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A SEROLOGICAL TEST FOR THYMOAMA IN PATIENTS WITH MYASTHENIA GRAVIS

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Ten to fifteen percent of patients with myasthenia gavis (MG) have an underlying thymoma. Such patients do less well and it may be important to detect them early. Conventional tests for thymoma such as immunofluorescent demonstration of skeletal muscle antibodies and CT scanning of the anterior mediastinum may give false positive and false negative results. We have attempted to validate a report that antibodies to a citric acid extract (CAE) of muscle, demonstrated by an indirect haemagglutination technique, are specific for thymoma. We studied four groups of subjects — normal controls, patients with other neuromuscular disease (OND), MG patients with known thymic histology, and MG patients with unknown thymic histology. CAE antibodies were not detected in any normal controls or patients with OND. In the group with known thymic histology they were found in all those with thymoma and none of those with other histology. They were found in about 40% of those with unknown thymic histology. Our experience so far suggests that demonstration of CAE antibodies is a specific and sensitive test for thymoma in patients with MG.

RHEUMATOID ARTHRITIS AND MOTOR NEURONE DISEASE — AN ASSOCIATION?

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Three patients with rheumatoid arthritis (RA) and motor neurone disease (MND) are presented. They had had “classic” RA (American Rheumatism Association criteria) for 2, 19 and 23 years respectively before they developed neurological symptoms. Lower limb weakness was the presenting complaint in all patients, followed by footdrop, distal upper and lower limb wasting and bulbar symptoms in two. Tongue fibrillation was evident in these two patients whereas all had a brisk jaw jerk and a combination of upper and lower motor neurone signs in the limbs with intact sensation. Serum creatine kinase was moderately elevated in one. There were electromyographic signs of widespread chronic partial denervation with abundant spontaneous activity in the presence of normal motor conduction velocities and sensory action potentials. The CSF contents were normal. Quadriceps muscle biopsies revealed angular fibres and small fibre type grouping characteristic of partial denervation. Relentless progression of the disease resulted in the death of two patients after 20 and 34 months respectively, the surviving patient being wheelchairbound 23 months after presentation.

This association raises important issues regarding the aetiology of so-called motor neuropathies in collagen disorders and the possibility of immunological mechanisms in some forms of MND.

CONTROLLED TRIAL OF A TRH ANALOGUE (RX77368) IN PATIENTS WITH MOTOR NEURON DISEASE

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Following a pilot study on five patients, twenty-six patients entered a double blind trial of intravenous L-pyroglutamyl-L-histidyl-L-3,3 dimethyl prolineamide (RX77368) 300 μg/kg over two hours randomly crossed over with physiological saline after seven days. RX77368 was preferred to placebo by 10 of 13 patients with bulbar syndrome. Temporary improvement in dysarthria in eight patients was documented with phonemic analysis; four with anarthria did not improve. Other bulbar mediated functions assessed included vital capacity, peak flow, maximal inspiratory and expiratory pressures, swallowing, palatal and tongue movements. Dynamometry measurements showed significant change in coefficient of variation (CV) of maximal isometric voluntary contraction in some muscle groups. Trend analysis showed increase or decrease in force in muscle groups with change in CV. Changes in force were seldom clinically significant. Tone changed in eight patients and fasciculations increased in 18. No detectable change in reflexes, fatigability nor Norris scale were seen. Neurological effects lasted up to 72 hours. There was significant increase in fibre density and median macro EMG amplitude but not in compound muscle action potential of biceps. Thirteen patients had no significant side effects. Serum thyroxine increased and returned to basal levels within seven days.

A TWO CENTRE STUDY OF THE ELECTROTRETINOGRAM (ERG) IN MULTIPLE SCLEROSIS

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To investigate the possibility of retinal involvement in MS 10 patients with positive McAlpine criteria, monocular retrobulbar neuritis and duration of disease between 1 and 5 years, were studied in Thessaloniki and 5 in Bristol.

The ERG to white light flash from light adapted eyes was recorded with infraorbital skin electrodes using a method previously reported (Papakostopoulos 1982. In GA Chiarenza and D Papakostopoulos (Eds) Clinical Application of Cerebral Evoked Potentials in Paediatric Medicine. Exerpta Medica, Amsterdam). The PR VEPs from Oz, referred to Fz, were also recorded.

All patients in Thessaloniki had abnormal PR VEP latencies when the abnormal eye was stimulated. The ‘b’ wave of the ERG of the abnormal eye (x = 6.4 μV + 1.8) was consistently smaller (x = 10.5 μV ± 2.3) in amplitude compared with the normal eye (p < 0.001) or 10 normal control subjects’ eyes (x = 11.2 μV ± 2.9) (p < 0.001). The recordings in Bristol yielded similar results. These results, obtained in two different laboratories, provide neurophysiological evidence of damage additional to demyelination in the central nervous systems in multiple sclerosis.

AN INVESTIGATION OF NEUROLOGICAL, PSYCHOLOGICAL AND PSYCHIATRIC IMPAIRMENT IN MULTIPLE SCLEROSIS

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The presence of clinically silent lesions in multiple sclerosis (MS) is a well recognised feature of the disease, but raises the question whether resultant signs might remain undetected because of limited testing procedures. This present study attempted to explore such a possibility by under-taking detailed assessment using a range of diverse investigative techniques, including neurological, psychological and psychiatric tests.

In this study, 82 patients with “definite MS” (53 females and 29 males, age range 20-60 years with mean of 42 years) were assessed using the Kurtzke Disability Status Scale, a standard intelligence scale with tests of selected neuropsychological functions, the Beck’s Depression Scale and the Goldberg Standardised Interview. They were compared with 42 control patients (21 females and 21 males, age range 20-60 with a mean of 46 years) suffering from chronic disabling non-cerebral neurological conditions.

Results showed both groups to be intellectually below average with no significant differences on estimated premorbid IQ, or neuropsychological functions, where both groups performed below expected levels for their age groups. The MS patients showed a higher degree of psychopathology which consisted predominantly of depressive symptoms, including irritability and lack of concentration, as well as a characteristic feeling of excessive fatigue.

THE CLINICAL AND PATHOLOGICAL FEATURES OF CORTICAL LEWY BODY DISEASE

Severe loss of pigmented substantia nigra cells with the presence of Lewy bodies are the characteristic histological features of L-dopa responsive Parkinson’s disease. Small numbers of Lewy bodies may also be found in the hippocampus in about a quarter of cases. A possibly distinct clinicopathological entity termed diffuse Lewy body disease has also recently been described in the literature, with multiple Lewy bodies present in the fifth and sixth layers of the cerebral cortex. The clinicopathological features of four patients with this condition will be reported and a review of the literature given.

CSF INTERFERON IN NEUROLOGICAL DISORDERS
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There are three antigenically distinct sub-types of interferon (IFN). Studies using bio-assays have suggested that IFN-α and IFN-β are produced in response to viral infection, whereas IFN-γ production is induced by immunological mechanisms. IFN-γ will induce the expression of class II MHC antigens in tissues which do not normally express them. It has been suggested that this mechanism may trigger autoimmunity.

Using highly sensitive and specific immunoradiometric assays (IRMA) we have measured IFN-α and IFN-γ in CSF of patients with infectious and immunologically mediated neurological disorders. Both immunoreactive IFN-α and IFN-γ were present in the CSF in the acute phase of viral meningitis, but no IFN was found in other neurological disorders such as multiple sclerosis and Guillain-Barré Syndrome.

IRMAs have not been previously applied to the study of IFN in CSF, and IFN-γ has not previously been detected in CSF. Its presence in CSF following viral infection gives support to the hypothesis that a preceding viral infection may trigger autoimmune disorders which involve the nervous system.

ENCEPHALITIS DUE TO INFLUENZA B VIRUS SA Hawkins, JH Connolly, JA Lyttle. Department of Neurology, Royal Victoria Hospital, Belfast

During an epidemic of Influenza B/Singapore/222/79 in Belfast, two cases of severe encephalitis were seen with diagnostic rises of antibody titres to the specific virus strain during the course of the illness. One was in a 37-year-old woman who had generalised encephalitis with generalised EEG slowing, and lymphocytic pleocytosis in the CSF. She was hospitalised for four months with prolonged stupor, epilepsy and myoclonus. She eventually made a full recovery. The second case was a 38-year-old woman who had a four day prodromal illness, became dysphasic, with associated right arm weakness. Two days later she had a solitary convolution. CT scan was normal, EEG showed generalised changes in keeping with encephalitis, maximal in the left temporal region. CSF showed a lymphocytic pleocytosis. She made a rapid recovery, was discharged within two weeks and was back to work three months later.

The features of the illness and timing of the rises in antibody titres are more in keeping with encephalitis than post-infectious encephalomyelitis. Other neurological syndromes have in the past been rarely associated with Influenza B infection. We are not aware of any other similar cases of Influenza B encephalitis in the literature.

A COMPARATIVE STUDY OF PROGABIDE, VALPROATE AND PLACEBO AS ADD-ON THERAPY IN PATIENTS WITH REFRACTORY EPILEPSY
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Progabide is a gaba agonist with anti-epileptic properties in animal models of seizures and epilepsy. Its efficacy in human epilepsy is less certain.

A three way single blind cross-over comparison of progabide, valproate and placebo, as adjunctive therapy for 6 months each, was undertaken in 64 patients with therapy resistant partial and generalised seizures. The study was not completed because of the incidence of elevated hepatic enzymes on progabide. Analysis of efficacy showed progabide to be inferior to valproate against all seizure types, and particularly against tonic-clonic seizures. Valproate was superior to placebo against all seizure types, partial and tonic-clonic seizures. Progabide did not differ significantly from placebo in any instance. In addition progabide caused elevation of hepatic enzymes which was symptomatic in one case, and was associated with an interaction with phenytoin which results in intoxication in some cases.

PROPOSED RESEARCH DIAGNOSTIC CRITERIA FOR PARKINSON’S DISEASE
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In the absence of pathognomonic markers, the diagnosis of Parkinson’s disease (PD), and its distinction from other Parkinsonian syndromes, depends on clinical observation. Published descriptions of the motor syndrome of Parkinsonism are often unnecessarily ambiguous. There is a lack of consistency in the use of even the three major terms, “tremor” “rigidity”, akinesia”. We present the first detailed proposals for research diagnostic criteria for PD, based on review of published clinical series and studies relating clinical features of Parkinsonian syndromes to pathology. Clinical information is assigned to four categories; 1) background (eg genetic); 2) Prodromal and presenting features other than Parkinsonism; 3) The motor syndrome of Parkinsonism; 4) Additional features. Findings are further classified as typical, atypical or incompatible. We have designed a diagnos-
tic form which facilitates the assessment and description of both individuals and series of patients. The scheme is necessarily tentative but will, we hope, be refined in future discussions.

BILATERAL OCCLUSION OF THE INTERNAL CAROTID ARTERIES PRESENTING SYMPTOMS IN 74 PATIENTS AND A PROSPECTIVE STUDY OF 34 MEDICALLY TREATED PATIENTS
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Seventy-four patients out of the total of 1377 subjects entered into the International EC/IC Bypass Study had atherosclerotic occlusion of both internal carotid arteries. All had suffered either ischaemic hemisphere infarcts (80%) and/or transient ischaemic attacks (80%) involving one (78%) or both (22%) carotid territories. In addition, 10 subjects (14%) incurred recurrent vertebrobasilar or presyncopal episodes, many of which appeared secondary to haemodynamic insufficiency. The prevalence of risk factors and concomitant vascular disease was high; 93% gave a history of heavy smoking.

Thirty-four subjects were treated conservatively and prospectively followed for a mean period of 42 months. Eighteen patients (52.9%) suffered further cerebrovascular events, giving a rate of 15.1% per patient year; these were isolated TIAs in seven subjects and stroke in 11 cases. The stroke rate was 9.2% per patient year. Patients who had presented with ischaemic events involving more than one carotid territory were significantly more prone to subsequent cerebral infarction than those in whom symptoms had been confined to one carotid territory (p < 0.04). Deaths per year amounted to 8.4%. Seventy-one per cent survived, of whom half were either symptom-free or minimally disabled at the end of follow-up.

In the group of pre-selected patients, which excludes those with severe deficits at presentation, bilateral occlusion of the carotid arteries may be a condition compatible with useful existence.

THE CLINICO-PATHOLOGICAL CORRELATION OF LACUNAR SYNDROMES: THE OXFORDSHIRE COMMUNITY STROKE PROJECT
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Several distinct clinical syndromes have been noted to occur in the presence of restricted areas of infarction within the vascular territory of deep penetrating arteries ("lacunes"). However, several reports have suggested that similar clinical syndromes may occur in the presence of lesions at other sites. Both the original observations on lacunar stroke and subsequent reports have been based on very few cases. We have studied prospectively the clinico-pathological correlation of lacunar syndromes in a community based sample of stroke patients.

Over a three year period, 515 first ever strokes were assessed of whom 108 (21%) were considered to have one of the recognised lacunar syndromes — 49 (45%) pure motor stroke, seven (6%) pure sensory stroke, nine (8%) ataxic hemiparesis and 43 (40%) sensory-motor stroke. A CT scan or necropsy examination was performed in 95 (88%) cases. In 30 (32%) cases there was a small, deep infarct appropriate to the clinical features, in 59 (62%) cases the CT scan was normal and in three (3%) cases the CT scan showed primary intra-cerebral haemorrhage. In two other cases there was both deep and cortical infarction which might have caused the clinical features and in one case there was infarction in the territory of the pericallosal artery. These findings allow the significance of individual case reports to be assessed.

MAGNETIC RESONANCE IMAGING IN EXPERIMENTAL CEREBRAL OEDEMA
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MRI readily detects abnormalities in many CNS diseases. The specificity of abnormal images is unknown. We have, therefore, investigated two different types of cerebral oedema in cats: vasogenic cold oedema, where the expanded extracellular space contains variable amounts of plasma protein, and cytotoxic oedema induced by triethyltin, characterised by the accumulation of protein-free fluid in intramyelinic vacuoles.

NMR images, quantitative changes in relaxation times T1 and T2, and magnetisation decay characteristics were correlated with ultrastructural features of the lesion.

MRI was sensitive to these lesions but the images lacked specificity. The ratio of changes in T1 and T2, however, was characteristic. In early vasogenic oedema associated with large amounts of protein, T1 and T2 increased in approximately the same proportion. As the protein content diminished over a period of days, T2 tended to be more elevated than T1.

In cytotoxic oedema, the proportional increase in T2 was approximately twice that in T1. The magnetisation decay characteristics of each lesion showed specific features.

The images and the quantitative data together distinguish the two lesions and provide an insight into the nature of underlying pathological processes.

X-LINKED BULBO-SPINAL NEURONOPATHY
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In 1968, Kennedy and colleagues reported 11 males from two families with a distinct form of bulb and spinal muscular atrophy which was slowly progressive and inherited as an X-linked recessive. Since then a further 31 patients have been described in five separate reports, 10 being described by Harding and colleagues in 1982. As well as reporting similar findings to Kennedy they found reduced or unrecordable sensory nerve action potentials in seven patients and because of this abnormality they named it X-linked recessive bulbo-spinal neuronopathy.

The clinical features of two brothers and one nephew with X-linked recessive bulbo-spinal neuronopathy will be described. The neurophysiological investigations and sural nerve biopsy, previously unreported confirmed that both motor and sensory nerve are affected.

Because of the genetic implications we wish to stress the importance of recognising fascio-scapulo-humeral muscular atrophy (FSH) and spinal muscular atrophy (SMA) as separate entities which should not be classified with the spinal muscular atrophies.

THE ROLE OF CT SCANNING AND THE EVALUATION OF SPINAL MUSCULAR ATROPHY
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Adolescent and adult onset spinal muscular atrophy (SMA) may present as a limb girdle, Fascio-scapulo-humeral or Scapuloperoonal syndrome. Histopathological verification of the diagnosis is obtained from muscle biopsy but this only provides information on the abnormalities in the biopsied muscle. Clinical examination provides information on muscle groups, for example, posterior lower limb muscles, but does not permit differentiation of the relative contribution to muscle strength from individual muscles.
The development of modern generations of CT scanners has permitted more detailed assessment of the extent of the disease process.

CT scanning has been applied to 75 patients with histologically verified SMA of varied presentation and disease duration. CT evaluation was carried out without knowledge of the clinical features or disease duration.

This study has shown there appears to be a recognisable CT appearance in SMA. This was seen irrespective of the clinical mode of presentation. Abnormalities have been demonstrated in mildly affected individuals within families whose older members have shown marked clinical and CT abnormalities, suggesting that the degree of CT abnormalities depends on the disease duration.

Further studies of CT and SMA may obviate the need for muscle biopsy of more than one family member.

SERIAL QUANTITATIVE ELECTROMYOGRAPHY (EMG) AND MAXIMUM QUADRICEPS STRENGTH IN PERIPHERAL NEUROMUSCULAR DISORDERS
DJ Short, CM Wiles. Department of Neurology, St Thomas' Hospital, London

A comparison has been made between serial measurement of mean potential duration (MPD) and knee extension force in patients with peripheral neuromuscular disorders.

The maximum voluntary isometric knee extension force (MVC) was measured with the subject seated in a special chair. EMG was recorded from vastus medialis using a concentric needle electrode through 2 skin insertions between 5 and 10 cm proximal to the upper border of the patella. Action potentials from at least 20 individual motor units recruited at low force were recorded on photosensitive paper and subsequently analysed manually to give the mean potential duration (MPD). In addition patients completed a visual analogue scale of their subjective impression and a functional assessment made. A normal range for MPD was established in 25 subjects (aged 28–65). In 10 subjects the coefficient of variation for paired measurements was 3%.

Satisfactory studies were obtained on at least 3 occasions from 20 patients with various myopathies and diabetic amyotrophy. MPD and MVC changed in the expected direction during clinical improvement or deterioration but in only a few patients was there close correlation. Changes in MPD were a less sensitive quantitative guide to clinical status than maximum voluntary knee extensor force.

THE EFFECTS OF TRH ON PRIMARY LATERAL SCLEROSIS
P Pinelli, A Villani, F Pisano. Medical Center, Neurological Department, Veruno (NO) Italy

Two patients of the same family (CM, f, 56 years old; AG, m, 35 years old) affected by Strümpell-Lorrain disease and one (CR, m, 30 years old) affected by primary lateral sclerosis since 11 years were evaluated by means of clinical, dynamometric, and electromyographic investigations (quadriceps, biceps femoris, tibialis ant. and triceps surae): motor unit voluntary maximal recruitment (Vmx), Mnx response, T reflex and H response were recorded with macro-electrodes, and the Wartenberg test was evaluated with simultaneous goniometric recording.

The investigations were repeated thrice before and 20–45’ after each TRH-T adminis-
differing doses (300 mg, 600 mg, 900 mg/day) for 2 months each, was undertaken in 25 patients with resistant partial and generalised epilepsies.

There was a dose-related reduction in seizure frequency compared with a baseline period. (P > 0.0001, Wilcoxon signed rank test). At the highest dose, 43% of patients showed a greater than 50% reduction.

No serious adverse effects or drug interactions were noted. The compound appears worthy of further evaluation.

NORMA LCELLULAR SENSITIVITY TO X-RAYS IN PARKINSON'S DISEASE AND ALZHEIMER'S DISEASE

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It has been claimed that cells from patients with one of several sporadic neurological disorders, including Parkinson’s disease and Alzheimer’s disease, are hypersensitive to X-rays, implying deficiency of DNA reparative processes. We have been unable to confirm increased cellular radiosensitivity in these two conditions. Forearm skin biopsies from three patients with Parkinson’s disease (PD) and four with Alzheimer’s disease (AD) were cultured and survival of fibroblasts following exposure to graded doses of X-rays was measured by counting cell colonies and assessing the fraction surviving. PD cells (patients aged 41–76) showed a mean D0 of 1-21 Gy (12 experiments). AD cells (patients aged 48–62) showed a mean D0 of 1-24 Gy (11 experiments). Control cells grown in parallel showed a mean D0 of 1-29 Gy (22 experiments). These findings do not give support to the idea that DNA repair deficiency is a major pathogenetic mechanism in degenerative neurological disease.

IMMUNOELECTRON MICROSCOPIC EVIDENCE OF DUAL HORMONE PRODUCTION IN PITUITARY ADENOMA CELLS

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A pituitary adenoma was surgically removed from a 42-year-old male presenting with classical symptoms of acromegaly plus decreased libido and impotence. The lowest serum growth hormone (GH) level during oral glucose tolerance test was 26-5 mu/1. Prolactin (PRL) levels ranged from 1990–4790 mu/1.

Histologically the adenoma was predominantly acidophilic. With immunoperoxidase, a significant number of cells stained positively for PRL, while only occasional scattered cells show reactivity for GH. Staining for all other hormones was negative. The tumour had a uniform ultrastructural appearance. The cells showed good cytoplasmic differentiation in keeping with a prolactinoma. Immunoelectronmicroscopy, including double labelling techniques using selected colloidal gold particles as markers, not only demonstrated PRL and GH in each of the tumour cells, but also within the same granules.

The results indicate the presence of a pituitary adenoma in which the cells are capable of simultaneously producing GH and PL and packaging them within the same secretory granule. This is thought to represent a mammosomatotroph cell adenoma. Although such a mechanism for the production of two or more hormones by a single tumour cell has previously been postulated, we believe our report is the first time this has been shown by this technique.

CLINICAL, HISTOLOGICAL AND ULTRASTRUCTURAL FINDINGS IN A FAMILIAL MUSCLE DISEASE WITH TUBULAR AGGREGATES

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Tubular aggregates (TAs) are an unusual histological finding in muscle disease. They most often occur in type 2 fibres in patients with aches, cramps and pains but may also be found in small numbers in a variety of other conditions. Two families with muscle disease in which TAs were the dominant biopsy feature have recently been described and we report a third family of what seems to be a distinct condition. A father and daughter had symptoms of arm and leg weakness starting in their early teens with very slow progression. Both had proximal weakness with some limitation of eye movements and Achilles tendon contractures. Creatine kinase was 5–10 times normal. Histology and histochemistry of muscle biopsies showed vacuoles in almost all fibres and electron microscopy revealed that these were filled with TAs. These consisted of closely packed parallel tubules and differed from the TAs most commonly reported in other conditions. The pathogenesis of these remarkable structures is not clear.
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