ABN abstracts

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001 ABNORMALITIES IN CARDIAC RHYTHM REVEALED IN PATIENTS WITH REFRACTORY EPILEPSY

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Background: In the United Kingdom over 500 deaths per year are attributable to sudden unexpected death in epilepsy (SUDEP). SUDEP may be caused by potentially avoidable fatal cardiac arrhythmias and asystole following seizures.

Methods: We implanted REVEAL Plus cardiac rhythm monitoring devices into 11 male and 8 female patients with severe focal epilepsy who had had diagnostic video and EEG. Each volunteer kept a prospective seizure diary and attended our clinic for regular downloading of the recorded cardiac rhythm data over a median 16 month period.

Results: In all patients habitual seizures were associated with increased heart rate. Six patients consistently recorded ictal heart rates of greater than 120 beats per minute (bpm). Ictal bradycardia (30 bpm) was observed in two patients and prolonged in one. Significant episodes of sino-atrial (SA) node arrest occurred in two patients and lasted five and 13 seconds respectively. The first occurred peri-ictally while in the second a seizure was not noted at the time. Permanent pacemaker insertion has since been performed in both these patients and is planned for the patient with the prolonged ictal bradycardia.

Conclusions: A potentially life-threatening cardiac rhythm abnormality was recorded in three of 19 patients, requiring permanent pacemaker insertion. These findings necessitate a profound re-evaluation of the role of long-term cardiac monitoring in patients with epilepsy.

002 THE VALUE OF THE ELECTROCARDIOGRAPH (ECG) IN A FIRST SEIZURE CLINIC

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Current guidelines recommend recording a standard 12 lead ECG in patients presenting with suspected seizures. The yield from this investigation is unknown. We reviewed 163 (of 164) consecutive cases seen in a First Seizure Clinic retrospectively. Referrals were from GPs (69% patients), hospital physicians (20%) and A&E (11%). Average age was 33 years and 55% were male.

Diagnoses after the history and examination were: seizure (50%), syncope (30%), uncertain (13%), others (7%). Electrocardiographs (ECGs) were recorded with computer analysis and read by a consultant cardiologist. 130 patients had an ECG, 15% were abnormal. Abnormal ECGs were found in 12 patients with seizures, 3 with syncope, and 2 with an uncertain diagnosis. Abnormalities included: long QT (one patient with diagnosis of seizure, two with unknown diagnosis), short PR interval (reflex anoxic seizure patient) and unexplained bradycardia (heart rate <60, 4 patients with seizures). The ECG led to further investigations (echocardiogram, prolonged ECG, cardiac electrophysiological studies) on the advice of the cardiologist.

Cardiac abnormalities can cause blackouts which may be difficult to distinguish from epileptic seizures. ECGs can be useful in suggesting cardiac causes. Close co-operation between first seizure clinics and cardiological services is essential.

003 PHYSIOLOGICAL IMAGING OF INTERICTAL EPILEPTIFORM ACTIVITY USING SIMULTANEOUS EEG-CORRELATED FUNCTIONAL MRI

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Aim: To characterise and map bloody oxygen level dependent (BOLD) signal changes linked to interictal epileptiform discharges (IEDs), a large group of patients with focal epilepsy.

Methods: 50 patients with localisation-related epilepsy and frequent IEDs were studied on a GE Horizon 1.5T scanner using whole-brain EPI (TE/TR 40/3000, 64×64 matrix). 700 scans were acquired continuously over 35 minutes. Ten channels of scalp EEG, plus ECG, were recorded simultaneously using an MR-compatible system, with on-line artefact subtraction. IEDs were classified, labelled, and used to perform an event-related analysis of the fMRI data using SPM99.

Results: Good quality EEG was obtained in all patients and IEDs were successfully captured from 29: 12 (41%) had BOLD activations concordant with electroclinical data across a range of pathologies, 4 (14%) activation of uncertain significance, and in 7 (24%) no activation was observed. In this group, there was a tendency to abnormal background rhythms, head motion, and subtle myoclonus. In 4 patients (14%) IEDs were too frequent for fMRI and in 2 patients, the study was terminated due to seizures.

Conclusion: Simultaneous EEG/fMRI can provide novel localising information in selected patients, namely those with frequent stereotyped high-amplitude unifocal IEDs readily identifiable from the background EEG.

004 DIFFERENT PATTERNS OF ELECTROPHYSIOLOGICAL DEFICIT IN MANIFESTING AND NON-MANIFESTING CARRIERS OF THE DYT1 GENE

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Background: A mutation in the DYT1 gene on chromosome 9q34 causes early-onset primary torsion dystonia (PTD) with autosomal dominant inheritance but low phenotypic penetrance. The aim of the present study was to assess the functional consequences of the DYT1 gene, by comparing the electrophysiology of cortical and spinal circuits in clinically affected and unaffected carriers of the DYT1 mutation.

Method: We assessed intracortical inhibition and facilitation (ICI/ICF), the cortical silent period (SP), and spinal reciprocal inhibition (RI) in 10 manifesting carriers (MDYT1), 7 non-manifesting gene carriers (NMDYT1) and 13 healthy controls.

Results: The MDYT1 subjects had abnormalities similar to those seen in previous studies of non-genetically characterised individuals with primary dystonia with reduced ICI, shorter SP and absent presynaptic phase of RI compared with the healthy controls. NMDYT1 subjects had a similar significant reduction in cortical inhibition (ICI, SP), but their spinal RI was not different from controls.

Conclusions: We conclude that clinical expression of dystonia depends on widespread electrophysiological deficits, and the presence of the DYT1 mutation itself leads only to a subset of these changes. This is consistent with the hypothesis that additional environmental/genetic insults may be needed in to reveal clinical symptoms in DYT1 gene carriers.

005 PD LIFE—A PROSPECTIVE MULTI-CENTRE LONGITUDINAL AUDIT OF QUALITY OF LIFE IN PARKINSON'S DISEASE ACROSS THE UK

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Background: PDLIFE is a clinician led multicentre prospective national audit monitoring (a) changes in Quality of Life in response to treatment (QoL), (b) prescribing trends of anti-PD drugs across the United Kingdom (UK) and (c) identify changes in QoL, which may trigger changes or initiation of treatment in Parkinson's disease (PD).

Methods: Using the validated PDQ-39 QoL scale and clinical assessment form monitoring changes in treatment, and co-morbidity annually for 5 years. All PD patients (irrespective of age, drug naïve or receiving monotherapy) at an early (diagnostic and maintenance) stage

are included. Additionally sleep function, restless legs are also being evaluated.

Results: In the pilot phase 10 core UK centres have recruited 250 patients since 2002. 79 have attended first follow up (mean duration follow-up period of 297 days). It is expected that by 2004 we will obtain baseline data on 500 patients and follow-up data on 200 patients.

Conclusions: Preliminary pilot data suggest that in the UK, dopamine agonists are rarely used as monotherapy in older people (65–86 yrs) even in mild PD. Patients left untreated at diagnosis deteriorate significantly in several domains of QoL assessment even after 6 months.

006 PARKIN IS RECRUITED INTO AGGRESOMES IN A STRESS-SPECIFIC MANNER AND ITS OVER-EXPRESSION REDUCES AGGRESOME FORMATION

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Mutations in the parkin gene cause autosomal recessive juvenile parkinsonism (AR-JP). Parkin is present in Lewy bodies (LBs) of sporadic Parkinson's disease (PD) brains. However, LBs are not a feature of AR-JP brains suggesting that parkin may play a critical role in the formation of LBs. We investigated the role of parkin in aggresome formation in human dopaminergic neuroblastoma cells. We now report that endogenous parkin is recruited into aggresomes under a variety of stresses. However, we found the protein unfolding stress, tunicamycin, did not induce the formation of parkin-positive aggresomes. Confocal studies show that vimentin surrounds parkin in aggresomes and that Hsc70 and ubiquitin are also found in the aggresomes formed during proteosome inhibition. We established stable cell lines over-expressing human parkin. The formation of aggresomes was markedly reduced in cell lines over-expressing parkin compared to the vector alone for all stresses examined. We further show that the reduction in aggresomes does not correlate well with parkin's neuroprotective properties. In summary we show that although endogenous parkin may be a necessary component of aggresomes, excess levels of parkin may lead to increased removal of misfolded proteins by its ubiquitin ligase activity and thereby abrogate aggresome formation.

007 HIGH DENSITY SINGLE NUCLEOTIDE POLYMORPHISM MAPPING OF PROTEIN KINASE C ALPHA GENE IN A UK POPULATION OF MULTIPLE SCLEROSIS PATIENTS

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Introduction: Linkage studies in multiple sclerosis (MS) families have implicated a 2.5 Mb region of chromosome 17q22–24. Protein kinase C alpha (PRKCA) maps to this interval and is involved in both T cell regulation and proliferative responses. Hence, it is a prime candidate MS susceptibility gene.

Methods: Association of 35 SNP markers mapping at approximately 10 Kb intervals within the PRKCA gene was investigated in 184 unrelated UK MS patients and 340 controls. Genotyping was performed with Assays-on-Demand (ABI, UK) allelic discrimination assays on a Taqman™ platform. Haplotype frequencies were estimated using HelixTree software (Golden Helix Inc, USA) and compared between cases and controls.

Results: A cluster of SNPs mapping to the telomeric portion of the PRKCA gene showed evidence for association by genotype and this association appeared confined to DR*15 carriers. A haplotype of 2 SNPs mapping to the promoter region of the gene showed evidence for association (Bonferroni corrected p value = $9.3\times10-4$).

Conclusion: Our results provide further support for association of the 17q22–24 region with MS and implicate PRKCA as a possible MS disease gene. Association in a subgroup of patients supports the concept of genetic heterogeneity within MS cases.

008 THE RELATIONSHIP BETWEEN FUNCTION AND STRUCTURE OF THE POSTERIOR VISUAL PATHWAYS FOLLOWING OPTIC NEURITIS

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Introduction: Previous MRI studies have independently demonstrated functional changes in the visual cortex and structural changes in the optic radiations following optic neuritis. We investigated how visual cortex function and optic radiation structure are related in patients with previous optic neuritis.

Methods: Seven patients one year after isolated unilateral optic neuritis and seven controls underwent visual functional MRI (fMRI) and whole brain DTI (diffusion tensor imaging). DTI based tractography was used to extract each optic radiation from which the mean fractional anisotropy (FA) was calculated. Regression analyses were performed between the fMRI images and optic radiation FA values.

Results: The optic radiation FA was positively correlated with the visual cortex fMRI response for the unaffected eye in patients ($p=0.002$) and the matched eye in controls ($p=0.02$). This relationship was stronger in patients than controls ($p=0.07$). For the affected eye, there was weak evidence for a positive correlation in patients ($p=0.08$) and controls ($p=0.06$) with no difference between the two groups.

Conclusions: A novel relationship has been demonstrated between the visual fMRI response and the structure of the subserving optic radiations. This is stronger for the unaffected eye in the patient group and suggests function-structure plasticity following recovery from optic neuritis.

009 OLIGOCLONAL BAND NEGATIVE MS—DOES IT EXIST

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Objective: To study the features and reliability of the diagnosis of oligoclonal band (OCB) negative cerebrospinal fluid (CSF) multiple sclerosis (MS), with reference to the diagnostic criteria for MS.

Method: A retrospective, sex-matched, case-controlled study of patients diagnosed with OCB negative MS over a 6-year period from one major neurology centre.

Results: 19 OCB negative patients were identified from 539 cases and compared with an equal number of OCB positive controls. Several features in the OCB negative group were unusual with a higher frequency of headaches, generalised seizures, depression, cognitive impairment and psychosis. Although a ''better explanation'' was not obvious in these patients, there still remained the possibility of alternative pathology in 6 cases. MRI abnormalities were frequent but non-specific, with a higher rate of abnormal visual evoked potential studies compared to controls. 58% of OCB negative cases had either moderate or severe neurological disability.

Conclusion: The lower importance allowed for CSF studies in the new McDonald criteria results in a significantly greater proportion of patients being labelled ''clinically definite'' compared to the Poser criteria, which may decrease vigilance regarding alternative diagnoses. The presence of atypical clinical features is much commoner in this group and the previous benign implication for OCB negative MS may not be true.

010 DISTINCT PROFILES OF CHEMOKINE RECEPTOR EXPRESSION IN PATTERN II AND III MULTIPLE SCLEROSIS LESIONS

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Introduction: Four subtypes (pattern I–IV) of multiple sclerosis were identified based on neuropathological features. Pattern II and III account for 83% of cases. The mechanisms of myelin injury in subtypes of MS are not well understood. Monocytes, microglia and macrophages are present in all MS lesions and the expression of chemokine receptors is important to their recruitment, differentiation and function.

Aims: To determine the profile of CCR1, CCR3 and CCR5 expression on mononuclear phagocytes relative to demyelinating activity of pattern II and III lesions using immunohistochemistry.

Results: The numbers of cells expressing CCR1 and CCR5 varied significantly and consistently in relation to demyelinating activity of pattern II but not III lesions. A novel population of CCR3 expressing rod-shaped microglia was detected in pattern III but not pattern II lesions. Recently recruited monocytes co-expressed CCR1 and CCR5 in pattern II and III lesions.

Conclusion: Tissue environments in pattern II and III lesions are strikingly different. The profiles of CCR1 and CCR5 are consistent with pro-inflammatory cytokine mediated tissue damage in pattern II lesions. Pattern III lesions contained a population of CCR3-positive rod-shaped microglia, implying a distinct mechanism of microglial activation in pattern III lesions.

011 SPINAL CORD ATROPHY IN EARLY PRIMARY PROGRESSIVE MULTIPLE SCLEROSIS

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Background: Spinal cord symptoms are a common presenting feature in Primary Progressive Multiple Sclerosis (PPMS) and may result from underlying neurodegenerative processes. This study assesses cord atrophy in early PPMS using two techniques and examines the relationships between spinal cord atrophy, brain atrophy and disability.

Methods: 43 patients with early PPMS (within 5 years of disease onset) were assessed clinically and with 3D volumetric scans of brain and spinal cord. Spinal cord atrophy was assessed by (1) calculating the area of five slices axially reconstructed at the level of C2 and (2) measuring the total volume of extracted cervical cord, comparing the results obtained with 25 age and sex matched controls.

Results: Mean cervical cord area was less in patients than controls (73.4 mm^2 (SD 8.8):79.6 mm^2 (SD 7.5), $p=0.007$) and associations were found between cord volume and total brain volume ($r=0.5$, $p<0.001$) and brain white matter fraction ($r=0.4$, $p=0.021$). There was no relation between cord size and disability.

Conclusion: Spinal cord atrophy is present early in the disease course in PPMS and, at this stage, appears to relate to brain atrophy but not disability. This study suggests that spinal cord neurodegeneration is an early event in PPMS.

012 THE ORIGIN AND EVOLUTION OF THE ARTHROPOD-BORNE VIRUS, JAPANESE ENCEPHALITIS

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Encephalitides caused by arthropod-borne viruses are becoming increasingly important globally, with the spread of West Nile virus to Europe and the United States, and the continuing spread of Japanese encephalitis in Asia. However, the origins, evolution, and factors governing the wide variation in clinical features are poorly understood. Japanese encephalitis was first described in Japan in the 1870s, and has spread across Asia to cause large summer epidemics in northern regions, and year round endemic disease in southern regions. Differences in the distribution of the four genotypes of virus have been postulated to explain the differing clinical epidemiology. We have determined the complete nucleotide sequence of an Indonesian strain of virus (which represent the oldest lineage), compared it with other full-length genomes, and examined the geographical distribution of all known isolates. We show that Japanese encephalitis virus originated in the Indonesia-Malaysia region and evolved here into the different genotypes, which then spread across Asia. No association between genotype and phenotype was seen in a mouse model of Japanese encephalitis. Our data suggest that southeast Asia may be an important zone for emerging viruses, and have implications for the spread of other arthropod-borne viruses.

013 NEITHER BLINDSIGHT NOR OVERSIGHT BUT MINDSIGHT: PATHOLOGICAL COMPLETION WITHOUT EVIDENCE OF NEGLECT FOLLOWING DAMAGE TO OCCIPITAL CORTEX

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Homonymous scotomata may be accompanied by the subjective experience of completion of forms that ''should'' be occluded by the visual defect, a symptom termed Pathological Visual Completion. We report a single case whose experience of completion has been studied systematically by manipulating the parameters of the stimulus display. His disorder could not be explained by residual vision nor an attentional disorder. Pattern masking, varying the contrast characteristics of stimuli and changing visible cues to structural symmetry all had precise effects whereas familiarity and structural coherence did not. We conclude that pathological completion may be a positive cognitive event implicating processes that underlie the normal analysis of occluded forms.

014 FOCAL VENOUS INFARCTION OF THE SUPPLEMENTARY EYE FIELD REVEALS ITS FUNCTION

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The specific contribution of the 'supplementary' eye field (SEF) to the control of eye movements has eluded both electrophysiological investigations in monkeys and functional imaging studies in healthy humans. Here, we present detailed imaging and behavioural data on a rare patient who suffered extremely focal venous infarction of the medial frontal cortex limited to the SEF.

Although the patient showed no impairment in making simple reflexive saccades, he encountered severe difficulty when required to change saccadic plans. Importantly, however, he was aware of his errors and corrected them. Similarly, when required to switch between rules linking a visual stimulus with a saccadic response, he was significantly impaired, but again corrected errors well. He also experienced difficulty learning new saccadic stimulus-response associations when selecting between four competing responses. Analogous experiments requiring hand, rather than eye movements, did not reveal any impairment. Finally, he showed deficits when required to make memory-guided saccadic sequences.

These findings suggest that the SEF normally acts to implement volitional control over saccades, particularly in situations of response conflict when there are competing saccadic plans. Such self-control over eye movements provides a model system to study the supervisory or 'executive' control functions of medial frontal areas.

015 THE CLINICAL PHENOTYPE OF NON-PARANEOPLASTIC VOLTAGE GATED POTASSIUM CHANNEL ANTIBODY (VGKC AB) ASSOCIATED CNS DISEASE

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VGKC-Ab associated limbic encephalitis with titres above 400 pM has recently been described. Here we screened patients with unexplained cognitive and/or behavioural symptoms for VGKC Abs, over a 4 year period in a general neurology clinic serving a population of 150 000 patients. Eight patients were positive. Two with classic non-paraneoplastic limbic encephalitis had high titres (>1500 pM); the other six had lower titres (100–500 pM) and presented with sub-acute cognitive syndrome with features of mania (n=1), prolonged transient global amnesia (n=1), severe post-ictal psychosis after a single cluster of four seizures associated with elevated thyroid antibodies (n=1), chronic symptoms of cognitive/behavioural impairment (n=1) and refractory epilepsy (n=2). Some patients responded to immunotherapies and some spontaneously resolved. VGKC antibodies were not identified in patients with destructive or inflammatory CNS diseases such as a Rasmussen's Encephalitis or MS, or in other disease controls.

Thus a range of cognitive disorders can be associated with VGKC Abs. This raises the possibility that other conditions such as transient global amnesia, Hashimoto's encephalopathy and non-Herpes Simplex encephalitis include VGKC Ab mediated disease. We believe VCKC Ab associated CNS disorders are usually non-paraneoplastic, relatively common and the majority are currently undiagnosed.

016 PRECISE VOLUME MEASUREMENTS OF LOW-GRADE GLIOMAS. SOME SURPRISING FINDINGS

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Background: Little is known about the growth rates of low-grade gliomas (LGGs) during their 'premalignant' phase. We have developed a technique that can measure tumour volumes semi-automatically and hence determine tumour growth rates.

Methods: Patients with LGGs were scanned on a 1.5 T Signa LX MRI scanner (GE Medical Systems). Semi-quantitative volumes were determined on coronal FLAIR sequences using DispImage® software, which automatically 'contours' and calculates the area of a region of interest. Volume measurements were obtained twice by two observers blinded to the clinical status of the patients. Transformation was defined by clinical (significant deterioration) and/or radiological (new gadolinium enhancement) criteria.

Results: 27 patients have been followed up with six monthly scans for a mean of 20 (range 11–30) months. Seven have transformed, of whom one has died and twenty are stable. Intra- and inter-rater intra-class correlations are 0.99 (95% CI 0.98–0.99) and 0.98 (95% CI 0.97–0.98) respectively. Tumour volumes in the stable group were not significantly lower than in the transformers at baseline but the average growth rate was greater amongst the transformers than amongst the stable group (35%/year (95 CI 24–47%) vs 17%/year (95% CI 11–22%)) [p = 0.003].

Conclusions: Low-grade gliomas that are 'premalignant' grow faster than stable tumours.

017 FUNCTIONAL PARESIS—PARADOXES IN ILLNESS BELIEFS AND DISABILITY IN 107 SUBJECTS

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Objective: (1) To describe distress, disability and illness beliefs in consecutive patients presenting to neurologists with functional paresis and (2) to compare with these with patients who have neurological paresis.

Methods: Consecutive patients with recent onset functional or neurological paresis diagnosed by neurologists. Assessment included a semi-structured interview, a structured psychiatric interview and questionnaire assessment of distress, illness beliefs and disability.

Results: 107 subjects with functional paresis (mean age 39 years, 79% female, mean duration 11 months) were compared with 46 subjects with neurologically defined paresis (mean age 39 years, 83% female, mean duration 14 months). Although self-rated distress was similar, patients with functional paresis had significantly more psychiatric disorder at interview. Despite this, they were less likely to agree that stress was a cause of their symptoms (24% vs. 57%, $p<0.001$) and were twice as likely to have given up work because of their symptoms (59% vs. 29%, $p<0.001$), despite similar levels of self-rated disability.

Conclusions: Compared to patients with neurologically defined paresis, patients with functional paresis are less likely to blame stress for their symptoms (despite a higher rate of psychiatric disorder) but more likely to stop working (despite similar self-rated disability).

018 POTASSIUM CHANNEL ANTIBODY ASSOCIATED ENCEPHALITIS: A POTENTIALLY TREATABLE NON-PARANEOPLASTIC LIMBIC ENCEPHALITIS

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Background: Three cases of non-paraneoplastic reversible limbic encephalitis (LE) associated with voltage-gated potassium channel antibodies (VGKC-Ab) have previously been reported. We aimed to define the phenotypic features of this syndrome in more detail.

Methods and results: We studied 10 patients (9 male; age 44–79 yrs) positive for VGKC-Ab who presented over a 15-month period with memory loss, confusion and seizures. One patient had neuromyotonia. Syndrome of inappropriate anti-diuretic hormone secretion (SIADH) was present in eight. Eight patients had temporal lobe MRI signal change at presentation; paraneoplastic antibodies and CSF virology were negative in all. VGKC-Ab titres ranged from 450 to 5128 pM (cut-off <100 pM). Treatment with steroids, plasma exchange and intravenous immunoglobulin resulted in variable improvement, from slight to marked, coincident with the induced fall in VGKC-Ab, but medial temporal lobe atrophy and residual cognitive impairment were common. Over the same period, one case of paraneoplastic LE was identified in the two main centers.

Conclusions: VGKC-Ab-associated encephalopathy is a relatively common form of autoimmune, non-paraneoplastic LE. VGKC-Ab testing should be considered in patients presenting with LE, especially those with seizures, hyponatraemia and MRI signal change. Future work should aim to identify the frequency of this condition and establish optimal immunotherapy.

019 SYNTHETIC DISIALYL-GALACTOSE IMMUNOABSORBENTS CLEAR PATHOGENIC ANTI-GQ1B GANGLIOSIDE AUTOANTIBODIES FROM SERUM IN GUILLAIN BARRÉ SYNDROMES

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Guillain Barré syndrome frequently follows *Campylobacter jejuni* enteritis and molecular mimicry between carbohydrate epitopes on nerve gangliosides and the lipopolysaccharides (LPS) of *C. jejuni* accounts for the harmful autoimmune responses that result in impaired nerve function. Miller Fisher syndrome is associated with anti-GQ1b ganglioside autoantibodies in over 95% of cases and *C. jejuni* species isolated from affected cases bear GQ1b-like epitopes on their LPS. Non-specific plasma exchange ameliorates the severity and duration of the disease; however, removal of specific antibody by affinity plasma exchange might achieve superior outcomes since only the pool of harmful antibodies would be removed. A significant limiting factor to this therapeutic approach is the structural complexity and limited availability of ganglioside epitopes. Here we demonstrate that a proportion of anti-GQ1b antibodies that characterize MFS sera bind to the synthetic trisaccharide, alphaNeuAc(2–8)alphaNeuAc(2–3)betaGal covalently attached to BSA. Human polyclonal sera and murine monoclonal anti-GQ1b antibodies are inhibited by this trisaccharide epitope. The same trisaccharide immobilized on a Sepharose column depletes human serum of anti-GQ1b antibody. This proof of principle establishes that oligosaccharide-specific immuno-absorption therapy provides a novel approach to treating anti-ganglioside antibody-associated GBS and could be readily applied to clinical practice in conjunction with conventional plasma exchange.

020 OPHTHALMOPLEGIA: WHEN ALL THE TESTS ARE NEGATIVE

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The differential diagnosis of ophthalmoplegia can be difficult. Mitochondrial disease is a common cause of ophthalmoplegia in those patients without a demonstrable neuromuscular junction abnormality. Muscle biopsy is considered diagnostic in mitochondrial disease and classically shows a mosaic of cytochrome oxidase negative (CNF) and ragged red fibres (RRF).

In our patients with chronic external ophthalmoplegia (CPEO), there was disparity between extra-ocular muscle (EOM) and quadriceps, with much greater numbers of CNF in the clinically affected tissues (EOM). Subsequent quadriceps biopsies showed higher numbers of CNF. Of 115 patients with CPEO and a mitochondrial disease, four patients presented with entirely normal muscle histochemistry yet were found to have pathogenic mitochondrial DNA (mtDNA) mutations. In one patient 10 years elapsed before a second biopsy was abnormal and prompted the discovery of a mtDNA deletion. We believe that many patients may exist who have bypassed mitochondrial investigations on the basis of normal muscle histochemistry.

This has important implications for the diagnosis of patients with ophthalmoplegia. A quadriceps biopsy devoid of CNF or RRF does not exclude the possibility of mitochondrial disease. Detection of such by specific molecular analysis may prevent further unnecessary investigation, misdiagnosis and inappropriate treatment strategies.

021 INVOLUNTARY MOVEMENTS, SENSORY SYMPTOMS AND EARLY PSYCHIATRIC FEATURES IN SPORADIC VERSUS VARIANT CREUTZFELDT JAKOB DISEASE

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Background: Variant CJD (vCJD) typically presents with psychiatric features, early involuntary movements and sensory symptoms whereas sporadic CJD (sCJD) typically presents with rapid cognitive decline. Atypical sCJD is the most important differential of vCJD.

Aims: To identify the incidence in sporadic CJD of early clinical features typical of vCJD.

Methods: A case note review of all pathologically proven UK sCJD cases (1990–2002).

Results: Of 486 patients with sCJD 25 (5.4%) presented with sensory disturbance, 20 (4.1%) with involuntary movements and eight (1.6%)

with pure psychiatric features. Eight of these (15%) fulfilled the criteria for ''possible'' vCJD.

The mean age at onset was 62 years (vCJD: 28 years). Mean duration of illness was nine months (vCJD: 13 months). None (including those with early prominent sensory features) had the MRI pulvinar sign. 6/27 (22%) had MRI changes characteristic of sCJD. Periodic EEG complexes were seen in 12/49 (25%). PRNP codon 129 data are available in 29 (66% MM, 14% MV, 20% VV).

Conclusions: 11% of sCJD cases presented with symptoms common at onset in vCJD. Prolonged diagnostic confusion with vCJD is unlikely given the usual clinical progression of symptoms. Investigations (EEG and MRI) are helpful.

022 THE CRITICAL TIME WINDOW FOR REORGANISATION OF THE CORTICOSPINAL TRACTS ENDS CLOSE TO THE PERINATAL PERIOD IN MAN

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Aim: To investigate the critical time window for plasticity of the ipsi-lesional and contra-lesional corticospinal tract (CST) in man.

Subjects: All sustained unilateral stoke; 32 perinatally, 15 in childhood (>0.1–13 years), 13 as adults. All were >2 years after the stroke.

Methods: Surface EMG recorded from biceps brachii. Transcranial magnetic stimulation (TMS) to excite the CST. Ipsilateral and contralateral central motor conduction delays (CMCDs) measured. Topographical mapping of the areas of the cortex evoking responses.

Results: ***Contra-lesional CST*** Significant shortening of contralateral and ipsilateral CMCDs was observed only in subjects with perinatal stroke (Z scores: contralateral CMCD, mean −0.85; 95% confidence limits −1.38 to −0.30; ipsilateral CMCD, mean −6.1, 95% confidence limits −6.98 to−3.62). ***Ipsi-lesional CST*** A significant shift in the cortical site evoking responses was observed only following perinatal stroke (displacement laterally and posteriorly in comparison to the non infarcted hemisphere: mean lateral +1 cm, 95% confidence limits +0.45 to +1.54 cm; mean posterior +1.17 cm, 95% confidence limits +2.11 to +0.24 cm). 4/15 who suffered stroke in childhood showed a large shift (range −2 to +2 cm laterally and −2 to +4 cm posteriorly).

Conclusion: The critical time widow for contra-lesional tract reorganization ends near the perinatal period but ipsi-lesional cortical reorganization may occur later.

023 GENETIC EPIDEMIOLOGY OF ISCHAEMIC STROKE

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To design molecular genetic studies of stroke we need reliable genetic epidemiology. To determine whether family history (FHx) of stroke is a predictor of incident ischaemic stroke we studied unpublished data from the ongoing Oxford Vascular Study (OXVASC) and the Oxfordshire Community Stroke Project (OCSP) and performed a systematic review of published studies.

FHx of stroke was a risk factor for stroke in case-control (overall OR=1.67, 95% CI 1.6–1.8, p<0.00001, 26 studies) and cohort studies (1.29, 1.2–1.4, p<0.00001, 8 studies) but there was major heterogeneity between studies (p<0.00001) and significant (p=0.01) evidence of publication bias. Moreover, FHx of MI (1.50, 1.4–1.6, p<0.00001) and hypertension (1.52, 1.4–1.7, p<0.0001) were equally strong risk factors for stroke. However, FHx of stroke was more predictive if the analysis was confined to probands or relatives under 70. Only OXVASC, OCSP, and two published studies phenotyped strokes in detail. FHx of stroke was equally frequent in large and small vessel stroke (1.06, 0.8–1.4, p=0.7), but less frequent in cardioembolic stroke (0.69, 0.5–0.9, p=0.01).

Reliable interpretation of published FHx studies is difficult because of heterogeneity and probable publication bias. However, FHx appears to be associated with large and small vessel strokes in patients <70.

024 USE OF QUANTIFIED ACETAZOLAMIDE ACTIVATED XENON ENHANCED COMPUTERIZED TOMOGRAPHY (aXeCT) IN THE SELECTION OF PATIENTS FOR EXTRACRANIAL TO INTRACRANIAL (ECIC) BYPASS SURGERY

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Objective: To determine the outcome following ECIC bypass in patients with symptomatic carotid occlusive disease who display markedly reduced cerebrovascular reserve on aXeCT. Indication for surgery was the absence of significant cerebral blood flow (CBF) activation (<5%) from baseline values, and/or the presence on intra-cranial CBF steal.

Patients: Patients with chronic symptomatic cerebrovascular occlusive disease were assessed using aXeCT and comparing baseline CBF values with those obtained after 1g(iv) acetazolamide. 8 patients with extracranial carotid occlusions, and one young patient with extensive intracranial (Moya Moya) disease were selected for surgery in this way. Bypass was with a superficial temporal artery.

Outcome measures: 3 month i) clinical outcome ii) post-operative aXeCT iii) graft patency.

Results: There were no immediate postoperative complications. All patients reported marked improvements in preoperative symptoms and general well being at 3 months. Graft patency was 100%. All postoperative aXeCT scans demonstrated a return to normal reactivity.

Conclusion: aXeCT is a useful and convenient tool in the selection of patients suitable for ECIC bypass surgery. The indications remain rare, hence a multi-centre randomized study based on a activation studies is indicated for assessing long-term efficacy.

025 NEURAL CORRELATES OF INITIAL SEVERITY AFTER STROKE: A CROSS SECTIONAL fMRI STUDY

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Cerebral reorganisation after stroke may be studied in the human brain using functional magnetic resonance imaging (fMRI). It has recently been demonstrated that chronic stroke patients with poorer outcome are more likely to recruit non-primary motor networks during motor tasks. In order to determine whether this relationship holds true early after stroke, we studied eight patients with subcortical cerebral infarction 10–14 days after stroke onset. Patients underwent fMRI whilst performing isometric dynamic handgrip. Target force was individually set for each patient at 20% of affected hand maximum grip strength on the day of scanning, so that results would not be confounded by differences in effort exerted across subjects. Initial severity of stroke was assessed using several outcome measures.

A negative correlation between early outcome scores and size of handgrip related brain activation was observed bilaterally in primary motor cortex, supplementary motor area, cingulate motor areas, premotor cortex, posterior parietal cortex, visual cortex, and cerebellum. A positive correlation was observed in ipsilesional superior temporal sulcus and contralesional inferior parietal cortex. These results are similar to those in chronic stroke patients and suggest that non-primary motor networks are recruited early after stroke during attempted hand movement, particularly by those with greatest deficit.

026 ARE THERE DIFFERENCES IN THE RISK FACTOR PROFILES OF LACUNAR AND NON-LACUNAR INFARCTS? A SYSTEMIC REVIEW

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Background: The arterial pathology of lacunar infarction (LACI) is poorly understood. Comparing risk factor profiles of LACI and non-lacunar infarction (non-LACI) may improve our understanding.

Methods: We performed a systematic review of studies comparing the prevalence of risk factors in LACI and non-LACI. For each risk factor, we calculated study-specific and, where appropriate, pooled relative risks for LACI versus non-LACI.

Results: We found 34 relevant studies. 10 used the TOAST classification, in which hypertension and diabetes favour a LACI diagnosis. Hypertension and diabetes appeared commoner among patients with LACI, but analyses of studies not including risk factors in stroke subtype definitions showed no association hypertension or diabetes and LACI (pooled RRs LACI vs non-LACI: hypertension=1.09, 95% CI 1.01 to 1.17; diabetes=0.93, 95% CI 0.81 to 1.08). Atrial fibrillation and carotid stenosis were less common in LACI than non-LACI. No other risk factors assessed differed in prevalence.

Conclusions: Many studies investigating differences in risk factor profiles between stroke subtypes used classification methods that included risk factors in the definitions, which leads to biased results. When these studies are excluded, the results do not support the assertion that hypertension and diabetes predispose to LACI more than non-LACI.

027 THE ANAL REFLEX CAN BE ELICITED BY COUGH AND SNIFF—VALIDATION OF A CLINICAL SIGN

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It is unclear whether contraction of the external anal sphincter (EAS) following a voluntary cough is an integral component of the cough response itself, or a reflex response to the abdominal and pelvic floor dynamics induced by the cough. We addressed this question by comparing motor latencies for intercostal, abdominal and EAS muscle contraction after trans-cranial magnetic stimulation with those following a voluntary cough. We also studied the responses to sniff. Our results suggest that EAS responses following a voluntary cough or sniff represent a polysynaptic reflex with characteristics resembling the conventional scratch-induced anal reflex. Since the cough-induced anal reflex response is both highly consistent and easily elicited its use in clinical neurological examination is appropriate.

028 CELLULAR STUDIES OF SPASTIN, THE PROTEIN COMMONLY MUTATED IN AUTOSOMAL DOMINANT HEREDITARY SPASTIC PARAPLEGIA (SPG4)

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Hereditary spastic paraplegia (HSP) is a neurodegenerative condition characterised by progressive lower limb spasticity. It is often inherited in an autosomal dominant fashion, and 40% of these cases are caused by mutations in the SPG4 gene, encoding spastin, whose function remains unclear. Nuclear localisation was reported in one study, and cytoplasmic localisation with transient microtubule binding altered by mutations in another one. We have studied human cells transfected with two isoforms of spastin (full length [FL], and alternatively spliced [AS] lacking exon 4), both wild type and with the well-characterised K388R mutation. Prolonged overexpression of all constructs in neuroblastoma (SH-SY5Y) cells led to cell death. A stable clone expresses AS wild type in a punctate cytoplasmic distribution. The mictrotubule network in these cells appears disrupted, and spastin colocalises with tubulin in growth cones. Transiently transfected SH-SY5Y and epithelial (HEK293) cells have a cytoplasmic localisation of FL and AS spastin. The staining is irregular and punctate, with frequent aggregates. The mutant forms have a similar distribution, but prolonged expression appears to lead to a filamentous pattern of staining. The disrupted microtubules in the stable clone and the toxic effects of overexpression are consistent with the postulated microtubule-severing function of spastin.

029 NARATRIPTAN MODULATES TRIGEMINOVASCULAR NOCICEPTIVE TRANSMISSION IN THE VENTROPOSTEROMEDIAL (VPM) THALAMIC NUCLEUS OF THE RAT

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Objectives: To investigate whether naratriptan can modulate trigeminovascular nociceptive transmission in the VPM nucleus of the rodent thalamus.

Methods: Trigeminovascular nociceptive afferents were identified in the VPM by electrical stimulation of the superior sagittal sinus (SSS). The ability of naratriptan administered both intravenously (5 mg/kg) and by microiontophoresis to inhibit this response was studied. In addition, to investigate a potential post-synaptic site of action, $_L$-glutamate was microiontophoresed onto the cell bodies of relay cells in 5s pulses and the response was studied during co-administration of saline (control), and naratriptan.

Results: Naratriptan (5 mg/kg) was able to inhibit the response to SSS stimulation after intravenous ($n=8$, $P=0.003$, $t_7=4.44$) and microiontophoretic ($F_{2,14}=16.55$, $P<0.0001$) application. In all cells tested naratriptan suppressed the response to $_L$-glutamate ($F_{1,8}=34.72$, $P<0.001$) in comparison to the control.

Conclusions: The response of VPM thalamic relay cells activated by trigeminovascular nociceptive afferents can be modulated by naratriptan. Furthermore this action appears to be post-synaptic. Triptans may therefore have a site of action in the thalamus, in addition to those already described in the trigeminal nucleus caudalis.

030 THE DIAGNOSIS OF SPATIAL NEGLECT IN ACUTE STROKE

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Spatial neglect following stroke is a disabling syndrome. Although numerous clinical tests have been developed to diagnose the syndrome, none is 100% sensitive, so the diagnosis of neglect is often based on overall clinical impression.

150 acute stroke patients were prospectively assessed for personal, peripersonal, extrapersonal, representational and motor neglect using a battery of standard bedside tasks. 67% of right hemisphere patients demonstrated signs of left neglect. Of the 45 left hemisphere patients whose speech and language ability allowed them to be tested, only 3 showed signs of severe right neglect while 8 others manifested mild elements of neglect. 4 patients (1 with left and 3 with right hemisphere damage) showed visual extinction without any signs of spatial neglect.

The three types of test that were most sensitive in detecting neglect were dense cancellation (sensitivity 58–65%), line bisection (61%) and naming 10 objects around the room (52%). Importantly, we found that the combination of these three types of test were sufficient to diagnose 90% of cases of left sided neglect. These findings demonstrate that two thirds of right hemisphere patients may suffer from neglect which can be diagnosed swiftly at the bedside by a combination of three simple tests.

031 A SYSTEMIC REVIEW OF STUDIES OF PROGNOSIS OF UNTREATED BRAIN CAVENOUS MALFORMATIONS

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Background: Despite a considerable volume of literature about cavernous malformations (CMs) of the brain, there is little information about the prognosis of untreated CMs.

Methods: We searched Medline and Embase from 1966 and 1980 respectively to July 2002, using a 12-line electronic search strategy. We sought prognosis studies that met our pre-defined selection criteria: population-based, prospective, clearly defined diagnostic criteria, inception cohort, >50 patients, complete follow-up, relevant outcome events

Results: No study met all of our selection criteria and there were no population-based studies. Most were subject to selection bias, had short follow-up and retrospectively collected data. Variable definitions of CM haemorrhage, and calculation of haemorrhage rates as a lifetime risk, or as a rate based on the period of follow-up, make outcomes difficult to compare. Another difficulty is, whether haemorrhage rates are calculated per patient or per lesion. The published data on annual rate of first symptomatic haemorrhage vary from 0.4% to 2.7%/person/year. Re-bleed rates vary from 3.8%/person/year to 22%/lesion/year. Being young, female and presenting with haemorrhage may increase re-bleed rates.

Conclusion: A prospective, population-based study of the long-term morbidity and mortality for people affected by cavernous malformations is needed. Accepted epidemiological methods must be used.

032 eNOS HAPLOTYPES AND RISK OF CEREBRAL SMALL VESSEL DISEASE

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Introduction: Genetic influences are important in multifactorial cerebral small vessel disease (SVD), possibly acting via endothelial dysfunction. We tested 3 polymorphisms located towards the 5′ end of the endothelial nitric oxide synthase (eNOS) gene (T-786C, intron 4ab, G894T) as risk factors for SVD and different SVD subtypes; isolated lacunar infarction and ischaemic leukoaraiosis.

Methods: 300 SVD patients and 600 community controls were genotyped. Polymorphisms were tested individually and together using haplotype analysis software. Nitrate (NO_x) levels were measured in a subgroup.

Results: The intron 4a variant protected against isolated lacunar infarction, OR 0.55 (95% CI 0.35–0.86), $p=0.01$. Haplotypes encountered were different in this subtype vs. controls ($p=0.001$) with the −786C promoter/intron 4a combination particularly under-represented. NO_x levels were associated with a promoter polymorphism, T-786C ($p=0.03$), whilst the intron 4a allele appeared to modify NO_x levels associated with T-786C genotype.

Conclusion: The intron 4ab genotype was associated with isolated lacunar infarction. The protective influence of intron 4a could involve

changes in eNOS promoter activity and increased NO. The specific association with isolated symptomatic lacunar infarction and not ischaemic leukoaraiosis supports different aetiopathogenesis of the 2 subtypes. Absence of NO could lead to localised microatheroma in proximal arterioles rather than diffuse arteriosclerosis affecting distal perforating vessels.

033 LEUCOCYTE-PLATELET COMPLEX FORMATION IS INCREASED IN PATIENTS WITH ACUTE SYMPTOMATIC COMPARED WITH ASYMPTOMATIC SEVERE CAROTID STENOSIS

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Introduction: The mechanisms responsible for the disparity in stroke risk between patients with recently symptomatic and asymptomatic severe carotid stenosis are not understood.

Methods: Flow cytometry was used to measure the platelet expression of CD62P, CD63 and PAC1 binding, and the % leucocyte-platelet complexes in acute (n = 19) and convalescent (n = 16) symptomatic compared with asymptomatic severe carotid stenosis patients (n = 16). Most patients were on aspirin monotherapy, although combination antiplatelet therapy was more commonly used in the symptomatic group.

Results: The median % neutrophil-platelet ($p = 0.004$), monocyte-platelet ($p = 0.046$) and lymphocyte-platelet complexes ($p = 0.02$) were higher in acute symptomatic compared with asymptomatic severe carotid stenosis patients. The other platelet activation markers were not significantly higher in the symptomatic group. In patients on aspirin monotherapy, the % neutrophil-platelet complexes ($p = 0.03$), and the % monocyte-platelet complexes ($p = 0.03$) were higher in acute symptomatic (n = 11) compared with asymptomatic severe carotid stenosis patients (n = 14).

Conclusions: Leucocyte-platelet complex formation is increased in patients with recently symptomatic compared with asymptomatic severe carotid stenosis. This study improves our understanding of the potential mechanisms involved in the pathogenesis of ischaemia in severe carotid stenosis.

034 THE PRESENTATION OF ADULTS WITH ARTERIOVENOUS MALFORMATIONS OF THE BRAIN: PROSPECTIVE, POPULATION-BASED STUDY

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Background: Population-based data about adults with brain arteriovenous malformations (AVMs) are sparse, and hospital-based series vary in their composition.

Methods: Since 1999 a population-based cohort of adults with brain AVMs has been prospectively recruited using multiple overlapping sources of case ascertainment in Scotland. Radiological diagnosis is validated by independent review, and clinical data are collected from case notes.

Results: 92 adults were first diagnosed with a brain AVM in 1999 and 2000. 19 (21%) brain AVMs were incidental findings. Of the 73 symptomatic adults, 42 (58%) presented with intracranial haemorrhage, 25 (34%) presented with epilepsy, and 6 (8%) presented with focal neurological deficits. The overall mean age of presentation was 45 ± 16 years; whilst the mean ages of presentations with haemorrhage or epilepsy were comparable, those with focal deficits were ~10 years older, and individuals with incidental brain AVMs were ~20 years older ($p = 0.0001$). Prior to the incidental brain AVM diagnoses, 21% of these adults had an intracranial haemorrhage ($p = 0.01$), 21% had ≥ 1 epileptic seizure ($p = 0.04$) and 32% had epilepsy or haemorrhage.

Conclusions: One fifth of prospectively detected adults with brain AVMs are diagnosed incidentally, of whom one third have prior symptomatic events, which might have led to earlier detection.

035 THE MRC's ASYMPTOMATIC CAROTID SURGERY TRIAL (ACST)—RESULTS AFTER 5 YEARS FOLLOW UP

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Background: Although endarterectomy (CEA) may be indicated in symptomatic carotid stenosis exceeding 70%, the place of asymptomatic CEA in stroke prevention remains to be established. This was the main objective of this study.

Methods: Since 1993, 3101 patients in over 100 European centres have been randomised to best medical treatment (BMT) + immediate CEA or BMT + deferred CEA, i.e. surgery reserved for those cases who later developed appropriate symptoms. Nearly all patients entered had over 80% carotid stenosis. Randomization, by the Clinical Trials Service Unit, was within each centre. Surgeons became eligible to take part with a good ''track record'' on at least 50 CEAs. Surgical technique and medical treatment was left to each centre.

Results: The early surgery group had a highly significant reduction in stroke risk compared with the deferred group. The overall peri-operative risks were 2.6%. The benefit was clear under 75 years. In subjects over 75, deaths from other causes removed the value of surgery. CEA proved to be particularly valuable in subjects with higher cholesterol. No significant difference in benefit has been found 80–89% and 90–99% stenosis.

Discussion: These findings are likely to increase the numbers considered for CEA and have important economic implications.

ABN abstracts

Proceedings of the Association of British Neurologists Autumn Meeting, 1–3 October 2003

ABN MEDAL AWARD 2003

David Aitken Shaw. *NEF Cartlidge*

Like most Englishmen who have held high office, David Shaw is a Scot. In common with many of his generation he was late into medicine, having served in the Navy in the latter part of the war. His seafaring career was cut short when his landing craft was sunk by a torpedo and he moved to train in medicine. The Navy's loss has definitely been neurology's gain.

His early training in Edinburgh with J K Slater excited his interest in neurology and he subsequently became Lecturer at The National Hospital with John Marshall and was one of the earliest neurologists to develop an interest in cerebrovascular disease and stroke.

Henry Miller recognised his talents and brought him to Newcastle to expand research activities into cerebrovascular disease, but David's interests soon turned to undergraduate education and he rapidly progressed up the medical school hierarchy, becoming Clinical Sub-Dean, and Dean.

His manifest experience and enthusiasm in this area became recognised when as a member of the GMC, he became Chairman of the Education Subcommittee and was largely responsible for the production of the document ''Tomorrow's doctors''.

The statutory recommendations of this document have transformed medical education, resulting in—among other things—a shift of emphasis from factual information to clinical skills. Tomorrow's doctors are indebted to David Shaw.

He has made considerable contributions to the JCHMT, the University Hospitals Association, the Association of the Study of Medical Education and of course, our own Association, serving as Council member, being Treasurer for many years, and becoming President in 1988.

The Association has chosen wisely to honour David Shaw with the award of its medal for his contributions to neurology, to the Association itself, and to medical education in general. Professor Shaw, we look forward with interest to your presentation on ''Pupils of Argyll-Robertson''.

001 ABNORMALITIES IN CARDIAC RHYTHM REVEALED IN PATIENTS WITH REFRACTORY EPILEPSY

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Background: In the United Kingdom over 500 deaths per year are attributable to sudden unexpected death in epilepsy (SUDEP). SUDEP may be caused by potentially avoidable fatal cardiac arrhythmias and asystole following seizures.

Methods: We implanted REVEAL Plus cardiac rhythm monitoring devices into 11 male and 8 female patients with severe focal epilepsy who had had diagnostic video and EEG. Each volunteer kept a prospective seizure diary and attended our clinic for regular downloading of the recorded cardiac rhythm data over a median 16 month period.

Results: In all patients habitual seizures were associated with increased heart rate. Six patients consistently recorded ictal heart rates of greater than 120 beats per minute (bpm). Ictal bradycardia (30 bpm) was observed in two patients and prolonged in one. Significant episodes of sino-atrial (SA) node arrest occurred in two patients and lasted five and 13 seconds respectively. The first occurred peri-ictally while in the second a seizure was not noted at the time. Permanent pacemaker insertion has since been performed in both these patients and is planned for the patient with the prolonged ictal bradycardia.

Conclusions: A potentially life-threatening cardiac rhythm abnormality was recorded in three of 19 patients, requiring permanent pacemaker insertion. These findings necessitate a profound re-evaluation of the role of long-term cardiac monitoring in patients with epilepsy.

002 THE VALUE OF THE ELECTROCARDIOGRAPH (ECG) IN A FIRST SEIZURE CLINIC

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Current guidelines recommend recording a standard 12 lead ECG in patients presenting with suspected seizures. The yield from this investigation is unknown. We reviewed 163 (of 164) consecutive cases seen in a First Seizure Clinic retrospectively. Referrals were from GPs (69% patients), hospital physicians (20%) and A&E (11%). Average age was 33 years and 55% were male.

Diagnoses after the history and examination were: seizure (50%), syncope (30%), uncertain (13%), others (7%). Electrocardiographs (ECGs) were recorded with computer analysis and read by a consultant cardiologist. 130 patients had an ECG, 15% were abnormal. Abnormal ECGs were found in 12 patients with seizures, 3 with syncope, and 2 with an uncertain diagnosis. Abnormalities included: long QT (one patient with diagnosis of seizure, two with unknown diagnosis), short PR interval (reflex anoxic seizure patient) and unexplained bradycardia (heart rate <60, 4 patients with seizures). The ECG led to further investigations (echocardiogram, prolonged ECG, cardiac electrophysiological studies) on the advice of the cardiologist.

Cardiac abnormalities can cause blackouts which may be difficult to distinguish from epileptic seizures. ECGs can be useful in suggesting cardiac causes. Close co-operation between first seizure clinics and cardiological services is essential.

003 PHYSIOLOGICAL IMAGING OF INTERICTAL EPILEPTIFORM ACTIVITY USING SIMULTANEOUS EEG-CORRELATED FUNCTIONAL MRI

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Aim: To characterise and map bloody oxygen level dependent (BOLD) signal changes linked to interictal epileptiform discharges (IEDs), a large group of patients with focal epilepsy.

Methods: 50 patients with localisation-related epilepsy and frequent IEDs were studied on a GE Horizon 1.5T scanner using whole-brain EPI (TE/TR 40/3000, 64×64 matrix). 700 scans were acquired continuously over 35 minutes. Ten channels of scalp EEG, plus ECG, were recorded simultaneously using an MR-compatible system, with on-line artefact subtraction. IEDs were classified, labelled, and used to perform an event-related analysis of the fMRI data using SPM99.

Results: Good quality EEG was obtained in all patients and IEDs were successfully captured from 29: 12 (41%) had BOLD activations concordant with electroclinical data across a range of pathologies, 4 (14%) activation of uncertain significance, and in 7 (24%) no activation was observed. In this group, there was a tendency to abnormal background rhythms, head motion, and subtle myoclonus. In 4 patients (14%) IEDs were too frequent for fMRI and in 2 patients, the study was terminated due to seizures.

Conclusion: Simultaneous EEG/fMRI can provide novel localising information in selected patients, namely those with frequent stereotyped high-amplitude unifocal IEDs readily identifiable from the background EEG.

004 DIFFERENT PATTERNS OF ELECTROPHYSIOLOGICAL DEFICIT IN MANIFESTING AND NON-MANIFESTING CARRIERS OF THE DYT1 GENE

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Background: A mutation in the DYT1 gene on chromosome 9q34 causes early-onset primary torsion dystonia (PTD) with autosomal dominant inheritance but low phenotypic penetrance. The aim of the present study was to assess the functional consequences of the DYT1 gene, by comparing the electrophysiology of cortical and spinal circuits in clinically affected and unaffected carriers of the DYT1 mutation.

Method: We assessed intracortical inhibition and facilitation (ICI/ICF), the cortical silent period (SP), and spinal reciprocal inhibition (RI) in 10 manifesting carriers (MDYT1), 7 non-manifesting gene carriers (NMDYT1) and 13 healthy controls.

Results: The MDYT1 subjects had abnormalities similar to those seen in previous studies of non-genetically characterised individuals with primary dystonia with reduced ICI, shorter SP and absent presynaptic phase of RI compared with the healthy controls. NMDYT1 subjects had a similar significant reduction in cortical inhibition (ICI, SP), but their spinal RI was not different from controls.

Conclusions: We conclude that clinical expression of dystonia depends on widespread electrophysiological deficits, and the presence of the DYT1 mutation itself leads only to a subset of these changes. This is consistent with the hypothesis that additional environmental/genetic insults may be needed in to reveal clinical symptoms in DYT1 gene carriers.

005 PD LIFE—A PROSPECTIVE MULTI-CENTRE LONGITUDINAL AUDIT OF QUALITY OF LIFE IN PARKINSON'S DISEASE ACROSS THE UK

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Background: PDLIFE is a clinician led multicentre prospective national audit monitoring (a) changes in Quality of Life in response to treatment (QoL), (b) prescribing trends of anti-PD drugs across the United Kingdom (UK) and (c) identify changes in QoL, which may trigger changes or initiation of treatment in Parkinson's disease (PD).

Methods: Using the validated PDQ-39 QoL scale and clinical assessment form monitoring changes in treatment, and co-morbidity annually for 5 years. All PD patients (irrespective of age, drug naïve or receiving monotherapy) at an early (diagnostic and maintenance) stage are included. Additionally sleep function, restless legs are also being evaluated.

Results: In the pilot phase 10 core UK centres have recruited 250 patients since 2002. 79 have attended first follow up (mean duration follow-up period of 297 days). It is expected that by 2004 we will obtain baseline data on 500 patients and follow-up data on 200 patients.

Conclusions: Preliminary pilot data suggest that in the UK, dopamine agonists are rarely used as monotherapy in older people (65–86 yrs) even in mild PD. Patients left untreated at diagnosis deteriorate significantly in several domains of QoL assessment even after 6 months.

006 PARKIN IS RECRUITED INTO AGGRESOMES IN A STRESS-SPECIFIC MANNER AND ITS OVER-EXPRESSION REDUCES AGGRESOME FORMATION

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Mutations in the parkin gene cause autosomal recessive juvenile parkinsonism (AR-JP). Parkin is present in Lewy bodies (LBs) of sporadic Parkinson's disease (PD) brains. However, LBs are not a feature of AR-JP brains suggesting that parkin may play a critical role in the formation of LBs. We investigated the role of parkin in aggresome formation in human dopaminergic neuroblastoma cells. We now report that endogenous parkin is recruited into aggresomes under a variety of stresses. However, we found the protein unfolding stress, tunicamycin, did not induce the formation of parkin-positive aggresomes. Confocal studies show that vimentin surrounds parkin in aggresomes and that Hsc70 and ubiquitin are also found in the aggresomes formed during proteosome inhibition. We established stable cell lines over-expressing human parkin. The formation of aggresomes was markedly reduced in cell lines over-expressing parkin compared to the vector alone for all stresses examined. We further show that the reduction in aggresomes does not correlate well with parkin's neuroprotective properties. In summary we show that although endogenous parkin may be a necessary component of aggresomes, excess levels of parkin may lead to increased removal of misfolded proteins by its ubiquitin ligase activity and thereby abrogate aggresome formation.

007 HIGH DENSITY SINGLE NUCLEOTIDE POLYMORPHISM MAPPING OF PROTEIN KINASE C ALPHA GENE IN A UK POPULATION OF MULTIPLE SCLEROSIS PATIENTS

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Introduction: Linkage studies in multiple sclerosis (MS) families have implicated a 2.5 Mb region of chromosome 17q22–24. Protein kinase C alpha (PRKCA) maps to this interval and is involved in both T cell regulation and proliferative responses. Hence, it is a prime candidate MS susceptibility gene.

Methods: Association of 35 SNP markers mapping at approximately 10 Kb intervals within the PRKCA gene was investigated in 184 unrelated UK MS patients and 340 controls. Genotyping was performed with Assays-on-Demand (ABI, UK) allelic discrimination assays on a Taqman™ platform. Haplotype frequencies were estimated using HelixTree software (Golden Helix Inc, USA) and compared between cases and controls.

Results: A cluster of SNPs mapping to the telomeric portion of the PRKCA gene showed evidence for association by genotype and this association appeared confined to DR*15 carriers. A haplotype of 2 SNPs mapping to the promoter region of the gene showed evidence for association (Bonferroni corrected p value = $9.3 \times 10-4$).

Conclusion: Our results provide further support for association of the 17q22–24 region with MS and implicate PRKCA as a possible MS disease gene. Association in a subgroup of patients supports the concept of genetic heterogeneity within MS cases.

008 THE RELATIONSHIP BETWEEN FUNCTION AND STRUCTURE OF THE POSTERIOR VISUAL PATHWAYS FOLLOWING OPTIC NEURITIS

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Introduction: Previous MRI studies have independently demonstrated functional changes in the visual cortex and structural changes in the optic radiations following optic neuritis. We investigated how visual cortex function and optic radiation structure are related in patients with previous optic neuritis.

Methods: Seven patients one year after isolated unilateral optic neuritis and seven controls underwent visual functional MRI (fMRI) and whole brain DTI (diffusion tensor imaging). DTI based tractography was used to extract each optic radiation from which the mean fractional anisotropy (FA) was calculated. Regression analyses were performed between the fMRI images and optic radiation FA values.

Results: The optic radiation FA was positively correlated with the visual cortex fMRI response for the unaffected eye in patients ($p = 0.002$) and the matched eye in controls ($p = 0.02$). This relationship was stronger in patients than controls ($p = 0.07$). For the affected eye, there was weak evidence for a positive correlation in patients ($p = 0.08$) and controls ($p = 0.06$) with no difference between the two groups.

Conclusions: A novel relationship has been demonstrated between the visual fMRI response and the structure of the subserving optic radiations. This is stronger for the unaffected eye in the patient group and suggests function-structure plasticity following recovery from optic neuritis.

009 OLIGOCLONAL BAND NEGATIVE MS—DOES IT EXIST

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Objective: To study the features and reliability of the diagnosis of oligoclonal band (OCB) negative cerebrospinal fluid (CSF) multiple sclerosis (MS), with reference to the diagnostic criteria for MS.

Method: A retrospective, sex-matched, case-controlled study of patients diagnosed with OCB negative MS over a 6-year period from one major neurology centre.

Results: 19 OCB negative patients were identified from 539 cases and compared with an equal number of OCB positive controls. Several features in the OCB negative group were unusual with a higher frequency of headaches, generalised seizures, depression, cognitive impairment and psychosis. Although a ''better explanation'' was not obvious in these patients, there still remained the possibility of alternative pathology in 6 cases. MRI abnormalities were frequent but non-specific, with a higher rate of abnormal visual evoked potential studies compared to controls. 58% of OCB negative cases had either moderate or severe neurological disability.

Conclusion: The lower importance allowed for CSF studies in the new McDonald criteria results in a significantly greater proportion of patients being labelled ''clinically definite'' compared to the Poser criteria, which may decrease vigilance regarding alternative diagnoses. The presence of atypical clinical features is much commoner in this group and the previous benign implication for OCB negative MS may not be true.

010 DISTINCT PROFILES OF CHEMOKINE RECEPTOR EXPRESSION IN PATTERN II AND III MULTIPLE SCLEROSIS LESIONS

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Introduction: Four subtypes (pattern I–IV) of multiple sclerosis were identified based on neuropathological features. Pattern II and III account for 83% of cases. The mechanisms of myelin injury in subtypes of MS are not well understood. Monocytes, microglia and macrophages are present in all MS lesions and the expression of chemokine receptors is important to their recruitment, differentiation and function.

Aims: To determine the profile of CCR1, CCR3 and CCR5 expression on mononuclear phagocytes relative to demyelinating activity of pattern II and III lesions using immunohistochemistry.

Results: The numbers of cells expressing CCR1 and CCR5 varied significantly and consistently in relation to demyelinating activity of pattern II but not III lesions. A novel population of CCR3 expressing rod-shaped microglia was detected in pattern III but not pattern II lesions. Recently recruited monocytes co-expressed CCR1 and CCR5 in pattern II and III lesions.

Conclusion: Tissue environments in pattern II and III lesions are strikingly different. The profiles of CCR1 and CCR5 are consistent with pro-inflammatory cytokine mediated tissue damage in pattern II lesions. Pattern III lesions contained a population of CCR3-positive rod-shaped microglia, implying a distinct mechanism of microglial activation in pattern III lesions.

011 SPINAL CORD ATROPHY IN EARLY PRIMARY PROGRESSIVE MULTIPLE SCLEROSIS

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Background: Spinal cord symptoms are a common presenting feature in Primary Progressive Multiple Sclerosis (PPMS) and may result from underlying neurodegenerative processes. This study assesses cord atrophy in early PPMS using two techniques and examines the relationships between spinal cord atrophy, brain atrophy and disability.

Methods: 43 patients with early PPMS (within 5 years of disease onset) were assessed clinically and with 3D volumetric scans of brain and spinal cord. Spinal cord atrophy was assessed by (1) calculating the area of five slices axially reconstructed at the level of C2 and (2) measuring the total volume of extracted cervical cord, comparing the results obtained with 25 age and sex matched controls.

Results: Mean cervical cord area was less in patients than controls (73.4 mm^2 (SD 8.8):79.6 mm^2 (SD 7.5), $p=0.007$) and associations were found between cord volume and total brain volume ($r=0.5$, $p<0.001$) and brain white matter fraction ($r=0.4$, $p=0.021$). There was no relation between cord size and disability.

Conclusion: Spinal cord atrophy is present early in the disease course in PPMS and, at this stage, appears to relate to brain atrophy but not disability. This study suggests that spinal cord neurodegeneration is an early event in PPMS.

012 THE ORIGIN AND EVOLUTION OF THE ARTHROPOD-BORNE VIRUS, JAPANESE ENCEPHALITIS

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Encephalitides caused by arthropod-borne viruses are becoming increasingly important globally, with the spread of West Nile virus to Europe and the United States, and the continuing spread of Japanese encephalitis in Asia. However, the origins, evolution, and factors governing the wide variation in clinical features are poorly understood. Japanese encephalitis was first described in Japan in the 1870s, and has spread across Asia to cause large summer epidemics in northern regions, and year round endemic disease in southern regions. Differences in the distribution of the four genotypes of virus have been postulated to explain the differing clinical epidemiology. We have determined the complete nucleotide sequence of an Indonesian strain of virus (which represent the oldest lineage), compared it with other full-length genomes, and examined the geographical distribution of all known isolates. We show that Japanese encephalitis virus originated in the Indonesia-Malaysia region and evolved here into the different genotypes, which then spread across Asia. No association between genotype and phenotype was seen in a mouse model of Japanese encephalitis. Our data suggest that southeast Asia may be an important zone for emerging viruses, and have implications for the spread of other arthropod-borne viruses.

013 NEITHER BLINDSIGHT NOR OVERSIGHT BUT MINDSIGHT: PATHOLOGICAL COMPLETION WITHOUT EVIDENCE OF NEGLECT FOLLOWING DAMAGE TO OCCIPITAL CORTEX

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Homonymous scotomata may be accompanied by the subjective experience of completion of forms that ''should'' be occluded by the visual defect, a symptom termed Pathological Visual Completion. We report a single case whose experience of completion has been studied systematically by manipulating the parameters of the stimulus display. His disorder could not be explained by residual vision nor an attentional disorder. Pattern masking, varying the contrast characteristics of stimuli and changing visible cues to structural symmetry all had precise effects whereas familiarity and structural coherence did not. We conclude that pathological completion may be a positive cognitive event implicating processes that underlie the normal analysis of occluded forms.

014 FOCAL VENOUS INFARCTION OF THE SUPPLEMENTARY EYE FIELD REVEALS ITS FUNCTION

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The specific contribution of the 'supplementary' eye field (SEF) to the control of eye movements has eluded both electrophysiological investigations in monkeys and functional imaging studies in healthy humans. Here, we present detailed imaging and behavioural data on a rare patient who suffered extremely focal venous infarction of the medial frontal cortex limited to the SEF.

Although the patient showed no impairment in making simple reflexive saccades, he encountered severe difficulty when required to change saccadic plans. Importantly, however, he was aware of his errors and corrected them. Similarly, when required to switch between rules linking a visual stimulus with a saccadic response, he was significantly impaired, but again corrected errors well. He also experienced difficulty learning new saccadic stimulus-response associations when selecting between four competing responses. Analogous experiments requiring hand, rather than eye movements, did not reveal any impairment. Finally, he showed deficits when required to make memory-guided saccadic sequences.

These findings suggest that the SEF normally acts to implement volitional control over saccades, particularly in situations of response conflict when there are competing saccadic plans. Such self-control over eye movements provides a model system to study the supervisory or 'executive' control functions of medial frontal areas.

015 THE CLINICAL PHENOTYPE OF NON-PARANEOPLASTIC VOLTAGE GATED POTASSIUM CHANNEL ANTIBODY (VGKC AB) ASSOCIATED CNS DISEASE

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VGKC-Ab associated limbic encephalitis with titres above 400 pM has recently been described. Here we screened patients with unexplained cognitive and/or behavioural symptoms for VGKC Abs, over a 4 year period in a general neurology clinic serving a population of 150 000 patients. Eight patients were positive. Two with classic non-paraneoplastic limbic encephalitis had high titres (>1500 pM); the other six had lower titres (100–500 pM) and presented with sub-acute cognitive syndrome with features of mania (n=1), prolonged transient global amnesia (n=1), severe post-ictal psychosis after a single cluster of four seizures associated with elevated thyroid antibodies (n=1), chronic symptoms of cognitive/behavioural impairment (n=1) and refractory epilepsy (n=2). Some patients responded to immunotherapies and some

spontaneously resolved. VGKC antibodies were not identified in patients with destructive or inflammatory CNS diseases such as a Rasmussen's Encephalitis or MS, or in other disease controls.

Thus a range of cognitive disorders can be associated with VGKC Abs. This raises the possibility that other conditions such as transient global amnesia, Hashimoto's encephalopathy and non-Herpes Simplex encephalitis include VGKC Ab mediated disease. We believe VCKC Ab associated CNS disorders are usually non-paraneoplastic, relatively common and the majority are currently undiagnosed.

016 PRECISE VOLUME MEASUREMENTS OF LOW-GRADE GLIOMAS. SOME SURPRISING FINDINGS

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Background: Little is known about the growth rates of low-grade gliomas (LGGs) during their 'premalignant' phase. We have developed a technique that can measure tumour volumes semi-automatically and hence determine tumour growth rates.

Methods: Patients with LGGs were scanned on a 1.5 T Signa LX MRI scanner (GE Medical Systems). Semi-quantitative volumes were determined on coronal FLAIR sequences using DispImage® software, which automatically 'contours' and calculates the area of a region of interest. Volume measurements were obtained twice by two observers blinded to the clinical status of the patients. Transformation was defined by clinical (significant deterioration) and/or radiological (new gadolinium enhancement) criteria.

Results: 27 patients have been followed up with six monthly scans for a mean of 20 (range 11–30) months. Seven have transformed, of whom one has died and twenty are stable. Intra- and inter-rater intra-class correlations are 0.99 (95% CI 0.98–0.99) and 0.98 (95% CI 0.97–0.98) respectively. Tumour volumes in the stable group were not significantly lower than in the transformers at baseline but the average growth rate was greater amongst the transformers than amongst the stable group (35%/year (95 CI 24–47%) vs 17%/year (95% CI 11–22%)) [p = 0.003].

Conclusions: Low-grade gliomas that are 'premalignant' grow faster than stable tumours.

017 FUNCTIONAL PARESIS—PARADOXES IN ILLNESS BELIEFS AND DISABILITY IN 107 SUBJECTS

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Objective: (1) To describe distress, disability and illness beliefs in consecutive patients presenting to neurologists with functional paresis and (2) to compare with these with patients who have neurological paresis.

Methods: Consecutive patients with recent onset functional or neurological paresis diagnosed by neurologists. Assessment included a semi-structured interview, a structured psychiatric interview and questionnaire assessment of distress, illness beliefs and disability.

Results: 107 subjects with functional paresis (mean age 39 years, 79% female, mean duration 11 months) were compared with 46 subjects with neurologically defined paresis (mean age 39 years, 83% female, mean duration 14 months). Although self-rated distress was similar, patients with functional paresis had significantly more psychiatric disorder at interview. Despite this, they were less likely to agree that stress was a cause of their symptoms (24% vs. 57%, $p<0.001$) and were twice as likely to have given up work because of their symptoms (59% vs. 29%, $p<0.001$), despite similar levels of self-rated disability.

Conclusions: Compared to patients with neurologically defined paresis, patients with functional paresis are less likely to blame stress for their symptoms (despite a higher rate of psychiatric disorder) but more likely to stop working (despite similar self-rated disability).

018 POTASSIUM CHANNEL ANTIBODY ASSOCIATED ENCEPHALITIS: A POTENTIALLY TREATABLE NON-PARANEOPLASTIC LIMBIC ENCEPHALITIS

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Background: Three cases of non-paraneoplastic reversible limbic encephalitis (LE) associated with voltage-gated potassium channel antibodies (VGKC-Ab) have previously been reported. We aimed to define the phenotypic features of this syndrome in more detail.

Methods and results: We studied 10 patients (9 male; age 44–79 yrs) positive for VGKC-Ab who presented over a 15-month period with memory loss, confusion and seizures. One patient had neuromyotonia. Syndrome of inappropriate anti-diuretic hormone secretion (SIADH) was present in eight. Eight patients had temporal lobe MRI signal change at presentation; paraneoplastic antibodies and CSF virology were negative in all. VGKC-Ab titres ranged from 450 to 5128 pM (cut-off <100 pM). Treatment with steroids, plasma exchange and intravenous immunoglobulin resulted in variable improvement, from slight to marked, coincident with the induced fall in VGKC-Ab, but medial temporal lobe atrophy and residual cognitive impairment were common. Over the same period, one case of paraneoplastic LE was identified in the two main centers.

Conclusions: VGKC-Ab-associated encephalopathy is a relatively common form of autoimmune, non-paraneoplastic LE. VGKC-Ab testing should be considered in patients presenting with LE, especially those with seizures, hyponatraemia and MRI signal change. Future work should aim to identify the frequency of this condition and establish optimal immunotherapy.

019 SYNTHETIC DISIALYL-GALACTOSE IMMUNOABSORBENTS CLEAR PATHOGENIC ANTI-GQ1B GANGLIOSIDE AUTOANTIBODIES FROM SERUM IN GUILLAIN BARRÉ SYNDROMES

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Guillain Barré syndrome frequently follows *Campylobacter jejuni* enteritis and molecular mimicry between carbohydrate epitopes on nerve gangliosides and the lipopolysaccharides (LPS) of *C. jejuni* accounts for the harmful autoimmune responses that result in impaired nerve function. Miller Fisher syndrome is associated with anti-GQ1b ganglioside autoantibodies in over 95% of cases and *C. jejuni* species isolated from affected cases bear GQ1b-like epitopes on their LPS. Non-specific plasma exchange ameliorates the severity and duration of the disease; however, removal of specific antibody by affinity plasma exchange might achieve superior outcomes since only the pool of harmful antibodies would be removed. A significant limiting factor to this therapeutic approach is the structural complexity and limited availability of ganglioside epitopes. Here we demonstrate that a proportion of anti-GQ1b antibodies that characterize MFS sera bind to the synthetic trisaccharide, alphaNeuAc(2–8)alphaNeuAc(2–3)betaGal covalently attached to BSA. Human polyclonal sera and murine monoclonal anti-GQ1b antibodies are inhibited by this trisaccharide epitope. The same trisaccharide immobilized on a Sepharose column depletes human serum of anti-GQ1b antibody. This proof of principle establishes that oligosaccharide-specific immuno-absorption therapy provides a novel approach to treating anti-ganglioside antibody-associated GBS and could be readily applied to clinical practice in conjunction with conventional plasma exchange.

020 OPHTHALMOPLEGIA: WHEN ALL THE TESTS ARE NEGATIVE

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The differential diagnosis of ophthalmoplegia can be difficult. Mitochondrial disease is a common cause of ophthalmoplegia in those patients without a demonstrable neuromuscular junction abnormality. Muscle biopsy is considered diagnostic in mitochondrial disease and classically shows a mosaic of cytochrome oxidase negative (CNF) and ragged red fibres (RRF).

In our patients with chronic external ophthalmoplegia (CPEO), there was disparity between extra-ocular muscle (EOM) and quadriceps, with much greater numbers of CNF in the clinically affected tissues (EOM). Subsequent quadriceps biopsies showed higher numbers of CNF. Of 115 patients with CPEO and a mitochondrial disease, four patients

presented with entirely normal muscle histochemistry yet were found to have pathogenic mitochondrial DNA (mtDNA) mutations. In one patient 10 years elapsed before a second biopsy was abnormal and prompted the discovery of a mtDNA deletion. We believe that many patients may exist who have bypassed mitochondrial investigations on the basis of normal muscle histochemistry.

This has important implications for the diagnosis of patients with ophthalmoplegia. A quadriceps biopsy devoid of CNF or RRF does not exclude the possibility of mitochondrial disease. Detection of such by specific molecular analysis may prevent further unnecessary investigation, misdiagnosis and inappropriate treatment strategies.

021 INVOLUNTARY MOVEMENTS, SENSORY SYMPTOMS AND EARLY PSYCHIATRIC FEATURES IN SPORADIC VERSUS VARIANT CREUTZFELDT JAKOB DISEASE

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Background: Variant CJD (vCJD) typically presents with psychiatric features, early involuntary movements and sensory symptoms whereas sporadic CJD (sCJD) typically presents with rapid cognitive decline. Atypical sCJD is the most important differential of vCJD.

Aims: To identify the incidence in sporadic CJD of early clinical features typical of vCJD.

Methods: A case note review of all pathologically proven UK sCJD cases (1990–2002).

Results: Of 486 patients with sCJD 25 (5.4%) presented with sensory disturbance, 20 (4.1%) with involuntary movements and eight (1.6%) with pure psychiatric features. Eight of these (15%) fulfilled the criteria for ''possible'' vCJD.

The mean age at onset was 62 years (vCJD: 28 years). Mean duration of illness was nine months (vCJD: 13 months). None (including those with early prominent sensory features) had the MRI pulvinar sign. 6/27 (22%) had MRI changes characteristic of sCJD. Periodic EEG complexes were seen in 12/49 (25%). PRNP codon 129 data are available in 29 (66% MM, 14% MV, 20% VV).

Conclusions: 11% of sCJD cases presented with symptoms common at onset in vCJD. Prolonged diagnostic confusion with vCJD is unlikely given the usual clinical progression of symptoms. Investigations (EEG and MRI) are helpful.

022 THE CRITICAL TIME WINDOW FOR REORGANISATION OF THE CORTICOSPINAL TRACTS ENDS CLOSE TO THE PERINATAL PERIOD IN MAN

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Aim: To investigate the critical time window for plasticity of the ipsi-lesional and contra-lesional corticospinal tract (CST) in man.

Subjects: All sustained unilateral stoke; 32 perinatally, 15 in childhood (>0.1–13 years), 13 as adults. All were >2 years after the stroke.

Methods: Surface EMG recorded from biceps brachii. Transcranial magnetic stimulation (TMS) to excite the CST. Ipsilateral and contralateral central motor conduction delays (CMCDs) measured. Topographical mapping of the areas of the cortex evoking responses.

Results: ***Contra-lesional CST*** Significant shortening of contralateral and ipsilateral CMCDs was observed only in subjects with perinatal stroke (Z scores: contralateral CMCD, mean −0.85; 95% confidence limits −1.38 to −0.30; ipsilateral CMCD, mean −6.1, 95% confidence limits −6.98 to−3.62). ***Ipsi-lesional CST*** A significant shift in the cortical site evoking responses was observed only following perinatal stroke (displacement laterally and posteriorly in comparison to the non infarcted hemisphere: mean lateral +1 cm, 95% confidence limits +0.45 to +1.54 cm; mean posterior +1.17 cm, 95% confidence limits +2.11 to +0.24 cm). 4/15 who suffered stroke in childhood showed a large shift (range −2 to +2 cm laterally and −2 to +4 cm posteriorly).

Conclusion: The critical time widow for contra-lesional tract reorganization ends near the perinatal period but ipsi-lesional cortical reorganization may occur later.

023 GENETIC EPIDEMIOLOGY OF ISCHAEMIC STROKE

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To design molecular genetic studies of stroke we need reliable genetic epidemiology. To determine whether family history (FHx) of stroke is a predictor of incident ischaemic stroke we studied unpublished data from the ongoing Oxford Vascular Study (OXVASC) and the Oxfordshire Community Stroke Project (OCSP) and performed a systematic review of published studies.

FHx of stroke was a risk factor for stroke in case-control (overall OR=1.67, 95% CI 1.6–1.8, $p<0.00001$, 26 studies) and cohort studies (1.29, 1.2–1.4, $p<0.00001$, 8 studies) but there was major heterogeneity between studies ($p<0.00001$) and significant ($p=0.01$) evidence of publication bias. Moreover, FHx of MI (1.50, 1.4–1.6, $p<0.00001$) and hypertension (1.52, 1.4–1.7, $p<0.0001$) were equally strong risk factors for stroke. However, FHx of stroke was more predictive if the analysis was confined to probands or relatives under 70. Only OXVASC, OCSP, and two published studies phenotyped strokes in detail. FHx of stroke was equally frequent in large and small vessel stroke (1.06, 0.8–1.4, $p=0.7$), but less frequent in cardioembolic stroke (0.69, 0.5–0.9, $p=0.01$).

Reliable interpretation of published FHx studies is difficult because of heterogeneity and probable publication bias. However, FHx appears to be associated with large and small vessel strokes in patients <70.

024 USE OF QUANTIFIED ACETAZOLAMIDE ACTIVATED XENON ENHANCED COMPUTERIZED TOMOGRAPHY (aXeCT) IN THE SELECTION OF PATIENTS FOR EXTRACRANIAL TO INTRACRANIAL (ECIC) BYPASS SURGERY

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Objective: To determine the outcome following ECIC bypass in patients with symptomatic carotid occlusive disease who display markedly reduced cerebrovascular reserve on aXeCT. Indication for surgery was the absence of significant cerebral blood flow (CBF) activation (<5%) from baseline values, and/or the presence on intra-cranial CBF steal.

Patients: Patients with chronic symptomatic cerebrovascular occlusive disease were assessed using aXeCT and comparing baseline CBF values with those obtained after 1g(iv) acetazolamide. 8 patients with extracranial carotid occlusions, and one young patient with extensive intracranial (Moya Moya) disease were selected for surgery in this way. Bypass was with a superficial temporal artery.

Outcome measures: 3 month i) clinical outcome ii) post-operative aXeCT iii) graft patency.

Results: There were no immediate postoperative complications. All patients reported marked improvements in preoperative symptoms and general well being at 3 months. Graft patency was 100%. All postoperative aXeCT scans demonstrated a return to normal reactivity.

Conclusion: aXeCT is a useful and convenient tool in the selection of patients suitable for ECIC bypass surgery. The indications remain rare, hence a multi-centre randomized study based on a activation studies is indicated for assessing long-term efficacy.

025 NEURAL CORRELATES OF INITIAL SEVERITY AFTER STROKE: A CROSS SECTIONAL fMRI STUDY

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Cerebral reorganisation after stroke may be studied in the human brain using functional magnetic resonance imaging (fMRI). It has recently been demonstrated that chronic stroke patients with poorer outcome are more likely to recruit non-primary motor networks during motor tasks. In order to determine whether this relationship holds true early after stroke, we studied eight patients with subcortical cerebral infarction 10–14 days after stroke onset. Patients underwent fMRI whilst performing isometric dynamic handgrip. Target force was individually set for each patient at 20% of affected hand maximum grip strength on the day of scanning, so that results would not be confounded by differences in effort exerted across subjects. Initial severity of stroke was assessed using several outcome measures.

A negative correlation between early outcome scores and size of handgrip related brain activation was observed bilaterally in primary motor cortex, supplementary motor area, cingulate motor areas, premotor cortex, posterior parietal cortex, visual cortex, and cerebellum. A positive correlation was observed in ipsilesional superior temporal sulcus and contralesional inferior parietal cortex. These results are similar to those in chronic stroke patients and suggest that non-primary

motor networks are recruited early after stroke during attempted hand movement, particularly by those with greatest deficit.

026 ARE THERE DIFFERENCES IN THE RISK FACTOR PROFILES OF LACUNAR AND NON-LACUNAR INFARCTS? A SYSTEMIC REVIEW

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Background: The arterial pathology of lacunar infarction (LACI) is poorly understood. Comparing risk factor profiles of LACI and non-lacunar infarction (non-LACI) may improve our understanding.

Methods: We performed a systematic review of studies comparing the prevalence of risk factors in LACI and non-LACI. For each risk factor, we calculated study-specific and, where appropriate, pooled relative risks for LACI versus non-LACI.

Results: We found 34 relevant studies. 10 used the TOAST classification, in which hypertension and diabetes favour a LACI diagnosis. Hypertension and diabetes appeared commoner among patients with LACI, but analyses of studies not including risk factors in stroke subtype definitions showed no association hypertension or diabetes and LACI (pooled RRs LACI vs non-LACI: hypertension = 1.09, 95% CI 1.01 to 1.17; diabetes = 0.93, 95% CI 0.81 to 1.08). Atrial fibrillation and carotid stenosis were less common in LACI than non-LACI. No other risk factors assessed differed in prevalence.

Conclusions: Many studies investigating differences in risk factor profiles between stroke subtypes used classification methods that included risk factors in the definitions, which leads to biased results. When these studies are excluded, the results do not support the assertion that hypertension and diabetes predispose to LACI more than non-LACI.

027 THE ANAL REFLEX CAN BE ELICITED BY COUGH AND SNIFF—VALIDATION OF A CLINICAL SIGN

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It is unclear whether contraction of the external anal sphincter (EAS) following a voluntary cough is an integral component of the cough response itself, or a reflex response to the abdominal and pelvic floor dynamics induced by the cough. We addressed this question by comparing motor latencies for intercostal, abdominal and EAS muscle contraction after trans-cranial magnetic stimulation with those following a voluntary cough. We also studied the responses to sniff. Our results suggest that EAS responses following a voluntary cough or sniff represent a polysynaptic reflex with characteristics resembling the conventional scratch-induced anal reflex. Since the cough-induced anal reflex response is both highly consistent and easily elicited its use in clinical neurological examination is appropriate.

028 CELLULAR STUDIES OF SPASTIN, THE PROTEIN COMMONLY MUTATED IN AUTOSOMAL DOMINANT HEREDITARY SPASTIC PARAPLEGIA (SPG4)

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Hereditary spastic paraplegia (HSP) is a neurodegenerative condition characterised by progressive lower limb spasticity. It is often inherited in an autosomal dominant fashion, and 40% of these cases are caused by mutations in the SPG4 gene, encoding spastin, whose function remains unclear. Nuclear localisation was reported in one study, and cytoplasmic localisation with transient microtubule binding altered by mutations in another one. We have studied human cells transfected with two isoforms of spastin (full length [FL], and alternatively spliced [AS] lacking exon 4), both wild type and with the well-characterised K388R mutation. Prolonged overexpression of all constructs in neuroblastoma (SH-SY5Y) cells led to cell death. A stable clone expresses AS wild type in a punctate cytoplasmic distribution. The mictrotubule network in these cells appears disrupted, and spastin colocalises with tubulin in growth cones. Transiently transfected SH-SY5Y and epithelial (HEK293) cells have a cytoplasmic localisation of FL and AS spastin. The staining is irregular and punctate, with frequent aggregates. The mutant forms have a similar distribution, but prolonged expression appears to lead to a filamentous pattern of staining. The disrupted microtubules in the stable clone and the toxic effects of overexpression are consistent with the postulated microtubule-severing function of spastin.

029 NARATRIPTAN MODULATES TRIGEMINOVASCULAR NOCICEPTIVE TRANSMISSION IN THE VENTROPOSTEROMEDIAL (VPM) THALAMIC NUCLEUS OF THE RAT

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Objectives: To investigate whether naratriptan can modulate trigeminovascular nociceptive transmission in the VPM nucleus of the rodent thalamus.

Methods: Trigeminovascular nociceptive afferents were identified in the VPM by electrical stimulation of the superior sagittal sinus (SSS). The ability of naratriptan administered both intravenously (5 mg/kg) and by microiontophoresis to inhibit this response was studied. In addition, to investigate a potential post-synaptic site of action, $_{L}$-glutamate was microiontophoresed onto the cell bodies of relay cells in 5s pulses and the response was studied during co-administration of saline (control), and naratriptan.

Results: Naratriptan (5 mg/kg) was able to inhibit the response to SSS stimulation after intravenous ($n = 8$, $P = 0.003$, $t_7 = 4.44$) and microiontophoretic ($F_{2,14} = 16.55$, $P < 0.0001$) application. In all cells tested naratriptan suppressed the response to $_{L}$-glutamate ($F_{1,8} = 34.72$, $P < 0.001$) in comparison to the control.

Conclusions: The response of VPM thalamic relay cells activated by trigeminovascular nociceptive afferents can be modulated by naratriptan. Furthermore this action appears to be post-synaptic. Triptans may therefore have a site of action in the thalamus, in addition to those already described in the trigeminal nucleus caudalis.

030 THE DIAGNOSIS OF SPATIAL NEGLECT IN ACUTE STROKE

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Spatial neglect following stroke is a disabling syndrome. Although numerous clinical tests have been developed to diagnose the syndrome, none is 100% sensitive, so the diagnosis of neglect is often based on overall clinical impression.

150 acute stroke patients were prospectively assessed for personal, peripersonal, extrapersonal, representational and motor neglect using a battery of standard bedside tasks. 67% of right hemisphere patients demonstrated signs of left neglect. Of the 45 left hemisphere patients whose speech and language ability allowed them to be tested, only 3 showed signs of severe right neglect while 8 others manifested mild elements of neglect. 4 patients (1 with left and 3 with right hemisphere damage) showed visual extinction without any signs of spatial neglect.

The three types of test that were most sensitive in detecting neglect were dense cancellation (sensitivity 58–65%), line bisection (61%) and naming 10 objects around the room (52%). Importantly, we found that the combination of these three types of test were sufficient to diagnose 90% of cases of left sided neglect. These findings demonstrate that two thirds of right hemisphere patients may suffer from neglect which can be diagnosed swiftly at the bedside by a combination of three simple tests.

031 A SYSTEMIC REVIEW OF STUDIES OF PROGNOSIS OF UNTREATED BRAIN CAVENOUS MALFORMATIONS

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Background: Despite a considerable volume of literature about cavernous malformations (CMs) of the brain, there is little information about the prognosis of untreated CMs.

Methods: We searched Medline and Embase from 1966 and 1980 respectively to July 2002, using a 12-line electronic search strategy. We sought prognosis studies that met our pre-defined selection criteria: population-based, prospective, clearly defined diagnostic criteria, inception cohort, >50 patients, complete follow-up, relevant outcome events

Results: No study met all of our selection criteria and there were no population-based studies. Most were subject to selection bias, had short follow-up and retrospectively collected data. Variable definitions of CM haemorrhage, and calculation of haemorrhage rates as a lifetime risk, or as a rate based on the period of follow-up, make outcomes difficult to compare. Another difficulty is, whether haemorrhage rates are calculated per patient or per lesion. The published data on annual rate of first symptomatic haemorrhage vary from 0.4% to 2.7%/person/year.

Re-bleed rates vary from 3.8%/person/year to 22%/lesion/year. Being young, female and presenting with haemorrhage may increase re-bleed rates.

Conclusion: A prospective, population-based study of the long-term morbidity and mortality for people affected by cavernous malformations is needed. Accepted epidemiological methods must be used.

032 eNOS HAPLOTYPES AND RISK OF CEREBRAL SMALL VESSEL DISEASE

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Introduction: Genetic influences are important in multifactorial cerebral small vessel disease (SVD), possibly acting via endothelial dysfunction. We tested 3 polymorphisms located towards the 5′ end of the endothelial nitric oxide synthase (eNOS) gene (T-786C, intron 4ab, G894T) as risk factors for SVD and different SVD subtypes; isolated lacunar infarction and ischaemic leukoaraiosis.

Methods: 300 SVD patients and 600 community controls were genotyped. Polymorphisms were tested individually and together using haplotype analysis software. Nitrate (NO_x) levels were measured in a subgroup.

Results: The intron 4a variant protected against isolated lacunar infarction, OR 0.55 (95% CI 0.35–0.86), p = 0.01. Haplotypes encountered were different in this subtype vs. controls (p = 0.001) with the −786C promoter/intron 4a combination particularly under-represented. NO_x levels were associated with a promoter polymorphism, T-786C (p = 0.03), whilst the intron 4a allele appeared to modify NO_x levels associated with T-786C genotype.

Conclusion: The intron 4ab genotype was associated with isolated lacunar infarction. The protective influence of intron 4a could involve changes in eNOS promoter activity and increased NO. The specific association with isolated symptomatic lacunar infarction and not ischaemic leukoaraiosis supports different aetiopathogenesis of the 2 subtypes. Absence of NO could lead to localised microatheroma in proximal arterioles rather than diffuse arteriosclerosis affecting distal perforating vessels.

033 LEUCOCYTE-PLATELET COMPLEX FORMATION IS INCREASED IN PATIENTS WITH ACUTE SYMPTOMATIC COMPARED WITH ASYMPTOMATIC SEVERE CAROTID STENOSIS

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Introduction: The mechanisms responsible for the disparity in stroke risk between patients with recently symptomatic and asymptomatic severe carotid stenosis are not understood.

Methods: Flow cytometry was used to measure the platelet expression of CD62P, CD63 and PAC1 binding, and the % leucocyte-platelet complexes in acute (n = 19) and convalescent (n = 16) symptomatic compared with asymptomatic severe carotid stenosis patients (n = 16). Most patients were on aspirin monotherapy, although combination antiplatelet therapy was more commonly used in the symptomatic group.

Results: The median % neutrophil-platelet (p = 0.004), monocyte-platelet (p = 0.046) and lymphocyte-platelet complexes (p = 0.02) were higher in acute symptomatic compared with asymptomatic severe carotid stenosis patients. The other platelet activation markers were not significantly higher in the symptomatic group. In patients on aspirin monotherapy, the % neutrophil-platelet complexes (p = 0.03), and the % monocyte-platelet complexes (p = 0.03) were higher in acute symptomatic (n = 11) compared with asymptomatic severe carotid stenosis patients (n = 14).

Conclusions: Leucocyte-platelet complex formation is increased in patients with recently symptomatic compared with asymptomatic severe carotid stenosis. This study improves our understanding of the potential mechanisms involved in the pathogenesis of ischaemia in severe carotid stenosis.

034 THE PRESENTATION OF ADULTS WITH ARTERIOVENOUS MALFORMATIONS OF THE BRAIN: PROSPECTIVE, POPULATION-BASED STUDY

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Background: Population-based data about adults with brain arteriovenous malformations (AVMs) are sparse, and hospital-based series vary in their composition.

Methods: Since 1999 a population-based cohort of adults with brain AVMs has been prospectively recruited using multiple overlapping sources of case ascertainment in Scotland. Radiological diagnosis is validated by independent review, and clinical data are collected from case notes.

Results: 92 adults were first diagnosed with a brain AVM in 1999 and 2000. 19 (21%) brain AVMs were incidental findings. Of the 73 symptomatic adults, 42 (58%) presented with intracranial haemorrhage, 25 (34%) presented with epilepsy, and 6 (8%) presented with focal neurological deficits. The overall mean age of presentation was 45 ± 16 years; whilst the mean ages of presentations with haemorrhage or epilepsy were comparable, those with focal deficits were ~10 years older, and individuals with incidental brain AVMs were ~20 years older (p = 0.0001). Prior to the incidental brain AVM diagnoses, 21% of these adults had an intracranial haemorrhage (p = 0.01), 21% had ⩾1 epileptic seizure (p = 0.04) and 32% had epilepsy or haemorrhage.

Conclusions: One fifth of prospectively detected adults with brain AVMs are diagnosed incidentally, of whom one third have prior symptomatic events, which might have led to earlier detection.

035 THE MRC's ASYMPTOMATIC CAROTID SURGERY TRIAL (ACST)—RESULTS AFTER 5 YEARS FOLLOW UP

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Background: Although endarterectomy (CEA) may be indicated in symptomatic carotid stenosis exceeding 70%, the place of asymptomatic CEA in stroke prevention remains to be established. This was the main objective of this study.

Methods: Since 1993, 3101 patients in over 100 European centres have been randomised to best medical treatment (BMT) + immediate CEA or BMT + deferred CEA, i.e. surgery reserved for those cases who later developed appropriate symptoms. Nearly all patients entered had over 80% carotid stenosis. Randomization, by the Clinical Trials Service Unit, was within each centre. Surgeons became eligible to take part with a good ''track record'' on at least 50 CEAs. Surgical technique and medical treatment was left to each centre.

Results: The early surgery group had a highly significant reduction in stroke risk compared with the deferred group. The overall peri-operative risks were 2.6%. The benefit was clear under 75 years. In subjects over 75, deaths from other causes removed the value of surgery. CEA proved to be particularly valuable in subjects with higher cholesterol. No significant difference in benefit has been found 80–89% and 90–99% stenosis.

Discussion: These findings are likely to increase the numbers considered for CEA and have important economic implications.

036 THIRD INTERNATIONAL STROKE TRIAL (IST-3). THROMBOLYSIS FOR ACUTE ISCHAEMIC STROKE

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Design: IST-3 is a multicentre, randomised, controlled trial of intravenous rt-PA (0.9 mg/kg) in patients with acute ischaemic stroke <6 hours of onset. Full protocol can be found at www.ist3.com. The small start up phase (2000–2002) is complete. The expansion phase (2003–2004) aims to: establish up to 50 well organised centres capable of administering rt-PA; further streamline trial procedures; randomise up to 400 patients. The main trial (2005–2009) aims to involve at least 6000 patients from up to 400 centres worldwide.

Results: By 13 May, 107 patients had been recruited from 13 centres in the UK, Italy, Norway, and Belgium. The median time to randomisation was 3.7 hours and median onset to treatment 4.1 hours. At baseline: 75% were aged >70 years; 52% of the patients had total

anterior circulation, 38% partial anterior, 7% lacunar, and 3% posterior circulation stroke syndrome. The Data Monitoring Committee has reviewed the accumulating data in confidence and urged us to increase recruitment as rapidly as feasible.

Conclusion: The trial is recruiting patients that might benefit from thrombolysis, but do not precisely meet the current criteria for treatment within the product licence. UK neurologists are invited to support the trial.

037 VASCULAR RISK FACTORS IN CADASIL

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Background: Notch 3 mutations on 19p13 cause cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). Role of vascular risk factors on the clinical phenotype is unclear.

Methods: Individuals from genetically confirmed CADASIL pedigrees reviewed and details entered on a Progeny 4.5 Database. History of conventional vascular risk factors (diabetes, ethanol excess, smoking, hypercholesterolaemia, ischaemic heart disease, peripheral vascular disease, and hypertension) was sought from the database. These factors were entered into a logistic regression model to predict the onset of vascular events below age 40.

Results: 25 patients (17 male, 9 pedigrees, 21 alive) were reviewed. The age at onset of first vascular event varied from 25–61 years. Six patients had onset of vascular events before age 40. No cases had a history of IHD, PVD, or hypertension. No factors significantly predicted early onset of vascular symptoms. Diabetes and alcohol excess were associated with increased risk of early onset (DM hazard ratio 2.71 (95% CI 0.13 to 55.9), alcohol HR 1.59 (0.04–59.6)) while smoking and hypercholesterolaemia were associated with reduced risk (smoking HR 0.30 (0.02–5.34), cholesterol HR 0.31 (0.03–3.36)).

Discussion: Few cases with a history of conventional vascular risk factors were identified from the database. Age at onset—even within pedigrees—was confirmed to be highly variable in the Scottish CADASIL population. Preliminary analysis suggests that conventional risk factors may exert divergent effects on age at onset.

038 MULTISLICE CT ANGIOGRAPHY AT A TIA CLINIC

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Background: TIA clinics endeavour to promptly identify risk factors amenable to intervention (for example, significant carotid stenosis). Multislice CT angiography (CTA) offers rapid assessment of cervical and intracranial vasculature.

Methods: Retrospective review of patients assessed at a TIA clinic (11 months, 2001–2002). Cerebral imaging was performed using plain CT and CTA covering the aortic arch to circle of Willis. CTA images were reconstructed and analysed by a neuroradiologist.

Results: 168 patients (mean age 64 (SD 12) years) were reviewed. 108 had stroke or TIA (28 stroke, 80 TIA). 64/105 (62%) plain CT scans and 57/80 (71%) CTAs were abnormal, including significant carotid stenosis in 16 (including two complete occlusions), and 41 with other abnormalities (non-significant carotid stenosis, atheromatous disease without stenosis, and one intracranial stenosis). One required additional MR angiography (due to artefact from calcific plaque). Doppler ultrasound detected significant stenosis in only two of the four (with significant stenosis on CTA) examined. All examinations were tolerated. There were no adverse reactions.

Discussion: CT angiography is a safe and well tolerated method of evaluating intra and extracranial vasculature with superior anatomical coverage to Doppler examination.

039 TIME SINCE EVENT AND OTHER DETERMINANTS OF LESION PRESENCE ON DIFFUSION WEIGHTED MR BRAIN IMAGING

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Background: We have previously showed that ischaemic lesions are often seen on diffusion weighted MR brain imaging (DWI) several weeks after a TIA or minor stroke. However, this may reflect asymptomatic recurrences rather than the presenting event. We therefore performed a longitudinal study with T2 and DW imaging at baseline, 2, 4, 8, and 12 weeks in 10 minor stroke patients with an acute infarct and a cross sectional study in 243 consecutive outpatients, who all had T2 and DWI at a median of 17 days (range 3–60 days) after a TIA or minor stroke. A neurologist and a neuroradiologist reviewed the scans independently.

Results: In the follow up study, the initial lesion was present on the 4 week scan in all patients, and on the 2 month scan in five patients, and no asymptomatic new lesions occurred. In the cross sectional study, DWI was positive in 81/126 stroke patients and 16/117 TIA patients (OR = 10.3; 95% CI 4.8 to 22.0; $p \leqslant 0.0001$). Lesions were associated with persisting neurological signs (OR = 6.9; 95% CI 3.3 to 14.6; $p \leqslant 0.0001$), increasing NIH score ($p = 0.002$), increasing age ($p = 0.01$), and negatively associated with time since event ($p = 0.01$).

Conclusion: Ischaemic lesions on DWI commonly persist for several weeks after minor stroke and asymptomatic new lesions are rare. DWI is therefore useful in lesion localisation in outpatients with minor stroke.

040 IS RAPID STROKE ASSESSMENT CLINIC RAPID ENOUGH?

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Objective: The incidence of early stroke after TIA may be higher than previously accepted, later interventions targeting a low risk population. The Sheffield Nurse Led Rapid Stroke Assessment Clinic (RSAC) aims to see patients from general practice with TIA, minor stroke, or amaurosis fugax within five working days. Information was gathered over 26 months from non-attendees to establish the incidence of early stroke.

Methods: A single observer identified all non-attendees and reviewed the notes of those admitted to hospital. GPs were contacted when information was not obtainable and death certificates reviewed. All those with stroke were identified and when possible categorised.

Results: Between October 2000 and December 2002 there were 1452 referrals from GPs to the RSAC. There were 121 non-attendees, 38 of whom (31.4%) had a stroke within 90 days of referral, 27 (71%) within the first 3 days. Thirteen (34.2%) were fatal. 80% were due to cerebral infarction.

Conclusion: Non-attendees had a high risk of stroke in the first few days after TIA, suggesting that highest risk patients were not seen in time; clinical trials are needed to establish whether immediate intervention with antiplatelet drugs, statins, or antihypertensive agents have an impact in these patients.

041 ACUTE CEREBRAL CT EVALUATION OF STROKE STUDY

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Background: CT scans are difficult to interpret in acute stroke.

Aims: (1) Improve reliability of CT scan interpretation in early stroke and (2) develop a web based CT viewing and coding tool for randomised trials.

Design: We have developed an internet based, interactive CT reading tool. Several hundred readers of different nationalities (European, Canadian, Australian), specialties (general and neuroradiologists, neurologists, geriatricians), and experiences (trainees, consultants) are interpreting about 60 CT scans, to test interobserver and intraobserver reliability. Test CT scans are from several sources and include various acute infarct signs; assessments are entered directly into a database for analysis.

Trial status: By 7 May 2003, 463 physicians had registered and been assigned a test scan (ensures good scan visualisation on local PCs). Of the 463, 269 had successfully completed the test scan. Of the 269, 173 had completed their first 10 scans; 27 have completed 54 scans. The median time for all participants to date, to interpret one scan, is 3 minutes.

Conclusion: Web based CT classification is practical and allows access to large groups of readers. Image quality is good. Further information and registration can be found at www.neuroimage.co.uk. The study is ongoing; we welcome new participants.

042 ''FUNNY'' STROKES IN EAST ANGLIAN SIBLINGS

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Our first patient presented at age 11 with jerking episodes affecting right arm and leg. CT and EEG were normal and symptoms resolved with carbamazepine. Aged 19 she represented with a clumsy right side and transient aphasia. Her younger brother presented with sudden headache and left visual field disturbance at age 25. Detailed history revealed headache and transient dysphasia 2 years earlier. Cerebral angiography in both siblings showed extensive bilateral moyamoya disease (MMD) affecting both anterior and posterior circulation.

The sister underwent left extradural-intradural synangiosis in 1996 followed by contralateral surgery at 3 months. At recent follow up she had mild clumsiness in right hand and mild migraine like headaches. Her brother recently underwent left external carotid-internal carotid bypass surgery and contralateral surgery is planned. He currently has mild persistent left upper quadrantonopia and mild pyramidal weakness affecting his left arm.

In Japan the familial incidence of MMD is 7–10%. There are few reports in the white population and rarer reports of familial MMD. Sibling pair linkage analysis indicates a gene on 3p 24.2–26 in one Greek and several Japanese families and to 17q25 in other Japanese families. Our siblings are white from unrelated parents and MRA screening of family members is underway.

043 RETRIEVING MEANING AFTER TEMPORAL LOBE INFARCTION

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We investigated the effects of ''Wernicke's area'' infarction on function within intact downstream cortical regions involved in accessing word meaning. Nine patients and 19 normal subjects underwent PET activation studies. All subjects made decisions based on the meaning of heard words (Sem) with the control task requiring retrieval of word sound structure. Both groups heard words presented as clear speech (Cl). In addition, the normals heard degraded speech (Deg), making the stimuli more difficult to comprehend. Although the patients' performance was impaired compared with normals on SemCl, it was no different from normals on SemDeg. SemCl in normals activated the left ventromedial temporal cortex (VMTC) and left prefrontal regions. Comparing patient and control groups, prefrontal involvement was no different, but patients showed significantly less left VMTC activation. Reduced left VMTC activity was also observed when normals performed SemDeg. Further, increasing activity in the *right* VMTC in the patients predicted accuracy on SemCl. Thus, activation of the left VMTC during controlled retrieval of meaning is reduced by either damage to ipsilateral auditory cortex or degradation of the speech signal; the result of impaired mapping of sound to meaning. Following chronic aphasic stroke, there was evidence for compensatory plasticity within right VMTLC.

044 EARLY ONSET ALZHEIMER'S DISEASE IN A SIB PAIR WITH THE PRESENILIN-1 GENE R269G MUTATION

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Objective: Clinical and neuropsychological findings in two siblings with early onset Alzheimer's disease (EOAD) with the R269G point mutation in the presenilin-1 (PSEN-1) gene are presented. To our knowledge this is only the second family to be reported with this specific mutation. Findings were compared with previous reports of mutations at this codon.

Results: Age at onset (AAO) was 49 years in both siblings. The brother presented with major depressive disorder resistant to standard pharmacotherapy and requiring ECT. Obsessional behaviour traits, cognitive decline with prominent aphasia, auditory hallucinations, myoclonus, and seizures developed thereafter. The sister presented with cognitive decline with prominent visuospatial dysfunction, associated with behavioural features (agitation with pacing, shadowing behaviour), myoclonus, and tonic-clonic seizures.

Discussion: Behavioural and psychiatric features were prominent in our patients. Clinical details were sparse in the single previously reported family with PSEN-1 R269G mutation (Perez-Tur *et al*, *Neurodegeneration* 1996;**5**:207–12): AAO was 47 years in the proband, with memory loss, dysfluent speech, and seizures. Another mutation at the same codon, R269H, has been reported in one individual, with AAO 47 years, and visual and auditory hallucinations (Gomez-Isla *et al*, *Ann Neurol* 1997;**41**:809–13).

Conclusions: EOAD cases with the R269G PSEN-1 mutation show phenotypic heterogeneity within and between families, as seen in EOAD families with other PSEN-1 mutations. Both genetic and epigenetic factors may contribute to phenotype modulation.

045 MEDICAL AND SURGICAL INTERVENTIONS IN THE FIRST 100 CASES OF VARIANT CJD IN THE UK—A RISK FACTOR FOR THE DEVELOPMENT OF THE DISEASE?

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Introduction: The most likely cause of variant Creutzfeldt-Jakob disease (vCJD) is dietary transmission of abnormal prion protein. However, other routes of infection and the possibility of secondary iatrogenic transmission must be considered. This paper evaluates the evidence for primary or secondary transmission via medical or surgical interventions.

Method: Information regarding the number, type, timing, and place of all medical and surgical interventions was obtained from the families, hospital, and general practice records of the first 100 cases of vCJD referred to the National CJD Surveillance Unit, 60 hospital controls, and 127 community controls.

Results: There may be a trend towards a higher number of medical interventions in cases than controls but this is not significant and numbers are small ($p = 0.4$). Commonest medical interventions were psychiatric, neurological, and respiratory; the most frequent surgical interventions were abdominal-pelvic, minor surgery, and dentistry. Cases had no excess of higher risk procedures. 16 cases had interventions post-symptom onset. Twelve patient pairs had interventions in the same hospital; mean time between interventions was 13.33 years (range 0.25–38 years).

Conclusion: There is currently no evidence that primary or secondary transmission of vCJD has occurred via these routes. However, many people may be incubating the disease and monitoring must continue in the future.

046 SIGNIFICANT WEIGHT LOSS ASSOCIATED WITH LEVETIRACETAM: FOUR CASE REPORTS

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Background: Levetiracetam is indicated in refractory partial epilepsy. It has so far shown a favourable side effect profile. We report four cases of significant weight loss associated with levetiracetam. We have not identified any other cases reported in the literature of weight loss associated with levetiracetam.

Results: All four patients (3 female, age range 20–49 years) had localisation related epilepsy. Levetiracetam was introduced as an add on therapy. Within 5–12 months of starting levetiracetam the four patients reported significant weight loss (range 20–35 kg). None of the patients reported decreased appetite during the period of weight loss, however one developed pica craving only toast, cereal, scallops, and caviar. No other change of anti-epileptic treatment was made during the treatment period and no other cause of weight loss was identified. The commencement of levetiracetam was clearly related to the period of weight loss. All patients' weight was stabilised or increased after reducing the dose of levetiracetam.

Conclusion: Anti-epileptic drugs with a recognised tendency to produce significant weight loss include topiramate and zonisamide. Levetiracetam should also be considered as a potential cause of significant weight loss.

047 VALPROATE INDUCED PARKINSONISM

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Following reports of a reversible valproate induced extrapyramidal syndrome, we wanted to determine the incidence in patients in Greater Manchester. Patients were recruited from hospital and community settings. All patients had taken valproate or carbamazepine monotherapy for at least 12 months. Patients with previous neuroleptic, antiemetic, or antidepressant use were excluded. Patients were questioned about their drug history and examined for parkinsonism. Screening examinations were videoed and reviewed blind by a movement disorders specialist. Patients with signs of parkinsonism were scored using the Unified Parkinson's Disease Rating Scale (UPDRS).

Fifty six patients were assessed (40 valproate, 16 carbamazepine). The mean age, duration of treatment, duration of epilepsy, and seizure

frequency was statistically comparable for each group. Three (7.5%) of the patients receiving valproate had unequivocal signs of parkinsonism. Parkinson's disease in these patients was ruled out by DAT scan. Two patients ceased valproate treatment and their symptoms remitted. There was a significant correlation between the UPDRS score and age ($r=0.409$). UPDRS score was not correlated with any other variable. No control patients exhibited extrapyramidal signs. We conclude that there is a low incidence of extrapyramidal signs in patients receiving valproate, but that the presence of these signs is age dependent.

048 WHY DO PSYCHIATRISTS REQUEST EEG?

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Ninety eight questionnaires were mailed with EEG (electroencephalogram) reports to general adult psychiatrists who had referred patients to West of Scotland EEG departments over a six month period. 89% (87) questionnaires were returned.

The most common reasons for requesting EEG were suspected epilepsy (40%), organic cause of psychosis or depression (20%), exclude epilepsy (14%), exclude structural lesion (2%), and atypical behaviour or psychosis (6%). The referral information suggested a plausible diagnosis of epilepsy in only 5%. 50% of EEGs were reported as normal, 39% showed minor non-specific abnormalities, and 11% showed unequivocal abnormalities.

There was considerable difference between the perceived usefulness of the EEG result by the referring psychiatrist and the neurophysiologist (91% *v* 17%). However, following EEG, in 50% of patients psychiatrists felt that a psychiatric diagnosis was more secure and epilepsy less likely in 39%.

Recent SIGN guidelines stress the importance of the clinical diagnosis of epilepsy and avoidance of inappropriate EEG. In many cases the reasons for requesting EEG were not clear. EEG was also requested for reassurance that patients did not have epilepsy. The EEG cannot do this.

049 THE UK EPILEPSY AND PREGNANCY REGISTER: INTERIM RESULTS

A. J. C. Russell, J. J. Craig, P. Morrison, B. Irwin, R. Waddell, L. Parsons, I. Robertson, E. Guthrie, J. I. Morrow.

The UK Epilepsy and Pregnancy register is a prospective observational follow up study of the relative risks of antiepileptic drugs (AEDs) in pregnancy. The main outcome measures are the risk of major congenital malformation with exposure to different AEDs. 3206 women with epilepsy have been registered to date, with full outcome data on 2544. Major malformation rates with monotherapy exposure are 3.5% and with polytherapy 6.9%. Lamotrigine monotherapy exposures compare well with those of carbamazepine (2.1% *v* 2.2%) but rates associated with valproate are significantly higher (6.1%). Numbers for specific polytherapy combinations are still small, but trends include a higher malformation rate of 10% with lamotrigine in combination with valproate.

Although this is now the largest prospective register of its kind and we continue to recruit widely in the UK, we still need more pregnancies to examine other recently licensed AEDs. Greater numbers are also needed to look for drug specific malformation, the effects of specific combinations, and of different drug dosage. The register has stimulated interest and awareness of pregnancy issues over the last seven years, encouraging more informed pre-pregnancy counselling and also leading to follow up studies of child development as well as active collaboration with the international study EURAP.

050 FAMILY HISTORY OF EPILEPSY IN EPILEPSY AND OTHER NEUROLOGICAL CONDITIONS

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Aim: To determine the frequency of a family history (FH) of epilepsy in patients with epilepsy and other neurological conditions.

Methods: 3386 patients were included. 993 had epilepsy, 2393 had other neurological conditions including headaches, multiple sclerosis, movement disorders, cerebrovascular accidents, and polyneuropathies.

Results: 62 patients with a FH of epilepsy were identified. 54 of the 62 patients had epilepsy. A FH of epilepsy was common in idiopathic generalised epilepsy (22.8%) and uncommon in all other forms (cryptogenic partial epilepsy 2.3%, epilepsy with neurological deficit from birth 2.9%, symptomatic post-natal epilepsy 0.9%). Eight neurological patients with a FH of epilepsy had other neurological conditions without seizures (0.3%). Two patients had tension type headaches, one migraine, one facial nerve palsy, one stroke, two intermittent dizziness and unsteadiness, and one a single simple faint.

Conclusion: Our data suggest that genetic factors contribute to the development of idiopathic generalised epilepsy. A limited role for genetic factors in cryptogenic partial epilepsies and in epilepsies associated with neurological deficits from birth remains possible. Genetic factors appear to be least important in symptomatic postnatal epilepsies. A FH of epilepsy is not more common in patients with neurological conditions without seizures than in the general population.

051 USE OF ANTI-EPILEPTIC DRUG LEVELS: A RETROSPECTIVE AUDIT

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Introduction: Pharmacokinetic factors and narrow therapeutic index mean that measuring antiepileptic medications may be useful. Scottish Intercollegiate Guidelines identify phenytoin dose changes, possible toxicity, or adherence problems as indications to consider drug level measurement. We undertook an audit to examine adherence to these guidelines.

Method: All Cardiff patients who had undergone antiepileptic drug level measurement in October/November 2002 (total, 114; notes available, 102) were included. We noted the requesting team, test indications, interpretation, effect on management, and results documentation.

Results: Requests for phenytoin (50), lamotrigine (8), valproate (27), carbamazepine (22), phenobarbitone (7) were made from physicians (39), paediatricians (26), neurologists (14), neurosurgeons (14), psychiatrists (7), ITU (2). Toxicity and compliance were queried in 29 (25%) and 10 (9%) respectively. Management decisions were not always logical—for example, toxicity confirmed but dose not changed. All phenytoin levels (except one) were random. Written indication and results were documented in 50% and 48% respectively.

Conclusion: Few indications were compliant with guidelines (34%) in this audit, and some results were not interpreted logically. Widely adopted practices—for example, measuring random phenytoin levels and levels measured directly following loading—require further discussion. This local failure to adhere to national guidelines may well reflect practice elsewhere in the UK.

052 PREGNANT WOMEN WITH PSYCHOGENIC NON-EPILEPTIC SEIZURES

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Background: Psychogenic non-epileptic seizures (PNES, pseudoseizures) may make up 10–20% of patients thought to have intractable epilepsy. The high rate of misdiagnosis and the risks of anti-epileptic drug (AED) use in pregnancy are major concerns. These two issues come together whenever a woman with non-epileptic attacks or suspected non-epileptic disorder becomes pregnant on AED.

Methods: The Glasgow PNES clinic database records prospectively acquired information. We identified 125 women of childbearing age who had attended since 2000. Of these, 23 had had one or more pregnancies on AED. The number of pregnancies ranged from 1–6. Sixteen patients had a final diagnosis of PNES, four had PNES and epilepsy, and three had a clinical diagnosis of PNES awaiting confirmation. All pregnancies in patients with a confirmed diagnosis to date had good outcomes, although all four patients in the process of diagnosis had reported previous miscarriages.

We cross referenced our patients with Scottish registrations to the UK Epilepsy and Pregnancy Register. Twenty three of 709 pregnancies occurred in women suspected of or confirmed as having PNES. Three of these patients appeared on the Glasgow PNES database.

Conclusion: Pregnancy in patients with PNES on AED appears to be common. This highlights the need for improved diagnostic services.

053 GUIDELINES FOR THE INVESTIGATION AND MANAGEMENT OF BONE DISEASE IN EPILEPSY

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Patients with epilepsy are at increased risk of sustaining fractures. Predisposing factors include accidental injury and bone disease. Falls may be due to seizures, drug side effects, and reduced mobility. Bone disease may be due to abnormal bone structure (osteoporosis) or poor mineralisation (osteomalacia) and is asymptomatic until a fracture occurs. Epileptic patients appear to have increased bone turnover

necessitating a good supply of metabolites. Anti-epileptic drugs (AEDs) contribute to the risks of bone disease through a number of mechanisms. Hepatic enzyme inducing drugs increase the breakdown of vitamin D to inactive metabolites and lead to lower calcium and vitamin D levels, which may still be within the quoted normal range. They also increase the production sex hormone binding globulins, leading to reduced free testosterone and consequently increased osteoclast activity. AEDs may also have direct effects on gut absorption and bone metabolism.

Clinicians advising patients with epilepsy need to be more proactive in the prevention and detection of epilepsy associated bone disease. We propose guidelines and patient information leaflets to aid the clinician in the management of bone disease in epilepsy, highlighting those patients most at risk and providing a structure for their investigation and management.

054 VIDEO EEG RECORDING IN CORK UNIVERSITY HOSPITAL: REPORT OF A FOUR YEAR AUDIT

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A clinical audit of 122 video EEG recordings performed over a four year period in a regional neurological unit was carried out in order to provide data regarding the yield of diagnostically helpful and unhelpful recordings done in this setting and in a single centre. A subanalysis of the diagnostically helpful group in terms of the information gained was also carried out. The majority (77%) of recordings were found to be clinically unremarkable; 9.8% of recordings showed non-epileptic seizures. The epileptic recordings were extratemporal (6.5%), temporal (2.5%), myoclonic (1.6%) and absence (0.8%). 1.6% of recordings were diagnostically equivocal. The degree of diagnostic uncertainty as to the nature of a seizure is therefore high when a seizure is captured; the explanation for the high rate of negative recordings is likely to be multifactorial.

055 BOTULINUM TOXIN A: AN EFFECTIVE SYMPTOMATIC TREATMENT FOR SELECTED PATIENTS WITH INTRACTABLE EPILEPSIA PARTIALIS CONTINUA

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We report a patient with intractable epilepsia partialis continua involving the left arm, which was symptomatically controlled with intramuscular injections of botulinum toxin A.

A 53 year old man with a 14 year history of drug resistant epilepsy secondary to Rasmussen's encephalitis had virtually continuous and distressing jerking of his left arm. Scalp EEG recording confirmed the diagnosis of epilepsia partialis continua. His medical treatment included five antiepileptic agents. Alterations to his drug regimen failed to control his symptoms. After 1000 μ of botulinum toxin A (Dysport) split between flexor muscles of his left arm, the power and amplitude of the myoclonic jerks diminished greatly, relieving his severe pain and allowing some return of function. This benefit was sustained after reduction of his anti-epileptic medication. Symptomatic relief continued for 5 months and further injection cycles have also been effective.

Though previous attempts to control epilepsia partialis continua with botulinum toxin have not been successful, our case suggests that this approach may be beneficial in a carefully selected patient population.

056 AN AUDIT OF THE USE OF INTRAVENOUS IMMUNOGLOBULIN IN A REGIONAL NEUROSCIENCE CENTRE

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Background: We developed local guidelines for the use of intravenous immunoglobulin (IVIg) for neurological disease, following the recent publication of national guidelines by the ABN (2002) and the RCN (1999).

Methods: One of us (DB) prospectively monitored compliance with our local guidelines in every adult receiving IVIg via the neurology service over 6 months (November 2002–April 2003). Data were collected from case notes and the electronic laboratory results system.

Results: Twenty nine adults received a total of 69 infusions in the 6 month period. 15 adults (52%) were first time recipients of IVIg, of whom 14 (93%) received an information leaflet. Of the new recipients, the indication for IVIg use was unlicensed in eight (53%), six (75%) of whom had a signed consent form in their notes. 11 (73%) of the new recipients had serum stored prior to IVIg administration. All new recipients had pre and post IVIg investigations, but in seven (47%) the battery of tests was incomplete. Every new recipient received sucrose based, non-IgA depleted IVIg, without major side effects.

Conclusions: Although a sizeable proportion of new IVIg users received information leaflets and signed a consent form following the introduction of our local guidelines, blood test monitoring was poor.

057 BRAIN MRI APPEARANCES IN FABRY DISEASE

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Background: Fabry disease (alpha galactosidase deficiency) is a lysosomal storage disorder in which glycolipids accumulate in the kidneys, heart, endothelium, skin, peripheral nerves, and other tissues. Cerebrovascular manifestations of Fabry disease are largely due to dilated arteriopathy, predominantly in the vertebrobasilar circulation.

Results: We performed brain MRI scans in 15 male (hemizygote) Fabry patients, before and after enzyme replacement therapy (ERT). None of these patients (aged 23–50 years) had clinical evidence of CNS disease. Scan appearances were normal in eleven patients. In the other four, there were widespread small lesions of high T2 signal in the cerebral white matter. In one patient, some of the lesions showed enhancement with intravenous gadolinium and punctate enhancement in the brainstem was attributed to an ectatic vessel. Three patients showed intriguing high T1 signal in the posterior thalami, raising the possibility of localised parenchymal abnormality.

Conclusion: Brain MRI abnormalities are therefore common in Fabry disease, even in asymptomatic individuals. The scan appearances did not alter systematically with short duration (<1 year) of ERT.

058 THE VALIDITY OF SELF REPORTED DIAGNOSES IN PATIENTS WITH NEUROLOGICALLY UNEXPLAINED SYMPTOMS

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Objective: To assess the validity of past medical diagnoses reported by patients with neurologically unexplained symptoms (NUS) compared with patients with confirmed neurological disease without suspicion of somatoform illness (ND).

Methods: Twenty one patients with NUS and 16 with ND were interviewed about their current and past medical problems and diagnoses. The accuracy of the reported diagnoses was assessed through examination of their complete general practice notes.

Results: The median total number of previous diagnoses reported by patients with NUS was higher than in controls (6 *v* 3, $p=0.001$). There was no difference in the number of confirmed diagnoses (2 *v* 2.5). The excess diagnoses reported by patients with NUS not only included functional syndromes (6%), but also organic diagnoses which had either been (1) unequivocally excluded (5%), (2) were based on equivocal findings often found after multiple investigations (9%), or (3) had only been diagnosed clinically (51%).

Conclusion: Reported previous diagnoses should not be taken at face value when the current differential diagnosis includes a functional/somatoform neurological syndrome. Confirming the validity of previous diagnoses from alternate sources may contribute to a diagnosis of somatoform disorder, allowing appropriate management strategies for the current (and past) complaints to be initiated.

059 CONGENITAL HEMIPLEGIA: A POTENTIALLY TREATABLE DISORDER?

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Following perinatal damage to one motor cortex, fast conducting ipsilateral corticospinal (CS) projections from the *undamaged* hemisphere are present in adulthood. Our hypothesis is that during development ipsilateral CS projections from the *undamaged* hemisphere, which would normally be withdrawn, competitively displace surviving contralateral CS projections from the *damaged* hemisphere. Subjects with unilateral perinatal stroke involving the motor cortex were studied: (A) 12 longitudinally from birth and (B) 31 when aged between 3–5 years. EMG was recorded from biceps brachii. Transcranial magnetic stimulation (TMS) estimated central motor conduction delays (CMCD). (A) Initially TMS of the infarcted hemisphere evoked responses

in contralateral biceps in *all* subjects. By 2 years responses could not be evoked in six. (B) There were significant positive correlations between severity of hemiplegia and absent or prolonged contralateral CMCDs from the infarcted hemisphere ($r^2 = 0.66$, $p < 0.001$) and abnormally fast ipsilateral CMCDs from the undamaged hemisphere ($r^2 = 0.63$, $p < 0.001$). Withdrawal of surviving contralateral CS projections from the damaged hemisphere and persistence of fast ipsilateral CS projections from the undamaged hemisphere is associated with poor outcome. By analogy with amblyopia, interventions to improve the competitiveness of CS projections from the infarcted hemisphere may improve outcome.

060 CLINICAL TRIALS IN NEUROLOGY: ARE RATING SCALES STABLE ACROSS EUROPEAN COUNTRIES?

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Background: Clinical trials in neurology are frequently multicultural, and increasingly use patient completed rating scales as outcome measures. It is, therefore, essential that rating scales prove they generate stable measurements across different languages and cultures. Such studies are rare and difficult using tradition psychometric methods. We used Rasch technology, a new psychometric method, to examine the stability of the Multiple Sclerosis Impact Scale (MSIS-29) across eight European countries.

Methods: The UK developed MSIS-29 was administered to 50 MS patients in Finland, France, Holland, Ireland, Italy, Spain, and Sweden. Clinical settings and sample characteristics differed across countries. Data from each country were Rasch analysed. Cross cultural stability of item difficulties (differential item functioning (DIF)) was examined by comparing country specific with UK derived ($n = 1725$) MSIS-29 item calibrations, and examining the impact of differences on person measures (linear transformations of patients' raw scores).

Results: The MSIS-29 satisfied Rasch measurement criteria in all countries. There was some DIF across countries but in the vast majority of cases these were within accepted limits. Importantly, differences had no impact on the resulting person measures. Rasch technology may have an important role in the evaluation of cross cultural validity. The MSIS-29 may be used in multicentre trials of therapeutic agents across these countries.

061 A MULTIPLEX ASSAY FOR DETECTION OF MICROBE SPECIFIC OLIGOCLONAL IGG IN CEREBROSPINAL FLUID

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Introduction: The diagnosis of viral CNS infections requires the detection within the CSF of either a pathogenic organism or local synthesis of microbe specific antibodies. We present a novel screening and confirmatory assay to detect microbe specific antibody within CSF.

Methods: CSFs were screened against HSV, VZV, CMV, EBV, *Mycoplasma pneumoniae*, measles, and enterovirus antigen using a qualitative immunosorbent assay. Where reactivity was found to a specific antigen, paired CSF and serum samples underwent IgG isoelectric focusing (IEF) and antigen specific immunoblotting. Intrathecal synthesis of antigen specific IgG was recorded when bands were found within CSF but not serum.

Results: 120 CSF samples from 98 adults were studied of which 20% had intrathecal synthesis of oligoclonal IgG. 71 samples were from patients thought clinically possible to have a CNS viral infection, and 49 samples were from patients with CNS diseases unlikely to be of viral aetiology. The most frequent positive screen findings were for VZV and HSV, where 70% and 47% showed reactivity. However, IEF and immunoblotting showed local synthesis of HSV or VZV IgG in <10% of these cases. In only one sample was intrathecal synthesis of IgG to more than one organism found.

Conclusion: This sensitive assay detects microbe specific IgG in CSF and its application in clinical practice may improve diagnosis of CNS viral infections, particularly where CSF is obtained late in the disease process.

062 IMPROVEMENT IN COGNITIVE FUNCTION FOLLOWING LIVER TRANSPLANTATION

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Introduction: Patients with chronic liver disease frequently experience cognitive dysfunction. The effect of liver transplantation on this dysfunction is uncertain.

Methods: Consecutive patients attending St James's University Hospital for transplant assessment were invited to participate in the study. Cognitive function was assessed using the MMSE, the Rey auditory verbal learning test, trail-making tests A and B, the Stroop test, and the Benton visual retention test. This assessment was repeated 3–6 months after transplantation. A 10% change in cognitive function scores was defined as clinically significant, giving a sample size of 50. The study was approved by the local research ethics committee.

Results: The median age at transplantation was 51.5 years (IQR 44–58 years) and patients had spent a median of 11 years (IQR 10–16 years) in education. The most common indications for transplantation were alcoholic liver disease ($n = 18$) and primary biliary cirrhosis ($n = 15$).

There was a significant improvement ($p < 0.01$) across all the areas of cognitive function tested. Patients remained significantly different from normal controls, however, on all tests other than verbal learning and trail A.

Conclusion: Cognitive function in patients with end stage liver disease improves following liver transplantation, but does not return to normal.

063 OVARIOLEUKODYSTROPHY: A NEW CASE AND FURTHER DESCRIPTION OF THE SYNDROME

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Ovarioleukodystrophy is a syndrome of primary ovarian failure (POF) associated with white matter changes on cerebral magnetic resonance imaging (MRI). Very recently, this condition was shown to be related to mutations in the eukaryotic initiation factor 2B (eIF2B). We now describe another case of this rare syndrome in an unrelated patient.

The case is that of a 25 year old woman with a normal birth history. Initial developmental milestones were normal but cognitive impairment was apparent at school age. Endocrine evaluation for short stature and delayed puberty was consistent with primary gonadotrophin deficiency and pelvic ultrasound showed the presence of streak ovaries. Her karyotype was normal. At 17 years, she developed dystonic head posturing and progressive ataxia and spasticity. MRI brain revealed diffuse white matter abnormalities in the cerebral hemispheres bilaterally. Extensive investigations for the known leukodystrophies and for causes of ovarian failure were unrewarding.

We describe a case of POF associated with white matter disease, both of unknown origin. The clinical and radiological features bear striking resemblance to previous reports. Primary ovarian failure should be sought in cases of leukodystrophy of unknown cause. Better recognition of this association will allow better patient characterisation and description of the syndrome.

064 SIR ROBERT CARSWELL (1793–1857): PATHOLOGICAL ANATOMIST, ARTIST, AND FIRST TO DESCRIBE THE LESIONS OF MULTIPLE SCLEROSIS

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A 41 year old man was treated by orchidectomy and adjuvant paraaortic radiotherapy for a testicular seminoma in February 2001. Five months later he presented with symptoms and signs of lumbosacral intrathecal radiculopathy supported by neurophysiological studies and gadolinium enhanced MRI scan of the lumbosacral roots and plexus. Intravenous methyl prednisolone was administered for 5 days followed by oral prednisolone for 8 weeks. Ten sessions of hyperbaric oxygen was also instituted. Over the next year the neurological complaints fully resolved. We report this case of post irradiation lumbosacral radiculopathy because of the unusually short latency, short duration, and the recovery. Usually the course is relentlessly progressive, often to severe disability, although some cases may stabilise. A literature search reveals only one similar case with spontaneous resolution. There is no effective treatment so far and steroid administration has not shown any benefit in

the past, and so is unlikely to explain the resolution in this patient. Hyperbaric oxygen corrected a sacral plexopathy caused by pelvic radiation in a single reported case. Further trials with a combination of intravenous methyl prednisolone and hyperbaric oxygen are required and may hopefully reveal promising results.

065 ABNORMAL VOLTAGE GATED SODIUM CHANNEL DISTRIBUTION: A NOVEL MECHANISM OF AXONAL INJURY IN EAE SPINAL CORD?

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Objective: To identify and delineate the abnormal distribution of voltage gated sodium channels in an experimental model of MS and examine their relation with axonal injury.

Methods: Through application of immunohistochemistry, we examined the distribution of sodium channels $Na_v1.2$ and $Na_v1.6$ in spinal cord of EAE mice and their association with β-APP immunoreactivity, a marker of axonal injury.

Results: Our results show a significant attenuation of $Na_v1.6$ at nodes of Ranvier compared with control that is maximal during relapse (33.2 (SD 8.5)%) compared with remission (69.9 (SD 4.7)%). We observed an increased number of demyelinated axonal profiles with diffuse immunoreactivity for $Na_v1.2$ and $Na_v1.6$ in EAE spinal cord. Moreover we observed that in EAE β-APP^{+ve} axonal profiles were associated with a significant difference in $Na_v1.6^{+ve}$ (87.7 (SD 2.7)%) compared with $Na_v1.2^{+ve}$ profiles (45.8 (SD 2.6)%).

Conclusions: Axonal loss in MS plays a key role in the development of non-remitting disability and yet the molecular mechanisms that underlie this process are not clearly delineated. These findings extend the evidence implicating that a perturbation of sodium channel expression may not only contribute to the development of conduction block but also subserve a pathway of axonal injury and thereby represents a potential novel therapeutic target.

066 ABNORMALITIES IN NORMAL LOOKING BRAIN TISSUE ARE PRESENT IN EARLY PRIMARY PROGRESSIVE MULTIPLE SCLEROSIS AND CORRELATE WITH DISABILITY: A MAGNETISATION TRANSFER IMAGING STUDY

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Background: Primary progressive multiple sclerosis (PPMS) patients often develop severe disability despite low levels of abnormality on conventional MRI. This may relate to diffuse pathological processes occurring in the normal appearing white matter (NAWM) and grey matter (NAGM). These can be studied with magnetisation transfer imaging (MTI).

Aim: To assess NAWM and NAGM using MTI in early PPMS and to correlate these findings with disability and other MRI measures.

Methods: We studied 43 patients within 5 years of disease onset and 59 controls. Expanded Disability Status Scale (EDSS) and Multiple Sclerosis Functional Composite were scored. Mean, peak height, and peak location from NAWM and NAGM magnetisation transfer ratio histograms (MTR) were measured. PD, T2, T1, and gadolinium enhancing lesion loads were also calculated.

Results: Statistically significant differences were found between patients and controls in MTR parameters. Correlations were found between MTR parameters and disability (EDSS) in both NAWM ($r=-0.34$, $p=0.024$) and NAGM ($r=-0.34$, $p=0.034$). Strong correlations between MTR parameters and T2 lesion loads were found, particularly in NAWM ($r=-0.94$, $p<0.001$).

Conclusion: MTR abnormalities are seen in early PPMS, affect both NAWM and NAGM, and are associated with disability. NAWM MTR abnormalities are more closely related to conventional MRI measures than those seen in NAGM.

067 BRAIN METABOLITE CHANGES IN THE EARLY CLINICAL STAGES OF PRIMARY PROGRESSIVE MULTIPLE SCLEROSIS

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Background: Magnetic resonance spectroscopic imaging (MRSI) offers information on chemical components of the normal appearing areas of the brain and could help explain the mechanisms of disease in multiple sclerosis (MS), which are particularly relevant in primary progressive MS (PPMS).

Aim: To evaluate the mechanisms underlying disease progression in PPMS.

Methods: Forty three patients within five years of symptom onset of PPMS and 44 control subjects were studied. MRSI data were acquired from a grid placed above the roof of the lateral ventricles. Concentrations of five metabolites were obtained: choline, creatine, inositol, N-acetyl-aspartate, glutamate-glutamine. Voxels in the grid were considered grey matter (GM) or normal appearing white matter (NAWM). Expanded Disability Status Scale (EDSS) and Multiple Sclerosis Functional Composite (MSFC) scores were recorded in all patients.

Results: Concentrations of N-acetyl-aspartate and glutamate-glutamine in GM were lower in patients than in controls. In NAWM, inositol levels were higher and N-acetyl-aspartate levels were lower in patients than in controls. EDSS correlated with N-acetyl-aspartate in GM ($r=-0.444$, $p=0.03$) and with inositol ($r=0.412$, $p=0.011$) and glutamate-glutamine ($r=0.406$, $p=0.013$) in NAWM.

Conclusions: Metabolite changes occur in early PPMS and differ in GM and NAWM. N-acetyl-aspartate in GM and inositol in NAWM are related to disability in PPMS.

068 NEUROMYELITIS OPTICA (DEVIC'S DISEASE): A 10 YEAR EXPERIENCE IN A REGIONAL CENTRE

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Objectives and Methods: Neuromyelitis Optica (NMO) or Devic's disease is a rare demyelinating syndrome regarded by some authors as a variant of multiple sclerosis (MS). As a preliminary to a planned UK wide study, a retrospective assessment of cases diagnosed within the Walton Centre over the last 10 years was undertaken.

Results: Eight patients (7 female) were identified; mean age of onset was 46.4 years. Five had a relapsing course and three were monophasic. Four patients had other immunologic abnormalities, three of five had positive anticardiolipin antibodies. All patients received steroids and five patients were treated in addition with immunosuppressive and or immunomodulatory agents (azathioprine-5, mitoxantrone-1, betainterferons-1, cyclophosphamide-2, cyclosporin-1). In these five patients, observed relapse rate was substantially reduced on treatment, mean follow up period on treatment was 3.4 years. Early initiation of immunosuppressive treatment tended to favour improved functional outcome.

Conclusions: NMO is a rare disease with a distinct clinical phenotype. Immunological abnormalities, particularly anticardiolipin antibodies, are often associated. Despite the small size of the cohort, outcomes in this group suggest that early immunosuppressive treatment is of benefit. The ongoing nationwide study, which will also explore immunological and genetic markers, will hopefully shed more light on this distinctive disease.

069 CORTICAL MOTOR REORGANISATION IN PRIMARY PROGRESSIVE MULTIPLE SCLEROSIS

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Introduction: Previous work has reported differences between patients with primary progressive multiple sclerosis (PPMS) and normal subjects in the functional MRI (fMRI) response to active hand movements. Lower limb function has not been investigated in PPMS despite its importance in determining disability. We developed a lower limb fMRI paradigm which employs active and passive foot movements and applied it to patients with PPMS.

Methods: fMRI was performed on 13 patients and 16 controls for each foot. Active and passive dorsi and plantar flexion was performed using a special bipedal wooden apparatus. SPM99 was used for the analysis.

Results: Cortical regions, including the contralateral cerebellum, showed greater activation in patients than controls during both active and passive tasks. Other regions showed greater activation during active movement alone, such as the ipsilateral supplementary motor cortex, or during passive movement, such as the ipsilateral putamen and thalamus.

Conclusion: Patients with PPMS showed functional changes during active and passive foot movements compared with controls. The use of passive tasks allows the identification of cortical areas that are genuinely adaptive as these are independent of voluntary recruitment, and has the potential to assess the efficacy of rehabilitation.

070 A COMMUNITY BASED STUDY OF RESOURCES, NEEDS, AND WELLBEING OF PEOPLE WITH MULTIPLE SCLEROSIS

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Few studies of the needs of people with MS have been performed in a primary care setting. In Northern Ireland there is a network of general practitioners (GPs) with computerised records. Patients were identified by their GP, consent obtained, and the diagnosis verified. Participants were interviewed in their own homes, according to our protocol by representatives of a market research firm. 149 patients participated. Of these two thirds were female. For the purposes of analysis, we divided the participants into three groups as follows: 23% able to walk more than 500 metres, 41% moderately disabled, and 36% severely disabled (wheelchair or bed bound).

Level of disability was significantly related to employment, receipt of benefits, house alterations, receipt of nursing and personal care, GP attendances, and medication use. The moderately disabled were most likely to attend neurology outpatients.

Unmet needs were greatest for the moderately affected group suggesting a lag time from identification of need to provision of help. Overall physiotherapy was the most common unmet need. More advice and information was also wanted. Scores relating to fulfilment and quality of life did not correlate with disability or resources accessed but did correlate with unmet needs particularly unmet needs for care.

071 META-ANALYSIS OF DOPAMINE AGONIST TRIALS IN EARLY PARKINSON'S DISEASE

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Introduction: Although levodopa (LD) remains the standard treatment for Parkinson's disease (PD), long term therapy leading to motor complications has encouraged increased use of dopamine agonists (DA). We undertook a meta-analysis of 28 published randomised trials of DA in early PD to quantify more reliably the benefits and risks.

Methods: Data on mortality, motor complications, side effects, and withdrawals from treatment were analysed.

Results: There was no significant difference in mortality between DA and non-DA patients (relative risk = 1.03, 95% CI = 0.84 to 1.26; p = 0.8). The risk of developing dyskinesia (0.48, 0.40 to 0.57; p<0.00001), dystonia (0.64, 0.49 to 0.84; p = 0.001), and motor fluctuations (0.74, 0.62 to 0.89; p = 0.002) were significantly lower in patients randomised to DA compared with LD. However, DA patients were more likely to develop oedema (2.90, 2.01 to 4.21; p<0.00001), somnolence (2.73, 2.12 to 3.51; p<0.00001), hallucinations (2.21, 1.50 to 3.27; p = 0.00007), constipation (1.81, 1.35 to 2.41; p = 0.00006), dizziness (1.58, 1.23 to 2.01; p = 0.0003), and insomnia (1.41, 1.07 to 1.86; p = 0.01) compared with non-DA patients. Furthermore, DA treated patients were significantly more likely to drop out of the trial due to adverse events (2.77, 2.26 to 3.40; p<0.00001).

Conclusions: This meta-analysis confirms that patients receiving DAs are less likely to develop motor complications. However, other side effects—which may be more important for patients—are substantially increased. To determine reliably the balance between benefits and adverse effects of DAs, larger trials comparing DAs with levodopa and/or selegiline are needed with patient rated global quality of life as the primary outcome measure.

072 THE MOTOR RESPONSE TO LEVODOPA IN DEMENTIA WITH LEWY BODIES: A COMPARISON TO PARKINSON'S DISEASE WITH AND WITHOUT DEMENTIA

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Background: A core clinical feature of dementia with Lewy bodies (DLB) is an extrapyramidal syndrome (EPS). Levodopa (Ldopa) is gold standard oral therapy for Parkinson's disease (PD) but its use in DLB is tempered by concerns of exacerbating neuropsychiatric symptoms.

Aims: To assess the efficacy and tolerability of Ldopa to manage the EPS in DLB and compare the motor response with that in PD and PD with dementia (PDD).

Method: EPS assessment consisted of motor subsection Unified PD Rating Scale (UPDRS), finger tapping (FT), and walking tests (WT). Patients with DLB commenced Ldopa. After 6 months, patients were examined in the ''off'' state, given Ldopa, and assessed for motor responses. Identical assessments were performed in patients with PD and PDD on Ldopa.

Results: 18 DLB patients commenced Ldopa. Two withdrew prematurely with gastrointestinal symptoms and two with worsening confusion. 14 fasting DLB assessments demonstrated 12.6% (p<0.001) improvement in UPDRS score compared with 20% PD (n = 28, p<0.0001) and 25% PDD (n = 30, p<0.0001) respectively. FT increased 14.5% versus 20% and 28% while WT decreased by 36% versus 41% and 66% respectively

Conclusion: Ldopa was reasonably tolerated in DLB. Patients showed an improvement in EPS most strongly in general mobility. Ldopa therapy may be considered in DLB with troublesome parkinsonism.

073 PARKINSON'S DISEASE AND RESTLESS LEGS SYNDROME: AN UNDER RECOGNISED CAUSE OF DAYTIME MORBIDITY

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Introduction: Restless legs syndrome (RLS) is the commonest movement disorder during sleep and relaxed wakefulness and its occurrence in Parkinson's disease (PD) remains controversial. Chronic RLS is known to cause severe sleep disruption.

Methods: All PD patients that were part of an UK prospective audit (PDLIFE) and those attending regional PD clinics at King's and Lewisham hospitals were screened for RLS using validated questionnaire and polysomnography (PSG) in selected cases. Data were compared to a cohort of idiopathic RLS patients (n = 25).

Results: 46 cases of RLS (mean age 66 years (49–90), mean duration of PD 60.5 months, mean duration of RLS 77 months) were identified among PD using the International RLS Study Group (IRLSSG) criteria. All had symptomatic daytime somnolence and notable sleep disruption. None were diagnosed to have RLS in spite of symptoms prior to current diagnosis. PSG in selected cases showed periodic limb movements and awakening. Specific additional treatment for RLS was required in 39 cases. 11 (24%) had RLS before diagnosis of PD.

Conclusions: RLS is an important cause of sleep disruption in PD and needs to be recognised. The occurrence of RLS preceding PD supports a central dopaminergic basis for origin of RLS.

074 META-ANALYSIS OF SELEGILINE TRIALS IN EARLY PARKINSON'S DISEASE

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Introduction: Increased mortality has been reported with selegiline, and there remains uncertainty about its clinical role in Parkinson's disease (PD). We undertook a meta-analysis of 13 published randomised trials of selegiline in early PD to quantify more reliably the benefits and risks.

Methods: Data on mortality, motor complications, side effects, need for LD, and treatment withdrawals were analysed.

Results: There was no evidence of increased mortality with selegiline compared with no selegiline: 24% *v* 22% died, relative risk = 1.14; 95% CI 0.96 to 1.36; p = 0.1. In the few studies reporting motor complications, there was no significant reduction in dyskinesia (0.96; 0.73 to 1.28; p = 0.8), although fewer patients experienced motor fluctuations (0.75; 0.58 to 0.95; p = 0.02) with selegiline. Selegiline patients were less likely to require LD than placebo patients (0.48; 0.40 to 0.58; p<0.00001). There was no significant difference between groups in numbers suffering side effects (1.37; 0.85 to 2.23; p = 0.2) or withdrawing from trial treatment (1.07; 0.87 to 1.31; p = 0.5). However, withdrawals due to adverse events appeared higher in selegiline patients (2.16; 1.44 to 3.22; p = 0.0002), although most of this excess came from just one trial.

Conclusions: Selegiline reduces the requirement for levodopa, and possibly motor fluctuations, without substantial side effects or increased mortality. Because few trials have compared selegiline with levodopa or dopamine agonists, uncertainty remains about the relative benefits and risks of selegiline. Further trials including patient rated quality of life measures are needed.

075 THE CLINICAL UTILITY OF DATSCAN IMAGING OF THE BASAL GANGLIA IN THE ASSESSMENT OF PARKINSON'S SYNDROME

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Introduction: To demonstrate the utility of I^{123}-FP-CIT (DaTSCAN) in the assessment of suspected Parkinson's syndrome.

Materials and Methods: Fifty five patients with suspected Parkinson's syndrome were recruited into the study. A neurologist assessed all patients and symptom severity was recorded using the Unified Parkinson's Disease Rating System (UPDRS) Correlation was made imaging findings, disease severity, side of symptom onset, and modification of patient treatment based on imaging findings.

Results: Thirty five presented with unilateral symptoms, of these 33 had abnormal scans. Within this group 31 had reduced isotope uptake on the contralateral side. Three patients had low UPDRS scores but grossly abnormal scans. These patients were atypical in presentation none had any evidence of a Parkinson Plus syndrome (MSA or PSP). Of the two patients who progressed to show evidence of PSP both had grossly abnormal scans. Of the five patients with normal scans, four responded well to alternative therapy. A general trend of increasing UPDRS score reflecting worsening image findings was observed.

Conclusion: DaTSCAN proved useful in the assessment of patients with Parkinson's syndrome. It showed strong correlation with side of symptom onset and also allowed appropriate characterisation of each patient's symptomatology.

076 WORKING MEMORY ABILITY IN PARKINSON'S DISEASE IS ASSOCIATED WITH THE COMT VAL$^{108/158}$MET POLYMORPHISM

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Parkinson's disease patients show a range of working memory and executive deficits involving dopaminergic transmission in the prefrontal cortex. In this study, we have investigated the impact of catechol-O-methyl-transferase (COMT) val$^{108/158}$met polymorphisms on performance of the Tower of London test of planning by Parkinson's disease patients. This task has a complex relation with dopaminergic function, in that both high and low levels of dopamine in the dorso lateral prefrontal cortex impair performance. Patients with high activity COMT genotypes performed significantly better at the task than those with low activity genotypes. We hypothesise that the inferior performance in patients with the low activity COMT genotype is attributable to a state of relative hyperdopaminergic activity in the dorso lateral prefrontal cortex. We suggest that polymorphisms of common genes, which regulate central nervous system dopaminergic transmission, can influence some of the phenotypic manifestations of Parkinson's disease.

077 A CROSS SECTIONAL MAGNETIC RESONANCE SPECTROSCOPY STUDY IN PSP AND INDETERMINATE PARKINSONISM

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Reduction in N-acetyl-aspartate concentration ([NAA]), a neuronal marker detectable by in vivo magnetic resonance spectroscopy (MRS), may indicate neuronal loss or dysfunction. We measured brainstem [NAA] in PSP patients, controls, and patients with unclassifiable parkinsonism to determine the diagnostic utility of this technique and also correlated [NAA] with measures of disease severity.

Methods: Midbrain [NAA] was measured in 17 PSP patients (eight probable and nine possible according to NINDS-SPSP criteria), 13 patients with neurodegenerative parkinsonism of uncertain cause (''indeterminate''), and 13 healthy age matched controls. A $2\times2\times1$ cm voxel of interest (VOI) was placed to include the superior colliculi and as much midbrain as possible. [NAA] was calculated for the volume of brain within the VOI.

Results: Two subjects (one PSP, one indeterminate) were excluded, as their spectra were technically unsatisfactory. In the remaining subjects, mean [NAA] was significantly reduced in the whole PSP group versus controls ($p<0.015$) and versus indeterminates ($p<0.007$), and in probable PSP patients compared with indeterminate and control groups ($p<0.0001$). There were no significant correlations between disease rating scales (Golbe PSP Scale, UPDRS-motor, FAB) and [NAA].

Discussion: Midbrain [NAA] is reduced in PSP and may assist with clinical diagnosis. Longitudinal studies are needed to support this and evaluate potential prognostic application.

078 THE EFFECT OF DIAGNOSIS ON NEED FOR SERVICES: A COMPARISON OF MULTIPLE SCLEROSIS AND PARKINSON'S DISEASE

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Background: People with multiple sclerosis (MS) and Parkinson's disease (PD) demand diagnosis specific services, but how different are their needs? To address this question, we analysed data from a community sample.

Method: For a randomised controlled trial, we ascertained people with MS and PD from Nottingham GPs. We interviewed them at home, using a symptom checklist, the Nottingham Extended Activities of Daily Living schedule, the Braden Scale for skin sore risk, the Nutritional Risk Assessment (NRA), a falls risk checklist, a Self-Efficacy scale, the General Health Questionnaire (GHQ) administered to patients and carers, and the Carer Strain Index (CSI).

Results: There were 53 with PD and 45 with MS. The only striking contrast was in mean ages (70.4 and 49.0 years respectively). The spectrum of symptoms and of disabilities was similar, suggesting comparable needs for services such as continence advice, psychiatry, therapy, and equipment. The proportions reporting at least one fall in 12 months (around 50%) and the frequency of falling risk factors were similar, as were Braden, NRA, self efficacy, CSI, and GHQ scores.

Conclusions: Our findings suggest close parallels between service needs generated by MS and by PD. The case for diagnosis specific services should be based on detailed comparative investigations rather than on assumptions derived from single diagnosis studies.

079 THE ROLE OF TWO SIMPLE QUESTIONS IN IDENTIFYING ELDERLY PATIENTS WITH UNDIAGNOSED PARKINSONISM

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Background: Elderly patients who develop parkinsonism may not present to their general practitioner. We assessed the usefulness of two questions in identifying elderly patients with undiagnosed parkinsonism as part of an incidence study.

Methods: We added two validated questions about tremor and gait to the annual nurse led check on people over 75 in five general practices. We also collected details of their past medical history and medications. Patients who screened positive to either question, in whom there was no alternative explanation, were invited for an examination by a neurologist who diagnosed parkinsonism according to the UK Brain Bank criteria.

Results: In four months 503 patients were screened (12% of over 75s) of whom 24 refused to participate. 52 (10%) patients gave a positive answer to $\geqslant1$ question, of whom 15 declined further follow up, and 15 had an explanation other than undiagnosed parkinsonism. To date 10 of the remaining 22 patients have been examined and four (0.8% of those screened) had undiagnosed parkinsonism (16% of all incident patients identified so far).

Conclusions: Screening the elderly for undiagnosed parkinsonism has a low pick up rate but can identify a significant number of new patients who would otherwise be missed in an incidence study.

080 DIFFERENTIATING VASCULAR PARKINSONISM FROM TRUE PARKINSONISM: AUDIT OF FP-CIT SPECT IMAGING IN CLINICAL PRACTICE

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Background: Vascular parkinsonism (VP) is classically considered as lower body parkinsonism (LBP) due to subcortical ischaemia. However, atypical cases and overlap with Parkinson's disease (PD) often cause clinical uncertainty. Striatal FP-CIT-SPECT uptake reflects presynaptic dopaminergic function and is progressively reduced in PD but normal in VP (or focally reduced by infarction).

Methods: A prospective Glasgow movement disorder clinic audit of FP-CIT-SPECT, clinical diagnosis, and antiparkinson therapy response in 22 patients with clinical uncertainty between VP and true parkinsonism.

Four had LBP. All had structural imaging (small vessel disease/infarctions, n=15; normal/atrophy, n=7) and vascular risk factors.

Results: Baseline diagnosis was probable PD in 11 of 22 (50%) (10 had therapy trial; one good response, nine poor). Ten of these 11 had abnormal SPECT (final diagnosis PD); one of 11 had normal uptake, later diagnosed as essential tremor. VP was the baseline diagnosis in 11 (nine no therapy trial, two poor response). Of these 11 cases, four had normal FP-CIT, two had focal striatal lesions interpreted as infarction (final diagnosis VP), and five had dopamine deficit (final diagnosis PD). Six of 22 (30%) had unexpected SPECT results.

Conclusion: Clarification of dopamine status is helpful in clinical practice in differentiating between VP and PD.

081 SUBACUTE PRESENTATION OF MORVAN'S SYNDROME POST-THYMECTOMY

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Morvan's syndrome represents the clinical features of neuromyotonia (Isaacs syndrome) presenting as myokymia, muscle stiffness, cramps, and hyperhidrosis in combination with autonomic dysfunction and encephalopathy. The encephalopathy fluctuates with visual hallucinations, insomnia, and agitation. We describe a case of Morvan's syndrome presenting subacutely after thymectomy, with unusual clinical symptoms representing a difficult diagnostic challenge. The diagnosis was made on clinical grounds, neurophysiology, and the finding of serum voltage gated potassium channel antibodies (VGKC). This is the first reported case of Morvan's syndrome presenting post-thymectomy. Thymectomy has previously been proposed as a treatment for Morvan's syndrome. Morvan's syndrome normally presents with a slow insidious onset over months to years—some spontaneously remit, others require repeated plasma exchanges (PE), thymectomy, and maintenance high dose immunosuppression; however, most cases have proved fatal. Our case is unique in that presentation was over days and responded to a single course of PE with low dose maintenance immunosuppression. We hypothesise that the surgical procedure may have precipitated a rise in the serum levels of the VGKC antibodies, which were cleared by one course of PE. Although potentially this is a low risk to thymectomy, it is an important complication to recognise because of the dramatic reversibility to treatment.

082 COGAN'S LID TWITCH REVISITED

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Cogan first reported this clinical sign in myasthenia in 1965. He described a transient over shoot or twitching of the lids on making a saccade from depression to the primary position. It has also occasionally been reported in other brainstem and oculomotor disorders. Two mechanisms have been suggested: (1) rapid recovery of Levator function on depression, with subsequent rapid fatiguability and (2) central nervous system adaptation to the neuromuscular junction transmission defect.

The incidence of Cogan's Lid Twitch (CLT) sign has previously only been reported in one small group. Recent observation of CLT in the Miller-Fisher syndrome led us to re-evaluate the use of this test.

We compared the incidence of CLT in myasthenia in patients with other oculomotor/brainstem disorders with a ''normal'' group. Fifty patients were recruited to each group, from a neuroophthalmology clinic (Dr Metcalfe) and an orthoptic clinic (Marie Cleary).

60% of myasthenics displayed a positive CLT, compared with 6% of those with other oculomotor/brainstem disorders, and none of the ''normals''. Myasthenics always showed a transient over shoot, while lid twitch was typical for the non-myasthenics.

This characteristic response makes it a useful clinical test when performed correctly (illustrated by video recordings).

083 CLINICAL EVALUATION OF AUTONOMIC FUNCTION IN PATIENTS WITH GUILLAIN-BARRE SYNDROME

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Autonomic dysfunction in Guillain-Barre Syndrome (GBS) is well recognised but not well described. In a cross sectional multicentre study, 50 patients with GBS were studied for evaluation of autonomic dysfunction (AD) according to methods described by Ewing and Clarke. Mean age at presentation was 21.1 years (range 1–60 years). All patients were studied for symptoms and signs of AD. None of them received IVIG or plasmaphoresis. Autonomic function tests (AFT) were performed in 30 patients. 20 patients (40%) had symptoms of AD, 27 patients (54%) had signs, and 14 patients (28%) had symptoms and signs of AD. Abnormality in AFT was detected in 15 patients (50%) and showed that the parasympathetic derangement was the most frequent followed by sympathetic and combined derangement. Derangement in AFT battery had a highly significant correlation with the development of respiratory paralysis $p \leqslant 0.001$ and death $p = 0.008$.

All patients with GBS should be observed for evidence of autonomic dysfunction and nursing care has to be adjusted to take into account the autonomic status of the patient.

084 BRACHIUS PLEXUS HYPERTROPHY IN CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY

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We present the clinical, MRI, and nerve biopsy findings in three patients with chronic inflammatory demyelinating polyneuropathy (CIDP) which predominantly affected the upper limbs. All had slowly progressive disease over many years. One patient had bilateral shoulder pain as an initial presenting feature with a disease that mainly affected sensation. The other two patients had predominantly motor involvement. In all cases, the lower limbs have not been significantly affected, and the patients remain ambulant. Nerve conduction studies in the upper limbs of both patients demonstrated F wave abnormalities and conduction block consistent with a diagnosis of CIDP. All patients demonstrated significant brachial plexus abnormalities on MRI scanning. In one patient, the brachial plexus nodularity led to a diagnosis of neurofibromatosis being considered, although subsequent nerve biopsy showed onion-bulb hypertrophy. The second patient had a radial nerve biopsy which showed the inflammatory features of CIDP. None of the patients responded significantly to immunomodulatory treatment. The different appearances of the brachial plexus on MRI, in conjunction with the clinical presentations of these patients, suggest that they are unusual variants within the spectrum of CIDP.

085 A PILOT RANDOMISED, DOUBLE BLIND, PLACEBO CONTROLLED EXPLORATORY SAFETY STUDY OF THE USE OF INTERFERON-β 1A IN THE TREATMENT OF GUILLAIN-BARRE SYNDROME

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Objective: The immunomodulatory profile of interferon-beta (IFN-β) predicts a beneficial effect in Guillain-Barré Syndrome (GBS). In this pilot study we aimed to discover whether IFN-β is safe in GBS.

Methods: We recruited non-ambulant GBS patients to a double blind, randomised, placebo controlled trial. In addition to intravenous immunoglobulin (IVIg), patients received placebo or IFN-β1a (Rebif ^{R}) subcutaneously three times weekly, 22 μg for the first week, and then 44 μg until they were able to walk 10 metres, or for 24 weeks (whichever was sooner).

Results: We recruited 19 patients between 1999 and 2002. Four of the 13 IFN-β patients and two of the six placebo patients had serious adverse events. We did not encounter any unexpected adverse events and did not consider that any of the serious adverse events were probably or definitely attributable to the study drug. The improvement in disability grades at one month and six months did not differ significantly between the treated and placebo groups.

Conclusions: IFN-β was tolerated and did not have any unexpected adverse interaction with IVIg in GBS.

086 CRITICAL ILLNESS LUMBOSACRAL PLEXOPATHY

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Acute diffuse weakness in critically ill patients in intensive care units has been well described and attributed to critical illness polyneuropathy, myopathy, or defects of neuromuscular transmission. We report two patients who developed acute weakness confined to the lower limbs only during their stay in the intensive care unit. Electrophysiological findings were consistent with lumbosacral plexopathy. Absence of any other pathology was confirmed by laboratory and imaging investigations. We propose a new clinical diagnosis, critical illness lumbosacral plexopathy.