



Proceedings of the Association of British Neurologists Autumn Meeting, 22–24th September 2004

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ABN abstracts

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ABN Medal Award 2004

David Stevens

The ABN Medal was established in 1996 and in the past has been awarded to such neurological giants as PK Thomas, John Walton, Ian McDonald, and John Newsom-Davis, so why is it being presented to David Stevens—a jobbing neurologist from the West Country? The answer is simple: it is because he is a unique, multi-talented neurologist who has given outstanding service and made a number of seminal contributions to our Association.

David trained at the neurological feet of Bryan Matthews, Hugh Garland, and Maurice Parsonage before taking up his appointment as consultant neurologist at the Gloucester Royal Infirmary in 1973. There, as a single-handed neurologist, he provided a neurological service for a population of 522 000, reported all the electroencephalograms and evoked response studies, carried out the electromyographic and nerve conduction studies for the county, and he was also the consultant in charge of Ermin House—a unit for the younger physically handicapped. This heavy clinical workload was not carried out with two SHOs, a registrar and a senior registrar, but with a single SHO who was on a medical rotation. His first registrar arrived in 1991 and he was joined by a second neurological colleague in 1994, 21 years after taking up his appointment. David has an infectious enthusiasm for clinical neurology. He loves not only teasing out the diagnosis but also caring for his patients with chronic neurological disorders. He is a meticulous observer of the old school, but he is always ready and prepared to use the latest advances in neurological investigation. He is also, I suspect, the only neurologist who has a record of every outpatient, inpatient, ward consultation, and domiciliary that he has seen.

Despite his exceptionally heavy clinical workload he maintained a continuing interest in teaching and research, and also took on numerous administrative activities at local, regional, national, and international levels. His MD thesis was on Huntington's disease—a disorder on which he has written extensively. He was a member of the World Federation of Neurology's research group on Huntington's disease for many years. He organised their Ninth International Conference and was their Secretary General for eight years. He has also written papers on a wide variety of topics, including the first description of CADASIL, which he presented to this Association in 1976, and it is of interest that he was a coauthor of a paper with Carleton Gajdusec—a Nobel Prize winner. He has contributed chapters to a number of books, including five to the *Handbook of Clinical Neurology*, as well as serving on the editorial boards of the *British Journal of Hospital Medicine* and the *Journal of Neurological Sciences*.

David has lectured widely throughout the world, from Kyoto to Vancouver as well as at the Royal Colleges of London and Edinburgh, and in 1996 he was invited to give the Sydney Watson Smith lecture at the Royal College of Physicians in Edinburgh. In 1997 he was invited to become the President of the Advanced Course in Neurology in Lille, and in 1998 he was awarded the Faculté de Médecine Medal for his services to the postgraduate education in neurology in France.

David's administrative activities are too numerous to document, but in our Association he was a member of the Services Committee during which time he was author or coauthor of four important discussion documents. In 1997 he became treasurer of the Association, Chairman of the Finance Committee, and a member of both the International and the Local Organising Committees for the very successful 17th World Congress of Neurology, which was held in London in 2001.

This of course tells you little about David Stevens the person. Although now an old age pensioner, I can assure you that he is only old on the outside. He is still as articulate, artistic, imaginative, innovative, and enthusiastic as ever, particularly if there are gadgets involved.

He has an infectious and at times wicked sense of humour, though on a rather sad note I have to report that he was turned down for a walk-on part in the sequel to the film Bridget Jones' Diary, which was being filmed earlier this year in Lech—a part carried out by his wife with distinction and panache. Needless to say, Ute has given him considerable support over the years. David now rightly takes his place with the other ABN medallists and he has demonstrated what can be achieved from a District General Hospital. He has done what he wanted to do, he has enjoyed it, and he has made the most of every opportunity. The ABN owes him much and has been fortunate to have him as such an active member, but the people who have been most fortunate are his patients and those of us who have benefited from his warm friendship.

D C Thrush
23 September 2004

001 A CASE CONTROL STUDY INVESTIGATING DIETARY RISK FACTORS FOR VARIANT CJD

C. A. Heath, S. A. Cooper, K. Murray, D. Everington, B. Smith-Bathgate, M. Leitch, P. Smith, S. N. Cousens, R. S. G. Knight, R. G. Will, H. J. T. Ward. *National CJD Surveillance Unit, Edinburgh*

Background: In 1996, variant CJD, a disease with a novel clinicopathological phenotype was recognised. Subsequent research has established a causal relationship between BSE and variant CJD. The most likely route of transmission of the BSE agent is through oral ingestion of "infected meat" products. However, to date, epidemiological evidence of dietary transmission is lacking.

Methods: Active surveillance of variant CJD in the UK has been ongoing since 1996. Definite and probable cases were recruited into a case control study. Controls were recruited from a community setting. A close relative was interviewed using a standard semi-structured questionnaire and detailed dietary history was obtained. Cases and controls were frequency matched for both age and gender.

Results: 136 cases of variant CJD and 924 controls were recruited. There was a significant association between the risk of variant CJD and consumption of mechanically recovered products, including sausages, burgers, and meat pies (test for trend, $p < 0.01$, $p < 0.001$, and $p < 0.001$, respectively).

Conclusion: These results support the hypothesis that dietary exposure to BSE may have resulted in transmission to humans. However, recall and selection bias prevent definitive conclusions from being reached.

002 BELL'S PALSY: A STUDY OF THE TREATMENT ADVICE GIVEN BY NEUROLOGISTS

M. Shaw, I. Bone, F. Nazir. *Glasgow Southern General Hospital, Glasgow*

Background: Recent Cochrane reviews have noted the lack of evidence for the use of steroids and acyclovir in the treatment of Bell's palsy.

Objective: To study the treatment advice given by neurologists.

Methods: A questionnaire was emailed to all consultant neurologists and specialist registrars in Scotland.

Results: 5% of neurologists would see the patient. 76% of neurologists would advise steroids within 24 hours decreasing to 28% at 7 days. 20% would advise acyclovir. Consultants and registrars gave similar advice, although 42% of consultants would prescribe steroids up to 7 days compared with 6% of registrars (Fisher's exact $p = 0.009$). 95% of Glasgow neurologists advised steroids within 24 hours as compared with 42% of Edinburgh neurologists ($p = 0.002$).

Conclusions: The uncertainty regarding the treatment of Bell's palsy was reflected in the results of our questionnaires and in the comments made

by neurologists. A Scotland based trial comparing four treatment arms (comprising steroids, acyclovir, and placebo) is starting later this year and may address the need for a well conducted randomised controlled trial.

003 CLINICAL IMPROVEMENT FOLLOWING BILATERAL GLOBUS PALLIDUS INTERNA DEEP BRAIN STIMULATION FOR GENERALISED DYSTONIA

S. Tisch, P. Limousin, N. Quinn, K. Bhatia, M. Hariz. *Institute of Neurology, Sobell Department of Motor Neuroscience and Movement Disorders, National Hospital for Neurology and Neurosurgery, Queen Square, London*

Chronic high frequency stimulation of globus pallidus interna has emerged as an effective treatment for dystonia. We report our experience in a consecutive series of 14 patients with generalised dystonia (eight female, six DYT1+, five idiopathic and three secondary; mean age 37 years, range 17–63). All patients improved following surgery. Initial improvement occurred on average 3.9 days (range 1–7) after commencement of stimulation with mobile dystonia showing the earliest improvement. The mean Burke-Fahn-Marsden (BFM) movement score was 50 pre-operatively and decreased to 31 (n = 14) 1 month after surgery, with a 38% improvement. By 3 months there was a 45% improvement (n = 13) and by 6 months 55% (n = 6). At 3 months the greatest improvement occurred in DYT1+ patients (71%), followed by idiopathic (57%) and secondary (20%) patients. In four patients (three DYT1+, one idiopathic), all with axial flexor spasms triggered by walking, almost 90–100% improvement has occurred, suggesting that this pattern is particularly amenable to DBS. Stimulation in all patients is monopolar with an average current of 47 micro amps (range 28–85), suggesting that moderate currents are effective.

Pallidal DBS is an effective treatment for generalised dystonia in adults, including idiopathic cases, which respond almost as well as DYT1+ cases. Secondary generalised dystonia responds less well but DBS may improve function and comfort in these severely affected patients.

004 PROGRESSIVE DETERIORATION IN QUALITY OF LIFE OF PARKINSON'S DISEASE PATIENTS LEFT UNTREATED IN COMPARISON TO THOSE RECEIVING MONOTHERAPY: RESULTS FROM PDLIFE, A MULTI-CENTRE PROSPECTIVE STUDY ACROSS THE UK

K. Ray Chaudhuri, L. Taurah, D. MacMahon, D. Grosset, D. Burn, L. Kelly, L. Findley, K. Turner, A. Forbes, A. Bowron, K. Patel, O. J. Foster, and members of the UK PDLIFE committee. *Kings College and University Hospital Lewisham, London; Royal Cornwall NHS Trust; Southern General Hospital, Glasgow; Newcastle General Hospital; Essex Neurosciences Centre, Romford; St Georges Hospital, London; The Parkinson's Disease Society of the UK; Havering PCT & South Bank University; Staffordshire NHS Trust, Staffs; Northumbria Healthcare NHS Trust*

Background: Starting treatment in Parkinson's disease (PD) is often based on clinician discretion and in early PD, treatment may be delayed. The effect of this strategy on the quality of life (QoL) is unknown.

Aims: Serially assess the changes in overall QoL in untreated (drug naïve) PD persons (DNPD) and those on monotherapy (MTPD). To our knowledge this is the first study addressing this issue.

Methods: Demographic, drug histories and QoL (using PDQ 39 scale) in DNPD and those on monotherapy since 2002.

Results: 304 PD (mean age 66.3 years; Hoehn and Yahr score 1.74; mean duration of PD 4 years) have been assessed. 36 DNPD remain untreated after first consult (at 10.5 months) with significant deterioration in overall QoL ($p < 0.01$) while 91 MTPD on monotherapy had stable QoL ($p > 0.05$). At second follow up (mean period of 18.5 months), in 10 remaining DNPD there was a further significant deterioration in overall QoL ($p < 0.05$).

Conclusions: Approximately 11.5% of patients with PD referred to specialist clinics are not given treatment based on clinician/patient decision. The QoL of these patients deteriorate significantly if left untreated. This data questions the merits of a "watch and wait strategy" for treating PD.

005 AN ATYPICAL TETRA NUCLEOTIDE EXPANSION IN DM2 (PROMM)

J. Ealing, L. A. Mavrogiannis, H. Kingston, D. J. Cockburn, G. R. Taylor, C. Moore, M. Roberts. *Greater Manchester Centre for Neurosciences, Hope Hospital, Salford; Dept Neurogenetics, St Mary's Hospital, Manchester; Yorkshire Regional DNA Laboratory, St James's Hospital, Leeds*

Clinical and molecular data define at least two types of myotonic dystrophy. DM2, caused by CCTG expansions in the ZNF9 gene and often presenting clinically as PROMM, is distinct from DM1. We report a patient with manifestations compatible with DM2 and an unusual DM2 expansion.

A 38 year old female presented with a recent history of fluctuating proximal muscle weakness and myalgia, with a past history of paroxysmal atrial fibrillation. Examination revealed mild quadriceps wasting and weakness, without clinical myotonia; CK ranged from 300–3000; EMG showed spontaneous myotonic discharges in the right vastus, and myopathic features in both quadriceps muscles. No cataracts were seen, and brain MRI scan, echocardiogram, and lung function tests were all normal. Muscle biopsy revealed an increased number of central nuclei, but no inflammation. The patient's mother's EMG showed myotonic discharges, and two brothers suffer from muscular aches and symptomatic myotonia. DM1 was excluded and standard DM2 testing failed to detect an expansion. However, non-inheritance of the normal maternal DM2 allele indicated an expansion, which was found to be of atypical, non-pure CCTG composition.

This case indicates that the DM2 mutation spectrum might not be homogeneous, uncovers sensitivity limitations in current molecular testing, and has implications for DM pathophysiology.

006 THE ROLE OF ASSESSMENT IN THE PROFESSIONAL DEVELOPMENT OF NEUROLOGY TRAINEES

A. J. Wills. *Queen's Medical Centre, Nottingham*

The European Working Time Directive and similar legislation in the USA, have led to concerns that the consequent reduction in trainees' hours of work will have a negative impact on postgraduate medical training. It has been proposed that various curricular alterations are necessary to equip trainees for self-directed and more efficient learning.

There is a strong lobby urging the introduction of summative procedures, including an exit examination, prior to entry to the consultant grade. The public demands reassurance that robust mechanisms are in place, which can consistently identify poorly performing doctors. Meanwhile, there is intense political pressure (in the UK at least) to further shorten the duration of postgraduate training so that pledges vis a vis consultant numbers can be met. How these conflicting demands can be reconciled is a major challenge for the future.

Additional assessment procedures such as the "mini-CEX", "DOPS", and 360 degree method should be piloted forthwith; coupled with locally based multiple response questions and OSCEs.

To successfully introduce these changes trainees and trainers will need to work in partnership. Course evaluation and student feedback should be formalised and overseen by committees structured around consensus and predicated on minimum educational qualifications combined with competitive interviews for places.

007 THE SIGNIFICANCE OF SENSORY SYMPTOMS IN PATIENTS PRESENTING TO A SPECIALIST CEREBROVASCULAR CLINIC

R. S. Nicholas, R. P. White, T. P. Enevoldson, P. R. Humphrey. *Walton Centre for Neurology & Neurosurgery, Liverpool*

Background: The diagnosis of a vascular event (VE) is based on clinical assessment subject to intra- and inter-observer disagreement. The subjective nature of sensory symptoms presents additional difficulty.

Objectives: To quantify the incidence and relationship of sensory symptoms to the diagnosis of VE and >70% significant internal carotid stenosis (SCS).

Methods: New patients prospectively assessed over 1 year in a vascular clinic.

Results: In 421 patients, 209 VEs were diagnosed—70 as possible VEs and 142 as not VEs. Sensory symptoms were present in 40.1% of all patients and in 37.7% of VEs. Sensorimotor symptoms accounted for 25.8% of VEs and sensory symptoms alone for 11.9% of VEs. SCS incidence was 17.4% in the population rising to 29.3% in physician-diagnosed anterior circulation events. SCS incidence increased from 25.6% to 34.6% with sensori-motor symptoms and from 9% to 31.3% with sensory symptoms alone. Numbness was the commonest word used by patients; no words used were associated with a rise in SCS.

Conclusions: Sensory symptoms commonly lead to the diagnosis of VE with similar frequency of SCS as in other anterior VEs. The precise words used to describe sensory symptoms were unhelpful. A detailed history helps identify those more likely to have SCS.

008 MUTATIONS IN PKC GAMMA IN A UK FAMILY WITH SPINOCEREBELLAR ATAXIA

K. Talbot, G. Doran, A. Nemeth, P. Oliver, P. James. *Departments Clinical Neurology & Human Anatomy and Genetics, University of Oxford, Oxford*

There are now 26 assigned genetic loci and nine identified genes, five of which contain expanded polyglutamine repeats. However, in as many as 50% of patients with inherited ataxia a molecular diagnosis cannot be made in a clinical setting.

We have identified a large UK family with pure autosomal dominant cerebellar ataxia (ADCA III) presenting with slowly progressive gait and limb ataxia, dysarthria, and minor visual disturbance with an age of onset from 20–50 years. DNA was collected from 30 individuals over four generations, 19 of whom were affected. After exclusion of mutations in the genes for SCA1,2,3,6,7, selected markers from the ABI PRISM version 2.5 linkage-mapping set were used to investigate known loci. Multipoint analysis produced a LOD score of 3.23 at D19S571, a region coinciding with the previously identified SCA 14 locus. Sequencing of the gene for Protein Kinase C gamma identified a C→G transition at nucleotide 303 that leads to a H101Q amino acid substitution in protein sequence in all affected individuals.

This is the fourth family described in the world with mutations in PKC γ and the first from the UK. We found two individuals carrying the mutation but not manifesting ataxia, suggesting that this disorder is not fully penetrant.

009 TYPICAL CORTICAL LESIONS IN AN ANIMAL MODEL OF MS

I. M. Pomeroy, M. M. Esiri, P. M. Matthews, J. Palace. *Department of Clinical Neurology, University of Oxford, Oxford*

Introduction: Recent work using immunohistochemical methods has highlighted that cortical lesions are common in multiple sclerosis (MS). These lesions are poorly detected by magnetic resonance imaging (MRI) and thus further studies are limited by their requirement for post mortem tissue. The use of an animal model may overcome these limitations but cortical lesions have not previously been described in a model of MS. The work presented here forms part of a research project, which aims to investigate the prevalence, content, and significance of cortical lesions in marmoset experimental allergic encephalomyelitis (EAE).

Methods: EAE was induced by injecting six marmosets with 100 μ g of myelin oligodendrocyte glycoprotein in adjuvant with bordatella pertussis vaccine. 26–70 days post EAE induction, brains were fixed in formalin and set in paraffin blocks. Sections were stained using antibodies to myelin.

Results: 2/14 blocks per animal were selected for examination. A total of 45 demyelinating cortical lesions were identified representing all three morphological subtypes previously described in MS: leucocortical, intracortical, and subpial. No lesions were present in four controls.

Conclusions: This study demonstrates that typical MS-like cortical lesions are found in this model. This tool is now being exploited to further study the aetiology, development, and clinical significance of cortical lesions in MS.

010 SYNAPTIC LOSS AND IMPAIRED SYNAPTIC PLASTICITY IN CORTICAL LESIONS OF MULTIPLE SCLEROSIS

C. Wegner, M. M. Esiri, J. Palace, P. M. Matthews. *University of Oxford, Oxford*

The significance of cortical lesions (CL) in multiple sclerosis (MS) is unclear. The aim of this histological study was to investigate CL in MS and their effect on synapses.

Brain tissue was obtained from 10 MS patients. 30 blocks were removed from predefined areas and 29 blocks were selected for the visible presence of subcortical white matter (WM) lesions. Synaptophysin and growth associated protein-43 (GAP-43, synaptic remodelling marker) were measured quantitatively by immunautoradiography.

Fifty-seven CL were detected on sections stained for myelin from 59 blocks. The majority of CL were leucocortical-type I lesions (49%). Intracortical-type II CL (16%) and subpial-type III CL (35%) accounted for the remainder. Of the 30 samples from defined regions, 14 contained 39% of all CL (n=21), (38% leucocortical-type I CL, 14% intracortical-type II, 48% subpial-type III). Of those, 66% type II CL and 60% type III CL did not show nearby WM changes. Synaptophysin and GAP-43 were significantly reduced in CL (only measurable for type I) compared to non-lesion cortex.

We confirm that CL are common in MS, particularly subpial or leucocortical CL. Synaptic loss and impaired synaptic plasticity is also associated. Such consequences are likely to contribute to clinical expression of the disease.

011 SODIUM CHANNELS CONTRIBUTE TO MICROGLIA/MACROPHAGE ACTIVATION AND FUNCTION IN EAE AND MS

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Objective: To examine the novel hypothesis that sodium channels contribute to activation of microglia and macrophages in EAE and MS lesions.

Methods: Utilising immunohistochemistry and in situ hybridisation we examined the expression of sodium channels and their relationship to microglia/macrophage activation in EAE and MS lesions. To further delineate the role of sodium channels in microglial activation we examined the phagocytic capacity of cultured rat and med mice microglia following sodium channel blockade by tetrodotoxin.

Results: We demonstrate a robust increase of sodium channel Nav1.6 expression in activated microglia and macrophages in EAE and MS. We further demonstrate that phenytoin treatment, a sodium channel blocker, ameliorates the inflammatory cell infiltrate in EAE by 75%. We show that tetrodotoxin, a specific sodium channel blocker, reduces the phagocytic function of activated rat microglia by 40%. To confirm a role of Nav1.6 in microglial activation, we examined phagocytic capacity of microglia from med mice, which lack Nav1.6 channels, and show a 65% reduction in phagocytic capacity compared to wildtype mice microglia.

Conclusion: Our in vivo and in vitro results indicate that sodium channels play a role in microglia/macrophage activation and sodium channel blockade may interfere with inflammatory mechanisms in EAE and MS.

012 WE ARE JUDGED BY OUR PEERS—BUT WHO ARE THEY?

W. F. Durward. *Institute of Neurological Sciences, Southern General Hospital, Glasgow*

“Yes, you have ravish’d justice;
Forced her to do your pleasure”.

John Webster (1580–1625), *The White Devil* (1612), Ill.i.271–272

We have job titles, job descriptions and job plans. In medicolegal work peer groups have conventionally been identified by job title rather than by job description. Expert witness evidence may be discredited by claiming that the source is inappropriate rather than the content. The author has been informed in the witness box that he is not competent to comment about (criticise) performance of others practising neurology because of non-congruent job titles.

The author’s experience in giving evidence at two fatal accident inquiries (Scotland) will be described, with comment about need to recognise expert witnesses by job description rather than by job title. The conflict of interest that arises when expert witnesses and those subject to adverse comment have membership of the same medical defence organisation will be discussed.

013 IMPACT OF CYBERMEDICINE IN THE NEUROLOGY OUTPATIENT CLINIC

A. J. Larner. *Walton Centre for Neurology & Neurosurgery, Liverpool*

Objective/Methods: To report internet use for medical information by consecutive new referrals prior to consultation with a neurologist.

Setting: Outpatient clinics at two district general hospitals in north-west England, surveyed in first quarter of 2001–2004 inclusive.

Results: Of 854 patients seen, 335 (39% of total) had home internet access and 92 (11%) had searched for medical information; only five volunteered this before questioning. 37 (4%) had accessed information judged inappropriate to their final neurological diagnosis. Analysis of data by age and sex showed the highest proportional use was in the 31–40 year age group (18%), and greater proportional use by men than women (31% v 25% of those with access).

Discussion: In this study, around one in 10 neurology outpatients had accessed “cybermedicine” prior to consultation but very few volunteered

information thus found. 40% had accessed material or reached conclusions inappropriate to their eventual diagnosis.

Conclusion: Although the internet has many potential benefits for "e-patients" with established neurological diagnoses, searches undertaken prior to consultation may frequently be liable to error. Since these may shape health beliefs and expectations, inquiry for these searches might improve patient satisfaction with consultation.

014 GLUTEN NEUROPATHY: CLINICAL, EPIDEMIOLOGICAL, AND NEUROPHYSIOLOGICAL CHARACTERISTICS, AND THE EFFECT OF GLUTEN FREE DIET

M. Hadjivassiliou, R. Kandler, R. Grünwald, J. Jarratt, A. Chattopadhyay, B. Sharrack, D. S. Sanders, G. A. B. Davies-Jones. *Departments of Neurology, Neurophysiology and Gastroenterology, The Royal Hallamshire Hospital, Sheffield Teaching Hospitals NHS Trust*

Ataxia and neuropathy are the commonest neurological manifestations of gluten sensitivity. We investigated the prevalence of gluten sensitivity in patients with axonal neuropathies and the effect of gluten free diet in those with gluten neuropathy.

215 patients with axonal neuropathy were screened (141 symmetrical sensorimotor neuropathy, 47 mononeuropathy multiplex, 17 motor, and 10 small fibre). The aetiology was established in 123/215 (57%). Antigliadin antibodies were found in 56/215 (26%) of all, or 56/148 (38%) of the idiopathic neuropathies (12% prevalence of antigliadin antibodies in 1200 healthy controls). Other causes included DM 22/215 (10%), connective tissue disease/vasculitis 17/215 (8%), paraneoplasia 9/215 (4%), and B12 deficiency 9/215 (4%). MGUS, alcohol, drug related, and hypothyroidism accounted for 6 (3%), 4 (2%), 3 (1%), and 3 (1%), respectively. The clinical characteristics of gluten neuropathy (100 patients) include a mean age at onset of 55 years (range 24–77), mean duration nine years (range 1–33), and evidence of enteropathy in 26/89 (29%) of patients who underwent duodenal biopsy. The HLA types associated with coeliac disease were seen in 80%.

Neurophysiological evidence of improvement was apparent in 12 patients adhering to a strict gluten-free diet when compared to five patients off diet over one year.

015 ABN HISTORY: KATHLEEN CHEVASSUT AND THE "GERM" OF MULTIPLE SCLEROSIS

S. Casper, M. O'Brien. *Wellcome Trust Centre for the History of Medicine, University College London, London*

The story of Kathleen Chevassut (1897–1983) and "germ" of multiple sclerosis has been infrequently told (Compston, 1998; Thomson, 1987). These sources rightly tell the tale of a woman sponsored (1928–1932) by the MRC to examine the CSF of patients with disseminated sclerosis. Using new ultraviolet microscopy methods, Chevassut searched CSF cultures for a causative micro-organism, and in 1930 published "The Aetiology of Disseminated Sclerosis" in the *Lancet*. Rumours soon suggested she had faked her data. Her efforts to defend herself (widely seen as contumacy) incurred animosity. Yet historical evidence indicates that much of the derision towards Chevassut was actually aimed at the physician Sir James Purves Stewart. Purves Stewart had used Chevassut's cultures (without either her consent or the approval of the MRC) to generate a vaccine. In an era with few guidelines for the treatment of patients, and with no standardised protocols for controlling experiments, the ethics of Chevassut's and Purves Stewart's experiments are difficult to judge. That both were subsequently vilified cannot be doubted. Yet, Chevassut's role as a woman in science reminds us of their difficulties in this period.

Another unappreciated aspect of the Chevassut story is its role in British neurological specialisation. Indeed, evidence in Edwin Bramwell's diaries, indicates that it was one reason for the founding of the ABN.

016 IDENTIFYING AND CLASSIFYING A SEIZURE CLINICALLY: HOW ACCURATE ARE WE?

R. Renganathan, C. Monks, B. McNamara. *Cork University Hospital, Cork, Ireland*

Background: The International Classification of Seizures classifies seizures into partial seizures and generalised seizures.

Objective: Our objective was to assess the clinical ability of health professionals involved in the management of patients with seizures to accurately identify and classify a seizure.

Methods: A neurophysiologist reviewed 10 events from telemetry recordings. These were shown to groups of health professionals who were asked to identify and classify each event.

Results: 50 individuals participated. Neurophysiology technicians, consultant neurologists, neurology registrars, and nurses were more than 85% diagnostically accurate in identifying an epileptic seizure; medical students, senior house officers, interns, and general practice trainees had a diagnostic accuracy of 60–80%. Similar results were seen in classifying the seizure. There was a significant difference in proportion of correct answers among professionals with at least 6 months experience in neurology compared to those without a similar duration of experience. Absence seizure was the most easily identified seizure. Older terms like "petit mal", "grand mal" and "Jacksonian seizure" were used.

Conclusion: Although the study had a sample size, it shows that exposure in neurology plays a part in accurate diagnosis and classification of epileptic seizures. We plan to develop a teaching tool on identifying and classifying seizures.

017 FIRST SEIZURE CLINICS: OPPORTUNITIES AND IMPLICATIONS

J. P. Leach, R. Mohanraj, A. Mallik, R. Duncan, J. Greene. *Department of Neurology, Southern General Hospital, Glasgow; Epilepsy Unit, Western Infirmary, Glasgow*

Rationale: Misdiagnosis of epilepsy is an important long-term health issue. Prevention may be best done by providing rapid access "First Seizure Clinics". One such clinic was started in Glasgow in 2003; this paper examines the workload implications, diagnostic yield, benefits, and challenges of such a set up.

Results: The first 500 patients will be presented. All were reviewed at least once by the same consultant neurologist (JPL). Standard investigation protocols were followed.

Waiting times have remained encouragingly low: 85% of patients are given an appointment for less than 2 weeks following receipt of the referral. 24% of all referrals had an ictal cause for their initial presentation. Syncope was the initial diagnosis in 25%.

Assessment of patients elicited a history of other previously undiagnosed events in 17% of referrals. This allowed a proper assessment of the risk of recurrence for these individuals. Of 65 patients commenced on antiepileptic drug (AED) treatment by referring physicians, 81% required immediate change.

Conclusions: Rapid access first seizure clinics are a valuable resource for physicians from primary and secondary care. Such a service allows accurate diagnosis of the cause of first episode of loss of consciousness, which reduces inappropriate AED use and unnecessary restriction for non-ictal blackouts.

018 FACTORS MODIFYING PHENOTYPE IN CADASIL (CEREBRAL AUTOSOMAL DOMINANT ARTERIOPATHY, SUBCORTICAL INFARCTS AND LEUKOENCEPHALOPATHY)

S. Singhal, S. Bevan, T. Barrick, P. Rich, H. Markus. *St George's Hospital Medical School, London*

Background: CADASIL is an autosomal dominant cause of recurrent stroke, migraine, and presenile dementia due to notch3 mutations. It is now realised there is marked phenotypic heterogeneity. Factors determining genotype could include notch3 mutation site, modulating genes, or environmental factors.

Method: 127 CADASIL subjects from 65 families were prospectively recruited through a British prevalence study. All but one family showed a typical notch3 mutation, the remaining family being diagnosed on skin biopsy. Phenotype was assessed clinically (by presence and age of onset of major disease features), and by MRI lesion load. The site (amino acid position) of notch3 mutations and presence or absence of an apoE4 allele were recorded. Risk factors recorded were hypertension, cholesterol, smoking, diabetes, and homocysteine.

Results: No relationships between notch3 or apoE genotypes and either clinical outcome or radiological lesion load were identified. Current smoking at time of TIA/stroke was associated with earlier age of onset of TIA/stroke on Cox regression (hazards ratio (HR): 2.1 (1.3–3.6) per year, $p=0.004$). Homocysteine level was associated with age of onset of migraine on Cox regression (HR: 2.7 (1.4–5.3) per unit, $p=0.005$).

Conclusions: Neither notch3 nor apoE genotype appear to modulate CADASIL phenotype or extent of radiological brain damage. Smoking may hasten onset of ischaemic events. Elevated homocysteine is associated with an increased risk of migraine.

019 EFFECTS OF BLOOD PRESSURE (BP) REDUCTION AND OF CHOLESTEROL REDUCTION ON DIFFERENT PATHOLOGICAL TYPES AND ISCHAEMIC SUBTYPES OF STROKE: A SYSTEMATIC REVIEW OF RANDOMISED CONTROLLED TRIALS

J. Bell, A. Usher, C. L. M. Sudlow. *University of Edinburgh, Edinburgh*

Background: We performed systematic reviews of randomised controlled trials to assess whether the effects of pharmacological blood pressure (BP) reduction or cholesterol reduction with a statin varied for different pathological types and ischaemic subtypes of stroke.

Methods: We identified trials with a comprehensive search strategy and sought sub-group analyses of the effects of treatment on different pathological types and ischaemic subtypes of stroke.

Results: There were 12 trials (64 000 subjects) of BP reduction. Three (20 000 subjects) published effects of treatment on different pathological types of stroke and two (11 000 subjects) published effects on different ischaemic subtypes. There were eight trials (71 000 subjects) of cholesterol reduction. Four (38 000 subjects) published effects on different pathological types of stroke and two (13 000 subjects) published effects on different ischaemic subtypes. BP reduction decreased overall stroke risk, with no clear differences between ischaemic and haemorrhagic stroke, or between ischaemic stroke subtypes. Cholesterol reduction had no definite effect on haemorrhagic stroke, but reduced ischaemic stroke risk, with no clear difference between ischaemic stroke subtypes.

Conclusions: Data from randomised trials suggest that the effects of BP reduction on different pathological types and ischaemic subtypes of stroke are similar, as are the effects of cholesterol reduction on different ischaemic stroke subtypes.

020 TIMELINES IN MITOCHONDRIAL DNA DISEASE: GENOTYPES, PHENOTYPES, AND DISEASE PROGRESSION

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Mitochondrial DNA disease is a common cause of chronic morbidity and mortality in neurological practice. Clinical and genetic diversity has hampered attempts to study the natural history of these disorders and little is known regarding disease progression or effective therapeutic intervention.

We have investigated 250 patients with defined mitochondrial DNA defects in an ongoing natural history study. Each patient was clinically assessed at the Newcastle Mitochondrial Centre and prospective follow up maintained. Specifically designed data record sheets were used to record progression of clinical disease and all documented investigations. Symptom progression was analysed using a total of over 11 000 years of data. Progression of biochemical, neurophysiological, and radiological markers of disease were also assessed.

Our results confirm the progressive nature of mitochondrial DNA disease. Despite the clinical and genetic heterogeneity of these disorders we show clear genotype/phenotype correlations and address the contribution of heteroplasmy to disease severity. Our data has allowed us to construct clinical timelines, which we believe may act as useful templates when addressing the issue of prognosis in a clinical setting.

021 CONFOUNDING OF HERITABILITY OF STROKE BY HYPERTENSION IN PATIENTS WITH TIA

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Background: Family history of stroke (FHxstroke) is a risk factor for ischaemic stroke and TIA. However, more data are required on the relationship between FHxstroke and clinical subtype, baseline clinical characteristics, intermediate phenotypes (IP), and outcome.

Patients and Methods: We studied FHxstroke and MI (FHxMI) in a series of 783 TIA patients from two local population-based TIA incidence studies and two prospective series of consecutive hospital-referred TIA patients. We related FHx to baseline characteristics, clinical subtype, IP, and outcome.

Results: FHxstroke was less common than FHxMI ($p=0.0008$): 193 cases (24.6%, 95% CI 21.6 to 27.7) v 253 (32.3%, 95% CI 29.0 to

35.6). FHxstroke was strongly related to hypertension in the proband ($p<0.0001$). Maximum recorded pre-morbid systolic ($p=0.05$) and diastolic ($p=0.01$) blood pressure was significantly higher in cases with FHxstroke and increased with the number of affected FDRs ($p=0.009$). There was no association between FHxstroke, age, diabetes, smoking, glucose and cholesterol, clinical subtype of TIA, or risk of stroke during follow up (2593 patient years).

Conclusions: The strong association between hypertension and FHxstroke (suggesting that familial susceptibility to cerebrovascular ischaemia is due, at least partly, to heritability of hypertension) should be taken into account in molecular genetic studies of ischaemic stroke.

022 RISKS OF DEATH AND RECURRENT VASCULAR EVENTS AFTER LACUNAR AND NON-LACUNAR ISCHAEMIC STROKE (LACI AND NON-LACI)—A SYSTEMATIC REVIEW OF FOLLOW-UP STUDIES

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Background: We compared risks of vascular events after lacunar versus non-lacunar ischaemic stroke in a systematic review.

Methods: We identified inception cohort studies of patients with different ischaemic stroke subtypes followed up for death, recurrent stroke, and/or myocardial infarction (MI). For death and recurrent stroke, we calculated odds ratios (OR) for non-lacunar v lacunar infarction at 1 month, from 1–12 months, and from 6 months to 5 years. We also extracted data on recurrent ischaemic stroke subtypes following lacunar and non-lacunar infarction.

Results: Data from seven studies (2600 patients) showed that 1 month mortality risk was over three times greater in non-lacunar than lacunar patients, but in the long term there appeared to be no difference. Only nine of 19 studies defined recurrent stroke and no two definitions were the same. Data from three studies (900 patients) showed that 1 month recurrence risk was around three times greater in non-lacunar than lacunar patients, but in the long term there appeared to be no difference. After lacunar infarction, less than half of recurrences were lacunar. Long term risk of MI after stroke has hardly been studied.

Conclusions: Existing studies of prognosis after lacunar versus non-lacunar infarction provide little support for differences in arterial pathology.

023 OCCULT AND SYMPTOMATIC SUBARACHNOID HAEMORRHAGE IN CEREBRAL AMYLOID ANGIOPATHY

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Primary subarachnoid haemorrhage (SAH) is rarely reported in cerebral amyloid angiopathy (CAA); secondary extension from intracerebral haemorrhage (ICH) is familiar. Yet CAA involves leptomeningeal vessels more frequently than cortical vessels.

Three cases are described to illustrate primary SAH in CAA. Two are occult and presented with brief stereotypical sensorimotor symptoms correlating with MR evidence of cortical superficial siderosis (CSS)—a new MR sign in CAA.

Case 1: Clinically definite CAA with primary SAH: a 58 year old with headache, dysphasia, and CT and CSF positive for blood. Angiography negative. MR evidence of leukoaraiosis but no subcortical haemorrhage. Right frontal leptomeningeal biopsy positive for CAA.

Case 2: Clinically probable CAA with occult SAH: a 72 year old with an 8 month history of multiple attacks per day, short duration (seconds to minutes) left sided sensory disturbances, presenting acutely with headache and confusion. Bi-frontal ICH on CT. Negative MRV. CSS of right sensory motor cortex on gradient echo MRI.

Case 3: Clinically possible CAA with occult SAH: a 75 year old with multiple attacks per day, short duration (seconds to minutes) left sided faciobrachial numbness over a 6 month period. CSS of right sensory cortex and clinically silent left subcortical ICH on GE MRI.

024 CONTROLLING HYPERTENSION AND HYPOTENSION IMMEDIATELY POST STROKE (CHHIPS)—ONGOING TRIAL

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Introduction: Abnormal blood pressure (BP) levels are common following acute stroke. Up to 60% of patients are hypertensive (SBP>160 mmHg)

and nearly 20% relatively hypotensive (SBP<140 mmHg), within few hours of ictus. Both conditions are associated with adverse prognosis. Presently, the acute management of these post-stroke BP changes is debatable.

Methodology: CHHIPS is a multicentre, prospective, randomised, double-blind, placebo-controlled, titrated-dose trial, which aims to recruit 2050 patients in UK Teaching/District General Hospitals, with clinically suspected stroke (confirmed by brain imaging) who have no compelling indication/contraindication for BP manipulation. Hypertensive patients (SBP>160 mmHg) will receive labetalol, lisinopril, or placebo, and relatively hypotensive patients (SBP<140 mmHg) phenylephrine or placebo.

Results: The trial will assess the effects of acute pressor and depressor BP manipulation on early (<72 hours) neurological deterioration and 2 week death and dependency, and the influence of stroke subtype and time to treatment on BP control and outcome measures.

Conclusion: There is uncertainty about the management of BP changes in acute stroke. However, the effects of acute BP manipulation on cerebral blood flow and the penumbra are unclear, as is the appropriate treatment regime. It therefore remains for the risks and benefits of BP manipulation to be clearly established.

Centres interested in participating, please email: chhips@le.ac.uk.

025 APOLOPROTEIN E GENOTYPE AND OUTCOME AFTER STROKE: A SYSTEMATIC REVIEW

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Background: We performed a systematic review of studies assessing the effect of apolipoprotein E (APOE) genotype on outcome several months after acute stroke.

Methods: We used a comprehensive search strategy to identify studies and extracted information on: patient population and pathological type(s) of stroke studied; method and duration of follow up; numbers of patients dead/dependent or dead among those with and without the APOE *4 allele.

Results: We included eight studies among 1671 patients (1182 ischaemic stroke (IS), 213 primary intracerebral haemorrhage (PICH), 276 subarachnoid haemorrhage (SAH)). Possessing an *4 allele was associated with worse outcome after SAH (OR for death/dependency with versus without an *4 allele 2.4, 95% CI 1.3 to 4.3) and a trend towards worse outcome after PICH (OR 2.6, 95% CI 0.8 to 8.4), but not after IS (OR 0.95, 95% CI 0.7 to 1.2). Results for mortality were similar.

Conclusions: These results suggest that APOE genotype may influence outcome after SAH and PICH, but not after IS. Further, large studies are required to confirm or refute these findings, and to investigate reasons for the apparent difference in effects on haemorrhagic and ischaemic stroke.

026 TIME—A STUDY OF EPILEPTIC AMNESIA

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Memory problems are common among people with epilepsy. Seizure activity, underlying brain pathology, drugs, and psychosocial factors have all been implicated. The TIME study, with the help of the BNSU, is investigating three relatively unexplored phenomena that may contribute to the impairment of memory in epilepsy:

(1) In transient epileptic amnesia (TEA) the sole or main manifestation of seizure activity is recurrent, brief amnesia. 48 patients with a suspected diagnosis of TEA have so far been referred to the study. 13/16 patients assessed meet our diagnostic criteria. Subjects undergo clinical, neuropsychological, neuropsychiatric, and radiological assessment designed to clarify features of the condition including its structural basis and aetiology.

(2) Some patients with TEA, including 7/13 so far assessed, complain of accelerated forgetting of newly acquired memories, perhaps due to interruption of memory consolidation by seizure activity. Patients and controls are trained to criterion on verbal and visual tasks; long term retention is tested at 1, 3, and 6 weeks.

(3) 10/13 patients complain of a dense but patchy impairment of remote autobiographical memory. We are using detailed neuropsychological study and neuroimaging to establish whether these deficits reflect impaired memory encoding, storage or recall and whether they result from epilepsy per se or from a common underlying pathology.

027 NON-EPILEPTIC ATTACKS AFTER SUCCESSFUL EPILEPSY SURGERY

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It is well known that a proportion of those with epilepsy will also experience non-epileptic attacks. However, new onset nonepileptic attacks may emerge for the first time after epilepsy surgery, a fact not well recognised. Such attacks have a favourable prognosis particularly if recognised early as in the case described.

K.B. an 8 year old girl presented to the paediatric neurology service with a history of partial seizures. As the patient's seizures remained intractable and an MRI scan demonstrated right hippocampal sclerosis, she was referred for epilepsy surgery. After surgery she developed twitching of either or both upper limbs along with flickering of the eyelids and complaints of double vision (video available). A 24 hour videotelemetry study was carried out during which a number of these attacks were captured. No EEG change was noted during the attacks suggesting that they were non epileptic in nature. It is recognised that non-epileptic events in children have a good prognosis. Prognosis deteriorates with age and the outcome is poor with a long history of non-epileptic events.

It was therefore of great importance to our patient that an early diagnosis was made and videotelemetry plays a vital role in allowing a prompt diagnosis to be made. Clinicians should be aware of the possibility and make use of videotelemetry where uncertainty exists.

028 COUGH SYNCOPE IN HEAVY GOODS VEHICLE LICENCE HOLDERS

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Background: Road traffic accidents (RTAs) are sometimes the result of a medical condition. Physicians have a duty to recognise illness that can have implications for driving. The following illustrates how cough syncope, a medical condition that physicians need to recognise, can have disastrous consequences for drivers.

Methods: We were involved in a medico legal case in which a heavy goods vehicle (HGV) licence holder suffered an episode of cough syncope, which resulted in a fatality of another road user. Enquiries were made to the Driving Vehicle Licence Authority (DVLA) to see if similar cases existed.

Results: Four cases of serious RTAs were discovered, three with fatalities, over the last five years, each involving a HGV licence holder. In each case the expert medical opinion diagnosed cough syncope from the driver's history. This formed the basis of each drivers defence in court. The drivers were all obese and male. Three were smokers and in two investigations revealed evidence of chronic obstructive pulmonary disease (COPD).

Conclusion: The condition of cough syncope is easily recognisable. It commonly occurs in male, middle aged, overweight, smokers. Often findings reveal COPD. The history is of brief syncope, lasting only seconds. It always precipitated by coughing or even a single cough and recovery is rapid. Cough syncope has important implications for fitness to drive. The DVLA recently updated its guidelines, in part, due to these cases. Normal licence holders should stop driving until liability to attacks has been successfully controlled. HGV licence holders may have their licence withdrawn for 10 years if there is any chronic lung condition and/or a significant history of smoking. By highlighting these cases we hope to raise awareness of cough syncope and its implications for driving.

029 DIFFUSION TENSOR IMAGING WITH LOW AND HIGH B VALUES IN EPILEPSY

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Aim: Standard MRI with T1- or T2-weighted contrast often fails to identify a structural abnormality in patients with localisation related epilepsy. We used diffusion tensor imaging (DTI) at conventional and high b values in patients with temporal lobe epilepsy (TLE) to increase the yield of imaging.

Methods: We scanned five patients with refractory TLE. Four patients had unilateral (HS) determined by hippocampal volumetric measurements on T1-weighted images and measurements of the T2 relaxation time. We also scanned 10 control subjects. DTI was performed using a

1.5T GE (Milwaukee, USA) LX/NVi Neuro-Optimised system (maximum gradient strength 40 mTm⁻¹). The DTI pulse sequence was based on a single shot echo planar imaging (EPI) sequence. The DTI protocol employed 25 diffusion directions with b values of 1000 s mm⁻² and 3000 s mm⁻². TR 6 s, TE 92 ms, FOV 24 cm², matrix 962, slice thickness 5 mm, 2NEX.

Results: Diffusion in the hippocampus was significantly increased (>mean+3 standard deviations of normal controls) in nine of 10 measurements. The increase was bilateral but asymmetrical in four of five patients and unilateral in one patient. The increase corresponded with the presumed seizure onset and the standard MRI changes in all four asymmetrical patients. The changes were more conspicuous on maps generated with high b values.

Conclusion: Bilateral but asymmetrical diffusion abnormalities were common in the hippocampi of TLE patients. DTI at high b value may increase lesion conspicuity.

This work was funded by the Epilepsy Research Foundation.

030 GAMMA OSCILLATIONS INDUCED BY SPEECH RECOGNITION

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Aim: To determine EEG characteristics associated with speech recognition.

Subjects: Nine right handed adults with consent and ethical approval.

Methods: "Ben drove fast cars", degraded by vocoding into 3, 5 and 15 channels, was played binaurally using headphones and presented as follows while recording 28 channel EEG. Log event-related spectral power (ERSP) changes from baseline were determined.

Results: Before, 3 or 5 channels were not recognised as speech; 15 channels was, but words were misheard. After, all subjects correctly identified the sentence with 3, 5 and 15 channels. Comparing Before and After, there no significant changes in baseline; a significant increase in gamma frequency ERSP occurred over left centroparietal electrodes for 3 and 5 channels at 338–474 ms and 600–800 ms, and a decrease occurred for 15 channels at 338–474 ms.

Conclusions: Lateralised induced gamma oscillations have been reported previously and thought to reflect perception and higher order speech processing speech. Those studies were confounded by physical differences between stimuli and behavioural responses. Our study controls for confounders and demonstrates lateralised gamma oscillations induced purely to speech recognition.

031 CLINICAL AND GENETIC ANALYSIS OF "TYPICAL" FRIEDREICH'S PATIENTS WITHOUT GAA EXPANSION

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We conducted an in-depth clinical and genetic assessment of 42 patients with progressive ataxic syndromes from 20 families in Ireland. All patients had a prior clinical diagnosis of Friedreich's ataxia but tested negative for the GAA trinucleotide expansion. All patients underwent a full clinical and neuro-ophthalmological examination. Blood tests included serum vitamin E levels, phytanic acid, serum immunoglobulin levels, α -fetoprotein level, celiac screen, blood glucose, lipid profile, liver function tests, screening for SCA (spinocerebellar ataxia) 1, 2, 3 & 6. Further genetic testing depended on clinical findings and the blood picture.

The following are the results so far. One patient had raised α -fetoprotein, oculomotor apraxia, and multiple myeloma. He had mutations on the ATM gene diagnostic of ataxia telangiectasia, although he did not show increased radiosensitivity. Four patients had raised α -fetoprotein and neuropathy. Two of these had in addition high cholesterol and have been shown to have mutations in the aprataxin gene, which leads to ataxia with ocular apraxia type 1 (AOA1). Onset of the ataxia in the other two patients with raised α -fetoproteins were in the late teens and they are awaiting testing for AOA 2. There was diurnal fluctuation of symptoms in five patients with the added finding of dystonia, especially of the lower extremities. Four have been genetically proven to have dopa-responsive dystonia while one patient is exquisitely responsive to levodopa but awaits definitive diagnosis. Six patients were found to have early onset spastic ataxia but without retinal striations. We plan to search for linkages to the ARCAS (autosomal recessive ataxia of Charlevoix Saguenay) gene locus. Five other patients fitted the phenotype of AOA 1 but without all of the described accompanying metabolic derangements. They will nonetheless be tested for AOA1.

None of the patients in the study has raised levels of α -gliadin or anti-glutamic acid decarboxylase (anti-GAD) antibodies. The study is on going.

032 CLINICAL FEATURES OF OPTIC NEUROPATHY ASSOCIATED WITH TOXIC AND NUTRITIONAL FACTORS

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Background: Epidemic optic neuropathy has been described for over 100 years amongst malnourished patients in the tropics.

Aim: To define clinical characteristics of patients in the UK with optic neuropathy presumed to be of toxic or nutritional origin.

Methods: A prospective, observational case series of painless, bilateral visual loss due to optic neuropathy in the context of poor nutrition (with the exclusion of other causes).

Results: Forty patients were included. Thirteen (33%) were women. Mean age at onset was 41 years. There were nine (23%) vegetarian/vegans and 25 (70%) alcoholics. Twenty four (65%) smoked tobacco. Twenty six (65%) were Caucasian, 10 (25%) were of Afro-Caribbean/Caribbean descent and three (8%) were Asian. Optic atrophy was observed in 50/80 eyes (63%) and central scotoma in 44 eyes (55%). Ishihara testing was abnormal in 58/60 eyes (97%). Five eyes (6%) demonstrated relative afferent papillary defects. Fifteen patients (38%) described peripheral sensory symptoms. Vitamin B12 was low in three (9%). Folate was low in eight (20%). Three male alcoholics (31, 49 and 58 years) had Leber's hereditary optic atrophy (LHON) mutations.

Discussion and conclusions: Cases similar to those observed in the tropics are seen in temperate zones. Poor nutrition and LHON mutations may interact.

033 VISUAL LOSS AT ONSET OF SPORADIC CREUTZFELDT JAKOB DISEASE: MAKING SENSE OF THE "HEIDENHAIN VARIANT"

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Background: In some cases of Creutzfeldt Jakob Disease (CJD) visual symptoms are present in isolation at onset, but these cases have not been clearly defined.

Aims: To identify the prevalence of sporadic CJD (sCJD) with visual symptoms in isolation at onset and to clarify their clinical parameters.

Methodology: A retrospective review of all pathologically proven sCJD cases referred to the National CJD Surveillance Unit, 1990–2002, identifying those with visual symptoms in isolation at onset. Clinical features were compared with a "reference group" of 126 consecutively selected sCJD cases.

Results: 19 patients (4%) had a pure visual onset. 80% were initially referred to an ophthalmologist. The median age at onset was 65 years (range 55–88) and the median illness duration was 3 months (range 1–17). The majority exhibited an extremely rapid mental and physical decline after the initial focal onset. In comparison with the reference group these cases exhibited less cerebellar or extrapyramidal signs.

Thirty-nine per cent had a typical EEG. 13/19 had genetic testing (all of the PRNP-129 MM genotype). sCJD was suspected in all. 90% were referred to the NCJDSU in life.

Conclusions: Heidenhain cases are distinct by their presentation, but prolonged diagnostic confusion was not evident. An association with codon 129 MM homozygosity exists.

034 LATE ONSET EPISODIC ATAXIA TYPE 2 DUE TO AN IN-FRAME INSERTION IN CACNA1A

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Episodic ataxia type 2 (EA2) is a brain channelopathy with onset before 20 years. Patients experience disabling paroxysmal ataxia, vertigo and nystagmus, which lasts hours and often describe migraine-like headaches. The true incidence of this disease is unknown, but we suspect it is often misdiagnosed as basilar migraine. EA2 usually associates with point mutations in the brain P/Q-type calcium channel gene α 1A-subunit, CACNA1A. The precise mechanism of channel

dysfunction and its relation to the pathophysiology of attacks is uncertain.

We have identified a novel genetic mechanism in a case of EA2 with very late onset at 61 years. Analysis of CACNA1A did not reveal the SCA6 repeat expansion; however, an insertion (3687 ins 9bp), duplicating the previous nine nucleotides, was identified in exon 20 of the CACNA1A gene. This is the first multiple base-pair insertion mutation described in CACNA1A. Functional expression in *xenopus* oocytes revealed reduced current density and a shift in the voltage-dependent activation to more positive potentials, demonstrating partial loss of function.

This study identifies a novel mutational mechanism resulting in decreased brain calcium channel function in late onset EA2. We suggest CACNA1A gene analysis should be considered in late onset EA2 and basilar migraine.

035 ALTERATIONS OF THE BCL-2 FAMILY ONCOPROTEIN MEMBERS IN A CELL CULTURE MODEL OF FAMILIAL SOD1-RELATED MOTOR NEURONE DISEASE

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Motor neurone disease (MND) affects approximately 5000 people at any one time in the UK. Of the 10% of familial cases, one-fifth is linked to mutations in the gene encoding the free radical scavenging enzyme superoxide dismutase-1 (SOD1). Good evidence exists that apoptosis, a programmed mechanism of cell death, is involved in the degeneration of motor neurones in MND.

A key upstream signal regulator of apoptosis is the Bcl-2 family of proapoptotic and antiapoptotic oncoproteins, which control the activation of downstream caspases (cysteine proteases).

Using the well-established NSC34 motor neuronal cell line transfected with G93A mutant SOD1, normal human SOD1, or empty vector, we examined with immunoblotting the cytosolic and mitochondrial levels of a range of Bcl-2 members, under basal culture conditions, and in the presence of oxidative stress, the latter being an important pathogenetic mechanism in MND.

The study demonstrated that alterations of the "multidomain" proapoptotic group (Bak, Bax), proapoptotic members of the BH3-only group (Bad, Bid, Bnip3), and "multidomain" antiapoptotic members (Bcl-xL, Bcl-2) in the cytosol and mitochondria of motor neurones promote the activation of the caspase cascade in MND.

036 PRAMIPEXOLE INDUCED AGGRAVATION OF RETROPERITONEAL FIBROSIS SYMPTOMS INDUCED BY PERGOLIDE IN A PATIENT WITH PARKINSON'S DISEASE

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Introduction: There has been concern related to use of ergot dopamine agonists (DA) and fibrotic side effects in Parkinson's disease (PD). However, sporadic reports suggest that non-ergot agonists may also be implicated.

Methods: A PD patient, aged 67 years, disease duration 8 years, presented with back pain and swollen, painful left leg after being on pergolide 3 mg/day for 3 years. Initial diagnosis was infective cellulitis, which progressed in spite of treatment with antibiotics. Duplex scanning venogram ruled out deep vein thrombosis. Lymphoscintigraphy suggested secondary lymphoedema. Retroperitoneal fibrosis (RPF) was confirmed on CT guided percutaneous peritoneal biopsy (mixed inflammatory cell infiltrate with fat necrosis) and high erythrocyte sedimentation rate. Discontinuation of pergolide and bilateral ureteric stent placement, with prednisolone therapy led to reversal of symptoms. After 1 year, a brief exposure to pramipexole (1.5 mg tds) for 3 months led to recurrence of similar symptoms that he had experienced at the onset of RPF.

Results: Symptoms resolved on discontinuation of pramipexole.

Conclusions: WHO drug monitoring survey reports cases of fibrotic side effects with ropinirole and pramipexole, both non-ergot DA.¹ Our case highlights this problem.

1. Muller T, Fritze J. Fibrosis associated with dopamine agonist therapy in Parkinson's disease. *Neuropharmacol* 2003;26(3):109-111.

037 A DOUBLE-BLIND PLACEBO CONTROLLED CROSSOVER TRIAL OF TOPIRAMATE IN ESSENTIAL TREMOR

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The anti-epileptic drug topiramate has been reported to improve essential tremor, but clinical trials have been small and of unsatisfactory design. We undertook a double-blind placebo controlled crossover study of topiramate in essential tremor, using accelerometry, spirometry, and activities of daily living (ADL) questionnaire (Bain and Findley, 1993). Sixteen subjects were recruited between January and June 2002. Three withdrew consent, 13 commenced the study, and 10 finished it. Subjects were assessed at baseline and after 2, 4, and 6 weeks of treatment (placebo or topiramate doses 25 mg, 50 mg, and 100 mg daily). Following a wash-out period of 1 week, patients crossed over to the alternate arm of the study. Statistical analysis followed the method described by Altman (1991).

There was no period effect or treatment-period interaction. No outcome measure improved significantly in the active treatment period as compared with the placebo control period. Four of 10 patients improved in at least two of the three outcome measures during the active treatment phase, and none did during the control treatment phase.

In order to achieve a study with power of 80% to exclude the null hypothesis, at least 17 patients would be required using accelerometry, 19 using spirometry, and 2100 using an ADL questionnaire.

038 MEDICINE TAKING IN PARKINSON'S DISEASE: DEFINING BASELINE COMPLIANCE

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Background: Therapy intake in Parkinson's disease (PD) exceeds prescribed amounts in selected advanced cases. We hypothesised that suboptimal therapy compliance could occur at any stage of PD because of drug regimen complexity.

Methods: Patients were randomised to one of (a) electronic monitoring of pill intake for 3 months using the MEMS system (Aardex, Switzerland), (b) simple tablet count (STC), and (c) no additional monitoring. All patients completed a self-report assessment of therapy compliance.

Results: Data as mean (SD) were available for 42 patients (26 male, 62%), age 61.3 years (11), disease duration 6.3 years (3.9), with motor PD score 28 (13.2) and Hoehn and Yahr stage 2.3 (0.7). Median number of PD drugs per patient was two (interquartile range IQ 2-3). MEMS data for 13 patients taking 31 drugs was as follows (all median, IQ): overall compliance 94% (84-100%); doses taken in correct number on 73% of days studied (43-87%); doses taken at correct time intervals for 16% of doses (10-42%). STC in 13 patients on 31 drugs was 94% (84-100%). Patient self-reporting using visual analogue scale gave compliance 100% (90-100%).

Conclusions: Therapy compliance is imperfect in PD and timing of medicine intake is erratic. These observations have potential significance in understanding therapy responses in PD patients.

039 CLINICAL VIRAL ENCEPHALITIS IN ADULTS: A 10 YEAR RETROSPECTIVE STUDY

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Background: The aetiological agent is not identified in most cases of suspected encephalitis presenting to a neurology department.

We were interested in the differences in presentation and prognosis between clinically definite and clinically probable viral encephalitis.

Methods: We identified adult patients who had a clinical discharge diagnosis of viral encephalitis over the past 10 years.

Results: Forty-nine cases of viral encephalitis were identified: in 14 patients the diagnosis was confirmed; in 35 patients the diagnosis was made on clinical grounds. There were no differences on presentation or other investigation between these groups. Of the cases with no identified pathogen, paired serology was requested in 17%. Of the patients with definite HSE, two patients had negative PCR and two had acellular CSF. There was no difference in treatment between the two groups. 60% of patients received acyclovir within 24 hours, 22% of the patients with confirmed encephalitis died, and 63% were discharged home, compared with 3% and 91% respectively of those with no identified pathogen.

Conclusions: There are no clinical features on admission to distinguish those patients in whom the diagnosis of viral encephalitis is likely to be confirmed. Patients in whom there is no identified pathogen have a better outcome.

040 GLUTAMIC ACID DECARBOXYLASE AS A TARGET ANTIGEN IN GLUTEN SENSITIVITY: THE LINK TO NEUROLOGICAL MANIFESTATIONS?

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The observation that four of six patients with stiff-person syndrome (SPS) had circulating anti-gliadin antibodies led us to investigate the relationship between anti-glutamic acid decarboxylase (GAD) and gluten sensitivity. Using an ELISA assay we investigated the prevalence and levels of anti-GAD in patients with gluten ataxia, in patients with coeliac disease (CD) only, using as controls patients with familial and idiopathic sporadic ataxias, SPS, non-immune mediated neurological diseases, immune mediated neurological diseases, and healthy subjects. The prevalence of anti-GAD in patients with gluten ataxia was 47/77 (61%), in patients with CD only 53/82 (65%), in familial ataxia 4/46 (9%), in sporadic idiopathic ataxia 26/107 (24%), in immune mediated neurological disease 6/74 (8%), in non-immune mediated neurological disease 2/48 (4%), and in healthy controls 5/58 (9%).

The difference in prevalence and levels of anti-GAD in gluten ataxia and CD groups was significantly higher when compared to controls. Significant reduction in the level and prevalence of anti-GAD was observed in both groups after introduction of gluten-free diet. Confirmation of the results was achieved by using western blotting. No cross-reactivity was found between anti-gliadin and GAD.

GAD may be an important antigen in gluten sensitivity providing the link between gluten sensitivity and neurological dysfunction.

041 NEUROPSYCHOLOGICAL OUTCOME AND APOE POLYMORPHISM IN MULTIPLE SCLEROSIS

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Neuropsychological impairments occur in 40–60% of multiple sclerosis (MS) patients; there is a good relationship between neuropsychological impairment and cerebral hemisphere atrophy.

The epsilon 4 polymorphism of the APOE gene (E4 allele) is hypothesised to influence neuronal disease via changes in efficacy of neuronal maintenance and repair. Relationships have been found between the APOE E4 allele and MRI findings relating to axonal loss in MS.

Ninety-six MS patients were assessed using a schedule covering five key neuropsychological modalities that are impaired in MS. This schedule included the following: Wisconsin card sorting test 64 version (executive function), Rey auditory verbal learning task immediate and delayed (learning and memory), controlled oral word association task (word retrieval), judgement of line orientation (visual-spatial processing), and symbol digit modalities task (processing speed/working memory). A regression model with summed z scores and potential covariates was developed.

Compared with normative data, the study population was significantly impaired. The mean total score of the APOE E4 allele carriers ($n=21$, mean=0.47, SD=4.3) and non-carriers ($n=75$, mean=-0.22, SD=4.4) were not significantly different ($p=0.30$ corrected). These groups did not differ in baseline characteristics. This study does not support a role for the APOE E4 allele in disease progression in MS.