XXVIIth Meeting of the
Canadian Congress of Neurological Sciences
Winnipeg, June 1992
Scientific Program

Wednesday, June 24

Canadian Association for Child Neurology — Annual Meeting (08:30-17:00)

Cerebral Palsy

Introduction — Shashi Seshia (Winnipeg)
Intrapartum Issues
The Obstetrician and Cerebral Palsy — Christopher Harman (Winnipeg)
Neonatal Perspectives
The Neonatologist and Cerebral Palsy — Molly Seshia (Winnipeg)
Antecedents and Epidemiology of Cerebral Palsy — Karin Nelson (Bethesda)
Clinical Spectrum and Differential Diagnosis — Peter Humphreys (Ottawa)
Question Period — All morning speakers
Medical Treatment — Peter Rosenbaum (Hamilton)
Posterior Rhizotomy in Cerebral Palsy — Warwick J. Peacock (Los Angeles)
Question Period
Case Presentations
Summary — Karin Nelson (Bethesda)

Satellite Symposium: Spinal Instrumentation for Neurosurgeons (08:00-19:00)

Cervical Spine Instrumentation
Indications for Cervical Spine Instrumentation
Charles Tator (Toronto) Renn Holness (Halifax)
Practical Applications
Intra-oral Approaches — Alan Crockard (London, England)
Caspar Anterior Cervical System — Charles Tator (Toronto)
Synthes AO Anterior Cervical Plates — Marie Long (Calgary)
Halifax Interlaminar Clamps — Renn Holness (Halifax)
Posterior Cervical Plates — Michael Fehlings (New York)
Luqué Rods — Mahmood Fazl (Toronto)
Occipital Cervical Fixation — Michael Fehlings (New York)

Thoracic Spine Instrumentation
Indications for Thoracic Spine Instrumentation
Michael Fehlings (New York) Marie Long (Calgary)
Practical Applications
Postero-lateral Approaches — Dennis Maiman (Milwaukee)
Anterior Approaches
Michael Fehlings (New York) Marie Long (Calgary)
Transpedicular Approaches — Richard Perrin (Toronto)
Cotrel-Dubousset System — Michael Fehlings (New York)
Zielke Pedicular Screw Fixation — Michael Fehlings (New York)

Lumbar Spine Instrumentation
Indications for Lumbar Spine Instrumentation
George Sypert (Ft. Myers) Dennis Maiman (Milwaukee)
Practical Applications
Postero-lateral Approaches — Dennis Maiman (Milwaukee)
Anterior and Retroperitoneal Approaches — Michael Fehlings (New York)
Cotrel-Dubousset System — George Sypert (Ft. Myers)
Zielke Pedicular Screw Fixation — Michael Fehlings (New York)
Luqué Wires and Rectangles — George Sypert (Ft. Myers)

Satellite Symposium: Primary Generalized Epilepsy (17:00-19:30)

Primary Generalized Epilepsy: Syndromes or Biological Continuum — Fred Andermann (Montreal)
Treatment of Primary Generalized Epilepsy — Joseph Bruni (Toronto)
Mechanism of Action of Anti-epileptic Drugs — Jack Schneiderman (Toronto)
Side Effects and Toxicities of Antiepileptic Drugs and Quality of Life of Patients with Seizures — Alan Guberman (Ottawa)

Satellite Symposium: Cerebral Ischemia — A Clinical Dilemma (19:00-21:30)

The Surgical Treatment of Cerebral Aneurysms and AVM's — Charles Drake (London)
The Role of Free Radical Mechanisms in Ischemic Neuronal Injury — Ed Hall (Kalamazoo)
Excitatory Receptors and Ischemic Neuronal Injury — Alastair Buchan (Ottawa)
Calcium Channels and Ischemic Brain Injury — Antoine Hakim (Montreal)

Thursday, June 25

Morning

COURSE I: Current Neuroimaging Techniques

Essentials of MRI Scanning — Introduction — Blake McClarty (Winnipeg)
MRI of Pediatric Neurological Conditions — Derek Harwood-Nash (Toronto)
MRI Angiography — Gerhard Laub (Isilen)
MRI Spectroscopy — *in vivo* studies of cerebral ischemia
James Peeling (Winnipeg) Garnette Sutherland (Winnipeg)
Clinical MRI Spectroscopy — Douglas L. Arnold (Montreal)
SPECT Scanning — Masanori Ichise (Toronto)

COURSE II: Current Issues in Neuromuscular Disease

Role of Clinical Genetics in the Assessment of Neuromuscular Disease — Cheryl Greenberg (Winnipeg)
Update on Duchenne Muscular Dystrophy — Michael Brooke (Edmonton)
Clinical Approach to the Diagnosis and Management of Peripheral Neuropathies — Woon-Chee Yee (St. Louis)
Waveform Analysis in Nerve Conduction Studies: Facts, Fallacies and Fancies — Jun Kimura (Kyoto, Japan)
Muscle Fatigue and Myalgia — Michael Brooke (Edmonton)

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Afternoon

COURSE III: Controversies in Neurological Practice

Epilepsy: Management of First Seizure and Indications for Surgery — Warren Blume (London)
Stroke: Role of Anticoagulation in Acute Cerebral Ischemia — Vladimir Hachinski (London)
Multiple Sclerosis: Role of Steroids in Relapses — John Noseworthy (Rochester)
Migraine: Can We Diagnose It and Treat It? — Brian Anderson (Winnipeg)
Management of Low Grade Gliomas — Edward Laws (Washington, D.C.)

COURSE IV: Electrophysiological Studies in the Critical Care Unit

Introductory Remarks — Charles Bolton (London)
The Cerebral Hemispheres — Bryan Young (London)
The Brainstem and Spinal Cord — Jun Kimura (Kyoto, Japan)
Peripheral Nerve, Neuromuscular Junction and Muscle — Douglas Zochodne (Kingston)
The Respiratory System — Francois Grand'Maison (Sherbrooke)

COURSE V: Neurosurgical Conditions of Childhood

Craniofacial Surgery: How it Works — Bruce Hendrick (Toronto)
Prevention and Management of the Slit-Ventricle Syndrome — James Drake (Toronto)
Surgical Treatment of Epilepsy in Children — Warwick J. Peacock (Los Angeles)
A Panel Discussion: Management of Cerebral Palsy:
Medical Treatment — Paul Steinbok (Vancouver)
Therapeutic Electrical Stimulation — Karen Pape (Toronto)
Surgical Treatment — Warwick J. Peacock (Los Angeles)

Friday, June 26

Morning

Poster Session I — all day

Plenary Session I

Welcoming address — André Olivier (Montreal)
Opening of the Congress
Richardson Lecture
The Pathogenesis of the Alcohol Withdrawal Syndrome
Maurice Victor (White River Junction)
Penfield Lecture
Pediatric Neurosurgery in Canada — Infancy to Adolescence
Bruce Hendrick (Toronto)
Canadian Society of Clinical Neurophysiologists Lecture
Multifocal Motor Neuropathy with Persistent Conduction Block: Clinical, Physiological, and Histological Aspects
Jun Kimura (Kyoto, Japan)
President's Prize

Afternoon

Meet the Expert Lunch — Neurology
Maurice Victor and Lewis Rowland
Free Communications — General Neurology, Neurosurgery, Neuro-oncology, Cerebrovascular Disease, Pediatric Neurology

Saturday, June 27

Morning

Poster Session II — all day

Plenary II

Welcome address — Richard Riopelle (Kingston)
Canadian Association for Child Neurology Lecture
Current Advances in Pediatric Neuroradiology
Derek Harwood-Nash (Toronto)
Speaker of the Royal College of Physicians and Surgeons (Neurosurgery)
The Surgical Management of Craniopharyngioma
Edward Laws (Washington, D.C.)
Speaker of the Royal College of Physicians and Surgeons (Neurology)
The Immunology of Amyotrophic Lateral Sclerosis
Lewis P. Rowland (New York)
1992 K.G. McKenzie Memorial Prize
Special Lecture: Transoral Surgery for Midline Skull Base Tumours and Bony Anomalies
Alan Crockard (London, England)

Afternoon

Meet the Expert Lunch — Neurosurgery
Edward Lewis and Bruce Hendrick
Free Communications — Epilepsy, Cerebrovascular Disease, Neurobiology, Neurosurgery, Neuromuscular Disease, Neuroimaging

Sunday, June 28

Morning

President's Symposium: Controversial Aspects in the Medical and Surgical Treatment of Epilepsy
•who to treat •when to treat •how to treat
Panel Participants:
F. Andermann (Montreal) J. Bruni (Toronto)
A. Guberman (Ottawa) J. Girvin (London)
P. Gloor (Montreal) D. Keene (Ottawa)
A. Olivier (Montreal)

Afternoon

Satellite Course: Neurobiology Review Course (14:00-21:00)
The Spinal Cord — Modern Concepts of Function
Introduction — Brian Schmidt (Winnipeg)
Physiology of Relexes — David McCrae (Winnipeg)
Micturition — Susan Sefchuk (Winnipeg)
Modern Concepts of Motor Control — Larry Jordan (Winnipeg)
Molecular Biology
Introduction: Terminology and Techniques
Guy Rouleau (Montreal)
Genetic Predisposition: Prion Proteins
Peter St. George-Hyslop (Toronto)

(course continued on Monday, June 29)

Monday, June 29

Morning

Satellite Course: Neurobiology Review Course (08:00-12:00)

(Continued from Sunday, June 28)

Linkage Analysis in Neurologic Disease
Guy Rouleau (Montreal)
Genetics of Alzheimer Disease
Peter St. George-Hyslop (Toronto)
C. elegans — an Animal Model of Neural Degeneration
Genetics of Malignancy
Basic concepts; terminology — Guy Rouleau (Montreal)
Oncogenes, anti-oncogenes — Guy Rouleau (Montreal)
Glial tumours, neurofibramatosis — Guy Rouleau (Montreal)

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XXVIIth Meeting of the Canadian Congress of Neurological Sciences

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Platform Sessions
FRIDAY, JUNE 26, 1992 – P.M.

A. General Neurology

1.

Quantitative Behavioral Differences Between Alzheimer's and Vascular Dementia

A. KERTESZ and S. CLYDESDALE (London, Ontario)

Considerable controversy exists concerning differentiation of Alzheimer's disease (AD) and vascular dementia (VD). Careful selection of AD and VD subjects, matched for age, education, age at onset, duration of illness and degree of dementia, is combined with comprehensive neuropsychological testing, in an effort to distinguish these dementias.

Methods: Patients were screened with neurological and behavioral examination, which included the Mattis Dementia Rating Scale (MDRS), a modified Ischemic Score, detailed memory (WMS-R), intelligence (WAIS-R), and language tests (WAB).

Results: Comparisons with all subtests indicated significantly worse VD (n = 25) performance on Motor Performance, Picture Arrangement, Object Assembly and Writing subtests, and worse AD (n = 75) performance in sentence Repetition. When the data of severely demented patients were analyzed separately, discriminant function analysis (DFA) correctly classified 81% of AD and 88% of VD patients, employing Motor Performance, Writing and Drawing subtests, all performed significantly better by the AD group. In mildly demented patients, DFA predicted 78% of AD and 90% of MID membership using Digit Span and Construction tasks. Digit span was preserved in AD patients, but they were worse on the construction tasks.

Conclusion: Tests demanding motor activity consistently discriminate AD from VD. In early dementia, the differences are less obvious but construction tasks are more difficult for AD patients. These differences support a subcortical-cortical dichotomy between VD and AD.

2.

Olfactory Dysfunction in Alzheimer's Disease

S. COHEN, T. SHERRI and M. FREEDMAN (Toronto, Ontario)

Olfactory impairment has been shown to be an early sign of Alzheimer's disease. Olfactory discrimination, in particular, may decline early in the disease at a time when olfactory thresholds are still intact. Although this suggests a central rather than peripheral olfactory disorder, the nature of the olfactory discrimination disturbance has not been adequately explored. Furthermore, reports as to whether smell discrimination continues to decline throughout the disease and whether this correlates with degree of cognitive impairment are contradictory.

In this study, 14 of a proposed 50 patients with mild to moderate probable Alzheimer's disease (NINCDS-ADRDA criteria) have been tested to date and were given the University of Pennsylvania Smell Identification Test (UPSIT) plus a series of neuropsychological tests including those of attention, memory, language, mood and behaviour. The patients with Alzheimer's disease were significantly impaired relative to controls on the

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UPSIT ($p < .00001$) using a binomial test of proportions. Furthermore, olfactory discrimination scores were significantly correlated with performance on the Mini Mental State Examination ($r = .68$), Word List Generation ($r = .62$), Digit Symbol Test ($r = .72$) and Relative's Assessment of Global Symptomatology - Elderly (RAGS-E) ($r = .62$). On early analysis, the tests with the greatest predictive value were the Bushke Selective Reminding Test and the RAGS-E, each explaining approximately 30% of variation in the UPSIT scores. For female patients, additional correlations were found with the Global Deterioration Scale ($r = .97$) and verbal fluency using categories ($r = .97$). The results suggest that there is not only a striking deficit in olfactory discrimination in Alzheimer's disease but that the mechanisms underlying these deficits may be selectively dependent upon a breakdown in specific cognitive functions.

3.

The Type of TIA Does Not Predict the Degree of Carotid Stenosis

R. MAZAGRI, M. HRAPCHAK, F. DENATH, C. WALLACE and A. SHUAIB (Saskatoon, Saskatchewan)

In patients with transient ischemic attacks (TIAs) investigations for a potential carotid source may frequently be normal. There is some suggestion in the literature that the type of TIA may predict the degree of carotid narrowing. In patients with symptoms suggestive of a cortical TIA, investigations may show more than 50% stenosis of the carotid artery in up to 67% of patients. On the other hand, patients with presumed lacunar TIAs may have carotid narrowing in approximately 6% of patients (Lancet 1991; 337: 335-338). To test whether the concept of cortical versus lacunar TIAs is predictive of the degree of carotid narrowing, we looked at 71 patients prospectively enrolled in our stroke registry. All patients had carotid transient ischemic attacks, all had carotid ultrasounds, and where indicated, four vessel angiography was also done. Cortical TIAs were considered when speech difficulty was present in addition to motor or sensory symptoms or it the patient presented with amaurosis fugax. We considered the site to be "lacunar" if the patient had pure motor or sensory symptoms. The patients were divided into 2 groups based on the symptoms with 41 patients with presumed cortical TIAs and 28 patients with presumed lacunar TIAs. Doppler ultrasound or angiography was abnormal, suggesting over 50% stenosis, in 20 of 41 patients with lacunar symptoms. The difference between the two groups was not significant.

Our data suggests that the concept of cortical versus lacunar TIAs is not very useful. All patients with TIAs should have assessment for carotid stenosis.

4.

Incidence of Injuries Caused By Seizures

S. KIRBY and R.M. SADLER (Halifax, Nova Scotia)

There is little information in the literature regarding the incidence of injuries resulting from seizures.

We surveyed all patient visits to the four emergency departments serving adults (16+ years) in Halifax County, Nova Scotia (adult population 254,900) for the year Sept. 1, 1990 - Aug. 31, 1991 for patients presenting with possible seizures. The Medical Examiner's reports were also surveyed. We identified 599 patient visits precipitated by seizures of all types and etiologies. Seizures secondary to acute trauma were excluded. Data collection included age, sex, seizure type (when possible), first or recurrent seizure, antiepileptic drugs, drug levels, possible precipitants, treatment and types of injury (except tongue biting).

Injuries or death were identified in 83 of 559 visits (14.8%). Some seizures resulted in more than one injury so that 95 separate injuries were seen in total. The most common types of injuries were head contusions in 41/83 visits (49%), head lacerations 23/83 (27.7%), and fractures 8/83 (9.6%). There were six deaths. Seven patients had multiple visits with injuries. In 33.7% of the visits no treatment was required. The most common predisposing factors for seizures were a past history of epilepsy, alcohol abuse and noncompliance with medication.

We conclude that the incidence of injury as a result of seizures in patients that present to an emergency department was 14.8%. Most injuries were not serious and often did not require treatment. However, death was the outcome for six patients indicating that seizures remain a life threatening event.

A review of the literature and further details will be presented.

5.

Neurological Sequelae of Electrical Injury

D.N. BLACK, T. BOTEZ and L. BÉRUBÉ (Montreal, Quebec)

The literature contains only sporadic references to the effects of electrical injury on the nervous system. Pain and paralysis are often cited. Behavioural and cognitive disturbances are rarely recognized and are often attributed to hysteria, malingering or neurosis. In our recent experience with 8 patients, of whom 7 suffered shocks of 120 to 69,000 volts (+ 1 lightning injury), we recognize a syndrome of extreme fatigue, psychomotor slowing, disturbed memory and concentration, causalgic pain, and subjective numbness and weakness. Each of these features may be variably present. The syndrome can occur without burns, head injury, or loss of consciousness. Characteristically, patients' complaints are not matched by abnormalities on formal examination. There are no consistent abnormalities of EEG, CT and SPECT scan, EMG, or evoked potentials. 6/8 patients who had neuropsychological evaluation had abnormal visual and auditory memory and attention, visuoperceptual disorganization, and frontal type deficits; 3/4 had abnormal reaction times. These findings suggest an organic, possibly subcortical, basis for the syndrome. The pathogenesis is unknown. Modulation of neurotransmitter systems is of theoretical and therapeutic interest. In the absence of definable radiological or electrophysiological abnormalities, patients' complaints should be given prime consideration by clinicians. All patients should undergo neuropsychological testing and reaction time studies after serious electrical injury.

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6.

Neurological Illness Among Native North American Indians

D.N. BLACK (Montreal, Quebec)

A wide range of neurological diseases occurs among native North American Indians. Particular genetic, cultural and social factors influence the spectrum of diseases relative to Caucasian North Americans. Although geographic isolation and fragmented record-keeping make global estimates of prevalence difficult, neurological trauma, infections (bacterial meningitis, otitis), toxins (glue, gasoline, alcohol, mercury). and neurological complications of diabetes are prevalent. Certain genetic diseases such as Cree encephalitis and leukoencephalopathy, mutilating Navajo neuropathy and leukoencephalopathy are confined to North American Indians. Others are clustered among them; e.g., glutaric aciduria, familial chronic acidosis, Vogt-Koyanagi-Harada syndrome, thyrotoxic periodic paralysis, oculo-cerebral-renal syndrome of Lowe, and phenylketonuria. Trauma is a leading cause of death. A "fetal gasoline syndrome" has been described. Changing dietary habits and hypertension may be linked to the higher incidence of stroke relative to Caucasians. Cultural patterns influence complaints of pain and pain localization. The choice of words to describe symptoms may conceal other problems. Psychotic behaviour, including hallucinations, may be culture-specific. Neurologists practising in native communities should be sensitive to these issues.

7.

Folate Supplementation and Blood Folate Levels in Pregnant Epileptic Patients Taking Anti-Epileptic Drugs: Correlation With Outcome of Pregnancy

E. ANDERMANN, I. LOPES-CENDES, L. DANSKY, M. OGUNI, F. CENDES, E.L. SIAVALAS and F. ANDERMANN (Montreal, Quebec; Tokyo, Japan)

The decrease in blood folate levels due to anti-epileptic drugs (AEDs) has been described. It is well known that folate is essential for the cellular replication, specially during embryogenesis. Therefore, low folate levels, particularly in the first trimester, increase the risk of developmental embryonic malformations.

In order to analyze the influence of blood folate levels and of low dosage folate supplementation on the outcome of pregnancy in offspring of treated epileptic women, we studied 161 pregnancies prospectively, (mean maternal age 27 Years).

Serum folate (SF) and Red blood cell folate (RBCF) were monitored monthly throughout pregnancy, and intake of multivitamin preparations with low folate content (less than 3 mg) was recorded.

We divided the patients into 4 major groups according to the pregnancy outcome: (1) normal children (n = 122), (2) postural defects (n = 10), (3) developmental defects (n = 8) and (4) spontaneous abortion (SA) (n = 11) (Dansky, 1989).

Fifty-two percent of mothers in group (1), 30% in group (2), 12.5% in group (3) and 27% in group (4) took folate supplements in the first trimester. This number increased significantly for all groups in the second and third trimester, with no statistical difference among them. The mean SF and RBCF levels were found to increase from the first to the third trimesters, but overall there was no statistical difference among the 3 groups. However, when we analyzed the number of patients with folate level below the normal range (SF < 4.0ng/ml and RBCF < 175.0ng/ml), we found abnormal SF: 16% in group (1), 0% in group (2), 57.2% in group (3) and 20% in group (4) for the first trimester ($p < 0.05$). Similar differences were recorded for RBCF. The same trend was seen in the second trimester, but not in the third. Supplementation with multivitamins containing small doses of folate resulted in a normal or above normal SF and RBCF.

In conclusion, lack of folate supplementation in the first trimester and abnormal SF and RBCF levels were most frequent in women with the worst pregnancy outcomes (SA and DD). Thus multivitamin supplementation containing small doses of folate should be administered as soon as possible during pregnancy and preferably before pregnancy, to decrease the risk of these abnormal outcomes.

8.

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) in Diabetics

R. McKELVEY, L. DURCAN, J. STEWART, G. KARPATI and S. CARPENTER (Montreal, Quebec)

Diabetics can develop a variety of peripheral neuropathies. We report eight diabetic patients with features of chronic inflammatory demyelinating peripheral neuropathy (CIDP). This has been reported once before.[1]

Five of the patients required insulin for control. Two others had mild diabetes diagnosed *after* the onset of neuropathy. All patients developed a motor greater than sensory neuropathy, involving the legs more than arms, evolving over two months to five years, and causing major disability.

Electrophysiological tests showed combinations of demyelinative and axonal changes. CSF protein levels were high, above one gram per litre in seven cases. Nerve biopsies done in seven of the patients showed demyelination and remyelination, as well as some axonal changes. Inflammatory changes were present in one.

In seven patients treatment was instituted with varying combinations of corticosteroids, plasmapheresis, and azathioprine. Six patients had some improvement during their treatment, one regaining the ability to walk.

This report shows that diabetic patients can develop CIDP, and that recognizing this is important because this is a treatable peripheral neuropathy.

[1]Cornblath, DR, Drachman, DB, Griffin, JW. Demyelinating motor neuropathy in patients with diabetic polyneuropathy. Ann of Neurol 22: 1987, 126.

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9.

Post Stroke Seizures

A. ALEXANDROV, J.W. NORRIS and the SEIZURES AFTER STROKE GROUP (CANADA, ISRAEL, AUSTRALIA, ITALY) (Toronto, Ontario)

The cause and effect of seizures on stroke remains unclear, partly because they are infrequent and no single centre accumulates enough cases for meaningful analysis. Therefore, we are pooling data prospectively amongst 11 university hospitals for 2000 patients.

So far, we have entered 366 consecutive stroke patients. 16 (4%) had previous seizures, and 33 (9%) of the remaining 350 had new seizures. 13% (6/45) of patients had seizures in the cerebral hemorrhage group, and 9% (27/305) in the infarct group (N.S.). No seizures occurred in brain-stem strokes. 58% of seizures occurred on the first day. Cortical lesions produced more seizures than subcortical ($p < 0.02$). Size of lesion measured on CT made no difference (52 cm^3 in seizure group vs 31 cm^3 in non-seizure group, N.S.). Embolic strokes were not more likely to have seizures. Seizure patients fared worse than non-seizure patients.

Most seizures due to stroke occur in the immediate post-stroke period. Pathology and site of lesion are important causes of seizures which may secondarily affect prognosis.

10.

Etiology of Parkinson's Disease: A Test of the Multifactorial Hypothesis

K.M. SEMCHUK, E.J. LOVE and R.G. LEE (Saskatoon, Saskatchewan; Calgary, Alberta)

This population based case-control study of Parkinson's disease was conducted in the city of Calgary in 1989 to determine the relative etiologic importance of occupational exposure to herbicides and other compounds, exposure to ionizing radiation, genetic factors, smoking history, and history of various common viral and other health conditions.,

Cases (n = 130) with neurologist-confirmed idiopathic Parkinson's disease were identified through contacts with the 5 general hospitals, 24 long-term care facilities, 16 neurologists, the Movement Disorder Clinic, and the Parkinson's Society. Two matched (by sex and age ± 2.5 years) community controls were selected for each case by random digit dialing. We obtained lifetime occupational histories (including information on work-related chemical exposures), health and smoking histories, and family history of Parkinson's disease and essential tremor, by personal interview, and analyzed the data using conditional logistic regression for matched sets.

In the univariate analysis, family history of Parkinson's disease, head trauma, previous herbicide use, and family history of essential tremor were associated with an increased Parkinson's disease risk, while history of smoking resulted in significantly decreased risk. Cases and controls did not differ in their previous occupational contact with aluminum, carbon monoxide, cyanide, manganese, mercury, or mineral oils; exposure to ionizing radiation; or history of arteriosclerosis, chicken pox, encephalitis, hypertension, hypotension, measles, mumps, rubella, or spanish flu.

In the multivariate analysis, which controlled for potential confounding or interaction between the exposure variables, family history of Parkinson's disease was the strongest predictor of Parkinson's disease risk (OR = 5.07, $p < 0.001$), followed by head trauma (OR = 4.01, $p < 0.001$), and previous herbicide use (OR = 2.83, $p = 0.026$). History of smoking and family history of essential tremor did not achieve statistical significance.

These data support the multifactorial hypothesis that Parkinson's disease results from the combined effect of genetic and environmental factors, and concur with previous reports of parkinsonism amongst herbicide-exposed workers.

11.

The Significance of Epileptiform Activity in Comatose Adults in the General Intensive Care Unit (ICU)

G.B. YOUNG, J. DEMELO, J. KREEFT and R. McLACHLAN (London, Ontario)

We reviewed 306 consecutive comatose adults in the ICU who had electroencephalograms (EEGs). Of these, 23 (7.5%) had EEG epileptiform activity, excluding those with burst-suppression patterns. There were 14 men and 9 women from 24-86 years of age. Only 3 (13%) had clinical seizures or myoclonus.

Twelve patients had anoxic-ischemic encephalopathy. Brainstem reflexes were all present in 7, partially present in 3 and all absent in 2. The 11 with generalized epileptiform activity all died in coma, while 1 with focal spikes survived.

Six patients had septic-metabolic encephalopathy. All had intact brainstem reflexes, 2 of 3 with generalized epileptiform activity and 1 of 3 with focal spikes died in coma.

One of each had the following: herpes simplex encephalitis, bacterial endocarditis, trauma, thrombotic thrombocytopenic purpura and vertebrobasilar stroke. All had focal spikes and all but the latter patient survived.

EEGs are valuable in the assessment of comatose ICU patients as a significant number have epileptiform activity without clinical seizures; this could alter management. Further, prognosis is dependent on EEG classification and etiology.

B. Neurosurgery

12.

Activation-PET Scanning for the Assessment of Cerebral Arteriovenous Malformations

R. LEBLANC, E. MEYER, R. ZATORRE, D. BUB and A. EVANS (Montreal, Quebec)

Background: A major determinant in the successful treatment of cerebral arteriovenous malformations (AVMs) is their proximity and relationship to eloquent cortex. We report our

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ongoing assessment of activation-PET scanning in establishing this relationship and in helping to choose treatment modalities.

Patients and Methods: Five patients with an AVM localized by computed tomography (CT), magnetic resonance imaging (MRI) and angiography to the central region (2 cases) and to a putative speech area (3 cases) underwent activation-PET scanning during vibrotactile stimulation and reading and speaking of simple words. Areas of significant peak activation ($p < 0.05$ compared to baseline PET scans) resulting from the sensory stimulation or from the language tasks were superposed on the corresponding MRIs, and the x, y, and z coordinates of peak activity were localized using a stereotactic atlas. Results of activation-PET scanning were confirmed by Amytal testing and operative findings.

Results: Analysis of the superposed activation-PET scans and the MRI demonstrating the AVM following vibrotactile stimulation localized the AVMs to the pre- and post-central face and hand region in one case each; and language tasks activated areas 44 and 45 (Broca's area) and 21 (Wernicke's area) establishing the relationship of the AVMs to these speech regions. Based on these analyses patients were treated by surgery, embolization, and stereotactic radiosurgery, or not treated.

Conclusions: Activation-PET scanning is useful for deciding which treatment to use for AVMs in eloquent brain regions especially in putative language areas which can be quite variable in AVM patients.

13.

Pre-Operative Embolization of Brain and Spinal Hemangioblastomas

D. TAMPIERI, R. LEBLANC and K. TERBRUGGE (Montreal, Quebec; Toronto, Ontario)

Background: Large hemangioblastomas can be difficult to resect because of excessive bleeding. We report our experience with 2 patients whose large hemangioblastomas were embolized pre-operatively and totally resected with minimal blood loss and satisfactory post-operative outcome.

Patients and Methods: Embolizations were carried out within 3 days of surgery, under general anaesthesia, using 150-250 μCoutour emboli. A 65-year-old woman with progressive, severe myelopathy from a 4 × 2 cm intramedullary hemangioblastoma at T4 underwent embolization of the left T2 and T3 intercostal arteries; and a 29-year-old man with Lindau's syndrome and posterior fossa hemorrhage from a 3.2 × 1.5 × 1.5 cm right cerebellar hemangioblastoma underwent embolization of the right PICA, 2 right AICAs and a dural branch of the right vertebral artery.

Results: Embolization led to the complete obliteration of the tumoural blush without neurological sequelae. Both lesions were completely resected with a blood loss of 100 to 150 cc, bleeding occurring mainly from the pseudocapsule of the lesion. A new medullary syndrome resulted in the second patient.

Conclusions: Pre-operative embolization of hemangioblastomas is a relatively useful and safe procedure that reduces blood loss at surgery and allows complete resection.

14.

Radiosurgical Treatment of Angiographically Occult Vascular Malformations

A.F. SADIKOT, A. OLIVIER, G. BERTRAND, L. SOUHAMI and E. PODGORSAK (Montreal, Quebec)

Focal stereotactic radiosurgery is now a well-accepted part of the neurosurgical armamentarium for the treatment of surgically inaccessible arteriovenous malformations. Initially in our program of radiosurgery for vascular malformations, we treated 10 patients with angiographically occult vascular malformations involving the brainstem using a linear accelerator based dynamic stereotactic radiosurgical unit. The dose planning was done on the basis of magnetic resonance imaging and computed axial tomography, lesion sizes varying from 7 to 22 mm (mean 14.1 mm) in maximum diameter. Presenting symptoms were related to hemorrage in 7 patients and to mass effect in 3 patients. Treatment doses ranged from 2250cGy to 5500cGy (mean 2195cGy), prescribed at the 90th percentile isodose surface, with collimator sizes ranging from 5 to 15 mm (mean 8 mm). Follow-up time ranged between 11 and 33 months (mean 25.4 months). 2 lesions decreased in size on follow-up MRI whereas 8 did not show a change. 6 patients are symptomatically better whereas 3 showed no improvement. One patient, who had a malformation involving the lenticular nucleus, had delayed transient oedema surrounding the lesion at 18 months post-radiosurgery. The same patient had an episode of bleeding occurring at 33 months after radiosurgery resulting in death. Autopsy examination revealed evidence of a cavernous angioma with extensive histologic changes compatible with radiation effect. Longer follow-up periods and multi-centre trials should help better define the role of radiosurgery in the treatment of cavernous angiomas. In the interim surgery should be considered the first line treatment for cavernous angiomas of the brainstem that have bled. Radiosurgery may be reserved for treatment of surgically inaccessible lesions or for patients who are considered a poor surgical risk.

15.

Stereotactic Radiosurgery for Cerebral Arteriovenous Malformations With a Linear Accelerator

A.F. SADIKOT, A. OLIVIER, G. BERTRAND, R. LEBLANC, L. SOUHAMI and E. PODGORSAK (Montreal, Quebec)

The overwhelming majority of experience with radiosurgery for arteriovenous malformations has been obtained with the cobalt-60 gamma unit or heavy particle sources. The accessibility of linear accelerators has lead to their widespread use in radiosurgery of arteriovenous malformations but there are few reports of long-term results. Between April 1986 and December 1988, 36 patients with arteriovenous malformations had stereotactic radiosurgery at McGill University, of which 28 were treated with a single fraction dynamic rotation technique using a 10MV linear accelerator. Twenty-seven of these cases have had angio-

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graphic and clinical follow-up at two years. The AVM niduses varied in maximum diameter from 0.8 cm to 5 cm (mean 2.1 cm), and in volume from 0.2 cm^3 to 65 cm^3 (mean 6.9^3). The dose prescribed at the center of the nidus varied from 40 Gray (Gy) to 56 Gy (mean 51 Gy). At two years, 11 AVMs (41%) were completely obliterated, 7 (26%) had 50-99% obliteration and 9 (33%) had 0-49% obliteration. Angiography at three years on 5 of 16 patients with incomplete obliteration at two years, has shown complete obliteration in 4 cases. Analysis of possible factors determining success of treatment revealed that the size of the nidus and the dose delivered to its margin are the most significant factors in determining success of treatment ($p < 0.005$, Chi square). The complete obliteration rate of AVMs ≤ 3 cm and receiving a marginal dose ≥ 25 Gy was 64% at two years and at least 86% at three years. Two complications occurred among the 27 patients during the clinical follow-up period, one from rebleeding and the other from delayed edema. We conclude that dynamic stereotactic radiosurgery is a safe and effective method for the treatment of AVMs with a high surgical risk. As is the case with other methods used for radiosurgery, size and treatment dose are important factors related to successful treatment.

16.

Brain Arteriovenous Malformations (AVMs) Treated With Radiosurgery

M.L. SCHWARTZ, C.S. YOUNG and P.F. O'BRIEN (Toronto, Ontario)

After radiosurgical treatment, AVMs undergo a progressive obliterative process cluminating in the disappearance of most AVMs by two years. Accordingly, we obtain follow-up MRI scans at one year and cerebral angiography at two years. Thirty patients have now undergone treatment for AVMs ranging in size from 0.7 cm in diameter to 3 cm, and including one exceptional elongated lesion measuring 5 cm in its longest diameter. Radiosurgery was the unique treatment in 12 patients. Radiosurgery followed embolization in 13 patients and surgery in two patients. In three patients, embolization and surgery preceded radiation. Early morbidity has been limited to a 48 hour period of dysphasia starting 6 hours after treatment in one patient with a left angular gyrus AVM and to increased frequency of epileptic seizures in one patient with a right frontal lesion. So far, two patients are proven cured by angiography. In one case, the arteriovenous malformation has disappeared but there is still an early filling vein. By June, 1992, 7 patients will be available for two year follow-up and an additional 14 cases will be one year post-treatment. Their results will be presented.

17.

Teaching Neurosurgical Residents Aneurysm Surgery: Retrospective Review of 97 Resident Operated Cases

M.C. WALLACE and M. BERNSTEIN (Toronto, Ontario)

The repair of an intracranial aneurysm remains a significant technical challenge in neurosurgery and a formidable teaching responsibility in postgraduate neurosurgical training programmes. This report is a retrospective review of intracranial aneurysms treated surgically at The Toronto Hospital by two surgeons between July 1988 and December 1991. Surgery was supervised by one of two surgeons (MCW, MB) but the dissection and clipping was performed by the resident or fellow.

The series includes 97 aneurysm procedures in 94 patients. Twenty-one posterior circulation aneurysms of one author (MCW) are excluded. Eighty-two patients had bled previously while 15 unruptured aneurysms were repaired. Giant aneurysms were present in 8 cases. The distribution included aneurysms of the anterior communicating artery (28), posterior communicating artery (27), middle cerebral artery (23), carotid artery (9), pericallosal artery (3) or the vertebral or posterior cerebellar artery (7). Clinical grade at presentation: 0 (n = 15), 1 (n = 39), 2 (n = 9), 3 (n = 18), 4 (n = 10), 5 (n = 6). Outcome for the entire series was 61 excellent (63%), 16 good (17%), 5 poor (5%), 1 vegetative (1%), and 14 dead (14%).

In 95 cases, dissection and clipping of the aneurysm was performed by the fellow (8), senior resident (83), or the junior resident (4). In 2 cases the staff surgeon completed the clipping.

Morbidity and mortality was reviewed. Poor outcome or death (n = 20) occurred in 5 grade 1 patients and 1 grade 0 patient. In only 2 cases did the staff surgeons feel that the outcome grade was a result of the responsibility delegated to the resident or fellow. The good or excellent outcome in 80% of patients with all clinical grades of presentation is comparable to other surgical series. Anterior communicating artery aneurysms proved to be the most difficult in this residents' series, with 7 poor or dead results (25%). Poor or dead outcomes with posterior communicating or middle cerebral artery aneurysms were all but two in poor grade patients.

This review supports the concept that intracranial aneurysm surgery can be taught effectively and safely with significant surgical responsibility delegated to the trainee. Caution must be exercised with ruptured anterior communicating artery aneurysms, as morbidity and mortality was elevated in this group. A careful balance between teaching and clinical care responsibility must be maintained, producing a mixture of high quality care and well trained neurosurgeons.

18.

Aneurysmal Surgery Between the 4th and 10th Day After Subarachnoid Hemorrhage

M.W. BOJANOWSKI, M.C. PARE and R.A. MOUMDJIAN (Montreal, Quebec)

Recent studies have suggested that surgery between the 4th and 10th day after subarachnoid hemorrhage (SAH) following intracranial aneurysm rupture might be associated with higher morbidity and mortality rates. Although not proven, increased brain susceptibility to ischemic damage is the main reason evoked to explain these poorer results.

In order to assess these observations, we have retrospectively reviewed a consecutive series of 120 patients treated surgically for ruptured aneurysms between August 1987 and December 1991. In this population, 25 patients were operated between the 4th and 10th day (intermediate group) after the SAH. The latter

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was compared to other patients operated on early (1-3 day post SAH: 85 patients), or late (>10 days: 10 patients) in terms of the incidence of clinical complications and outcome.

Late referral was the main reason for the delay of surgery. All patients, including those in advanced clinical grades, were operated within 48 hours after admission if they were medically stable. Volume expansion was maintained for at least 10 days or until there was no evidence of clinical vasospasm. Calcium channel blockers were used in all patients.

In this series, 80% of patients in the intermediate group were in good clinical grade prior to surgery. Twenty (20%) of patients had evidence of radiological vasospasm at the time of surgery.

We found no significant difference in the incidence of radiological vasospasm nor delayed ischemic damage in the intermediate group compared to those patients operated earlier. There was also no significant difference in the long term outcome regardless of either the timing of surgery or the clinical grade.

Our results suggest that with our actual medical and surgical management, there is no evidence to delay surgery in those patients based on the time interval between SAH and patient evaluation.

19.

Role of Angiography Following Aneurysm Surgery

R.L. MacDONALD and M.C. WALLACE (Toronto, Ontario)

A policy of routine postoperative angiography was instituted in a consecutive series of 88 patients with ruptured or symptomatic cerebral aneurysms. This study reviews the postoperative angiograms to determine how often unexpected vessel occlusions or incomplete aneurysm clippings occurred and how often results of postoperative angiography altered patient management.

Ninety-two aneurysms were clipped in 90 separate operations (70 anterior and 22 posterior circulation aneurysms). Postoperative angiography was obtained in all but 10 cases. Exceptions were due to early patient death (6 cases), poor patient condition (3 cases), and patient refusal (1 case). No complications were attributed to postoperative angiography. At surgery, residual aneurysm was thought to be left in 3 cases and this was confirmed angiographically, altering patient care in that further angiographic followup will be necessary in these cases. Unsuspected vessel occlusions or incomplete aneurysm clippings were documented in 7 cases, prompting reoperation in 3 cases. These reoperations were to remove a clip from a middle cerebral artery branch, to clip a second aneurysm at the anterior communicating artery complex which was not recognized at the first surgery for clipping of an aneurysm at that location, and to replace a slipped clip on a giant carotid-ophthalmic aneurysm.

We conclude that routine postoperative angiography shows that unsuspected vessel occlusions and incomplete aneurysm clippings are not uncommon. In about half the cases where such findings were documented, patient management will be altered. This appears to be particularly common following surgery for giant aneurysms arising from the internal carotid artery.

20.

The North American Symptomatic Carotid Endarterectomy Trial (NASCET): Surgical Results

G.G. FERGUSON (FOR THE NASCET COLLABORATORS) (London, Ontario)

The initial results from NASCET provide incontrovertible evidence that carotid endarterectomy is highly effective in reducing the risk of future ipsilateral stroke in symptomatic patients with a linear stenosis of 70% or greater (NEJM 325: 445-453, 1991). The purpose of this report is to present the details of the surgical results in the 328 patients with high grade stenosis randomized to surgery.

The 30 day perioperative death rate was 0.6% and the major stroke rate was 2.1% (7/328). By 90 days, the time used for the assessment of a stroke as major or minor in the final analysis of results, 2 major perioperative strokes had become minor, giving a combined death and major stroke rate for the surgical group of 2.1%, the comparable rate at 90 days in the medical group being 1.2%. Of the 2 deaths, one was sudden, presumably cardiac in origin, while the other was the result of cerebral infarction complicating acute occlusion at the endarterectomy site. Of the 7 major strokes, 3 resulted from acute occlusion, 2 from delayed intracerebral hemorrhage, 1 from a presumed intraoperative embolus, and 1 from a delayed VB stroke at 26 days. Two of the 4 cases of acute occlusion were likely the result of intimal dissection from shunt insertion. None of the major perioperative events could be related to hemodynamic intolerance to carotid cross-clamping. The minor perioperative stroke rate was 3.7% (12/328) giving an overall rate of perioperative stroke and death of 5.8%. There were no other disabling perioperative complications.

The value of carotid endarterectomy in high grade symptomatic stenosis is proven. Technical failure is the leading cause of major perioperative events, the elimination of which is the challenge for cerebrovascular surgeons in the future.

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21.

Carotid Microendarterectomy

J.M. FINDLAY (Edmonton, Alberta)

The operating microscope has been used to improve the technical performance of carotid endarterectomy and thereby minimize operative stroke risk. The magnification and improved illumination of the operating microscope allow for more complete removal of small, loosely adherent plaque remnants following gross plaque removal, for more precise plaque separation and arterial repair at the distal end of the internal carotid endarterectomy, and for a finer, nonstenosing arteriotomy closure.

This technique was employed in a series of 35 symptomatic patients (TIA, 16; minor stroke, 15; amaurosis fugax, 4), all but

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5 of whom had carotid stenoses 70% or greater, and 14 of whom were preoperatively assessed as Sundt grades II or higher in terms of operative risk. Intraoperative shunts were used in 3 patients with contralateral carotid occlusions, vein patches were inserted in 3 and distal intimal tack-down sutures were used in 12. In this series there were no deaths and only one postoperative stroke, occurring 12 hours after surgery and found to be due to occlusion at the operative site. Although no structural cause for the occlusion was found at exploration, vein-patch angioplasty restored blood flow and the patient made a complete recovery. In this and all other patients restoration of normal postoperative carotid patency has been confirmed (angiography in 4 and carotid Doppler examination in 31). The microsurgical approach to carotid endarterectomy will be described in detail.

Carotid endarterectomy has optimum efficacy when administered with maximum safety. While perioperative stroke risk is dependent upon many factors, we feel that the technical refinements afforded by the operating microscope help reduce this risk to a minimum.

22.

Dural Arteriovenous Fistulas of the Cribriform Area

R.O. HOLNESS and S.E. BRIEN (Halifax, Nova Scotia)

Two patients are presented with arteriovenous fistulas of the cribriform area fed by branches of the ethmoidal arteries. One patient presented with proptosis and orbital pain which were reversed by coagulation of the fistula via an anterior craniotomy. The second patient had presented seven years previously with a dominant intracerebral frontal hematoma and the fistula was suggested by a follow-up MRI scan and subsequent angiogram. This patient was also cured by coagulation at the fistula site. These lesions are rare but are significant in that they may present with intracerebral hemorrhage which usually occurs from the venous drainage which takes place by way of pial veins into the superior sagittal sinus. Ninety-one percent of 33 cases of this entity reported up until 1990, presented with hemorrhage. As surgery for this entity is straight forward and usually curative, it is advocated as the treatment method of choice. The diagnosis of these lesions depends on the clinician having a high index of suspicion and, as illustrated by case 2, can only be made with certainty utilizing angiographic subtraction techniques.

C. Neuro-Oncology

23.

Childhood Brain Tumours Presenting as Seizure Disorders: Results of Simple Tumour Excision

R. MUNN, D. COCHRANE, P. STEINBOK and K. FARRELL (Vancouver, British Columbia)

The purpose of this study was to review the clinical features, pathologic findings, and seizure control following excision in children with supratentorial neoplasms who presented with seizures.

Between April 1983 and September 1991 twenty-eight children (14 girls) presented with seizures as a manifestation of brain tumours. 13 tumours were temporal in location and 15 were extratemporal. Simple tumour excision without formal cortical resection was performed in all patients. Pathology revealed ganglioglioma in 16 (4 associated with cortical dysplasia), low grade astrocytoma in 9 and malignant tumours in 3.

The average age of the first seizure was 5.8 years (3 months-16.3 years) and the average duration of seizures prior to operation was 3.7 years (1 week-14.7 years). Partial onset seizures, with and without generalization, occurred in 22 patients and 6 patients had generalized seizures only. Five children had partial motor seizures that clinically localized to the involved hemisphere prior to operation. Three children presented with a single seizure, 11 had multiple daily seizures, 6 had multiple weekly and the remaining had monthly seizures. Preoperative EEGs were abnormal in 15 of 16 patients studied. Nine of these patients had focal abnormalities that localized to the site of the lesion.

Average duration of followup was 20.9 months (2-96 months). 19 patients were seizure free and 1 reported the occasional aura. One patient died and the remaining 7 patients reported seizures (2 had single provoked seizures, 4 had a greater than 50% reduction in seizure frequency and one was unchanged). Nineteen patients remain on anticonvulsants.

This study suggests that most tumours presenting with seizures in childhood are benign and that the outcome after simple tumour excision is favorable. Longer followup is required to analyze whether seizure free children can be weaned from their anticonvulsants post tumour excision.

24.

Optic Pathway/Hypothalamic Gliomas: A Continuing Dilemma in Management

H.J. HOFFMAN, R.P. HUMPHREYS, J.M. DRAKE, J.T. RUTKA, L.E. BECKER, DEREK JENKIN and MARK GREENBERG (Toronto, Ontario)

Optic pathway gliomas have a highly unpredictable course. Some will remain static and quiescent for many years whereas others take an aggressive course, rapidly increasing in size and frequently leading to the demise of the patient. Despite this marked difference in behaviour these tumors are histologically similar and this had led to marked controversies in management.

We have reviewed the results of management of all patients with a diagnosis of optic pathway/hypothalamic glioma treated at the Hospital for Sick Children during the years 1976 to 1990. During this period 62 children with optic pathway/hypothalamic gliomas were managed at the Hospital for Sick Children. Twelve patients received no direct treatment to their tumor. Three patients only received a biopsy. Six patients were treated with radiotherapy alone. Eight patients received radiotherapy following on a biopsy. Seventeen patients were treated by resection alone and 16 patients had a resection followed by radiotherapy. Eight patients received chemotherapy and in five of these patients the chemotherapy was given as an initial therapy.

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Forty-eight patients are well with their visual deficits but seven of these patients are receiving hormone replacement therapy. Six patients have significant neurologic deficits and eight patients have died.

Among the thirty patients who received radiotherapy 21 are well. Two patients have significant neurologic deficits and seven patients have died. In contrast among the 37 patients who have not received radiotherapy, 27 are well, four have neurologic deficits, and one has died.

Our present policy is to resect anteriorly placed tumors which are restricted to one orbit and are producing unsightly proptosis and significant visual loss. Posteriorly placed tumors in patients with neurofibromatosis providing vision is stable and there is no neurologic deficit are treated symptomatically but receive no surgical or adjunctive therapy. Posteriorly placed tumors in patients without neurofibromatosis are all operated upon and a resection carried out. Following resection the patients are observed unless vision is badly compromised. In patients with badly compromised vision or in patients who show progression of the disease on neuro-imaging and/or clinical evaluation following resection, further therapy is given. In children under the age of five this further therapy consists of chemotherapy and in children over the age of five radiotherapy is administered.

25.

Presentation and Management of Tectal Glioma

C. LAURYSSEN, M. HAMILTON, M.E. MacRAE and N.A. HAGEN (Calgary, Alberta)

While the diagnosis of non-pilocytic adult onset brainstem glioma can impart an ominous prognosis, subgroups of patients with brainstem glioma have a more favourable course. Identification of such patients may alter treatment. We report 5 adult patients who presented with hydrocephalus as the only manifestation of tectal glioma. Magnetic resonance imaging was particularly helpful in distinguishing between tumor and idiopathic aqueductal stenosis. 2 of 5 patients demonstrated enhancement of tumor on CT scan. Treatment consisted of ventriculo-peritoneal shunting (5 patients) and radiation therapy (2 patients). One of the 2 patients who received radiation therapy was unable to complete the treatment due to the development of interstitial pneumonitis. The course of tumor seemed unaffected by radiation treatment. The only death in the cohort was neither related to the tumor not its treatment, with a followup ranging from 12 to 144 months (median: 90 months). No patient developed evidence of tumor growth during this time.

We conclude that patients who present with hydrocephalus as the only manifestation of tectal glioma can have a favourable prognosis. Management should consist of ventricular shunting, and radiation therapy should be withheld until focal brainstem signs or symptoms develop.

26.

A Multidisciplinary Approach to Skull Base Surgery at Notre-Dame Hospital

R.A. MOUMDJIAN, M.W. BOJANOWSKI, F. LAVIGNE, D. ROY and M. PARE (Montreal, Quebec)

With the increasing popularity of skull base surgery, our interest was arisen by the large number of skull base lesions referred to Notre-Dame Hospital. Our association with ENT and interventional neuroradiology rendered these lesions more accessible and radically resectable with encouragingly low mortality morbidity.

All cases were investigated with CT-scans, MRI, angiography and most cases underwent pre-op embolisation, then combined surgery including 2 neurosurgeons and one ENT surgeon. This intimate collaboration allowed us to plan optimally these operations as well as shorten the operative time per surgeon rendering these procedures appealing, comfortable and rewarding.

We present here a selection of 8 most interesting cases. These include 2 anterior approaches (transfrontal reconstruction of the skull base and transoral odontoid resection), 4 lateral approaches (orbito zygomatic mandibular and transpetrosal surgery and cavernous sinus dissection), 2 posterior approaches (suboccipital lateral transcondylar approach and retrosigmoid suboccipital approach) and a combined retrosigmoid subtemporal approach with splitting of the tentorium. The technical aspects essential to the success of such procedures will be discussed.

27.

Surgery of Benign Tumors of the Cavernous Sinus

F. DEMONTE and O. AL-MEFTY (Maywood, U.S.A.)

With recent advancements in surgical techniques, tumors involving the cavernous sinus are being treated with increased facility. In our series of 16 patients treated from April 1 through December 31, 1991, 7 had meningiomas, 3 had pituitary adenomas, 2 had chordomas, 2 had hemangiomas, and one each had a dermoid and trigeminal schwannoma. Total removal was achieved in all patients except 3 with meningiomas and one with a pituitary adenoma. In all patients with subtotal removal, pieces of tumor were left adhering to the carotid wall. No deaths occurred in this series but one patient experienced a major stroke not related to cavernous sinus surgery. Ocular motility was improved in two patients, unchanged in ten and worse in four. Although it is too early to predict decreased recurrence rates, the fact remains that benign tumors of the cavernous sinus frequently can be removed with low morbidity.

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28.

Multivariant Analysis of 52 Cases of Primary Brain Tumors Treated With Photodynamic Therapy

P. MULLER, B. WILSON and G. JONES (Toronto; Hamilton, Ontario)

The patient parameters [sex, age, pathology, new/recurrence, Karnofsky score, survival status, and survival time], and, treatment parameters [volume resected, tumor cavity surface area, total photic energy administered in Joules [J] and energy density [J/cm^2] in 52 consecutive cases of primary malignant supratentorial brain tumors treated with PDT were assessed using multivariant analysis. The light dose of 80 J/cm^2 was commensurate with a doubling of median survival in comparison to lower doses.

The only variables associated with survival in the 20 malignant astrocytomas were Karnofsky [p = 0.001] and light dose > 80 J/cm^2 [p = 0.115]. All other variables had a univariant p-values over 0.42. Doses of 40-80 and > 80 J/cm^2 were assessed together also and their p-values were 0.89 and 0.13, respectively; thus a threshold effect was identified. The only variables associated with survival in the 25 glioblastomas were dose > 80 J/cm^2 [p = 0.09] and volume [p = 0.07]. All other variables had univariate p-values over 0.33. Doses of 40-80 and > 80 J/cm^2 were assessed together and their p-values were 0.74 and 0.09, respectively; again a threshold effect was shown. The only variables associated with survival in the 9 other primary tumors were dose > 80 J/cm^2 [p = 0.18] and volume [p = 0.17]. All other variables had univariant p-values over 0.23.

The median, %1-yr and %2-yr survival rates for patients with malignant gliomas who received > 80 J/cm^2 was 60 weeks, 70% and 30%, respectively; the survival rates for those that received < 80 J/cm^2 were 29 weeks, 25, and 10, respectively.

It is concluded that PDT doses have an effect on malignant primary brain tumors and that effective treatment requires high light doses.

29.

Brain Growth Failure Following Radiation Therapy of Childhood Brain Tumours

C. LAURYSSEN and S.T. MYLES (Calgary, Alberta)

Radiation therapy is acknowledged to be an important adjunct in the treatment of brain tumours. However, therapeutic irradiation can lead to brain injury, with adverse effects on intelligence and endocrine function. Growth hormone deficiency, with reduced linear growth, has been well-documented following irradiation of brain tumours in children. This paper describes 4 patients who received whole brain radiation therapy and have had failure of brain growth on long term followup. Of these patients 2 had growth hormone deficiency but 2 have had normal linear growth patterns.

The first child received 3,500 rads in 25 fractions in 1979, at 8 months of age, to treat a recurrent frontal teratoma. The next child received 5,000 rads in 29 fractions in 1983, at 7 years of age, for a presumed glioma of the left cuadate nucleus. The third patient was treated with 6,000 rads in 75 fractions in 1983, at age 22 months, for a recurrent left temporal malignant astrocytoma. The final patient received 2,205 rads in 23 fractions in 1980, at 1 year of age, for a medulloblastoma. In addition she received a 6 week course of chemotherapy. The first 2 patients had almost complete cessation of brain growth with normal linear growth, and the latter 2 patients had almost complete cessation of brain growth with associated growth hormone deficiency, following radiation therapy. In each case brain and linear growth were normal prior to radiation therapy.

All 4 patients show differing degrees of intellectual impairment.

Details of these unusual clinical cases, including MRI imaging results will be presented.

30.

Stereotactic Biopsy: A Review of Indications, Success Rate, and Complications in 230 Cases

A. PARRENT and M. BERNSTEIN (Toronto, Ontario)

Two hundred and thirty (230) CT-guided stereotactic biopsies performed by one surgeon (MB) were reviewed retrospectively to critically assess the indications, success rate, and complications. All procedures were performed under local anesthetic using the BRW system between January 1986 and January 1992.

Decision to perform stereotactic biopsy as opposed to craniotomy for any individual patient was based on the perceived lack of need for cytoreduction and/or characteristics of the lesion felt to render it too dangerous for an open procedure. This includes lesions which are very deep and/or small, and lesions located in eloquent cortex. Multiple lesions and those with diffuse and indistinct boundaries were also felt to be better suited for stereotactic biopsy than for open craniotomy.

Eighty-four percent of lesions were neoplastic of which 3/4 were gliomas. Non-neoplastic lesions were diagnosed in 11% of patients of which 2/3 were of infectious etiology. In 11 patients (5%) a definitive diagnosis could not be made on the basis of the stereotactic biopsy and in 6 patients the original diagnosis was proven incorrect at subsequent craniotomy or autopsy.

Complications were seen in 14 patients (6%) but approximately half of these were minor and/or transient. Symptomatic intracerebral hemorrhage occurred in 9 patients (4%) and there was one death. Overall, major morbidity and mortality for the procedure was 2.8%.

Stereotactic biopsy is a relatively low risk, high yield technique for providing diagnosis of intracranial lesions. In general it should be used in cases where open craniotomy poses a high risk of morbidity and/or cases in which the value of cytoreductive surgery is questionable (e.g., invasive neoplasms without mass effect or lesions with probable infectious or inflammatory etiology).

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31.

Toronto Brachytherapy Update: What Have We Learned?

M. BERNSTEIN, N. LAPERRIERE and S. McKENZIE (Toronto, Ontario)

Since embarking on stereotactic high-activity iodine-125 brachytherapy over 5 years ago, we have treated 93 patients to date; 40 recurrent malignant astrocytoma, 45 "up-front" malignant astrocytoma, and 8 solitary recurrent brain metastases. 105 patients have been entered into the randomized study to determine the efficacy of brachytherapy when used as part of the initial management of patients with malignant astrocytoma. Three additional patients have been treated for recurrent skull base tumours (one meningioma, one malignant pituitary adenoma, one plasmacytoma).

We have yet to resolve a number of issues regarding brachytherapy, particularly certain technical and dosimetric aspects. We are however, able to draw some conclusions based on our experience to date: 1) patient selection is paramount and based on radiological and clinical criteria, only about 30% of new patients with malignant astrocytoma and 10% of those with recurrent disease are eligible for brachytherapy; 2) in patients with recurrent disease, brachytherapy confers a median additional survival of approximately one year post implant; 3) in new patients treated "up-front" the results of our and one other randomized study will hopefully determine if there is definite merit to using brachytherapy as part of the initial therapy for malignant astrocytoma; 4) complications of brachytherapy can be significant and have occurred in 16% of our patients; 5) reoperation for intractable mass effect due to "radiation necrosis" has been required in 27% of our patients; 6) pattern of recurrence after brachytherapy appears to be different than in patients not treated with brachytherapy; 7) quality of life and seizure activity are not significantly worsened by brachytherapy but decadron dependency is common. These results will be discussed in the context of experience of other groups active in brachytherapy, and in the context of other experimental modalities for malignant brain tumours.

32.

Coexistence of Cerebrovascular Hamartomas and Astroglial Tumours

R. LEBLANC, Y. ROBITAILLE, S. DYVE and G. GOPLEN (Montreal, Quebec)

Background: Anaplastic gliomas are frequently associated with neovascularization and angiogenesis. The coexistence of these neoplasms with cerebrovascular malformations is therefore of interest. We report 7 cases of such an association seen at our institution.

Methods: Our surgical and autopsy files were reviewed using arteriovenous malformation (AVM), cavernous angioma, aneurysm, and cerebral tumour as keywords. Four patients with a cerebral AVM and 3 with a cavernous angioma with coexisting glioma were identified. There were no cases of coexistent glioma and cerebral aneurysm.

Results: Three males and 4 females aged 39 to 72 years had a total of 3 AVMs and 4 cavernous angiomas coexisting with a glioblastoma in 6 cases and a gliosarcoma in one. One patient with a cavernous angioma and glioblastoma also had a capillary telangiectasia, and one cavernous angioma was a mixed form with a capillary telangiectasia. The initial diagnosis was of AVM in 2 cases and neoplasia in 5. In the former the diagnosis of tumour was made at autopsy or at subsequent surgery and in the latter the diagnosis of AVM or cavernous angioma was made at autopsy. All patients died within 1 to 6 months of the diagnosis of the glioma. The lesions were in the same hemisphere in 4 cases (same site or close proximity in 2), in 2 cases they were in contralateral hemispheres and in 2 others they were supra and infratentorial.

Conclusions: The coexistence of cerebrovascular hamartomas (AVMs and cavernous angiomas) and cerebral gliomas in a large number of patients from one institution suggests that this association is more than fortuitous, and that the hamartomas and gliomas may be submitted to common trophic influences.

33.

Metabolic Characterisation and Discrimination of Brain Tumours Using ^{1}H MR Spectroscopic Imaging (MRSI)

M.C. PREUL, D.L. ARNOLD and W. FEINDEL (Montreal, Quebec)

We used MRSI to study changes in MRI signals from choline, creatine, lactate, N-acetylaspartate, alanine, lipid in 10 biopsy-proven brain tumours (3 glioblastomas, 3 low grade gliomas, 3 metastases, 1 meningioma) and 3 normal controls. Proton MRI and MRSI examinations of brains were obtained using a 1.5T MRI unit. Regions in and around the tumours were classified according to appearance on MRI in 4 zones: lesion centre; peripheral tissue within lesion; adjacent to lesion, abnormal MRI appearance; adjacent to lesion, normal MRI appearance. Contralateral homologous voxels and normals were controls. Only voxels that fulfilled the criteria on MRI throughout their volume were included in the analysis. Results were analysed as relative metabolite ratios (ipsilateral lesion/contralateral control) of choline/creatine (CH), creatine/creatine (CR), N-acetylaspartate/creatine (NA) lactate/creatine (LA), alanine/creatine (AL), and lipid/creatine (LI). Maximal abnormalities in all metabolites were measured in the tumour centre. Meningiomas showed a unique signal from AL and the lowest CR levels. Metastases displayed a prominent LI peak, not apparent in other tumours. Metastases and glioblastomas had high LA levels. Glioblastomas had higher LA levels than low grade gliomas. CH was high in glioblastomas, low grade gliomas, and meningiomas. Abnormally high CH was observed outside glioblastomas (as defined by MRI), but not outside other tumours. NA was low in all tumours and also abnormally low in contralateral brain that appeared normal on MRI. The metabolic abnormalities extended outside the tumour as defined on MRI. NA, a neuronal marker, is low or absent in tumours either

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because they do not contain neurons or there is neuronal damage. The decrease of NA in contralateral brain probably results from damage to axonal projections. Increased LA implies increased glycolysis. It may be increased in and around more malignant tumours because they: have outgrown their nutritional supply, are intrinsically more glycolytic, or compromise metabolism of surrounding brain. AL appears to be specific marker for meningiomas. Metastatic tumours are characterised by an LI peak not prominent in malignant glial tumours. MRSI is a major advance over single-voxel MR spectroscopy for non-invasive evaluation of metabolism in tumours because it allows immediate appreciation of regional heterogeneity of chemico-pathological changes. This preliminary data suggests that there are characteristic spectra associated with different major intracranial tumour types.

D. Pediatric Neurology

34.

Multisystem Involvement in the Term Newborn With Hypoxic-Ischemic Encephalopathy

I. CORDES, E.H. ROLAND, B.A. LUPTON and A. HILL
(Vancouver, British Columbia)

Perinatal hypoxic-ischemic brain injury is a major cause of longterm neurological sequelae. Following such injury, there may be variable involvement of organ systems other than the brain. The purpose of this study is to determine the incidence and significance of involvement of other organ systems in term newborns with hypoxic-ischemic encephalopathy (HIE).

We reviewed the clinical and laboratory data obtained during the first week of life in 54 consecutive term newborns with HIE. In 52 of 54 infants (96%) there were clinical and/or laboratory abnormalities which implied injury to other organs. In 40 infants (75%), 2 or more organs other than the brain were affected. The frequency of multisystem involvement correlated with the severity of HIE during the newborn period and with outcome, e.g., mild HIE was associated with involvement of an average of two other organs whereas in severe HIE there was involvement of an average of four other organs. Infants who developed severe neurological abnormalities at 18 months of age usually had multiple organ involvement (at least 4 other organs affected).

The most common single systemic abnormality was renal dysfunction which occurred in 48 infants (89%). Renal dysfunction was diagnosed on the basis of hematuria (32 infants; 59%), oliguria < 0.5 ml/kg/hour for > 24 hours (22 infants; 41%) and elevated serum creatinine > 120 µmol/L after day 2 (14 infants; 26%). Metabolic disturbances occurred in 33 infants (61%). These included hyponatremia ≤ 130 µmol/L (6 infants; 11%), hypocalcemia < 2 mmol/L; (21 infants; 39%) and hypoglycemia (≤ 30 mg/dl) (18, 33%). Abnormal coagulation (thrombocytopenia ≤ 100 × 10 g/L or disseminated intravascular coagulation) was observed in 17 newborns (32%). Other abnormalities included pulmonary complications, e.g., oxygen requirement > 40% for 6 hours, pleural effusion and "shock lung" (18 infants; 33%), cardiovascular problems, e.g., persistent fetal circulation, hypotension, cardiac dilatation (17 infants; 31%), gastrointestinal dysfunction, e.g., ileus, necrotizing enterocolitis (5 infants; 9%) and elevated hepatic enzymes, e.g., AST, ALT (4 infants; 7%).

Although HIE may occur in isolation, these data suggest that multisystem abnormalities may occur commonly in the context of severe hypoxic-ischemic cerebral injury.

35.

Validity of Electrophysiological Criteria Used in Selective Functional Posterior Rhizotomy for Spastic Cerebral Palsy

P. STEINBOK, R. KEYES, L. LANGILL and D. COCHRANE
(Vancouver, British Columbia)

The purpose of this study was to determine the validity of the intra-operative electrophysiologic criteria used to select posterior rootlets for sectioning in the procedure of selective functional posterior rhizotomy (SFPR).

Intra-operative stimulation of posterior lumbosacral nerve roots and rootlets, using a 50 hz stimulus at threshold intensity, was performed in 5 non-spastic children (controls) undergoing laminectomies for cord untethering and 32 spastic patients during SFPR. EMG responses were recorded in the lower and upper limbs, neck and face. In 6 patients and 5 controls, the H4/H1 ratio in the responses and the pattern of sustained responses were assessed in detail.

Sustained responses with ipsilateral lower limb extra-segmental spread occurred in both spastic patients and controls. Contralateral lower limb spread and suprasegmental spread to the upper limbs, neck and face were found only in spastic children. Sustained responses with an incremental pattern and H4/H1 of > 100% were noted only in the spastic population, but the occurrence of such responses did not necessarily correlate with the extent of contralateral spread.

It is concluded that a sustained response with ipsilateral lower limb spread is not a valid criterion of abnormality associated with spasticity and should not be used to determine the rootlets to be cut in SFPR. Contralateral and suprasegmental spread into the upper limbs, neck and face, and incremental responses with H4/H1 > 100% are probably valid criteria of abnormality, but may reflect different neurophysiologic perturbations in the spastic patient.

36.

Assessing the Medical and Non-Medical Needs of Children With Seizure Disorders and Their Families

I.G. MANION, D. KEENE, J. CHAMPAGNE, H. LACROIX, B. KANNON, K. TATARYN, M. VEZINA and B. ALLEN
(Ottawa, Ontario)

Children and adolescents with seizure disorders can present with a variety of adjustment problems both related and unrelated to their medical condition. These can affect medical management as well as the quality of life for both the patient and his/her family. Families attending the Neurology Clinics of a major

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pediatric center were surveyed to evaluate parent perceptions of child adjustment and child and family needs. Parents were approached during regular clinic visits and were asked to complete: the Child Behaviour Checklist, a Service Utilization Questionnaire, a Needs Questionnaire, and a Demographic Questionnaire. The neurologist seeing the child also completed a fact sheet identifying medical as well as nonmedical concerns.

Out of the 214 families approached during consecutive clinic visits over the four month study period, 158 (74%) participated in the survey. This sample represents roughly 40% of the total clinic population. Results suggest that as a group, these seizure disordered patients present with greater psychosocial adaptation problems than the norm. Such difficulties include behaviour management problems, academic and learning problems, individual and family adjustment problems as well as a variety of social concerns. A subgroup of patients identified as developmentally disabled appear to have greater adaptation problems, consume more resources, and have parents who express the greatest future needs for their child and family.

37.

High Level Phenobarbital Maintenance (HLPBM) Therapy for Infants and Children Prone to Status Epilepticus

H.Z. DARWISH and V. LANGE (Calgary, Alberta)

The adverse effect of Phenobarbital (PB) on learning in the child has been well documented. Several studies have also identified recurrent status events (RSEE) with later poor cognitive outcome.

We have treated 9 children with HLPBM (Blood levels = 160-200 μM/L - Therapeutic range 70-120 μM/L). 6 have been followed for a mean of 3 years (2-5 years) and 3 for less than 1 year. All had RSEE on regular therapeutic levels of Phenobarbital, Carbamazepine and Phenytoin. 4 were tried on Valproic acid and failed even in levels above the maximal therapeutic range. Clonazepam in maximum dose of 0.3 mgm/kg failed to control (RSEE) in the 6 children it was tried on.

8/9 had symptomatic partial onset seizures with secondary generalization, 1/9 had idiopathic primary generalized convulsions. In 3/9 (HLPBM) was started before 1 year of age. The remaining 6/9 were over 3 years old when this strategy was used. 3/6 are of normal congitive ability, but the other 3 followed for over 2 years are moderately handicapped. It has been possible to discontinue the (HLPBM) regime in 4/6 without recurrence of status events.

This strategy of keeping the PB level 50% higher than the high end of the therapeutic range was clearly effective in controlling (RSEE), when all other strategies failed. It still was tolerated and allowed the children to continue to learn and gain in development. A further improvement in alertness and learning indeed was seen when it was successfully discontinued after 2 or more years of use.

38.

Fentanyl or Sufentanil Citrate Use in Electrocorticography in Children Under 8 Years of Age

H.Z. DARWISH, S.T. MYLES (Calgary, Alberta)

Local analgesia cannot be used in young children undergoing surgery for refractory epilepsy. Fentanyl or Sufentanil citrate are potent opioid analgesics which can produce analgesia or deep anesthesia depending on the dose used.

We have performed electrocorticography (ECOG) on 5 children varying in age from 1 month to 8 years for a total of 7 ECOGs. Intraoperatively, nitrous oxide in combination with Sufentanil or Fentanyl was used for the initial surgical procedure sometimes with Halothane or Thiopentone. All agents were then discontinued and only Fentanyl or Sufentanil were used as the principle agent during the ECOG.

ECOG clearly revealed grouped spikes in 3, and electrographic seizure patterns in 2, and random spikes in 2 associated with focal slowing. The foci identified were as expected in the regions of abnormality demonstrated by MRI and or preoperative Ictal surface EEG recording.

One child had a ganglioglioma of the parietal and temporal lobes. Two children had low grade astrocytomas of the parietal lobe. One child had a forme Fruste of tuberous sclerosis affecting the parietal and frontal regions and an infant had hemimegalencephaly.

To date 4 of 5 children have had significant improvement in seizure control of whom 1 is completely seizure free.

39.

Xenon Computed Tomography (XE-CT) in Children With Intractable Epilepsy

M.B. CONNOLLY, K. POSKITT, R. MUNN and K. FARRELL (Vancouver, British Columbia)

Xenon computed tomography (Xe-CT) is a technique which permits the measurement of absolute regional cerebral blood flow. This abstract describes the preliminary data from a study comparing Xe-CT with HMPAO-SPECT and MRI in children with intractable seizures.

Six children (4 males; 2 females) with refractory epilepsy have been studied to date. The mean age was 7 years; range 3 years, 2 months to 12 years, 9 months. The mean time interval from onset of seizures to time of study was 4 years. Four patients had partial epilepsy and one had severe myoclonic epilepsy of infancy, and one patient Lennox-Gastaut syndrome. All patients were studied in the interictal state except one patient who had a seizure during the Xe-CT examination.

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CT scans were normal in all children. MRI was normal in five and in the sixth patient, an area of increased signal on T2 weighted imaging was demonstrated in the left temporal lobe. Interictal HMPAO-SPECT demonstrated abnormalities in four patients. Three patients had focal areas of hypoperfusion in a temporal lobe and one patient had hypoperfusion in the left temporal and frontal areas. Xenon-CT was abnormal in five patients demonstrating areas of hypoperfusion in a temporal lobe in four patients and increased flow in the left frontal lobe in one patient who had a seizure during the Xe-CT study. One patient with a normal HMPAO-SPECT study had an area of hypoperfusion in a temporal lobe on Xe-CT study.

Functional neuroimaging using HMPAO-SPECT and Xe-CT were superior to anatomical neuroimaging techniques in demonstrating focal abnormalities. Xe-CT demonstrated superior spatial resolution than HMPAO-SPECT and enabled calculation of absolute regional cerebral blood flow. These data suggest that Xe-CT may be useful in the localization of epileptogenic regions in children with intractable epilepsy.

40.

Idiopathic Non-Hemorrhagic Ischemic Stroke in Children

M. NGUYEN and P. HUMPHREYS (Ottawa, Ontario)

We reviewed all non-hemorrhagic strokes in children aged 28 days to 18 years seen at the Children's Hospital of Eastern Ontario between 1979 and 1991. Of 39 cases meeting our inclusion criteria, 20 had definable causes: congenital heart disease (6), neck vessel injury (3), vasculitis (3), complicated migraine (2), sickle cell anemia (2), cardiomyopathy (1), air/fat embolism (1), fever/dehydration (1), mitochondrial encephalopathy (1). An underlying etiology could not be determined in the remaining 19 cases, including a case with radiologic evidence of the "moya-moya" phenomenon. Extensive review of the idiopathic cases revealed that 11/19 (58%, or 28% of all stroke cases) had sufficiently similar clinical and radiological findings to suggest a common pathogenesis. The 11 patients ranged in age from 2.5 to 16 years; 5 were male. All had an abrupt onset, predominantly motor hemiplegia; those with left hemisphere lesions (7 cases) were also transiently aphasic. In all patients, C.T. scanning revealed an area of infarction corresponding to the area of supply of the lenticulostriate arteries (i.e., caudate, putamen, internal capsule). 9/11 had abnormal angiograms showing irregular narrowing of the supraclinoid portion of the appropriate internal carotid, proximal middle cerebral, and anterior cerebral arteries, usually with occlusion of the latter. In addition, one case had a double lumen phenomenon in the internal carotid suggestive of dissecting aneurysm. Follow-up over 1-12 years has shown no evidence of progressive carotid stenosis and no recurrence of stroke. Our findings suggest that an idiopathic (thus far) non-progressive, stenotic arteriopathy of the distal internal carotid and its principal branches is the commonest cause of non-hemorrhagic stroke in childhood.

41.

Infantile Spasms: Outcome and Prognostic Factors in Cryptogenic and Symptomatic Cases

B. KOO, P. HWANG and A. HUNJAN (Toronto, Ontario)

We reviewed 57 cases of infantile spasms (17 cryptogenic and 40 symptomatic) at the Hospital for Sick Children, Toronto, from 1987 to 1991.

Eight out of seventeen (47%) cryptogenic and thirty-three out of forty (83%) symptomatic case had unfavourable developmental outcome. Neurological deficit was present in 42.5% of symptomatic cases. The presence of other forms of seizure was observed in 41% of cryptogenic and 60% of symptomatic cases. All cases in the cryptogenic group and 76% in the symptomatic group responded to ACTH treatment but both groups showed 20% relapse rate on discontinuation of therapy. Factors affecting outcome include: co-existence of other forms of seizures, relapse on cessation of ACTH treatment, the presence of abnormal neurological findings and the EEG pattern. The character of spasms, time lag in initiation of treatment and treatment duration have no significant effect on outcome.

Patients with infantile spasms need to be fully assessed to differentiate between cryptogenic and symptomatic groups as the outcome is significantly different.

42.

Benign Familial Infantile Epilepsy

W.L. LEE (Toronto, Ontario)

Fourteen patients with familial epilepsy during infancy appear to constitute a distinct epileptic syndrome. Seizures started between the ages of 3 to 7 months and stopped between the ages of 4 to 18 months. Seizure type varied and three patients had more than one type of seizures. Most patients had very few seizures, but one had multiple seizures daily for many months. All the patients were neurologically and developmentally normal. EEG was normal in 12 patients. One patient had a clinical seizure during the recording and EEG showed an electrographic seizure with onset over the left hemisphere and secondary generalization. No metabolic or neuroradiological abnormalities were found. Response to anticonvulsants was variable. All patients have been followed for more than 15 months after their last seizure. They have remained seizure-free without anticonvulsants. All patients have one or more first, second and/or third degree relatives with afebrile seizures during infancy which stopped before school age. Affected family members have remained seizure-free and neurologically normal up to adulthood. Afebrile seizures starting between 3 to 7 months of age with normal neurological and developmental examination and a family history of similar infantile seizures probably represents a distinct clinical syndrome with benign outcome.

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43.

Congenital Muscular Dystrophy: A Review of 20 Cases

B. BEN ZEEV and E.G. MURPHY (Toronto, Ontario)

A review of 20 cases of congenital muscular dystrophy that were diagnosed at the Hospital for Sick Children, Toronto from 1982 till 1991 is presented.

The review includes clinical aspects: birth history, developmental milestones, presenting symptoms, physical findings, long term follow-up and outcome. It also includes biochemical, electrophysiological, neuro-imaging, genetic and pathological findings.

This group of patients is compared to previous groups of patients with CMD that were described in the literature (J. of Paediatrics, May 1982, J.B. McMenamin et al., J. of Paediatrics 1989, 115, Q.H. Leyten, et al.) in order to examine whether the known classification of these cases still holds or a modified one, based on both clinical and pathological findings, should be proposed.

We also emphasize specific clinical aspects of CMD of which, in our view, the non-neurologist may not be sufficiently aware, and which may be of help in obtaining a more sensitive diagnostic approach to CMD.

44.

Protective Effects of Mild Hypothermia During But Not Following Hypoxia-Ischemia (H-I) on the Immature Rat Brain

J.Y. YAGER, J. TOWFIGHI and R.C. VANNUCCI (Hershey, U.S.A.)

Small reductions in temperature (T) following H-I significantly decreases brain damage in experimental adult animals. Unlike adults, thermoregulatory mechanisms are not fully developed in the immature rat. During normoxia, 7-day postnatal rat pups maintain their T at 35 ± 1.5°C irrespective of ambient T. During hypoxia, rat pups become poikilothermic. We have previously shown that in the immature rat, reductions of intra-ischemic T by 3-6°C dramatically improves neurologic outcome. Thus, no brain damage occurred with an intra-ischemic T of 31°C. Recovering animals, without brain damage, retain the ability to regulate Ts within normal limits (Ped Res 29: 366, 1991). To further determine the effects of small decreases in T following H-I, 7-day post-natal rats underwent unilateral common carotid artery ligation and exposure to hypoxia in 8% oxygen for 3 hrs at 37°C. Following H-I, rat pups were immediately placed in chambers at either 37 (n = 22), 34 (n = 20) or, 31 (n = 26)°C and allowed to recover for 3 hrs. They were then returned to their dams to 30 postnatal days, at which time neuropathologic alterations were assessed. Brain and rectal Ts were recorded under the same experimental conditions in separate groups of 7-day postnatal rats. A strong correlation existed between brain and core Ts during H-I and recovery at 37 (r = .7), 34 (r = .95) and 31 (r = .99)°C. Brain damage occurred in all animals, 90% of which had cerebral infarctions. There was no difference in the extent of cerebral injury between rat pups recovered at 37, 34 or 31°C ($p > 0.75$). Rat pups displaying cortical infarction were no longer capable of maintaining their core T. Thus 1) reductions in T of 3-6°C immediately following H-I is not protective to the immature brain, as it is in adults, and 2) immature rats displaying significant cerebral injury lose the ability to thermoregulate. The findings have important implications regarding the value of therapeutic intervention following H-I in the newborn.

E. Cerebrovascular

45.

Outcome Evaluation Methods in Models of Focal Ischemia in the Rat

M. UNO and M.C. WALLACE (Toronto, Ontario)

An enormous increase towards the understanding of the mechanisms of ischemic cell death has prompted intense investigation of a wide range of potential therapeutic agents in animal models of focal ischemia. The purpose of this study was to evaluate and compare methods of tissue perfusion in 2 models of focal ischemia.

Fischer rats (n = 40) underwent permanent focal ischemia by coagulation and transection of the middle cerebral artery (MCA) via craniectomy[1] or by insertion of a silk thread into the intracranial carotid via the common carotid artery[2] Sham controls (n = 12) were included. Physiological monitoring of arterial blood gases, blood pressure and temperature were recorded for the four hour ischemic period. After 4 hours, animals underwent perfusion fixation with tetrazolium chloride (TTC)[3] or neutral red.[4] Infarction area was determined by pathology, TTC or neutral red evaluation at predetermined coronal levels and a volume of infarction calculated.

Physiological variables were not different between groups. No infarction, TTC defect or perfusion deficit with neutral red was noted in control animals. The volume of ischemic damage by TTC perfusion correlated well with pathological evaluation in both methods of ischemia. The volume of TTC defect in animals subjected to suture catheterization was 87.5 ± 37.2 mm^3, representing 20.2 ± 8.6% of the hemisphere, and was consistently lower than these animals undergoing MCA occlusion by craniectomy (NS). Variability of infarction was higher with the suture method. Neutral red evaluation of ischemic tissue consistently produced a smaller volume of change compared to TTC or pathological evaluation ($P < 0.05$ Fischer).

This study found the suture method a less reliable/more variable method of inducing focal ischemia than permanent occlusion of the MCA. This sheds doubt on its useful role in studying either permanent or focal ischemia. Neutral red perfusion study underestimated pathological damage volumes at 4 hours after ischemia and may have to be restricted to earlier time periods after the onset of ischemia.

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[1] Tamura et al.: J Cereb Bl Flow Metab, 1: 53-60, 1981

[2] Longa et al.: Stroke, 20: 84-91, 1989

[3] Park et al.: Neuropath Appl Neurobiol, 14: 289-298, 1988

[4] Selman et al.: Neurosurgery, 21: 825-830, 1987

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46.

Oxygen Free Radicals and Antioxidant Status During Acute Ischemic Stroke

R. MOSEWICH, A. SHUAIB, J. KALRA, S. MANTHA, M. PRASAD and R. MAZAGRI (Saskatoon, Saskatchewan)

Oxygen free radicals (OFR) have been implicated in the pathogenesis of cerebral ischemia. OFR exert their cytotoxic effects by lipid peroxidation resulting in production of malondialdehyde (MDA). Their role is not well studied in acute cerebral infarction in humans. The objective of this study was to compare the enzyme activity of superoxide dysmutase (SOD), catalase (CA) and glutathione peroxide (GHS-Px) and generation of OFR in acute stroke and age-matched controls.

Blood was collected from patients with acute stroke within 48 hours and compared to age-matched controls free of acute ischemic injury. SOD, CA and GHS-Px activities were measured in serum and erythrocytes. OFR-producing activity of polymorphonuclear leukocytes was measured by chemiluminescene. There were 30 patients and 25 controls studied in a one year period. There was a significant increase in activity of GHS-Px and MDA ($p < 0.05$). SOD and CA were not significantly increased in stroke although there was a trend for higher values in acute stroke. Our study shows that there is an increase in GHS-Px and MDA and this would indicate that there is increased OFR activity in acute stroke. Further studies are needed in the initial 4 to 6 hours after an acute stroke to better understand the role of OFR in acute stroke.

47.

Effects of Hypothermia in Repetitive Cerebral Ischemia: A Cell Culture and *In-Vivo* Study

A. SHUAIB, E. SOCHOCKA and M.S. IJAZ (Saskatoon, Saskatchewan)

There is evidence that damaging effects of repetitive ischemia at one hour intervals are cumulative and exceed injury produced by a similar single insult. In gerbils, severe damage is seen in the striatum, thalamus, hippocampus, medial geniculate nucleus (MGN) and the substantia nigra reticulata (SNr). Damage secondary to repetitive ischemia has not been studied in cell cultures. We report our results with repetitive ischemia in *in-vivo* and astrocytic cell cultures, and the effects of hypothermia on this damage. In cell cultures, repetitive ischemic episodes of 3 hours each with 1 hour of "reperfusion" was compared to a single 9 hours duration insult. Repetitive ischemia revealed more severe damage in cell culture (LDH [units per gram protein] 45 versus 220). Hypothermia (32 degrees) was very effective in reducing damage in both experiments. In the *in-vivo* series, all 6 gerbils in whom temperature was reduced between the ischemic insults showed minimal damage in the hippocampus and SNr compared to damage in normothermic animals. Similarly, LDH activity was significantly less in hypothermic cultures (30 versus 220). We show for the first time that hypothermia is protective in repetitive ischemia and that this effect is apparent in *in-vivo* and cell cultures.

48.

Gamma-Vinyl Gaba When Used via Alza Pumps Prevents Hippocampal Damage in Repetitive Ischemia

A. SHUAIB, S. HASAN, M.S. IJAZ, R. MAZAGRI and W. HOWLETT (Saskatoon, Saskatchewan)

There is now considerable evidence that neuronal damage during repetitive ischemia is cumulative and exceeds the damage from a similar duration single insult. In gerbils, repetitive ischemia results in neuronal damage in the hippocampus, striatum, thalamus, substantia nigra reticulata (SNr) and the medial geniculate nucleus (MGN). We postulated that SNr damage was a result of a loss of the inhibitory input from the striatum. Using Alza pumps, we infused a constant rate (.5 micol/h of Gamma-vinyl gaba (GVG) (10 ng/ml) into the 3rd ventricle to test if this would prevent cell loss in the SNr. Damage was scored on a scale of 1 to 4 (1 < 25% damage and 4 a complete infarction). Three episodes of ischemia for two minutes were used as the repetitive insult. Six animals served as controls (with saline infusion) and a similar number of animals had GVG infusion. Damage was similar in the striatum, MGN and thalamus in both groups. There was a mild decrease in SNr damage in the treated group. The CA1 region of the hippocampus was however completely protected in 5 of 6 animals treated in the treated group. Our results suggest that Gabaergic agents may be protective to the hippocampus and substantia nigra reticulata when used intraventricularly during repetitive ischemia.

49.

Post-Ischemic AMPA Receptor Blockade Reduces Hippocampal CA1 Neuronal Injury

H. LESIUK, K. BARNES and A.M. BUCHAN (Ottawa, Ontario)

NBQX, a competitive antagonist of the AMPA class of glutamate receptor was used to probe the effect of post-ischemic blockade of AMPA receptors, in the 2-vessel occlusion (plus hypotension) model of transient global ischemia, which reliably induces hippocampal CA1 neuronal injury. Male Sprague-Dawley rats (n = 20) were subjected to 10 min. of cerebral ischemia (under general anaesthesia with mechanical ventilatory support and meticulous control of temperature, arterial blood gas composition and fluid balance) and seven days of reperfusion. Animals were randomly assigned to treatment with NBQX (30 mg/kg, i.p.) 0, 15 and 30 min. post-ischemia, or equivalent injections of sterile water. After 7 days, animals were sacrificed and histologic sections of hippocampus prepared. CA1 neurons of the septal hippocampus were counted and the ratio of damaged to total neurons calculated. The percentage of damaged CA1 neurons in the NBQX treated group (n = 10) (mean ± S.D.) was 9% ± 9%. In the control treatment group (n = 10) percent CA1 injury was 73% ± 8%. Thus, NBQX treatment, even though delayed to the onset of reperfusion, resulted in highly significant ($p < 0.001$, Mann-Whitney U) protection of hippocampal CA1 neurons from ischemic injury, in this model of

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transient forebrain ischemia. Given the failure of NMDA antagonists to prevent neuronal injury following severe ischemia, this result suggests that the AMPA class of glutamate receptor may play a more critical role in the pathogenesis of ischemic neuronal injury.

50.

AMPA Receptor Antagonists But Not NMDA Antagonists Reduce Neocortical Infarction Following Transient Focal Ischemia

D. XUE, Z.G. HUANG, K.E. SMITH, H. LESIUK and A.M. BUCHAN (Ottawa, Ontario)

NMDA and AMPA receptor antagonists protect against moderate ischemia in focal stroke models. Our initial report on NBQX (AMPA antagonist) suggested AMPA receptors may be more important mediators of ischemic injury than NMDA receptors.[1]

The present study compares delayed treatment with MK-801 (NMDA antagonist) to NBQX in a rodent model of transient middle cerebral artery occlusion. Male SHR rats (n = 41) were subjected to 2 h of reversible ischemia followed by 22 h of reperfusion (RP). Saline, MK-801 (1 mg/kg), or NBQX (30 mg/kg) were administered IP 30 min. before, at the time of, and 30 min. following RP. Animals were sacrificed at 24 h. Regional cerebral blood flow (%) was recorded at the ischemic core area (R3) and its edge (R2). Infarcted cortical volume was calculated, and an ANOVA followed by Scheffe's test was used to compare the damage between treatment groups.

Groups (n)	rCBF(R2) (% ± SE) Post-I	Pre-RP	Post-RP	Mean Volume of Cortical Infarction (MM3±SE)	Reduction (%)
Saline (15)	14 ± 2	16 ± 2	83 ± 17	181 ± 8	—
MK-801 (11)	14 ± 2	20 ± 5	58 ± 8	169 ± 10	7
NBQX (15)	16 ± 2	18 ± 3	78 ± 18	137 ± 6*	24*

* $p < 0.001$

There was no change in intra-ischemic rCBF using these drugs in a delayed treatment paradigm. However, NBQX but not MK-801 significantly reduced infarct size.

[1]Buchan et al., Neuroreport 2, 473-476, 1991

51.

Are AMPA Receptors More Important Than NMDA Receptors in Selective Neuronal Death?

H. LI and A.M. BUCHAN (Ottawa, Ontario)

Glutamate released following brain ischemia is considered to be an important factor in inducing neuronal degeneration. Antagonists of AMPA (NBQX) and NMDA (MK-801) glutamate receptors prevent neuronal calcium entry into neurons and have been proposed as cytoprotectants against cerebral ischemia *in vivo*. NBQX and MK-801 were tested in the 4-vessel occlusion model of severe forebrain ischemia. Adult male Wistar rats (n = 44) were subjected to 10 min. of forebrain ischemia and seven days of reperfusion. NBQX (30 mg/kg), MK-801 (1 mg/kg) or a combination of the two were injected IP at the time of reperfusion, and 15 and 30 min. post-ischemia. Damaged CA1 neurons of the dorsal hippocampus in surviving animals (n = 37) were counted and the percentage of injured cells calculated. Deaths (n = 7) were equally distributed between groups.

Group (n)	% CA1 Injury (Mean ± SD)
Saline (8)	81 ± 28
NBQX (11)	21 ± 27*
MK-801 (9)	83 ± 18
Combination (9)	54 ± 34

* $p < 0.001$ Mann-Whitney U with Bonferoni correction.

Post-ischemic administration of NBQX, but not MK-801, prevented the death of CA1 neurons following severe forebrain ischemia in adult rats. The addition of MK-801 to NBQX is detrimental.

52.

Calcium Channel Activation in Transient Forebrain Ischemia

M.J. HOGAN, S. TAKIZAWA, A.M. BUCHAN and A.M. HAKIM (Montreal, Quebec; Ottawa, Ontario)

Calcium movement into neurons through activated calcium channels is postulated to be a major mechanism of cell injury and death in cerebral ischemia. *In-vivo* binding of the voltage sensitive calcium channel antagonist [^{3}H]-nimodipine is saturable and specific to ischemic brain and may be predictive of the eventual fate of ischemic tissue. Therefore we measured *in-vivo* nimodipine binding to brain in a rat model of transient forebrain ischemia to assess the relationship of binding to selective vulnerability observed in this model.

The *in-vivo* distribution of [^{3}H]-nimodipine in brain was determined autoradiographically following 30 minutes of nimodipine circulation. Measurements were performed at 0.5, 2, 24 and 48 hours after 20 minutes of transient forebrain ischemia. Histology was assessed at these times and at 72 hours.

Nimodipine binding was increased in all ischemic regions at 0.5 hours after transient ischemia but returned to normal by 2 hours of reperfusion. A second increase in binding was observed at 24 hours in cortex, caudate and hippocampus. This increase was highest in caudate which showed the greatest ischemic injury at this time. There was less binding in regions showing less intense or later appearing ischemic injury.

We postulate the initial increase in nimodipine binding to be a consequence of cell membrane depolarization occurring during ischemia. This is consistent with previous observations that increased binding is a sensitive indicator of impending ischemic injury. The reversal of increased binding after 2 hours of reperfusion suggests restoration of cell membrane potentials has occurred. The second rise in binding occurring at 24 hours coincides with the appearance of ischemic injury in those selectively vulnerable regions. The biphasic response of nimodipine binding in this model may define a window of opportunity for therapeutic manoeuvres aimed at preventing delayed neuronal injury

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following transient ischemia. This information may be relevant to post-cardiac arrest patients.

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53.

Blood Brain Barrier Permeability in a Focal Stroke Model

Z.G. HUANG, E. PRESTON, D. XUE, K.E. SMITH and A.M. BUCHAN (Ottawa, Ontario)

This study was conducted to explore the time course of changes in blood-brain barrier (BBB) permeability in a rodent model of transient middle cerebral artery occlusion (MCAO). Anesthetized male SHR rats (n = 24) were subjected to 2 h of reversible right focal ischemia followed by reperfusion of 2 min. or 1, 4, 22, or 46 h (4-5 rats per group). At these time points, a H^3-sucrose solution (20μCi/100 g) was administered IV, circulated for 30 min., and the animals immediately sacrificed. Regional transfer constants (Ki) for BBB permeation of sucrose were calculated from the ratio of parenchymal ($dpm \cdot g^{-1}$) and time-integrated plasma ($dpm \cdot s^{-1} \cdot mL^{-1}$) sucrose concentrations. Mean Ki values (± SE) for right cortex ($mL \cdot g^{-1} \cdot s^{-1} \times 10^6$) were: 17.3 ± 5.3* (2 min.), 5.7 ± 1.8 (1 h), 5.9 ± 1.3 (4 h), 13.1 ± 0.9 (22 h), and 59.0 ± 5.3* (46 h). Group Ki values for left cortex ranged from 2.3 ± 0.2 to 3.0 ± 0.6. Right striatum and hippocampus were not affected until a significant increase in Ki occurred between 22 and 46 h, e.g., striatum: 5.3 ± 0.4 (22 h) vs 14.4 ± 2.9 (46 h) ($p < 0.05$). The data indicate a biphasic opening of the cortical BBB. The acute opening after reperfusion (2 min.) argues for delivery and testing of therapies at this time even though they may not normally be BBB permeable. Apparent worsening and spread of cerebrovascular insult in this model was demonstrated by increasing Ki 24-46 h post-MCAO. *$p < 0.05$ compared to 1 and 4 h data (ANOVA).

54.

The Effect of Focal Cerebral Ischemia in Experimental Models as Monitored by MRI

J.K. SAUNDERS, A. BUCHAN, A. JASINSKI, D. XUE, K. BUTLER and P. KOZLOWSKI (Ottawa, Ontario; Krakow, Poland)

The first objective of this work was to determine the usefulness of Magnetic Resonance Imaging (MRI) for determining infarct volume following focal cerebral ischemia [middle cerebral artery occlusion of spontaneously hypertensive rats]. The infarct volumes measured by MRI were compared with those determined by histopathology. The agreement between the two methods was excellent at a specific timepoint (24 hours) following the insult. A major advantage of MRI is that maturation of the infarct can be observed in each animal since many images can be obtained serially. In light of the excellent correlation the imaging techniques were then used to obtain supplementary information including temporal profiles as well as information on the state of water in various regions of the brain. After 3 hours each of transient ischemia and reperfusion the brain appears normal in T_2 weighted images. With longer periods of reperfusion the infarct becomes apparent and continues to grow in volume over the next 18 hours. The degree of hyperintensity in the infarcted region as measured by the T_2 values also increases over this time period. Using diffusion weighted images the infarcted area can be observed earlier than the T_2 weighted images and is again evidenced by hyperintensity in the infarcted area. The temporal profile of infarct volume and intensity is essentially the same for 3 hour transient occlusions followed by 21 hours of reperfusion or for permanent occlusions. The infarcted area could also be detected using magnetisation transfer weighted images. In comparison to the above results which were obtained for ischemic insults at 37°C little or no evidence of damage was observed if the insult was performed at 34°C.

In conclusion MRI can be used to determine infarct volume, the amount of swelling in the infarcted volume and to follow the temporal profile of the evolution of the infarct. Furthermore, details of the motion of water molecules and their interactions with macromolecules in the infarct (core relative to penumbra) can also be probed using the various imaging modalities.

55.

^1H and ^{31}P Localized NMR Spectroscopy Studies of a Focal Ischemia in the Rat Brain

P. KOZLOWSKI, D. BOURGEOIS, A. BUCHAN, A. JASINSKI, D. XUE and J.K. SAUNDERS (Ottawa, Ontario; Krakow, Poland)

Non-invasive NMR spectroscopy *in-vivo* has proven to be a powerful tool in studying biochemical processes in living systems. Acquiring both ^1H and ^{31}P spectra allows to obtain a complementary information about the concentrations of high energy phosphates, inorganic phosphate, N-acetyl aspartate, choline, creatine, glutamine/glutamate and lactate, as well as intracellular pH. Transient or permanent focal ischemia induced in spontaneously hypertensive rats (SHR) results in well localized neocortical infarction in the brain. Therefore localized spectroscopy gives an opportunity to compare the biochemical information from normal, ischemic, reperfused and infarcted cortex.

Focal ischemia was induced in fasted SHR rats by permanent occlusion of the right common carotid artery and either permanent or temporary occlusion of the right middle cerebral artery. The head temperature was monitored for each animal and held constant at 37.5°C.

Inductively coupled surface coils of elliptical shape tuned either to proton's or to phosphorus' frequencies were placed at the top of the rat's head to receive the signal mainly from the brain. Spectroscopic Imaging (SI) was used to acquire either 64 (^{31}P) or 256 (^1H) spectra with the voxel volume of either 125μl or 20μl respectively.

Acquired spectra show significant amount of lactate and reduction in concentration of N-acetyl aspartate in the infarcted region as compared to nonaffected part of the brain. Also the level of high energy phosphates is decreased and the resonance from inorganic phosphate is elevated in the infarct area.

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Intracellular pH measured 24 hours after ischemic insult appears to be normal (7.2). To confirm the presence of the lactate in the ischemic part of the brain one shot lactate editing sequence was used.

The results show that the localized NMR spectroscopy *in-vivo* allows to study biochemical events in ischemic tissue and evaluate the effects of different factors on the stroke severity.

F. Epilepsy

56.

Characteristics of Adult Epileptic Patients With a Sustained Excellent Response to Clobazam Compared to Those Developing Tolerance

A. GUBERMAN and M. COUTURE (Ottawa, Ontario)

Clobazam, a new antiepileptic benzodiazepine recently released for clinical use in Canada, produces a sustained excellent response in up to 1/3 of intractable epileptic patients when used as an add-on agent. In Canadian studies tolerance occurred in 10-20% of patients as opposed to most European studies where rates were twice as high. The discrepancy has not been resolved but may depend in part on varying definitions of tolerance, different patient populations and falling drug serum levels.

From a population of 115 adult intractable epileptic patients in whom clobazam was added, we identified 16 patients who remained seizure-free, or almost so, followed for a period of 37.6 ± 11 months. Five additional patients who initially were seizure-free, or nearly so, relapsed to a level of 50% or more of their pre-clobazam seizure frequency despite a constant clobazam dose (tolerance) after a mean interval of 11.5 months (range 10-40). The 2 groups were compared with respect to seizure types and frequency, duration and etiology of epilepsy, concomitant drugs and serum levels, method of initiation of clobazam, clobazam dose, clobazam and n-desmethylclobazam serum levels. The only difference found was in the serum drug levels: clobazam 0.4 ± 0.27 micromol/L and N-D-clobazam 6.4 ± 3.73 micromol/L in the sustained responders vs means of 0.2 (range 0.1-0.31) and 3.3 (range 2.3-4.6) respectively in the tolerance group. These findings suggest that higher dosages may be associated with a lower incidence of tolerance.

57.

Anti-Epileptic Drug Levels in Pregnant Epileptic Patients: Correlation With Changes in Seizure Frequency

I. LOPES-CENDES, E. ANDERMANN, L. DANSKY, A. SHERWIN, M. OGUNI, M.H. SENI, F. CENDES and F. ANDERMANN (Montreal, Quebec)

Falling total blood levels of anti-epileptic drugs (AEDs) during pregnancy have been well documented in the literature (Yerby, 1990), as has an increase in seizure frequency (Canger, 1982). There are several hypotheses to explain this, including: increase in total blood volume, increase in metabolic clearance, and changes in plasma protein binding. Clinicians frequently tend to increase the dosage of AEDs based only on the lower total blood levels.

This study attempts to analyze the correlation, if any, between the decrease in mean total blood levels of AEDs and an increase in the frequency of seizures during pregnancy. We studied 76 patients who had not changed the dosage of AED during pregnancy. The mean total blood concentrations for each trimester for 3 major drugs: Carbamazepine (CBZ) (N = 38), Phenytoin (PHE) (N = 28) and Valproic acid (VAL) (N = 10), all of them in monotherapy, were analyzed.

We divided the patients into 2 groups: (1) 41 patients with complete control of major seizures in the year prior to pregnancy, and (2) 35 patients presenting with major seizures in the same period. Group (1) was classified into 2 classes: Unchanged and increased and group (2) into 3 classes: Unchanged, increased and decreased, based on seizure frequency during pregnancy (Canger, 1982).

In group (1), there were 34 unchanged (82.9%), and 7 increased (17.1%); in group (2) 25 unchanged (71.4%), 8 increased (22.8%) and 2 decreased (5.8%).

The mean blood levels for all 3 drugs decreased significantly ($p < 0.05$) from the first to the third trimester: 30% for PHE, 25% for CBZ and 45% for VAL. The difference in the degree of the decrease was not significant among the three AEDs. When analyzing the percentage of falling blood levels for the 2 seizure classes we found, for unchanged frequency: 27% PHE, 12% CBZ and 39% VAL; and for increased frequency: 45.5% PHE, 44% CBZ and 46.7% VAL. Although there appeared to be a correlation for PHE and CBZ, these differences were not statistically significant.

These results confirm the decrease of AED total blood levels during pregnancy. The proportion of patients with increased seizure frequency was smaller than previously reported (Knight, 1975). The importance of assessing the clinical parameters together with the laboratory data, and not only the total blood levels, in the management of these patients during pregnancy, is emphasized.

58.

Mesial Temporal Atrophy: Cause or Consequence of Repeated Seizures? Evidence from Computerized MRI Volumetric Studies

F. CENDES, F. ANDERMANN, P. GLOOR, I. LOPES-CENDES, A. OLIVIER, A. EVANS, D. MELANSON, M. JONES-GOTMAN and T. PETERS (Montreal, Quebec)

Atrophy of mesial temporal structures in temporal lobe (TL) epilepsy has been studied for over a century and has led to much controversy. Pathological changes within hippocampal formation (HF) and amygdaloid body (AB) have been well established over the years, but whether this represents a cause or effect of repeated seizures remains uncertain. Recent experimental animal models and *in vitro* studies suggest that repeated seizures are sufficient to induce neuronal loss (Cavazos and Sutula 1990, 1991). It has also been suggested that frequent

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seizures originating in extratemporal areas may produce hippocampal cell loss as well. Recent studies using computerized MRI volumetric measurements of TL structures indicate that this technique is sensitive and specific in detecting mesial temporal atrophy (Jack et al.; Cascino et al.). In patients who underwent surgical treatment there was a good correlation between reduction in MRI volume and hippocampal neuronal loss.

If repeated seizures lead to HF and AB damage and thus to mesial TL atrophy, one would expect a correlation between the number of years of uncontrolled seizures and the degree of atrophy. In order to assess this issue, we studied 27 patients with intractable TL epilepsy and 6 with extra-temporal epilepsy (age range 11-68 years, mean 32 y), using MRI based volumetric measurements of AB and HF. We found significant atrophy of these structures, as compared to normal control values, in all patients with TL epilepsy, coinciding with the side of EEG seizure onset, but not in the extra-temporal patients.

We then performed a linear regression analysis, plotting the number of years of recurrent seizures in each of the 27 TL patients versus the degree of atrophy of the AB and HF. There was no correlation between these two parameters ($p > 0.9$). There was also no correlation between the patient's age and the degree of atrophy of these structures. On the other hand we confirmed the well known association between a history of prolonged febrile convulsions (present in 33.3% of the TL patients) with atrophy of the AB and HF. In this group the atrophy was more pronounced as compared to other patients with TL epilepsy ($p < 0.05$).

These findings suggest that mesial temporal atrophy is a cause rather than a consequence of repeated seizures. Studies of larger series may provide further clarification.

59.

The Role of Intraoperative Recording and Stimulation of the Amygdala in the Surgical Treatment of Temporal Lobe Epilepsy

R. LEBLANC, W. FEINDEL, R. DESBIENS, D. TAMPIERI and Y. ROBITAILLE (Montreal, Quebec)

Background: Clinical and experimental studies suggest that the amygdala is responsible for most of the manifestations of temporal lobe epilepsy (TLE). We report our most recent experience with the intraoperative recording and stimulation of the amygdala during surgery for the treatment of TLE.

Methods and Findings: Twenty-five consecutive patients operated on under local anesthesia for TLE underwent intraoperative recording (all cases) and stimulation (13 cases) of the amygdala via a multicontact depth electrode during continual electrocorticographic and clinical assessment. The 16 males and 9 females aged 15-45 years (mean 28.9) had TLE for an average of 20.4 years. The dominant temporal lobe was involved in 13 cases. Epileptic activity was recorded from the amygdala in 24 of 25 cases. Stimulation produced the usual aura or seizure in 7 of 13 cases and/or an epileptic seizure or after discharge in 10 cases. Pre-resection epileptic activity was recorded behind the proposed resection margin in 14 cases but was no longer apparent after resection of the amygdala in 8 cases, thereby avoiding further cortical resection in the latter. Hippocampal resection was limited to the pes; mean maximum dominant cortical resection was 4.1 cm and nondominant resection 5.2 cm. There was no epileptic activity from the hippocampal resection margin. Gliosis was present in 11 of 12 periamygdaloid specimens studied histologically. Twenty-three of 25 patients are seizure-free or have > 80% reduction in seizures (mean follow-up 19.3 months).

Conclusions: Intraoperative recording and stimulation of the amygdala is useful in the surgical treatment of temporal lobe epilepsy and can guide the extent of cortical resection.

60.

Selective Transcortical Amygdalo-Hippocampectomy. Surgical Technique and Preliminary Results

A. OLIVIER, A. CUKIERT and F. ANDERMANN (Montreal, Quebec)

Thirty out of 600 patients that were submitted to temporal lobe operations as part of the treatment of medically refractory epilepsy underwent a selective transcortical removal of the amygdala and hippocampus. The rationale for this modality of treatment derived from our own experience with depth electrode recording in over 150 cases of temporal foci which has shown that in an overwhelming number of cases the onset of the seizures was at the region of the amygdala and hippocampus. The technique was inspired by Niemeyer's 1958 approach to the mesio-limbic structures. The procedure consists of exposing the lateral temporal neocortex by means of pterional craniotomy. Electrocorticography is then carried out by means of surface and depth electrodes. A small cortical incision (2.0 cm) in the second temporal gyrus or through the depth of the second temporal sulcus is made. A thin corridor is fashioned through the temporal subcortical white matter until the roof of the temporal horn is reached. Self retractors are used to provide a good view of the hippocampus and collateral eminence. Using a sequence of clear landmarks, the hippocampal formation is dissected using an extrictly subpial cortical resection with the ultrasound dissector (CUSA). The parahippocampus is then removed. The hippocampus is tilted laterally and transected at the level of the tail and removed "en bloc". The removal is carried forward with the resection of the amygdala and whole uncus. The results were comparable with those of standard temporal resection. No complications have occurred. The purpose of the presentation is to discuss the surgical anatomy of the procedure, its indications and preliminary results.

61.

Surgical Treatment of Epilepsy: The Problem of Lesion/Focus Incongruence

D. CLARKE, A. OLIVIER, D. FISH and F. ANDERMANN (Montreal, Quebec)

The surgical approach to the treatment of epilepsy has been to remove the epileptogenic focus. In instances where a radio-

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graphic lesion is detected in a surgically acceptable location which corresponds to the epileptogenic focus, there has been no dilemma in terms of treatment. Removal of the lesion in such cases is, at the same time, a removal of the focus. This study suggests an alternative strategy for treating patients with intractable epilepsy in whom a radiographically visualized lesion is not congruent with the electroencephalographic focus. Sixty seizure patients (divided into three groups of twenty), all of whom have had surgical resection for intractable epilepsy, are reviewed. Group A patients represent the most common situation of an electroencephalographic focus and radiographic lesion which are congruent (lesion sites: 13 temporal, 6 frontal, 1 parietal); these patients underwent resection of the lesion/focus tissue with very good results. Group B consists of patients in whom the focus and the lesion are incongruent (lesion sites: 14 temporal, 4 parietal, 2 occipital); these patients underwent resection of the focus only. Group C patients are those whose focus and lesion are incongruent (lesion sites: 12 temporal, 7 frontal, 1 parietal); these patients underwent resection of the lesion only. The very good surgical outcome, in terms of seizure control, of Group C compared with the very poor outcome of Group B leads the authors to conclude that, where a choice between a focus and a lesion is imperative, the radiographic lesion should be given priority in terms of surgical resection.

62.

Influence of Age at Surgery and Interval Between Onset of Seizure and Surgery, on Seizure Control Following Temporal Lobectomy

J.G. VILLEMURE, K. WORSLEY, W. CHOI and T. RASMUSSEN (Montreal, Quebec)

Two hundred fifty-five charts of patients having had a temporal lobectomy for control of seizures, with a follow-up of at least two years, were reviewed to determine the influence of the age of the patient at surgery or the influence of the interval between the onset of seizure and surgery on the success of the operation.

There were 99 females and 156 males; 131 temporal lobectomies were left, 124 were right. Age at onset of seizures varied from birth to 46 years old (median 10); age at operation ranged from 5 to 55 years (median 23) and interval between onset of seizures and surgery was from 1 to 42 years (median 13).

Follow-up ranged from 2 to 25 years (median 12). Seizure outcome was graded (0 to 4) according to Rasmussen's classification. 36.5% have become and remained seizure free; 25.5% have had continuous or late recurrence of seizures following surgery, but at a frequency of less than 2% their original seizure frequency; 38% have continued to have seizures at a frequency greater than 2% their pre-operative seizure frequency. Statistical treatment of these data does not show any relationship between the age at time of surgery or the interval between onset of seizures and surgery, on the seizure control following temporal lobectomy.

63.

Frontal Lobe Resections in Epilepsy

A. CUKIERT, A. OLIVIER and F. ANDERMANN (Montreal, Quebec)

Forty-nine patients who underwent frontal lobe surgery for epilepsy with a minimum of 1 year follow-up were studied. Group 1 consisted of 33 patients submitted to a frontal resection alone and Group II of 13 patients submitted to a frontal resection associated to an anterior callosotomy. Partial and generalized seizures were present in both groups but generalized seizures prevailed in Group II. Group II also disclosed more generalized EEG patterns. Early post-operative seizures occurred in 45% of the cases in patients in Group II. The main neuropathological findings were gliosis and scars. No pathology was present in 27% of the specimens in Group 1 and in 31% in Group II. There was a statistically significant relationship between the presence of spikes on the post-operative ECoG and/or early post-operative seizures to a bad outcome in both groups. Traumatic epilepsies disclosed a significantly better outcome. There was no relationship between the size of resection and outcome. Group II results are similar to those obtained in a similar population of patients submitted only to a callosal section. There seems to be no advantage in performing a frontal cortical resection in this situation.

64.

The Role of Corpus Callosum in the Synchronization of Epileptiform Discharges During Wakefulness and Sleep

R. DESBIENS, L.F. QUESNEY and A. OLIVIER (Montreal, Quebec)

Inter-Hemispheric Synchronization (IHS) of epileptiform discharges is dependent upon cortico-callosal and subcortico-cortical mechanisms. The latter are most likely operational during sleep. We decided to study, during wakefulness and sleep, the mechanism of IHS in patients with secondary generalized epilepsy submitted to total callosotomy.

Methods: We studied 2 patients with unilateral and bilaterally synchronous spike-wave discharges who underwent total callosotomy. Prolonged EEGs including wakefulness and sleep were obtained before and after callosal section. EEGs were visually analyzed. Spike-wave discharges were classified in 2 groups: unilateral (focal, regional, hemispheric) or bilaterally synchronous. The ratio of synchrony (RS) (number of bilaterally synchronous discharges/total discharges) was calculated during wakefulness and sleep, before and after total callosotomy.

Results: 4483 epileptic discharges were studied, 2201 during wakefulness, 2282 during sleep. The mean RS during wakefulness before and after callosotomy was 0.86 and 0.24 respectively. During sleep, corresponding values were 0.84 and 0.51. The decrease in the RS after total callosotomy was statistically sig-

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nificant both during wakefulness and sleep. After total callosotomy, the RS during sleep (0.51) was higher ($p < 0.005$) than during wakefulness (0.24).

Conclusions: Total callosotomy decreases the incidence of bilaterally synchronous epileptiform discharges during wakefulness but does not abolish them. The ratio of synchrony, remains high during sleep after total callosotomy. Our findings support the role of cortico-callosal and subcortico-cortical mechanisms of inter-hemispheric synchronization in patients with secondary generalized epilepsy. The former mechanism occurs mostly during wakefulness and the latter is evidenced mostly during sleep after callosotomy.

65.

Proportional Systems Based on the Corpus Callosum for Cerebral Localization and Reporting the Extent of Cortical Resection

A. OLIVIER and A. CUKIERT (Montreal, Quebec)

A horizontal callosal line was defined by means of two points located at the most inferior aspect of the rostrum and splenium.

Anterior and posterior callosal planes (ACP and PCP) were created perpendicular to the horizontal callosal plane (HCP) and passing through the most anterior part of the rostrum and the most posterior region of the splenium (PS) respectively. A middle callosal plane (MCP) was then created between the two. The central sulcus can be delineated by a line starting at the intersection between the MCP and HCP laterally and a point 0.5 cm in front of the PCP mesially, thus defining the fronto-parietal border. A temporal line was created by joining PS to the most antero-inferior part of the temporal horn.

Anterior and posterior temporal planes (ATP, PTP) were created passing through the top of the temporal lobe and PS respectively and perpendicular to the temporal plane. A middle temporal plane (MTP) was created between them. The volumes between the most anterior part of the frontal lobe and ACP, ACP and MCP, MCP and PCP, ATP and MTP, MTP and PTP were further subdivided in four by means of 3 additional planes parallel to the original ones. The frontal and temporal volumes were then divided in 4 at the respective perpendicular coronal plane. This methodology created volumes that could be studied using computer-assisted MRI/DSA/CT/PET analysis in terms of anatomy (normal and pathological), localization and volumetric measurements. The technique can also be used for pre-operative planning, for placement of depth electrodes, of callosotomy, cortical excisions and lesionectomies and for reporting the extent of epilepsy surgery.

SATURDAY, JUNE 27, 1992 – P.M.

G. Cerebrovascular

66.

Repetitive Forebrain Ischemia in Gerbils: PEG-SOD Does Not Attenuate Neuronal Damage in the Hippocampus

M.S. IJAZ, A. SHUAIB, R. MAZAGRI, J. KALRA and W. HOWLETT (Saskatoon, Saskatchewan)

Oxygen free radicals (OFR) have been implicated in the pathogenesis of neuronal damage in cerebral ischemia and OFR scavengers have been shown to decrease injury when used in transient global ischemia. It has been postulated that the increased neuronal damage with repetitive ischemia may be secondary to activation of OFR in the reperfusion period. To test for the role of OFRs in repetitive ischemia in gerbils, we used a free radical scavenger superoxide dismutase (PEG-SOD) in these experiments. Repetitive ischemia (3 minutes times 3) was used in all animals and two doses of PEG-SOD were infused intravenously (600 and 1200 units per animal). Six animals were used for each dose and damage was assessed using the silver impregnation method. Damage score was 1 = < 25% damage, 2 = 25 to 75% damage, 3 = > 75% damage, and 4 = infarction. When compared to control animals (N = 6) the extent of damage was no different in the animals treated with the two doses of PEG-SOD (N = 6 at each dose). The extent of damage was similar in the cortex, hippocampus, striatum, medial geniculate nucleus, thalamus, and the substantia nigra reticulata. Our study therefore shows that in the doses tested, PEG-SOD does not appear to offer protection in repetitive ischemia in gerbils when used intravenously.

67.

Cerebral Damage Following Repetitive Ischemia of Differing Durations in Gerbils

B.M. KEEGAN, A. SHUAIB, M.S. IJAZ and W. HOWLETT (Saskatoon, Saskatchewan)

A reliable model that covers the full spectrum of cerebral damage following repetitive ischemia is needed to evaluate possible protective interventions.

Ischemic episodes of short duration (SHORT) (2 or 3 min.) and long duration (LONG) (4 to 5 min.) were repeated 3 times on each gerbil with 1 hour of reperfusion allowed between the episodes. The ischemia was induced by bilateral clamping of the carotid arteries and damage was observed by silver impregnation staining methods. A 4 point scale was used where 0 = no damage and 4 = infarction. Significantly more damage was found in the LONG group (n = 7) than in the SHORT group (n = 9) in the cortex (LONG = 3.00, SHORT = 1.33, p = .008), striatum (LONG = 3.50, SHORT = 1.83, p = .01), hippocampus CA-1 (LONG = 3.29, SHORT = 2.44, p = .006) and the medial geniculate nucleus (LONG = 2.21, SHORT = 1.22, p = .003).

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No difference was found in the substantia nigra reticulata (LONG = 2.00, SHORT = 2.33, p = .64).

Our results suggest that the extent of damage after ischemia is proportionate to its duration. The short duration ischemia may be useful for testing therapies with limited benefits whereas the longer duration of ischemia may prove helpful for testing more potent therapies.

68.

Hypothermia in the Post-Ischemic Period Protects Hippocampal Neurons in the Repetitive Model of Global Ischemia

D. TRUELOVE and A. SHUAIB (Saskatoon, Saskatchewan)

Transient global ischemia results in predictable damage to the hippocampus (CA1, CA4), the cerebral cortex and the striatum. There is recent evidence that the extent of neuronal damage from repetitive ischemia is greater than the damage from a single insult of similar duration. Furthermore, in addition to the damage in the hippocampus, striatum and the cortex, neuronal injury is also evident in the thalamus, medial geniculate nucleus and substantia nigra reticulata. Previous studies have established that mild intra-ischemic hypothermia has a marked neuroprotective effect in transient global ischemia. The present study was carried out to evaluate whether mild post-ischemic hypothermia affords the same degree of protection as this is more clinically relevant. We used 10 Mongolian gerbils whose brain temperature was kept at approximately 38 degrees Celsius and rectal temperature was kept at 36 degrees Celsius while subjected to three two minute episodes of global brain ischemia with 20 minutes of reperfusion allowed between each ischemic episode. Five of these animals were then set aside as controls. The other five animals received three hours of mild post-ischemic hypothermia which commenced immediately after the insult. During these three hours, brain temperature was maintained at between 35 and 36 degrees Celsius and rectal temperatures at 33 to 34 degrees Celsius. Both sets of animals were sacrificed 7 days afterwards and were examined for histological evidence of damage with the silver staining method. The damage from repetitive ischemia was completely attenuated by mild post-ischemic hypothermia. Our results suggest that hypothermia, when applied immediately after repetitive ischemia, is protective to the brain and may be of use in certain clinical settings.

69.

Intracellular Calcium Concentration is Different in Ischemia Sensitive and Ischemia Resistant Primary Cultures of Cerebellar Granule Neurons

W. CODE, Z. ZHAO, L. PENG, A. SHUAIB and L. HERTZ (Saskatoon, Saskatchewan)

A number of mechanisms cause neuronal damage secondary to ischemia, including ATP depletion, free radical formation and excitotoxicity leading to receptor activated accumulation of calcium. We have previously demonstrated a difference in ischemia sensitivity of neurons between normal (NK:5.4 mM) or elevated (HK:25.4 mM) potassium concentration. (Soc. for Neuroscience abstract 1991). We hypothesize that this increased sensitivity may be secondary to increased build-up of free intracellular calcium. Cultures grown in HK respond to 50 uM glutamate with a 160% increase in free intracellular calcium concentration as demonstrated with Indo-1 and a microfluorimeter. Meanwhile, NK cultures increased free intracellular calcium concentration by significantly less at 110%. In HK cultures, but not NK cultures, the increase can be blocked by using a calcium free buffer (with EGTA). Similarly, experiments with ^{45}Ca corroborate the above showing increased calcium uptake secondary to glutamate with HK cultures and dependent on calcium containing medium. NK cultures showed no increase in ^{45}Ca uptake secondary to 50 uM glutamate. These findings are consistent with NMDA receptor preponderance on HK neurons and AMPA receptors on NK neuron (Cox et. al., 1990 Neuron, 4:941), and again link the NMDA receptor with glutamate neurotoxicity.

70.

A ^{31}P Magnetic Resonance Spectroscopy Study of the Effect of Mannitol on Forebrain Ischemia

F.E. HRUSKA, P. HAZENDONK, F.W. YANG, R. BUIST, R. TYSON, G. SUTHERLAND and J. PEELING (Winnipeg, Manitoba)

Mannitol has been shown to protect against ischemic neuronal injury. This has been attributed to improvement in cerebral blood flow (CBF) during ischemia secondary to decreased blood viscosity and/or to direct vessel dilation, so that energy/membrane failure is delayed or prevented. In this study ^{31}P magnetic resonance (MR) spectroscopy has been used to evaluate the effect of mannitol administered prior to transient ischemia on brain energy status, exploring the above hypothesis.

Thirty-two male Sprague-Dawley rats weighing 250-320 g were used. Groups of 8 rats received lg/kg mannitol, .25g/kg mannitol, saline, or no treatment 5 min. prior to forebrain ischemia (bilateral carotid occlusion plus hypotension to 50 mmHg for 10 min.). Pre- and post-ischemia blood glucose and gases were normalized. ^{31}P MR spectra were obtained in 1 min. blocks prior to, during, and for 40 min. following ischemia. Changes in pH and the Pi, PCr, and ATP peak heights were compared between groups.

No differences were found between groups prior to ischemia. During ischemia all animals experienced profound cerebral energy failure and acidosis (pH = 6.2). No differences in pH were observed between groups. In the lg/kg mannitol group the fall in PCr and ATP differed slightly compared to other groups, and a difference in the rise of Pi was observed. No differences in recovery of pH, Pi, PCr or ATP were observed post-ischemia, although in all groups ATP recovery was impaired, reaching only 80% of pre-ischemic level.

These results do not support the hypothesis that mannitol treatment improves CBF and prevents ischemic energy failure. Any protective effect of mannitol may be due to its effect on brain edema or its free-radical scavenging properties. Post-ischemia brain mitochondrial function is not fully restored.

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71.

Effect of Altering Blood Glucose Levels in Cerebral Ischemia Studied Using ^{31}P NMR Spectroscopy

R. TYSON, J. PEELING and G. SUTHERLAND (Winnipeg, Manitoba)

^{31}P nuclear magnetic resonance spectroscopy was used to study the effect of blood glucose on high-energy phosphate metabolite levels and tissue pH prior to, during and following transient forebrain ischemia (bilateral carotid occlusion plus controlled hypotension at 45 mmHg for 10 min.) in hypo-, normo- and hyperglycemic rats. Blood glucose in each group was further altered to give post-ischemic hypo-, normo- and hyperglycemic subgroups, maintained for 1 hr.

During ischemia, the decrease in tissue pH and hydrolysis of high-energy phosphate metabolites depended on the pre-ischemia blood glucose concentration. ATP and PCr decreased more rapidly in hypoglycemic rats compared to normo- or hyperglycemic animals ($p < 0.0023$), which showed no differences. Post-ischemic hyperglycemia delayed recovery of tissue pH, ATP and PCr in all groups, while insulin administration immediately following ischemia increased the rate of recovery of ATP in hyperglycemic animals ($p = 0.0009$). ATP remained significantly below pre-ischemia level in all subgroups at 1 hr post-ischemia ($p < 0.0003$), while PCr was lower in those subgroups hyperglycemic prior to and/or following ischemia ($p < 0.0002$). In animals maintained severely hypoglycemic throughout the experiment, cardiac function was compromised post-ischemia.

Maintenance of normoglycemia following ischemia optimizes the recovery of phosphate metabolites and pH. No additional benefit is gained by inducing severe hypoglycemia post-ischemia. The administration of glucose following ischemia is detrimental to recovery of high-energy metabolites and pH, and may enhance injury. Manipulating post-ischemic blood glucose concentration in the clinical setting may therefore be of benefit.

72.

^{31}P Magnetic Resonance Spectroscopy Study of Forebrain Ischemia in Diabetic and Non-Diabetic BB Rats

G. SUTHERLAND, J. PEELING, E. SUTHERLAND, R. TYSON, F. DAI, P. KOZLOWSKI and J. SAUNDERS (Winnipeg, Manitoba; Ottawa, Ontario)

Using spontaneously diabetic BB rats, the effect of chronically maintained blood glucose levels on the degree of energy failure and the brain pH change during an ischemic insult, and on the subsequent recovery following reperfusion, has been studied using *in vivo* ^{31}P magnetic resonance spectroscopy. Short duration forebrain ischemia (10 min. carotid occlusion plus hypotension of 50 mmHg) was induced in diabetic and non-diabetic male BB rats whose blood glucose levels were maintained with insulin. Spectra were obtained in one minute blocks before, during and for one hour following ischemia. Prior to ischemia, hypoglycemic (blood glucose < 3 mM) diabetic rats showed an increased inorganic phosphate peak intensity, with no significant pH change, compared to other groups. During ischemia, the decrease in tissue pH and the hydrolysis of high energy phosphate metabolites depended on pre-ischemic blood glucose concentrations. Among hyperglycemic BB rats, similar ischemia-induced changes were found for subgroups with blood glucose levels of 13.7 ± 1.2 and $20.3 \pm .6$ mM, in keeping with the known down-regulation of glucose transport in diabetes. The decline in the phosphocreatine level during ischemia was not significantly different between groups. With reperfusion both inorganic phosphate and pH values rapidly returned to pre-ischemia values. Phosphocreatine levels, however, did not recover in hyperglycemic diabetic animals, with the degree of residual impairment dependent on the pre-ischemia glucose level. The results indicate that optimal management of diabetes may lessen the degree of injury within the ischemic penumbra, which is of greater size in diabetic patients.

73.

Ischemic Neocortical Protection With U74006F - A Dose Response Curve

G. SUTHERLAND, J. PEELING and N. HAAS (Winnipeg, Manitoba; Ottawa, Ontario)

In a previous report we showed that while ischemic neocortical injury is alleviated by the pre-ischemia administration of U74006F, a lipid peroxidation inhibitor, injury within either the hippocampus or striatum is not significantly changed. This study examines the extent of ischemic neuronal protection afforded by administration of various pre-ischemic doses of U74006F.

Fifty-four male Sprague-Dawley rats weighing 250-300 g were used. Nine control rats received vehicle (0.02 M citrate buffer pus 0.8% NaCl) intravenously (IV) while groups of 9 rats received U74006F (IV) at a dosage of 0.3, 1, 3, 7 or 10 mg/kg, 30 min. prior to ischemia. Forebrain ischemia was induced by bilaterial carotid occlusion plus controlled hypotension (50 mmHg) for 10 min. while brain temperature was maintained at 37.7°C. Brains were perfusion fixed on day 7 post-ischemia for histopathological examination.

For both the hippocampus and striatum neuronal injury was not significantly different between groups. In the frontal neocortex (watershed zone between that supplied by the anterior and middle cerebral arteries) the frequency of ischemic neurons was significantly decreased ($p < 0.05$) in the 7 mg/kg group (0.32 ± 0.07) compared to the control group (0.54 ± 0.07). The reduction in ischemic neuronal injury in the other groups (0.3 mg/kg (0.52 ± 0.05); 1 mg/kg (0.42 ± 0.7); 3 mg/kg (0.54 ± 0.09); 10 mg/kg (0.47 ± 0.08)) was not significant.

These results indicate that the pre-ischemia dose of U74006F that affords optimal neocortical protection in this rat forebrain ischemia model is 7 mg/kg.

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74.

The Effect of Deoxycoformycin on Forebrain Ischemia in Rat

S. DELANEY, G. SUTHERLAND, J. PEELING, J. GEIGER and F. YANG (Winnipeg, Manitoba)

Adenosine, an important neuromodulator, has been found to be neuroprotective. One approach to increase endogenous adenosine levels is by inhibition of adenosine deaminase, the major catabolic enzyme of adenosine. Accordingly we tested whether deoxycoformycin (DCF), a potent inhibitor of adenosine deaminase, protects against ischemic neuronal damage.

Thirty-one male Sprague-Dawley rats weighing 220-350 gm were used. Seven sham-operated rats received an intraperitoneal (IP) injection of DCF (5 mg/kg) while the three remaining groups of 8 animals each received DCF 0.5 mg/kg, DCF 5 mg/kg or saline two hours prior to transient forebrain ischemia [bilateral carotid occlusion plus controlled hypotension (50 mm/Hg) for 10 min.]. Brains were perfusion fixed on day 5 post-ischemia for histopathological examination.

For all regions examined (hippocampus, striatum and neocortex), there was no significant difference in the degree of neuronal injury between the DCF and saline treated groups. Anesthetic management, together with surgical manipulation and DCF treatment, had no adverse neuronal effect.

These results suggest that enhancing adenosine levels during or following transient forebrain ischemia is of no significant benefit in protecting against neuronal injury. It is possible that the neuroprotective effect of adenosine is limited by the adenosine receptor level rather than by the level of the receptor agonist.

Supported by: the Canadian Heart and Stroke Foundation

75.

Streptokinase in the Treatment of Cerebral Vasospasm After Subarachnoid Hemorrhage in Dogs

F.J. ESPINOSA, P.M. GROSS, J.-H. TAO, K.O. GREEN, D.S. WAINMAN and J.J. PANG (Kingston, Ontario)

Intrathecal thrombolysis with use of t-PA and rt-PA after SAH has proved effective in preventing chronic vasospasm in monkeys. Also, within 24 hr. after hemorrhage in cats streptokinase (SK) and streptodornase proved effective in lysing the SAH clots but produced diffuse meningoencephalitis. Streptokinase, however, had not been studied singly in chronic experiments to assess whether VSP may be prevented and the meningoencephalitis that develops when used with streptodornase does not occur. We studied 33 dogs of either sex under general anesthesia; they were randomly assigned to receive SK 150,000 μ (1 ml) or saline (1 ml) intrathecally. Six animals died immediately after creation of the SAH and before they received SK or saline. Of the remaining 27 dogs available for analysis, 15 received SK and 12 saline 24 hr after the SAH via an Ommaya reservoir implanted at the time of the craniotomy. Variables measured or observed before and 7 days after SAH included neurological status, BP, vessel caliber on cerebral angiograms, structural and morphological changes of the cerebral arteries on electron microscopy, permeability of cerebral vessels to horseradish peroxidase, and the presence or absence of hematomas in the subarachnoid space and/or meningoencephalitis. In the placebo group delayed neurological deficit developed in 2 dogs 2 and 4 days after clot placement. In the SK group such deficit occurred in 1 dog 2 days after the SAH. Overall, vasospasm was more common and more severe in the SK group. Significant VSP (31% to 100% reduction in vessel calibre) developed in 25% (3/12) of the dogs in the placebo group, and in 66% (10/15) of the dogs in the SK group. The average percentage reductions in vessel calibre of the maximally constricted vessel in each dog was 23% in the placebo group and 37% in the SK group. The electron microscopic and pathological findings will be discussed.

76.

Efficacy of Retrograde Perfusion of the Cerebral Vein with LY2316175 Hours After Occlusion of the Middle Cerebral Artery in Rat Brain

N. INOUE, T. NAGAO and Y.L. YAMAMOTO (Montreal, Quebec)

Our previous study showed that treatment after 3 hrs. focal ischemic brain using transvenous perfusion of the brain (TVPOB) with the antioxidant, LY231617, was effective, while IV treatment was not effective. In addition, we have now extended our study for the effect of TVPOB with LY231617, starting treatment 5 hrs. after occlusion of the left middle cerebral artery (MCAO).

Male Sprague-Dawley rats with MCAO were assigned to one of three groups. Control group: MCAO without any treatment for 7 hrs. IV and TVPOB treated groups: LY231617, 10 mg/kg/hr., starting 5 hrs. after MCAO for 2 hrs. Cerebral blood flows (CBF) with ^{14}C-iodoantipyrine, infarct volume, and protein kinase C (PKC) activity by ^{3}H-phorbol ester, were measured. Data were analyzed by ANOVA followed by Tukey test.

TVPOB group showed a significant increase of CBF (Table) with significant reduction (37%) of infarct volume (mm^3) (208.9 ± 61.8 to 130.6 ± 34.6, $p < 0.05$), but there was no significant reduction of infarct volume in IV group. The effect for PKC activity revealed significant preservation in the cortical and subcortical ischemic areas associated with increase of CBF.

Table. Measurement of CBF (ml/100g/min.) (mean ± SD)

	Control (n = 7)		IV (n = 7)		TVPOB (n = 7)	
	LT	RT	LT	RT	LT	RT
SMC	7 ± 8	126 ± 15	9 ± 7	111 ± 25	43 ± 25#	123 ± 17
APC	4 ± 4	119 ± 17	4 ± 4	109 ± 24	37 ± 25#	116 ± 16
PPC	10 ± 13	119 ± 15	15 ± 18	111 ± 23	43 ± 24*	117 ± 18
Caudate	11 ± 13	122 ± 20	18 ± 20	103 ± 24	74 ± 27##	112 ± 21

SMC: sensorimotor cortex, APC: anterior parietal cortex, PPC: posterior parietal cortex *: $p < 0.05$ significant difference from the control #: $p < 0.05$, ##: $p < 0.01$ significant difference from control and IV groups

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These observations indicate that TVPOB with LY231617 has therapeutic effects even after a 5 hr delay in the initiation of treatment following MCAO in rat.

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H. Neurobiology

77.

Phagocytosis and Lymphocyte Emperipolesis in Human Astrocytes and Microglia

M. FURER, V. HARTLOPER and A. NATH (Winnipeg, Manitoba)

Astrocytes ingest cellular debris and myelin in pathological conditions and may contain viable lymphocytes within their cytoplasm (emperipolesis) in Multiple Sclerosis and some brain tumors.

An *in vitro* system was developed to study the properties of phagocytosis, lymphocyte adhesion and emperipolesis in human astrocytes, microglia and macrophages. Cultures of human fetal astrocytes (HFA), adult astrocytes (AA) and fetal microglia were established. Glial cells and macrophages from peripheral blood were cocultured with zymosan and different types of lymphocytes.

Zymosan phagocytosis was first seen at 2.5 hrs., and at 4 days, 80% of microglia and 76% of macrophages engaged in phagocytosis. Two percent of HFA and no AA ingested zymosan. A mean of 27 particles were ingested per cell.

Lymphocyte adhesion to astrocytes was observed at 20 min., and at 1 hr., lymphocytes were seen inside the cytoplasm of both HFA and AA. At 3 days, 20% of AA and 16% of HFA were engaged in emperipolesis. This phenomenon was not seen in microglia or macrophages. A mean of 3 lymphocytes were internalized by each astrocyte. Different T-cell populations varied in their ability to engage in emperipolesis in HFA. At 8 hrs., CD8+ lymphocytes were internalized in 83% and CD4+ lymphocytes in 10% of HFA.

Lymphocyte emperipolesis in HFA was temperature- and calcium-dependent. A range of adhesion molecules and cell surface antigens were assessed as potential mediators of this phenomenon. Lymphocyte adhesion was mediated by CD8 antigen.

Lymphocytes either proliferated within the cytoplasm of the astrocytes, underwent lysis or caused disruption of intermediate filaments of the astrocytes.

This lymphocyte-astrocyte interaction may be important in the pathogenesis of certain inflammatory diseases of the brain, in the transmission of viral infections to the central nervous system, or as a mechanism of host defence and tumor surveillance.

78.

Three-Dimensional Analysis of the Microvasculature in the Normal and Injured Rat Spinal Cord: Microangiography and Scanning Electron Microscopy with the Corrosion Cast Technique

I. KOYANAGI and C.H. TATOR (Toronto, Ontario)

The purpose of this study was to investigate normal vascular patterns in the rat spinal cord and the alterations by clip compression injury. Female Wistar rats were transcordially perfused with silicone rubber (Microfil, Flow Tec, Inc.) for microangiography. The perfused spinal cords were cleared with alcohol-methylsalicylate. For scanning electron micrography (SEM), perfusion with polyester resin (Mercox, Dai-nihon, Inc.) was performed. The spinal cords were digested in alkaline solution, and the resulting microvascular casts were observed with SEM. For analyzing the injured spinal cord, the perfusion was carried out at 15 minutes, 1, 4 or 24 hours after a 53g compression injury at C8-T1. Twenty-eight rats were used for silicone rubber microangiography, and nine rats were examined with SEM.

In the normal rats, the centrifugal arterial system from the sulcal arteries provided the major blood supply to both the gray and white matter. Large veins, which coursed obliquely to the dorsal surface, were identified in the posterior columns. The injured spinal cord showed marked ischaemia and hemorrhages at the injury site. The hemorrhages predominated in the posterior columns and extended rostrally and caudally for 2-7 mm from the injury site. The remote hemorrhages originated from the large veins in the posterior columns. Disruption of sulcal arteries and their branches produced extensive ischaemia in both gray and white matter.

We conclude that these techniques provided an excellent method of assessing the three-dimensional distribution of the vasculature in the normal and injured rat spinal cord.

79.

Ca^{2+} Neurotoxicity is not Solely Dependent on a Sustained Suprathreshold Rise in Intracellular Ca^{2+}

M. TYMIANSKI and C.H. TATOR (Toronto, Ontario)

It is widely believed that neurotoxicity is triggered by CA^{2+} influx causing a sustained rise in the free cytoplasmic calcium concentration ($[Ca^{2+}]_i$). If this is true, then neurotoxicity should depend only on the magnitude- and the time-course- of the elevation in $[Ca^{2+}]_i$, a view which conflicts with frequent observations that elevated $[Ca^{2+}]_i$ is not easily related to cell death. We tested this hypothesis in spinal neurons using the fluorescent CA^{2+} indicator fura-2 $[Ca^{2+}]_i$, its time-course, and its neurotoxic effects were monitored while evoking the same sustained $[CA^{2+}]_i$ elevations through two independent pathways; through voltage-sensitive calcium channels by depolarization with 50 mM potassium (high-K^+) and through glutamate activated channels with the application of 250 μM glutamate (high-glu^-). An analysis of neuronal survival coupled with several indices of neuronal CA^{2+} homeostasis revealed that the neurotoxic effects

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of high-glu⁻ were 4-5 fold greater, and occurred much more rapidly, than those of high-K^+ when $[Ca^{2+}]_i$ was elevated to the same degree (log-rank $\chi^2 = 58.44$, $p < 0.0001$). Thus, we conclude that the extent of CA^{2+}-mediated neurotoxicity is amplified when CA^{2+} influx occurs through glutamate-activated channels, and does not depend solely on a sustained rise in $[Ca^{2+}]_i$. This result explains the frequent failure of conventional Ca^{2+} channel blockers (e.g., nimodipine) in improving outcome from experimental neuronal injury (e.g., Sanada et. al. 1990, Steen et. al. 1984, Kobayaski et. al. 1988), as these blockers impede only Ca^{2+} influx through VSCC's (see above) which cause relatively less neurotoxicity. Our results indicate that future research on neuroprotection by Ca^{2+} channel blockade should be centred on blockers of glutamate-activated channels.

80.

A Novel Approach to Preventing Ca^{2+} Neurotoxicity with Membrane-Permeant Calcium Chelators

M. TYMIANSKI and C.H. TATOR (Toronto, Ontario)

CNS ischemia and trauma cause excessive mortality and morbidity among neurosurgical patients. The damage to central neurons is thought to be partly mediated by a toxic rise in intracellular calcium concentration ($[Ca^{2+}]_i$). To date, the philosophy of managing Ca^{2+} neurotoxicity was to isolate and to block the many known pathways of calcium entry into neurons by a polypharmaceutical approach. We hypothesized that BAPTA/AM (1,2-bis(2-aminophenoxy) ethane-N,N,N′,N′-tetraacetic acid), a membrane permeant buffer with high Ca^{2+} affinity, will chelate intracellular Ca^{2+} irrespective of its source, thus circumventing the problem of neurotoxicity due to calcium influx through multiple pathways. Spinal neurons in explant cultures were challenged with a 45 minute exposure to 250μM glutamate, causing a massive Ca^{2+} influx. $[Ca^{2+}]_i$ was measured with the Ca^{2+} indicator fura-2, and cell survival was assessed with trypan blue. In control experiments (121 neurons), glutamate caused a large fraction of and neuronal death (77 ± 5.7%). When glutamate-challenged neurons were preloaded with 10μM BAPTA/AM (139 neurons), the peak rise in $[Ca^{2+}]_i$ was unaltered ($t = 0.578$, $p = 0.564$), but there was less neuronal death (45 ± 14%; $t = 2.0589$, $p = 0.073$). With 100μM BAPTA/AM (111 neurons), the calcium chelator significantly attenuated the glutamate-evoked peak $[Ca^{2+}]_i$ ($t = 6.774$, $p < 0.0001$), and produced a dramatic neuroprotective effect-lowering neuronal death to 13 ± 1.2% ($t = 12.01$, $p < 0.0001$). The results strongly indicate that the Ca^{2+} buffer BAPTA/AM is a powerful neuroprotective agent. We believe that protection of neurons from injury using Ca^{2+}-buffers provides an alternative in situations where conventional approaches to neuroprotection have failed. As a consequence, we are currently planning experiments *in vivo* to assess the neuroprotective effects of BAPTA/AM in a rat spinal cord injury model, and in a rat ischemia model.

81.

An Evaluation of Direct Current Stimulation in the Rodent Spinal Cord

R.J. HURLBERT and C.H. TATOR (Toronto, Ontario)

Direct current (DC) fields have been shown to be of benefit in the treatment of acute spinal cord injury in several animal models. The purpose of this experiment was to evaluate the safety and efficacy of two methods of DC stimulation (disc vs cuff electrodes) in the normal rat spinal cord.

Experiments were divided into two groups: toxicity analysis and field mapping. In the first group, 64 normal rats were implanted with DC stimulators (0-50 μA) and followed for a period of two days to 12 weeks. The current was delivered by epidural disc or cuff electrodes positioned at C7 and T2. Severe pathological changes occurred in the spinal cords of animals with disc electrodes subjected to currents as low as 3 μA. Stimulation with cuff electrodes significantly reduced the amount of neurotoxicity caused by the applied fields. However, pathological changes could still be found with currents as low as 1.5 μA.

In the second set of experiments, 10 animals (5 with disc electrodes, 5 with cuff electrodes) underwent field mapping within the spinal cord from C7 to T2. Stimulation with disc electrodes produced a large dorsal to ventral voltage gradient especially high in the vicinity of the stimulating electrodes. Similar gradients were not present with the cuff electrode configuration.

We conclude that even small amounts of DC stimulation can be detrimental to the uninjured rat spinal cord. However, the use of cuff electrodes can improve the tolerance of the CNS to these currents. In addition, cuff electrodes more evenly distribute the electrical field. These findings have important implications for the continued study of DC fields and acute SCI.

82.

Functional Motifs of the Nerve Growth Factor Receptor Heterodimer: Molecular Modelling and Predictive Testing

R.J. RIOPELLE, S. MYERS, S. DOSTALER and D. WEAVER (Kingston, Ontario)

Cytoplasmic regions of the two proteins constituting the receptor heterodimer for Nerve Growth Factor ($p75^{ngfr}$ and $p14^{prototrk}$) were searched for motifs resembling the predicted secondary structure of the tetradecapeptide mastoparan. Potential sequences were modelled using a semi-empirical molecular mechanical force field approach. The sequence $p75^{ngfr}$ 367-379 represents a highly conserved domain predicted to be involved in NGF signal transduction involving G-protein mechanisms. Biological testing of a peptide homologous to $p75^{ngfr}$ 367-379 with NGF-responsive cellular targets supports this prediction.

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83.

Actions of Ciliary Neurotrophic Factor on a Teratocarcinoma Cell Line

S.K. GUPTA, A. HAGGARTY, R.J. RIOPELLE, R.J. DUNN, P.M. RICHARDSON and S. CARBONETTO (Kingston, Ontario; Montreal, Quebec)

CNTF (ciliary neurotrophic factor), one of the few neurotrophic factors with known amino-acid sequence, is of potential clinical interest for several reasons including its ability to support the survival of injured motor neurons. Little is yet known about the CNTF receptor or its second messenger systems for neuronal survival and differentiation. The P-19 teratocarcinoma cell line has been investigated as a possible source of tissue for studies of CNTF signal transduction. CNTF, at picomolar concentration, prevents the death of P-19 cells that usually follows withdrawal of serum from the culture medium. CNTF induces not only survival but differentiation of P-19 cells, causing them to lose a primitive cell-surface antigen and express neurofilament genes. In other studies, P-19 cells were incubated with ^{125}I-CNTF and affinity cross-linking studies were performed to demonstrate a ligand-receptor complex of approximately 170 kilodaltons. These observations on P-19 cells suggest that the cell line will be useful in studying the mechanisms of action of CNTF and raise the possibility that CNTF is involved at a very early stage of neural differentiation.

84.

Autism and Adenylosuccinate Lyase: Cloning of a cDNA Fragment of the Human Gene

E.A. FON, S.K. GUPTA, M. LUTCHMAN, S. SHEVELL, R. PALMOUR and G.A. ROULEAU (Montreal, Quebec)

Autism is a neuropsychiatric syndrome defined essentially by clinical criteria. Various lines of experimental data seem to point to a biologic etiology but no comprehensive hypothesis has emerged that fully explains the pathophysiology of the disorder. This may reflect the heterogeneity of the syndrome. We are interested in investigating the role of adenylosuccinate lyase (ADSL), an enzyme essential in two independent steps of de novo purine biosynthesis. There have been several reports of autistic children found to be deficient in ADSL. In the chicken, a complete 1.5 kb cDNA of the ADSL gene has recently been cloned using functional complementation with a liver cDNA expression library. The human ADSL gene has been localized to chromosome 22 using a chinese hamster ovary cell line (Ade-I) deficient in ADSL. In an attempt to clone the human ADSL gene, we have isolated from human muscle RNA a 200 bp fragment using reverse transcriptase PCR with primers chosen from the chicken cDNA sequence. This fragment was subcloned and showed 75% nucleic acid sequence homology and greater than 90% deduced amino acid sequence homology with the corresponding portion of the chicken cDNA. Furthermore, this fragment was localized to human chromosome 22 using a somatic cell hybrid mapping panel and it gave a specific 1.5 kb band on hybridization to a Northern blot of human RNA. In addition, using primers selected within this human fragment, we have now also isolated an 890 bp contiguous fragment that seems to represent the 3' end of gene and that gives an identical 1.5 kb signal on Northern blot of human RNA. With the cloning of the human ADSL gene, it will be possible to screen autistic children and their families for mutations and potentially elucidate the role of this enzyme in the pathogenesis of autism.

85.

ND6 Region Polymophisms in Mitochondrial Diseases

R.K. MOSEWICH, S. SHANSKE and S. DIMAURO (Saskatoon, Saskatchewan; New York, U.S.A.)

A recent report suggests that myoclonic epilepsy with ragged-red fibers (MERRF), mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS), fatal infantile cardiomyopathy (FICM) and Parkinson's disease are related mitochondrial diseases due to shared mitochondrial DNA (mtDNA) point mutations (pm) which occur in clusters. It was postulated that 3 pms in the NADH dehydrogenase subunit 6 (ND6) region shared by all diseases may be particularly important by causing electron transport chain defects and leading to further mtDNA mutations including a 4,977 bp deletion (Ozawa et al. Biochem Biophys Res Commun 1991; 176: 938-946).

We analyzed mtDNA isolated from muscle biopsies from 5 MELAS patients, 5 MERRF patients and 7 controls utilizing the polymerase chain reaction and restriction enzymes recognizing 2 of the 3 putative ND6 region sites. One of the mutations, at site 14368, was found in all patients with MELAS and MERRF as well as 6 controls. Another mutation, at site 14199, was not found in any of our patients or controls.

Our results indicate that the two ND6 mtDNA mutations studied are polymorphisms not contributing to the pathogenesis of these diseases.

86.

Specificity of Anti-Myelin Basic Protein from MS-CSF for Selected Synthetic Peptides of MBP

K.G. WARREN and I. CATZ (Edmonton, Alberta)

Eighteen synthetic peptides containing 8-25 residues and covering the length of human-MBP (h-MBP) were synthesized by the Fmoc method. Anti-MBP were isolated and purified from CSF of patients with MS by two-step affinity chromatography. Purified anti-MBP was reacted with increasing amounts of h-MBP as well as each of the 18 synthetic peptides in an initial phase assay, and then titers of free anti-MBP in the resulting mixtures were determined by a solid phase radioimmunoassay. Purified anti-MBP was neutralized by h-MBP and 6 of the 18 synthetic peptides. The antibody was completely neutralized by peptides containing overall residues 75-106 of h-MBP and was partially neutralized by peptides containing overall residues 61-75 of h-MBP. Peptides covering both the amino and carboxyl terminals of h-MBP did not neutralize purified anti-MBP. This suggests that anti-MBP purified from MS-CSF have affinity for

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discontinuous epitopes located between residues 61 and 106 on the h-MBP molecule. Alternatively anti-MBP may be polyspecific recognizing different amino acid sequences.

87.

Deafferentation Results in Reorganization of the Somatosensory Thalamus

D.F. LOUW, S.A. NORTHGRAVE and D.D. RASMUSSON (Halifax, Nova Scotia)

The deafferentation resulting from spinal cord injury or amputation may frequently provoke a variety of sensory disturbances, including debilitating chronic pain. The underlying physiological mechanisms remain cryptic. Electrophysiological events in the thalamus may contribute to the genesis of these syndromes, and it has been suggested that the increased burst activity noted in stereotaxic thalamic surgery may underlie these phenomena. We studied this in the raccoon thalamus immediately after or two months following digit amputation. Single- and multi-unit recordings were made using Parylene-coated tungsten electrodes (impedance 2-5 MΩ) and the data were analyzed using a BrainWave system.

Cutting the digital nerves or injecting lidocaine into the base of a digit (n = 11) resulted in immediate unmasking of strong lateral inhibition from adjacent digits. This inhibition was seen as either a decrease in spontaneous activity or an off-response. In the lidocaine experiments these events were reversible with recovery of the on-focus response. In the case of chronic deafferentation (amputation of the fourth digit in four animals), however, neurons in the presumptive fourth digit lobule did not exhibit this inhibition but were excited by stimulation of the adjacent digits. This is consistent with findings in the somatosensory cortex of the raccoon at similar intervals after deafferentation and may in fact be responsible for the cortical events.

These results indicate that chronic cortical plastic changes may result from subcortical reorganization. Furthermore, this plasticity must overcome the lateral inhibition that is initially unmasked as a first step in the reorganization of excitatory inputs.

Supported by: MRC.

I. Neurosurgery

88.

Spinal Cord Stimulation for Control of Ischemic Pain and Perfusion in Advanced Peripheral Vascular Disease

K. KUMAR, J.J. BURGESS and A.K. VERMA (Regina, Saskatchewan)

Epidural spinal cord stimulation (SCC) was used in 42 patients for pain associated with lower extremity ischemic vascular disease considered to be nonreconstructable. 24 patients who had a follow up between 6 to 20 months form the basis of this report. 17/24 (70%) of the cases were considered successful. 7/24 (30%) cases failed, 6 necessitating below knee amputation. The presence of diabetes 10/24 did not affect the outcome. Mean pain relief in successful group was 80% vs. 30% in the failure group. The transcutaneous oxygen partial pressure (TcP02) increased 122% with success vs. –3% with failures. These results were not universal however, as > 50% pain relief resulted in a > 50% increase in TcPOs in only half of the success group. Patients with TcPO2 at less than 3 or transcutaneous carbon dioxide partial pressure (TcPCO2) > 95 invariably end up in amputation within the first three months. Trophic ulcers did not heal if TcPO2 was less than 20. The improvement in pain and TcPO2 values also correlate with increased blood flow velocities (doppler studies) and improvement in pulse wave patterns. A tendency was also seen for ankle pressures to increase with an increase in TcPO2 and 6 patients had significant increases in the ankle/brachial ratio (> 0.15).

SCS appears to be a useful therapeutic modality in select patients of end-stage ischemic vascular disease by controlling pain and improving perfusion with the best results seen in patients with severe claudication/rest pain without trophic changes in the foot.

89.

Preliminary Experience with Halifax Clamps for Non Traumatic Indications

K. REDDY and P. MISSIUNA (Hamilton, Ontario)

The authors review their experience with seven patients using the Halifax clamps for non traumatic indications: Rheumatoid arthritis in 5,Os odontoideum in 1 and Down's syndrome in another. Five patients were female and two were male. Mean age was 46 yrs, and range was 14-70 yrs. In six patients the indication for surgery was intractable neck and suboccipital pain. One patient was symptomatic. None of the patients had significant neurologic deficits. All the patients had a predental space over 5 mm, the mean being 7.7 mm. Six patients underwent preoperative magnetic resonance (MR) imaging studies preoperatively. Five showed mild to moderate compression of the craniovertebral junction. All patients had bilateral Halifax clamps implanted. In one of our early cases, no bone graft was used, and in one other case, onlay graft (obtained from spinous processes locally) was used. The inferior clamp became unhooked on one side in one of the patients prompting us to modify our technique. We now use a bovine bone strut along with an 18 gauge wire to link the two clamps, in spite of this modification, in a 14-year-old boy with Os odontoideum, one of the inferior hooks slipped off, requiring a reoperation. The authors wish to point out that though the advantages of avoiding sublaminar wires and being relatively MR compatible prompt us to continue using this system, the Halifax clamp system does have disadvantages. We propose that bilateral clamps be used in conjunction with a bony strut for distraction and a wire to join the two clamps to avoid rotation.

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90.

Anterior Cervical Discectomy Without Fusion

P.J.M. MARCOTTE, J.G. GOLFINOS and V.K.H. SONNTAG (Phoenix, U.S.A.)

It is unclear whether patients undergoing anterior cervical discectomy have better outcomes with or without fusion. We reviewed 150 consecutive patients (mean age, 49.9 years; 62%, male; 38%, female) who underwent ACD without fusion for cervical disc disease over a 5-year period. Of these, 11 patients were excluded because of inadequate follow-up; the remaining patients were followed clinically from 1 to 44 months (mean = 8.8 months). Altogether, 194 discs were removed from 139 patients. Of these, ACD was performed at a single level in 86 patients (61.9%), at two levels in 49 (35.3%), at three levels in 3 patients, and at four levels in one. Of these 139 patients, 69.8% were operated upon for radiculopathy, 23.7% for myelopathy, and 6.5% for a combination. At operation, 55.4% had herniated disc material alone removed, while 44.6% had both disc material and osteophytes removed. Based on Odom's criteria, 38.1% had an excellent outcome, 30.9% a good outcome, 20.9% a fair outcome, and 10.1% a poor outcome. The poor outcome group included 8 patients who underwent reoperation for persistent symptoms. Of these, 3 had repeat ACD at the same or additional levels, and 5 underwent interbody fusion. Of the 86 patients with single-level ACDs, 73.3% had excellent or good outcomes compared with 61.3% with 2-level ACDs. Patients with radiculopathy tended to have better outcomes than those with myelopathy. The mean postoperative length of stay was 3.4 days. Only 4 patients had complications, none with permanent sequelae. We conclude that patients undergoing ACD at single and multiple levels without interbody fusion have clinical outcomes comparable to those with ACD and fusion; this problem should be studied in prospective trials of ACD with and without fusion.

91.

Cervical Corpectomy: Indications, Complications, and Results of 35 Cases

P.J.M. MARCOTTE and V.K.H. SONNTAG (Phoenix, U.S.A.)

A retrospective review of 35 consecutive patients undergoing anterior cervical corpectomies and fusions was made. The patients had symptomatic spinal stenosis or kyphosis, caused by degenerative disease (29%), previous cervical surgery (34%), trauma (26%), or vertebral invasion by tumor or infection (11%). Myelopathy was present in 80% of patients, 17% had radiculopathy, and 1 patient had pain only. One or two level procedures were carried out on 86% of the patients (range 1 to 4 levels), with an average of 1.7 vertebral bodies resected. Trauma patients usually underwent 1 level corpectomy. The number of levels removed conformed to no pattern in the other diagnostic groups. Plating was considered a preferred adjunct and was applied unless contraindications existed (20%). There was one death (3%) from medical complications and five patients required another procedure for treatment of complications; there were no failed fusions. The referral pattern and the nature of retrospective data, limited the average 6.9 month follow-up data to 30 patients. Seventy-six percent improved clinically and realignment of the cervical spine was documented in 90% of patients. Myelopathy improved in 80% of the patients with total resolution in one. Despite cord atrophy, 7 of 8 patients improved clinically. Data indicated no relation between the number of vertebrae resected and outcome. Patients with non-malignant disease showed improvement in 84% of cases. This retrospective series demonstrates that cervical corpectomy can be used to treat various causes of cervical stenosis and/or kyphosis, and that realignment, decompression, and neurological improvement can be expected.

92.

Posterior Transarticular Screw Fixation. A Preliminary Report

P.J.M. MARCOTTE, V.K.H. SONNTAG, B. FITZPATRICK and C.A. DICKMAN (Phoenix, U.S.A.)

Posterior wire fixation/fusion represents conventional treatment of atlas-axis complex instability requiring operation. Alternative methods of operative fixation, using screw fixation by both anterior and posterior approaches, have been devised. A series of 9 patients who underwent posterior interarticular screw fixation, by a modified Magerl technique, is presented. The screw fixation method was used to supplement posterior wire and bone fusion as a halo substitute. Operative indications, patient selection, technical details, and follow-up results are presented. Successful screw fixation was achieved in all patients without neurological or vascular complications. Suboptimal screw placement occurred, without accompanying morbidity, in 2 patients early in the series. All fusion constructs remained reduced and stable at follow-up, which averaged 1 month for the group. The study demonstrates the safety and effectiveness of interarticular screw fixation as a halo substitute. Longer follow-up is required to evaluate the incidence of screw and/or fusion failure before broader application of the technique is undertaken.

93.

Transcranial Oxygen Extraction Following Severe Head Injury

R.J. MOULTON and P. SHEDDEN (Toronto, Ontario; Houston, U.S.A.)

The cerebral metabolic rate for oxygen (CMRO2) is the product of cerebral blood flow (CBF) and the arterial-jugular oxygen difference (AVDO2). Because of the expense and inconvenience of bedside measurement of CBF, AVDO2 measurement has been proposed as a substitute for CBF monitoring. We hypothesize that changes in AVDO2 values are more reflective of changes in CMRO2 than in CBF. This paper describes the results of serial measurement of AVDO2 in 51 patients following severe head injury.

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Serial AVDO2 measurements were carried out at 12 hourly intervals for periods ranging from 12 hours to 7 days. Seventy-three percent of patients underwent initial measurement within 24 hrs. of injury and 90% within 48 hrs. of injury. All patients underwent hourly serial somatosensory evoked potential (SSEP) monitoring. Glasgow Outcome Scores were measured at 3 months.

Mean AVDO2 fell in all outcome groups over the period of serial measurement. Means for good/moderate and severe groups fell less than those for dead/vegetative patients. Due to the large variance in AVDO2 values within patient groups, these trends were not statistically significant. Thirteen patients had improvement in serial SSEPs. AVDO2 values increased over the period of maximum SSEP improvement by an average of 43% over baseline values in these patients. In 20 patients with deteriorating SSEPs, AVDO2 values fell by 29.1%, $p < .001$.

It is unlikely that increased AVDO2 would indicate ischemia in a patient with improving SSEPs. We feel that the changes in AVDO2 observed in patients with deteriorating or improving SSEPs more likely indicate decreasing or increasing CMRO2. Unfortunately, due to the large amount of within and between patient variance in measured values, AVDO2 measurement does not appear to be a terribly useful clinical measurement in the absence of simultaneous measures of electrophysiologic function.

94.

Excitatory Amino Acids in Cerebrospinal Fluid After Severe Closed Head Injury

A.J. BAKER, R.J. MOULTON, P.M. SHEDDEN and V.H. MACMILLAN (Toronto, Ontario)

Much evidence has accumulated to support the notion that the excitatory amino acids (EAAs) glutamate and aspartate contribute to ischemic neuronal injury. Additionally there is evidence to suggest that ischemia plays an important role in the delayed neuronal injury following closed head injury (CHI). However, the role of the EAAs in human CHI has not been elucidated. We have preliminary data that supports the hypothesis that EAAs contribute to post-traumatic brain injury (PTBI). We have found significant concentrations of glutamate and aspartate in the cerebrospinal fluid (CSF) of severely head injured patients.

All severely head injured patients at our institution receive an external ventricular drain to monitor and treat raised intracranial pressure (ICP). CSF is then drained in order to control ICP. The drained CSF, which would otherwise be discarded, was collected at regular intervals and analyzed for the EAAs employing high performance liquid chromatography. The results were tabulated along with detailed clinical information including the ICP, continuous somatosensory evoked potentials, cerebral oxygen extraction, serum glucose, CSF lactate production, mannitol requirements, discharge status and status at 3, 6 and 12 months.

Initial results show that in all eight severely head injured patients studied, CSF concentrations of glutamate and aspartate are significantly elevated compared to control CSF from normal patients. Data from additional patients will allow a more detailed comparison of the temporal pattern and degree of release of EAAs with the other variables.

The problem of ischemia after CHI is becoming increasingly evident. The synergism of axonal injury and ischemia has been described. Our findings of elevated CSF levels of EAAs suggest that ongoing ischemia is present. Given the known neurotoxicity of the EAAs, the demonstration here that EAAs are found in significant concentrations after CHI is supportive evidence that they are involved in PTBI. Since EAA antagonists are available, there exists the possibility of therapeutic intervention in PTBI.

95.

Clinical Presentation and Treatment of Adult Chronic Subdural Hematomas: A Review of 88 Patients

J.B. FRIZZELL, M. HAMILTON and B.I. TRANMER (Calgary, Alberta)

The management of chronic subdural hematomas (CSDH) in the adult patient is approached with a wide variety of surgical techniques. The trend in recent years has, however, been toward treatment with burr holes rather than craniotomy. The rationale for this assumes that the management of CSDH with burr holes offers equivalent efficacy but with lower morbidity and mortality and a shorter post-operative hospital stay.

A retrospective review was undertaken at the University of Calgary examining all adult patients, over a 3 year period (1988-1990), with unilateral CSDH. There were 88 patients treated by eight neurosurgeons. Patients were classified according to the clinical grading scheme of Markwalder, et al. (J Neurosurg, 55: 390-396, 1981): 48 were Grade 1 (mild symptoms), 28 Grade 2, 5 Grade 3 and 7 were Grade 4 (comatose). Patients were subdivided according to treatment type: 28 had burr hole(s), 12 had burr hole with closed drainage, 28 had craniotomy and 28 had craniotomy with a drain.

There were no significant differences in the distribution of the clinical grades among the treatment groups. Among the entire group there were 4 wound infections (4.5%), 8 hematoma reaccumulations requiring reoperation (9%) and two deaths (2.3%). There were no significant differences among the 4 treatment groups with respect to patient outcome (Glasgow Outcome Scale), incidence of postoperative complications, reoperation for reaccumulation of hematoma or length of hospital stay. Previous reports concerning the superiority of burr holes over craniotomy are not substantiated by this review: craniotomy has a valid role in management of patients with CSDH. A randomized prospective trial is indicated to adequately reassess this issue.

96.

The Role of Corticosteroids in the Treatment of Subacute Subdural Hematoma

K. REDDY and D. FEWER (Hamilton, Ontario; Winnipeg, Manitoba)

Seventy-two contemporary and consecutively treated subacute subdural hematomas treated by the authors were reviewed. In 43 (60%) corticosteroid administration was the first treatment modality. In 11/43 (26%) this was the only form of therapy

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needed. In 7/32 (22%) there was a partial or temporary response, but a drainage procedure was required. In those who responded completely, symptoms and signs always reversed within one week, usually within 48 hours. CT improvement was much slower, most often extending many weeks after cessation of the 2-3 weeks treatment schedule. In 3/11 there was clearly associated hemispheric edema. In 4/11 the subdurals were bilateral. In no case was a patient's neurological outcome compromised by this therapy. In one case, pre-existent diabetes mellitus was aggravated by steroids, but this was successfully managed and did not require cessation of therapy. The authors conclude that in those cases with progressive symptoms and signs and whose subdurals are less than 2.5 cm in thickness, corticosteroid therapy is a safe, practical alternative to conventional drainage procedures.

97.

A Comprehensive Program for the Brain Injured - Early Results

N.C. HILL (Winnipeg, Manitoba)

A comprehensive program for all patients who suddenly develop a brain injury from a non-progressive cause (trauma, intracerebral hemorrhage, anoxia, benign tumor) has been designed for Manitoba following consultations at local, provincial and national levels.

The program classifies patients into patients who will return to the community and those unlikely to do so. Those returning to the community progress through facilities (hospital rehabilitation centres, temporary homes with support, outpatient vocational centres) and programs (impact and outreach) to either independent living, or to supervised community homes. This portion of the program, aided by independent community organizations, is in the final stages of preparation.

Those patients unlikely to return to the community because of their unacceptable behaviour, will enter regional behavioural treatment centres, and will eventually be cared for in special care secure facilities if they are unable to return to their homes. This portion of the program is also about to be implemented.

Those patients unlikely to return to the community because of a vegetative neurologic condition, progress through a sensory stimulation program in the acute care ward, to special care wards in a chronic hospital, then to supervised homes and to regional rural special care centres. This portion of the program has been instituted, and a report is given on the results of the first 25 patients participating in the program. These results indicate a significant improvement in patient care, family satisfaction and funding costs. A secondary benefit is the subsequent improvement in efficiency of acute wards formerly housing these patients.

Early results indicate that a comprehensive program has been designed which can be made operable, with significant improvement in patient care.

98.

Hydrocephalus Associated with Acoustic Schwannoma: Incidence and Management

E.G. DUNCAN and C.H. TATOR (Mississauga, Ontario; Toronto, Ontario)

Review of 212 patients with acoustic schwannoma revealed that both the incidence and management of secondary hydrocephalus (SH) were related to tumour size, classified as small (< 1.0 cm; n = 76), medium (1.0 to 2.5 cm; n = 91) and large (> 2.5 cm; n = 45).

SH occurred in 30 patients (14%). Only one patient (1%) with a small tumour had SH, while 10 patients (11%) with medium and 19 patients (42%) with large tumours had SH.

For these 30 patients management was: tumour excision (25), VP shunt only (4) and no treatment of tumour or SH (1). Of the 25 undergoing tumour surgery, 14 required prior shunting; 0 of 1 with small, 3 of 6 with medium and 11 of 18 with large tumours.

For the 11 patients not shunted before tumour excision, the SH resolved in the one patient with a small tumour but persisted in 2 of 3 patients with medium tumours (one shunted) and 3 of 7 patients with large tumours (all shunted). Thus, overall, no patient with a small tumour was shunted while 4 of 6 (66%) with medium and 14 of 18 (78%) with large tumours required shunts.

A further 17 patients (8%) without SH pre-operatively developed hydrocephalus after tumour surgery: 6 each in the small and medium groups and 5 in the large group. Five (29%) required shunts, 1 in the small, and 2 each in the medium and large groups.

Thus, the incidence of SH rose with increasing tumour size. Patients with SH and small tumours were not shunted but those with larger tumours often required a shunt. A smaller number of patients developed hydrocephalus after tumour surgery, unrelated to tumour size, but only infrequently needed shunts.

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99.

Dominant Hereditary Spinocerebellar Ataxia Associated with Motor Neuron Disease: A Clinical and Genetic Study in a Large Saskatchewan Kindred

I. LOPES-CENDES, E. ANDERMANN, F. CENDES, J. DONAT, F. OOSMAN, D. KIRCHGESNER, T. NUNAN and F. ANDERMANN (Montreal, Quebec; Saskatoon, Saskatchewan; Humbolt, Saskatchewan; Lanigan, Saskatchewan)

The spinocerebellar ataxias, represent a very wide spectrum of disease, which includes the olivoponto-cerebellar degeneration. They are usually a familial disorder, with an autosomal recessive or dominant pattern of transmission. The classification of these conditions remains controversial (Harding, 1986), and will only be resolved when the specific mutations are identified. To date, the gene in certain autosomal dominant families has

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been mapped to markers linked to the HLA region on chromosome 6p (Zoghbi, 1988).

We have studied one family of Austrian origin, with 229 individuals in 6 generations, 23 of whom were clinically affected, (10 females and 13 males). The mean age of onset was 38.8 ± 14 y (range 16-61). We have estimated that 98 family members are still at risk of developing the disease. There is a strong correlation between the generation and age of onset, with a mean onset age of 50 y for generation III, 33 for generation IV, and 20 for generation V. We also noted a weak correlation between age of onset in the parental generation and in the offspring. However no correlation between sex and age of onset was found. The progression and intensity of symptoms were also clearly related to the age of onset: the later the onset, the more benign the evolution. The disease was very disabling and rapidly progressive in patients with onset in the early 20's and mild when the onset was after 40 y.o. The same was found with the age of death. The first symptoms were problems with balance, but one interesting and constant initial complaint was the presence of muscular cramps related to physical exercise. The clinical examination showed cerebellar ataxia (gait and limb ataxia, dysarthria, dysmetria). The following associated features were frequently found: Facial impassivity 80%, some degree of sensory loss 70%, tremor of tongue 60%, ophthalmoplegia 50%, dysphagia 25% and fasciculations 40%. The later was rarely described in the Harding series. On the other hand, we did not find some of the more commonly associated features, such as dementia, optic atrophy or retinal degenerations. CT scans showed enlargement of the 4th ventricle associated with cerebellar atrophy, in 4 patients. Autopsy obtained in one patient revealed cerebellar atrophy, with Purkinje cell loss and atrophy in the inferior olive, as well as signs of inflammatory motor neuron degeneration.

In an attempt to further delineate this condition, and to provide improved genetic counselling, we are now performing DNA studies for genetic linkage.

100.

Age of Onset of Amyotrophic Lateral Sclerosis Predicts Length of Survival

A. EISEN, M. MacNEIL, M. SCHULTZER and B. PANT
(Vancouver, British Columbia)

At the time of initial diagnosis one of the major concerns of patients with amyotrophic lateral sclerosis (ALS) relates to their overall survival. Functional and physiological testing have predictive value only when clinical manifestations have been present for several months. This precludes survival prediction at the time of disease onset.

Between 1985 and 1991 we prospectively followed 246 patients with sporadic ALS. 138 patients (86 men and 52 women) died making it possible to analyze factors relating to the total duration of their disease. Mean disease duration was 4.0 ± 3.8 years for men and 3.2 ± 2.5 years for women. There was an inverse, quadratic, exponential, relationship between onset age and disease duration (goodness of fit $p > 0.05$). Mean duration at onset age = < 40 years was 8.2 ± 5.0 years compared to 2.6 ± 1.4 years for patients aged 61-70 years ($p > 0.001$). The ratio of young (≤ 40 years) men to women was 3.6:1. When matched for age, disease duration was the same for patients with bulbar and non-bulbar onsets.

We conclude that onset age of sporadic ALS is the most significant predictor determining disease duration. Sex and bulbar onset are not relevant. Longer survival in younger patients probably reflects a greater reserve of the corticomotoneuronal system which this study suggests normally declines with advancing age. The preponderance of young men with ALS may give an etiological clue to the disease.

101.

Fasciculation as an Initial Feature of Amyotrophic Lateral Sclerosis (ALS)

A. EISEN, B. PANT, M. MacNEIL and H. STEWART
(Vancouver, British Columbia)

Fasciculation is generally considered to be benign, unless it is associated with a neurological deficit. Most frequently it is then a manifestation of amyotrophic lateral sclerosis (ALS).

Of 246 patients with ALS seen and followed between 1985-1991, 17 (6.9%) had fasciculation as a sole presenting feature. This symptom had been present 3-18 months (mean 9.5 months) preceding other symptoms. Fasciculations were usually noticed by the patient and spouse to initially involve a single muscle. Muscle cramping was an associated symptom in 11 patients; but there was no weakness or limitation of daily activities.

All were men with a mean age of 55.2 years. Mean duration of disease from onset to Dec.'91 (N = 15) or death (N = 2) was 5.5 ± 4.4 years (range 1.5-18). This compared to a mean duration of 3.6 ± 3.1 years for the total cohort of 246 patients.

Recent evidence indicates that there is a presymptomatic phase of Parkinson's disease which lasts about 5 years (Brain 1991; 114: 2283). It is likely that the same holds true for ALS and fasciculations may be one manifestation of the "preclinical" stage. Development of fasciculations over the age 50 years may herald the onset of ALS and should not be ignored. Mean survival of ALS in patients who have fasciculation as a presenting feature is longer and its recognition as an early manifestation of ALS may offer a better chance for therapeutic intervention.

102.

Motor Neuron Disease Presenting as Ventilator Dependency

J. HOSTETLER, S. LUDWIN, V. SALY and D. ZOCHODNE
(Kingston, Ontario)

Motor neuron disease (MND) is usually diagnosed prior to the onset of severe respiratory symptoms. However, it may be the cause of weaning failure in patients presenting with acute respiratory failure (ARF) of unknown origin. We report two patients with ARF in whom MND was diagnosed after difficulty in weaning from ventilation was encountered.

A 77-year-old female had been investigated for anorexia and a 20 kg weight loss, with no diagnosis established, some five months prior to onset of hypercapneic ARF requiring intubation and ventilation. Electromyography and nerve conduction studies

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(EMG/NCS) were highly suggestive of MND, and muscle biopsy identified denervation. With follow up, further clinical signs of MND emerged and she remained ventilator dependent.

The second patient, a 65-year-old female, had a one year history of progressive shortness of breath but deteriorated acutely after taking a benzodiazepine hypnotic and required mechanical ventilation. The diagnosis was obscured by the presence of COPD, SLE that had transformed to mixed connective tissue disease, and chronic steroid administration. EMG/NCS indicated widespread denervation which was confirmed regionally by muscle biopsy and led to the diagnosis of MND.

Unsuspected MND is an unusual but important cause of "failure to wean" and is usually accompanied by a history of previous bulbar dysfunction. The diagnosis of MND early in the course of ARF requires a high index of suspicion, but once made, can facilitate subsequent management.

103.

Measurement of IgM Antibodies to Gm1 Gangliosides in the Evaluation of Motor Neuronopathies

M.S. FREEDMAN, J.P. ANTEL, T. DEGUZMAN and J. MINUK (Montreal, Quebec)

In previous studies, patients with a clinical picture of motor neuropathy (MN) and evidence of multifocal nerve conduction block (MCB) were noted to have very high levels of anti-GM1 antibodies (Ab) in their sera. The ELISA method for quantitating anti-GM1 Ab is very sensitive, detecting measurable titers of anti-GM1 Ab in patients with many types of neurological diseases, as well as in normal controls, but with titers rarely exceeding serum dilutions of 1:1000. Titers of Ab in patients with classical ALS exceed those of "controls". We have used the ELISA technique and serum from a patient (H.U.) with established MN and MCB and high titer anti-Gm1 Ab as a standard in order to evaluate patients with predominantly motor neuropathies and motor neuronopathies for the presence of IgM Abs. We have identified 3 groups of patients: those with low titer (< 10 U/ml), medium titer (10-20 U/ml) and high titer (> 20 U/ml) Ab levels, based on the presence of measurable Ab at serum dilutions of 1:1000. High titers were found in 5 patients, 4 who had a clinical picture consistent with MN and MCB, and 1 with a clinical diagnosis of CIDPN and IgM monoclonal gammopathy. Patients with medium titers at 1:1000 serum dilution had high titers at 1:200, whereas the low titer group was still low at 1:200 serum dilution. These patients comprised a mixture of motor neuropathies/neuronopathies, such as ALS or polio. Identification of a "high" titer of Ab to Gm1 is of importance, given its possible role in the pathogenesis of motor nerve disease and its potential for treatment.

104.

Incidence of Guillain-Barré Syndrome in Ontario and Quebec, 1983-1989, Using Hospital-Service Databases

M.E. McLEAN (Ottawa, Ontario)

To ascertain the incidence of GBS in the Canadian provinces of Ontario and Quebec for the years 1983 - 1989 and to demonstrate the feasibility of measuring the incidence of GBS through internal record linkage of Canadian hospital-service data, we conducted a record linkage study using two hospital discharge databases: Hospital Medical Records Institute (HMRI) database and Med-Écho (the hospital-service database of the Ministère de la santé et des services sociaux du Québec). Records containing the ICD-9 code for GBS, or one of the diagnoses most likely to harbour misclassified GBS cases were extracted from both databases. HMRI and Med-Écho databases records were internally linked using two specific sets of algorithms, linking records to the same case of GBS on a probabilistic basis. A total of 1,302 and 1,031 incident cases of GBS admitted in Ontario and Quebec hospitals, respectively, were identified., The mean annual GBS incidence in each province after age-and-sex-standardization to the 1986 Canadian census population was 2.02 per 100,000 person-years in Ontario and 2.30 in Quebec. The incidence was higher in older age-strata in both provinces (70-80 years), and was higher in males. No seasonal nor geographic pattern could be detected.

105.

Anti-Neutrophil Cytoplasmic Antibodies in Vasculitic Peripheral Neuropathy

C.H. CHALK, H.A. HOMBURGER and P.J. DYCK (Montreal, Quebec; Minnesota, U.S.A.)

Serum autoantibodies to neutrophil cytoplasmic antigens (ANCA) have been reported to be useful in the diagnosis and followup of systemic necrotizing vasculitis. Most patients have had lung or kidney involvement. Peripheral neuropathy is an important manifestation of necrotizing vasculitis. Patients with vasculitic neuropathy are important to distinguish from other types of neuropathy because the prognosis and treatment are different. We asked, therefore, whether detection of ANCA would be useful in the diagnosis of vasculitic neuropathy and prospectively evaluated 145 patients referred to the Mayo Clinic's Peripheral Nerve Centre (6 had biopsy-proven vasculitic neuropathy, 27 had other inflammatory neuropathies, 46 had other acquired neuropathies, 30 had inherited neuropathies, 20 had other neurological diseases and 16 had symptoms only). ANCA were sought by immunofluorescence (IFA) and by ELISA for antibodies to myeloxperoxidase (MPO) and serine protease 3 (PR3).

Four of the 6 patients with vasculitic neuropathy had positive results, 2 by ELISA-MPO, 1 by IFA and 1 by both. No other patients had positive IFA but a small number in each of the other diagnostic groups had positive ELISA-MPO. Most of these were low level titres, but several patients in the other diag-

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nostic groups had markedly elevated titres. No patients had positive ELISA-PR3. We conclude that while ANCA may be relatively common in vasculitic neuropathy, their use in the differential diagnosis of neuropathy is limited by low specificity.

106.

Anti-Cholinesterase Agents in Post-Poliomyelitis Syndrome

D.A. TROJAN, D. GENDRON and N.R. CASHMAN (Montreal, Quebec)

The anticholinesterase agent pyridostigmine has been reported to improve fatigue in patients with post-poliomyelitis syndrome (PPS). In 17 fatigued PPS patients, we measured jitter on stimulation single-fibre electromyography (S-SFEMG) for at least 3.5 minutes before and after intravenous injection of 10 mg edrophonium. Following this test, patients were treated with pyridostigmine 180 mg per day, and fatigue level was quantified on the Hare fatigue scale before and one month after administration of the medication. Intravenous injection of edrophonium produced a reduction in jitter (defined as a significant difference in jitter means before and after edrophonium, unpaired t-test, $p < 0.05$) in 7 patients, no change in 8, and a significant increase in 2 patients; pyridostigmine was associated with decreased fatigue in 9 patients. Edrophonium-induced reduction of jitter on S-SFEMG was significantly associated with pyridostigmine induced subjective improvement of fatigue (Fisher's exact test, $p < 0.05$). Significant reduction in fatigue with pyridostigmine was observed only in the 7 patients who experienced significant reduction in jitter with edrophonium (Hare scale 3.0 pre vs 1.5 post, Wilcoxan signed rank sum test, $p = 0.03$). The 9 patients reporting decreased fatigue with pyridostigmine experienced decreased jitter on endorphonium injection, compared to pre-edrophonium norms (100% vs 88%, Bonferroni corrected, $p < 0.001$), which was not observed in the 8 patients not responding to pyridostigmine. Because subjective patient response to pyridostigmine is associated with objective amelioration of S-SFEMG jitter with edrophonium, we conclude that fatigue in some patients with PPS is due to anti-cholinesterase-responsive neuromuscular junction transmission defects.

107.

Muscle Biopsy in Critical Illness: Electro-Physiological and Morphological Correlations

C.E. PRINGLE, C.F. BOLTON, D.A. RAMSAY, J.J. GILBERT, S. CAMPBELL and F. RUTLEDGE (London, Ontario)

Patients in the intensive care unit (ICU) may develop neuromuscular disorders. The nature of these is controversial. Much evidence suggests that many are due to an axonal neuropathy (critical illness polyneuropathy) but a few cases of primary myopathy have been reported.

Between 1981 and 1989, 11 patients underwent muscle biopsy because of clinical and electro-physiological evidence of neuromuscular disease. All suffered from sepsis and multiple organ failure. Neurological consultation was sought at 21 (10-61) days after admission to the ICU because of failure to wean from the ventilator.

The patients showed varying degrees of muscle weakness and reduced or absent deep tendon reflexes. Because of difficulties in assessing sensation, clinical distinction between neuropathy and myopathy was uncertain. Consequently, muscle biopsies were performed at 28 (16-78) days.

Muscle biopsies and electrophysiological studies (EPS) were assessed independently of each other and without prior knowledge of the clinical details, and were graded.

EPS in all cases were suggestive of a neuropathy (5 mild, 4 moderate and 2 severe) with reduced compound muscle action potentials and abnormal spontaneous activity. Biopsy supported a neuropathy with findings of diffuse and small group atrophy predominating (5 mild, 2 moderate and 1 severe). In only one patient were rare necrotic fibres identified. Creatinine kinase levels were near normal in all except one case.

We conclude that the weakness in these critically ill patients was due to a neuropathy. Sepsis was the likely underlying factor, steroids were not, but neuromuscular blocking agents may have been a contributing factor in one unusually severe case.

108.

A Local Opiate-Sensitive Peripheral Nerve Trunk Peptidergic Flare

D.W. ZOCHODNE and L.T. HO (Kingston, Ontario)

Neurogenic inflammation is associated with local vasodilatation (flare) and plasma extravasation mediated by Substance P (SP), CGRP (Calcitoningene related peptide) and other peptides. Local capsaicin probably replicates these features by releasing peptides from sensory nerve terminals. The peripheral nerve trunk might be susceptible to neurogenic inflammation because its vasa nervorum are innervated by afferent peptidergic fibres.

We studied features of a local flare response of vasa nervorum induced by epineurial capsaicin in the rat sciatic nerve. Animals were anaesthetized, paralyzed and ventilated and serial changes in endoneurial blood flow (EBF) were measured using an endoneurial microelectrode sensitive to hydrogen clearance. In previous work, we reported that capsaicin vasodilatation of vasa nervorum was probably largely mediated by CGRP but was blocked by specific antagonists of both CGRP and SP. In this work, we confirmed the importance of SP release in the flare response by noting that an additional and newer SP antagonist, Spantide II, also blocked capsaicin hyperemia locally. We verified that central nociceptive pathways were not required for capsaicin flare because proximal sciatic nerve section did not alter the response. Systemic injection of morphine sulfate did not change baseline EBF but also completely blocked the capsaicin hyperemia. Combined treatment with the opiate antagonist, naloxone and morphine, however, restored capsaicin hyperemia.

The peripheral nerve trunk appears capable of sustaining neurogenic inflammation because it possesses features observed in other tissues including local opiate sensitivity. Peripheral nerve trunk "neurogenic" inflammation could be of importance in injury and in the generation of neuropathic pain.

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109.

A Syndrome of Acute and Severe Rhabdomyolysis in Intensive Care Unit Patients

D.W. ZOCHODNE, D.A. RAMSAY, S. MOFFATT and E.S. SHELLEY (Kingston; London, Ontario)

Failure to wean patients from ventilators in the intensive care unit may occur as a result of neuromuscular disease, either previously recognized or arising as a secondary complication. Bolton et. al. (1984) first drew attention to critical illness polyneuropathy, a complication of sepsis and multiple organ failure with associated muscle denervation. We describe a distinct, myopathic disorder that developed in 6 intensive care unit patients without pre-existing neuromuscular disease. The patients were referred with "failure to wean" and had severe flaccid paralysis of the limbs, wasting, loss of deep tendon reflexes but preserved sensation. All had markedly elevated serum CK levels and 3 developed myoglobinuria with acute renal failure. Electrophysiological features included very low amplitude or absent motor responses with preserved conduction velocity, relatively preserved sensory conduction and mild abnormal spontaneous activity on needle electromyography. In two patients studied early in their course, there was a marked electrodecremental response to repetitive stimulation identifying a neuromuscular transmission defect (despite previous discontinuation of muscle blocking agents). Only one patient survived and was discharged to the ward 80 days after admission. Muscle biopsy in the survivor and postmortem examination in 4 patients identified a severe necrotizing myopathy without inflammation. All 6 patients had received a nondepolarizing muscle blocking agent (vecuronium, pancuronium or atracurium) before the myopathy developed. All patients had also been septic and 5 had received high dose corticosteroids.

Clinical, biochemical, electrophysiological and histological features distinguish this myopathy from critical illness polyneuropathy and use of nondepolarizing blocking agents and steroid may be important factors in its development. In some patients, muscle fibre necrosis is accompanied by a neuromuscular transmission defect.

SATURDAY, JUNE 27, 1992 – P.M.

K. Neuroimaging

110.

The Role of MRI in the Investigation of Spinal Dural Arteriovenous Fistula

R. WILLINSKY, K. TERBRUGGE, W. MONTANERA and D. MIKULIS (Toronto, Ontario)

A retrospective review was done of the MR findings in 15 patients with spinal arteriovenous malformations (AVMs) explored and/or treated at The Toronto Hospital, Western Division between 1984 and 1991. Five of these patients were excluded since they had intramedullary AVMs. Eight had dural arteriovenous fistula (AVF) and 2 had retromedullary or extramedullary AVMs.

In the 8 patients with dural AVF there were 5 males and 3 females with ages ranging from 28 to 71 with a mean of 52 years. All but 1 presented with a myelopathy. Five of these 8 had MRI, 2 with gadolinium (Gd). MR showed abnormal vessels on the surface of the cord in 3 of 5, cord swelling in 2 of 5, and increased T2 signal in 3 of 5. With Gd the abnormal subarachnoid vessels were more evident and enhancement of the cord was seen in 2 of 2.

In both patients with extramedullary AVMs, MRI was done without and with Gd. One was a 15-year-old female with progressive scoliosis and the other a 39-year-old male with myelopathy. MR showed abnormal subarachnoid vessels in both which was more conspicuous after Gd. One showed an increased signal in the cord on T2-weighting. Neither patient had cord enhancement with Gd.

In summary, MR with Gd can suggest the diagnosis of a spinal dural AVF or retromedullary AVM. The MR findings include abnormal subarachnoid vessels, cord swelling, increased signal within the cord on T2-weighting, and cord enhancement.

111.

MRI of Familial Cavernous Angiomas

R. VANDORPE, D.H. LEE, J.P. GIRVIN and A.J. FOX (London, Ontario)

Introduction and Purpose: Familial occurrence of cerebral cavernous angiomas is rare. Since 1947 only 20 families have been reported. Comparison of spin echo (SE) and gradient echo (GE) imaging in MRI screening of family members has been studied.

Material and Methods: A midbrain lesion causing hydrocephalus was detected on MRI in a 16-year-old girl with headaches. This was pathologically shown to be a cavernous angioma. The mother, who complained of vertigo, had an MRI showing multiple lesions consistent with cavernous angiomas. Other family members were then screened with MRI. SE and GE MRI at 1.5T was obtained in 8 family members over 3 generations.

Results: Cavernous angiomas were observed with a pattern consistent with autosomal dominant inheritance. More lesions were identified on GE imaging compared to SE imaging. Also, one patient had a single lesion detected only on GE sequences, but not on SE sequences.

Conclusion: Family members with suspected familial cavernous angiomas of the brain should be imaged with MRI. A GE pulse sequence should be obtained in addition to SE sequences. GE imaging is superior to SE imaging in the detection of cavernous angiomas.

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112.

Complications of Endovascular Treatment of Brain Arteriovenous Malformations (BAVMs) with Cyanoacrylate

R. WILLINSKY, P. HALLACQ, D. FOURNIER, K. TERBRUGGE, W. MONTANERA and P. LASJAUNIAS (Toronto, Ontario; Paris, France)

Embolization is a widely accepted treatment of BAVMs as a single treatment, or as part of a multidisciplinary approach including surgery and/or radiotherapy. However, embolization procedures are not without risks. We report on the complications which occurred in a series of 95 patients with BAVMs, embolized with liquid adhesives between 1984 and November 1991. One to eleven vessels were embolized in these patients (240 procedures).

Complications from endovascular treatment occurred in 17 patients (17.8%) There was 1 death (1.1%) from acute hemorrhage. Sixteen patients experienced a neurological deficit (16.8%), 3 of which were permanent (3.1%): 2 hemiparesis, 1 superior visual field defect. Only 1 of these 16 patients had a documented hemorrhage, with a transient deficit. There were 3 minor technical complications where catheter components were left *in situ* and proved no consequence to the patient. Therefore our mortality rate is 1/95 patients (1.05%) or 1/240 procedures (0.4%). The significant morbidity rate is 4/95 patients (4.2%) or 4/240 procedures (1.7%).

Risks of new techniques have to be balanced with the benefits of these techniques relative to the "natural history" of the lesion and to other therapies.

113.

Endovascular Treatment of Cerebral Aneurysms with Platinum Coils

T.R. MAROTTA, A.J. FOX, D.M. PELZ and S.P. LOWNIE (London, Ontario; Los Angeles, U.S.A.)

Problem: Some aneurysms are not clippable due to anatomic or clinical difficulties. While these can be endovascularly treated using balloons, platinum coils are better, safer, and easier to use.

Methods: Seven patients were treated with intraneurysmsal placement of platinum coils, 6 pushable and 1 detachable. Coils were placed via a Tracker 18 microcatheter. Patients have been followed clinically, angiographically, and in 1 case by autopsy.

Results: In all cases multiple coils with various total lengths (23-90 cm) were deposited without complication. Aneurysms treated with the pushable coils were partially filled to prevent coil migration, which did not occur. In each of these cases, neck remnant remained. In 1 case there was regrowth of the aneurysm. The aneurysm treated with the detachable coil was filled to capacity without significant evidence of neck remnant. There has been no delayed subarachnoid hemorrhage. Two patients, Grade IV when treated, died from the original hemorrhage.

Conclusions: Platinum coils can be easily and safely placed within aneurysms. Temporary partial treatment is achievable with pushable coils. Detachable coils are safer, and aneurysm sacs can be fully packed. This has a possibility to evolve as an alternative to surgical repair, without craniotomy or general anesthesia.

114.

Angioplasty for Vasospasm following Subarachnoid Haemorrhage

T.R. MAROTTA, A.J. FOX, D.M. PELZ, D.H. LEE and S.P. LOWNIE (London, Ontario; Los Angles, U.S.A.)

Problem: Development of vasospasm following subarachnoid haemorrhage is a determinant of morbidity and mortality. On occasion, spasm is resistant to hemodilution, hypervolemia, hypertension, and vasodilator therapy and angioplasty of affected major cerebral vessels can be performed.

Methods: Nine patients have been angioplastied using the ITC .85 silicone non-detachable balloon. Preliminary CTs were performed to evaluate for infarction. Clinical assessment and angiograms were done pre and post angioplasty. All patients were followed clinically. Two patients did not recover, and died. They both had autopsy. One patient has had a delayed cerebral angiogram.

Results: Twenty-one vessels (internal carotid, proximal middle and anterior cerebral, vertebral and basilar arteries) were successfully angioplastied in 7 patients with immediate neurologic improvement in 5. One patient could not be angioplastied because access was impeded by aneurysm clips. Angioplasty was unsuccessful in 1 who was referred months after spasm infarction and had fibrotic arachnoiditis in the cisterns. Two patients died, 1 from severe subarachnoid hemorrhage and the other from a large middle cerebral artery infarct. Histology showed patchy endothelial loss in the angioplastied vessels. One balloon burst and fragmented with no clinical sequelae. There were no vessel ruptures. One delayed angiogram showed normal caliber vessels.

Conclusion: Angioplasty is a useful adjunct to the treatment of intractable vasospasm.

115.

Angiographic Followup of Severe Stenosis without Endarterectomy

A.J. FOX, M. ELIASZIW, R.N. RANKIN and H.J.M. BARNETT (FOR THE NASCET COLLABORATORS) (London, Ontario)

Introduction: The North American Symptomatic Carotid Endarterectomy Trial (NASCET) has shown benefit of endarterectomy in patients with severe (70-99%) stenosis. Followup analysis of the medical arm enables study of evolution of stenosis.

Materials and Methods: Of 331 patients in the medical arm, 290 remained alive and without endarterectomy upon ter-

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minating randomization of severe stenosis. Of these 55 had followup angiography to date. On average initial and followup reviews were done within 20 months. Degree of stenosis was determined by comparing residual luminal diameter with that of normal artery well beyond the bulb.

Results: Nineteen (35%) carotids showed occlusion on followup angiography, 3 (5%) showed more narrowing, 25 (45%) showed no change and 8 (15%) improved. 20% (11/55) patients had ipsilateral strokes, 8 of the 11 showed angiographic carotid occlusion while 3 were similar in degree.

Among the 8 cases with stenosis improvement, none suffered stroke before followup. Among the 19 that progressed to occlusion, 8 had strokes. Only 35% (19/55) with followup angiography had duplex ultrasound performed, 8 were identified to have occlusion.

Conclusions: These patients are unique. With the published NASCET results, most patients with severe stenosis will have endarterectomy in the future. The 15% who showed improvement, most likely improved because of resorption of plaque hemorrhage.

116.

Carotid Ultrasound: Correlation with Angiography in a Multicentre Trial

R.N. RANKIN, A.J. FOX, K. THORPE, M. ELIASZIW and H.J.M. BARNETT (FOR THE NASCET COLLABORATORS) (London; Hamilton, Ontario)

Ultrasound is used as the imaging method of followup for carotid atherosclerosis in the North American Symptomatic Carotid Endarterectomy Trial (NASCET). For this purpose, an initial ultrasound was obtained prerandomization within 6 days (median) of the carotid angiogram on 936 patients. These were reviewed at the NASCET central office. It has been proven that endarterectomy is indicated for lesions > 70% stenosis.

Ultrasound findings of carotid stenosis were classified according to standard criteria of frequency change or velocity at peak systole, stenotic velocity ratio, and spectral broadening. An angiographic linear diameter measurement of minimal residual lumen and diameter of the internal carotid well beyond the bulb quantified the stenosis. Comparison with the angiographic measurements yields a sensitivity of 59.3%, a specificity of 80.4% for detection of severe stenosis (> 70%), and a coefficient of agreement (kappa) of 0.40.

Specific criteria for severe stenosis detection, are an intrastenotic peak systolic frequency change of > 10 kHz, velocity of > 310 cm/s, and stenotic ratio of > 5.2. Using these criteria sensitivity changes to 37.8%, specificity to 92.7% and kappa to 0.34.

While the agreement between ultrasound and angiography is good, for individual cases the ultrasound alone does not have sufficient accuracy for determining treatment.

117.

MRI Volumetric Measurements of Amygdaloid Body and Hippocampal Formation: Inter and Intra Rater Differences

F. CENDES, F. ANDERMANN, G. WATSON, A. EVANS, P. GLOOR, M. JONES-GOTMAN, D. MELANSON, A. OLIVIER, G. LEROUX and T. PETERS (Montreal, Quebec; Sacramento, U.S.A.)

Volumetric studies of mesial temporal lobe structures are non invasive and an accurate method for lateralization in surgical candidates evaluated because of intractable temporal lobe epilepsy. This technique in combination with all other currently employed methods, can decrease the necessity for using invasive methods of investigation (Jack et al.; Lencz et al.).

MRI volumetric measurements of amygdaloid body (AB) and hippocampal formation (HF) were performed in 32 epileptic patients and in 13 healthy volunteers (mean age 32.2 years), using an interactive semiautomated software package developed at MNI and following a protocol previously described (Watson et al., Neurology, in press).

Repeated measurements at least one week apart were done on the same scan by one rater (F.C.) and by 2 different raters (F.C. and C.W.), to assess intra-rater and inter-rater average differences, in order to determinate the accuracy of the method.

For intra-rater assessment 42 AB and 33 HF drawings were analyzed. Average differences in measurements were 3.2% of the total AB volume and 1.2% of the total HF volume. For inter-rater assessment 24 AB and 33 HF drawings were analyzed. Average differences in measurements were respectively 9.1% and 3.4% of the total volume of the AB and the HF.

Abnormality is defined as values at least 2SD below the mean normal control group, which for AB represents 19.5% of the mean AB volume and for HF represents 10.3% of the mean HF volume. Thus despite intra and inter-rater differences, one obtains reliable volume measurements of the drawings of the Amygdala and Hippocampus, providing a valid and reproducible result, when performed by an examiner familiar with the boundaries of these structures as seen on MRI and following a specific protocol.

118.

Endovascular Treatment of Saccular Intracranial Aneurysms using Detachable Platinum Coils

S.P. LOWNIE, G. GUGLIELMI, G. DUCKWILER and F. VINUELA (Los Angeles, U.S.A.)

Since April 1990, 42 patients have undergone treatment of 43 saccular intracranial aneurysms using a detachable microcoil system developed at the University of California at Los Angeles. 31 females and 11 males, mean age 52 years (range 29 to 75 yr) have been so treated. 23 presented with SAH, 13 with mass effect, and in 6 the aneurysm was an incidental finding. The indications for an endovascular approach included: anticipated surgical difficulty due to aneurysm size and/or location (14 cases), failed surgery (11), medical conditions precluding surgery (7), poor clinical grade (5), and refusal of surgery (2).

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23 aneurysms were located on the posterior circulation, including 14 at the basilar bifurcation and 4 at the vertebrobasilar junction. Of 20 on the anterior circulation, 7 were carotid-ophthalmic or paraophthalmic.

The average angiographic occlusion of the aneurysm was 90% (range 70% to 100%). In 10 cases (26%), 100% angiographic occlusion was obtained.

Excellent or good clinical outcomes were seen in 33 out of 42 patients (79%). Of the 3 poor outcomes (7%), 2 were related to Grade IV patients, and 1 occurred in a patient with recurrent aneurysm growth which necessitated surgery, with a subsequent hemiparesis. Of the 6 deaths (14%), 3 were due to poor grade, 1 due to concurrent endocarditis, 1 due to catheter perforation of the aneurysm, and 1 due to delayed hemorrhage in an inoperable partially occluded aneurysm.

At angiographic followup, the degree of occlusion was stable or unchanged in 15 out of 35 aneurysms (43%). Further decrease in the residual aneurysm lumen was seen in 3 cases (9%). Evidence of increased aneurysm lumen was noted in 13 cases (37%), necessitating further coil placement in 8 (23%). Followup status is unknown in the remaining 4 cases (11%).

Poster Session
FRIDAY, JUNE 26, 1992 – ALL DAY

A. Neurobiology

P1.

Synapse Formation and Preferential Distribution in the Granule Cell Layer by Regenerating Retinal Ganglion Cell Axons Guided to the Cerebellum of Adult Hamsters

T.J. ZWIMPFER, H. INOVE, G.M. BRAY and A.J. AGUAYO (Toronto, Ontario; Montreal, Quebec)

After optic nerve transection in adult rodents, retinal ganglion cell (RGC) axons can regenerate through a peripheral nerve (PN) graft that joins the eye and the superior colliculus (SC) and establish functional synapses in the SC, a normal target of RGC axons. To further investigate synaptogenesis in the injured mammalian CNS, regenerating RGC axons of adult hamsters were guided through a PN graft to one of 4 targets they do not usually innervate: the cerebellum (Cb), inferior colliculus, visual cortex or somatosensory cortex. Regenerated RGC axons were identified by HRP anterogradely transported from the retina.

When examined 2 to 9 months after grafting, RGC axons were found to have extended into the grey matter of each of these 4 novel targets for distances of up to 650 μm, while generally avoiding the white matter. By EM, regenerated RGC terminals formed long-term synapses with neurons in all 4 targets. Within the Cb, there was a marked preference for growth and synaptogenesis in the granule cell layer (GCL) that could not be explained by the position of the PN graft in the Cb, a selective denervation of the GCL, local damage to other neurons, or the distribution of reactive gliosis in the vicinity of the graft. These results indicate that in adult mammals, regenerating CNS axons can form persistent synapses with novel targets. The preferential synaptogenesis in the GCL of the Cb suggests that such axons are capable of responding to molecular determinants of synaptogenesis.

P2.

New Insight on the Factors Orienting the Axonal Outgrowth of Grafted Purkinje Cells in the PCD Cerebellum

M. KEEP, R-M ALVARADO-MALLART and C. SOTELO (Montreal, Quebec; Paris, France)

The pcd (Purkinje cell degeneration) mutant mouse is a model of cerebellar heredo-degenerative disease, with loss of nearly all Purkinje cells (PC). Reconstitution of neural architecture with grafted PCs has been attempted. In prior studies, PC replacement repaired the cortical circuit, but reestablishment of corticonuclear projections only occurred rarely. The sole cerebellar output is PC axons projecting to deep nuclei. To assess competition between PC targets of host and graft deep nuclei, and the role of distance between implants and deep nuclei, new experiments were performed.

E13/14 embryo grafts free from contaminating co-graft deep nuclei were implanted into pcd cerebella. With cortical implants, absence of donor nuclear neurons is not sufficient to allow axons of grafted PCs in the host molecular layer to leave this layer. With grafts located near the host deep nuclei, PCs project massively into the host deep nuclei. When the grafts are positioned in the central white matter, some PCs invade the molecular layer, most of them remaining within the implant. Some axons of the cortically integrated PCs, using nearby graft as a bridge, seem to innervate the host deep nuclei. The latter receive a massive projection from the non-integrated PCs. Thus grafted PCs are able to specifically and massively innervate their target host deep nuclei when in proximity, or through a permissive microenvironment.

P3.

Evaluation of the Direct Effects of Nimodipine on Cytoplasmic Calcium in Spinal Neurons

M. TYMIANSKI and C.H. TATOR (Toronto, Ontario)

Irreversible damage to CNS neurons poses a barrier to the optimal recovery of neurologically injured patients. In physical trauma, rapid changes in extracellular ionic composition (a rise in potassium ($[K^+]_e$) and a fall in sodium concentrations) activates calcium channels, and is thought to cause a deleterious rise in intracellular calcium concentration ($[Ca^{2+}]_i$). We hypothesized that Ca^{2+} channel blockers might help maintain normal cellular Ca^{2+} homeostasis. A spinal cord explant model was used to study the effects on ($[Ca^{2+}]_i$ of rapid switches from baseline ($[K^+]_e$ = 4.5 mM, $[Na^+]_e$ = 135 mM) to iso-osmotic high-K^+, low-Na solutions (50 mM and 65 mM respectively). $[Ca^{2+}]_i$ was determined in explant neurons with fura-2/AM. Brief exposures (30 s) to high-K^+ caused a rise in $[Ca^{2+}]_i$. Ca^{2+} channel ligands were used to probe the route of calcium influx. The changes in

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$[Ca^{2+}]_i$ were mediated through dihydropyridine (DHP)- sensitive calcium-channels, with no measurable contribution to $[Ca^{2+}]_i$ from channels sensitive to ω-conotoxin. Bay-K 8644 and nimodipine respectively increased and decreased the rise in $[Ca^{2+}]_i$ evoked by high-K^+ ($p < 0.0001$). Nimodipine blocked the rise in $[Ca^{2+}]_i$ in a dose-dependent fashion (EC_{50} = 170 nM), with saturating concentrations (1 μM) blocking up to 78% of the total rise. A fraction of the rise in $[Ca^{2+}]_i$ was unresponsive to nimodipine or to ω-CgTx. When neurons were exposed to high-K^+ for prolonged periods (> 20 min), nimodipine administered before-, simultaneously with-, but not long after- the high-K^+ challenge helped to restore intracellular calcium homeostasis. This report establishes: 1) the responses of explanted spinal neurons to high-K^+, 2) the significance of DHP-sensitive calcium channels to neuronal $[Ca^{2+}]_i$, and 3) the narrow time-window in which nimodipine can be used to normalize neuronal calcium homeostasis.

P4.

Ultrastructural Features of Spinal Cord Axons and Microvasculature following Experimental Compression Injury

D.L. ANTHES, E. THERIAULT and C.H. TATOR (Toronto, Ontario)

One of the most common mechanisms of traumatic human spinal cord injury (SCI) is acute compression of the cord following fracture-dislocation or burst fractures of the spine. Accordingly, to study the ultrastructural features of SCI we have used an experimental SCI model which produces acute extradural compression of the cord by means of a modified aneurysm clip. The specific ultrastructural consequences of the clip compression injury during the acute post-injury phase were investigated. Three rats were sacrificed at each time point: 15 minutes, 2 hours and 24 hours post-injury as well as uninjured controls. The cords were harvested and prepared for electron microscopy with analysis focused on the region of the rubrospinal tract located in the lateral funiculus. Myelin changes indicative of axonal degeneration included lamellar separation, vesiculation, vacuolization, disintegration and rupture. Axoplasmic changes associated with traumatic injury included granular degeneration and the accumulation of intracellular organelles around a neurofilamentous core. Microvascular disruption was apparent by extensive perivascular oedema and extravasation of erythrocytes. Endothelial cells exhibited intracellular vacuoles and intraluminal projections or blebs. The vessels of the microcirculation showed vasostasis, distension, compression and thrombosis. These axonal and microcirculatory features provide evidence for specific mechanisms of secondary injury in traumatic spinal cord injury such as autolysis by lysosomes released from ruptured axons and ischemia due to intravascular thrombosis and vascular compression.

P5.

Effect of 21-Aminosteroid U74389 (Lazaroid) on Experimental Acute Spinal Cord Compression Injury

S.S. HAGHIGHI, J.J. ORO, X. GENG and T. STIENS (Columbia, U.S.A.)

The effect of bolus injection of Lazaroid (U74389f) on acute spinal cord compression trauma in rats was studied. The cortical somatosensory evoked potentials (CSEPs) were abolished after a static compression injury of 120 grams for 10 minutes in all vehicle-treated animals. Intravenous bolus administration of Lazaroid were given at 1, 2, and 3 hours post-injury in the treated group. All the Lazaroid-treated rats demonstrated a return of the evoked cortical activities within the 2nd hour post-injury. No return of the CSEPs occurred in the vehicle-treated animals within 5 hours post-injury observation.

We concluded that the bolus administration of Lazaroid given one hour after the traumatic spinal cord injury facilitated the return of the spinal cord function in the static compression model of acute spinal cord trauma.

P6.

Amino Acid Changes in Thiamine Deficiency Monitored with Intracerebral Microdialysis

A.S. HAZELL, R.F. BUTTERWORTH and A.M. HAKIM (Montreal, Quebec)

Wernicke-Korsakoff syndrome is a metabolic disorder resulting from thiamine deficiency (TD) in which symmetrical histological lesions appear in selectively vulnerable regions of the brain including the thalamus. In experimental TD, recent evidence suggests that decreased activity of the thiamine-dependent enzyme, α-ketoglutarate dehydrogenase (KGDH), is the major contributor to many of the reversible changes accompanying this illness and may lead to localized areas of increased glutamate release resulting in an adverse effect on cellular integrity.

To examine this possibility, cerebral microdialysis was performed on TD rats (n = 5) at the acute clinical stage (loss of righting reflex). Similar studies were carried out in normal (n = 4) and pair-fed (n = 5) control animals. Rats were anesthetized with pentobarbital and 1 mm dialysis probes implanted stereotaxically into the right ventral posterior medial thalamus (VPMT) and non-vulnerable left frontoparietal cortex (FPC). The probes were perfused at a constant rate of 2 μL/min. Dialysate (10 min) samples collected 4-6 h later were analyzed by HPLC for amino acid content. Levels of glutamate (glu), aspartate (asp), glycine (gly) and taurine (tau) were assessed in all groups.

A comparison of normal and pair-fed controls showed no significant differences in any of the amino acids for either region. Combining these two groups and comparing with TD animals produced the following results:

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Group/ Region	Asp	Glu	Gly	Tau (μM)
Controls				
VPMT	0.02 ± 0.00	1.00 ± 0.13	1.67 ± 0.15	0.98 ± 0.15
FPC	0.04 ± 0.02	1.02 ± 0.11	1.95 ± 0.13	1.30 ± 0.08
Clinical				
VPMT	0.09 ± 0.02[a]	4.78 ± 0.28[b]	2.11 ± 0.13[a]	1.71 ± 0.04[b]
FPC	0.11 ± 0.00	1.84 ± 0.07[b]	1.43 ± 0.03	0.67 ± 0.04

(means ± S.E.M.; [a]$p < 0.05$, [b]$p < 0.01$ compared with controls)

These findings provide evidence for a 400-500% increase in extracellular glutamate in one vulnerable region of the TD brain accompanied by more moderate elevations of asp, gly, and tau. Prolonged exposure to such levels of glu may further compromise functional integrity at a stage when glucose metabolism is known to be severely depressed in these areas.

Supported by: MRC (Canada).

P7.

Inhibition of Normal Process Formation in Cultured Oligodendrocytes by Protein Kinase C Inhibitors

P.G. NOBLE and V.W. YONG (Montreal, Quebec)

We have previously reported that phorbol esters that stimulate protein kinase C (PKC), 4β-phorbol-12,13-dibutyrate (PDB) and phorbol-12-myristate-13-acetate (PMA), promoted process formation in cultured bovine, rat and human oligodendrocytes (OL) (Yong et al., 1988 and 1991). Furthermore, the age-dependent decrease of process formation by cultured rat OL was prevented by PKC stimulation (Yong et al., 1991). These results are of potential relevance to remyelination since the processes of OL wrap and compact around axons to form myelin.

The current experiments were designed to further implicate PKC in process formation by OL. Firstly, adult rat OL were treated with relatively selective inhibitors of PKC, H-7 and Staurosporine (SP) (10, 50 and 100 uM and 5, 10, 50 and 100 nM respectively), and process formation determined by immunofluorescence for galactocerebroside. Secondly, measurements of PKC enzyme activity were performed on PDB-treated OL cultures using a histone phosphorylation assay. The results show that H-7 (50 and 100 uM) and SP (at all concentrations) inhibited normal OL process formation ($p < 0.05$ compared to untreated controls by ANOVA with Duncan's multiple comparisons). Treatment with these inhibitors also produced regression of previously well-formed processes ($p < 0.05$ for H-7 at 100 uM and for SP at 100 nM). These effects of H-7 and SP were not mediated by a direct toxic effect to OL as determined by 51Cr labelling. Measurements of enzyme levels showed that PKC activity of OL was increased after phorbol ester treatment and did not readily undergo downregulation in contrast to other cell types (astrocytes, gliomas and fibroblasts).

These results provide further evidence that stimulation of PKC in OL is important in triggering as well as maintaining OL process formation.

P8.

Influence of Astrocytes, Insulin and Insulin-Like Growth Factor-I (IGF-I) on Neuritic Growth of Spinal Motoneurons *In Vitro*

L.C. ANG, B. BHAUMICK, J. SASS and B.H. JUURLINK (Saskatoon, Saskatchewan)

Recently we have shown that both insulin and IGF-I promote the survival of motoneurons in culture but such effect is only observed in the presence of living astrocytes (Ang et al., 1991). In this experiment we examine the effect of astrocytes, insulin and IGF-I on the neuritic growth of spinal motoneurons *in vitro*. Motoneurons were isolated from E15 dissociated mouse spinal cord by density centrifugation. The neurons were planted onto polyornithine-coated coverslips in a growth medium (DMEM/F12) supplemented with progesterone, transferrin, selenium, horse serum (10%) and muscle extract. The neuritic growth was determined at day 8 of culture by counting with the light microscope, the intersections produced by neurites radiating from the perikaryon placed centrally in a graticule of concentric circles (Sholl, 1953). Counts were performed on motoneurons on one strip extending from one edge through the center to the opposite edge of a coverslip and the mean intersections per neuron was worked out. The mean for cultures without addition of astrocytes, insulin or IGF-I was 12.75 ± 0.54. When astrocytes on a separate coverslip were introduced from day 1 into the dish containing coverslips of motoneurons, there was definite increase in neuritic branching (15.0 ± 0.816) at day 8. The branching was further increased with addition of 5 ug/ml of insulin (15.5 ± 1.021) or 100 ng/ml of IGF-I (30.0 ± 2.944) to cultures with astrocytes. Insulin or IGF-I in the absence of astrocytes did not increase the neurite branching of motoneurons. We conclude that living astrocytes increase the neuritic growth of motoneurons *in vitro* and that insulin and IGF-I further promote neuritic growth through actions mediated by astrocytes.

B. Neurosurgery

P9.

Withdrawn.

P10.

Spontaneous Thrombosis of a Galen Aneurysm following Ventricular Drainage

D.L. LADOUCEUR (Sherbrooke, Quebec)

Primary aneurysms of the vein of Galen are due to arterial vessels emptying directly into the vein of Galen. Usually, in infancy the malformation is associated with uncontrollable cardiac failure. The prognosis in this age group is poor with very few survivors.

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The present case showed the unusual favorable prognosis in a 2-month-old female infant admitted with an intracerebral hemorrhage. Following investigations with CT-scan of the head and cerebral angiogram, a diagnosis of true aneurysm of the vein of Galen was confirmed and disclosed as responsible for the hemorrhage. The patient never had before and following her admission any cardiac symptom or sign. Hydrocephalus subsequently developed in the few days after the hemorrhage and a ventricular shunting was performed. Clinical improvement in the following weeks was observed and serial CT-scan of the head suggested a thrombotic process of the aneurysm which was confirmed by cerebral angiogram and NMR study three months later.

P11.

Complete Removal of a Dumbbell Schwannoma in the Lower Cervical Spine Using a Modified Verbiest Approach: A Case Report

K. REDDY and S.D. ARCHIBALD (Hamilton, Ontario)

A 43-year-old lady was seen because of an incidental finding of an enlarged right C6-7 intervertebral foramen. The patient reported having three episodes of "her legs giving way", along with episodes of numbness and weakness in the right hand. Neurologic examination revealed slight weakness of the right wrist and finger extensors along with hyperreflexia and absent vibration sense in the right lower limb. Plain cervical spine x-rays showed a grossly enlarged 6-7 intervertebral foramen. Magnetic resonance imaging showed a large dumbbell shaped lesion involving the right C-7 nerve root, extending well outside the spinal canal.

Complete resection of the tumor was attempted using a modification of the lateral cervical approach of Verbiest. Using a transverse cervical skin crease incision the scalenus anticus and the phrenic nerve were identified and preserved. The proximal subclavian artery and the vertebral artery identified and traced cranially. The tumor was found to be enmeshed with the fascicles of the nerve root, necessitating its section. Complete resection was achieved. The patient had no neurologic deficits at all post-operatively, suggesting some "plasticity" of the nervous system at the radicular level. To our knowledge this is the first time this approach has been documented to have been used to completely remove a dumbbell schwannoma of the lower cervical spine.

P12.

Spinal Angiolipomas

M. PREUL, R. LEBLANC, Y. ROBITAILLE, R. POKRUPA and D. TAMPIERI (Montreal, Quebec)

Spinal angiolipomas are distinct, benign lesion composed of mature lipocytes and abnormal blood vessels. Most are extradural, some are intramedullary, and some infiltrate the surrounding bone. We report two cases of spinal angiolipomas and analyse previous reports. The 22 females and 12 males were aged 17 to 73 years (mean age 43 years). Females were significantly older than males (mean 44.9 vs 41.5 years; $p < 0.0001$; student t-test). The patients had back pain (39%), sensory dysfunction (97%), weakness (100%) of the lower extremities, hyperreflexia and spasticity (82%), and sphincter dysfunction (47%) for 1 to 180 months (mean 28.6 months) before diagnosis. Four patients (18% of females) were pregnant and 2 had significant weight gain coincident with the onset of symptoms. Thirty-four angiolipomas were extradural and 2 were intramedullary. Six of the extradural lesions infiltrated the surrounding bone. The tumours extended from C6 to L4 and had a predilection for the midthoracic region (53% of cases). Plain radiographs were abnormal in 36% and in all patients with bony infiltration. All myelograms were abnormal and showed a complete block in 69% of patients. Computed tomography (CT) and magnetic resonance imaging (MRI) revealed fat density lesions that enhanced in 50% of cases on infused CT and in the gadolinium-infused MRI study. All patients improved following resection of the epidural lesions and internal decompression of the intramedullary ones.

Spinal angiolipomas affect women by a 2:1 ratio. They involve the thoracic, especially the midthoracic region, produce spinal compression, and, in some cases, bony erosion and pathological fractures. The can be exacerbated by pregnancy and weight gain, suggesting that vascular engorgement, hormone response, and participation in general obesity may be important for their development and maintenance. MRI is the investigation of choice.

P13.

Mature Teratomas of the Central Nervous System at Atypical Sites in the Adult Central Nervous System: Report of 5 Cases

K. REDDY, J.B. SCHNITTAKER and A.M. KAUFMAN (Hamilton, Ontario; Winnipeg, Manitoba)

Mature teratomas are distinctly uncommon tumors in the adult central nervous system. The sites that these uncommon tumors have been shown to arise from within the central nervous system are the pineal region and the fourth ventricle. The authors have combined 5 cases of mature teratomas of the central nervous system at atypical sites in adults. The clinical presentation and management of these patients have been examined retrospectively and the previously available literature reviewed. Three of the patients were female and two were male. The mean age at presentation was 37.6 yrs. Three were located within the spinal cord and two intracranially. The clinical presentation varied considerably depending on the location of tumor, all the spinal lesions presenting with progressive neurologic compromise of varying degrees, and the lower spinal lesions presenting also with back pain. The patient with metastatic malignant teratoma presented with symptoms of impending herniation caused by hemorrhage into the tumor. The one patient with the cerebellar hemispheric lesion presented with progressive ataxia, facial paresis and hearing loss. No radiologic features specific to these tumors could be identified. Morphologically all but one of the lesions were cystic, and histologically all contained more than one germ cell layer derived tissue foreign to the site. Three of the patients improved significantly following surgery and one

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patient was unchanged. The patient with the cerebellar teratoma worsened post-operatively but has returned to the premorbid functional level but with residual neurologic deficits. A review of the available literature reveals that all the lesions presented in this report are distinctly rare, especially in adults. The majority of our patients presented with slowly progressive symptoms were histologically benign and responded well to surgical therapy. We conclude that mature teratomas in the adult central nervous system can occur at unusual sites, and respond well to appropriately directed surgical therapy.

P14.

Postoperative Pain in Acoustic Neuroma Patients: Some Observations on its Nature, Possible Etiology and Modification

D.W. ROWED, D.A. SCHESSEL and J.M. NEDZELSKI (Toronto, Ontario)

Postoperative interviews were conducted with 98 acoustic neuroma patients. Fifty-eight of these were consecutive cases operated by a suboccipital hearing conservation approach (SOHC) and 40 were patients operated on by a translabyrinthine (TL) approach, and matched for age, sex, tumor size and mean follow-up (5 years). There was an unpromoted complaint of pain in 37/58 (64%) of the SOHC group compared with 0/40 (0%) in the TL group. Pain was portrayed as severe (7/10 mean), often incapacitating and unimproved with the passage of time in a majority. In some cases exacerbation with manoeuvres which increase intracranial pressure was described.

In attempting to reduce postoperative pain, we initially changed to a small trifurcate incision which entails less muscle incision and dissection than the standard sigmoid incision, but 9/13 patients (69%) managed in this fashion still complained of chronic postoperative pain. A further modification consisted of the same incision with an underlying 2.5 cm craniotomy with replacement and stabilization of the bone flap. To date only one of 8 patients managed in this fashion has experience mild to moderate postoperative pain (3/10) ($p < .005$). Though follow-up is limited, our previous observation that chronic postoperative pain always begins within a month leads us to be optimistic that freedom from pain will continue. Excellent initial pain relief in one patient from cranioplasty is encouraging.

We believe that adherence of healing nuchal soft tissues to dura may result in pain and that performance of a small craniotomy with replacement and stabilization of the bone flap may reduce the incidence of postoperative pain.

P15.

Haemorrhagic Complications of Arachnoid Cysts: Report of 2 Cases

F.B. MAROUN, J.C. JACOB, M. MANGAN, R.E. REDDY and A. BADEJO (St. John's, Newfoundland)

Intracranial arachnoid cysts are rare, accounting for 1 to 5% of all non-traumatic intracranial mass lesions. Whether symptomatic or not their management is still controversial. We report two cases of arachnoid cyst presenting with intracranial haemorrhage following trauma. The first patient suffered an intracystic haemorrhage which was treated initially by drainage and later because of persisting headache by cysto-peritoneal shunt. The second patient suffered a subacute subdural hematoma following head injury which was evacuated. On follow-up scan the arachnoid cyst gradually disappeared.

P16.

Hemifacial Spasm and Neoplastic Lesions: Report of Two Cases and Review of the Literature

F.B. MAROUN, J.C. JACOB, M.A. MANGAN and R.E. REDDY (St. John's, Newfoundland)

Despite major advances in the understanding of hemifacial spasm its pathogenesis is still controversial. The incidence of neoplastic lesions producing hemifacial spasm is extremely rare. We report two cases of CP angle cholesteatoma who presented with hemifacial spasm. Symptoms disappeared after the removal of the cholesteatoma. Extensive review of the literature revealed forty cases of neoplastic lesions producing hemifacial spasm. A review of those and other theories of pathogenesis of hemifacial spasm will be discussed.

P17.

Direct Spinal Cord Evoked Potential to Localize Root Entry Zone

M. FAZL and D. HOULDEN (Toronto, Ontario)

Direct spinal cord evoked potential can provide accurate localization of dorsal root entry zone (DREZ) during radiofrequency lesion making to treat severe pain in patients with brachial plexus avulsion. This procedure helps accurate localization of root entry zone which prevents complication related to this procedure as a result of coagulation of adjacent structures.

Corticospinal tract conduction velocity is faster than dorsal column and also threshold for producing action potential is much lower. This physiological phenomenon helps to accurately localize root entry zone right in between corticospinal tract and dorsal column. This procedure has been performed in five patients with brachial plexus avulsion with no complications. Animal experimentation as well as procedures that have been used in humans to perform this procedure will be discussed.

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C. Neuro-oncology

P18.

In Vivo Phosphorous (^{31}P) Chemical Shift Imaging (CSI) of Untreated Human Brain Tumours

H. HUGENHOLTZ, A. RUTTER, M.T. RICHARD, V. MONTPETIT, I.C.P. SMITH and J.K. SAUNDERS (Ottawa, Ontario)

We tested the hypothesis that differences in ^{31}P spectra can discriminate CNS tumours from each other and from non-neoplastic lesions.

Patients with intracranial mass lesions underwent one-dimensional ^{31}P CSI with a surface coil, using a 1.5 T Siemens Magnetom within 24 hours of surgical biopsy/excision.

Each study required approximately 90 minutes for completion. A proton image of the lesion under study was first obtained. A surface coil was then applied to the cranial vault over the lesion and the CSI was performed.

The acquired spectra correlated to disc-shaped voxels (1.0-1.5 cm thick, approx. 9 cm diam.) beneath the surface coil. In turn, these voxels correlated with the configuration of the CNS lesions, determined from the corresponding proton images. Therefore, the acquired spectra reflected predominantly tumour, brain adjacent to tumour (BAT), "normal" tissues and combinations thereof.

The tumours included glioblastomas, astrocytomas, meningiomas and metastatic tumours. The phosphorous spectra from tumour were distinctly abnormal for all tumour types as well as those from BAT glioblastomas and astrocytomas. All tumours contained an alkaline pH. Gliomas had a high ratio of phosphodiesters over ATP and metastatic adenocarcinomas had a low ratio of phosphocreatine over ATP.

In-vivo CSI may contribute to the diagnosis of brain tumours in human subjects.

P19.

Proton (^{1}H) Magnetic Resonance Spectroscopy (MRS) Studies of Human Brain Tumours

H. HUGENHOLTZ, A. RUTTER, M.T. RICHARD, V. MONTPETIT, I.C.P. SMITH and J.K. SAUNDERS (Ottawa, Ontario)

Previous studies have shown that punch biopsies from cervix could be categorized from normal to malignant, using high resolution ^{1}H MRS. The applicability of this technique was tested on samples of human brain tumours.

Samples of human brain tumours (approx 0.5 ml) were placed in PBS D_2O buffer and immediately frozen by immersion in liquid nitrogen within 15 seconds of surgical biopsy and then stored at –70°C. When possible, separate samples of normal tissue were also obtained.

360 MHz 1D and 2D COSY spectra were then taken at 37°C at the Institute for Biological Sciences, National Research Council. The MRS data was then compared to the histopathological diagnosis of the tumour.

Specimens from glioblastoma and metastatic tumour could be discriminated from each other and from astrocytoma and normal tissue by the presence or absence of crosspeaks in the 2D COSY. Astrocytoma and normal samples are discriminated with 1D COSY data.

These parameters in the 1D and 2D COSY spectra may be utilized in future *in-vivo* MRS studies.

P20.

Intraoperative Somatosensory Evoked Potential (SSEP) Recording and Ultrasonography as Aids in the Resection of Subcortical Rolandic Tumours

D.W. ROWED, D.A. HOULDEN and K.A. KLETTKE (Toronto, Ontario)

Surface anatomy of sensorimotor cortex may be defined by topographical changes in SSEP wave form recorded from the cortical surface and correlated with subcortical lesions localized by intraoperative ultrasonography. Phase reversal of short latency SSEP components recorded from the pre- and post-central gyri is particularly useful and is probably underutilized in neurosurgical procedures.

Use of intraoperative SSEP in 8 patients with either astrocytomas or solitary metastases lying deep to the central fissure resulted in identification of pre- and post-central cortex in 6, post-central cortex in 1, and neither in 1. In the latter patient the grossly abnormal SSEP present pre-operatively could not be recorded intraoperatively.

Subtotal (astrocytomas) or grossly complete (metastases) resections were carried out with only one patient developing a new or increased sensorimotor deficit postoperatively. In this patient a hemorrhage developed near the operative site during tumour removal, and this was suggested by changes in the intraoperative SSEP and confirmed by ultrasound.

Intraoperative SSEP monitoring is a simple, widely applicable technique which facilitates maximal resection of deep rolandic tumours under general anaesthesia with minimal morbidity. Craniotomy size may be decreased and sensorimotor cortex may be defined in most cases, even if displaced.

Technical details and case samples will be discussed.

D. Pediatric Neurology

P21.

Supernumerary Fragment of X Chromosome in a Learning Disabled Boy

E.A. MacDONALD, P.B. SUTTON and A.M.V. DUNCAN (Kingston, Ontario)

An 11-year-old boy presented with dyslexia, dysgraphia and poor mathematic ability, but normal social and physical devel-

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opment. Head circumference and stature were normal. Motor coordination was poor and mirror movements prominent. Hypotonia and joint laxity were present. He had right-left confusion and graphesthesia. Physical examination was otherwise normal. The parents are separated and the father has learning disabilities; the mother has a university education.

Chromosomal analysis of stimulated lymphocytes revealed a supernumerary marker chromosome in 80% of metaphases studied. The rest of the karyotype appeared normal. *In situ* hybridization revealed the marker to be of X chromosomal origin with an X centronese-specific alpha satellite sequence. Recent information suggests that this may be a ring consisting of the juxtacentric region of Xp11.1 and Xq11.

In population surveys marker chromosomes occur in 1 in 1000 people, with 40% being familial. Many are asymptomatic. In our case familial origin cannot be excluded but further studies will be directed at determining if the marker is genetically active and contains material present in other X-linked mental retardation syndromes.

P22.

Hepatomegaly in Duchenne Muscular Dystrophy

G.A. deVEBER and L.E. BECKER (Hamilton; Toronto, Ontario)

"Dystrophin", the protein deficient in skeletal muscle in Duchenne Muscular Dystrophy (DMD) has been reported to be expressed in other organs including brain, cornea and intestine. Mental retardation in DMD demonstrates functional involvement of brain possibly due to deficiency of normal dystrophin expression in that organ. Hepatomegaly has never been reported in DMD to our knowledge. We report 2 patients with clinical, neuro-physiological, biochemical and muscle biopsy features of DMD who also had clinical hepatomegaly. Both presented in the second or third year of life with cognitive and motor development delay, hepatomegaly (5 cm below costal margin in both cases) mild splenomegaly and hypertrophic, weak muscles. Liver enzymes including gamma-glutamyl transpeptidase (GGT), bilirubin and alkaline phosphatase were normal in both. Investigation for storage disease, extensive in one case did not reveal a specific metabolic disorder. Marked calf hypertrophy and striking elevation of creatine kinase (CK) (31,000 in one and 6,435 in the other) led to electromyography and muscle biopsy which confirmed the diagnosis of DMD in both. We reviewed liver autopsy reports from 8 boys in Toronto who died at ages 14 - 16 yrs from DMD and found, as previously observed that the majority (6 of 8) had small liver weights (range 491 to 950 gm, mean 745 gm). Histological findings were of "mild fatty changes" in one small liver and "hepatic fibrosis" in one large liver, the rest were normal.

Liver enlargement in our two patients with DMD is of unknown etiology and functional significance but its presence suggests liver involvement in this disease, at least early in its course. Subtle liver biochemical alterations in animal muscular dystrophy including esterase alterations, low unsaturated fatty acids and elevated catalase (CAT) activity have been reported but human liver biochemistry in DMD has not been well characterized.

DMD should be considered in the differential diagnosis of developmental delay with hepatosplenomegaly. Liver imaging studies and biopsy in such cases proven to have DMD may elucidate an underlying abnormality.

P23.

Does Early Diagnosis of Herpes Simplex Virus Encephalitis Affect Prognosis?

E.P. WOOD and P. HWANG (Toronto, Ontario)

Herpes Simplex Virus Encephalitis (HSVE) is the most common cause of fatal viral encephalitis. Early treatment is reported to improve outcome but there is controversy over diagnostic criteria and the need for brain biopsy.

A retrospective chart review of all cases from the Hospital for Sick Children in Toronto covering 1981-1990 with HSVE as the discharge diagnosis was done. There were 21 cases, 9 in neonates and 12 in older infants and children.

The EEG was almost always abnormal, showing focal slow waves predominantly in the temporal regions, and frequent epileptiform discharges, but periodic lateralized (PLEDS) activity was encountered only in the minority. Neuroimaging studies such as CT scans were relatively insensitive early in the course of the disease but may be specific late in the evolution. Radionuclide scanning showed early focal uptake suggestive of a disruption of the blood-brain barrier.

In conclusion, early diagnosis of HSVE is essential to optimize neurologic outcome. Electro-physiologic and appropriate neuroimaging studies may obviate the need for brain biopsy. This would allow for earlier diagnosis and thus efficacious treatment resulting in improved intact survivorship.

P24.

Treatment of Rasmussen's Encephalitis with Ganciclovir

S.D. LEVIN and R.S. McLACHLAN (London, Ontario)

Rasmussen's chronic encephalitis is characterized by intractable focal and generalized seizures, progressive hemiparesis and cognitive decline. Pathological findings of perivascular inflammation and microglial nodules suggest a viral encephalitis. Cytomegalovirus (CMV) DNA has been demonstrated in the brains of these patients.

We report the use of ganciclovir, a potent anti-CMV drug in 3 patients with pathologically proven Rasmussen's encephalitis. Two patients ages 8 years and 24 years who were positive for CMV genome were treated with a two week course of ganciclovir 10 mg/kg bid for two weeks immediately following epilepsy surgery. Both improved significantly. A 3-year-old boy treated after brain biopsy showed Rasmussen's encephalitis and whose *in situ* hybridization and gene amplification studies showed no CMV genome, had no improvement.

Whether ganciclovir is effective in Rasmussen's encephalitis remains unproven. Our limited experience suggests that biopsy confirming the diagnosis and treatment with granciclovir should be tried early in the disease to determine efficacy.

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P25.

Peroneal Muscular Atrophy as the Presentation of Chiari I Malformation with Hydrosyringomyelia

G.A. deVEBER (Hamilton, Ontario)

Peroneal muscular atrophy is a clinical entity with onset in late childhood or adolescence of distal muscular atrophy and weakness in the feet and legs with mild distal sensory loss. Forearm and hand muscles are eventually involved. It is classically associated with Charcot-Marie Tooth disease (hereditary sensory motor neuropathy type II) but can be seen in other peripheral nerve or predominantly distal anterior horn cell degenerations or rarely in distal muscular dystrophies.

We describe a 15-year-old boy who presented to neuromuscular clinic with a two year history of progressive "foot drop". He had also had minimal left hand weakness for the previous 18 months. Clinical examination showed mild pre-tibial and calf atrophy, muscle weakness of right greater than left foot intrinsics and ankle dorsiflexors, invertors and evertors (all were grade 3/5 or less), absent tendon reflexes at the knees and elbows but intact ankle tendon reflexes and flexor plantar responses. There was slight wasting and weakness of the left hand thenar group, isolated impairment of vibration at the toes and a slight decrease in light touch perception of the fingertips and in a patch over the right shoulder. He had a history of moderately severe head trauma 10 years earlier with subsequent non-progressive mild cognitive impairment and no family history of neuromuscular disease. Motor and sensory nerve conduction velocities and late responses were normal and concentric needle examination showed evidence of active and chronic denervation (giant polyphasic potentials) in proximal and distal muscles in all four limbs and paraspinal muscles at multiple levels. Craniospinal MRI showed moderate hydrocephalus, Chiari I malformation and extensive hydrosyringomyelia extending from foramen magnum to conus medullaris.

This patient exhibits an unusual presentation of syringomyelia with no long tract symptoms or signs and minimal upper limb dysfunction, but severe distal leg weakness and wasting characteristic of peroneal muscular atrophy. This presumably represents loss of lumbosacral anterior horn cells supplying distal leg and foot muscles due to the syrinx. Spinal cord pathology should be considered in the differential diagnosis of this clinical syndrome.

P26.

Central Nervous System Malignancy Mimicking Mitochondrial Encephalopathy

F.A. BOOTH and W.C. HALLIDAY (Winnipeg, Manitoba)

Mitochondrial encephalopathy is often considered in the differential diagnosis of neurological disorders with abnormalities of eye movements and ptosis. Central nervous system malignancy is considered less likely. We present an adolescent boy in whom the presumptive diagnosis of mitochondrial encephalopathy was made who in the final phase of his disorder was shown to have an infiltrating anaplastic astrocytoma. The patient, who had a longstanding history of cognitive and motor dysfunction of unknown etiology, presented at age 15 years with a drooping right eye-lid, dizziness, headaches and worsening coordination. Initial examination revealed a right ptosis, a partial right third nerve palsy with pupillary sparing, in-coordination and developmental delay. Extensive investigation showed only mild lateral ventricular dilatation, right greater than left. Over the next four years, he developed progressive brainstem dysfunction including bilateral ptosis and external ophthalmoplegia, cerebellar and motor dysfunction and intellectual regression. On one occasion, blood pyruvate and a lactate/pyruvate ratio were mildly elevated. Biopsies of muscle and skin were normal. CT and MRI changes, which occurred late during the period of deterioration, prompted a brain biopsy which revealed an infiltrating anaplastic astrocytoma. At autopsy, there was no evidence of mitochondrial encephalopathy. Our case suggests caution in making a diagnosis of mitochondrial disease in the absence of consistent biochemical or morphological abnormalities and illustrates that the diagnosis of a CNS neoplasm can be difficult, even with modern imaging technology.

P27.

Progressive Familial Myopathy with Deposits of Desmin Aggregates

J. VAJSAR, G.E. MURPHY and L.E. BECKER (Toronto, Ontario)

Two siblings who presented with cardiomyopathy several years before they developed slowly progressive muscle weakness had unique clinical and pathological findings. Skeletal muscle biopsies displayed subsarcolemmal crescents of dark eosinophilic material in both type I and type II fibres. Immunohistochemically, the subsarcolemmal material stained positively for the intermediate filament (IF) protein desmin and for the heat shock protein ubiquitin, but for no other cytoskeletal proteins. Ultrastructurally, the subsarcolemmal deposits consisted of aggregates of granular and filamentous material arising from Z-bands. Follow-up muscle biopsies 6 years later showed an increased number of the muscle fibres containing subsarcolemmal desmin-ubiquitin-positive aggregates.

These clinical and pathological features characterize a rare familial myopathy associated with an unusual pattern of distribution of desmin IF proteins in skeletal and probably also cardiac muscle.

P28.

Neuronal Hamartoma, Cortical Dysplasia and Neuronal Heterotopias in a Patient with Intractable Complex Partial Seizures

H. OTSUBO, V. JAY, L. BECKER, P. HWANG, H. HOFFMAN and D. ARMSTRONG (Toronto, Ontario)

Unusual pathology was encountered in an anterior temporal lobectomy specimen from a 9-year-old boy with intractable

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complex partial seizures and behavior problems. EEG showed active epileptiform discharges from left anterior temporal and generalized epileptiform paroxysms interictally, while ictal onset was detected from the left temporal including inferior mesial temporal region with sphenoidal electrodes. MRI showed a slightly enlarged left temporal lobe, and diffuse high signal intensity over the cortical region as well as poor differentiation of gray and white matter on T2 imaging. Interictal SPECT using 99 m Tc HMPAO demonstrated decreased rCBF over the left temporal region.

Pathologically, the left temporal cortex revealed focal polymicrogyria and focal cortical dysplasia with extensive disorganization of neuronal morphology, layering and orientation. The cortical-white matter junction was indistinct with extensive neuronal heterotopias in white matter. A hamartomatous nodule in the white matter revealed abnormal neurons with penetration of cell bodies by capillaries. Two years postoperatively, the patient had no seizures on medication with improvement in behavior. The EEG shows no focal epileptiform activity. This unusual pathological phenomenon is attributed to a developmental disturbance affecting neuronal, glial and vascular elements.

P29.

Clinical Correlates of Sagittal Spikes in Children

S. EARL, M. HUGHES and N. LOWRY (Saskatoon, Saskatchewan)

Sagittal (midline) spike discharges are said to occur in 0.1 - 0.5% of all EEG's. In children the frequency is higher (2 - 3%). Such spikes may spread to various surface areas and be difficult to localize if vertex electrodes are not employed routinely. They may appear and disappear over time in the same patient. Over a 3 year period we recorded sagittal spikes in 18 children over the age of 1 month. 9/18 had generalized seizures, 6 had partial seizures, 1 had mixed seizures and 2 were not having seizures when the spikes were recorded. 8 had no neurological abnormalities, 4 had cerebral palsy, 2 had primary microcephaly, 2 had tuberous sclerosis and 2 had Landau-Kleffner syndrome.

Of the 8 patients with normal intelligence, 3 had generalized motor seizures, 2 had typical absences and 3 had partial seizures. These seizures were all easily controlled with medication.

Sagittal spikes may have a wide variety of underlying etiologies, however, in patients with normal intelligence they likely represent a benign type of epilepsy which responds well to treatment and has a good prognosis.

E. Neuroimaging

P30.

Endovascular Treatment with Cyanoacrylate of Brain Arteriovenous Malformations (BAVMs) Supplied by the Anterior Choroidal Artery (AChA)

P. HALLACQ , K. TERBRUGGE , P. WILLINSKY , W. MONTANERA and P. LASJAUNIAS (Toronto, Ontario)

For many years the AChA has been considered as one of the most dangerous arteries for intervention procedures. Embolization is reputed as safe when performed beyond the choroidal point, after the AChA has given off most of its branches to the optic tract, internal capsule and basal ganglia. Stroke in AChA's territory results in variable hemiplegia associated with hemianopsia and sensory deficit.

We report our experience with endovascular treatment of BAVMs fed by the AChA. In 22 (11%) of 200 patients with BAVMs referred for assessment, the AChA was one of the feeders to the malformation. In 6 patients the angioarchitecture and hemodynamics of the lesion were favorable for selective catheterization and embolization with liquid cyanoacrylate based material. In the six patients undergoing embolization, excellent penetration of the BAVM nidus was obtained, and no neurological deficit occurred. Interestingly, 4 patients had proximal catheter tip position at embolization and did not have a neurological complication.

The conventional principles in embolization procedures is not to inject embolic material proximal to vessels leading towards healthy territory. This was not evident in 4 of our patients. We believe that a detailed analysis of the vascular territorial balance between AChA, posterior communicating artery, middle cerebral artery and internal carotid artery is important for determination of the safety of embolization procedures in the AChA territory.

P31.

Endovascular Treatment of Spinal Arterio-Venous Malformations: Review of Our 7-year Experience

K. TERBRUGGE , S. AGGARWAL, R. WILLINSKY and W. MONTANERA (Toronto, Ontario)

Over the past 7 years, we have performed 16 endovascular therapeutic procedures on 8 patients (5 males and 3 females, aged 21-64 years) with spinal arteriovenous malformations (AVMs). Six patients had dural while 2 had intramedullary AVMS. A tissue adhesive (NBCA) was utilized for embolization in all patients. However, additional use had to be made of PVA particles in 3 patients when the catheter tip placement was unsatisfactory to permit NBCA's use. Results of the embolization were considered fair to excellent in 7 patients; it was unsuccessful in one. Surgery was necessitated in this patient, and also in 2 others who demonstrated either less-than-satisfactory occlusion of the nidus (1 patient) or because of the AVM's recurrence after initial good occlusion (1 patient). A review of our experience will be presented.

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P32.

Usefulness and Limitations of Modern Neuroimaging Techniques in the Recognition and Differential Diagnosis of Focal Cortical Dysplasia

R. DESBIENS, F. ANDERMANN, F. DUBEAU, D. TAMPIERI , D. MELANSON, A. OLIVIER, Y. ROBITAILLE and P. LANGEVIN (Montreal; Quebec City, Quebec)

Better understanding of Neuronal Migration Disorders (NMDs) was derived from the development of neuroimaging techniques like CT, MRI, PET and SPECT: they permitted a comprehensive classification of these disorders and insight into the timing and sequence of events leading to these brain malformations.

Schizencephaly, nodular and band heterotopia, hemimegalencephaly, diffuse cortical dysplasia and bilateral perisylvian polymicrogria are entities recognizable by imaging, but clinical syndromes are less specific (epilepsy, mental retardation, focal or diffuse sensory and motor signs).

However, some defects in neuronal migration, especially focal cortical dysplasia, may be difficult to demonstrate or visualize. The imaging abnormalities may also be misinterpreted or not recognized.

The MNI series of cortical dysplasias now includes 52 patients; this series was reviewed recently by Palmini et al. (Can J Neurol Sci 1991; 18: 580-587). Among these patients, two had no detectable preoperative MRI changes but eventually proved to have focal cortical dysplasia and one with focal MRI changes was found to have a double diagnosis (remote post-traumatic occipital contusions and subcortical nodular heterotopias).

The clinical, electrophysiologic and pathologic features of these patients will be reviewed. The role of functional neuroimaging techniques, in the early recognition of these less obvious forms of NMDs, will be stressed.

F. Multiple Sclerosis

P33.

Prevalence of Multiple Sclerosis (MS) in Westlock County: Another Excess Risk Area Confirmed in Alberta

S.A. WARREN and K.G. WARREN (Edmonton, Alberta)

Until recently the highest MS prevalence rate reported in Canada was 111/100,000 in Saskatoon (Hader, CMA 1982; 127: 295). Now Klein et al. (CJNS 1990; 17: 241) have observed a prevalence rate of 202 in Crows Nest Pass, southern Alberta, and Warren and Warren (CJNS 1991; 18: 252) a rate of 196 in Barrhead County, north-central Alberta. Both areas were reputed to be of excess risk before being formally studied. The University of Alberta's MS Clinic has begun to study other suspected excess risk areas, to determine if their reputations can be confirmed.

MS patients living in Westlock Country, which is adjacent to Barrhead County, were ascertained through the files of the MS Clinic (the major referral centre for the area); all doctors in the county; the county's 1 general hospital and 1 nursing home.

Twenty-five MS patients were identified among the county's 11,455 residents. Using probable/definite cases only (N = 23), a prevalence rate of 201/100,000 was observed for January 1, 1991. Considering all patients, 48% were relapsing-remitting and 60% were walking without aids. Patients' mean age was 47, mean onset age 30, and mean illness duration 18 years. The female to male ratio was 1.5:1; 24% of patients reported another MS relative; and 88% were living in Westlock County or vicinity at onset. Westlock County patients did not differ from Barrhead County patients on any of these factors. Incidence rates were also stable during the 1960's, 70's and 80's in each area, suggesting a constant environmental risk factor.

Because of their similarities regarding prevalence, disease features and incidence patterns, Westlock and Barrhead Counties should probably be considered parts of the same excess risk pocket in north-central Alberta. Most prevalence studies in other provinces have been conducted in major cities not suspected excess risk areas, so it is not clear whether risk pockets with similarly high prevalence rates exist elsewhere in Canada or are unique to Alberta.

P34.

Balo's Concentric Sclerosis and Multiple Sclerosis in an East Indian Woman

A.J.E. PROUT, K. BERRY and J. OGER (Vancouver, British Columbia)

A 24-year-old East Indian woman presented with a four year history of remitting and relapsing multifocal neurological dysfunction. Clinical features, neurophysiologic testing and magnetic resonance imaging supported a diagnosis of multiple sclerosis (MS), despite the persistent absence of oligoclonal banding (OCB) in the cerebrospinal fluid. She developed psychomotor retardation and rapidly progressive brainstem dysfunction which led to her death despite intravenous cyclophosphamide and cortiosteroid therapy. Pathological examination of the brain revealed multiple demyelinated areas frequently containing concentric bands of preserved myelin typical of Balo's concentric sclerosis (BCS), in addition to other lesions more typical of MS. This case represents a pathologic association between BCS and MS, which may be related to the absence of OCB and the patient's race. The relationship between BCS and MS could be explained by the specificity of the immunogenetic background encountered in a Caucasian of non-European origin.

P35.

Gelastic Seizures: An Unusual Manifestation of Multiple Sclerosis

J. RAVINDRAN and C.L. VOLL (Saskatoon, Saskatchewan)

A 25-year-old female with multiple sclerosis presented with gelastic seizures as her initial symptom. Her seizures comprised stereotyped attacks of uncontrollable laughing, generally per-

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sisting for several minutes, accompanied by depersonalization, partial unresponsiveness, inability to speak and masticatory movements, followed by postictal confusion. Magnetic resonance imaging showed multiple focal areas of increased density in the periventricular white matter bilaterally on T2 weighted images. In addition a prominent focal area of increased density was noted along the mesial aspect of the right temporal lobe. The lesion correlated with a slow wave focus shown on spectral frequency analysis of EEG. We believe that gelastic seizures have not been previously reported as a presenting symptom of multiple sclerosis. The most common EEG finding in multiple sclerosis patients with seizures is a gross delta or theta focus without spiking. On the basis of EEG frequency analysis, we believe that the mesial temporal lesion was the probable epileptogenic focus.

P36.

Spasmodic Torticollis and Foot Dystonia with Internal Capsule Plaque in Multiple Sclerosis

S. GANGULI, C.L. VOLL, W.J. HADER and I. GULKA (Saskatoon, Saskatchewan)

A young woman with clinical definite multiple sclerosis developed spasmodic torticollis abruptly, coincident with left hemiparesis and subsequently left foot dystonia which persisted during the next five years and failed to respond to a variety of medications, including carbamazepine. In addition to multiple periventricular lesions, magnetic resonance imaging (MRI) showed a dominant plaque in the posterior limb of the right internal capsule, abutting on the thalamus. The sustained focal dystonic movements in our patient differed from paroxysmal dystonia which occurs more typically in multiple sclerosis. Paroxysmal dystonia is suppressed with carbamazepine, and almost invariably subsides spontaneously after weeks or months. There are few reports of MRI findings in patients with focal dystonia in multiple sclerosis. One study reports paroxysmal dystonic head turning with arm and leg spasms with a demyelinating plaque in the contralateral internal capsule. A plaque in the mesencephalon was identified as the likely responsible lesion causing non-paroxysmal spasmodic torticollis in another patient with multiple sclerosis. We report this case because we believe it is the first MRI-correlated description of non-paroxysmal spasmodic torticollis and foot dystonia in multiple sclerosis associated with a demyelinating plaque in the contralateral internal capsule.

G. Neuro-Ophthalmology

P37.

Blindness Due to Extramedullary Hematopoiesis in Thalassemia

G. FRIEDMAN, N. PELED, J. ROARTY, P. HWANG, W. LOGAN and N. OLIVIERI (Toronto, Ontario)

Extramedullary hematoporesis (EH) is a rare but well recognized complication of Thalassemia. It is the physiological response to the ineffective erythropoiesis and hemolysis, and represents a particular problem in patients not receiving regular transfusions. Expansion of the bone marrow leading to bony hyperplasia at extramedullary sites can lead to variable symptomatology on the basis of local compression. The sites of EH are most frequently the liver, spleen and lymph glands, although in extreme cases skeletal changes occur in the skull, thorax and pelvis. More recently, there have been several reports of neurological complications secondary to EH, including spinal cord compression, paraplegia, and low back pain.

We report a case of EH leading to subacute onset of blindness. This case is important, because to our knowledge, it is the first report of EH as a cause of blindness. Moreover, it represents a potentially reversible cause of blindness if recognized early. Current understanding of EH, as well as therapeutic options are discussed.

P38.

A Computerized Model for the Teaching of Pupil Testing

C.E. MAXNER, A. HOSKIN-MOTT, S. LEE and R. KO (Halifax, Nova Scotia)

In the neuro-ophthalmic education of undergraduates, postgraduates, and practising physicians, mastery of the pupil exam is made difficult by its dependence on the availability of patients with disease processes giving pupillary signs. As well, the education process is time consuming because it necessitates one-on-one teaching to ascertain that, in fact, the student *has* mastered the appropriate skills.

We have developed a program which allows a student to interact with a computerized model to teach normal pupillary function and then to master the identification of the afferent pupillary defect.

An overview of this program and its evaluation as a teaching instrument will be presented.

SATURDAY, JUNE 27, 1992 – ALL DAY

H. Neuromuscular

P39.

A Simple Test for the Detection of Dysphagia in Members of Families with Oculophyaryngeal Muscular Dystrophy (OPMD)

J.-P. BOUCHARD, S. MARCOUX, F. GOSSELIN, D. PINEAULT and G. ROULEAU (Quebec; Montreal, Quebec)

OPMD starts late in life with lid ptosis, dysphagia or both. As these symptoms are very slowly progressive, an early diagnosis of OPMD is often difficult to ascertain. The objective of the study was to develop a simple and objective diagnostic test for dysphagia. A total of 238 members of 20 French Canadian families, each of which included an index case of OPMD confirmed by biopsy were identified. They were classified according to symptoms and neurological examination as positive (n =

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46), probable (n = 12), possible (n = 47) or negative (n = 133) cases. Controls were 337 normal subjects with no familial history of OPMD.

All subjects were asked to drink as fast as possible 80 cc of cold water and time needed was recorded. Subject's age averaged 62.3, 54.7, 45.9, 42.2 and 48.4 years in positive, probable, possible, negative cases, and controls respectively. After adjustment of age, the average time required for the test was significantly longer ($p < 0.05$) in positive (27.9 seconds), probable (12.1 seconds) and possible (8.9 seconds) cases than in negative cases (5.7 seconds). Results in the latter group were similar to those in controls (5.9 seconds). With a cutoff set at ≥ 8 vs < 8 seconds, the sensitivity and specificity of the test for differentiating positive cases from other categories of cases were 87% and 77% respectively. Using ≥ 6 vs < 6 seconds as cutoff, the sensitivity and specificity of the test for differentiating *possible* and *probable* cases from *negative* cases were 70% and 71% respectively.

P40.

Isolated Respiratory Muscle Denervation in Myasthenia Gravis

J. MAHER, C.F. BOLTON and T. PARKES (London, Ontario)

We report a previously undescribed phenomenon of isolated denervation of the respiratory muscles in a patient with myasthenia gravis.

A 60-year-old housewife presented to hospital with respiratory failure which required emergency intubation and ventilation. There was a 6-month history of intermittent diplopia, progressive dysarthria, dysphagia, nasal regurgitation and mild proximal limb weakness. Examination revealed mild proximal limb weakness, an absent gag reflex and mild proximal limb weakness. Limb power declined and impairment of ocular movement increased with sustained exertion. Respiratory examination revealed paradoxical movement of the chest and abdomen. Vital capacity was 5 ml/kg. The clinical diagnosis of myasthenia gravis was confirmed with electro-physiological studies, using repetitive stimulation techniques and by the use of the edrophonium bromide test, both of which were positive. However, needle electromyography revealed active denervation (positive sharp waves and fibrillation potentials) in the chest wall and diaphragm and decreased recruitment of motor units. There was no evidence of denervation elsewhere. Respiratory failure and needle electromyographic evidence of denervation slowly resolved over 6 months. There was no evidence of thymoma.

The isolated denervation of the diaphragm and chest wall reflected the site of her major muscle weakness, which we believe contributed significantly to her slow recovery. Nonetheless, with aggressive management, recovery was complete.

P41.

Use of Intrathecal Baclofen in Three Patients with Intractable Lower Limb Spasticity Secondary to Diverse Diagnoses

G.M. KLEIN, W.J. BECKER, D. DeFORGE, M.L. LONG, O. DOLD, D. ABLETT and C. HARRIS (Calgary, Alberta)

We evaluated and treated three patients with intractable lower limb spasticity with long-term intrathecal baclofen. Primary diagnoses were multiple sclerosis, spinal cord trauma and closed head injury.

Neurologic evaluation included clinical examination, spasm frequency score, Ashworth score and bladder score.

Functional evaluation included resistance to passive stretch measured as torque at fixed velocities over a variety of joint angles using an isokinetic dynamometer (Kincom) device, and ADL assessments using the Klein-Bell ADL scale, Jebson hand test and video-taped performances, where appropriate.

Patients were evaluated prior to treatment, and after treatment with intrathecal baclofen delivered by a permanent intrathecal catheter. All patients had a positive clinical and functional response.

P42.

Electrophysiological Evidence That Some Fasciculations in ALS are Generated in Corticomotoneurons

H. STEWART, B. PANT and A. EISEN (Vancouver, British Columbia)

We have previously postulated that in ALS the corticomotoneuron (CM) is the initial cell to be involved and that the anterior horn cell (AHC) is affected secondarily by antegrade effects (Muscle & Nerve 15: 1992). Fasciculation in ALS may predate other symptoms, commonly occurs in strong, clinically unaffected, muscles and is seen relatively infrequently in other diseases selectively affecting anterior horn cells.

Using a concentric needle electrode and a narrow bandpass (500 Hz - 2 kHz) fasciculation potentials (FPs) were recorded from different muscles in 15 patients with ALS. The FPs had a fibre density that was 2-3 times that of the most complex voluntary activated motor units (MUPs) recorded at the same needle position. Employing transcranial magnetic stimulation we elicited motor evoked potentials again recorded with a concentric electrode from the resting hand muscles. Some of these were morphologically identical to FPs recorded at the same needle site.

These observations lead us to conclude that some fasciculations in ALS originate in hyperexcitable corticomotoneurons prior to their death. A single CM synapses monosynaptically with several or many AHCs which is anatomical support for the concept and would explain the complexity of some FPs in comparison to activated-motor units. Fasciculations frequently decrease in ALS as the disease progresses this may in part be the result of CM attrition.

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P43.

Haemochromatosis and Amyotrophic Lateral Sclerosis: Is There an Association?

J. RAVINDRAN, L. ANG and J.R. DONAT (Saskatoon, Saskatchewan)

A 59-year-old man was diagnosed to have haemochromatosis confirmed by liver biopsy. Two years later he presented with progressive muscular weakness, dysarthria and dysphagia. He had wasting, weakness and fasciculations in the tongue and both upper limbs. His deep tendon reflexes were symmetrically brisk with bilateral extensor plantar response. Autopsy findings confirmed cirrhosis of liver and increased iron deposition in the liver. Neuropathological findings showed loss of motor neurons in the brain stem and the anterior horns of the spinal cord and degeneration of the pyramidal tract consistent with amyotrophic lateral sclerosis.

The occurrence of these two diseases in this patient may be coincidental. It has been shown in animal studies that degeneration of motor neurons can occur with oxygen radical mediated cytotoxicity (Kim 1991). Iron dependent free radical reactions are involved in neurotoxicity (Halliwell 1989). The occurrence of these two diseases in our patient may be a point of interest in looking at free radical induced damage to motor neurons as one of the pathogeneses of amyotrophic lateral sclerosis.

P44.

Neurophysiological Monitoring of Sensory and Motor Function During Acetabular Fracture Surgery: Preliminary Report

K.A. KLETTKE, D.A. HOULDEN, A. SCHOPFER and J.N. POWELL (North York, Ontario)

Following surgery for acetabular fractures, 7-13% of patients wake up with new neurological deficits related to peripheral nerve injury.

Intraoperative damage to the sciatic nerve (SN) or femoral nerve (FN) is thought to be partly related to prolonged or improper retraction of these nerves. Few reports address neural monitoring during surgery for acetabular fracture and these are limited to monitoring sensory function by somatosensory evoked potentials (SSEP's).

We have monitored both sensory and motor nerve function in 8 patients undergoing acetabular fracture surgery with hopes of preventing nerve injury. SSEP's were recorded from sites proximal (cervical, cortical) and distal (popliteal fossa) to the surgical site following posterior tibial nerve stimulation at the ankle. For motor nerve monitoring a new technique was developed where we stimulated the L1-L2 interspace via needle electrodes placed in the interspinous ligaments and recorded the compound muscle action potential from tibialis anterior, gastrocnemius and rectus femoris. Once a baseline muscle recording has been obtained, only one stimulation is needed to observe a response giving the surgeon instant feedback. In contrast, the SSEP requires averaging which takes 2-4 minutes.

None of our patients developed new post-operative deficits. In one patient, the muscle response significantly deteriorated during surgery but improved to baseline after retraction was altered. No patient had permanent deterioration in muscle responses or SSEP's so the clinical utility of our monitoring techniques remains to be determined.

I. General Neurology

P45.

Paroxysmal Dyskinesia Associated with Hypoglycemia

B.J. SCHMIDT and N. PILLAY (Winnipeg, Manitoba)

The development of involuntary movements during insulin-induced hypoglycemic shock treatment was described by Golden in 1937 (Ann Int Med vol. 11). In recent decades, however, hypoglycemia has rarely been reported as a cause of dyskinesia. We report 2 patients with paroxysmal involuntary movements associated with hypoglycemia.

A 54-year-old male presented with a 4 year history of sporadic episodes of uncontrollable, chaotic, bilateral limb movements, mainly involving the legs. Adrenergic symptoms such as diaphoresis, tremor and tachycardia were absent. However, he regularly aborted the episodes by drinking orange juice. His random blood glucose measurements were low with inappropriately elevated insulin levels. Combined EEG-video monitoring of one of his attacks demonstrated relative preservation of consciousness and generalized slowing without epileptiform activity. His blood glucose level was 2.1 mmol/l during the attack.

The second patient is a 28-year-old insulin-dependent diabetic who presented with transient episodes of alternating hemiparesis occurring in the early morning hours. In addition she had episodes of unilateral or bilateral choreiform movements affecting the upper limbs. The attacks were not associated with adrenergic symptoms. During an EEG-video monitored event she suddenly developed choreiform movements following an injection of her usual dose of insulin. Her blood glucose fell to 2.0 mmol/l during the attack and the episode was aborted by the administration of intravenous glucose.

The possibility of neuroglycopenia should be considered in patients with unexplained attacks of neurological dysfunction, such as dyskinesia or hemiparesis, even if adrenergic symptoms of hypoglycemia are absent.

A videotape recording of the first patient will be presented.

P46.

Leukoaraosis and Tardive Encephalopathy After Acute Carbon Monoxide Poisoning

L.-Y. FENG, L. JIAN-MING, W. XIAO-QI, L. YING, F. KE and C. JIAN-YUAN (Shijiazhuang, China)

We had studied 12 consecutive patients with tardive encephalopathy after acute carbon monoxide poisoning. Computed tomograms in 11 (mean age 53.8 years; aged 37 - 80

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years; 9 men, 2 women) of the 12 patients showed leukoaraosis (LA), 9 of the patients presented diffuse white matter lesions in periventricular region and the centrum semiovale in parietal, frontal and occipital regions. One patient presented in both frontal centrum semiovale and another presented occipital centrum semiovale as well as involved globus pallidus. All of the patients had dementia in some degree, fecal and urinary incontinence, and dysbasia. Clinical examination showed that 7 had Babinski's sign (+), 1 had general seizure. All the patients were treated with nicotinic acid intravenous transfusion (0.5 - 1.2 g every day for 30 days). After one month, 7 of the patients were completely cured, 2 significantly improved. These results suggest that LA may be cured at early stage treatment by improving microcirculation, which may be helpful for the treatment and prognosis in the patients with LA caused by other diseases.

P47.

Familial Postpartum Brachial Neuritis

J.-P. BOUCHARD, L. LALIBERTE, D. BRUNET and R. ROY (Quebec; Chicoutimi, Quebec)

In 1933, Ungley reported a recurrent neuropathy developing late in pregnancy and in puerperium in a mother and two daughters. Since then a number of familial cases of brachial neuritis have been described, with autosomal dominant inheritance, often associated with minor dysmorphic features such as hypotelorism. More than half of the women encountered in these families developed symptoms during pregnancy or postpartum, often with pain only and no amyotrophy.

A woman, age 33, had a normal first pregnancy and felt pain in her left shoulder immediately after delivery under epidural anesthesia. Weakness and atrophy of supra, infraspinatus and triceps muscles were soon noted on the left, accompanied by a severe winging of the right scapula. Pain disappeared shortly after local corticosteroid injection of left shoulder. Motor recovery was slow and EMG fibrillation potentials persisted in involved muscles up to 8 months after onset.

Her sister, age 31, had a normal third pregnancy and repeated cesarian section under general anesthesia. She complained of severe pain in the right arm of the third day postpartum, and to the left shoulder on the fifth, as well as dyspnea. Oral corticosteroids were started after two weeks and relieved the pain within three days. The distribution of muscles involved was almost the same as in case 1. EMG showed denervation signs in involved muscles after three months when function had almost returned to normal. Longstanding amyotrophy of the right arm of the deceased father is in agreement with reports of familial history of childhood brachial neuritis in such cases.

P48.

Creutzfeldt-Jakob Disease Combined with Binswanger's Disease: A Case Report

A. DUROCHER and J. MICHAUD (Montreal, Quebec)

We describe the case of a 74-year-old woman who presented with a dementing syndrome characterized by psychiatric disturbances, bizarre posturing and cognitive dysfunction progressive over a two-year period. EEGs during the evolution did not show any specific abnormalities. The neuropathological examination disclosed the following findings: 1) typical Creuzfeldt-Jakob disease (CJD) with spongiform changes and mild neuronal loss and gliosis involving mostly the cerebral cortical arteriolosclerotic encephalopathy (Binswanger's disease) with its classical white matter demyelination and gliosis associated with vascular sclerotic changes. The vascular pathology was also expressed by some Charcot-Bouchard microaneurysms and rare microhemorrhages. A clinical pathological correlation will be proposed. In recent years, white matter changes have been described in CJD. Radiologic and morphologic characteristics of these will be reviewed and compared with those found in Binswanger's disease in general. Their respective possible physiopathology will be explored. To our knowledge, the occurrence of CJD with Binswanger's disease has never been reported.

P49.

Femoral Neuropathy Complicating Renal Allograft Rejection

F.R. JACQUES and P.R. BOURQUE (Ottawa, Ontario)

Femoral neuropathy is a well documented but a rare complication of renal transplantation. It is postulated that nerve compression occurs during surgery (retractor blades) or in the immediate post-operative period (iliacus or peri-renal hematoma). We report the first case of delayed post-operative femoral neuropathy from allograft rejection.

The patient, a 59-year-old man, underwent uncomplicated transplantation of a cadaveric kidney in the right iliac fossa. On the tenth post-operative day, a severe right femoral neuropathy developed in the context of right lower quadrant pain, fever and progressive uremia. A CT scan of the pelvis showed inhomogeneous hyperdensity and marked swelling of the allograft. Electrodiagnostic studies were consistent with an acute femoral neuropathy superimposed on a mild axonal polyneuropathy. Despite intense immunosuppressive therapy, the transplant kidney had to be excised. Marked recovery of right femoral nerve function occurred over the subsequent week.

We propose that neuropraxic femoral nerve injury resulted from compression by an endematous renal allograft undergoing rejection.

P50.

Superior Sagittal Sinus thrombosis in a Post-Myelogram Patient with Anti-Thrombin III Deficiency

P. TUITE, I. GRANT, F. AHMED, J. STEWART and S. CARPENTER (Montreal, Quebec)

Superior sagittal sinus thrombosis (SSST) is a well recognized clinical and radiologic entity and only recently has been associated with anti-thrombin III (AT III) deficiency.[1] We report a case of SSST in a post-myelogram patient with AT III deficiency.

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A 24-year-old man, who was previously healthy except for chronic back pain, underwent myelography, which was normal. He subsequently developed headache, neck pain, nausea, vomiting and photophobia without meningismus. A focal seizure of his right arm occurred and CT revealed a left parietal hematoma. A family history of spontaneous deep venous thrombosis was obtained and cerebral angiography revealed SSST. Despite aggressive ICU management he deteriorated and was declared brain dead ten days later. He was not anticoagulated. Autopsy confirmed the SSST and demonstrated a previously unrecognized right hemispheric hematoma in addition to the left parietal hematoma seen on CT. No evidence of meningitis was found. Hematologic studies revealed AT III deficiency. The remainder of the family was tested and results are pending.

The mechanism of SSST development in this patient remains unexplained; however, there are several proposed theories.

We also review the causes of SSST and its relationship to AT III deficiency and various treatments for SSST.

[1]Ambruso DR, Jacobson LJ, Hathaway WE. Inherited antithrombin III deficiency and cerebral thrombosis in a child. Pediatrics 1980; 65: 125-131.

P51.

Prognostic Significance of Generalized Status Myoclonicus and Brain Stem Reflexes Following Acute Anoxia

J.M. MAHER (London, Ontario)

Generalized status myoclonicus after cardiorespiratory arrest has commonly been regarded as having a poor outcome. These seizures have been felt by some to reflect lethal damage to neurons. Limited data is available regarding the prognostic value of the immediate post-arrest neurological examination. We report a patient who made a complete recovery following a respiratory arrest despite generalized status mycolonicus and markedly impaired brain stem reflexes shortly after a respiratory arrest.

Case – a 72-year-old, white man had an acute respiratory arrest requiring intubation and ventilation. During the arrest he became markedly hypoxic and hypotensive. He arrested due to a pneumonia complicating impaired respiratory function due to post-polio syndrome. Following the resuscitation he developed generalized status myoclonicus. Neurological examination one hour post-arrest revealed him to be in coma, with no eye opening and decorticate posturing to painful stimuli. He had pinpoint, poorly reactive pupils, absent oculocephalic reflexes, markedly impaired oculovestibular response with only slight abduction of the left eye, and absent corneal and gag reflexes. Despite these findings he made a full recovery, the coma resolving in 8 hours, the new neurological abnormalities resolving within 12 hours and myoclonic seizures resolving within 24 hours.

Conclusion – the prognosis of post-anoxic coma associated with status myoclonicus is not always poor. Furthermore, the immediate post-arrest neurological examination, even if markedly abnormal, is of limited value in that it lacks prognostic significance.

P52.

Lower Cranial Nerve Palsies Secondary to Branchial Cleft Cyst

C. LAURYSSEN and M.E. MacRAE (Calgary, Alberta)

Cranial nerve palsy secondary to branchial cleft anomalies is a rare occurrence. We would like to report a case of multiple lower cranial nerve palsies secondary to a branchial cleft cyst in a 20-year-old female trumpeter.

P53.

Brachial Plexopathy: A Complication of Closed Reduction of Shoulder Dislocation

A. WILBOURN, R. LEDERMAN and P. SWEENEY (Cleveland, U.S.A.)

Attempted closed reduction of anterior humeral head dislocation (AHHD) has been a known cause of brachial plexus injury (BPI) for over 150 years. Nonetheless, instances of this BPI are unreported in the modern English language medical literature. Herein, we describe the clinical and electrodiagnostic findings in two such patients. 1) A 56-year-old woman with recurrent right AHHD sustained a lateral cord BPI during failed reduction under general anesthesia. Clinically: shoulder pain; lateral forearm, thumb and index finger paresthesias; biceps weakness. Electrodiagnostically: lateral antebrachial cutaneous (LAC) and median sensory responses - low amplitude/unelicitable; musculocutaneous motor response - low amplitude; fibrillation potentials/motor unit potential (MUP) loss in biceps, pronator teres, and flexor carpi radialis muscles. 2) A 70-year-old man fell and sustained a right AHHD with resulting pulseless, cold hand. Prompt successful reduction relieved limb ischemia but produced a severe, three cord BPI. Clinically: anesthesia below elbow; all limb muscles markedly paretic/paralyzed except spinati, rhomboids, and serratus anterior. Electrodiagnostically: sensory (ulnar, radial, LAC, and media - thumb, index and middle fingers) and motor (median, ulnar, radial, musculocutaneous) responses - all low amplitude/unelicitable; fibrillation potentials/severe MUP loss in all clinically affected muscles.

Conclusion: Cord lesions can occur during closed shoulder reductions.

P54.

Conduction Aphasia in Dementia

E.L. LALUMIERE, P. DEMERS and A. ROBILLARD (Montreal, Quebec)

Aphasia is seen in many degenerative diseases of the central nervous system (CNS) responsible for dementia; it will be a transcortical sensitive type (impaired auditory comprehension, fluent paraphasia output with preservation of the ability to repeat) in Alzheimer disease, associated with echolalia, palilalia

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in Pick's disease, and featuring more frequently dysarthria in multi-infarct dementia. We describe here the case of a 73-year-old woman presenting a 3 year history of progressive language abnormalities: mainly, literal paraphasia, abnormal repetition performance for words and sentences and impaired writing, consistent with conduction aphasia. Simultaneously, a progressive short-term memory disorder was noted, immediate recall (e.g., digitspan) being surprisingly more affected than delayed recall (demonstrated by the 15 words test of Rey): however, there was no disturbance of other cognitive functions in the first 2 years. The EEG was normal and brain CT SCAN showed moderate cortical and subcortical atrophy. This presentation of a probable degenerative disorder of CNS is quite unusual: we will discuss the neuropsychological explanation of this aphasia (e.g., a short-term auditory-verbal memory disorder as opposed to a pure language disorder) and the possible etiology of this likely dementia syndrome.

P55.

Central Sleep Apnea in Landau-Kleffner Syndrome

C.L. VOLL and N. LOWRY (Saskatoon, Saskatchewan)

We report a patient with typical Landau-Kleffner syndrome who developed central sleep apnea thirty months after initial presentation with seizures. The apneas were not associated with overt seizure activity and were unaccompanied by any discernable change in baseline EEG activity which showed continuous spike wave activity during sleep. We believe that this is the first reported association of central sleep apnea with the Landau-Kleffner syndrome. The mechanism underlying central sleep apnea in our patient is unknown. Sleep-related seizures may be accompanied by apneas, and it is possible that the central type sleep apnea syndrome observed in our patient is a clinical manifestation of sleep-related electrical status epilepticus which is an integral component of the Landau-Kleffner syndrome. Alternatively the development of central sleep apnea, which is associated on occasion with definable brainstem pathology, may be indicative of a pathological process involving respiratory centres in the brainstem. Although the neuropathology of Landau-Kleffner syndrome remains unknown, pathological and positron emission tomographic studies have suggested that it is associated with subcortical and/or brainstem abnormalities. The development of central sleep apnea in our patient, three years after initial presentation with seizures, may support previous speculation that the Landau-Kleffner syndrome is associated with brainstem pathology.

J. Cerebrovascular

P56.

Efficacy of Transvenous Perfusion of the Brain with LY231617 After Focal Ischemia in Rat Brain for 3 Hours With or Without Urethane Anesthesia

T. NAGAO, N. INOUE and Y.L. YAMAMOTO (Montreal, Quebec)

Urethane is a long-term anesthetic and up to now poorly studied. We examined the effect of urethane anesthesia on cerebral ischemia with or without treatment of transvenous perfusion of the brain (TVPOB) with the antioxidant, LY231617, which was started 3 hours after middle cerebral artery occlusion (MCAO). **Methods:** Adult Male Sprague-Dawley rats were used. Control group with (n = 6) or without (n = 10) urethane: Lt. MCAO for 5 hours. IV and TVPOB groups with (n = 6 each) or without (n = 10 each) urethane: LY231617, 10 mg/kg/hr by IV or TVPOB, starting 3 hours after Lt. MCAO for a period of 2 hours. Urethane (lg/kg) was intraperitoneally injected at the time of the surgical procedure prior to MCAO. Cerebral blood flow (CBF) using ^{14}C-iodoantipyrine and infarct volume were measured. Data were analyzed by one-way ANOVA. **Results:** infarct volume in both TVPOB groups was significantly reduced, but TVPOB group without urethane showed further significant reduction. CBF in ischemic regions in both TVPOB groups were significantly increased.

Table: Total infarction volume (mm^3)

	Control	IV	TVPOB
Urethane +	108 ± 16	02 ± 22	71 ± 37*
Urethane –	106 ± 26	99 ± 35	37 ± 9*, #

*: $p < 0.05$ significant difference from IV and Control groups
#: $p < 0.05$ significant difference from urethane + group

Conclusion: The treatment of TVPOB with LY231617, starting treatment 3 hours after MCAO with and without urethane, has a significant therapeutic effect. But without urethane group has a more beneficial effect on the infarct volume than that of with urethane group in spite of no significant difference in CBF between two groups.

This research was supported by: MRC (MT-3174) and Eli Lilly & Co.

P57.

The Changes in Extracellular Glutamate Concentration During Focal Ischemia in Rat

H. OSUGA and A.M. HAKIM (Montreal, Quebec)

Introduction: Energy failure in neurons after cerebral ischemia causes unregulated release of a number of neurotransmitters into the extracellular space, particularly the synaptic cleft. Glutamate, a neuroexcitatory amino acid, is presumed to promote calcium accumulation into the cell which leads to dete-

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rioration of neuronal cell function. We have already reported that CBF reduction was greater in striatum than in cortex in simultaneous middle cerebral and carotid artery occlusions. The aim of this study was to evaluate the changes in extracellular glutamate concentrations in the same ischemic model in both striatum and cortex using microdialysis. We hypothesized that glutamate levels would rise in proportion to the ischemic vulnerability of the brain region.

Materials and Methods: Day 1: Male Sprague-Dawley rats weighing 250 - 300 g were anesthetized with 2% halothane and breathed 30% oxygen-air mixture, and mounted on a Kopf stereotaxic device. After making two burr holes, two microdialysis probes (diameter 0.5 mm, membrane length 1.0 mm, Carnegie medicine) were implanted into left caudate nucleus and parietal cortex. Day 2: The probe-implanted rat was anaesthetized and the left femoral artery was cannulated to monitor blood pressure and blood gas. The proximal middle cerebral artery was then coagulated and the ipsilateral carotid artery was ligated. During and after surgery, Ringer's solution was perfused at 4 µl/min and dialysate was collected at 5 min interval. Body temperature was maintained at 37 ± 0.5°C.

Results: The pre-occlusion glutamate level in the dialysate was 0.96 µM in striatum and 1.32 µM in cortex. Immediately after the occlusions, glutamate levels in dialysate from striatum were increased to 11.38 µM and rose later in the cortex to 6.69 µM. About 20 min after this first peak in glutamate concentration, glutamate levels declined and remained depressed for 20 min, and then a second persistent increase in glutamate from cortex and striatum was noted.

Conclusion: The extracellular glutamate concentration rises biphasically in proportion to the regional severity of ischemia. This may confer ischemic vulnerability to the regions.

Supported by MRC, Canada and the Canadian Heart and Stroke Foundation.

P58.

Experimental Treatment of Angiographic Cerebral Vasospasm by Cervical Spinal Cord Stimulation in Rats

M.G. GIROUX and D. LADOUCEUR (Sherbrooke, Quebec)

Cerebral vasospasm secondary to subarachnoid hemorrhage following rupture of an aneurysm is a major cause of morbidity and mortality. The goal of this study is to assess the potential beneficial effect of cervical spinal cord stimulation (SCS) on experimental cerebral vasospasm. Autologous blood was introduced in the cisterna magna of 8 rats producing severe vasospasm of the posterior cerebral circulation documented angiographically.

Angiogram of the posterior circulation performed 48 hours later disclosed a filiform basilar artery. All rats were then stimulated for 20 minutes and cerebral angiogram was then repeated to evaluate the posterior circulation.

All stimulated rats showed a significant increase in basilar artery diameter (more than 50%) of compared angiograms.

These observations suggest that cervical SCS is effective in the treatment of experimental angiographic vasospasm and may have clinical implications for the future treatment of cerebral vasospasm.

P59.

The Rate of CA1 Cell Death is Dependant on the Duration of Severe Forebrain Ischemia in Adult Rats

H. LI, W.A. PULSINELLI and A.M. BUCHAN (Ottawa, Ontario; New York, U.S.A.)

Hippocampal CA1 neurons die in a delayed fashion following transient forebrain ischemia. We investigated the rate of cell death following different durations of ischemia. Adult male Wistar rats (n = 209) were subjected to 5, 15 or 30 minutes of ischemia using the 4-vessel occlusion (4-VO) model. The rats were sacrificed at 1, 2, 3, 7 or 14 days following reperfusion. Damaged CA1 neurons of the dorsal hippocampus were counted and the percentage of injured cells calculated.

Duration of Ischemia	% of CA1 Injury (Mean ± SD) Duration of Reperfusion				
	1 day	2 days	3 days	7 days	14 days
5 min	0 ± 0 (n = 6)	1 ± 1 (n = 3)	24 ± 26 (n = 75)	51 ± 28 (n = 37)	59 ± 25* (n = 9)
15 min	0 ± 0 (n = 7)	11 ± 19 (n = 3)	73 ± 30 (n = 42)	85 ± 16* (n = 5)	
30 min	1 ± 0 (n = 6)	47 ± 17 (n = 7)	84 ± 19 (n = 7)		

*: $p < 0.001$ Mann-Whitney U with Bonferoni correction

Necrosis of hippocampal CA1 neurons was delayed and could be very gradual. The rate of cell death was determined by the duration of ischemia.

P60.

Cardioembolic Caudate Infarction as the Cause of Hemichorea in Lupus Anticoagulant Syndrome

A. KIRK (Saskatoon, Saskatchewan)

An unexplained association between circulating antiphospholipid antibodies and chorea has been reported in systemic lupus erythematosus and lupus-like syndromes. As these antibodies are also associated with thrombotic tendency, it has been suggested that thrombosis or embolism might cause chorea. However, CT and MRI typically do not demonstrate focal basal ganglionic lesions in such patients. This negative finding has been used as support for an alternative hypothesis that antibodies bind directly to phospholipid in the basal ganglia. This report concerns a 21-year-old woman who presented with three months of left hemichorea and a week of dyspnea. There was a past history of venous thrombosis and spontaneous abortion. She was found to have lupus anticoagulant and IgG anticardiolipin antibodies. Echocardiography revealed very large aortic and tricuspid vegetations. Blood cultures were negative. Lung scan suggested multiple pulmonary emboli, presumably arising from the tricuspid vegetations as no evidence of current peripheral phlebothrombosis was found. The patient did not meet American Rheumatism Association criteria for SLE. CT showed a small round lucency in the head of the right caudate. MRI showed a 3

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mm T2 hyperintensity in the same location. Chorea resolved completely on low-dose haloperidol. She was anticoagulated and is asymptomatic 4 months later. The presence of a focal lesion on CT and MRI and of other embolic disease suggests that hemichorea was caused by a cardioembolic infarct. Local thrombosis within the basal ganglia cannot be ruled out but direct antibody binding to striatal antigens seems an unlikely explanation of this patient's chorea.

P61.

Leukoaraosis and Cerebrovascular Disorders

L.-Y. FENG, L. YING, Z. YU-FEN, F. KE, C. JIAN-YUAN and W. YU-JIN (Shijiazhuang, China)

Leukoaraosis (LA) was found in 86 (53 men, 33 women; mean age 62.7 years) of 161 patients with cerebrovascular disorders. Among the patients LA were found in 70 (54%) of 129 patients with cerebral infarct and in 16 (50%) of 32 patients with cerebral hemorrhage. Patients with LA were significantly older than those without it (latter cases, mean age 56.13 years, $p < 0.001$), were significantly higher in mean systolic blood pressure (20.98 kPa and 19.43 kPa, $p < 0.025$) and more likely to have a history of hypertension (49/86: 27/75, $p < 0.01$) and cardiovascular diseases (17/86: 7/75, $p < 0.10$). Our result also showed increasing age, multiple infarct (24/30), subcortical infarct (28/51), hemorrhagic infarct (4/6) and subcortical hemorrhage (11/22) were significant determinants of LA. These findings indicate that in patients with cerebrovascular disorders LA is associated with vascular diseases and suggest that LA be one of the determinants of a bad prognosis for stroke.

K. Neurosurgery

P62.

Transcranial Clipping of Recurrent Cerebral Aneurysms Following Endovascular Treatment

D.L. LADOUCEUR (Sherbrooke, Quebec)

Two cases are reported in which endovascular treatment of cerebral aneurysm (posterior communicating in both) was complicated two years later by a recurrence.

One patient presented a subarachnoid hemorrhage (SAH) following rupture of a posterior communicating (Pcom) aneurysm.

The other patient had an aneurysm diagnosed incidentally following a contrast-enhanced CT-scan of the head for an unrelated problem.

Endovascular balloon embolization of both aneurysms was performed without any immediate complication. Two years after the treatment, a cerebral angiogram showed recurrent aneurysms. Surgical clipping excluded both aneurysms definitely.

Discussion oriented toward the importance of control cerebral angiogram at long term follow-up is emphasizing the significance of balloon migration following endovascular treatment of aneurysms.

P63.

Brain Asteriovenous Malformations (BAVMs) and Associated Arterial Aneurysms

P. HALLACQ, K. TERBRUGGE, R. WILLINSKY, W. MONTANERA and P. LASJAUNIAS (Toronto, Ontario; Paris, France)

We report a series of 95 patients with BAVMs embolized with liquid tissue adhesives. In these patients, 30 BAVMs revealed associated aterial aneurysms or infundibula. The aneurysms can be classified into those that are on the feeding pedicles towards the AVM and those that are remote and therefore coincidental. The aneurysms on the feeding pedicles can be proximal or distal on the feeding artery or be intralesional, all of them being flow-related.

In our series 53 aneurysms or infundibula were found in 30 patients (1 to 5 per patient). Thirty-one aneurysms were located on the feeding artery, 3 were intralesional, 19 were remote. Six aneurysms on the parent feeder and the 3 intralesional ectasias were treated with cyanoacrylate at the time of embolization. Eleven flow-related aneurysms regressed after embolization performed more distally. Three were clipped surgically, 7 did not change after treatment. One aneurysm distally located on the feeding artery and not "glued", ruptured 3 hours after embolization and the patient subsequently died.

We strongly believe that the presence of flow related aneurysms, as part of the angioarchitectural changes encountered in the evolution of brain AVMs, increases the risk of intracranial hemorrhage. Although partial treatment of BAVMs is not yet proven therapy to erase the risk of hemorrhage from BAVMs, these high-flow angiopathy markers should be treated first. Intralesional and distal aneurysms on the feeding pedicles can be safely treated at the time of embolization.

P64.

Cardiac Pacing in the Management of the Bradyarrhythmias of Spinal Cord Injury

Z. KISS and C.H. TATOR (Toronto, Ontario)

The cardiovascular effects of acute spinal cord injury have been extensively studied in both animal models and humans. Although almost every kind of cardiac dysrhythmia has been described, the only consistent one in severe injuries is that of bradycardia. In clinical practice, it is treated with vagolytics and sympathomimetics when it is severe enough to compromise perfusion pressure. We describe two cases of life-threatening bradyarrhymias secondary to spinal cord injury, managed by early placement of permanent cardiac pacemakers. The factors predisposing these patients to develop symptomatic cardiac dysfunction, our indications for treatment and results will be discussed as well as a review of the limited literature concerning pacemaker use in the bradycardic acute spinal cord injured patient.

Sinus bradycardia is frequently the precursor to heart block, sinus arrest, supraventricular and ventricular arrhythmias in

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spinal cord injury and early treatment of the bradycardia should prevent some of the sudden cardiac deaths occurring in acute quadriplegics. We feel that cardiac pacing is a valuable therapeutic modality in the management of severe spinal cord injury bradycardia and may allow earlier mobilization of cord injured patients.

P65.

Continuous Intrathecal Baclofen Infusion for the Treatment of Adults with Spinal Spasticity

P.W. NANCE, B.J. SCHMIDT, H.I. DUBO, F. HU and D. FEWER (Winnipeg, Manitoba)

The use of intrathecal (IT) baclofen for the treatment of spasticity has been reported in the U.S. and Europe. However, the results of further studies are needed before this treatment can be made available for general clinical use. We have initiated a prospective trial of IT baclofen therapy for adults with spasticity due to spinal cord injury or multiple sclerosis.

Of the 70 patients with problematic spasticity assessed thus far, 6 met criteria for inclusion in the study with respect to increased muscle tone (Ashworth > 3, mean = 4.25), spasm frequency (spasm score > 2, mean = 3.5), and failure to respond to currently available oral antispasticity drugs (including baclofen, clonidine and cyproheptadine). All subjects responded to IT bolus injection of baclofen during the double blind, placebo controlled screening phase (bolus range: 12.5 - 100 μg; average dose: 58.3 μg).

Four of the subjects were implanted with programmable, battery powered Medtronic pumps and 2 subjects received non-programmable Infusaid pumps. All subjects reported a marked decrease in spasticity after IT baclofen, and a significant reduction of the Ashworth (mean = 1.5, $p < .005$) and spasm scores (mean = 0.5, $p < .005$) was recorded. The Achilles tendon and H-reflex were markedly suppressed, and the leg swing (pendulum) test scores improved. Bladder capacity, peak intracystic and urethral sphincter pressures were not significantly changed by IT baclofen. One subject regained independent wheelchair transfer ability and another is now able to walk 30 feet with electrical stimulation and a walker. The antispasticity effect has been maintained for up to 18 months (mean follow-up to date is 7 months) with an average infusion of 165 μg/day. Complications have been limited to single incidents of connector valve failure, IT catheter displacement, leg weakness, phlebothrombosis, aseptic knee effusion and aseptic seroma around the pump.

Our findings are consistent with the reported efficacy of IT baclofen for selected patients and extend previous observations on reflex suppression and bladder function.

(Support: Rick Hansen Legacy Fund, Health Sciences Centre Foundation and Manitoba Paraplegia Foundation)

P66.

Increase in Age of Patients with Histologically Proven Brain Tumours

P. SHEDDEN, P. MULLER, W. TUCKER and R. MOULTON (Toronto, Ontario)

Epidemiological research has shown an increase in the incidence of malignant brain tumours in the Canadian and U.S. populations especially among elderly patients. At St. Michael's Hospital, Toronto, 1604 patients with brain tumours were treated surgically between 1978 and 1990. We assessed their age, sex distribution and pathology in order to determine whether there had been an increase in age between the reference periods of 1978 - 1983 and 1984 - 1990.

There were 745 patients in the first reference period and 859 in the second. The mean age of the whole group was 53 ± 16 years; 401 were > 65 and 96 > 75 years of age. There were 779 males and 757 females. There were 742 neuroectodermal tumours, 327 meningiomas, 206 metastatic tumours, 144 pituitary adenomas, 68 acoustic neuromas and 117 others.

A small but significant increase in mean age was identified when all tumours were included in the analysis; the mean age and SD in the reference periods were 52.0 ± 15.6 and 54.3 ± 16.3, respectively ($p < 0.005$). An increase was identified for patients with meningiomas and metastatic disease but not gliomas.

The proportion of patients > 65 years in the first and second reference periods were 161/745 (22%) and 240/859 (28%), respectively ($p < 0.005$). No significant differences were noted for the pathology subgroups. A significantly higher proportion of patients were over the age of 70 in the second reference period when all cases were included and also when the neuroectodermal tumours were assessed independently.

No differences in sex distribution was identified. The differences in age may be attributed to an aging population; they are also consistent with epidemiological studies which have identified an increase in the incidence of malignant brain tumours in the elderly.

P67.

Combined Cranio-orbital Zygomatic and Petrosal Approaches for Extensive Cranial Base Neoplasms

F. DeMONTE and O. AL-MEFTY (Maywood, U.S.A.)

Because of their location, certain extensive tumors of the cranial base defy removal through a single surgical approach. Combined approaches are necessary for adequate exposure of these types of tumors.

The combination of a cranio-orbital zygomatic craniotomy with the petrosal approach exposes all three cranial fossae superbly. The technique used, results, complications, and outcomes, both oncologic and clinical, in a series of six patients will be discussed. This combined approach is a viable option in the treatment of patients with extensive basal lesions.

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P68.

Calvarial Masses in Infancy

O.R.T. WILLIAMS, S.T. MYLES and O.N.R. DOLD (Calgary, Alberta)

Calvareal masses in infancy are not infrequent causes for seeking neurosurgical consultation. We present three such cases, each with unexpected pathology. The children were aged 13 months (patient L), 2.5 years (patient A), and 5 months (patient W).

All three children presented with palpable calvareal mass lesions of short duration without history of antecedent trauma, two children (patients L, A) had significant pain and tenderness, and all three had lytic lesions on plain skull xray, CT scans demonstrated no evidence of intra-cranial extension.

Surgical exterpation demonstrated dural involvement as dense fibrous adhesions in all cases. Histopathological examination demonstrated Infantile Fibroma (patient A), Infantile Fibrosarcoma (patient B), and Infantile Myofibromatosis (patient C). All three children have been recurrence free since surgery.

This short series demonstrates the relative importance of pursuing a diagnosis in all skull lesions of childhood and infancy, as all were felt to be benign pre-operatively by radiological evaluation. Additionally the presence of pain should arouse heightened clinical concern as this symptom may suggest a more rapid growth pattern.

L. Neurophysiology

P69.

Abnormal Evoked Potentials in Clinically Normal Volatile Solvent Abusing Adolescents

N. PILLAY and M. TENENBEIN (Winnipeg, Manitoba)

Volatile solvent abuse by adolescents is prevalent worldwide. Chronic abuse results in devastating central nervous system damage. Reliable objective markers of solvent abuse are lacking largely because chemical analysis of body fluids is impractical due to the heterogeneity of abused substances. We obtained visual evoked potentials (VEPs), brainstem auditory evoked potentials (BAEPs), and somatosensory evoked potentials (SEPs) from clinically normal volatile solvent abusing children to investigate the possibility of identifying neurologic damage prior to its clinical appearance.

These three evoked potentials were obtained from 15 clinically normal children (9 boys), aged 9 - 17 years admitted to a child psychiatry service. All had significant history of volatile solvent abuse and most abused several products each of which were composed of multiple chemicals. These included aromatic, aliphatic, and halogenated hydrocarbons. Results were graded as mild, moderate, or severe. SEPs were normal in all 15 patients but eight had abnormal VEPs and/or BAEPs, 5 of which were severe.

These findings are notable because of the surprising frequency of abnormality and because they are subclinical suggesting that evoked potentials may be a sensitive indicator of nervous system involvement in volatile solvent abusers. They may serve as an objective marker of early neurologic damage with potential usefulness for counselling and intervention.

M. Epilepsy

P70.

"JAMAIS VU" Status Epilepticus: Clinical and EEG Study

A.O. OGUNYEMI and J. GOODWIN (St. John's, Newfoundland)

Localization of seizure onset is crucial when evaluating patients with uncontrolled partial seizures. Clinical assessment, CT scan or MRI and surface EEG recordings are the initial methods of evaluation. The ability to localize the initial symptom (aura) of a seizure is highly desirable. We are unaware of previous reports which clearly localized "jamais vu", a sense of strangeness for familiar places and people. We therefore present this patient with 2 episodes of "jamais vu" status epilepticus with EEGs showing well-localized ictal discharges.

This 37-year-old lady with uncontrolled complex partial seizures had previous EEGs showing interictal, bitemporal, independent spikes and sharp waves. While in her office, she suddenly became "confused". She complained that she was in a strange place and that her co-workers appeared different. She was noted to be apprehensive.

On arrival in the hospital about 2 hours later, she continued to feel that everything seemed strange. Her husband became unfamiliar as did her doctor. According to her, everyone including the nurses, doctors and even her husband spoke in a strange manner. On examination, she was alert and oriented to time, place and person. There were no neurological deficits. Specifically, tests of language, memory and recognition of faces were normal.

An emergency, prolonged EEG showed repetitive sharp waves localized to the right anterior-mid temporal region. The seizure was terminated with intravenous lorazepam and phenytoin. About 24 hours later, there was recurrence of the seizure, confirmed by EEG.

This lady then, had 2 episodes of simple partial status epilepticus of the "physical" type (jamais vu). The localized ictal discharges suggest that right anterior-mid temporal epileptogenic focus should be suspected in patients with the aura of "jamais vu".

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N. Pediatric Neurology

P71.

Parent Mediated Behaviour Management Training of Noncompliant Children with Epilepsy

I.G. MANION, D. KEENE, P.J. McGRATH, J.T. GOODMAN, P. HUMPHREYS, S. WHITING and P. CLOUTIER (Ottawa, Ontario; Halifax, Nova Scotia)

A between group comparison design with repeated measures was used to evaluate the effectiveness of a training program for parents of epileptic children displaying early behaviour problems. Thirty-one families with an epileptic child (4 - 11 years) were randomly assigned to either an experimental parent training group (n = 16) or to a standard practice, waiting list control group (n = 15). Training consisted of parent education, behaviour management training, and parent self-management training. It included a combination of group parent sessions (4 - 5 families per group) and individual family sessions. Treatment outcome was assessed by way of parent reports of child behaviour problems (i.e., Child Behaviour Checklist), parent self-reports of family and individual functioning, and home and clinic observations of parent and child behaviours.

Results suggest that both groups showed increases in compliance with differences being more pronounced in the treatment group. Treatment parents displayed significant changes in their style of parenting (i.e., fewer questions, increase in the use of praise and contingent praise) compared to controls. Parent and child behaviour change generalized to the home setting, and was maintained, although with less pronounced effects, over the six-month follow-up period. Both groups showed improvement in parent reports of child behaviour and of family stress over time. Positive changes on these measures were only slightly more pronounced for treatment families. Parent satisfaction with this psychosocial intervention was very high. Results are discussed with attention to a significant drop-out rate and to the ebb and flow of stressors (both medical and psychosocial) faced by these families.

P72.

Acanthocytosis, Myoclonic Epilepsy and Dysmorphic Features

M.B. CONNOLLY, E.H. ROLAND and K. FARRELL (Vancouver, British Columbia)

Acanthocytosis is associated with specific neurological syndromes including, abetalipoproteinaemia, chorea with acanthocytosis and McLeod syndrome. Rare associations include Hallevorden-Spatz disease and mitochondrial encephalomyopathy. One patient with myoclonic epilepsy has been reported previously. We describe a 3 1/2-year-old girl with acanthocytosis, myoclonic epilepsy, dysmorphic features and developmental delay.

The child was the first born of nonconsanguinous caucasian parents. Pregnancy was complicated by unexplained intrauterine growth retardation and delivery was by emergency cesarian section at 38 weeks due to fetal distress; birth weight 2.25 kgs. She was hypotonic in the perinatal period and there was delayed development from birth. Nocturnal tonic seizures started at one year of age and atypical absence and myoclonic-astatic seizures at 3 years of age.

On examination at 3 years of age, the head circumference was 45.4 cm (– 3 SD), height 87.5 cms (– 3 SD), and weight 9.9 kgs (– 4 SD). There was frontal bossing, deep set eyes, upward slanting palpebral fissures, and a thin upper lip. She had bilateral optic nerve hypoplasia, generalized hypertonicity, hyperreflexia and ankle clonus.

Computed tomography of the head was normal. EEG examination showed generalized atypical spike and wave activity. Nerve conduction studies were normal and EMG examination showed small polyphasic potentials in proximal and distal muscles. Karyotype analysis including high resolution chromosome banding was normal. Blood smear examination showed acanthocytosis; Kell and Lutheran red cell antigens were negative. Liver enzymes were normal; gammaglutamyl transferase was 29 u/L (6 - 19 U/L). Renal function was normal. Cholesterol was 5.52 mmol/L (1.15 - 4.7); triglycerides normal; plasma lipoproteins normal. Plasma and CSF lactate and amino acids, urine organic acids and oligosaccharides were normal.

This is the second report of a patient with acanthocytosis in association with myoclonic epilepsy. The relationship between the two disorders is unknown but may involve a membrane defect. Careful examination of a blood smear may identify other children with this red blood cell abnormality and epilepsy.

P73.

The Neuroradiological and Clinical Findings in 14 Patients with Early-Onset Peroxisomal Diseases

A.E. SLOANE, S. BLASER, I. TEIN, D. HARWOOD-NASH and L.E. BECKER (Toronto, Ontario)

The neuroradiological and clinical features of patients with Zellweger Syndrome (10 ZS), Infantile Refsum's Disease (3 IRD), and Rhizomelic Chondrodysplasia Punctata (1 RCP) are reported. Clinical and diagnostic characteristics were recorded by retrospective chart review. Ten ultrasounds (US), 14 CAT scans (CT) GE 9800/8800, and 3 MR imaging scans (MRI) were reviewed by 2 neuroradiologists blinded to the diagnosis.

Patients with ZS had a cavum septum pellucidum and vergae evident on US (2), CT (5), and MRI (2); subependymal cysts on US (6), CT (2), and MRI (1). Abnormal white matter was present on MRI (1 IRD, 2 ZS), and CT (6 ZS, 2 IRD), of whom 3 had normal US. Abnormal, diffusely delayed myelination on autopsy correlated with exaggerated white matter on CT (1 ZS). In another ZS necropsy, polymicrogyria confirmed CT findings. Pachgyria, polygria and/or agyria (6/10 ZS), and primitive Sylvian fissures lined by polygyria (unilaterally 1 ZS, bilaterally 4 ZS) were present on CT, and on MRI in both patients with ZS.

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US showed abnormal sulcation (1 ZS, 1 IRD). Arachnoid cysts in the choroid plexus (2/2 ZS), and abnormal dentate nuclei (1/1 IRD) were present on MRI.

Abnormal findings were present in all patients, being more severe in the ZS group. CT correlated with 2 of 3 ZS autopsies. With the exception of subependymal cysts, all findings were seen on CT, although MRI best defined the white matter abnormalities and cerebral dysgenesis in patients when both MRI and CT were available.

P74.

The Case of the Disappearing Brain Tumor

N. LOWRY, R. GRIEBEL and D. GEORGE (Saskatoon, Saskatchewan)

Peter presented in 1983 at the age of 12 years with headache, altered behavior and somnolence. CT of the brain showed a left parietal tumor, needle biopsy diagnosed a grade III astrocytoma and he was treated with radiotherapy and Dexamethasone. Eight months later CT showed no evidence of tumor. Three months later (February 1984) he developed memory loss and somnolence – CT showed a deep seated mid-line hypothalamic tumor which was then treated with Dexamethasone. CT showed marked improvement. In 1986 he developed a left sided weakness. CT showed a right thalamic tumor, with Decadron the tumor disappeared. In November of 1988 he had a recurrence in the right basal ganglia area. Repeat needle biopsy showed tumor which was suggestive either of lymphoma or eosinophilic granuloma but diagnostic of neither. He was treated with steroids and the right sided lesion shrunk on CT scan. In January of 1989 his condition worsened again. CT showed a left occipital tumor and also that the right basal ganglia lesion was gone. His parents decided against further treatment and no medication was given. The patient went home to die. In March of 1989 a CT showed that the left occipital lesion had increased in size with increased enhancement and increased edema. Palliative care only was given. In May of 1989, clinically, for no apparent reason there was a marked improvement. CT scan showed no evidence of active disease. In May of 1991 he died of pneumonia. Autopsy showed no residual tumor, no evidence of vasculitis, no evidence of multiple sclerosis.

Could this have been a spontaneously resolving eosinophilic granuloma of the brain?

P75.

Congenital Hereditary Motor Sensory Neuropathy (Type 1): A Rare Presentation

I. CORDES and E. ROLAND (Vancouver, British Columbia)

Hereditary motor sensory neuropathy Type 1 (HSMN 1) is a progressive neuropathy which begins during childhood with distal weakness, atrophy, and sensory loss, hyporeflexia, pes cavus and severe delay of motor and sensory nerve conduction velocities. The majority of cases have now been linked to genetic markers on chromosome 17. Congenital presentation of this disorder is rare and the clinical features of this subtype of HSMN 1 have not been well-described. We describe a five-year-old boy who had congenital presentation of HSMN 1 in association with a mosaicism of chromosome 17.

During the antenatal period, amniocentesis, performed for advanced maternal age, revealed chromosome mosaicism 46XY/47XY + 17. The pregnancy and delivery were otherwise uneventful. At birth, the patient had bilateral club feet, asymmetry of the chest and hirsutism of the lower back The gait was abnormal and he walked late at 17 months of age. He developed progressive pes cavus and distal leg weakness with marked weakness of peroneal and tibialis anterior muscles. Serial casting and manipulation resulted in minimal improvement of the clubfoot deformities. In addition, there was winging of the scapulae and minimal weakness of hands and shoulder girdle. Surgical lengthening of the tendoachilles was performed at five years of age.

Detailed metabolic investigations for heredodegenerative diseases and toxic disorders were normal. Cerebrospinal fluid analysis was normal. Electrocardiography and echocardiography were normal. Spinal myelography was normal. Electromyography/nerve conduction studies confirmed severe, generalized, demyelinating sensorimotor neuropathy involving all limbs with greater involvement of the legs. Sural nerve biopsy demonstrated demyelination. Transcranial magnetic stimulation revealed mild prolongation of central motor conduction times.

The family history was negative for neuromuscular disease. Electromyography/nerve conduction studies of parents were normal.

This patient has clinical and laboratory features of HSMN Type 1 of prenatal onset related presumably to a genetic mutation of chromosome 17. Transcranial magnetic stimulation suggested involvement of both upper and lower motor neurons in this disorder. Clinical abnormalities in congenital HSMN 1 appear to be more severe and progressive than in more typical varieties of HSMN 1.

P76.

MR Evaluation of Delayed Myelination in Down Syndrome

B. KOO, S. BLASER, D. HARWOOD-NASH, L.E. BECKER and E.G. MURPHY (Toronto, Ontario)

Magnetic resonance imaging (MRI) has been found to be useful in assessing brain myelination and provides information on brain maturation.

The normal pattern of brain myelination conforms to a fixed sequence with good pathological and MRI correlation. Neuropathological analysis of myelination has shown delayed central myelination in Down syndrome. Delayed myelination on MRI in Down syndrome has not previously been reported.

We report a case of Down syndrome with a significant delay in myelination as demonstrated on MRI. This 18-month-old child had brain myelination equivalent to that of a 11-month-old child.

MRI has the advantage of serial assessment of myelination during brain maturation.

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P77.

Diagnosis of Childhood Headache by International Headache Society Criteria

J. WOLSTEIN, F. BOOTH, J. REGGIN and S.S. SESHIA (Winnipeg, Manitoba)

Specific diagnostic criteria and characteristics for each class of headache have been proposed by the International Headache Society (IHS) (1988) to improve consistency and reliability of the diagnosis of headache. Several criteria, specifically for migraine without aura, require precise description of location, quality and intensity. We report on our experience with the IHS criteria and characteristics in children.

The 37 children in this prospective study were seen by any one of four pediatric neurologists because of headaches, between Oct and Dec 1991. Information was recorded on data sheets that included the IHS criteria. Data were missing in one case. The ages of the remaining 36 children ranged from 5.4 to 17.8 yrs (median 10.6 yrs). The causes of headache were: (i) Migraine without aura (n = 20); (ii) migraine with aura (n = 8); (iii) chronic and episodic tension type (n = 3); (iv) both migraine and tension type (n = 5).

The history was given primarily by the child in 10 cases, primarily by the guardian in 5 and by both in 21 cases. Information about: (i) location was obtained in all children; (ii) quality was obtained in 7 children; (iii) intensity was not obtained in 1 child.

The causes of headache could be classified using the IHS criteria in 31 of the 36 children.

We conclude that the criteria of the IHS can be used in children. However, children are often unable to provide detailed descriptions and the information provided by caregivers may be biased.

Supported by: Harry Medovy Fellowship and CHWRF.

P78.

Contact Thermography in the Diagnosis of Headache in Children

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Migraine occurs in 4 - 10% of all children (Hockaday, 1988). Migraine without aura is the most common type of migraine in this age group. Frequently, even adolescents are unable to describe their symptoms. Hence the diagnosis of migraine is often subjective and clinical validation unsatisfactory. For this reason we have prospectively evaluated the role of contact thermography in the diagnosis of childhood migraine. To the best of our knowledge this has not been done before.

Thermograms were done in 54 children aged 4.2 - 16.5 yrs (median 10.5 yrs), who were seen for headache by any one of four pediatric neurologists, between July and December 1991. Headaches were typed clinically and the information was recorded on data forms. 51 children were studied between headaches and 3 during a headache. 4 children served as controls.

Thermograms were interpreted by a "blinded" radiologist without any clinical information. Thermograms on 3 children were technically unsatisfactory. The results in the remaining 51 were: (i) Migraine without aura: 16 normal, 10 abnormal; (ii) Migraine with aura: 11 normal, 4 abnormal; (iii) Migraine and tension type: 6 normal, 1 abnormal; (iv) Other types of headache: 3 normal, 0 abnormal.

Controls: 3 normal, 1 abnormal. The "abnormal" control has a sibling with possible migraine.

Our study suggests that contact thermography may be useful in the diagnosis of childhood migraine. However, a larger sample, particularly of controls and those with tension type headache, needs to be assessed to more precisely characterize the relative sensitivity and specifity of the test.

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AMATINE®

(Midodrine Hydrochloride)
2.5 mg and 5.0 mg Tablets

PHARMACOLOGICAL CLASSIFICATION: Vasopressor

ACTION AND CLINICAL PHARMACOLOGY: Midodrine hydrochloride is a postsynaptic alpha adrenergic receptor stimulant with little effect on the beta-adrenergic receptors in the heart. The actions of midodrine on the cardiovascular and other organ systems are essentially identical with those of other alpha-adrenergic receptor stimulants, such as phenylephrine or methoxamine. The most prominent effects of midodrine are on the cardiovascular system, consisting of a rise in systolic and diastolic blood pressures, accompanied by a marked reflex bradycardia. The increase in blood pressure is due almost entirely to an increase in peripheral resistance. Midodrine slightly decreases cardiac output and renal blood flow; it increases the tone of the internal bladder sphincter and delays the emptying of the bladder.

Midodrine is a prodrug, i.e., the therapeutic effect of orally administered midodrine is due to and directly related to its conversion after absorption to desglymidodrine which differs chemically from methoxamine only by lacking in a methyl group on the side chain.

PHARMACOKINETICS: After oral administration, midodrine is rapidly and almost completely absorbed, with a mean absolute bioavailability (as desglymidodrine) of 93% for the oral tablets.

After the oral administration of 2.5 mg midodrine in a single dose to 12 volunteers, the mean peak concentration of unchanged midodrine is approximately 10 ng/mL and occur after 20-30 minutes, with a terminal plasma half-life of 0.4-0.5 hours. The mean plasma concentration of the active metabolite, desglymidodrine, peaks in approximately 1 hour, with a plasma half-life of approximately 3 hours after the oral administration of 2.5 mg midodrine.

Midodrine is poorly diffused across the blood-brain barrier. Both midodrine and desglymidodrine are quickly eliminated from the body, mostly by the kidneys. Approximately 91% of the administered dose is excreted in the urine in 24 hours. Of the urinary material, 50-60% is present as desglymidodrine and approximately 2%, as non-metabolized midodrine. Unidentified breakdown products do not exceed 3.9% of the urinary material.

INDICATIONS AND CLINICAL USE: AMATINE®(Midodrine Hydrochloride) tablets may be added to an established treatment regimen in order to attenuate symptoms in the primary neurogenic types of idiopathic orthostatic hypotension, that is in the Bradbury-Eggleston or Shy-Drager syndromes, in those cases when the response to the standard therapy is not adequate. The initiation of midodrine therapy should be undertaken under close medical supervision in a controlled clinical setting such as in hospital, in clinic or in the office.

CONTRAINDICATIONS: Midodrine is contraindicated in patients with severe organic heart disease, acute renal disease, urinary retention, pheochromocytoma, thyrotoxicosis or known hypersensitivity to midodrine.

WARNINGS: Supine Hypertension: The most serious and frequent (see **ADVERSE REACTIONS**) adverse reaction to midodrine in patients suffering from primary neurogenic hypotension is the unacceptable elevation of supine arterial blood pressure (supine hypertension), which, if sustained, may cause stroke, myocardial infarction, congestive heart failure, renal insufficiency or similar disorders which individually or collectively may be fatal. Symptoms of supine hypertension are more frequently detected at the initiation of midodrine therapy and during the titration period.

Control of supine blood pressure has been obtained by an adjustment in midodrine dosage with or without a 45-degree elevation of the patient's head. If supine hypertension persists, treatment with midodrine should be discontinued, and appropriate therapy (e.g., phentolamine, a specific antagonist of midodrine pressor activity) instituted immediately.

To minimize the incidence of supine hypertension, instruction how to initiate midodrine therapy should strictly be followed (see **DOSAGE AND ADMINISTRATION**). Patients should be cautioned to report symptoms of supine hypertension immediately. Symptoms may include cardiac awareness, pounding in the ears, headache, blurred vision, etc. If these occur, the patient should discontinue the drug and consult with the prescribing physician.

Bradycardia: Bradycardia may occur after AMATINE® (Midodrine Hydrochloride) tablets administration, primarily due to vagal reflex. Caution should be exercised when AMATINE is used concomitantly with cardiac glycosides (such as digitalis), psychopharmacologic agents, beta blockers or other agents which directly or indirectly reduce heart rate. Patients who experience bradycardia should be told to report immediately any signs or symptoms suggesting bradycardia (pulse slowing, increased dizziness, syncope, cardiac awareness) and to take no more drug until they have consulted with the prescribing physician.

AMATINE tablets should not be administered in the presence of uncorrected tachyarrhythmias or ventricular fibrillation.

PRECAUTIONS: Urinary Retention: Midodrine may induce an increase in the tone of the internal sphincter of the urinary bladder which may lead to urinary retention. Midodrine also may effect the bladder trigone which may result in a delayed response to bladder filling. Initial signs of urinary retention are manifested clinically as hesitancy or change in frequency of micturition. Patients should be told to report promptly any indication of urinary retention (e.g., hesitancy or frequency of micturition) which may be a sign of urinary retention.

When midodrine is used concomitantly with other vasoconstrictor sympathomimetic pressor agents, monitoring of blood pressure is necessary.

Midodrine should be used with caution in patients with urinary tract outflow obstruction, neurogenic bladder or similar conditions, since midodrine is eliminated by the kidneys and accumulation may occur in such patients.

Laboratory Tests: Evaluation of the patient should include assessment of renal and hepatic function prior to initiation of therapy, and during treatment, when appropriate.

Pregnancy: No teratogenic effects have been observed in studies in animals. At very high doses (20 mg/kg/day) the drug was toxic to dams and fetal loss occurred. There are no data on the use of midodrine on pregnant women. Therefore, midodrine should be used during pregnancy only when the benefit to the mother exceeds the possible harm to the fetus.

Nursing Mothers: It is not known if midodrine is excreted in human milk. Caution should be exercised when midodrine is administered to nursing mothers.

Children: Safety and effectiveness in children have not been established.

Drug Interactions: When administered concomitantly with Midodrine, cardiac glycosides may enhance or precipitate bradycardia, block or arrhythmia.

The use of drugs which stimulate alpha adrenergic receptors (e.g., phenylephrine, phenylpropanolamine or dihydroergotamine) may enhance or potentiate the pressor effects of midodrine. Therefore, when midodrine is used concomitantly with vasoconstrictor sympathomimetic agents, use caution.

Patients on salt-retaining steroids (e.g., fludrocortisone), with or without salt supplementation, may experience an excessive pressor effect after midodrine therapy, especially in the supine posture. The possibility of hypertensive effects with midodrine can be minimized by either reducing the dose of fludrocortisone or decreasing the salt intake prior to initiation of treatment with midodrine.

Alpha adrenergic blocking agents antagonize the vasopressor effect of midodrine.

ADVERSE REACTIONS: In 305 patients treated with midodrine for primary neurogenic types of idiopathic orthostatic hypotension (Bradbury-Eggleston or Shy-Drager Syndrome), the overall adverse reaction rate was 34%, and the drop out rate due to adverse reactions was 6.9%. The most serious and frequent adverse reaction to midodrine is supine hypertension (17.5%). The other frequent adverse reaction to midodrine (>10%) is pruritis (11.5%). The adverse reactions to midodrine grouped according to organ systems, are given below.

Organ System	Adverse Reaction	No. of Patients (%) n=305	
Cardiovascular:	Supine Hypertension	48*	(17.5)
	Palpitation/Tachycardia	1	(0.3)
	Chest Pain	1	(0.3)
	Angiitis	1	(0.3)
Gastrointestinal:	Nausea/Vomiting	3	(1.0)
	Abdominal Discomfort	1	(0.3)
	Diarrhea	1	(0.3)
Integumentary:	Pruritis	35	(11.5)
	Paresthesia (Scalp/Other)	22	(7.2)
	Piloerection	16	(5.2)
Urinary:	Urge/Full Bladder	14	(4.6)
	Dysuria	2	(0.7)
	Frequency	2	(0.7)
	Urinary Retention	2	(0.7)
Central Nervous System:	Weakness/Fatigue	3	(1.0)
	Headache	2	(0.7)
	Tremor	1	(0.3)
	Depression	1	(0.3)
Body as a Whole:	Flushing/Heat	1	(0.3)
	Chills/Cold	1	(0.3)

*n=275

SYMPTOMS AND TREATMENT OF OVERDOSAGE: We have had no reports of overdose with AMATINE® (Midodrine Hydrochloride) tablets. However, symptoms of overdose could include piloerection (goose flesh), a sensation of coldness, and urinary retention. The effects of midodrine can be treated with alpha sympatholytic drugs (e.g., phentolamine). In cutaneous hypersensitivity reactions, H_1-antihistamines should be administered.

DOSAGE AND ADMINISTRATION: Adults and Adolescents: Treatment with AMATINE® (Midodrine Hydrochloride) tablets should be started under close medical supervision in a controlled clinical setting such as in hospital, in clinic, or in the office. Hourly measurements of blood pressure (supine and sitting or standing, if possible) should be made for 3 hours following the first dose and also the second dose of a three times daily dosage regimen.

It is recommended that treatment begin at the lowest level and be titrated at intervals of three to several days until the optimal response is obtained. Upon escalating the dosage, the supine and standing blood pressure should be closely monitored in hospital, in clinic or in the office as for the initiation of therapy, hourly for 3 hours following the first two doses.

The usual starting dose of AMATINE tablets is 2.5 mg three times daily. Single doses of 2.5, 5 and 10 mg have been successfully employed. Most patients are controlled at or below 30 mg per day given in three or four divided doses. AMATINE tablets can be given up to six times per day. Some patients require a morning dose that is higher than that taken later in the day. In some instances AMATINE tablets have been given on a three times per day schedule as follows: 1 to 2 hours before arising in the morning, mid-morning and mid-afternoon. In order to reduce the potential for supine hypertension, it may be recommended that midodrine doses not be given after the evening meal. The maximum recommended dose should not exceed 30 mg daily.

During the period of close medical supervision, the patient or a relative should be trained to measure blood pressures. Supine and sitting blood pressures should be measured daily for at least a month after initiation of treatment and twice per week afterwards.

The administration of AMATINE tablets should be stopped and the attending physician notified immediately, if the blood pressure in either position increases above 180/100 mmHg.

Children: In view of the lack of experience in children, this drug is not recommended for patients under 12 years of age.

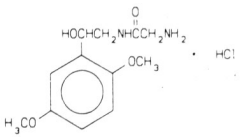
PHARMACEUTICAL INFORMATION:

Chemical name (USAN): (1) 2-amino-N-[2-(2,5-dimethoxyphenyl)-2-hydroxyethyl]-monohydrochloride, (±)-acetamide; (2) (±)-2-Amino-N-(beta-hydroxy-2,5-dimethoxyphenethyl) acetamide monohydrochloride

Molecular formula: $C_{12}H_{18}N_2O_4HCl$

Molecular weight: 290.74

Structural formula:



Description: Midodrine hydrochloride is an odorless, white crystalline powder.

Solubility in water: 9.3 g/100 mL

Solubility in methanol: 1.6 g/100 mL

pK: 7.8 (0.3% in water) **pH:** 3.5-5.5 (5% in water)

Melting point: 205-207°C

Composition:

Midodrine hydrochloride	2.5 mg	or	5 mg
Highly dispersed silicone dioxide			
Color FD&C Yellow #6 Lake (5 mg strength only)			
Microcrystalline cellulose (Avicel PH 101)			
Corn starch			
Talc			
Magnesium stearate			

Storage Recommendations: Store between 15°-25°C.

Availability of Dosage Forms: AMATINE® (Midodrine Hydrochloride) tablets are supplied as oral white tablets 2.5 mg and oral orange 5.0 mg scored on one side in brown glass bottles with plastic cap to cap LDPE closures of 100's.

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IMITREX®

(sumatriptan succinate)
100 mg Tablet
6 mg Subcutaneous Injection
and Autoinjector

THERAPEUTIC CLASSIFICATION

Migraine Therapy

PHARMACOLOGIC CLASSIFICATION

5-HT_1-like Receptor Agonist

CLINICAL PHARMACOLOGY IMITREX (sumatriptan succinate) is a selective 5-hydroxytryptamine$_1$-like (5-HT_1-like) receptor agonist shown to be effective in relieving migraine headache.

Activity of sumatriptan at the 5-HT_1-like receptor mediates selective vasoconstriction within carotid arterial circulation supplying intracranial and extracranial tissues such as brain and meninges. Dilatation of cranial blood vessels is thought to play important role in underlying mechanism of migraine.

Sumatriptan (0.01-100 μM) caused dose-dependent vasoconstriction in human isolated perfused dura mater as judged by increases in perfusion pressure. Activation of 5-HT_1-like receptors by sumatriptan suggests possibility that mechanism of anti-migraine action could involve vasoconstriction of dural blood vessels.

Sumatriptan has no effect at either 5-HT_2 or 5-HT_3 receptor subtypes.

Clinical response begins 10-15 min. after subcutaneous injection and around 30 min. after oral administration.

Cardiovascular Effects: *In vitro* studies in human isolated epicardial coronary arteries suggest that predominant contractile effect of 5-HT is mediated via 5-HT_2 receptors. However, 5-HT_1-like receptors also contribute to some degree to contractile effect. Transient increases in systolic and diastolic blood pressure (up to 20 mmHg) of rapid onset (within min.), have occurred after intravenous administration of up to 64 μg/kg (3.2 mg for 50 kg subject) to healthy volunteers. Changes not dose related and returned to normal within 10-15 min. Following oral administration of 200 mg, however, mean peak increases in blood pressure were smaller and of slower onset.

Pharmacokinetics: Rapidly absorbed after oral and subcutaneous administration with a mean bioavailability of 96% after subcutaneous dosing and 14% after oral dosing. Low oral bioavailability mainly due to hepatic metabolism and, to a lesser extent, incomplete absorption. Oral absorption is not significantly affected either during migraine attacks or by food.

Following oral dose of 100 mg, mean C_{max} of 54 ng/mL attained, while time to peak plasma level was variable (0.5-5 hours). However, 70% to 80% of C_{max} values attained within 30-45 min. of oral dosing. Mean plasma half-life approx. 2 h (range 1.9-2.2 h).

Following 6 mg subcutaneous dose (standard injection) in deltoid region of arm or thigh or autoinjection into thigh, mean C_{max} value of 60 ng/mL attained at approx. 15 min. Mean plasma half-life approx. 2 h (range 1.7-2.3 h).

Sumatriptan is extensively metabolized by the liver and cleared to a lesser extent by renal excretion. The major metabolite, indole acetic acid analogue of sumatriptan mainly excreted in urine where it is present as free acid (35%) and glucuronide conjugate (11%). No known 5-HT_1 or 5-HT_2 activity. Minor metabolites not identified. Plasma protein binding in humans is low (14%-21%).

No differences observed between pharmacokinetic parameters in healthy elderly volunteers compared with younger volunteers (less than 65 yrs).

INDICATIONS AND CLINICAL USES IMITREX (sumatriptan succinate) indicated for relief of migraine attacks with or without aura.

Not indicated for prophylactic therapy of migraine or for management of hemiplegic or basilar migraine.

CONTRAINDICATIONS In patients with known hypersensitivity to any components of formulation; in patients with ischemic heart disease, angina pectoris including Prinzmetal angina, previous myocardial infarction and uncontrolled hypertension; in patients taking ergotamine-containing preparations.

Until further data available, sumatriptan is contraindicated in patients with hemiplegic and basilar migraine, in patients receiving treatment with MAOI's, selective 5-HT reuptake inhibitors and lithium.

WARNINGS

No experience in patients with recent cerebrovascular accidents or cardiac arrhythmias (especially tachycardias). IMITREX is not recommended in these patients.

IMITREX Injection should not be given intravenously since it may cause coronary vasospasm and angina. Sumatriptan should be used with caution in patients in whom there is a concern of ischemic heart disease, as in patients with arteriosclerotic diseases such as peripheral and/or cerebral vascular disease.

Recommended dose should not be exceeded.

PRECAUTIONS:

Cluster Headache: There is insufficient information on the efficacy of sumatriptan in the treatment of cluster headache and on the safety of continuous use of sumatriptan over several days, to permit adequate dosage recommendations.

General: Prolonged vasospastic reactions reported with ergotamine. As these effects may be additive, sumatriptan should not be taken until 24 hrs. after any ergotamine-containing preparation. Conversely, ergotamine-containing preparations should not be taken until 6 hrs. after sumatriptan administration.

Sumatriptan may cause a short-lived elevation of blood pressure (see Clinical Pharmacology and Contraindications).

Drowsiness may occur as a result of treatment with sumatriptan. Patients should be advised not to perform skilled tasks eg. driving or operating machinery if drowsiness occurs.

Hepatic and Renal Impairment: Effects of renal and hepatic impairment on efficacy and safety of sumatriptan not evaluated. Not recommended in this patient population.

Use in Elderly (> 65 years): Experience of use of sumatriptan in patients over 65 yrs limited. Use in these patients is not recommended.

Use in Children (< 18 years): Safety and efficacy of sumatriptan in children not established. Use in this age group not recommended.

Use in Pregnancy: Reproduction studies performed in rats revealed no *evidence of impaired fertility or post-natal development due to* sumatriptan.

No adequate and well-controlled studies in pregnant women. Use is not recommended.

Lactation: Sumatriptan excreted in breast milk in animals. No data exists in humans, therefore, caution advised when administering it to nursing women.

Drug Interactions: Single dose pharmacokinetic drug interaction studies have not shown evidence of interactions with propranolol, flunarizine, pizotifen or alcohol. Multiple dose interaction studies not performed.

ADVERSE REACTIONS Most common adverse reaction associated with IMITREX administered subcutaneously is transient pain (local erythema and burning sensation) at site of injection.

Other side effects reported for both oral and subcutaneous routes, but more common for subcutaneous route, include sensations of tingling, heat, heaviness, pressure or tightness in any part of body, chest symptoms, flushing, dizziness and feelings of weakness. Transient increases in blood pressure arising soon after treatment recorded.

Fatigue and drowsiness reported at slightly higher rates for oral route, as were nausea and vomiting; relationship of latter adverse reactions to sumatriptan not clear.

Following table lists incidence of adverse reactions reported in clinical trials with oral formulation and the subcutaneous injection.

Most events transient in nature and resolved within 45 min. of subcutaneous administration and 2 hrs. of oral administration.

Incidence of Drug Related Adverse Events in Controlled Clinical Trials

Event	Tablets n = 1456	Placebo n = 296	Subcutaneous Injection n = 2665	Placebo n = 868
Gastrointestinal				
nausea/vomiting	12%	4%	8%	4%
gastric symptoms, abdominal discomfort	1%	≤1%	1%	<1%
dysphagia	1%	0%	1%	0%
gastro-oesophageal reflux, diarrhea and abnormal stools	<1%	≤1%	<1%	0%
Neurological				
tingling	1%	<1%	9%	2%
malaise/fatigue	8%	2%	2%	<1%
dizziness/vertigo	5%	2%	8%	3%
warm/hot sensation	1%	<1%	8%	3%
burning sensation	<1%	0%	5%	<1%
numbness	1%	<1%	3%	1%
drowsiness/sedation	3%	<1%	2%	<1%
paresthesia	1%	0%	1%	<1%
Cardiovascular				
flushing	<1%	1%	5%	2%
hypertension, tachycardia	<1%	0%	<1%	<1%
bradycardia	<1%	0%	<1%	0%
palpitations	<1%	<1%	<1%	<1%
hypotension	<1%	0%	<1%	<1%
pallor	<1%	0%	<1%	<0%
pulsating sensation	<1%	0%	<1%	<1%
Symptoms of Potentially Cardiac Origin				
neck pain/stiffness	2%	0%	3%	<1%
feeling of heaviness	3%	<1%	8%	1%
pressure sensation	1%	<1%	6%	1%
chest symptoms	3%	<1%	4%	<1%
throat symptoms (including sore or swollen throat or throat spasms)	2%	0%	2%	<1%
Musculoskeletal				
weakness	3%	<1%	3%	<1%
myalgia	2%	0%	1%	<1%
feeling of tightness	<1%	0%	3%	<1%
joint symptoms, backache, muscle stiffness or cramp	<1%	0%	0%	0%
Miscellaneous				
sweating	2%	<1%	2%	<1%
disorder of mouth and tongue	2%	<1%	4%	2%
disturbance of hearing	<1%	0%	<1%	0%
visual disturbance	<1%	0%	<1%	<1%

Minor disturbances of liver function tests occasionally observed. No evidence that clinically significant abnormalities occurred more frequently with sumatriptan than placebo.

SYMPTOMS AND TREATMENT OF OVERDOSE No reports of overdosage with IMITREX (sumatriptan succinate). Experience with doses outside the recommended labelling: One patient received two 6 mg subcutaneous doses within 30 mins. and 1 patient received four 100 mg tabs. within 24 hrs., with no adverse events.

If overdosage occurs, patient should be monitored and standard supportive treatment applied as required. Toxicokinetics not available.

Effect of haemodialysis or peritoneal dialysis on plasma concentrations of sumatriptan not known.

DOSAGE AND ADMINISTRATION Indicated only for intermittent *treatment* of migraine headache with or without aura. Should *not* be used prophylactically.

May be given orally or subcutaneously.

Equally effective when administered at any stage of migraine attack. However, it is recommended that it be given as early as possible after onset of aura or headache.

Clinical response begins 10-15 min. following subcutaneous injection and around 30 min. following oral administration.

Further doses of sumatriptan should not be taken if patient shows no response to initial treatment of single attack. However, analgesic medication other than ergotamine-containing preparations may be used for further pain relief. May be taken for subsequent attacks.

Sumatriptan should not be taken until 24 hrs. after an ergotamine-containing preparation. Conversely, ergotamine-containing preparations should not be taken until 6 hrs. following sumatriptan administration.

Tablets: Recommended adult dose one 100 mg tab.

Clinical trials have shown that approx. 50-75% of patients have headache relief within 2 hrs. after oral dosing, and that a further 15-25% have relief by 4 hrs. If no response within 4 hrs. patient is a non-responder and may use rescue medication except ergotamine-containing preparations.

Patients who have had a successful response (ie. no pain or mild pain) may treat a later recurrence of headache with additional dose of sumatriptan.

Maximum total dose in 24 hrs. is 3 x 100 mg tab (300 mg).

Patients who do not respond to first dose should not take second dose of sumatriptan for same attack. May be taken for subsequent attacks.

Tablet should be swallowed whole with water, not crushed or chewed.

Injection: Should be injected subcutaneously (on outside of thigh) using an autoinjector.

Recommended adult dose is one 6 mg subcutaneous injection.

Clinical trials have shown that patients continue to improve for at least 120 min. after single subcutaneous injection of sumatriptan. If no response within 2 hrs. patient is a non-responder and may use rescue medication except ergotamine-containing preparations.

Patients who have had a successful response (ie. no pain or mild pain) may treat later recurrence of headache with 1 additional dose. Maximum dose in 24 hrs. is two 6 mg injections (12 mg), with 1 hr. interval between each 6 mg dose.

Patients who do not respond to first dose should not take second dose for same attack. May be taken for subsequent attacks.

STABILITY AND STORAGE RECOMMENDATIONS

Tablets should be stored at 15°C to 30°C. Injection should be stored at controlled room temperature (15°C-30°C) and protected from light.

AVAILABILITY OF DOSAGE FORMS

Pink, film-coated tablets available in blister packs of 6 tabs, packed in cardboard carton. Each tab contains 100 mg sumatriptan (base) as succinate salt.

Injection available in prefilled syringes containing 6 mg of sumatriptan base, as succinate salt, in isotonic solution (total volume = 0.5 mL). Syringes placed in a tamper-evident carrying/disposal case. Two prefilled syringes plus autoinjector packed in patient starter kit. Refill pack *available containing 2 prefilled syringes in carton.*

Injection also available to physicians or hospitals in single dose vial (total volume = 0.5 mL) containing 6 mg of sumatriptan base, as succinate salt.

REFERENCES:

1. Pryse-Phillips W et al. A Canadian population survey on the clinical, epidemiologic and societal impact of Migraine and tension-type headache. *Can J Neurol Sciences.* In publication, Nov. 1991.
2. Angus Reid. The Migraine Diary Study. Data on File. Glaxo Canada Inc. November 1990.
3. Feniuk W et al. Rationale for the use of 5-HT_1-like agonists in the treatment of migraine. *J Neurol* 1991; 238:S57-S61.
4. Humphrey PPA et al. Preclinical studies of the anti-migraine drug, sumatriptan. *Eur Neurol* 1991;31:282-290.
5. Brown EG et al. The safety and tolerability of sumatriptan: An overview. *Eur Neurol.* 1991;31:339-344.
6. The Oral Sumatriptan International Multiple-dose Study Group. Evaluation of a multiple-dose regimen of oral sumatriptan for the acute treatment of migraine. *Eur Neurol.* 1991;31:306-313.
7. The Sumatriptan Auto-injector Study Group. Self-treatment of acute migraine with subcutaneous sumatriptan using an auto-injector device. *Eur Neurol.* 1991;323-331.
8. IMITREX® Product Monograph. Glaxo Canada Inc. January 1992.
9. Tansey MJB et al. Sumatriptan in the acute treatment of migraine. Data on File. Glaxo Canada Inc. December 1991.

Full Product Monograph Available on Request to Physicians and Pharmacists.

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IMITREX®
SUMATRIPTAN SUCCINATE
MAKING MIGRAINE HISTORY

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