A SYSTEMATIC AND STRUCTURED APPROACH TO THE INVESTIGATION OF ATAXIA

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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 result as part of a broader multisystem disease, eg 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 specialist 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, whereby 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 ENDEAVERS IN MUSCULAR DYSTROPHY: THE HOPE VERSUS THE HYPE

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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 steroids. A parallel critique is provided of the inordinate hype in the tabloid scientific press, such as Nature. On analysis, much of this hype relates to inappropriate and often emotive language used in the description of the results, both by the scientists and the press. A series of guidelines has been developed 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

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Three families are described in whom the cardinal clinical manifestations are those of androgen insensitivity (gynaecomastia, truncal obesity, small genitalia, long forearms, wide armpits, progressive infertility), and pectoral muscle wasting atrophy. Potas, mild to moderately lower limb proximal weakness and dysarthria 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; electron microscopy: non specific features; immunohistochemical staining: 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)

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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 symmetrical, apparently normal, defects (white matter) 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

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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 DM 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.

Alu I, Hinf I, and Taq I polymorphisms were determined in this family. Southern blot analysis and RFLP analysis of PCR products. The affected individuals were found to be Alu 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.
006 RADIOLOGICAL CHARACTERISTICS OF FOCAL BRAIN LESIONS IN HIV POSITIVE PATIENTS
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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 Toxoplasma encephalitis. Primary CNS lymphoma (PCNSL) is a fast growing cause and progressive multifocal leukoencephalopathy (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 FBLs.

Correlatives 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, cystercerosis, cryptococcosis, or toxoplasmosis.

Results: The CT scan appearances alone were found to be very non-specific. The collective combined data as proposed above were useful for diagnosis. Nineteen patients (59.4%) were diagnosed with tuberculosis, 5 patients (15.6%) were diagnosed with neurocysticercosis. 1 patient (3.1%) was diagnosed with cerebral toxoplasmosis. 1 patient (3.1%) was diagnosed with cerebral tuberculomas, 1 patient (3.1%) was diagnosed with tuberculous meningitis, 1 patient (3.1%) was diagnosed with tuberculoma and cystercerosis, and 1 patient (3.1%) was found to have intracranial abscess. One patient (3.1%) was diagnosed with PML. One patient (3.1%) was diagnosed with PCNSL. Two patients (6.3%) were found to have multiple infarcts.

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 presented. Tuberculosis was the commonest cause in our patients and may reflect the endemic nature of this illness in our population.

007 PROFILE OF NEUROLOGIC DISORDERS ASSOCIATED WITH HIV/AIDS IN HOSPITAL BASED PATIENTS AT THE CHRIS HANI BARAGWANATH HOSPITAL IN SOWETO, SOUTH AFRICA
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Current Actuarial Society of South Africa (ASSA) data show that 14% of 46.3 million South Africans are HIV positive (6.5 million people are infected). There are 1500-1800 new infections occurring each day. 22.8% of the sexually and economically active population are HIV positive. Nearly 1 in 10 South Africans aged 20–40 years are expected to die of AIDS by the year 2005.

Chris Hani Baragwanath Hospital (CHBH) is a 300 bed tertiary care teaching hospital affiliated to the Faculty of Health Sciences, University of the Witwatersrand. In 1999 the HIV sero-prevalence of adult admissions was 33% for female patients 28% for male patients. In the age group 25–34 years there was a 60% female and 37% male sero-positivity.

To determine the prevalence of neurological disease in these patients we undertook a prospective audit of adult inpatients in the medical wards of the hospital.

Results: 250 patients with HIV infection have to date been analysed in terms of clinical features, CD4 counts, viral loads in blood, and CSF. Eighty patients were found to have neurological illness (32%). The profile of these patients included meningitis/focal brain lesion; myelopathy with neuropathy and dementia; new onset seizures; and dementia. These data will be presented in detail.

008 PROTEIN S DEFICIENCY IN HIV ASSOCIATED STROKE
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The association between HIV and stroke remains unclear. We recently described 35 black South African patients with HIV and stroke (in and stroke). Protein S deficiency was in 11 of these patients. A previous retrospective case control study in an African–American population found a high prevalence of protein S deficiency associated with stroke regardless of HIV status.

To determine the relevance of the association between protein S deficiency and stroke in HIV positive patients we studied patients with stroke who were HIV positive and HIV negative, as well as HIV positive patients without stroke. The patients were matched in terms of age, sex, and CD4 count. This data will be presented.

009 CARDIAC PAPILLARY FIBROELASTOMA: AN UNUSUAL CAUSE OF EMBOLIC STROKE
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A 23 year old woman presented with sudden onset of hemiplegia. She had no significant vascular risk factors and was previously in good health. Computed tomography (CT) scan of her brain showed a right parietal hypodensity in keeping with an acute infarct. A thorough aetiological search was conducted. Transoesophageal echocardiography (TEE) showed a papillary fibroelastoma involving the non-coronary cusp of the aortic valve. Numerous case reports have described cardiac papillary fibroelastoma (CPF) with a remote embolic event, although the frequency with which this occurs remains to be established. CPFs are usually found incidentally during cardiac evaluation or at postmortem. With improved echocardiographic resolution small ill-defined lesions are increasingly recognised. Clinicians must decide how to manage such patients with either incidental or symptomatic CPF.

010 THE NON-SPECIFIC EFFECT OF LITHIUM ON INTERLEUKIN 2 RECEPTORS (IL2Rs) AND IL6Rs IN LYMPHOCYTES OF PERIPHERAL BLOOD IN BIPOLAR MANIA TYPE I
L. Kirkby, G. Modi. WITS University Medical School, South Africa

Activation of the immune system has been described in bipolar disorder and in schizophrenia. Macrophages and their products, most notably cytokines, have been implicated to play a role in the pathophysiology in these conditions. There is evidence to suggest that these immune cells are activated in these illnesses. There is increased production of cytokines and other products in these illnesses. In particular, plasma levels of interleukin receptors, IL2R and IL6R, have been found to be increased in bipolar mania. However, the results are not consistent and there have been reports where the levels of IL2R have been decreased. Typical antipsychotics apparently have no significant effects on plasma IL2R.

In order to determine the relevance of these findings and the relationship with lithium treatment, we evaluated 20 patients with bipolar mood disorder type I. Twenty normal age, sex, and race matched controls were used. Three groups of patients were identified. Group 1 consisted of patients with a first episode of mania (6 patients). Group 2 consisted of patients who relapsed after stopping lithium treatment (11 patients), and group 3 consisted of patients who relapsed on lithium treatment (3 patients). In the first group the mean value for IL6R was 6.12 then compared with a control of 21.2. The mean value for IL2R was 6.58 compared with the control mean of 23.4. In the second group the IL6R mean for the patients was 15.7 compared with the control mean of 24.3. The IL2R mean was 15.7 for the patients compared with the control mean of 24.5. In group 3 the IL6R mean for the patients was 25.8 compared with the control mean of 25.1. The IL2R mean was 32.2 compared with a control mean of 28.2.

These results show that in first episode manics, the IL2R and IL6R are reduced. In patients who relapse after stopping lithium, the receptor levels are also reduced (not as low as in first episodes) and in patients who relapse on lithium treatment, the levels remain normal. Thus, the effect of lithium is to normalise immune activation markers. The immune abnormalities seen in bipolar mood disorder are, therefore, a state dependent effect.
011 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 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 this study mRNA 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 7°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 (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.

012 OPTIC NEURITIS IN AN URBAN BLACK AFRICAN COMMUNITY
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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 neuropathy (such as ischaemic optic neuropathy, 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 black.

To determine DNA rearrangements in this patient as part of a genetic analysis revealed a compound heterozygote—the first to be described in South Africa.

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

Examination/Methods: This 50 year old male complained of weakness of the shoulder girdle since adolescence. The weakness was steady progressive, lately involving the hip joints and muscles of the lower legs as well. On examination, the patient showed atrophy of the shoulders and hips Bilateral Drop foot was present due to Tibialis anterior weakness. Southern blot analysis was performed to determine DNA rearrangements in this patient as part of a genetic/c 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.

013 NEMALINE MYOPATHY: A SURPLUS PROTEIN MYOPATHY
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Introduction: Nemaline myopathy is a genetically diverse group of conditions characterised by excess formation of Z disc material (rods). Four clinical types are described: a severe neonatal form, a milder congenital form, an adult form (all autosomal recessive), and a childhood autosomal dominant form. We describe the clinical and pathological features of a patient with the adult form.

Case description: A 29 year old female patient presented with mildly progressive proximal weakness of a year’s duration. 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.

Methods: A muscle biopsy was performed. Separate samples were processed for paraffin embedding, routine muscle histochemistry, immunocytochemistry, and electron microscopy. Immunocytochemistry was performed using monoclonal antibodies against dystrophin 1, 2 and 3; α, β, γ, and δ sarcoglycans, spectrin, laminin-α2, and α-actinin.

Results: Routine H/E showed variation in fibre size with normal sized and atrophic fibres. The modified gomori trichrome 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 components of the thin filament (TPM3, NBP, TPM2, ACTA1, and TNN1) and in the RYR1 (ryanodine receptor gene). No mutations have been described in the α-actinin gene. The mechanism by which such mutations lead to an excess production of α-actinin material (α-actinin), which is controlled by an unaffected gene, is unknown. This exemplifies a novel mechanism in congenital myopathies.

014 FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY IN A COMPpOUNd HETEROZYGOTE
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Background: Facioscapulohumeral muscular dystrophy (FSHD) is an autosomal dominant muscular dystrophy 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.

Aim: The aim of the study was to categorise clinically affected individuals is of great importance.

Examination/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.

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

Results: Deletions of the 3.3 kb repeat units occurred on both chromosomes in this patient, indicating a compound heterozygote.

Conclusion: This is the first patient with FSHD in South Africa showing deletions on both chromosomes. Genetic counselling of such individuals is of great importance.

015 DETECTION OF NOVEL POINT MUTATIONS IN NON-DELETION PATIENTS WITH DUCHENNE MUSCULAR DYSTROPHY USING DNA SEQUENCING
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Background: Duchenne muscular dystrophy is a severe X-linked recessive genetic disorder affecting 1:3500 live male births. Two thirds of cases have a familial basis, whereas the other one third of cases are due to spontaneous mutations within the Duchenne gene. In approximately 65% of cases, the patients 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 the study was to categorise clinically affected Duchenne and Becker muscular dystrophy patients into deletion and non deletion patients. A total of 90 patients with DMD and 20 patients with BMD were enrolled. The patients were divided into two groups: deletion and non deletion patients. The patients were further divided into two subgroups: new mutation and familial mutation patients. The deletions were first detected on multiplex PCR. The remaining cases were further analysed by DNA sequencing.
non-deletion groups. The DNA from the non-deletion group of patients was then 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 two 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 V3 Termination Kit. DNA sequence analysis was conducted using the Biotools 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 NcoI 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.

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**018 PRETORIA STROKE DATABASE—LET’S START AT THE BEGINNING**

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Previously, we looked at a group of young patients with stroke retrospectively. This is an extension of the study where we aimed to evaluate the risk factors of all patients of 60 years and younger who were admitted to the Pretoria Academic Hospital neurology ward with an ischaemic stroke as from March 2002 prospectively.

**Methods and Patients:** All patients (60 years or younger) who were admitted to the adult neurology ward of the Pretoria Academic Hospital with an ischaemic stroke from 1 March 2002 to the end of September 2002 were included in the study. The data were collected prospectively and registrars were asked to participate in the collection of data. A stroke form was drawn up, and the following investigations were done: ECG, CRP, heart and carotid Doppler, CT brain scan, and a battery of lab tests.

**Results:** In our population of patients, hypertension still came out as the most important risk factor, but most patients had more than one risk factor. The detailed results of the risk factors will be described on the poster.

**Conclusion:** Hypertension remains the most prominent risk factor for ischaemic stroke in the population of young patients at the Pretoria Academic Hospital.

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**019 MICROARRAY ANALYSIS AND MICROSATellite GENOTYPING IN SOUTH AFRICAN PATIENTS WITH MULTIPLE SCLEROSIS: IDENTIFICATION OF A SIGNIFICANT ASSOCIATION WITH THE GENE ENCODING MONOCYTE CHEMOTACTIC PROTEIN-3**

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Multiple genes and environmental factors are believed to contribute to the aetiology of multiple sclerosis (MS), a chronic inflammatory disease of the central nervous system. In this study microarray technology, which makes it possible to simultaneously study the expression of thousands of genes in a single experiment, has been applied to identify genes underlying susceptibility to MS in the genetically homogeneous African population of South Africa. RNA was extracted from cultured human fibroblasts, and fluorescently labelled single stranded cDNA was generated using either reverse transcriptase incorporation of Cy-3 or Cy-5 dCTP into first strand cDNA, or Klenow labelling following a cDNA amplification step. The fluorescently labelled cDNAs of the patients and control samples were hybridised to the immobilised DNAs on the array using an automated slide processor. Following hybridisation, the DNA microarrays were scanned to monitor the fluorescence of each target that was successfully hybridised to the immobilised probe. Data were interpreted using the Applied Biosystems Quantarray package, and further data analysis was performed in Genespring (Silicon Genetics) and Microsoft Excel. The resulting gene expression ratios indicated significant under and over expression of various genes involved in regulating macrophage function in the MS compared with the control samples. Over-expression of monocyte chemotactic protein-3 (MCP-3), known to attract immune cells to the site of inflammation, represented the most significant finding (p < 0.002). The results were confirmed with quantitative methods, including real-time PCR and northern blot analysis. Subsequent analysis of the CA/GA microsatellite polymorphisms in the promoter enhancer region of the MCP-3 gene revealed a significant difference in allelic distribution between 117 South African MS patients and 73 matched control samples (p < 0.001, 3df, χ²=7.14). Sequencing of the coding region of three MS patients showing over expression of MCP-3 did not reveal any sequence changes, which is in accordance with involvement of the promoter region in MCP-3 over expression. Since the data presented in this study confirm previous findings of a significant association between MS and the MCP-3 gene, a comprehensive genetic test based on these and related findings will be developed for diagnostic purposes.
NERVUS ACCESSORIUS NERVE CONDUCTION AS A TEST TO EVALUATE RESPONSE TO BOTULINUM TOXIN THERAPY

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Botulinum toxin therapy has become the main treatment option for patients suffering from torticolis. 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 developed and may be a useful tool as a method to measure drug response in patients treated with botulinum toxin. The technique is, however, difficult to use and high interest variability is a problem. We describe a technique in which motor nerve conduction study stimulating the accessory nerve and recording from the sternocleidomastoid muscle is used pre and post treatment as a measure of response to botulinum toxin. This technique has several advantages: in the majority of patients suffering from torticolis the sternocleidomastoid muscle is injected as part of the treatment regimen, and unilateral injection that allows for a normal control in the patient and the technique is simple with a low level of discomfort.

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. Since nerve conduction study might therefore be a useful tool to evaluate non-responders suspected to have antibodies to botulinum toxin.

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, paresthesias, abdominal discomfort, headaches, and weight loss. These were 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.

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

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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 5'-G>Tn 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 gene. MS patients were not confined to a specific SLC1A1 genotype, thereby excluding the possibility that SLC1A1 allele 2 previously implicated in susceptibility to infectious diseases, correlates with viral infection in MS patients. Expression of the pol gene of MSRV was detected in the PBMCs of 34/49 (69%) MS patients/49 (69%) of close relatives, whereas none of the unaffected close relatives, while absent in the serum of 39 unrelated healthy control individuals (p <0.001). No significant differences were observed with respect to presence or absence of EBV sequences. HHV6 sequences were detected at a significantly lower frequency (p <0.04) in the PBMCs of unrelated controls (5%) compared with the MS patients (22.5%), most of whom also expressed MSRV RNA. The data provided in this study indicated that virus infections affect the population risk but not the familial risk in MS.

A MULTIDISCIPLINARY APPROACH TOWARDS ELUCIDATING THE GENETICS OF MULTIPLE SCLEROSIS

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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 autoimmunity and infectious disease susceptibility, in order to investigate the role of genetic 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 divergent 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 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 for the 77C →G mutation in 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

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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, inability to sustain attention) 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 deficit 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 SHR. Glutamate activation of excitatory amino acid-3-hydroxy-5-methyl-4-isoxazoliopropionate (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 NEUROCYSTICERCOSIS IN EASTERN AND SOUTHERN AFRICA

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Through the monitoring of hospital based patients with neurocysticercosis, community based serological surveys of particular groups of patients, and surveys of porcine cysts in Southern Africa, 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 and sustainable methods of controlling and treating cysticercosis, taeniosis in humans. Finally, the promising results from Pilot Projects on vaccination of Pigs (Flisser Ann 2002, personal communication) have all brought forward the prospect of control and eventual eradication of human and porcine cysticercosis/taeniosis from the realms of theory to the possibility of application. In 1993 The International Task Force for Disease Eradication declared cysticercosis/taeniosis as one of only six infectious diseases deemed eradicable and an “International Action Planning Workshop on Taenia Solium Cysticercosis/ Taeniosis with special reference on Eastern and Southern Africa” was held on the 19–22 August 2002 in Arusha, Tanzania, with the above declaration in mind. This paper was presented at the workshop and the present presentation is to brief the congress on recent developments towards control and final eradication of cysticercosis/taeniosis in humans and pigs.

026 SPECTRUM OF CLINICAL PRESENTATION OF MITOCHONDRIAL ENCEPHALOPATHY AT RED CROSS CHILDREN’S HOSPITAL 1991–2001

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Background: Mitochondrial disorders have been diagnosed with increasing frequency since advances in genetics allowed identification of mutations within the mitochondrial genome. Quantification of mitochondrial DNA and analysis of respiratory chain enzyme activity have permitted the identification of mitochondrial dysfunction in the absence of known mutations in mitochondrial DNA (mtDNA). A few mutations in nuclear DNA encoding for mitochondrial proteins have also been identified. With this increase in knowledge it has become apparent that presentation is very variable, particularly in the absence of known mutations coding for characteristic phenotypes such as mitochondrial encephalopathy with lactic acidosis and stroke like episodes (MELAS).

Method: This study is a retrospective review of 45 cases of suspected mitochondrial encephalopathy, including Leigh syndrome, seen at the Red Cross Neurology Service in the past 10 years. Clinical presentation and course, laboratory findings, radiological, and genetic studies were documented.

Results: Confirmed genetically were three MELAS cases, one of Leigh syndrome, one of Leber hereditary optic neuropathy (LHON), and one of Leigh Syndrome with a previously undescribed mtDNA mutation. Three children had decreased pyruvate dehydrogenase activity. One presented with encephalopathy and had absent cytochrome C oxidase staining in muscle tissue. Five children had radiological and clinical features consistent with a diagnosis of Leigh syndrome. One child presented with features of Kearns Sayre syndrome.

Conclusion: The case series is large when compared with other degenerative neurological disorders. It is important to be aware of the full spectrum of mitochondrial-related dysfunction in the definitive biochemical or genetic diagnosis is not always possible but a compatible clinical presentation with supportive biochemical or radiological findings may suggest the diagnosis.

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

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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 a global developmental delay, the remaining children had normal neurodevelopment. The children presented with encephalopathy, acute, sub-acute and chronic (n=3), progressive multifocal leuкоencephalopathy (n=2), intractable seizures (n=1), ischaemic 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 NEUROIMAGING FEATURES OF TUBERCULOUS MENINGITIS IN CHILDHOOD

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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 TB meningitis. A total of 24 cases were identified. Clinical features were reviewed and the clinical radiological correlation was investigated.

Results: Neuroimaging features of tuberculous meningitis were divided into acute and chronic categories. Imaging features in the acute phase were more abrupt and associated with findings suggestive of a rapid progresive process. These included diffuse meningeal enhancement; obliteration of sulci and cisterns; hydrocephalus (100%); and ring-enhancing lesions in the brain parenchyma (50%). In the chronic phase the imaging features indicated chronic inflammation and fibrosis leading to atrophy of the brain. These included parenchymal atrophy; leptomeningeal enhancement; and subependymal enhancement. Conclusions: While the radiological features of tuberculous meningitis can be variable, they are usually very diagnostic. The radiological features form an important part of the diagnostic process and are important for follow up studies.
were assessed with regard to the presence of imaging features including basal cisternal enhancement, hydrocephalus, infarction and tuberculoma. 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 TB, 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 summarized and statistically compared with no significant difference found. The commonest positive CT finding of the affected patients was basal meningial enhancement, followed by hydrocephalus, infarction, cisternal high-density exude prior to IVI contrast, and TB granulomata.

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.

NEUROCRISTOPATHY: A CASE OF HADDAD DISEASE

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Haddad disease (Ondine-Hirschsprung) is characterised by a combination of congenital central hypoventilation syndrome and Hirschsprung disease (CCHS). It was first described by Haddad in 1978 and was confirmed on laparotomy. No structural or neuromuscular causes of PIND in this study. A relatively small proportion of targets to non-targets in tests 2–4 was approximately 0.8–1.5. 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 at a BAC of 0.05%.

Methods: Intergroup comparison of the consequences of sleep deprivation 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 1/7/32 (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 subjects in three tests, and two subjects in all four tests. Only 6/32 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. Sleep deprivation 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.

ATTENTION AND WORKING MEMORY IN REGISTRARS AFTER NIGHT DUTY

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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 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 anaesthesiology 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 assessment was conducted at either 08:15 or 08:55 preceding night duty and repeated 24–25 hours later, just after completion of duty.

Conclusion: Sleepiness Scale (SSS). Thereafter a battery of four reaction time (RT) tasks of increasing difficulty was administered on a personal computer. The tests 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 a digit 0–9 and the dimension of the flankers was altered to vary the range 0–9; (c) a sequential RT task that required the subject to respond to the second of any digit 0–9 occurring in a repeating sequence; and (d) 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 0.8–1.5. 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 at a BAC of 0.05%.

Results: Intergroup comparison of the consequences of sleep deprivation 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 1/7/32 (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 subjects in three tests, and two subjects in all four tests. Only 6/32 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. Sleep deprivation 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.

SURVEY OF STROKE RISK FACTORS SEEN IN GENERAL PRACTICE IN SOUTH AFRICA

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Introduction: The prevalence of stroke risk factors in a typical general practice population in South Africa is unknown.

Objectives: To assess, among all population groups consulting general practitioners in South Africa, the prevalence of stroke risk factors and the type and extent of pharmacotherapies used to modify these risk factors.

Design: Multicentre observational study by 200 randomly selected GPs throughout South Africa who were each requested to collect data, according to a preset questionnaire, on 50 consecutive patients attending their practice.

Outcome Measures: Prevalence of hypertension, current smoking history, diabetes, hypercholesterolaemia, atrial fibrillation, recent
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Risk factors

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<th></th>
<th>Black</th>
<th>Coloured</th>
<th>Indian</th>
<th>White</th>
<th>Total</th>
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<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>
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<tr>
<td>Lipids abnormal (on Rx or chol &gt;5 mmol/l)</td>
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<td>20.5%</td>
<td>22.1%</td>
<td>37.9%</td>
<td>27%</td>
</tr>
<tr>
<td>Smoking (current)</td>
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<td>30.9%</td>
<td>22%</td>
<td>22.5%</td>
<td>21%</td>
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<tr>
<td>Atrial Fib</td>
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<td>1.5%</td>
<td>6%</td>
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History of minor and major strokes, history of cardiac disease, and extent of pharmacotherapy use in risk factor management.

Results: 933 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; 318 (3%) of patients had previous minor strokes; 69 (0.7%) 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 angiotensin-converting enzyme (ACE) inhibitors (16%), angiotensin II blockers (4.5%), calcium channel blockers (2%), antiplatelet agents (15%), anti-diabetic agents (8.2%), and diuretics (21%).

Conclusions: Stroke risk factors are highly prevalent in general practice patients 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.

033 SYMPATHETIC NERVOUS SYSTEM IN MODULATING IMMUNE ACTIVITIES IN AUTOIMMUNE DISEASES

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Previous studies suggested that both the hypothalamus–pituitary axis and sympathetic nervous system (SNS) play significant roles in autoimmunity disease initiation and progression. This mini review concentrates on the issue of sympathetic nervous system in the modulation of natural immune response. The catecholaminergic (NA) and peptidergic nerve fibres are present in both primary and secondary lymphoid organs, distributing with the vasculature, trabecular, and capsular smooth muscle, and within the parenchyma among immune cells of the immune system. It has been reported that sympathetic nervous system plays an important role in primary antibody response, cytokine T cell responses, natural killer cell activity, and proliferation and differentiation of both T and B cells. There are plenty of articles reviewing the effects of the sympathetic nervous system on immune response in general. However, the articles reviewing the role of the sympathetic nervous system (SNS) in modulation of the immune response in natural situations, such as in autoimmune diseases and infectious diseases, have not come to the publication yet. The present article fills the blank. The studies reviewed showed that SNS regulated the immune activities of autoimmune diseases, which played pivotal roles in the onset and progression of the diseases. The mechanisms behind the regulations are yet undefined and remain to be clarified.

034 A NOVEL FAMILIAL TUBULAR AGGREGATE MYOPATHY ASSOCIATED WITH ABNORMAL PUPILS

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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.

035 BRITISH NEUROSCIENTISTS: A PHILATELIC TRIBUTE

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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 prosta- cyclin, aspirin is widely used in stroke prevention.

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

036 KLIPPEL-FEIL SYNDROME “PLUS”

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We report a case with Klippel-Feil (KFS) syndrome associated with hypertelorism, microtia, Sprengel deformity, hand and feet deformities, scoliosis, clinical manifestations of Klippel-Tranayau 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 anaesthesiologist’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.

037 BINSWANGER’S DISEASE AND NECROCYSTICERCOSIS

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We report seven patients who presented with clinical manifestations of ischaemic cerebrovascular disease (CVD) and dementia, and on CT
scan radiological signs of active neurocysticercosis and Binswanger's disease were found. Two patients died due to bilateral pulmonary thromboembolism secondary to deep venous thrombosis on lower limbs and the others remain alive. In almost all of them after one day of treatment with praziquantel (PZQ) some aggravation of the clinical manifestations of BD were observed. We have hypothesised about the Taenia solium microbial activation coagulation disorder and glial disorders, blood–brain barrier disturbances, Binswanger’s disease. We considered that anti-parasitic therapy for active NCC in patients with an associated BD should be prescribed for isolated cases when it's extremely necessary.

[038] DO CLINICIANS AGREE ABOUT THE DIAGNOSIS OF NEUROSYMPHILIS?

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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 unproven.

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 TPA 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 (exact ages 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 edges of our scale. Despite this, clinician one categorised 109/324 and 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.

[039] 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) poor 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 2001 were identified from an epilepsy surgery database. Outcome data were obtained from patient records and from telephonic 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. Intercal 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 T 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-Rolandi 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-mute-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.

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

J.M. Heckmann1, W.C. Low2, C.M. Morris1, C. de Villiers1, S. Rutherford1, R. Ramaee2, R. Kalaria3. Division of Neurology, Groote Schuur Hospital; Division of Neurology, University of Cape Town, South Africa

Objective: To determine the phenotypic features and molecular basis of a dementia 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: Thirteen individuals spanning three generations from an indigenous South African (Xhosa) family with Presenilin 1-linked familial AD were identified. 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.

Conclusion: This is the first documented indigenous South African (Xhosa) family with Presenilin 1-linked familial AD. The intrafamilial 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).

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

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Background: Thiopurine methyltransferase (TPMT) involved in metabolising azathioprine is encoded by a polymorphic gene. Consequently, the TPMT genotype can influence the potential for developing...
toxicity. The aim is to compare the TPMT genotype and enzyme activity in AZA patients and determine their possible predictive value in azathioprine related toxicity.

**Subject and Methods:** Clinical outcomes of patients treated with azathioprine for >6 months were assessed (n=118; 24 black; 76 mixed ancestry [M/A]; 13 white; 5 other). TPMT genotype was determined by PCR based methods to detect mutations at 238, 460, and 719 of TPMT cDNA defining the common mutant alleles [TPMT*2, *-3A, *-3C]. TPMT activity in packed RBCs determined phenotype (n=65).

**Results:** Four patients developing acute idiosyncratic reactions within 24 hours were excluded. In 33 patients azathioprine doses had to be reduced due to side effects, most frequently haematological (n=22) after a median period of 10.5 weeks. Five patients developed delayed gastrointestinal [GI] symptoms or deranged liver functions, three arthropathies, and one skin manifestation.

Seven patients were heterozygous for mutations [5/7 TPMT*3C] and had lower TPMT activity compared to those without mutations (p=0.003); haematologic toxicity developed in 5 and GI symptoms in 1. The predictive value for genotype was 86%. TPMT activity differed among the ethnic groups (p<0.04); in the largest group, M/A (n=36), patients with toxicity showed a trend towards lower activity compared to those without toxicity (p=0.07). Control values have not yet been established for African populations; using antimodes for African-American and Caucasians, the predictive value for “low/intermediate” TPMT activity in M/A patients is 40% and 45%, respectively. There was a trend towards lower doses of azathioprine being tolerated by patients with mutations (0.85 +/- 0.70 mg/kg) compared to those developing toxicity without mutations (1.80 +/- 0.55 mg/kg).

**Conclusion:** Preliminary data suggest that TPMT genotyping may be more predictive than TPMT activity in individualising azathioprine therapy. However, TPMT activity frequency distribution diagrams need to be established for local populations. Patients in whom mutations were identified finally tolerated on average a 65% lower than recommended dose.

This study is supported by research grants from the MRC (SA) and UCT.

**042 AZATHIOPRINE USE IN MYASTHENIA GRAVIS AND PREGNANCY**
1Division 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 patients with generalised myasthenia gravis (GMG). All new medications should be evaluated by testing in small numbers of patients.

**Aim:** To assess maternal and neonatal morbidity in patients with GMG who become pregnant while taking azathioprine and were maintained on this immunosuppressive during their gestational period. GMG status and pregnancy outcomes were compared to those of 22 non-pregnant GMG who became pregnant while taking azathioprine and were asymptomatic for “low/intermediate” TPMT activity in M/A patients is 40% and 45%, respectively. There was a trend towards lower doses of azathioprine being tolerated by patients with mutations (0.85 +/- 0.70 mg/kg) compared to those developing toxicity without mutations (1.80 +/- 0.55 mg/kg).

**Conclusion:** Preliminary data suggest that TPMT genotyping may be more predictive than TPMT activity in individualising azathioprine therapy. However, TPMT activity frequency distribution diagrams need to be established for local populations. Patients in whom mutations were identified finally tolerated on average a 65% lower than recommended dose.

This study is supported by research grants from the MRC (SA) and UCT.

**043 SPECTRUM OF LOWER MOTOR NEURONE SYNDROMES ENCOUNTERED IN HIV POSITIVE PATIENTS RECOMMENDATION FOR NEUROLOGICAL EVALUATION TO GROOTE SCHUUR HOSPITAL**
O. Ameer, J.H. Heckmann, R.W.E. Eastman. Division of Neurology, Department of Medicine, University of Cape Town and Groote Schuur Hospital, South Africa

**Aim:** To describe the clinical and electrophysiological presentation of lower motor neurone (LMN) syndromes encountered among a group of HIV positive patients.

**Method:** Case records of all consecutive HIV positive patients referred to GSH neurology department for evaluation of a suspected LMN syndrome from January 2000 until October 2002 were analysed. Functional class [F (x)] was defined as 1 = independent ambulation, 2 = ambulation with the use of an assistive device, 3 = wheelchair bound, and 4 = requiring ventilation.

**Results:** There were 43 patients. Three patients had received highly active anti-retroviral therapy (HAART). 21 patients had symptoms >6 weeks duration while 17 had symptoms <6 weeks. See tables for clinical presentations that were encountered.

**Conclusions:** A wide spectrum of lower motor neurone syndromes was seen. Inflammatory demyelinating neuropathies (AIDP, CIDP, LSPR) were most frequently encountered, while painful distal sensori-motor neuropathies were uncommon. This may reflect a referral bias. A wide range of lymphocyte and CD4+ counts were seen with individual neuropathies. Preliminary data suggest that in those patients in whom follow up was available, those with CIDP and LSPR who were treated with prednisone responded early and dramatically. In contrast, patients with sensori-motor axonal polyneuropathy responded poorly to prednisone. Spontaneous remissions were noted to occur in untreated patients with both inflammatory and sensori-motor axonal polyneuropathies.

**044 LONG TERM OUTCOME OF STREPTOCOCCAL MOVEMENT DISORDERS**
K.G. Walker, J.H. Wilmshurst. Department of Neuro-Sciences, Red Cross Children's Hospital, South Africa

Post-streptococcal conditions such as rheumatic carditis, Sydenhams chorea (SC), PANDAS, and other movement disorders remain major 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 effects that could be related to in utero azathioprine exposure.

**Conclusions:** In this small series, the continued use of azathioprine 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.

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1On 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 neuropathies.

n, Number of patients; mm, mean.

Outcome of patients treated with immunomodulatory therapy (prednisone N=9; IIG N=1).

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A REVIEW OF STROKE IN KWA-ZULU NATAL OVER A 15 YEAR PERIOD

V.B. Patel, Z. Sacoor, P.L.A. Bill. Nelson Mandela School of Medicine, University of Natal, South Africa

This is a retrospective analysis of all stroke patients admitted to the neurology unit at Wentworth Hospital over the past 15 years. A case control study comparison is made between age matched HIV positive and HIV negative patients.

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 papillomatous necrosis. The differential diagnosis and final aetiology will be presented on the poster.

LAFORA BODY DISEASE IN TWO PATIENTS PRESENTING WITH PROGRESSIVE MYOCLONIC 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 clinical and confirmed at autopsy, or occasionally by a brain biopsy. EEG changes, MRI findings, and immunoassay 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 myoinositol and later reduction in NAA. In conclusion these findings was noted. There were no retinal infiltrates. The EEG revealed a predominant beta background rhythm, upon which was thrusted generalised repetitive spike and polyspike waves followed by slow wave discharges. At times these discharges were asynchronous. ACT brain showed mild generalised atrophy. An auxiliary 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.

STROKE IN DEVON: THE NEED TO TRANSLATE 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 people at risk, re-enforcing the diagnosis of stroke and access of medical services.

052 SPECT PERFUSION IMAGING IN THE DIFFERENTIAL DIAGNOSIS OF PRESENILE DEMENTIA: A RETROSPECTIVE REGIONAL AUDIT
M. Doran1, S. Vinjamuri2, J. Collins2, D. Parker1, A.J. Lanner1. 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-HMPAO 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 assessed by five raters (2 neurologists, 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 neurologists 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 neuroscience centre, referring patients to two nuclear medicine centres.

Results: Inter-rater reliability in scan assessment was reasonable (κ=0.60), but inter-rater reliability was less good (30–63% for various conditions). Diagnostic accuracy for individual raters ranged from 32–58%. SPECT scan normality or abnormality in blind and informed views gave respective sensitivities of 77% and 71%, specificities of 58% 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 views. 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 stage.

053 DOES THE CAUSE OF MULTIPLE SCLEROSIS LIE BETWEEN THE ISLANDS OF MALTA AND SICILY?
M. Elian1, G. Dean2, A. Galea Debona3, N. Vella4, V. Mitsud5, J. Aquilina6, P. Asciak7. 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 annual incidence was 0.7 per 100 000. Among immigrants maltese born patients had clinically definite MS (CDMS) and 13 clinically probable MS (CPMS). The annual incidence was 0.7 per 100 000. Among immigrants and Maltese born patients had clinically definite MS (CDMS) and 13 clinically probable MS (CPMS). The annual incidence was 0.7 per 100 000. Among immigrants and Maltese born patients had clinically definite MS (CDMS) and 13 clinically probable MS (CPMS). The annual incidence was 0.7 per 100 000. Among immigrants and Maltese born patients had clinically definite MS (CDMS) and 13 clinically probable MS (CPMS). The annual incidence was 0.7 per 100 000. Among immigrants and Maltese born patients had clinically definite MS (CDMS) and 13 clinically probable MS (CPMS). The annual incidence was 0.7 per 100 000. Among immigrants and Maltese born patients had clinically definite MS (CDMS) and 13 clinically probable MS (CPMS). The annual incidence was 0.7 per 100 000. Among immigrants and Maltese born patients had clinically definite MS (CDMS) and 13 clinically probable MS (CPMS). The annual incidence was 0.7 per 100 000. Among immigrants and Maltese born patients had clinically definite MS (CDMS) and 13 clinically probable MS (CPMS). The annual incidence was 0.7 per 100 000. Among immigrants and Maltese born patients had clinically definite MS (CDMS) and 13 clinically probable MS (CPMS). The annual incidence was 0.7 per 100 000. Among immigrants and Maltese born patients had clinically definite MS (CDMS) and 13 clinically probable MS (CPMS). The annual incidence was 0.7 per 100 000. Among immigrants and Maltese born patients had clinically definite MS (CDMS) and 13 clinically probable MS (CPMS). The annual incidence was 0.7 per 100 000. Among immigrants and Maltese born patients had clinically definite MS (CDMS) and 13 clinically probable MS (CPMS). The annual incidence was 0.7 per 100 000. Among immigrants and Maltese born patients had clinically definite MS (CDMS) and 13 clinically probable MS (CPMS). The annual incidence was 0.7 per 100 000. Among immigrants and Maltese born patients had clinically definite MS (CDMS) and 13 clinically probable MS (CPMS). The annual incidence was 0.7 per 100 000. Among immigrants and Maltese born patients had clinically definite MS (CDMS) and 13 clinically probable MS (CPMS). The annual incidence was 0.7 per 100 000. Among immigrants and Maltese born patients had clinically definite MS (CDMS) and 13 clinically probable MS (CPMS). The annual incidence was 0.7 per 100 000. Among immigrants and Maltese born patients had clinically definite MS (CDMS) and 13 clinically probable MS (CPMS). The annual incidence was 0.7 per 100 000. Among immigrants and Maltese born patients had clinically definite MS (CDMS) and 13 clinically probable MS (CPMS). The annual incidence was 0.7 per 100 000. Among immigrants and Maltese born patients had clinically definite MS (CDMS) and 13 clinically probable MS (CPMS). The annual incidence was 0.7 per 0.000.

Conclusions: We were not able to conclude that the cause of MS lies between Malta and Sicily.

054 BETA-INTERFERON IN MULTIPLE SCLEROSIS: AN ASSESSMENT OF THE ABN STOPPING CRITERIA IN CLINICAL PRACTICE
G. Giannonnii, 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 IFNβ4. Although 40/101 (40%) patients satisfied the current (2001) ABN criteria for stopping IFNβ4 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 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

K.A.C. Harkness, A. Coles, U. Pohl, J. Xuereb, J.C. Baron, G. Lennox, Addenbrookes University Hospital, Cambridge, UK

We present an unusual cause of reversible dementia. This 72 year old lady presented with an 8 week history of a rapidly progressive frontal dementia. 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 white matter change. Two doses of dexamethasone given pre-operatively may have accounted for her clinical improvement. The co-occurrence of CAA and vasculitis is an infrequent observation. Whether these entities are genetically or pathophysiologically related is unresolved. Treatment with immunosuppressants can resolve symptoms and may lead to reduction of amyloid load.

056 MINERALOCORTICOID RECEPTOR EXPRESSION AND INCREASED SURVIVAL FOLLOWING NEURONAL INJURY: A NEW THERAPEUTIC TARGET IN CEREBRAL ISCHEMIA

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Acute ischaemic stroke is the leading neurological cause of death and disability. Therapeutic strategies based on inhibiting apoptotic or necrotic death pathways have yet to show efficacy in human studies. An alternative strategy is to augment endogenous protective mechanisms involved in the response to ischemia.

In neuronal culture, exposure to low levels of the neurotoxin staurosporine causes a 136±38% increase in mineralocorticoid receptor gene expression (p <0.05) and a 43±5% reduction in spontaneous neuronal death (p <0.05). This pathway is associated with activation of the MAP kinase cascade and increased phosphorylation of the transcription factor Elk-1, along with increased Elk-1 DNA binding activity in gel shift assays. In rat hippocampus, mineralocorticoid receptor expression increases by 43±5% following hypothermic transient global ischaemia (p <0.05), and the protective effect of hypothermia in this model is reversed (46±252% increase in death, p <0.05) by mineralocorticoid receptor antagonism.

In neuronal culture, treatment with caffeine leads to a rapid induction of mineralocorticoid receptor [49±15% at 30 mins, p <0.05]. Identification of those properties of caffeine responsible for this induction will provide a strategy for rational design of drugs that might augment endogenous neuroprotective responses in stroke.

We gratefully acknowledge the support of the Brain and Spine Foundation.

057 IS THE ENDOVASCULAR TREATMENT OF CAROTID STENOSIS IN HIGH RISK PATIENTS REALLY SAFER THAN CAROTID ENDARTERECTOMY?

F.M. McKevitt, S. Macdonald, G.S. Venables, T.J. Cleveland, P.A. Gaines, 1Neurology Department, Royal Hallamshire Hospital, Sheffield, UK; 2Sheffield Vascular Institute, Northern General Hospital, Sheffield, UK

The role of endovascular treatment of carotid artery stenosis remains controversial but there is consensus that it may be an alternative for those deemed at high risk for carotid endarterectomy (CEA). We reviewed the outcomes of patients undergoing endovascular treatment that would have been considered at high risk from CEA.

Methods: High risk patients were classed as those with occlusion of the contra-lateral internal carotid artery, recurrent stenosis post CEA, or previous neck irradiation, or coronary surgery. Patients treated by carotid angioplasty +/- stenting for >70% stenosis with at least one of these criteria were included. A neurologist assessed clinical outcome at 30 days.

Results: 89 procedures fulfilled at least one inclusion criterion of which 58.4% had symptomatic disease. The major stroke/death rate was 11.2%. The major stroke/stroke related death rate was 7.9%. 55 had a contra-lateral occlusion, 13 post-CEA, 16 post-radiation, and 25 pre-coronary surgery. The major stroke/stroke related death rates for each subset were 10.7%, 7.7%, 0%, and 4%, respectively. These differences were not significant.

Conclusion: These results suggest that this category of patient, particularly those with a contra-lateral occlusion, who undergo endarterectomy or endovascular treatment, are at high risk of stroke regardless of method of carotid intervention.

058 GENETIC ASSOCIATION STUDY OF IDIOPATHIC GENERALISED EPILEPSY

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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 being determined by specific gene combinations. We are conducting 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 broad phenotype, using the Kent sample, in a Ca channel gene (CACNA1A) and the opioid receptor gene (OPRM1). In CACNA1A 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=0.0000001). 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=0.000087). Fine mapping studies are currently being performed in order to identify the functional variants. Most 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 adolescence.
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 663 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.
AN ANTI-SPINAL ANTIBODY IN DERMATITIS HERPETIFORMIS PATIENTS

D.S.N.A. Pengiran Tengah1, A. Church2, G. Giovanni2, L Fry2, B. Turner1, A.J. Wills AJ, 1Department of Neurology, Queen’s Medical Centre; 2Division of Clinical Neurology, University Hospital, Nottingham NG7 2UH, 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

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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.

Methods: Over a 16 month period, two monthly DT, dual echo, and T1 relaxation time (T1) maps 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 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.

BETA-INTERFERON PRESCRIBING FOR MULTIPLE SCLEROSIS IN GREATER MANCHESTER: ARE ABN GUIDELINES HELPFUL?

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Aims: To determine whether ABN guidelines are helpful in predicting treatment response.

Methods: Retrospective audit of beta-interferon prescribing in Greater Manchester (population 2.8m) between April 1995 and September 2002. Patients were categorised according to whether they fulfilled original and current ABN guidelines, or neither. Annualised relapse rate (ARR) and expanded disability status scale (EDSS) were used as outcome measures. Treatment “responders” and “non-responders” were identified for sensitivity, specificity, and positive predictive values for both guidelines calculated.

Results: Female:male ratio 2:1; mean age 37.1 years (SD 9.1, range 13–66); disease duration 7.2 years (6.1, 0–32). At initial assessment, ARR was 1.2 (0.6, 0–3) and mean EDSS 3.5 (1.7, 0–6.5). At review mean 30.6 months (SD 27.6, 12–88), ARR was 0.45 (0.2, 0–16) and mean EDSS 4.4 (2.1, 0–7.5). The sensitivity, specificity, and positive predictive values for original and current ABN guidelines were 85%, 42%, 46%, and 92%, 21%, 38%, respectively. The test of treatment response as a two-tailed test of statistical significance was 0.05.

Conclusion: Caution is required in interpreting results due to potential misclassification of “responders” and “non-responders”. Nevertheless, results provide support for the notion that strict application of current ABN guidelines (in line with original ABN guidelines) may increase the likelihood of a good outcome.

LAMBERT EATON MYASTHENIC SYNDROME (LEMS) ASSOCIATED WITH THYMITIS

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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 facilitation or fatiguability on repeated muscle contraction. Nerve conduction studies revealed evidence of a mild axonal sensory polyneuropathy. Compound muscle action potential (CMAP) amplitudes following single 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 digitii minimi revealed an increment in the CMAP amplitude of 33%. Anti voltage gated calcium channel antibodies were present.
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 mediastinoscopy. Histological examination revealed no evidence of malignancy but typical changes of thymitis. Postoperatively his symptoms of muscle weakness have improved, including keratitis, conjunctival mycetome, endophthalmitis, and pan-ophtalmitis. However, reports of orbital involvement are rare.

In this paper we describe the case of a 57 year old well controlled 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 of the left eye, left proptosis and peri-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 m astoid 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.

**Case Report:** A 54 year old lady presented with late onset partial epilepsy. Following prolonged seizures 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, unilateral facial twitching, and crescendo flattening of the left 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.

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

**07D CONGENITAL MYASTHENIA—RAPSYN DEFICIENCY: HOW RARE?**

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Congenital myasthenic syndromes (CMS) comprise a heterogeneous group of inherited disorders characterised by impaired neuromuscular transmission. They arise from genetic defects in fundamental proteins involved in the production 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 43 kDa 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 a young age patients present 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 NEUROLOGICAL APOPTOSIS OCCURS IN PATIENTS WITH MITOCHONDRIAL DNA DISORDERS**

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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 anti-apoptotic factors and mutations in the mitochondrial DNA may be involved in neurodegeneration in a number of conditions. The frequency of apoptotic neurons was very low, in the order of one in 10,000. 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...
vivo and may contribute via a similar mechanism in other neurodegenerative conditions.

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

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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 dose 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

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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 (range 16–85) years]. Overall the patients improved significantly (p < 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; Barthel 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?

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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 acute 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 a further 10.8% of cases contact would have been appropriate 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.

**078** NEUROLOGICAL DISORDERS IN THE EMERGING HIV EPIDEMIC IN NORTHERN TANZANIA

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A total of 1628 adult neurology patients admitted to a consultant hospital in Northern Tanzania between 1984 and 1992 were examined by the author. The main neurological disorders were stroke 26.1%, infection 19.4%, neuropathy 13.8%, paraparesis 13%, coma and convulsions 8%, neurodegenerative 4.2%, tumours 3.2%, motor neurone disease 1.8% neuromuscular 1.4%, and others 9%. A total of 417/1628 selected patients, all of whom were asymptomatic for HIV disease, were tested serologically for HIV. 152/417 (36%) were HIV positive. HIV positive rates were highest in coma/convulsions 56%, infections 43%, stroke 43%, neuropathy 40%, and paraparesis 23%. In contrast rates were lowest in neurodegenerative disease 13%, tumours 13%, and neuromuscular disease and motor neurone disease 0%. The mortality rate was higher in HIV positives compared to HIV negatives (p < 0.04). The frequency of HIV infection increased from 1 in 1995 to 27 in the final 6 months of the study in 1992. During the final 6 months 102 consecutive neurological admissions were tested for HIV and 27/102 (26%) were HIV positive. This was significantly higher that the rates in corresponding blood donor’s 161/4687 (3.4%) p < 0.001. This study shows the main effects of the emerging HIV epidemic on neurological disorders in Northern Tanzania.

**079** TONIC GABA, RECEPTOR MEDIATED CURRENTS MODULATE CORTICAL EXCITABILITY

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Background: Action potential dependent release of GABA from presynaptic terminals gives rise to inhibitory postsynaptic currents (IPSCs). Another form of inhibition, described in granule cells of the rodent dentate gyrus, results from continuous activation of extrasynaptic GABA, receptors. We asked if such “tonic” inhibition exists in the hippocampus, and considered its role in regulating cortical excitability.

Method: We obtained voltage clamp recordings from interneurons and pyramidal cells in the CA1 subfield of acute guinea pig hippocampal slices. GABA, receptor mediated currents were isolated by applying glutamate and GABA, receptor blockers.

Results: The GABA, antagonist picrotoxin abolished spontaneous IPSCs (phasic inhibition) in both interneurons and pyramidal cells. It also reduced the steady state GABA, receptor mediated current (tonic inhibition) in interneurons but not in pyramidal cells. Tonic inhibition in interneurons was enhanced by zolpidem. Increasing the extracellular GABA concentration revealed a tonic current in pyramidal cells with a pharmacological spectrum identical to that seen in interneurons. Blocking the tonic current in interneurons with low concentrations of picrotoxin caused an increase in the frequency of spontaneous IPSCs (phasic inhibition) in pyramidal neurons.

Conclusions: Tonic GABA, receptor mediated inhibition in interneurons may contribute to homeostatic regulation of GABA release, by inhibiting interneurons when extracellular GABA is high,
PREVENTION OF SUDDEN UNEXPECTED DEATH IN EPILEPSY (SUDEP)

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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's, 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. Ten important 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.

PHARMACOKINETIC STUDY OF THE ANTISENSE OLIGONUCLEOTIDE EN101 IN PATIENTS WITH MYASTHENIA GRAVIS

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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 in their 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 reintroduced. 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.

A PHASE 1B SAFETY, EFFICACY, AND PHARMACOKINETIC STUDY OF THE ANTISENSE OLIGONUCLEOTIDE EN101 IN PATIENTS WITH INHERITED PRION DISEASE CAUSED BY OCTAPEPTIDE REPEAT INSERTION: GENETIC MODIFIERS AND HAPLOTYPE BACKGROUND IN LARGE UK AND SOUTH AFRICAN FAMILIES

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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. Subjects show that heterozygosity at polymorphic codon 129 accounts for 41.5% of the variance in age of onset by delaying disease onset by 10 years (p=0.0001) but has no effect on disease duration, suggesting different biological mechanisms determine these variables. Trials of prion disease therapeutic agents are being considered in those at risk.

EMAIL TRIAGE FOR NEW NEUROLOGICAL OUTPATIENT REFERRALS

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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 consultation, or investigations, or merely offering advice. In a 4 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% and 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

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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 outpatient 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

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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 307 820 people (152 932 aged below 15 years and 181 888 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 11 975 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 (7.9–9.5) 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 INFECTION EVOKE EXAGGERATED SICKNESS BEHAVIOUR IN MURINE PRION DISEASE

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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.