE 1
Primary and secondary headache syndromes.

Primary headache syndromes
- Migraine
- Cluster headache and related syndromes (including paroxysmal hemicranias and SUNCT (short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing))
- Thunderclap headache
- Hypnic headaches
- Benign exertional/sex headache
- Cough headache
- Exploding head syndrome (sensation not headache)

Secondary headache syndromes
- Traumatic
- Simple closed head injury
- Complex with subdural/subarachnoid/intracerebral haemorrhage
- Vascular disease
- Subarachnoid haemorrhage – aneurysmal, peri-mesencephalic, other vascular anomalies
- Unruptured aneurysm
- Acute cerebral ischaemia – TIA or stroke
- Non-traumatic subdural/extradural/intracerebral haemorrhage
- Dissection of carotid or vertebrobasilar arteries
- Cerebral venous thrombosis
- Vasculitis including giant cell arteritis
- CNS infection
- Meningo-encephalitis (bacterial, viral, fungal)
- Cerebral abscess
- Intermittant hydrocephalus (e.g. colloid cyst)
- Idiopathic intracranial hypertension
- Intracranial hypotension (spontaneous or post LP)
- Intracranial tumour
- Pituitary apoplexy
- Arnold Chiari malformations
- Optic neuritis
- Metabolic or toxic disturbance
- Phaeochromocytoma
- Thyroid disease
- Drug induced
- Withdrawal syndromes
- Hypercarbia
- Hypertensive encephalopathy
- Cervical spine disease
- Dental, ENT or ophthalmic disease (e.g. sinusitis, acute glaucoma)
- Secondary to general medical conditions (ischaemic heart disease, epilepsy, infection)

is shown in Table 1. The use of the diagnostic label of 'not subarachnoid haemorrhage' is unacceptable.

The odds of serious pathology in true AOH are high, reaching one in three in a community-based Dutch study in the under-60 age group, or one in eight in patients with headache as their only symptom.[5] Most of these serious diagnoses were of aneurysmal subarachnoid haemorrhage (SAH). As the prognosis for rebleeding in SAH is poor, GPs should refer AOH immediately to hospital. The history will identify which patient has had a true AOH and needs further investigation, but will not differentiate between sinister and benign sudden onset headache syndromes.

In SAH, the onset of headache is usually between seconds and a few minutes, and most experts believe it should last for at least an hour. Supporting features include vomiting, meningism, loss of consciousness, seizures and focal neurological signs, but 10–20% of patients with SAH have headache alone, and all of the above 'supporting' symptoms can occur with benign headache syndromes. The presence of a history of aneurysmal SAH in a first-degree relative increases the risk three to seven times. The concept of a sentinel bleed 'heralding' the onset of true SAH is outdated and probably represents a missed SAH. Missed SAH is very expensive, in terms of both the future care of the patient and medicolegal compensation.

The investigation of SAH should include biochemical and haematological blood tests, an electrocardiogram (ECG), chest X-ray, and an un-enhanced CT brain scan. Supplementary tests are a cerebrospinal fluid (CSF) examination in those with a normal scan but with a history of AOH, and angiography to identify an aneurysm in those with proven SAH. The management of SAH involves supportive measures, analgesia, nimodipine, and securing the aneurysm by surgical or endovascular means.

Late presentation of patients with sudden headaches suggestive of SAH is less clear-cut, as CT brain scans and CSF examination for xanthochromia are unreliable more than three weeks after the event. Formal angiography, CT angiography (CTA) or MR angiography (MRA) may be useful and the degree of suspicion helps to guide investigation. Computerised tomography angiography and MRA are less accurate than four-vessel angiography at visualising small aneurysms.

Neurologists should be assessing AOH, but unfortunately this does not happen for the majority of cases at present.

Acute Epilepsy

Dr Hannah Cock, The National Hospital for Neurology and Neurosurgery, London

The crux of appropriate clinical management of epilepsy is in accurate and timely diagnosis. The list of conditions in the differential diagnosis is large, including syncope, hypoglycaemia, sleep, anoxic seizures, hypnic jerks, sleep apnoea, parasomnias, restless legs, transient ischaemic attacks, tics, migraine and 'non-epileptic attack disorder'. The medical and social consequences of epilepsy are considerable and thus diagnostic accuracy is essential.

Diagnosis of epilepsy is fundamentally clinical, as a convulsive electroencephalograph (EEG) is the only truly confirmatory test. In differentiating between non-epileptic attack disorder and epilepsy, the presence or absence of tongue biting, other injury, incontinence, past psychiatric illness, female gender, drop attacks, prolactin levels and florid uncontrollable movements can be helpful, although there are no hard-and-fast rules, and most of the published evidence is anecdotal.

A full history (including a witness account) should be taken. If epilepsy is suspected, a referral should be made to a consultant with expertise in epilepsy.[9] The patient must refrain from driving for one year and inform the Driver and Vehicle Licensing Authority. An ECG and some baseline biochemistry should be obtained, and ideally an MRI brain scan ordered within three months.[6]

The value of an EEG is dependent on the context in which it is requested. Interictal EEG has a sensitivity of 50% and a specificity of 98% in patients who have a good clinical history of epilepsy, so has little role in diagnosis. It does, however, play a part in classification of epilepsy sub-type, and prognosis. It should not be requested if epilepsy is clinically improbable, as both the sensitivity and specificity are reduced in this situation. Ictal and post-ictal EEGs are useful in generalised or other convulsive attacks, but may be normal during partial seizures.

Clusters of seizures need to be addressed promptly, as they can be premonitory for status epilepticus. Possible precipitants are poor drug compliance, drug interactions, changing drug regimens or intercurrent illness. Appropriate treatment would be clobazam 10 mg or lorazepam 4 mg daily, for up to five days.

Status epilepticus is defined as epileptic activity continuing for 30 minutes or more. Early treatment is important as continued epileptic activity not only causes physiological damage, but also alters drug receptor sensitivity (such as benzodiazepine receptors), making treatment more difficult. These effects are variable from patient to patient. As many as 50% of patients diagnosed with status epilepticus may actually have non-epileptic status.[10, 11] The consequences include prolonged intensive therapy unit (ITU)/high dependency unit (HDU) stays (with resulting cost implications) and iatrogenic complications (such as respiratory arrest).[10] Diagnosis of non-epileptic status rests with EEG, and in an ideal world, this would be available at all hours in every district general hospital. The reality is that 60% of these hospitals do not have an EEG machine onsite, and fewer have adequately trained staff.[12, 13] The minimum acceptable standard should be EEG within 12–24 hours for all admissions with seizures or confusion, ideally prior to (or during) transfer to ITU, with trained staff available to give a provisional report.

The management of status epilepticus follows the rubric that 'time is brain'. Protocols are important, and the process is as important as the content:

1. Resuscitation and general medical support
2. Confirmation of diagnosis
3. Stop seizures
4. Identify and treat any cause
5. Establish maintenance anti-epileptic drugs

Premonitory and initial seizures may be terminated with benzodiazepines – lorazepam, diazepam or midazolam. Three RCTs and two retrospective studies compared lorazepam with diazepam (n>500), in both adults and children, and found that lorazepam was successful in 75% of cases, compared with 50% of those treated with diazepam.[11, 12, 16–18] Since use of lorazepam confers no extra cost per patient, has no significant adverse effects, and has superior efficacy to diazepam, it should be the drug of choice. Five studies have looked at the use of midazolam (administered buccally) in children (n=282 episodes). It had similar efficacy to rectal diazepam, and was easier to administer.[14, 19, 20]

For established status epilepticus, three drugs are used: phenytoin (£160/1 g), fosphenytoin (£800/1 g (phenytoin equivalents*)) and phenobarbitone (£4/700 mg). The efficacy of other anti-epileptic drugs (such as sodium valproate) is unknown.

Whichever drug is given, the dose must be adequate. Walker[8] showed that in 26 patients with status epilepticus, 18 had an inadequate loading dose of phenytoin, and Cascino showed that in 184 patients with status epilepticus, 28% had delayed or inappropriate treatment, and in 76% of those treated the first dose of the anti-epileptic drug was inadequate.[13] Propofol and/or midazolam are sometimes used in established status epilepticus, but a systematic review (28 studies, 193 patients) found that there was an increased chance of treatment failure on these drugs.[15]

SESSION 2

GENES AND MUSCLES

Chairman: Dr Richard Roberts, Consultant Neurologist, Western General Hospital, Edinburgh

Myotonic Dystrophy

Dr Douglas Wilcox, Royal Hospital for Sick Children, Glasgow

Myotonic dystrophy is caused by a CTG triplet expansion in the first intron of the dystrophin gene on chromosome 19. Ribonucleic acid (RNA) containing this

*Fosphenytoin is a metabolite of phenytoin, and dosages of it are marketed as the equivalent dose of phenytoin required to achieve the same blood level.

repeat cannot pass out of the nucleus to be processed and is detrimental to nuclear function. This dominant negative effect leads to abnormal up and down regulation of other genes. The number of CTG repeats varies in different tissues within the patient and with age, providing a wide clinical spectrum of disease.

Coordination of care for MD patients is problematic as it is a multisystem disease and some families harbour occult disease for generations prior to diagnosis with minor motor problems, learning difficulties and social and personal problems. Some patients present with sudden death in middle age from cardiac complications, whilst others present at birth with congenital MD. Patients often present with unrelated medical emergencies, and are at risk from anaesthetic agents.

In the West of Scotland, with a population of three million, there are 370 known MD patients. However, only 70 were seen in the Glasgow neurogenetic clinic last year, suggesting that resources do not meet need. Patients now hold Care Cards, which contain protocols for care, and advice and contact numbers for further information. These help to educate the patient, relatives, public and doctors, and they are downloadable from www.gla.ac.uk/muscle.

THE MARION BM LINDSAY LECTURE – PARKINSON'S DISEASE

Professor Andrew Lees, The National Hospital for Neurology and Neurosurgery, London

Parkinson's disease, 'people with Parkinson's disease', or synucleinopathy? The name of the disease varies, but in spite of the expansion in knowledge about the genetics and pathophysiology of the disease, the diagnosis is a clinical one. The early diagnosis of PD is often delayed by vague symptoms (including depression), and the patient can be incredulous of this diagnosis, which does not rely on tests (although PET scans show altered fluorodopa-uptake patterns five to ten years before motor symptoms appear).

Risk factors for developing PD are shown in Table 2.

TABLE 2
Risk factors for development of Parkinson's disease.

- Age >60
- Non-smoker
- Low caffeine intake
- Reduced olfaction
- Major depression
- Decreased arm swing/blink rate
- More than one first-degree affected relative
- Anhedonia, low mood, novelty-seeking personality, mental inflexibility
- Alcoholism

Dementia occurs in PD in 20–40% of cases, and common symptoms are visual hallucinations and daytime somnolence. Visual hallucinations in PD are associated with increasing age, and can be caused or aggravated by anti-Parkinsonian medication.

Dementia with Lewy bodies is a separate diagnosis. It presents with less tremor and more myoclonus than in PD, and has a faster natural history. L-Dopa is not usually beneficial but acetylcholinesterase inhibitors may help. The consensus criteria for probable dementia with Lewy bodies are as follows:

1. Dementia with attentional changes
2. Two of: a) Fluctuating cognitive changes
   b) Visual hallucinations
   c) Motor signs of PD[21]

Initial treatment of PD includes selegiline, anticholinergics, amantadine, dopamine agonists and levodopa. Amantadine may be useful for dyskinesia in 40–50% of patients. Subcutaneous apomorphine can be used continuously to reduce dyskinesia and as a rescue mechanism to avoid 'offs'. Subthalamic stimulation may be useful but is associated with depression and behavioural disturbance.

Falls are nine times more frequent in patients with PD compared to age-matched normal controls.[22] The risk of falling is thought to be related to turning, symptom severity, fear and anxiety of falling and concomitant use of benzodiazepines (the latter of which increases the risk five-fold), by mechanisms that are not fully understood. Physiotherapy can be beneficial.

The first genetic mutation to be described in PD was in α-synuclein, on chromosome 4. This genetic form of PD is inherited in an autosomal dominant fashion with incomplete penetrance in Greek and American-Italian families. The α-synuclein protein is thought to be involved in synaptic modification. In this form of PD there is accumulation of α-synuclein in the Lewy bodies, but even in sporadic PD, these are full of synuclein and ubiquitin. Older Drosophila flies, transgenic for α-synuclein, have difficulty climbing poles compared to wild-type flies, and are thought to represent a model of the disease.[23]

There are now three more genes with mutations and four loci described in PD families (Park 1–8). One of these genes, Parkin, is not associated with Lewy bodies in the brain. On the University of Pennsylvania smell test, patients with Parkin mutations had normal smell, but those with no Parkin mutations but PD had abnormal smell. This is proposed as a test to direct investigation for Parkin mutations.

Patients with subclinical or prodromal PD may in the future be identified earlier, due to heightened awareness,

better investigations and gene testing.

SESSION 3

CONTINUING PROFESSIONAL DEVELOPMENT FOR NEUROLOGISTS

Chairman: Dr Colin Mumford, Consultant Neurologist, Western General Hospital, Edinburgh

Neurology on the internet – the revolution will be televised

Dr R Al-Shahi, Western General Hospital, Edinburgh

The internet has been criticised as unsafe, unstructured and uncontrollable. However, as it is increasingly integrated into our everyday lives, it becomes more useful and reliable.

The origins of the internet (as a communications system and information resource) lie in the Cold War. It relies on the concept of a distributed network, whereby if one point is 'knocked out' it can be bypassed using a series of surrounding connections. The main data storage is on a number of 'super-computers' called servers, distributed around the world, linked digitally with optical communication cables.

Use of the internet relies on access to the necessary information, using a browser programme (Internet Explorer, Netscape Navigator) and a search engine (Google, Yahoo, Alta Vista). Search engines use customised directories or index lists to locate web pages, which are compiled using software which trawls the internet at all times. Google is the largest engine, with more than three billion web pages indexed to date. Some useful websites are listed in Table 3.

TABLE 3
Useful websites for the neurologist.

Knowledge bases
- National Electronic Library for Health (www.nelh.nhs.uk) – access to electronic forms of the BNF, Cochrane databases, Medline, Evidence Based Medicine, and general news and information.
- Neurosciences on the Internet (www.neuroguide.com) – up-to-date information on neuroscientific issues.

Textbooks
- eMedicine (www.emedicine.com) – a comprehensive general textbook (mainly American authors) on all aspects of medicine.

Professional websites
- Doctors.net (www.doctors.net.uk) – e-mail, library, discussion forums, Medline, shopping.
- ABN (www.theabn.org) – website of the Association of British Neurologists, with contact details, lists of meetings etc.

Patient information
- Brain and Spine Foundation (www.brainandspine.org.uk)
- Neurological Alliance (www.neurologicalalliance.org.uk)
- Patient.co.uk (www.patient.co.uk)

How not to misinterpret the data – evaluation of clinical trials in neurology

Dr C Counsell, University of Aberdeen

Randomised controlled trials are a key component of evidence-based medicine (becoming accepted as the gold standard for clinical practice), and they influence future research agendas, so it is important that we know how to evaluate them. To do this we need to know that:

1. The results are real
2. The results are clinically meaningful
3. The results are sufficient to change clinical practice

A significance of $p \leq 0{\cdot}05$ is generally taken as implying statistical significance (i.e. 'real'), but it means that there is only a 1:20 (or smaller) chance that the result is a false positive. Extreme results in small trials should be assessed in their clinical context, and ideally only after inclusion in meta-analysis.

Bias can affect results, and takes many forms:

1. Selection bias is removed by proper randomisation.
2. Co-intervention bias is negated by the use of placebo.
3. Attrition bias is factored out by minimising trial losses wherever possible, and by using an intention to treat approach (with last outcome carried forward) in the analysis.
4. Assessment bias can be removed with adequate blinding to randomisation.
5. Reporting bias is dealt with by identifying pre-defined outcome criteria.
6. Publication bias can be partly addressed by putting published results in clinical context, but there are still a considerable number of unpublished negative studies. This could be overcome by creating a compulsory register of clinical trials.

To know whether the observed effect is clinically meaningful, it is necessary to have an understanding of the outcome criteria. Is a pathophysiological change truly an effect, or a surrogate marker? Is a distinction made between disability (the actual physical impairment), handicap (the functional impairment) or quality of life (how the patient is affected)? How do all of these correlate to the expectations of patients? Whereas none of the measurements are more valid than another, they do mean different things, and an effect observed on one does not always directly correlate with an effect on another, or infer reliability or sensitivity to meaningful change.

For the results to be sufficient to change clinical practice, the evidence must be of high quality, generalisable, and the size of the evidence base must be relative to the frequency of the condition.

SESSION 4

DEBATE: 'PATIENT CONSENT IS ALWAYS REQUIRED BEFORE PATIENTS TAKE PART IN OBSERVATIONAL STUDIES AND RANDOMISED CONTROLLED TRIALS'

Chairman: The Right Reverend Richard Holloway, Edinburgh

FOR

Dr Andrew Fraser, Scottish Executive Health Department (Deputising for two speakers who were unable to attend due to ill-health)

Dr Fraser argued that the autonomy of the patient should be taken seriously, and each patient should be allowed the discretion to decide. He advocated justice for patients and felt that the medical profession was in a privileged position, should maintain a position of trust, and avoid being seen to misuse data. To accept the motion would be 'too high a price for the patients to pay'. However, consent in incapable patients is difficult and he agreed that implicit consent may be necessary, as long as the public as a whole were educated about the issues.

AGAINST

Professor Charles Warlow, Western General Hospital, Edinburgh; Dr Angus Nicholl, Communicable Disease Surveillance, London

Dr Nicholl argued that it is essential to pass on information to those responsible for public health issues without consent, to protect the public, promote health and prevent death. He cited the example of typing of Salmonella strains in enteritis and dissemination of the information without consent, as a population health issue.

Professor Warlow argued that RCTs are essential to genuinely compare groups, and therefore to determine best treatment. Informed consent may be impossible due to incapacity of the patient. The Adults with Incapacity Act in Scotland allows routine treatment but no other treatment until legal proxy consent is given which has eliminated research in incapacitated patients (e.g. in status epilepticus or cardiac arrest). In the US (under strict guidelines) approved research can be carried out in emergency situations on incapacitated patients.

The motion was put to vote before the debate with 41% for the motion and 59% against. After the debate, the vote was repeated with a swing away from the motion, with 26% for the motion and 74% against.

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