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A SYSTEMATIC AND STRUCTURED APPROACH TO THE INVESTIGATION OF ATAXIA
P.F. Worth1, N.W. Wood1. 1National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG, UK; 2Department of Molecular Pathogenesis, Institute of Neurology, Queen Square, London WC1N 3BG, UK

Ataxia is a common and often prominent feature of a large number of disparate neurological conditions, both hereditary and acquired. Ataxia may result from a primary neurological disorder or may present as part of a broader multisystem disease, e.g secondary to a metabolic abnormality. Therefore, establishing the correct diagnosis and aetiology often presents the clinician with a difficult challenge.

In this paper, we highlight particularly useful and important features of the history and clinical examination of patients with ataxia. We argue that the single most informative factor that guides the clinical approach is the age at disease onset. This establishes a framework for subsequent analysis of the clinical problem. Other important factors include family history, ethnic origin, rate of progression, and the association of other symptoms and signs. Each feature may itself point towards a particular diagnosis, or may help to direct and prioritise the large number of diagnostic tests and special investigations available in order to simplify what can be a lengthy and expensive diagnostic process. We give special attention to the problem of hereditary ataxia; if this is suspected, we suggest a means of prioritising genetic tests, thereby minimising costs. We hope to offer a practical and systematic strategy, if not an algorithm, which will be of use to both the specialist and general neurologist alike.

THERAPEUTIC ENDEAVOURS IN MUSCULAR DYSTROPHY: THE HOPE VERSUS THE HYPE
V. Dubowitz. Dubowitz Neuromuscular Unit, Dept of Paediatrics, ICSM Hammersmith Campus, Du Cane Rd, London W12 ONN, UK

A critical review is provided of the various therapeutic efforts in muscular dystrophy over the past decade, covering cell transfer, gene therapy, including gene replacement and more recently gene repair, protein upregulation, and pharmacological trials, particularly with muscle relaxants. A number of guidelines have been published for therapeutic scientists to try and avoid this hype, which is not in the interests of the patients and their families or of the scientists.

PECTORAL MUSCULAR ATROPHY/DYSTROPHY WITH ANDROGEN INSensitivity
G. Modi, M. Sur, V. Pans, B. Morar, H. Soodyall, B. Joffe. Department of Neurology, Johannesburg General Hospital, University of Witwatersrand, South Africa

Three families are described in whom the cardinal clinical manifestations are those of androgen insensitivity (gynaecomastia, truncal obesity, small genitalia, long slender limbs, wide armpit, progressive infertility), and pectoral muscle wasting/atrophy. Pitosis, mild to moderate lower limb proximal weakness and hypertrophied deltoids are other features.

EMG: non-specific myopathic and neurogenic potentials; CPK: normal to moderately elevated; biopsy: in severe case—features of a dystrophic process; in mild case—non-specific/normal; electron microscopy: non specific features; immunohistochemical stains: for dystrophin (C-terminal, N-terminal, and rod domain), merosin, sarcoglycan (including alpha, beta, and delta), beta-dystroglycan, caveolin 3, dysferlin, emerin, and spectrin (these stains were all positive or normal). Androgen receptor antibody staining was also performed and showed reduced binding which may be non-specific; androgen receptor: molecular analysis of the exons of the androgen receptor gene was sequenced and showed no mutations as well as the absence of trinucleotide expansion in exon 1; SMA gene: normal.

Conclusion: The clinical features described in these families as well as the laboratory data suggest that this is a novel neuromuscular disorder with androgen insensitivity. Alternatively it may still represent a variant of Kennedy’s disease.

MITOCHONDRIAL DNA POINT MUTATION IN INFANTILE BILATERAL STRIATAL NECROSIS (IBSN)
G. Modi, C. Eddy, M. Modi, A. Maharaj, H. Soodyall. University of the Witwatersrand, South Africa

Friede (1975) first used the term infantile bilateral striatal necrosis (IBSN) to describe a group of infantile encephalopathies characterised by bilateral symmetrical degeneration of the putamina, caudate nucleus, and less commonly the pallidum. IBSN is characterised clinically by psychomotor retardation, optic atrophy with abnormal eye movements, dystonia (with athetosis and myoclonus), spasticity, and ataxia. The illness is often familial (dominant or recessive) and rarely sporadic. Diagnostic findings on imaging are asymmetrical longitudinal oval defects (lens shaped) in both putamina.

We describe here a South African family with typical features of IBSN. The mother and her two daughters as well as a deceased son showed clinical and radiological features compatible with this diagnosis. IBSN has been associated with mutations in the mitochondrial ATPase 6 gene at positions 8851 and 9176. We therefore examined our family for mutations in the mitochondrial ATPase 6 gene and also searched for known mutations associated with Leigh’s disease, Leber’s disease, and other mitochondrial diseases.

A mitochondrial ATPase 6 mutation was identified at np 9053. This results in an amino acid change from serine to asparagine. IBSN is therefore a mitochondrial disease with mutations in the mitochondrial ATPase 6 gene.

MYOTONIC DYSTROPHY IN A GUJARATI INDIAN FAMILY—GENOTYPE/PHENOTYPE CORRELATIONS AND HAPLOTYPE ANALYSIS
G. Modi, H. Makkkan, K. Hari, H. Soodyall. University of the Witwatersrand, South Africa

A Gujarati Indian family from Durban, South African, with myotonic dystrophy (DM) was identified. Typical features of DM were noted clinically. These included myotonia, unique topography of muscular atrophy, and dystrophic changes in non-muscular tissues. These will be described.

Eleven individuals from the family were assessed and five members were diagnosed with DM. The affected members were tested for the CTG repeat expansion of the DMPK gene on chromosome 19 using PCR. Southern blot analysis of the expanded CTG repeat alleles was done to estimate expansion size. The expansions ranged from 200 to 1200 in the affected members (normal less than 20). The expansions were correlated with Mini Mental scores, fertility, and weakness in this family. Direct correlations were noted between the CTG expansions and all three clinical parameters.

A lu I, Hinf I, and Taq I polymorphisms were determined in this family by Southern blot analysis and RFLP analysis of PCR products. The affected individuals were found to be lu I +, Hinf I –, and Taq I +. This haplotype background is the same as the haplotype of non-Gujarati Indian DM and the Caucasian DM haplotype. This provides evidence for migration of the DM haplotype into India. It may also assist in predictive studies in individual pedigrees.
Focal brain lesions (FBLs) are a major diagnostic problem in HIV infected patients. The only accurate diagnosis of these lesions is by histology. In third world countries where resources for brain biopsies are limited by availability of neurosurgical and neuropathological services, radiological studies, in particular CT scans of the brain [MRI scans are also limited], play a pivotal role in diagnosis of these FBLs. In terms of the literature the commonest cause for FBL in HIV positive patients is toxoplasmosis encephalitis. Primary CNS lymphoma (PCNSL) is a fast growing cause and progressive multifocal leukencephalopathy (PML) is another emerging opportunistic infection of the CNS. The exact frequency of other FBL causing disorders has been poorly evaluated.

We describe here 32 HIV positive patients with FBL in an unselected series of hospital based patients. The CT scan characteristics of these lesions in terms of size, shape, thickness of wall, oedema, and enhancement characteristics were categorised in detail. No specific or clear distinguishable features were identified for the FBL.

Correlations were then made with blood investigations, CSF findings, chest x rays, and non-neurological illnesses. Empiric treatment was then instituted with regular CT scan follow up. Treatment modalities were adjusted according to the clinical and radiological responses.

Presumed diagnosis were made based on CT scan appearance and the parameters mentioned above as well as response to treatment. Diagnoses were positively made in those conditions that are readily diagnosed by serological tests, that is, syphilis, cisticercosis, cryptococcus or toxoplasmosis.

Results: The CT scan appearances alone were found to be very non-specific. The collective combined data as proposed above were readily diagnosed by serological tests, that is syphilis, cisticercosis, cryptococcus or toxoplasmosis.

Conclusions: The data provide a method for diagnosis of FBLs in HIV positive patients where histology is not possible. An algorithm is therefore proposed and will be followed. Cisticercosis was the commonest cause in our patients and may reflect the endemic nature of this illness in our population.
GENE EXPRESSION IN BIPOLAR MOOD DISORDER—A MICROARRAY GENEFILTER STUDY
L. Kirkby, K. Amoils, G. Modi. WITS University Medical School, South Africa

Microarrays are revolutionising gene expression research. The microarray, or GeneFilter, is based on a DNA cross linked to a membrane, autoradiography, and a software package called Pathways. The microarray provides the simultaneous analysis of changes in the steady state levels of mRNA transcripts of over 5000 genes. In our study, total RNA was extracted from lymphocytes in peripheral blood of 10 bipolar type I patients in the manic phase of the illness, and then blood was re-drawn after each patient stabilised on lithium therapy. The RNA was stored at 70°C. The RNA was labelled with DIG radiolabelled probe by reverse transcription, and then hybridised onto the membrane overnight and detected by colour detection using NBT/BCIP substrate.

A comparison analysis was performed between the pre and post lithium therapy patients using the Pathways software. The intensity ratios through colour overlays was used to analyse the differences in gene expression between the manic and the euthymic phases of bipolar illness. The top 500 genes that were overexpressed and showed differences were chosen. Further analysis was performed by choosing a ratio cutoff point of 100.

Thus, the manic phase produced three top expressor genes as compared with the euthymic phase: GTP/GDP dissociator inhibitor protein (ratio 127), integrin linked kinase (ILK) (ratio 125), and MTF-1 mRNA for metal regulatory transcription factor (ratio 118).

GTP binding proteins occur in the signal transduction pathway, and they regulate cellular processes as diverse as protein biosynthesis and intracellular membrane trafficking. Small G proteins cycle between the GDP bound inactive form and the GTP bound active form. They receive upstream signals through their regulators and transduce signals to downstream targets while they stay in the GTP bound form. Thus, G proteins serve as timers.

These results indicate that in bipolar mood disorder there may be an abnormality in signal transduction pathways.

OPTIC NEURITIS IN AN URBAN BLACK AFRICAN COMMUNITY
R. Pokroy, G. Modi, D. Saffer. WITS Medical School, South Africa

To describe the clinical profile of idiopathic optic neuritis in South African blacks. South African black patients with acute isolated idiopathic optic neuritis, treated and followed for at least 3 months at a large medical centre, were studied. Exclusion criteria were other causes of optic neuritis (such as ischaemic optic neuritis, toxins or Leber’s hereditary optic neuropathy); all causes of optic neuritis (such as HIV, neurosyphilis, and sarcoid or connective tissue disease); neurological disease outside of the optic nerves; and any race other than South African black. Patients underwent extensive ophthalmic, neurological, radiological, cerebrospinal fluid, and blood assessment.

Results: Eighteen eyes of 10 patients were studied. The mean age was 35.7 years and 9 patients were female. Only 2 patients had truly bilateral optic neuritis, the other 8 having either bilateral simultaneous or consecutive disease. Presenting visual acuity (VA) was less than 0.1 in all patients. Routine H/E showed variation in fibre size with normal axons and atrophic fibres. The modified gomori trichrom stain showed numerous rods within muscle fibres, most strikingly in the atrophic fibres. The α-actinin stain revealed fibres with a coarse granular appearance indicating the presence of excess Z disc material. Electron microscopy confirmed the presence of rods.

Discussion: This patient exemplifies the adult onset form of nemaline myopathy. Numerous mutations have been described in 5 genes coding for the proteins MEF2C, SRF, NEB, ACTA1, and TNN1). However, the specific gene causing FSHD has not been determined yet. Clinically, patients present with slowly progressive weakness involving mainly the face and shoulder muscles, usually starting in adolescence. In rare cases (5-10%) involvement progresses to a severity requiring wheelchair assistance in later life.

Conclusion: There were no dysmorphic features. The CK was normal and the EMG showed a myopathic pattern. There was no family history of any neuromuscular disorder.

FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY IN A PATIENT FROM SOUTHERN AFRICA
R. Pokroy, G. Modi, D. Saffer. WITS Medical School, South Africa

Facioscapulohumeral muscular dystrophy (FSHD) is a progressive genetic neuromuscular disorder commonly seen in South Africa. The disorder has been linked to chromosome 4q35, where DNA rearrangements due to deletions of 3.3 kb repeat units occur. However, the specific gene causing FSHD has not been determined yet. Clinically, patients present with slowly progressive weakness involving mainly the face and shoulder muscles, usually starting in adolescence. In rare cases (5–10%) involvement progresses to a severity requiring wheelchair assistance in later life.

Aim: To describe the clinical profile of FSHD in South African blacks.

Methods: In this presentation, a patient with FSHD is described whose genetic analysis revealed a compound heterozygote— the first to be described in South Africa.

Results: This 50 year old male complained of weakness of the shoulder girdle since adolescence. The weakness was steadily progressive, laterally involving the hip joints and muscles of the lower legs as well. On examination, the patient showed typical facial weakness, with pronounced winking of the scapulae and weakness of the shoulders and hips. Bilateral drop feet were present due to tibialis anterior weakness. Southern blot analysis was performed to determine DNA rearrangements in this patient as part of a genetic/clinical study of patients with FSHD.

Conclusion: This is the first patient with FSHD in South Africa showing deletions on both chromosomes in this patient, indicating a compound heterozygote.

DETECTION OF NOVEL POINT MUTATIONS IN NON-DELETION PATIENTS WITH DUCHENNE MUSCULAR DYSTROPHY USING DNA SEQUENCING
K.D. Pillay, P.L.A. Bill. Department of Neurology, Nelson R. Mandela School of Medicine, Durban, South Africa

Duchenne muscular dystrophy is a severe X-linked recessive genetic disorder affecting 1:3500 live male births. Approximately 65% of cases have detectable deletions on multiplex PCR. In the remaining cases, no deletions are present, therefore it has been postulated that other mutations such as single nucleotide polymorphisms or duplications are responsible for the disease phenotype.

Aim: The aim of this study was to categorise clinically affected Duchenne and Becker muscular dystrophy patients into deletion and non-deletion genotypes using DNA sequencing.
non-deletion groups. The DNA from the non-deletion group of patients was subjected to DNA sequence analysis to detect point mutations and/or duplications.

**Methods:** DNA extractions were conducted using the QIAamp mini blood kit. Multiplex PCR using 18 primer pairs spanning the deletion “hot-spots” throughout the dystrophin gene, were performed. The DNA of the non-deletion group of patients was subjected to PCR reactions using primers targeted at exons 47, 48, 50, and 51. DNA sequencing was performed on the PCR products from the non-deletion group of patients using the BigDye V.3 Termination Kit. DNA sequence analysis was conducted using the Biotoro and the Linux based Staden computer packages.

**Results:** DNA sequence analysis revealed three exonic polymorphisms and five intronic polymorphisms. A single nucleotide polymorphism that caused a change in the amino acid sequence was found in exon 47 of one patient and an insertion was found in another patient that produced a frame-shift in the translational reading frame in exon 47. A polymorphism was found in exon 48 of three patients, which changed the amino acid sequence and also destroyed the restriction endonuclease Msel recognition site. There were four intronic polymorphisms in intron 47. The first was a nucleotide substitution, the second was a single nucleotide insertion, the third was a four base pair deletion, and the last was another four base deletion. The other intronic polymorphism was found in intron 49.

**Conclusion:** On evaluation of the results from this study it is evident that Duchenne and Becker muscular dystrophy represent varying degrees of severity for a genetic disease that is essentially the same. Understanding the basis of these variable disease presentations is crucial for elucidating the causal nature of this progressive muscle weakness, hence multiplex PCR for deletion detection and DNA sequencing for polymorphism detection serve as valuable techniques.

# CULTURALLY INDEPENDENT COGNITIVE TEST—EVALUATION IN NORMAL INDIVIDUALS

C. Schutte, M. Kakaza. Department of Neurology, University of Pretoria, South Africa

**Introduction and Aim:** Testing cognitive function in illiterate individuals is difficult, as most cognitive tests require a standard Western education for completion and appropriate interpretation. A novel culturally independent cognitive test (CICT) has been devised previously and used to compare cognitive function in low CD4 count HIV positive and HIV negative patients. Subsequently, the CICT was applied to a group of diabetic patients with possible cognitive impairment and compared to the MMSE in these patients. The degree of agreement between the two tests was reasonable. The aim of the current study was to administer the CICT to a group of normally functioning individuals who did not have a standard Western education.

**Methods:** A group of 50 individuals who had no or minimum formal schooling was evaluated. The individuals selected were between 20 and 50 years of age, well adjusted, and productive in their work environment. The CICT consists of the following sub-categories: memory registration (four words), construction (simple diagrams, both drawing, and copying with matches), attention, memory recall, and finger tapping frequency (on a mechanical counter).

**Results:** The results of this study are currently being produced and analysed. Good scores in all the individuals are expected.

# NEW-ONSET EPILEPSY AT THE PRETORIA ACADEMIC HOSPITAL NEUROLOGY OUTPATIENT DEPARTMENT

S. Dommann, C. Schutte. Department of Neurology, University of Pretoria, South Africa

**Aim:** To review patients with new onset epilepsy who presented to the outpatient department at the Pretoria Academic Hospital over one year.

**Methods and Patients:** The records of all adult patients with new onset epilepsy who showed abnormalities on EEGs were analysed. Four specific aspects were investigated: incidence of epileptiform features on EEG in non-specific abnormalities, percentages of abnormalities on CT brain scans, clinic attendance over one year, and number of seizure recurrences over one year.

**Results:** Data are currently being analysed and will be presented on the poster.
020 NERVUS ACCESSORIUS NERVE CONDUCTION AS A TEST TO EVALUATE RESPONSE TO BOTULINUM TOXIN THERAPY

J.A. Smuts, P.W.A. Barnard Wilgers. Medical Centre, Pretoria, South Africa

Botulinum toxin therapy has become the main treatment option for patients suffering from torticollis. In some patients response in subsequent treatments is disappointing after initial good response. The reasons for this response failure can be attributed to many factors but the development of antibodies to the toxin is cited as the main mechanism. If antibodies are present this would inhibit denervation expected after injection of the toxin. Testing for these antibodies is available, but these tests are complex and very expensive and therefore of little practical value. The use of surface EMG as a method to measure denervation in the sternocleidomastoid muscle has been used to collect a seizure diary. This was followed by a 42 day study. A baseline phase of 28–56 days with optimal standard therapy. On the injected side we were able to show a statistically significant drop in the compound muscle action potential (CMAP) compared with the values obtained pretreatment. No significant changes were observed on the non-injected side. This nerve conduction study might therefore be a useful test to evaluate responders suspected to have antibodies to botulinum toxin.

021 LOW DOSE TOPIRAMATE TREATMENT AS ADJUNCTIVE THERAPY IN PATIENTS WITH INADEQUATE SEIZURE CONTROL


Objectives: To assess the efficacy of a low dose (150 mg/day) of topiramate as adjunctive therapy in patients with partial onset seizures with or without secondary generalisation who are inadequately controlled on other anti-epileptic therapy.

Methods: The study was designed as an open label multicentre study. A baseline phase of 28–56 days with optimal standard therapy was used to collect a seizure diary. This was followed by a 42 day titration phase of 25 mg/day of topiramate with a dose increase of 25 mg every week to a maximum of 150 mg/day. This was followed by a maintenance phase at this dose of topiramate for 84 days. Diary cards kept by the patients and monthly clinical follow up visits where vital signs were checked were used to monitor response.

Results: The efficacy of topiramate 150 mg/day as add on therapy was measured by the reduction in seizures from baseline to the end of maintenance phase. This was calculated in two ways: absolute reduction in seizure count and percentage reduction in seizure count. The primary efficacy variable was the percentage of patients that demonstrated at least a 50% reduction in their seizure counts from baseline to the end of the maintenance phase. Twelve of the 18 patients (66.7%) demonstrated a >50% seizure reduction over the last 6 weeks of the maintenance phase. The only other measured parameter where statistically significant change from baseline was observed was that of weight loss (average loss of 3.4 kg) at the end of maintenance.

The reported side effects included reduced concentration, paresthesia, abdominal discomfort, headaches, and weight loss. These were all only mild to moderate and only in two patients dose reduction was necessary.

Conclusion: The addition of a low dose of topiramate was effective to reduce seizures frequency by >50% in patients not adequately controlled on standard therapy.

022 ANALYSIS OF SOUTH AFRICAN PATIENTS WITH MULTIPLE SCLEROSIS: POPULATION VERSUS FAMILIAL RISK ASSOCIATED WITH THE PRESENCE OF VIRAL SEQUENCES

J.N.P. de Villiers1, F.K. Treurnicht, L. Warnich, M.J. Kotze2. 1Division of Human Genetics, Faculty of Health Sciences, University of Stellenbosch, Tygerberg, South Africa; 2GeneCare Molecular Genetics, Christiana Barnard Memorial Hospital, Cape Town, South Africa; 3Department of Medical Virology, Faculty of Health Sciences, University of Stellenbosch, Tygerberg, South Africa; 4Department of Genetics, University of Stellenbosch, Stellenbosch, South Africa

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS). Although current knowledge suggests that MS is associated with autoimmunity, and that genetic susceptibility and infectious agents may be involved in the disease process, the cause of MS remains unknown. Recent studies performed in the South African population demonstrated a significant association between MS and the functional S-LTI polymorphism in the promoter region of the SLC1A1 gene implicated in both autoimmune and infectious disease susceptibility. In this study serum and peripheral blood mononuclear cells (PBMCs) of MS patients, close relatives, and unrelated controls were screened for the presence of MS associated retrovirus (MSRV) and two herpes virus (HHV-6 and EBV) sequences, respectively, within the context of the SLC1A1 and the 5′-GT)n motif.

In this study a control group of 10 healthy volunteers was tested to show interest stability of the technique without the injection of botulinum toxin. In the presence of antibodies it is expected that the compound muscle action potential (CMAP) would be unchanged before and after botulinum toxin injections. We then tested 15 patients before and 6 weeks after injection of the sternocleidomastoid muscle. On the injected side we were able to show a statistically significant drop in the compound muscle action potential (CMAP) compared with the values obtained pretreatment. No significant changes were observed on the non-injected side. This nerve conduction study might therefore be a useful tool to evaluate non-responders suspected to have antibodies to botulinum toxin.

023 A MULTIDISCIPLINARY APPROACH TOWARDS ELUCIDATING THE GENETICS OF MULTIPLE SCLEROSIS

M.J. Kotze, J.N.P. de Villiers. Division of Human Genetics, Faculty of Health Sciences, University of Stellenbosch, Tygerberg, South Africa; GeneCare Molecular Genetics, Christiana Barnard Memorial Hospital, Cape Town, South Africa

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS). Clinically it is characterised by a relapsing–remitting or chronic progressive course, frequently leading to severe disability. Although current knowledge suggests that MS is associated with autoimmunity, and that infectious agents and hereditary factors may be involved, the cause of MS remains unknown. The demonstration of a higher recurrence risk of MS in families (4–5%) compared with the general population (0.1%) suggests a genetic basis. Extensive analyses of the entire human genome to identify new genes that may underlie MS have indicated that several genes may contribute to disease susceptibility. In this study specific candidate genes for MS have been analysed for the first time within the context of autoimmune and infectious disease susceptibility, in order to investigate the role of innate and viral factors implicated in the pathogenesis of MS. The Z-DNA forming repeat polymorphism in the promoter region of the solute carrier family 11 (proton-coupled divalent ion transporters) member 1 (SLC1A1) gene, associated with both autoimmune and infectious disease susceptibility, was found to be significantly associated with MS (p <0.01) in the genetically homogeneous Afrikaner population of South Africa. Significant differences in allelic distribution between German controls and MS patients with a secondary progressive disease course (p <0.05), and between the German patients with primary and secondary progressive MS (p <0.05) were furthermore observed. A point mutation (77C→G) in the gene encoding protein tyrosine phosphatase, receptor-type C (PTPRC), playing an essential role in the activation of T and B cells, was found to be associated with MS in the German population. Analysis of the Afrikaner population did not indicate a contribution of this mutation to MS. However, it seems likely that this mutation may contribute to disease expression, because in one of the South African families with two MS affected sibs; the most severely affected sister was heterozygous for the 77C→G mutation. The PTPRC mutation may therefore be of significance in disease prognosis, mainly within the family context. The
multidisciplinary approach used in this study to elucidate the aetiology of MS has led to a stepwise accumulation of scientific information, which forever changed our understanding of the disease process.

**024 DEFICIENT GLUTAMATE STIMULATED RELEASE OF DOPAMINE FROM NUCLEUS ACCUMBENS SHELL COMPARED WITH CORE OF SPONTANEOUSLY HYPERTENSIVE RATS**

V.A. Russell, Department of Human Biology, Faculty of Health Sciences, University of Cape Town, Observatory 7925, South Africa

Spontaneously hypertensive rats (SHR) are used as a model for attention deficit hyperactivity disorder (ADHD) because SHR are hyperactive and they are unable to sustain attention during behavioural tasks. ADHD symptoms (hyperactivity, impulsiveness, inattentiveness) have been suggested to result from impaired dopamine mediated reinforcement mechanisms involving the nucleus accumbens. Using an in vitro superfusion technique, we previously showed that electrical and/or K+ stimulated release of dopamine from dopaminergic nerve terminals in the prefrontal cortex, nucleus accumbens, and caudate-putamen of adult SHR was significantly lower than that of adult Wistar-Kyoto (WKY) control rats. We also showed that dopamine autoreceptor feedback inhibition is enhanced in adult SHR caudate-putamen and nucleus accumbens slices. A similar deficiency had been observed in nucleus caudatus slices of prepubertal SHR. Because SHR develop hypertension after puberty, subsequent investigations were carried out on prepubertal, 4–6 week old rats. Glutamate activation of extrasynaptic N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) receptors was shown to release significantly more norepinephrine from SHR prefrontal cortex slices than WKY, suggesting that neural circuits that use glutamate as a neurotransmitter exert greater stimulatory control of norepinephrine function in prefrontal cortex of SHR than WKY. In the present investigation we show that glutamate-stimulated release of [*3H*] dopamine from striatal slices is mediated by AMPA receptors and that glutamate stimulated release of [*3H*] dopamine is not significantly different in nucleus accumbens core and shell of WKY or core of WKY and SHR, whereas glutamate stimulated release of [*3H*] dopamine from SHR shell is significantly lower than SHR core. There is also a tendency for glutamate stimulated [*3H*] dopamine release from SHR shell to be lower than from WKY shell.

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**025 NEUROCYSTICEROSIS IN EASTERN AND SOUTHERN AFRICA**

N.A. Malojane, R. Krecek, L. Michael. Department of Neurology, Kalafong Hospital, University of Pretoria, South Africa

Through the monitoring of hospital based patients with neurocysticercosis, community based serological surveys of particular groups of people, and surveys of porcine cysticercosis in pigs, a lot of information has been gathered on the prevalence and incidence of neurocysticercosis in Eastern and Southern Africa. Projects on the accurate diagnosis and treatment of cysticercosis have established reasonable cost effective strategies which forever changed our understanding of the disease. Neurocysticercosis is one of the most common parasitic infections of man and goes under a compatible clinical presentation with supportive biochemical or neuroradiological features. Definitive biochemical or genetic diagnosis is not always possible but a probable clinical presentation with supportive biochemical or radiological features may suggest the diagnosis.

**027 NEUROLOGICAL COMPLICATIONS OF HIV IN PAEDIATRIC PATIENTS. THE SOUTH AFRICAN EXPERIENCE**

R. Von Toorn1, G. Riordan1, P. Roux1, B. Eley1, J.M. Wilmhurst1. 1Units of Paediatric Neurology; 2Infectious Disease; 3Red Cross Children’s Hospital, School of Child and Adolescent Health, University of Cape Town, South Africa

Background: Retroviral disease is endemic throughout Southern Africa. Neurologically the microcephalic globally delayed infant is well recognised. However, with the increased incidence and prevalence of this devastating disease more "atypical cases" are presenting.

**Patient audit:** Nine children (five female; four male), seen in the neurology service over a two year period, demonstrated a spectrum of neurological complications, occurring as part of, or in consequence to, HIV. Median age of presentation was 2 years and 5 months (range 7 months to 6 years) retroviral status was known in eight out of nine of the patients prior to their neurological complication. Two patients had global developmental delay, the remaining children had normal neurodevelopment. The children presented with encephalopathy, acute, sub-acute and chronic (n=3), progressive multifocal leucoencephalopathy (n=2), intratable seizures (n=1), isochromatic hemiplegia (n=1), myelopathy (n=1), and peripheral neuropathy (n=1). Neuroimaging was performed in eight patients, of whom three had evidence of basal ganglia calcification. All children had poor outcome with incomplete recovery or continued deterioration.

**Conclusion:** Ongoing research is needed to delineate the pattern of disease in affected children. Children who live beyond the first year of life may present with a broad spectrum of neurological complications. With the high prevalence of retroviral infection disease differentiation remains important, as other treatable diseases can occur in addition to the HIV.  

**028 NEURORADIOLOGICAL DIAGNOSTIC AND PROGNOSTIC FEATURES OF TUBERCULOUS MENINGITIS IN CHILDHOOD**

S. Andronikou1, B. Smith1, R van Toorn2, H. Douw1, J.M. Wilmhurst2. 1Departments of Pediatric Neurology and Pediatric Radiology; 2Red Cross Children’s Hospital, School of Child and Adolescent Health, University of Cape Town, South Africa

We present our clinical experience of patients with tuberculous meningitis and correlating neuroradiological features.

**Methods:** The study comprised a retrospective review of all CT scans and clinical and laboratory findings in children presenting with a provisional diagnosis of TBM between 1998 and 2001. CT scans...
were assessed with regard to the presence of imaging features including basal meningeal enhancement, hydrocephalus, infarction, and tuberculosis. Patients were defined as those with definite proof of TBM (TB CSF culture positive), those with circumstantial proof of TBM (clinical presentation and consistent CSF features), and those without evidence of TBM. Correlation was made between the presence and severity of meningeal enhancement with presentation, proof of TBM, and outcome, initially concentrating on the CSF culture positive group and then including the probable group.

Results: Sixty eight patients were reviewed, from the group 19 patients (7M:12F) were CSF culture positive and 40 (24M:16F) were clinically consistent with a diagnosis of TBM. The youngest patient was 3.3 months and the oldest was 12 years with a median of 16 months for the culture positive group. The clinical features in the two groups were summarised and statistically compared with no significant difference found. The commonest positive CT finding of the affected patients was basal meningeal enhancement, followed by hydrocephalus, infarction, cisternal high-density exudo prior to IV contrast, and TB granulomas.

Conclusion: From this an inclusion criteria has been suggested, including the neuroradiology, to enhance the early confirmation of TBM. Current established guidelines are lacking this.

029 NEUROCRISTOPATHY: A CASE OF HADDAD DISEASE

R. van Collier¹, M. Baker², S.A. Annandale³, G.I. Ionescu³. ¹Department of Neurology, UP; ²Department of Paediatrics, I Military Hospital; ³Division of Paediatric Surgery, South Africa

Haddad disease (Online-Hirschsprung) is characterised by a combination of congenital central hyperventilation syndrome and Hirschsprung disease (CCHS). It was first described by Haddad in 1978 and is believed to be a defect of the migration of the neural crest. 48 other cases could be found in the world English literature. We present a full term neonate who was referred from the Eastern Cape with no structural or neuromuscular causes were excluded. A full battery of four reaction time (RT) tasks of increasing difficulty was administered on a personal computer. The tasks were: (a) simple RT in which the subject had to respond as quickly as possible by depressing the spacebar after the appearance of any target (always a single digit 0–9) in the centre of the computer screen; (b) choice RT in which the target was one specific digit, the subject had to respond to the second of any digit 0–9 occurring in a repeating sequence; and (c) a further sequential RT in which the target was a digit 1–8 that represented an increase of one relative to the preceding digit. The proportion of targets to non-targets in tests 2–4 was approximately range 0–9:1. A significant change was regarded as >15% deterioration in respect of any RT measure or accuracy measure on the basis of a reported 8–15% deterioration in RT of a BAC of 0.05%.

Methods: Intergroup comparisons of the baseline compared after night duty mean RTs revealed significant prolongation with respect to the first three tests. The same trend applied to test 4 but did not attain significance. Accuracy was significantly lower in respect of tests 3 and 4. A >15% deterioration in any one of the eight RT measures occurred in 17/33 (51%) subjects, mostly in respect of RT. (16 subjects) as opposed to accuracy (four subjects). Only one subject had a significant deterioration in accuracy without a corresponding change in time. Significant deterioration was found in nine subjects limited to one test, while two subjects deteriorated in two tests, three tests in five subjects. Only 6/33 subjects (18%) had largely maintained performance levels by virtue of no variables deteriorating by >8%.

Conclusions: Our findings are in general agreement with previous group analyses. The speed of response was affected to a greater extent than the accuracy of responses by sleep deprivation. The data may mask the presence of some significantly compromised individuals as marked inter-individual differences in susceptibility to sleep deprivation were found. While most of the subjects with a meaningful deficit evinced fluctuating performance levels, a small number had sustained deficits across the test battery. The effects of sleep deprivation in registrars should not be minimised or overlooked.

030 WHAT CAUSES PROGRESSIVE INTELLECTUAL AND NEUROLOGICAL DETERIORATION IN ADOLESCENTS? FINDINGS FROM A PROSPECTIVE NATIONAL SURVEILLANCE STUDY

J. te Water Noudé¹, A. Nicoll¹, R. Will², G. Devereux¹, L. Stellitano¹, C. Verity¹. ¹Addenbrooke’s Hospital, Cambridge, UK; ²Communicable Disease Surveillance Centre, Colindale, UK; ³The National Creutzfeld-Jacob Disease Surveillance Unit, Edinburgh, UK

Objective: Dementia is an uncommon diagnosis to make in adolescence. We reviewed cases with progressive intellectual and neurological deterioration (PIND) referred to a prospective national surveillance study that has been running in the UK for 5 years.

Methods: Clinical details of adolescents (aged 12 or more) with PIND identified via the British Paediatric Surveillance Unit were reviewed and classified by diagnosis by the PIND Expert Group.

Results: 784 children were included in the PIND study between May 1997 and July 2002. Of these 563 had a confirmed diagnosis: 44 of this group were adolescents. All of the 44 adolescents were given a specific diagnosis. There were 24 different diagnoses in this group: the cause most familiar to adult neurologists is Huntington’s disease, which occurred in five. The leuкоdystrophies were the most common: this was a heterogenous group with eight cases, including five different specific conditions. The most common single diagnosis was variant Creutzfeld-Jacob disease (vCJD), which occurred in five adolescents.

Conclusions: Of the PIND children in this study, a relatively small proportion were adolescents. vCJD is an important diagnosis to make in the UK. It is striking that a diagnosis was made in all the adolescents with PIND in this study.

031 ATTENTION AND WORKING MEMORY IN REGISTRARS AFTER NIGHT DUTY

P.R. Bartel, W.J. Offermeier, F.J. Smith. Departments of Neurology and Anaesthesiology, University of Pretoria and Pretoria Academic Hospital, South Africa

Background and Objectives: The consequences and controversies surrounding sleep deprivation in medical registrars (residents) are currently in the spotlight. Psychomotor assessments have a role in informing this debate. Some previous studies have lacked sensitivity by utilising tests of short duration. We avoided this pitfall in a study of registrars upon completion of a single period of night duty. Both group and individual effects were considered. The reference point for individual deficits was the equivalent effect of a blood alcohol concentration (BAC) >0.05% determined by other researchers.

Methods: The subjects consisted of 33 registrars in anaesthesics at the Pretoria Academic Hospital. There were 17 men and 16 women, aged 26–42 years. Night duty was performed on a weekly basis commencing at 16:00 and ending at 08:00 the next day. This is a less onerous schedule than in many previous studies. The normal working hours preceding and following night duty were available for study purposes. Baseline cases were undetermined and assumed to be 08:55 preceding night duty and repeated 24–25 hours later, just after completion of duty. Questionnaires included: (a) items regarding habitual sleep, the amount of sleep obtained during the night before duty and that obtained during the duty period; and (b) the Stanford Sleepiness Scale (SSS). Thereafter a battery of four reaction time (RT) tasks of increasing difficulty was administered on a personal computer. The tasks were: (a) simple RT in which the subject had to respond as quickly as possible by depressing the spacebar after the appearance of any target (always a single digit 0–9) in the centre of the computer screen; (b) choice RT in which the target was one specific digit, the subject had to respond to the second of any digit 0–9 occurring in a repeating sequence; and (c) a further sequential RT in which the target was a digit 1–8 that represented an increase of one relative to the preceding digit. The proportion of targets to non-targets in tests 2–4 was approximately range 0–9:1. A significant change was regarded as >15% deterioration in respect of any RT measure or accuracy measure on the basis of a reported 8–15% deterioration in RT of a BAC of 0.05%.

Results: Intergroup comparisons of the baseline compared after night duty mean RTs revealed significant prolongation with respect to the first three tests. The same trend applied to test 4 but did not attain significance. Accuracy was significantly lower in respect of tests 3 and 4. A >15% deterioration in any one of the eight RT measures occurred in 17/33 (51%) subjects, mostly in respect of RT. (16 subjects) as opposed to accuracy (four subjects). Only one subject had a significant deterioration in accuracy without a corresponding change in time. Significant deterioration was found in nine subjects limited to one test, while two subjects deteriorated in two tests, three tests in five subjects. Only 6/33 subjects (18%) had largely maintained performance levels by virtue of no variables deteriorating by >8%.

Conclusions: Our findings are in general agreement with previous group analyses. The speed of response was affected to a greater extent than the accuracy of responses by sleep deprivation. The data may mask the presence of some significantly compromised individuals as marked inter-individual differences in susceptibility to sleep deprivation were found. While most of the subjects with a meaningful deficit evinced fluctuating performance levels, a small number had sustained deficits across the test battery. The effects of sleep deprivation in registrars should not be minimised or overlooked.
history of minor and major strokes, history of cardiac disease, and extent of pharmacotherapy use in risk factor management.

Results: 9133 patients (55% female and 45% male) were screened. 2130 (23%) were black, 657 (7%) were coloured; 922 (10%) were Indian, and 5424 (59%) were white. They were all over 30 years of age. 4715 (51.6%) were 49 years of age or less and 4418 (48.4%) were over 50 years of age. The overall prevalence of risk factors increased with age except smoking, which decreased with age. 6610 (72%) of the total group of patients had at least one risk factor; 3109 (34%) had two, 1686 (18%) had three risk factors; 318 (3%) of patients had previous minor strokes, 690 (7%) had major strokes; 429 (4.8%) had been in congestive cardiac failure, and 760 (8%) gave a history of ischaemic heart disease. Medications prescribed were anticoagulants (2%), antiplatelet agents (15%), anti-diabetic agents (8.2%), ACE inhibitors (16%), angiotensin 11 blockers (4.5%), calcium channel blockers (4.5%), and diuretics (21%).

Conclusions: Stroke risk factors are highly prevalent in general practice populations of all racial groups. This study has yielded unique data on the prevalence of stroke risk factors in patients attending South African general practices—both in metropolitan and rural communities. GPs can play an important role in stroke prevention.

### Abstract 32

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Black</th>
<th>Coloured</th>
<th>Indian</th>
<th>White</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension (&gt;140/90 or on Rx)</td>
<td>53%</td>
<td>48%</td>
<td>48%</td>
<td>53%</td>
<td>52%</td>
</tr>
<tr>
<td>Diabetes (on Rx; or fasting sugar &gt;7 mmol/l)</td>
<td>11.9%</td>
<td>13.2%</td>
<td>24%</td>
<td>8%</td>
<td>11%</td>
</tr>
<tr>
<td>Lipids abnormal (on Rx or chol &gt;5.16 mmol/l)</td>
<td>5.1%</td>
<td>20.5%</td>
<td>22%</td>
<td>37.9%</td>
<td>27%</td>
</tr>
<tr>
<td>Smoking (current)</td>
<td>14.8%</td>
<td>30.9%</td>
<td>22%</td>
<td>22.5%</td>
<td>21%</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>2%</td>
<td>2.2%</td>
<td>1.5%</td>
<td>6%</td>
<td>4.4%</td>
</tr>
</tbody>
</table>

### SYMPATHETIC NERVOUS SYSTEM IN MODULATING IMMUNE ACTIVITIES IN AUTOIMMUNE DISEASES

Y. Liu. Neurotec Department, Huddinge University Hospital, Karolinska Institute, 141 86-Stockholm, Sweden

Previous studies suggested that both the hypothalamic-pituitary axis and sympathetic nervous system (SNS) play significant roles in autoimmune disease initiation and progression. This mini review concentrates on the issue of sympathetic nervous system in the modulation of natural immune response in the general. However, the articles reviewing the role of sympathetic nervous system in the progression of autoimmune diseases have not come to the publication yet. The present article fills the blank. The studies reviewed showed that SNS regulated the immune activities in autoimmune diseases, which play pivotal roles in the onset and progression of the diseases. The mechanisms behind the regulations are yet undefined and remain to be clarified.

### A NOVEL FAMILIAL TUBULAR AGGREGATE MYOPATHY ASSOCIATED WITH ABNORMAL PUPILS

N. Shahrizaila1, J. Lowe2, A. Wills1. 1Department of Neurology, Queen’s Medical Centre, University Hospital NHS Trust, Nottingham NG7 2UH, UK; 2Department of Histopathology, Queen’s Medical Centre, Nottingham NG7 2UH, UK

We report a novel familial syndrome of myopathy and pupillary abnormalities associated with tubular aggregates compatible with either autosomal dominant or X-linked inheritance. We examined four members from two generations of a family who demonstrate myopathy and a marked miosis. Pharmacological pupillary responses suggested smooth muscle involvement. Pathological findings consisted of tubular aggregates in many fibres but predominantly type I. Tubular aggregates are inclusions within muscle fibres that have frequently been found in association with several myopathic disorders. However, an associated miosis has only rarely been described. We believe this is the first description of a familial syndrome of tubular aggregate myopathy with pupillary abnormalities.

### BRITISH NEUROSCIENTISTS: A PHILATELIC TRIBUTE

A. Dubb. University of the Witwatersrand, South Africa

C.E. Brown-Sequard (1817–1894) was born in Mauritius when it was a British colony. He thus qualifies as a British subject but furthermore was one of the first physicians to be appointed at Queen Square. His contributions to clinical neurology are well known.

C. Sherrington (1857–1952) was the doyen of neurophysiology. He described the pathway of nerve function and coined the terms “neuron” and “synapse”. In 1932 he shared the Nobel Prize with E.D. Adrian (1889–1977) for work on sensory nerve impulses.

H. Dale (1875–1968) shared the Nobel Prize in 1936 with Otto Loewi for “their discoveries relating to chemical transmission of nerve impulses.”

A. Hodgkin (1914–1998) and A. Huxley (1917– ) worked together to discover the ionic mechanisms in the passage of impulses along individual nerve fibres. They shared the 1963 Nobel Prize with the Australian J.C. Eccles (1903–1997).

Bernard Katz (1911– ) came to London as a refugee from Nazi Germany in 1934. At University College London he discovered the mechanism for the storage, release, and inactivation of the neurotransmitter acetylcholine. He received a third share of the 1970 Nobel Prize.

John Vane (1927–) contributed to the discovery of prostaglandins, which is inhibited by aspirin. With its effect on platelets and prostacyclin, aspirin is widely used in stroke prevention.

The persons mentioned will be featured on slides of postage stamps.

### KLIPPEL-FEIL SYNDROME “PLUS”

L.de.F. Ibáñez-Valdés, H. Foyo-Sábat. Department of Family Medicine, University of Transkei, South Africa

We report a case with Klippel-Feil (KFS) syndrome associated with hypertelorism, microtia, Sprengel deformity, hand and feet deformities, scoliosis, clinical manifestations of Klippel-Tranauanay syndrome, epilepsy, other congenital anomalies, and severe arterial hypertension secondary to renal artery stenosis. We have hypothesised that for patients with KFS and unilateral renal artery stenosis, medical treatment with ACE inhibitors can provide more benefits than surgery or percutaneous transluminal angioplasty. In order to get better results in the management of this patient all underlying problems should be identified before sending the patient for any kind of surgery, at this point it is important to bring these problems to the anesthesiologist’s attention for a very careful manipulation of the neck and head during induction of anesthesia, apart from other considerations.

We propose the term of Klippel-Feil syndrome “Plus” for those patients with cervical vertebral fusion and many other associated deformities rather than to add new eponyms to the long list that already exist. From our knowledge this is novel combination not previously reported to the medical literature.

### BINSWANGER’S DISEASE AND NEUROCYSTICEROSIS

H. Foyo-Sábat, L.de.F. Ibáñez-Valdés. Department of Neurology, Department of Family Medicine, University of Transkei, Private Bag X1 Umtata 5099, South Africa

We report seven patients who presented with clinical manifestations of ischaemic cerebrovascular disease (CVD) and dementia, and on CT...
DO CLINICIANS AGREE ABOUT THE DIAGNOSIS OF NEUROSYphilIS?

J.T. Butler, M. Timmermans, E. Jordaan, J.A. Carr. Department of Neurology, Tygerberg Hospital, University of Stellenbosch, South Africa

Introduction: The accuracy of the diagnosis of neurosyphilis cannot be determined with available techniques because no “gold standard” exists. In most patients the clinical presentation is not specific for neurosyphilis and the theoretical “point” of transition from syphilis to neurosyphilis defies definition. There are a plethora of publications concerning the sensitivity and specificity of laboratory data for the diagnosis of neurosyphilis but all suffer from the lack of a defined external standard, and published data therefore likely represent overestimates of the true properties of these tests. Published criteria for the diagnosis of neurosyphilis vary and their clinical usefulness remains unknown.

Aim: To determine how strongly clinicians agree about the diagnosis of neurosyphilis.

Method: Using the Tygerberg Hospital microbiology database, all patients with a positive CSF TFA serology seen at the same hospital in the period 1990–2000 were identified. The clinical records, serum and CSF serological results and other relevant information were abstracted from the hospital records by one investigator (MT) and entered onto a coded data sheet. Two neurologists were independently asked to view the clinical and laboratory data of 324 patients (all clinical data were known to be HIV positive) and to answer the question: “How likely is it that this patient has neurosyphilis requiring treatment?” Certainty of diagnosis was scored from −7 (definitely not) to +7 (definitely neurosyphilis). A score of 0 implies a position of equipoise, at the point of most uncertainty whether the patient does or does not have neurosyphilis. Agreement was assessed by weighted kappa values (to compensate for the ordinal nature of the data). Data were also analysed with tests of marginal homogeneity and log-linear modelling.

Results: The results indicate that for this data set there was “substantial” agreement (using Landis and Koch criteria) for the diagnosis of neurosyphilis (weighted kappa values of 0.76 and 0.9, using two different techniques). The two neurologists disproportionately classified patients at the extremes of certainty and agreement was best at the middle of the scale. Despite this, the clinician one categorised 109/324 and the clinician two categorised 92/324 patients in the range of certainty from −4 to +4, indicating that moderate to substantial uncertainty for the diagnosis of neurosyphilis is common. A survey of 12 neurologists in academic practice indicates that treatment thresholds vary from +2 to −2 on our scale, with 6 preferring to treat for neurosyphilis with a score of +1 or greater.

Conclusion: In a non-HIV population there appears to be “substantial” agreement between two neurologists about the diagnosis of neurosyphilis. Moderate to substantial uncertainty about the diagnosis in individual patients is common.

FRONTAL LOBE EPILEPSY SURGERY

J. Butler, R. Melvill. University of Stellenbosch, South Africa

Introduction: Localisation of seizures to the frontal lobes and lateralisation of frontal lobe seizures is complicated by (a) the plethora of symptoms and signs of frontal lobe seizures; (b) poor correlations of seizure symptomatology with specific regions of onset within the frontal lobes; (c) the large size of the frontal lobes; (d) rapid propagation patterns of seizures within the frontal lobes; (e) seizures propagating to the frontal lobes from other lobes may present with frontal lobe symptomatology; (f) poorly localising (and at times lateralising value) of scalp EEG; and (g) difficulties of localising and lateralising low amplitude high frequency ictal discharges on subdural EEG.

Aim: To assess the outcomes of epilepsy surgery in a prospectively identified cohort of patients undergoing frontal lobe epilepsy surgery.

Method: All patients who underwent epilepsy surgery of the frontal lobes prior to November 2000 were identified from an epilepsy surgery database. Outcome data were obtained from patient records and from telephone contact with all patients.

Results: A total of 21 patients (9 females and 12 males) were identified. Their ages ranged from 1 to 33 years (10 were <15 years old). All had medically refractory seizures and all underwent prolonged video EEG monitoring. Seizure symptomatology varied enormously between patients, and included limbic symptomatology, “frontal absence” mimicking temporal seizures, running, thrashing of the limbs, flapping the arms, hearing a noise and screaming, grunting, and posturing of the extremities. In 13 individuals there were no lateralising clinical findings. Intercital scalp EEG findings were absent in 7 patients and falsely localising in 5 patients (“temporal spikes” in 4). In 11 patients no lesion was evident on MRI (including FLAIR images and high resolution axial T1 weighted images). Six patients had dysplastic lesions, 2 post traumatic spongiosis, 1 an infant, and 1 a previously resected vascular malformation. Two patients had lesions in the contralateral frontal lobe that were unrelated to their seizures.

Subdural EEG was performed in all but 2 of the patients. One of the two patients not undergoing subdural EEG required a second surgical resection. Six patients had resections in the peri-Rolandic region and eight of the mesial frontal area that included the supplementary motor area.

Fifteen patients are seizure free (follow up of 6 months to 3 years). One patient had a bone-flap infection requiring grafting and 1 patient has clinically significant changes in behaviour. A transient, partial akinetic-mutism-like state occurred in all patients undergoing resections in the supplementary motor area.

Conclusion: Preliminary outcome data from a cohort of patients who had frontal lobe epilepsy surgery indicates that the majority have benefited substantially from surgery.

NOVEL PRESENILIN 1 MUTATION WITH PROFOUND NEUROFIBRILLARY PATHOLOGY IN AN INDIGENOUS SOUTH AFRICAN (XHOSA) FAMILY WITH EARLY ONSET FAMILIAL ALZHEIMER’S DISEASE

J.M. Heckmann, W.C. Low, C.M. Morris, C. de Villiers, S. Rutherford, R. Ramesar, R. Kalaria. Division of Neurology, Groote Schuur Hospital; High Resolution Centre, Institute for Ageing and Health, University of Newcastle upon Tyne, UK; ‘Neuropathology, Tygerberg Hospital, South Africa; ‘Division of Human Genetics, University of Cape Town, South Africa

Objective: To determine the phenotypic features and molecular basis of a dementing illness inherited as an autosomal dominant trait in an indigenous South African (Xhosa) family.

Background: Sporadic Alzheimer’s disease (AD) is rare among indigenous South Africans and familial AD has not been reported.

Design/Methods: Thirty individuals from an Xhosa family were investigated. Thirty-two individuals from a family of a South Indian origin were investigated as controls. Thirty-two South African individuals from the same population were investigated at random.

Results: The I143M mutation found in this family is novel and forms part of the mutation cluster on the second transmembrane domain of Presenilin 1. The phenotype is characterised by memory loss starting in the fifth to sixth decade, and a progressive dementing illness lasting on average eight years. Language and naming skills were preserved at a stage when other cognitive skills were profoundly affected. Only the proband suffered a generalised seizure a few months before death. The neuropathological findings in the proband are those of severe AD with profound neurofibrillary pathology in the brainstem.

Conclusions: This is the first documented indigenous South African (Xhosa) family with Presenilin 1-linked familial AD. The intragenomic variation in the course of the disease raises the possibility of as yet unknown environmental influences.

Supported by the MRC (UK), Alzheimer’s Research Trust (UK), Alzheimer’s Association (USA).

THIOPURINE METHYLTRANSFERASE DEFICIENCY AND HETEROZYGOSITY AND THE DEVELOPMENT OF SIDE EFFECTS TO AZATHIOPRINE THERAPY

J.M. Heckmann, L. Lambson, E.P. Owen. Division of Neurology, Groote Schuur Hospital; Division of Chemical Pathology, University of Cape Town, South Africa

Background: Thiopurine methyltransferase (TPMT) involved in metabolising azathioprine is encoded by a polymorphic gene. Consequently, the TPMT genotype can influence the potential for developing...
AZATHIOPRINE USE IN MYASTHENIA GRAVIS AND PREGNANCY

1Department of Neurology; 2Department of Obstetrics and Gynaecology; 3Paediatric Neurology and Child Health, University of Cape Town, South Africa

Background: Concerns about potential adverse effects of immunosuppressive drugs have limited their use in pregnant women with generalised myasthenia gravis (MGM).

Aim: To assess maternal and neonatal morbidity in patients with MGM who become pregnant while taking azathioprine and were maintained on this immunosuppressive during their gestational period.

Method: Group 1: MGM patients who became pregnant while on azathioprine continued to receive immunosuppressive doses in addition to symptomatic MGM treatment. MG status and pregnancy outcome were assessed. Children of mothers who received azathioprine during pregnancy were also developmentally screened by a paediatric neurologist. Group 2: a control group of MGM patients who did not receive azathioprine during their pregnancies was provided by maternal obstetric historical data (1965–1996 medical records). These patients received symptomatic therapy and prednisone if necessary.

Results: Group 1 consisted of 15 pregnancies and group 2 of 57 pregnancies. Both groups had similar duration of gestation, Caesarean section rates, and non-MG related antenatal and postnatal complication rates. 36% of group 1 and 39% of group 2 had worsening of their myasthenia during pregnancy. However, 20% of group 2 mothers required post-partum ventilation and 22% of group 2 infants had neonatal MG. These events tended to occur in those experiencing a deterioration of MG during pregnancy. No group 1 mothers required ventilation or delivered myasthenic neonates. Group 1 children are currently being screened for adverse affects that could be related to in utero azathioprine exposure.

Conclusion: In this small series, the continued use of azathioprine pregnancy was associated with a significant reduction in serious maternal myasthenic events. Additionally, azathioprine use appears to reduce the prevalence of neonatal myasthenia and was not associated with any significant neonatal morbidity.

Abstract 43 Table 1

<table>
<thead>
<tr>
<th>Defined syndrome</th>
<th>n</th>
<th>mn CD4+</th>
<th>MN lymphocyte (X106)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDP</td>
<td>8</td>
<td>299 (104–519)</td>
<td>1.30</td>
</tr>
<tr>
<td>CIDP</td>
<td>354 (112–638)</td>
<td>2.13</td>
<td></td>
</tr>
<tr>
<td>Lumbosacral radiculoneuropathy (LSPR)</td>
<td>6</td>
<td>326 (8–1174)</td>
<td>2.95</td>
</tr>
<tr>
<td>Mononeuropathy</td>
<td>243 (11–472)</td>
<td>1.42</td>
<td></td>
</tr>
<tr>
<td>Sensory axonal neuropathy</td>
<td>13</td>
<td>221 (12–489)</td>
<td>1.10</td>
</tr>
<tr>
<td>Sensory neuropathy</td>
<td>78 (1–225)</td>
<td>1.46</td>
<td></td>
</tr>
<tr>
<td>Myopathy</td>
<td>341 (156–225)</td>
<td>1.79</td>
<td></td>
</tr>
<tr>
<td>Brachial plexopathy</td>
<td>1</td>
<td>33</td>
<td>1.16</td>
</tr>
</tbody>
</table>

*p On CSF analysis, N=1 CMV PCR +ve, N=2 CMV PCR -ve, N=1 H. Zoster PCR +ve, N=2 PCR not done.
Two patients with myopathy also had neutropenia, n, Number of patients; mn, mean. Outcome of patients treated with immunomodulatory therapy (prednisone N=9; IVIG N=1).
public health problems in South Africa. Although the ideal goal is primary prevention, some measure of secondary prevention has been attained using prophylactic penicillin, but too many children’s lives are ruined by long term complications and morbidity. A retrospective study of 42 cases attending the rheumatic fever clinic (RFC) over the past 10 years has been undertaken in order to direct attention to possible means of preventing complications but also to emphasize the urgency of addressing primary prevention and penicillin prophylaxis. We are discharging children to the same predisposing conditions from which they come! 42 patients with movement disorders and a past history of group A beta haemolytic streptococcus were identified (21 females, 21 males). Average age of presentation was 9 years 1 month. 35 patients were socioeconomically deprived. Pharmacological interventions, results, and side effects have been reviewed. The natural history, long term morbidity, and association with penicillin prophylaxis and compliance have been addressed. A number of patients initially diagnosed with SC have now been diagnosed with Tourette’s syndrome and a number with PANDAS. This study emphasized the high morbidity of neuropsychiatric disorders in post streptococcal movement disorders. The need for clearly defined protocols using different medical regimens has been identified.

### Abstract 43 Table 2

<table>
<thead>
<tr>
<th>Clinical category</th>
<th>AIDP</th>
<th>CIDP</th>
<th>LSAPR</th>
<th>Polynephropathy</th>
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<tbody>
<tr>
<td>Total no. of patients</td>
<td>N = 8</td>
<td>N = 5</td>
<td>N = 6</td>
<td>N = 13</td>
</tr>
<tr>
<td>No. of patients treated</td>
<td>1*</td>
<td>3*</td>
<td>3*</td>
<td>4*</td>
</tr>
<tr>
<td>Baseline F (x) class-treated patients</td>
<td>1*</td>
<td>3 *</td>
<td>3 *</td>
<td>3*+2(N=2); 3*+2(N=2)</td>
</tr>
<tr>
<td>No of responders</td>
<td>1*</td>
<td>3 *</td>
<td>2 *</td>
<td>3 * + 2(N=2)</td>
</tr>
<tr>
<td>Post treatment functional class of responders</td>
<td>3 *</td>
<td>1 *</td>
<td>1 *</td>
<td>2 *</td>
</tr>
</tbody>
</table>

\*: Weaned but died of sepsis. In untreated patients, N=21 lost to follow-up; Spontaneous recovery N=6 (2=AIDP, 2=CIDP, 1=LSAPR, 1=polynephropathy). [All returned to F (x) 1]; No recovery N=5. 2=cranial mononeuritis/multiplex, (remained at F (x) 1, 2=polynephropathy, (remained at F (x) 3, 1=myopathy, death) was noted. There were no retinal infiltrates. The EEG revealed a predominant beta background rhythm, upon which was thrust generalised repetitive spike and polyspike waves followed by slow wave discharges. At times these discharges were asynchronous. ACT brain showed mild generalised atrophy. An axillary skin biopsy revealed numerous PAS positive, diastase resistant, Lafora bodies. No family history of a similar disorder was noted. No further genetic tests were done. Symptomatic therapy was continued.

### Patient 2: A 35 year old British national now resident in South Africa presented to GSH in May 2002 with poorly controlled generalised epilepsy since age 22, as well as more recent onset jerking and tremulousness. On examination he was noted to have myoclonic jerks involving all limbs, dysarthria, and ataxia. No cognitive dysfunction was noted. The EEG revealed a theta background, as well as multifocal spike and slow wave discharges, with extreme photosensitivity noted. MRI of the brain was normal. An axillary skin biopsy revealed Lafora bodies. No family history of a similar disorder was noted. The results of further genetic testing for the EPM2A gene are awaited. Symptomatic therapy was continued.

### Conclusion: Two patients diagnosed as having Lafora body disease have been presented. Although exact incidence figures are unavailable for South Africa, experience at our hospital suggests that this is a rare disease in our setting.

### Abstract 44

**METABOLIC PROFILE OF CREUTZFELD-JACOB DISEASE USING PROTON MAGNETIC RESONANCE SPECTROSCOPY**

A. Al-Memar\1, M. Murphy\1, F. Howe\1, K. L. Opstad\2, D. J. O. McIntyre\2, J. R. Griffiths\2, B. A. Bell\1. \1Dept of Neurology, Neurosurgery and Neuropathology, Atkinson Morley’s Hospital, Cape Hill, Wimbledon, SW20 ONE, UK; \2Cancer Research UK Biomedical Research Group, Dept of Biochemistry and Immunology, St George’s Hospital Medical School, London SW17 ORE, UK

Creutzfeldt-Jacob Disease (CJD) is one of the spongiform encephalopathies characterised by accelerated cognitive decline with or without myoclonus culminating in premature death. Diagnosis can be made clinically and confirmed at autopsy, or occasionally by a brain biopsy. EEG changes, MRI findings, and immunosassay of CSF 14–3–3 protein may be contributory towards the diagnosis. There are only a few reports in the literature describing proton magnetic resonance spectra (H-MRS) of patients with CJD at different stages of their illness and demonstrated an early elevation in myocinostol and later reduction in NAA. In conclusion these findings could be a useful tool for monitoring disease progression and might be useful to assess therapeutic responses in the future.

### Abstract 45

**LAFORA BODY DISEASE IN TWO PATIENTS PRESENTING WITH PROGRESSIVE MYOCLOTONIC EPILEPSY**

O. Ameen, R. Eastman. From The Division of Neurology, Department of Medicine, Groote Schuur Hospital and the University of Cape Town, South Africa

**Background:** The progressive myoclonic epilepsies (PMEs) are a group of rare inherited disorders usually characterised by myoclonic jerks, generalised epilepsy, and progressive neurological decline. Lafora body disease, an autosomal recessive disorder, is a distinct disease within the group of PME. The diagnosis is usually made on axillary skin biopsy. More recently genetic testing has become available.

**Patient 1:** A 17 year old female scholar, noted to have excellent grades previously, presented to GSH in June 2001 with generalised seizures and progressive cognitive dysfunction. On examination myoclonic jerks, severe cognitive, and mild pyramidal tract dysfunction was noted. There were no retinal infiltrates. The EEG revealed a predominant beta background rhythm, upon which was thrust generalised repetitive spike and polyspike waves followed by slow wave discharges. At times these discharges were asynchronous. ACT brain showed mild generalised atrophy. An axillary skin biopsy revealed numerous PAS positive, diastase resistant, Lafora bodies. No family history of a similar disorder was noted. No further genetic tests were done. Symptomatic therapy was continued.

**Patient 2:** A 35 year old British national now resident in South Africa presented to GSH in May 2002 with poorly controlled generalised epilepsy since age 22, as well as more recent onset jerking and tremulousness. On examination he was noted to have myoclonic jerks involving all limbs, dysarthria, and ataxia. No cognitive dysfunction was noted. The EEG revealed a theta background, as well as multifocal spike and slow wave discharges, with extreme photosensitivity noted. MRI of the brain was normal. An axillary skin biopsy revealed Lafora bodies. No family history of a similar disorder was noted. The results of further genetic testing for the EPM2A gene are awaited. Symptomatic therapy was continued.

**Conclusion:** Two patients diagnosed as having Lafora body disease have been presented. Although exact incidence figures are unavailable for South Africa, experience at our hospital suggests that this is a rare disease in our setting.

### Abstract 46

**MORE THAN MEETS THE EYE**

P. Francis, P. L. A. Bill. Nelson Mandela School of Medicine, University of Natal, South Africa

This is a case presentation of a 35 year old lady presenting with bilateral blindness. Brain imaging revealed bilateral haemorrhagic papilutinal necrosis. The differential diagnosis and final aetiology will be presented on the poster.

### Abstract 47

**STROKE IN DEVON: THE NEED TO TRANSFER KNOWLEDGE INTO ACTION**

C. Carroll, J. Hobart, C. Fox, L Teare, J. Gibson. Department of Neurology, Derriford Hospital, Plymouth, UK

**Background:** Implementation of early stroke treatment requires prompt admission to hospital. Heightened awareness should facilitate early admission, and can be increased by education. We identified local targets for an education programme.

**Methods:** Four groups completed questionnaires regarding their knowledge of stroke symptoms and risk factors, and the action planned or taken in the event of stroke. Patients (within 48 hours of stroke); at risk patients; general population; and nurses.
Results: 90% of the non-stroke group were able to list at least one stroke symptom, 73% of at risk respondents stated they would call an ambulance in the event of stroke. However, 60% of stroke patients did not identify their stroke. Median time from symptom onset to seeking medical help was 30 minutes. Medical help was sought by the patient in only 15% of cases. In 80% of cases the GP was called rather than an ambulance. Patients with self reported risk factors were unaware of their risk. Only 7.5% of at risk patients acquired their stroke information from their doctor.

Conclusions: Public knowledge about stroke is good, but stroke patients’ access of acute services is poor. A campaign should target these people at risk, re-enforcing the diagnosis of stroke and access of medical services.

**050**

**THALAMIC NEURODEGENERATION IN RELAPSING: REMMITING MULTIPLE SCLEROSIS**

A.I. Cifelli 1,2, M. Wylezinska 1, P. Jezzard 1, J. Palace 2, M. Alecci 1, P. Matthews 1,2. 1Centre for Functional Magnetic Resonance Imaging of the Brain, University of Oxford, UK; 2Department of Clinical Neurology, University of Oxford, UK

Recent histopathology and MR studies have demonstrated thalamic neurodegeneration in secondary progressive (SP) multiple sclerosis (MS). Our goal was to extend these previous observations to relapsing remitting (RR) MS patients. We studied 14 RR MS patients (EDSS, mean 3.25, range 2.0–6.0) and 14 age matched healthy controls. MR spectroscopy (MRS) and structural MR were performed in order to measure respectively thalamic N-acetylaspartate (NAA) concentra-
tions (a measure of the apparent neuronal density) and volume. This latter was divided by the intracranial volume in each subject, thereby obtaining a unit less parameter, normalised thalamic volume (NTV), which was not influenced by global brain size differences. NAA concentra-tions were decreased approximately 11% in the thalami of the RR patients relative to controls (p <0.05). The MS patients had an almost 25% lower NTV than controls (p <0.005). Decreases in thalamic NAA concentration correlated strongly with thalamic volume loss in the parietal lobes (r=0.849, p <0.001). Both the NAA concentra-
tion (r=0.54, p=0.0044) and NTV (r=0.60, p=0.011) correlated inversely with disease duration. The reduction of both NAA concentra-
tion and thalamic volume implies that a neurodegenerative component may contribute to the pathology of MS even in the earlier RR stage.

**051**

**UNDERSTANDING THE INFORMATION NEEDS OF WOMEN WITH EPILEPSY AT DIFFERENT LIFESTAGES: RESULTS OF THE “IDEAL WORLD” SURVEY**

P. Crawford, S. Hudson For the ‘Ideal World’ Steering Group, Dept of Neurosciences, York District Hospital, York UK. Epilepsy Action, Leeds, UK

**Purpose:** The British Epilepsy Association (BEA) survey aimed to (a) assess quality of treatment information provision to women with epilepsy at different lifestyles (childbearing age, pregnancy, menopause); and (b) identify information needs with a view to ensuring that all women with epilepsy are counselled appropriately about the impact of anti-epilepsy drugs (AEDs) and able to make informed choices about treatment.

**Methods:** The survey content was developed in 2001 and mailed to BEA UK female membership aged 19+ (approximately 12000) and posted on the BEA website during January 2002. 2690 responses were collected, from which a sample of 2000 were randomly selected and analysed.

**Results:** 38% of women aged 19–44 (n=1086) had not been told of possible interactions between their AED and the contraceptive pill. 91% of women aged 19–44 were not consulted about the use of oral contraceptives, the pill, the morning after pill or abortifacient drugs (ADEs) and anti-epilepsy drugs (AEDs) and risk of birth defects; yet only half of them [45%] remembering that their medication may affect the unborn child. 32% of women aged 19–44 who were not considering having children in the future (n=549) said the decision was linked to their epilepsy. 57% of women aged 19–44 were not consulted about the use of oral contraceptives, the pill, the morning after pill or abortifacient drugs (ADEs) and anti-epilepsy drugs (AEDs) and risk of birth defects on an ongoing basis, even if data are incomplete.

**Conclusions:** Women with epilepsy are not receiving important information regarding treatment, which could have profound implica-
tions for their health and that of their unborn child. Regular review and discussion should be encouraged about possible adverse effects of treatment—especially before conception—and where possible, provide the most up to date information.

The BEA ‘Ideal World’ survey was sponsored by an educational grant from GlaxoSmithKline.

**052**

**SPECT PERFUSION IMAGING IN THE DIFFERENTIAL DIAGNOSIS OF PRESENILE DEMENTIA: A RETROSPECTIVE REGIONAL AUDIT**

M. Doran 1, S. Vinjamuri 1, J. Collins 1, D. Parker 1, A.J. Lamer 1. 1Walton Centre for Neurology and Neurosurgery, Liverpool, UK; 2Department of Nuclear Medicine, Royal Liverpool Hospital, Liverpool, UK; 3Wrexham Maelor Hospital, UK

**Objective:** To assess the utility of brain perfusion imaging with Tc-99m-IMPACTO SPECT in presenile patients with apparent cognitive impairment, resistant to diagnosis by clinical, neuropsychological, and structural imaging methods.

**Methods:** A retrospective audit of SPECT scans (n=57) performed over a 4½ year period (1995–1999) was undertaken. Scans were carried out by five raters (2 neuroradiologists, 3 nuclear medicine specialists) on two occasions six months apart for normality/abnormality and diagnosis, firstly without clinical data (“blind”), secondly with brief clinical information (“informed”). Subsequently, the two neuroradiologists established “criterion” diagnoses based on all available clinical, neuropsychological, and imaging data. The criterion diagnoses were compared with SPECT diagnoses.

**Setting:** Cognitive Function Clinic at a regional neurosciences centre, referring patients to two nuclear medicine centres.

**Results:** Intra-rater reliability in scan assessment was reasonable (k=0.60), but inter-rater reliability was less good (k=0.30–0.63 for various conditions). Diagnostic accuracy for individual raters ranged from 32–58%. SPECT scan normality or abnormality and informed viewings gave respective sensitivities of 77% and 71%, specificities of 71% and 63%, positive predictive values of 88% and 87%, negative predictive values of 73% and 82%. Positive and negative likelihood ratios (LR) were 1.71 and 1.89, and 0.42 and 0.46, respectively for blind and informed viewings. Calculating pairwise disease group comparisons, likelihood ratios suggested some diagnostic gain (LR >5) in differentiating AD from non AD” and AD from FTD/local syndromes.

**Conclusion:** Compared to its reported use in senile dementia, SPECT scanning was less helpful in establishing diagnoses in this cohort of presenile patients.

**053**

**DOES THE CAUSE OF MULTIPLE SCLEROSIS LIE BETWEEN THE ISLANDS OF MALTA AND SICILY?**

M. Elian 1, G. Dean 1, A. Galea Debono 1, N. Vella 1, V. Mitsud 2, J. Aquilina 1, P. Asciak 1. 1Central Middlesex Hospital, London, UK; 2The Medico-Social Research Board of Ireland; 3St Luke’s Hospital, Guardamangia, Malta; 4Department of Health Information, Malta

We reviewed the deaths from multiple sclerosis (MS) in Malta since the last study in 1978 when the prevalence was 5 per 100 000 and ascertained the prevalence of the disease in 1999. Since 1978, 17 had died with a verified diagnosis of MS. They included 13 deaths with MS from the original study and two were immigrants. Fifty maltese born patients had clinically definite MS (CDMS) and 13 clinically probable MS (CPMS). The ratio of MS in men and women was 1.3 (2.2:1.6) per 100 000 (male 11.2, female 15.2). The prevalence of CDMS + CPMS combined was 16.7 per 100 000 (male 13.3, female 19.9). The annual incidence was 0.7 per 100,000. Among immigrants to Malta, there were also 12 MS patients, and the expected number at Maltese born rates was one.

There have been marked changes in the population distribution during the 21 years between the two studies, with a big increase in the age groups with a high risk of MS. There is a longer expectation of life and the diagnosis is now made earlier.

Malta still has a low MS prevalence in contrast with Sicily, for example Enna 120 per 100 000, and other Mediterranean countries of Europe. A study will now be undertaken to compare the genome of MS patients and of controls in Malta with those in Sicily and in other countries of Europe.

**054**

**BETA-INTERFERON IN MULTIPLE SCLEROSIS: AN ASSESSMENT OF THE ABN STOPPING CRITERIA IN CLINICAL PRACTICE**

G. Giavannoni, B.D. Dubois, E. Keenan, B.E. Porter, R. Kapoor, P. Rudge, A.J. Thompson, D.H. Miller. The Institute of Neurology and the National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG, UK

**Background:** The efficacy of interferon β (IFNβ) is well established in relapsing remitting multiple sclerosis (MS). However, the use of this
drug in clinical practice is complex because it is only partially effective. The disease has a variable natural history, and it is often difficult to decide when there is no longer a therapeutic benefit. The ABN has proposed stopping criteria to help clinicians address the above.

**Objectives and Methods:** Analysis of a prospectively followed series of 101 ambulant, relapsing MS patients treated at the National Hospital for Neurology and Neurosurgery with IFN-β therapy. A stopping criteria was undertaken in order to assess the proportion of patients fulfilling the current guidelines of the ABN for stopping IFN-β therapy.

**Results:** During a median treatment period of 26 months (range 12–85), the relapse rate decreased by 41% compared to the two years prior to the start of treatment. Although 40/101 (40%) patients satisfied the current (2001) ABN criteria for stopping IFN-β treatment at some stage during their treatment, only 6/101 (6%) stopped or switched compounds because of perceived lack of efficacy. 6/25 patients (24%) who had at least two disabling relapses in a 12 month period had a reduced relapse rate on treatment compared to the two years prior to starting treatment. Conversely, 5/61 patients (8%) who did not fulfill the ABN stopping criteria had an increased relapse frequency on treatment compared to the two years prior to starting treatment, however, a proportion of these latter relapses were non-disabling.

**Conclusion:** The high frequency of patients reaching the ABN stopping criteria within 26 months of commencing treatment raises doubts about the feasibility of these criteria in clinical practice.

**055 VASCULITIS COMPLICATING CEREBRAL AMYLOID ANGIOPATHY: A CAUSE OF REVERSIBLE DEMENTIA**


We present an unusual cause of reversible dementia. This 72 year old lady presented with an 8 week history of a rapidly progressive frontal lobe syndrome. She had no vascular risk factors and no relevant family history. On examination she was normotensive and disoriented with bilateral dyspraxia and poor sequencing. Her MMSE score was 20/30. Her ESR was at 35 mm/hr. CSF examination was normal. An EEG showed bilateral complex slow activity. MRI of the brain showed symmetrical, diffuse high signal with mild swelling involving the white matter of both frontal lobes with no abnormal enhancement. Right frontal brain biopsy demonstrated typical appearances of sporadic cerebral amyloid angiopathy (CAA) with additional features of a chronic inflammatory cell infiltrate within the walls of many vessels, consistent with vasculitis. The patient made a dramatic clinical improvement and repeat MRI scan showed significant resolution of the vessels, consistent with vasculitis. The patient made a dramatic clinical improvement and repeat MRI scan showed significant resolution of the white matter changes.

**Conclusion:** Idiopathic generalised epilepsies (IGE) comprise overlapping syndromes with a complex pattern of inheritance. Family and twin studies suggest some shared susceptibility genes, with particular syndromes determined by specific gene combinations. We are carrying out a candidate gene association study of IGE. The Kent cohort (with controls and parents where available) is being extended in collaboration with London, Liverpool, and Sheffield with 400 probands to date. We have previously reported significant associations with IGE as a broadly phenotypic, using the Kent sample, in a Ca channel gene (C4A1A), and the opioid receptor gene (OPRM1). In C4A1A, we found associations with 5 single nucleotide polymorphisms (SNPs) in a 30kb region between exons 6 and 9 and have identified a risk haplotype p<0.0000014. In OPRM1, 2 SNPs (in exon 1 and 290bp upstream) were associated with IGE but were not in LD with each other. Haplotype analysis identified a protective haplotype p<0.0000087. Fine mapping studies are currently being performed in order to identify the functional variants. More recently, we have also found suggestive evidence for association of the K channel gene KCNJ3 that appears to be specific to absence epilepsy. An update will be presented.

**058 GENETIC ASSOCIATION STUDY OF IDIOPATHIC GENERALISED EPILEPSY**

L. Nashel1,2, A. Oser-Lah1, B. Chioza1, H. Wilkie1, P. Asherson1, A. Makoff1. 1Kent & Canterbury Hospital, Canterbury, UK; 2King’s College Hospital, London, UK.

Idiopathic generalised epilepsies (IGE) comprise overlapping syndromes with a complex pattern of inheritance. Family and twin studies suggest some shared susceptibility genes, with particular syndromes determined by specific gene combinations. We are carrying out a candidate gene association study of IGE. The Kent cohort (with controls and parents where available) is being extended in collaboration with London, Liverpool, and Sheffield with 400 probands to date. We have previously reported significant associations with IGE as a broadly phenotypic, using the Kent sample, in a Ca channel gene (C4A1A), and the opioid receptor gene (OPRM1). In C4A1A, we found associations with 5 single nucleotide polymorphisms (SNPs) in a 30kb region between exons 6 and 9 and have identified a risk haplotype p<0.0000014. In OPRM1, 2 SNPs (in exon 1 and 290bp upstream) were associated with IGE but were not in LD with each other. Haplotype analysis identified a protective haplotype p<0.0000087. Fine mapping studies are currently being performed in order to identify the functional variants. More recently, we have also found suggestive evidence for association of the K channel gene KCNJ3 that appears to be specific to absence epilepsy. An update will be presented.

**059 WHAT CAUSES PROGRESSIVE INTELLECTUAL AND NEUROLOGICAL DETERIORATION IN ADOLESCENTS? FINDINGS FROM A PROSPECTIVE NATIONAL SURVEILLANCE STUDY**

J. te Water Naudé, A. Nicoll, R. Will, G. Devereux, L. Stellitano, C. Verity, Addenbrooke’s Hospital, Cambridge, UK, Communicable Disease Surveillance Centre, Colindale, UK; The National CJD Surveillance Unit, Edinburgh, UK

**Objective:** Dementia is an uncommon diagnosis to make in adolescence. We reviewed cases with progressive intellectual and neurological deterioration in the study of dementia. Four cases of dementia were identified: two cases of late-onset dementia, one case of Creutzfeldt-Jacob disease, and one case of herpes encephalitis.
neurological deterioration (PIND) referred to a prospective national surveillance study that has been running in the UK for 5 years.

Methods: Clinical details of adolescents (aged 12 or more) with PIND identified via the British Paediatric Surveillance Unit were reviewed and classified by diagnosis by the PIND Expert Group.

Results: 784 children were included in the PIND study between May 1997 and July 2002. Of these 123 had a confirmed diagnosis: 44 of this group were adolescents. All of the 44 adolescents were given a specific diagnosis. There were 24 different diagnoses in this group: the cause most familiar to adult neurologists is Huntington’s disease, which occurred in five. The leukodystrophies were the most common: this was a heterogenous group with eight cases, including five different specific conditions. The most common single diagnosis was variant Creutzfeldt-Jacob disease (vCJD), which occurred in five adolescents.

Conclusions: Of the PIND children in this study, a relatively small proportion were adolescents. vCJD is an important diagnosis to make in the UK. It is striking that a diagnosis was made in all the adolescents with PIND in this study.

Efficacy of Gabapentin in Essential Tremor: A Double Blind Placebo Controlled Trial

A. Osei-Lah, K. Bhattacharya, T. Britton, A. Wills, R. Chaudhuri, L. Halsted. 1Department of Neurology, King’s College Hospital, London, UK; 2Department of Neurology, Queen’s University Hospital, Nottingham, UK

Essential tremor (ET) is the commonest adult movement disorder. Treatment options are limited, with tolerance and side effects associated with commonly used medications. ET may be disabling enough to warrant deep brain stimulation. Gabapentin is well tolerated with few interactions. Results of previous studies evaluating its usefulness in ET have been mixed. We studied its efficacy in 31 patients with ET in a double blind placebo controlled trial using a standardised video assessment, accelerometry, and patient self-rating scores. Analysis was on an intention to treat basis. There was a modest trend in favour of gabapentin. Mean global disability scores improved by 14% in the gabapentin group and deteriorated by 6% in the placebo group (p=0.8 ANOVA; mean visual analogue scores improved 3.9% in the gabapentin group compared with a deterioration of 4% in the placebo group (p=0.3 ANOVA). Mean tremor scores and activities of daily living scores did not improve. No patients among the placebo group and 4 patients among 13 completing the study on gabapentin reported marked improvement, elective to continue on the study medication. Gabapentin appears to markedly benefit a subgroup of patients with essential tremor. In our small study, 4/13 had a worthwhile clinical response.

T1 Changes Detect the Progression of Pathology in the White Matter and Cortex of MS Patients


Objective: To test the sensitivity of whole brain T1 relaxometry to the evolution of changes in MS.

Methods: We studied 14 MS patients at baseline and after a median time of 19.5 months (14–22 months). Structural images and whole brain T1 maps were obtained. Changes were defined separately in the lesional and non-lesional white matter and cortical grey matter using histogram analysis.

Results: There was an inverse relationship between disease duration and the NAWM peak height T1 value at the initial visit (r=−0.711, p=0.048). The changes in the total white matter histogram over time could be accounted for by changes in the normal appearing white matter histogram (p=0.03). There also was a significant change in the grey matter histogram parameters between MRI visits (p < 0.001). Univariate testing showed a significant decrease (6%) in the mean (11/14 patients, p=0.004) and in the median (7%) (13/14 patients, p=0.001) T1 value at follow up.

Conclusions: T1 values in both the grey and the white matter at the baseline visit were related to disease duration, suggesting that T1 changes are likely to be clinically relevant. The role of T1 measurement as an MRI outcome measure in clinical trials now should be explored.

Eurap, an International Antiepileptic Drugs and Pregnancy Registry—An Invitation to Africa to Join This Global Venture

A.J.C. Russell, D. Battoo, T. Tomson. 1Institute of Neurological Sciences, Southern General Hospital, Glasgow, UK, on behalf of the Central Project Commission and the Scientific Advisory Board of EURAP; 2Neurological Institute Carlo Besta, Milan, Italy; 3Department of Neurology Karolinska Hospital, Stockholm, Sweden

The safety of antiepileptic drugs (AEDs) in pregnancy is of major concern due to lack of conclusive data. EURAP is a prospective international antiepileptic drugs and pregnancy registry set up to compare the teratogenic potential of different AEDs. Women taking AEDs for any indication at the time of conception are eligible for inclusion. Information sought includes patient demographics, details of underlying disease, seizure frequency, drug therapy, family history, and other potential risk factors. Follow up data are collected once in every trimester, at birth, and at one year. Anonymised data is sent electronically to the central registry in Milan.

As of August 2002, 269 collaborators in 25 countries from Europe, Asia, Australia, and South America have enrolled 1725 pregnant women. Of the 1270 (74%) prospective cases, 952 have delivered with a final outcome in 457. 76% were on carbamazepine monotherapy, followed by valproic acid, lamotrigine, and phenobarbionate. 44 major congenital malformations have been identified, a major malformation rate of 5%.

Extension protocols are being developed to address other important issues including the pharmacokinetics of new AEDs during pregnancy and the perinatal period, long term postnatal development, and pharmacogenetics.

We invite the fifth continent to join us in this international venture.

Dopamine Agonist Mediated Neuroprotection: Mechanisms of Action

A.H.V. Schapira, M. Gu, J. M. Cooper. Royal Free and University College Medical School, UCL, UK

Dopamine agonists are effective for the symptomatic control of motor features in Parkinson’s disease (PD), and have been shown to delay or prevent the onset of motor complications associated with levodopa use. Pramipexole and ropinirole have recently been shown to slow the rate of loss of the striatal imaging markers 18F-CIT and 18F-fluorodopa, respectively.

We have previously demonstrated that pramipexole can protect neuronal derived SHSY-5Y cells against MPP+ and roteneone toxicity. We now show that although 10 μM of pramipexole protects against MPP+ cell death, it does not prevent the declined in acinato activity, a marker of free radical damage. 10 μM of pramipexole was effective in reducing cell death in JK cells in response to 5 mm MPP+. Both of these cells have no dopamine receptors and this result supports functional studies showing that dopamine blockade does not prevent the neuroprotective action of pramipexole and implies that dopamine receptors are not necessary to mediate its neuroprotective action. We also show that pramipexole can protect against a fall in mitochondrial membrane potential, release of cytochrome c, caspase activation, and apoptotic cell death.

A Novel Familial Tubular Aggregate Myopathy Associated with Abnormal Pupils

N. Shahriarizai, J. Lowe, A.J. Wills. Department of Neurology, Queen’s Medical Centre, University Hospital NHS Trust, Nottingham, NG7 2UH, UK

We report a novel familial syndrome of myopathy and pupillary abnormalities associated with tubular aggregates compatible with either autosomal dominant or X-linked inheritance. We examined four members from two generations of a family who demonstrate myopathy and a marked miosis. Pharmacological pupillary responses suggested smooth muscle involvement. Pathological findings consisted of tubular aggregates in many fibres but predominantly type I. Tubular aggregates are inclusions within muscle fibres that have frequently been found in association with several myopathic disorders. However, an associated miosis has only rarely been described. We believe this is the first description of a familial syndrome of tubular aggregate myopathy with pupillary abnormalities.
AN ANTI-SPINAL ANTIBODY IN DERMATITIS QUANTITATIVE IMAGING MAPS, PYRAMIDAL TRACT AGE SPECIFIC PREVALENCE OF IMPAIRMENT AND DISABILITY RELATED TO HEMISPERIC STROKE IN THE HAI DISTRICT OF NORTHERN TANZANIA

AN ANTI-SPINAL ANTIBODY IN DERMATITIS HERPETIFORMIS PATIENTS

D.S.N.A. Pengiran Tengah1, A. Church2, G. Giovannoni3, L Fry4, B. Turner1, A.J. Wills1. 1Department of Neurology, Queen’s Medical Centre, 2Department of Neuroimmunology Institute of Neurology, University College London, National Autonomic Unit for Neurology and Neurosurgery, Queen Square, London, UK; 3Department of Dermatology, Imperial College School of Medicine, London, UK

Objective: To investigate the presence of anti-neuronal antibodies in patients with dermatitis herpetiformis (DH) and coeliac disease (CD) based on previous data suggesting that gluten is neurotoxic via immune mechanisms.

Methods: Serum was analysed from 35 patients with biopsy proven DH and 52 patients with biopsy proven CD who had undergone thorough neurological examination and detailed case-note review.

Results: We identified a novel antibody from peripheral blood in over 50% of the subjects with DH. On Western blot, this antibody reacted with a protein of 74 kDa from an extract of human spinal cord. Anti-neuronal antibodies were negative in all but one DH patient who had equivocally positive anti-Hu antibodies. Neurological conditions found in this cohort of gluten sensitive subjects were migraine (8), essential tremor (1), epilepsy (1), chorea (1), and benign fasciculations (1).

Conclusion: Further characterisation of this novel spinal antibody is required. It may suggest a potential mechanism for sensory ataxia, which has been previously described in patients with established gluten sensitivity. However, none of the patients had clinical evidence of dorsal column dysfunction, which may indicate that an additional co-factor (possibly a trace vitamin) is required for the development of symptoms. The absence of this spinal cord antibody in patients with CD may reflect greater gluten exposure in DH patients who often continue to consume gluten as their dermatological symptoms may be controlled by dapsone alone.

QUANTITATIVE IMAGING MAPS, PYRAMIDAL TRACT DISEASE, AND CLINICAL RECOVERY FOLLOWING A MOTOR RELAPSE OF MULTIPLE SCLEROSIS

L. Vaithianathan1, C.R. Tench1, P.S. Morgan2, L.D. Blumhardt3, C.S. Constantinescu4. 1Division of Clinical Neurology, University Hospital, Queen’s Medical Centre, Nottingham NG7 2UH, UK; 2Division of Academic Radiology, University Hospital Queen’s Medical Centre, Nottingham NG7 2UH, UK

Background: The case of a 47 year old lady with an acute motor relapse of multiple sclerosis (MS) is described, in whom serial diffusion tensor (DT) imaging was acquired enabling mapping of an evolving lesion in the corresponding pyramidal tract, in association with clinical recovery, through fibre tracking.

Method: Over a 16 month period, two monthly DT, dual echo, and T1 relaxation time (T1) sequences were obtained, and disability was assessed using the expanded disability status scale (EDSS), ambulation index (AI), and timed 25 foot walk. Trajectories delineating the course of the pyramidal pathways were defined, to allow sampling of diffusion indices and T1 at each month.

Results: T1 weighted coronal views revealed development of a band of high signal along the descending motor tract, consistent with a Wallerian degeneration pattern. A baseline EDSS of 2, peaked at 8.5 during the acute relapse before recovering to 4.5, 12 months later. Left pyramidal tract T1, trace, and relative anisotropy correlated significantly with the EDSS (p=0.006, r=0.85; p=0.027, r=0.73; p=0.013, r=0.80, respectively) and the timed 25 foot walk (p=0.016, r=0.79; p=0.03, r=0.74; p=0.01, r=0.84, respectively) but not AI. Early deficit following an MS relapse is probably due to reversible local factors. Here, mapping of quantitative indices reveals that degenerated pathways account for persisting neurological deficit.

LAMBERT EATON MYASTHENIC SYMPTOME (LEMS) ASSOCIATED WITH THYMINT

T.J. Walls1, M. Lai2, J. Forty1, M. Bennett3. 1Department of Neurology, Newcastle General Hospital, UK; 2Department of Clinical Neurophysiology, Royal Victoria Infirmary, Newcastle, UK; 3Cardiothoracic Centre, Freeman Hospital, Newcastle, UK; 4Department of Histopathology, Freeman Hospital, Newcastle, UK

A previously healthy 46 year old male presented with a 6 month progressive history of general lethargy and reduced exercise tolerance. He was a non-smoker, there was no history of autoimmune disease, personally or in his immediate family. Examination revealed mild bilateral triceps weakness and areflexia. There was no fatigability or fatigue on repeated muscle contraction. Nerve conduction studies revealed evidence of a mild axonal sensory polyneuropathy. Compound muscle action potential (CMAP) amplitudes were reduced, with no difference between proximal and distal testing. Sensory nerve stimuli were reduced. Repetitive nerve stimulation at 3 Hz revealed a 24% decrement in the CMAP amplitude recorded from abductor pollicis brevis. Nerve stimulation at 20 Hz, while recording from abductor digit minimi revealed an increment in the CMAP amplitude of 33%. Anti voltage gated calcium channel antibodies were

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strongly positive (252 pM) but no acetylcholine receptor antibodies were detected. Extensive investigations revealed no evidence of any underlying malignancy. On CT of the thorax an anterior mediastinal mass lying around the aortic arch was detected. This was completely removed via mediastinotomy. Histological examination revealed no evidence of malignancy but typical changes of thymitis. Postoperatively his symptoms of muscle weakness have defensibly resolved. Thymitis should be added to the list of non-malignant causes of LEMS.

**070 SCEDOSPORIUM APIOSPERMUM OPTIC NEUROPATHY; AN UNUSUAL PLACE FOR A COMMON FUNGUS**

P.F. Worth1, G.M. Scott2, G.T. Plant2. 1National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG UK; 2Department of Clinical Microbiology, University College London Hospitals, Cecil Fleming Way, Grafton Way, London WC1E 6SS, UK

Scedosporium apiospermum is an emerging fungal pathogen commonly found in soil and polluted water, which frequently causes mild skin infection. Central nervous system infection is rare but has been described in a diabetic lady with a year long history of deterioration of the visual acuity in her left eye, associated with left retro-orbital pain. Examination revealed perception of light in the left eye, left optoparesis and orbital oedema, limited elevation of the left eye, and reduced sensation in the first two divisions of the left trigeminal nerve with an attenuated left corneal reflex. MRI scan of the orbits revealed a diffuse enhancing mass at the left orbital apex compressing the left optic nerve with bilateral mastoid air cell disease. The patient underwent paranasal sinus exploration; washings and granulation tissue recovered from the left maxillary sinus yielded a growth of S apiospermum. The patient has now been taking systemic antifungal therapy (itraconazole) for 8 months. The patient’s vision has remained stable, and MRI scan appearances remain unchanged. To our knowledge, this is only the fourth case of orbital involvement by this unusual pathogen described to date.

**071 AUTOANTIBODIES AS A CAUSE OF EPILEPSY**

S. Wroe1, B. Lang2, K. McKnight3, Y. Jiang2, Y. Hart2, J. Palace3. 1Department of Neurosciences Group, Weatherall Institute of Molecular Medicine, John Radcliffe Hospitals, Oxford, OX3 9DU UK; 2Department of Clinical Neurology, Radcliffe Infirmary, Oxford, UK

The cause of epilepsy is unknown in the majority of patients. Auto-antibodies may modulate ion channels or receptors involved in central excitatory and inhibitory neurotransmission. Such antibodies may play a role in the pathophysiology of a number of seizure disorders. Although a range of antibodies in patients with epilepsy has been described, their specificity is uncertain. Sera was obtained from 106 patients with various epilepsy syndromes and screened for antibodies to voltage-gated calcium (VGCC) and potassium (VGKC) channels, neuronal AChR, glutamate receptor 3 (Glur3), ganglioside GM1, and glutamic acid decarboxylase (GAD).

Twelve patients (11%) had antibodies to VGKC. These included patients with post-viral encephalitis, ependymitis, Hashimoto’s Encephalopathy, limbic encephalitis, and cognitive problems. Three of these patients were treated with immunomodulation, two of whom improved. Nine patients (8%) had GAD antibodies. These patients tended to have epilepsy. Significant levels of antibodies were not detected in any of the other assays.

The presence of these specific and relevant antibodies in a subgroup of patients with epilepsy may allow more successful treatment regimes, such as immunomodulation and treatments targeted at specific ion channels, to be developed.

**072 ADULT ONSET RASMUSSEN’S ENCOPHALITIS PRESENTING WITH SECONDARY READING EPILEPSY**

K.W. Yeoh1, N. Mullatti1, M. Koutroumanidisa, I.K. Hart2, R.M. Morris3, L. Nashel1. 1King’s College Hospital, London SE5 9RS, UK; 2The Walton Centre, Liverpool L9 7UJ

Aim: We report a unique case of secondary reading epilepsy occurring in adult variant Rasmussen’s encephalitis (RE).

**Case Report:** A 54 year old lady presented with late onset partial epilepsy. Following a prolonged illness she relapsed with focal right arm jerking, variable dysphasia, and complex partial seizures. EEG revealed slowing of background activity over the left frontotemporal region with polyspike discharges, maximal over the left inferior frontal electrode. These were consistently provoked by meaningful spoken words. MRI showed a focal region of the hemisphere atrophy particularly of the left superior temporal gyrus and Sylvian fissure. Ictal SPECT showed markedly reduced blood flow of the left hemisphere. FDG PET showed reduced tracer uptake of the left hemisphere including the basal ganglia, consistent with RE. Western blotting studies revealed antibodies to two proteins at 60 and 110 kDa, seen in other cases of RE. The patient was treated with IVIG 160 g and 3 g methylprednisolone over 3 days, repeated monthly.

**Results:** There has been a dramatic improvement in seizure control and language. Video EEG will be demonstrated.

**Conclusion:** Intravenous IVIG is an effective treatment for arresting and partially reversing the epilepsy, functional deficit, and neuropsychological changes associated with Rasmussen’s syndrome.

**073 CONGENITAL MYASTHENIA—RAPSYN DEFICIENCY: HOW RARE?**

G. Burke1, D. Beeson1, J. Newsom-Davis1, S. Kobb2, D. Hilton-Jones1, J. Wroe1, 1Neurosciences Group, Weatherall Institute of Molecular Medicine, John Radcliffe Hospitals, Oxford, OX3 9DU UK; 2Department of Neurology, Guys Hospital, London SE1 9RT UK

Congenital myasthenic syndromes (CMS) comprise a heterogeneous group of inherited disorders characterised by impaired neuromuscular transmission. They arise from genetic defects in functional and post-synaptic proteins at the neuromuscular junction. Most CMS involve mutations of the muscle acetylcholine receptor (AChR) but recently a new postsynaptic protein, rapsyn, has been implicated.

Rapsyn is a 433kDa protein involved in clustering the AChR at the muscle endplate, and mutations in this protein have been shown to cause an AChR deficiency CMS. We have defined the genetic basis in a series of patients (n=19) with CMS due to rapsyn mutations and this has enabled us to define two distinct phenotypes. At an early onset phenotype presents at birth and is associated with arthrogryposis multiplex congenita, recurrent apnoea, and episodic crises precipitated by minor infections. A late onset phenotype presents with symptoms that may be mistaken for seronegative myasthenia gravis. This latter phenotype is likely, at present, to be underdiagnosed. By contrast with other forms of AChR deficiency CMS, patients with rapsyn mutations show no ophthalmoplegia. These phenotypic clues should help distinguish this form of CMS from others, should facilitate an early diagnosis, and avert inappropriate immunosuppression.

**074 NEURONAL APOPTOSIS OCCURS IN PATIENTS WITH MITOCHONDRIAL DNA DISORDERS**

D.A. Cottrell, A. Schaefer, G.M. Borthwick, R. Perry, D.M. Turnbull. Department of Neurology, The Medical School, University of Newcastle upon Tyne, UK; Department of Neuropathology, Newcastle General Hospital, MRC/University of Newcastle upon Tyne Centre for Clinical Brain Aging, UK

Neuronal loss is prominent in neurodegenerative disorders. One potential process for neuronal demise is that of programmed cell death or apoptosis and apoptotic neurons have been reported in several neurodegenerative disorders. Mitochondria contain both pro- and antiapoptotic factors and in vitro play a pivotal role in cell survival. Vulnerable populations of neurons in Alzheimer’s disease and motor neuron disease are prone to a mitochondrial biochemical deficiency indicative of mitochondrial DNA (mtDNA) damage. The role these mitochondrial enzyme deficient neurons play in the pathogenesis of these disorders is unclear. We have investigated the occurrence of apoptosis in cerebellar, hippocampal, and frontal cortical neurons of two patients with different mtDNA disorders. Apoptotic neurons were observed in both cases using both the TUNEL reaction as a marker of nuclear DNA fragmentation and the cleaved caspase 3 immunoreactivity an indicator of the activity of the apoptotic cascade. Both cases also contained numerous mitochondrial enzyme deficient neurons. The frequency of apoptotic neurons was very low, in the order of one in 10 thousand. This was not unexpected because the process of apoptosis is short lived, in the order of a few hours. This study supports the theory that impaired mitochondrial function can initiate neuronal apoptosis in
**075**

**INTERMITTENT, LOW DOSAGE PREDNISOLONE IN THE LONG TERM TREATMENT OF EARLY DUCHENNE MUSCULAR DYSTROPHY**

V. Dubowitz, M. Kinlaw, E. Mercuri, M. Main, F. Muntoni, Dubowitz Neuromuscular Unit, Dept of Paediatrics, ICSM Hammersmith Campus, Ducane Rd, London W12 ONN, UK

Six boys under the age of 5 years with Duchenne dystrophy have been treated with an intermittent, low dosage regime of prednisolone (0.75 mg/kg/day for 10 days per month, or 10 days on and 10 days off). Four of them have been followed for over 4 years and form the basis of this presentation. Clinically, they had classical Duchenne dystrophy, and an out of frame deletion in the Duchenne gene and absence of dystrophin in their muscle. All 4 showed a rapid and dramatic response in muscle function and strength. In 3 of the 4 there was an almost complete remission of all clinical signs of dystrophy. Their functional scores remained well above the average scores recorded in untreated Duchenne boys at the same age. There was no increase in weight, stunting of growth, decreased bone density, or any other significant side effects related to the prednisolone. Our current experience suggests that this intermittent, low dosage prednisolone regime is well tolerated and can be safely given long term in young children with Duchenne dystrophy. The striking response also suggests that there may be an optimal window for treatment of Duchenne dystrophy in the early stages of the disease.

**076**

**COMPARISON OF PHYSICIAN OUTCOME MEASURES AND PATIENTS’ PERCEPTION OF BENEFITS OF INPATIENT NEUROREHABILITATION**

S.G.M. Edwards1, E.D. Playford2, J.C. Hobart3, A.J. Thompson1. 1Neuro-rehabilitation Unit, National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG; 2Institute of Neurology, National Hospital for Neurology and Neurosurgery, UK; 3Derriford Hospital, Plymouth PL6 8DH, UK

Measuring rehabilitation is difficult. We evaluated how much the traditional, physician oriented measures reflect the benefit perceived by patients, as measured on a visual analogue scale (VAS; 0–10, the higher the better) at the time of discharge. Our study comprised 742 consecutive patients with length of stay greater than 10 days admitted to our neurorehabilitation unit (mean age 47 years range 16–88 years). Overall the patients improved significantly (<0.001, paired t tests) on all physician outcome measures. Patients’ perceived benefit from rehabilitation programmes was high, mean VAS 8.3 (SD 2.0). Correlations of visual analogue scores and disability change scores were low (Pearson’s coefficient for change in functional independence measure, motor score 0.240, cognitive score 0.072, total score 0.238; Barzel score 0.278).

Physician outcome measures relate poorly with patients’ perceived benefit from inpatient neurorehabilitation as measured on a visual analogue scale, indicating that these measures reflect only a small part of patients’ perceived benefit. Conventional outcome measures are likely to underestimate the benefit of rehabilitation, with issues such as patients’ coping strategies and self efficacy being ignored. Work is needed to more accurately define the areas of health that rehabilitation affects, so that interventions and services can be more specific and effective.


**077**

**DO WE NEED ACUTE NEUROLOGICAL SERVICES IN A&E?**

D.C. Heaney, N. Campbell, O.C. Cockerell. Department of Neurology, Royal London Hospital, Whitechapel, London E1 2AD, UK

**Background:** The ABN believes that a 24 hour neurological service should be available to all patients admitted with neurological illness. The potential demand for neurological services in A&E departments is uncertain.

**Objective:** To establish the prevalence of neurological illness among patients attending the A&E department of a London teaching hospital and determine contact with neurological services.

**Methods:** Retrospective case note study of 1000 A&E attendees. Consecutive cases during randomly selected week were examined. Contact with neurological services (defined as registrar/consultant review, telephone advice, referral to neurology outpatients) was recorded and further cases where management might have been improved by a neurologist were identified.

**Results:** 78/703 (11.1%) adult attendees presented with neurological symptoms of which 51 (65.4%) were sent directly home. Neurological services were contacted regarding 15.4% of cases presenting with neurological symptoms but review of case notes demonstrated that in further 10.8% of cases contact would have been inappropriate and in four cases management would have been significantly altered by a neurologist. 12/288 (4.3%) paediatric attendees presented with neurological symptoms of which nine (75%) were admitted. In four cases paediatric neurological services were contacted.

**Conclusions:** Neurological symptoms are common cause for presentation to A&E but only 26% of patients with such symptoms are likely to benefit from contact with neurological services. For the remainder of cases, satisfactory clinical outcome is achieved without contact with a neurologist.
and enhancing their firing when it is low. Pyramidal neurons are relatively insensitive to fluctuations in the GABA, possibly because they are shielded by GABA transporters. Elevation of ambient GABA, as occurs with tiagabine or vigabatrin, may paradoxically decrease the phasic release of GABA from interneurons, undermining the antiepileptic effects of these drugs.

**080 PREVENTION OF SUDDEN UNEXPECTED DEATH IN EPILEPSY (SUDEP)**

Y. Langan1, L. Nashef1, J.W.A.S. Sander2, 1Epilepsy Research Group, Institute of Neurology, Queen Square, London WC1N 3BG, UK; 2Department of Neurology, King’s College Hospital, London and East Kent Hospitals NHS Trust, UK

**Objective:** The commonest seizure related death is sudden unexpected death in epilepsy (SUDEP). We have undertaken a case control study to examine the influence of various parameters on the risk of sudden death for an individual with epilepsy.

**Methods:** Coroner, neurologists via the British Neurological Surveillance Unit (BNSU) and the charity “Epilepsy Bereaved” notified cases to the study. Each case had four controls, matched for age and geographical location, and chosen using the Medical Research Council General Practice Research Framework (GPRF).

**Results:** 154 definite cases of SUDEP were identified, 97 men and 57 women with a mean age of 32 years. A number of factors were found to increase the risk of sudden death, including a history of convulsive seizures and a higher frequency of such seizures. The presence of supervision at night was found to be protective.

**Conclusion:** This work lends support to the view that SUDEP is a seizure related phenomenon and that the optimisation of seizure control is highly important in its prevention. We have identified that supervision at night appears to offer protection against SUDEP, which is consistent with the established observation that the majority of these deaths are unwitnessed. Attention to recovery following a seizure and positioning or stimulation as necessary may be important in SUDEP prevention.

**081 A PHASE 1B SAFETY, EFFICACY, AND PHARMACOKINETIC STUDY OF THE ANTISENSE OLIGONUCLEOTIDE EN101 IN PATIENTS WITH MYASTHENIA GRAVIS**

D.H. McKee, J.D. Sussman. Greater Manchester Neurosciences Centre, Hope Hospital, Salford, UK, and University of Manchester UK (both authors)

We present results from the first clinical trial of EN101, a synthetic antisense oligonucleotide directed against acetylcholine receptor mRNA, in human subjects with stable myasthenia gravis requiring daily pyridostigmine for symptom control.

Patients stopped pyridostigmine for 18 hours, with subsequent deterioration, non-myasthenic symptoms, measured by the Quantitative Myasthenia Gravis score (QMG). Escalating oral doses of EN101 were given until a significant improvement in QMG occurred. Once daily dosing continued for three days, followed by a washout period during which the subjects’ clinical condition deteriorated and pyridostigmine was reinstated. Following treatment with EN101 subjects showed both statistically and clearly clinically significant changes in QMG scores, sustained for up to 28 hours following final dosing.

No serious adverse events were observed. By contrast with previous treatment with pyridostigmine, cholinergic side effects such as abdominal cramps and diarrhoea were conspicuous by their absence. Conversely, dryness of the mouth was reported in the majority.

Despite theoretical difficulties inherent in antisense oligonucleotide therapeutics, EN101 appears to be powerfully effective in reversing myasthenic symptoms, with significant advantages over cholinesterase inhibitors, particularly in the context of an acute deterioration. The results of this study justify proceeding to a double blind, randomised controlled trial.

**082 A COMPARISON OF CAROTID ENDARTERECTOMY AND CAROTID ANGIOPLASTY AND STENTING: A PARALLEL COHORT OF 600 PROCEDURES**

F.M. McKevit1, T.J. Cleveland1, P.A. Gaines1, J.D. Beard1, G.S. Venables1, 1Neurology Department, Royal Hallamshire Hospital, Sheffield, UK; 2Sheffield Vascular Institute, Northern General Hospital, Sheffield, UK

**Background:** Carotid endarterectomy (CEA) is the current gold standard for the treatment of carotid stenosis. Endovascular techniques (carotid angioplasty/carotid stenting), however after a minimally invasive alternative. We compare two parallel cohorts of patients undergoing both procedures at a single institution.

**Methods:** Data were collected prospectively and assessed on the first 300 cases undergoing each procedure for symptomatic atherosclerotic disease. Outcome measures were all stroke/death rate, major stroke/death rate, and haematoma rate. Assessment was by a neuroradiologist.

**Results:** Between 1990 and 2000 300 patients underwent CEA. 65.3% were male, median age 67, median stenosis 82%, and 6.7% had a contra-lateral occlusion. All stroke/death rate was 6.0%, the major stroke/death rate was 4.3%, and neck haematoma was 8.3%. Between 1993 and 2001, 295 patients underwent 300 endovascular procedures (86 angioplasty, 214 carotid stents). 70.7% were male, median age 68, median stenosis 85%, and 7.7% had a contra-lateral occlusion. All stroke/death rate was 5.0%, the major stroke/death rate was 2.7%, and groin haematoma rate was 9.7%. The differences were not statistically significant except for the haematoma rate, p=0.05.

**Conclusion:** If long term durability of endovascular techniques can be demonstrated, the gold standard for the treatment of carotid stenosis may be challenged.

**083 INHERITED PRION DISEASE CAUSED BY OCTAPEPTIDE REPEAT INSERTION: GENETIC MODIFIERS AND HAPLOTYPE BACKGROUND IN LARGE UK AND SOUTH AFRICAN FAMILIES**

S. Mead1, J. Heckmann1, S. Rutherford2, M. Poulter1, J. Collinge2, 1Department of Neurodegenerative disease and MRC Prion Unit, Queen Square, London, WC1N 3BG; 2Neuropathology Unit, Department of Anaatomical Pathology, University of Stellenbosch, Cape Town, South Africa; 3Neurology division, Groote Schuur Hospital and University of Cape Town

Inherited prion disease with octapeptide repeat insertion (OPRI) in the prion protein gene was the first described genetic mutation in neurodegenerative disease. Ten years on, by far the largest characterised OPRI prion disease family originates from south east England. Many other insertion mutations have been characterised in smaller pedigrees, of particular interest is a 5-OPRI from South Africa with a unique insertion type. Genealogical and clinical record work, together with characterisation of disease associated SNP and microsatellite haplotype suggests a single founder for English 6-OPRI families, probably from the 17th century. Other insertion mutations have unique haplotype backgrounds suggesting separate ancestral mutations. Clinical details have been collected for 73 affected individuals, 84 individuals are known to be at risk of inheriting the disease. Details of MRI, PrP immunocytochemistry, transmission studies, and PrP strain typing are available. For a classical genetic disease, the degree of variation in age of onset and disease duration is remarkable. Studies show that heterozygosity at polymorphic codon 129 accounts for 41.5% of the variance in age of onset by delaying disease onset by 12 years (p=0.0001) but has no effect on disease duration, suggesting different biological mechanisms determine these variables. Trials of OPRI disease therapeutic agents are being considered in those at risk.

**084 EMAIL TRIAGE FOR NEW NEUROLOGICAL OUTPATIENT REFERRALS**

V. Patterson, J. Humphreys, R. Chua. Royal Victoria Hospital, Belfast and Erne Hospital, Enniskillen

New outpatient referrals make up a large part of the work of consultant neurologists. There is often considerable delay between the referral being made and the patient being seen; this leads to frustration for the patient and referring doctor, and also for the neurologist, who may end up seeing someone whose symptoms have resolved. We wondered whether a triage system using email might reduce this frustration and set up a study with eight general practitioners (GPs) who agreed to refer all their patients with neurological symptoms who required hospital referral, to a neurologist, using email. The neurologist agreed to reply within 48 hours, either arranging a consultation, or investigations, or merely offering advice. In a 14 month period 76 referrals were received, 67 of which were replied to within 48 hours. 43 referrals were dealt with without the need for a consultation, 9 with investigations, and 34 without. Neurologist’s time was reduced by 38%. Satisfaction was high for both GPs and patients managed by email. Review of GPs’ records subsequent to email consultation showed good levels of initial safety. We conclude that email triage of new neurological referrals is possible, acceptable, safe, and has the potential to make the practice of neurologists considerably more efficient.
COPYING CLINIC LETTERS TO PATIENTS

P.E.M. Smith. University Hospital of Wales, Heath Park, Cardiff

Patients rarely receive written documentation of hospital consultations, yet this need is often expressed. The UK Department of Health plans to implement a policy of automatic copying of clinic letters to patients by April 2004; neurologists must prepare for this change.

Over 24 months from October 2000, copies of 1029 clinic letters on new outpatients to general neurology and epilepsy clinics (of a total of 1143 sent (90%)) were copied to them. During the second year, 96% of clinic letters were copied. A covering letter gave contact details for discussion, and invited feedback. Spontaneous feedback was generally favourable, expressing enthusiasm for the additional information and explanation. For example, one patient described using the letter to help disclose her Parkinson’s disease to relatives; another was helped by investigating the medical terminology with his family. Occasional adverse feedback helped to refine the method and format of copy letters. One patient’s objection to being defined by his occupation and handedness prompted a change in the routine opening sentence. Three patients reported letters sent first to an incorrect address. Seven identified incorrect clinical details. Four reported drug dose errors, although two of these were misunderstandings of “BD”. One patient used his copy letter without consent as a medicolegal report.

This feedback prompted improved clarity of letters, more careful checking of content (especially addresses and drug doses), and minimised the use of abbreviations. Clinic letters now solely report the consultation, encouraging more open and honest interactions.

STROKE MORTALITY IN URBAN AND RURAL TANZANIA

R.W. Walker, D.G. McLarty, H.M. Kitange, D. Whiting, G. Masuki, D.M. Mtsiwa, H. Machibya, N. Unwin, K.G.M.M. Alberti, on behalf of the Adult Morbidity and Mortality Project. Department of Medicine, North Tyneside General Hospital, Rake Lane, North Shields, Tyne and Wear NE29 8BH, UK; Department of Diabetes, University of Newcastle upon Tyne Medical School; Ministry of Health, PO Box 9083, Dar-es-Salaam, Tanzania; Adult Morbidity and Mortality Project (AMMP), PO Box 65243, Dar-es-Salaam, Tanzania

Background: Most data for stroke mortality in sub-Saharan Africa are hospital based. We aimed to establish the contribution of cerebrovascular disease to all cause mortality and cerebrovascular disease mortality rates in adults aged 15 years or more in one urban and two rural areas of Tanzania.

Methods: Regular censuses of the three surveillance populations consisting of 307820 people (152932 aged below 15 years and 181888 aged 15 or more) were undertaken with prospective monitoring of all deaths arising in these populations between 1 June 1992, and 31 May 1995. Verbal autopsies were completed with relatives or carers of the deceased to assess, when possible, the cause of death.

Results: During the 3 year observation period 11975 deaths were recorded in the three surveillance areas, of which 7629 (64%) were in adults aged 15 years or more (4088 (54%) of these in men and 3541 (46%) in women). In the adults, 421 (5.5%) of the deaths were attributed to cerebrovascular disease, 225 (53%) of these in men and 196 (47%) in women. The yearly age adjusted rates per 100 000 in the 15–64 year age group for the three project areas (urban, fairly prosperous rural, and poor rural, respectively) were 65 (95%, CI 39–90), 44 (31–56), and 35 (22–48) for men, and 88 (48–128), 33 (22–43), and 27 (16–38) for women, as compared with the England and Wales (1993) rates of 10.8 (10.0–11.06) for men and 8.6 (7.9–9.4) for women.

Conclusions: We postulate that the high rates in Tanzania were due to untreated hypertension. Our study assessed mortality over a single time period and therefore it is not possible to comment on trends with time. However, ageing of the population is likely to lead to a very large increase in mortality from stroke in the future.

PERIPHERAL INFECTIONVOKESEXAGGERATED SICKNESS BEHAVIOUR IN MURINE PRION DISEASE

M.I. Combrinck1, V.H. Perry1, C. Cunningham1. CNS Inflammation Group, School of Biological Sciences, University of Southampton, Southampton, SO16 7PX, UK;2University Department of Pharmacology, Mansfield Road, Oxford, OX1 3QT, UK

Peripheral infections in mammals are characterised by local, systemic, and CNS effects. The latter give rise to sickness behaviour. Pro-inflammatory cytokines such as interleukin 1β (IL-1β) are thought to be important mediators of this neuroimmune signalling (Cartmell et al, 1999). Peripheral infections in patients with Alzheimer’s disease are often said to have more severe behavioural consequences than those in cognitively normal elderly subjects, and it is well known that brain microglia are activated in the elderly and in Alzheimer’s disease (McGeer et al, 1987).

Using ME7 induced murine prion disease as a model of chronic neurodegeneration that displays chronic microglial activation, and the intra-peritoneal injection of bacterial lipopolysaccharide to mimic a peripheral infection, we showed that the temperature and activity responses of animals with pre-clinical prion disease were exaggerated compared with controls, and that this was associated with a significant increase in brain levels of IL-1β. We hypothesise that prior priming of microglia by the degenerative process, followed by further activation through signalling from the periphery, resulted in increased brain IL-1β synthesis and the consequent acute sickness behavioural responses.

These findings demonstrate an interaction between peripheral infection and pre-existing CNS inflammation and suggest that further stimulation of an already primed microglial population by a peripheral infection may drive disease progression in chronic inflammatory/degenerative conditions such as Alzheimer’s disease and prion disease.