# ABN abstracts

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### 001 ABNORMALITIES IN CARDIAC RHYTHM REVEALED IN PATIENTS WITH REFRACTORY EPILEPSY

R. J. Simister, F. J. Rugg-Gunn, M. Squirrell, M. S. Hall, D. Holdright, J. S. Duncan. *Department of Clinical and Experimental Epilepsy, Institute of Neurology, London; Department of Cardiology, Middlesex and Heart Hospitals, London; Medtronic Ltd, Watford*

**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

S. Wong, P. C. Adams, M. J. Jackson. *Dept Cardiology & Neurology, Royal Victoria Infirmary, Newcastle upon Tyne*

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

A. Salek-Haddadi, L. Lemieux, J. Duncan, D. R. Fish. *Dept Clinical & Experimental Epilepsy, UCL Institute of Neurology, London; MRI Unit, National Society for Epilepsy, Chalfont St Peter, Bucks*

**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

M. J. Edwards, Y. Z. Huang, J. C. Rothwell, K. P. Bhatia. *Sobell Department of Motor Neuroscience and Movement Disorders*

**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

K. R. Chaudhuri, L. S. Taurah, D. G. MacMahon, K. Turner, L. Kelly, D. Burn, A. Forbes, A. Bowron, O. J. Foster, members of the UK PD LIFE committee. *King's College Hospital London, University Hospital of Lewisham London, UK Parkinson's Disease Society, Camborne and Redruth Community Hospital, Atkinson Morley Hospital London, St Georges Hospital London, Harold Wood Hospital Romford, Newcastle General Hospital*

**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

M. M. K. Muqit, S. M. Davidson, M. D. Payne-Smith, L. P. MacCormac, N. W. Wood, D. S. Latchman. *Department of Molecular Neuroscience, Institute of Neurology, London; Medical Molecular Biology Unit, Institute of Child Health, London; Birkbeck, University of London, London*

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

J. A. Woolmore, A. Barton, S. John, J. Worthington, A. A. Fryer, R. C. Strange, C. P. Hawkins. *Keele MS Research Group, Institute of Science and Technology in Medicine, Keele University, Stoke on Trent; ARC Epidemiology Research Unit, and Centre for Integrated Genomic Research, University of Manchester*

**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

A. T. Toosy, O. Ciccarelli, S. J. Hickman, G. J. Parker, C. A. M. Wheeler-Kingshott, D. H. Miller, A. J. Thompson. *Institute of Neurology, London*

**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

F. G. Joseph, N. J. Scolding. *Institute of Clinical Neurosciences, Frenchay Hospital, Bristol*

**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

D. J. Mahad, C. Trebst, P. Kivisäkk, B. Tucky, J. Wujek, B. D. Trapp, C. F. Lucchinetti, H. Lassmann, R. M. Ransohoff. *The Cleveland Clinic Foundation, Dept Neurosciences, Cleveland, USA*

**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

G. T. Ingle, J. Sastre-Garriga, L. Ramio, D. H. Miller, A. J. Thompson. *Department of Headache, Brain Injury and Neurorehabilitation, Institute of Neurology, London*

**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

T. Solomon, H. Ni, D. W. C. Beasley, M. Ekkelenkamp, M. J. Cardosa, A. D. T. Barrett. *Department of Neurological Sciences and Medical Microbiology University of Liverpool, WHO Collaborating Center for Tropical Diseases, Sealy Center for Vaccine Development, and Department of Pathology, University of Texas Medical Branch, Galveston, Texas, USA and Universiti Malaysia Sarawak, Malaysia*

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

G. T. Plant, R. R. A. McCarthy, M. James-Galton. *National Hospital for Neurology and Neurosurgery, London; University of Cambridge, Department of Experimental Psychology, Cambridge*

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

M. Husain, A. Parton, T. Hodgson, D. Mort, G. Rees. *Imperial College, London; Institute Cognitive Neuroscience, London*

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

A. Seymour, J. Palace, B. Lang, L. Clover, A. Cavey, A. Vincent. *Horton Hospital, Banbury; Clinical Neurology, Radcliffe Infirmary, Oxford; Neurosciences, Institute of Molecular Medicine, John Radcliffe Hospital, Oxford*

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

J. H. Rees, C. Benton, H. Watt, N. C. I. Fox, A. Waldman, H. R. Jäger, J. Stevens, P. Tofts. *National Hospital for Neurology and Neurosurgery, London*

**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

J. Stone, M. Sharpe, I. Deary, C. Warlow. *Division of Clinical Neurosciences, Division of Psychiatry and Department of Psychology, University of Edinburgh*

**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

J. M. Schott, A. Vincent, L. Clover, C. Buckley, A. Gabel, B. Lang, S. Omer, C. G. Bien, J. Palace, M. N. Rossor. *Dementia Research Group, Institute of Neurology, London; Neurosciences Group, Department of Clinical Neurology, Weatherall Institute of Molecular Medicine, John Radcliffe Hospital, Oxford; Atkinson Morley Hospital, Wimbledon, London; Department of Epileptology, University of Bonn, Bonn, Germany; Department of Clinical Neurology, Radcliffe Infirmary, Oxford*

**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

H. J. Willison, K. Townson, J. Veitch, J. Boffey, N. Isaacs, S. Andersen, C. C. Ling, D. R. Bundle. *University Department of Neurology, Institute of Neurological Sciences, Southern General Hospital, Glasgow; Department of Chemistry, University of Glasgow; Department of Chemistry, University of Alberta, Edmonton, Alberta, Canada*

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

A. M. Schaefer, E. L. Blakely, M. J. Barron, P. G. Griffiths, R. W. Taylor, D. M. Turnbull. *Department of Neurology, University of Newcastle-upon-Tyne*

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

S. A. Cooper, C. A. Heath, R. G. Will, R. S. G. Knight. *National Creutzfeldt Jakob Disease Surveillance Unit, University of Edinburgh*

**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

J. A. Eyre, M. Smith, F. Villagra, F. Cowan, M. Rutherford, E. Mercuri, F. Kirkham. *School of Clinical Medical Sciences, Department of Child Health, University of Newcastle upon Tyne; Department of Child Health, Imperial College London; Institute of Child Health, London*

**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

E. Flossmann, U. G. R. Schulz, P. M. Rothwell. *Stroke Prevention Research Unit, Department of Clinical Neurology, Radcliffe Infirmary, University of Oxford*

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

P. J. Kirkpatrick, J. C. Baron, J. Golledge, P. Al-Rawi, I. McNamara. *University Department of Neurosurgery and Stroke Medicine*

**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

N. S. Ward, A. J. T. Thompson, M. M. Brown, R. S. J. Frackowiak. *Wellcome Department of Imaging Neuroscience & Department of Headache, Brain Injury and Rehabilitation, Institute of Neurology, London*

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

C. Jackson, C. Sudlow. *University of Edinburgh*

**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

M. Swash, C. L. H. Chan, S. Ponsford. *Queen Mary's School of Medicine, St Bartholomew's and The Royal London Hospital, London*

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)

C. Proukakis, J. W. Taanman, J. M. Cooper, T. T. Warner. *Department of Clinical Neurosciences, Royal Free & University College Medical School, London*

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

K. G. Shields, P. J. Goadsby. *Institute of Neurology, London*

**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

P. A. Malhotra, R. Greenwood, M. Husain. *Division of Neuroscience and Psychological Medicine, Imperial College London; Institute of Cognitive Neuroscience, University College London; National Hospital for Neurology and Neurosurgery, London*

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

J. M. Hall, R. Al-Shahi, C. P. Warlow. *University of Edinburgh*

**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

A. Hassan, K. Gormley, M. O'Sullivan, J. Knight, P. Sham, P. Vallance, J. Bamford, H. Markus. *Department of Clinical Neurosciences, St George's Hospital Medical School, London; Division of Psychological Medicine, Institute of Psychiatry, London; Centre for Clinical Pharmacology, University College, London; Department of Neurology, St James' University Hospital, Leeds*

**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

D. J. H. McCabe, P. Harrison, P. S. Sidhu, I. J. Mackie, G. Purdy, A. S. Lawrie, H. Watt, S. J. Machin, M. M. Brown. *Stroke Research Unit, Department of Headache, Brain Injury and Rehabilitation; Dementia Research Group, Institute of Neurology, The National Hospital for Neurology & Neurosurgery; The Haemostasis Research Unit, Department of Haematology, University College London*

**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

R. Al-Shahi, J. J. Bhattacharya, C. E. Counsell, V. Papanastassiou, V. R. Ritchie, R. C. Roberts, R. J. Sellar, C. P. Warlow, the SIVMS collaborators. *Department of Clinical Neurosciences, Western General Hospital, Edinburgh; Institute of Neurological Sciences, Southern General Hospital, Glasgow; Department of Neurology, Royal Infirmary, Aberdeen; Fauldhouse Health Centre, Fauldhouse, Edinburgh; Department of Neurology, Ninewells Hospital and Medical School, Dundee*

**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 $45 \pm 16$ 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 $\geq 1$ 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

D. J. Thomas, A. Halliday, A. O. Mansfield, R. Peto for the ACST collaborators. *St Mary's Hospital, London*

**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.