LETTERS TO
THE EDITOR

Creutzfeldt-Jakob disease presenting as complex partial status epilepticus: a report of two cases

Creutzfeldt-Jakob disease is a transmissible human spongiform encephalopathy which may be familial, iatrogenic, or sporadic. The classic clinical features include a rapidly progressive dementia with the patient retaining clear consciousness until the terminal stages of the disease. We report on two patients presenting with a rapidly declining level of consciousness, in whom the clinical picture and EEG were suggestive of complex partial status epilepticus.

The first patient was a 58 year old woman who was admitted to a psychiatric unit with a short history of mood disturbance, confusion, and unsteadiness. A provisional diagnosis of agitated depression was made and she was started on lofepramine. She then became unsteady on her feet and required support when walking. She had had occasional complex partial seizures for 30 years but at presentation was not taking any anticonvulsant drugs.

On examination, she appeared perplexed, tearful, and agitated, and was unable to give a coherent history. She was intermittently confused and her gait was ataxic. There were no other cerebellar signs. The rest of the neurological examination was unremarkable although limited by poor cooperation.

She became more withdrawn and uncommunicative with incontinence of urine. She would occasionally jump when sitting in a chair.

Brain CT and MRI were normal, as was her CSF. An EEG showed frequent, almost continuous variable amplitude sharp waves in all areas, although with a right sided emphasis, with a repetitive appearance up to 2 per second (figure). The record was thought to be in keeping with partial status epilepticus.

Her level of consciousness deteriorated despite intravenous valproate and phenytoin and she was transferred to the intensive care unit for continuous EEG monitoring. On arrival, she was deeply unconscious and despite aggressive management of her presumed complex partial status she died 3 weeks later. Histology of the brain was diagnostic of the sporadic form of Creutzfeldt-Jakob disease.

The second patient was a 68 year old man who was admitted with a short history of mood disturbance, confusion, and inappropriate behaviour. He appeared not to recognise his family. Initially he was dysphasic and obtunded. His consciousness then deteriorated and he became mute with evidence of right sided weakness.

All investigations including contrast enhanced brain CT and CSF examination were normal. An EEG was reported as showing frequent bilateral epileptiform activity, but there was no improvement in his clinical state after a loading dose of intravenous phenytoin. A repeat EEG was dominated by periodic lateralised epileptiform discharges (PLEDs), more marked on the left side. A third EEG 3 weeks later again showed frequent predominantly left sided epileptiform discharges, which were attenuated by a bolus of intravenous diazepam but without any improvement in his clinical condition.

He was transferred to this hospital for artificial ventilation because of the concern that he was in complex partial status. On admission he was mute, his eyes were closed, and he flexed to pain on the left side only. Intermittent twitching of both sides at a rate of between 1 Hz–2 Hz was seen. Reflexes were brisk and symmetric. His right plantar response was extensor, his left flexor.

A further EEG 5 days later showed generalised asynchronous continuous periodic sharp waves occurring at a frequency of 1.3 Hz, at times in the form of biphasic or triphasic complexes. Myoclonic jerks occurred during the recording.

It was considered that overall these features were consistent with a diagnosis of Creutzfeldt-Jakob disease. His condition continued to deteriorate and he died 2 weeks later. A request for a postmortem examination was refused.

These two cases illustrate a previously unrecognised presentation of Creutzfeldt-Jakob disease, namely presumed complex partial status.

In the first case, the interpretation of the EEG findings was made more difficult by the patient’s depressed conscious level and the previous history of complex partial seizures, albeit mild. The initial psychiatric presentation, with mood and behaviour disturbance, as well as fluctuating confusion, was compatible with complex partial status. The initial EEG report, suggesting partial status epilepticus, prompted treatment, unsuccessfully, with anticonvulsant drugs and subsequent transfer for continuous EEG monitoring. This disclosed marked fluctuations, including discrete runs of rhythmic sharp waves that were considered to be electrographic seizures. Even after sustained burst suppression, the recording fluctuated between generalised periodic discharges and periods of relative inactivity within a matter of seconds.

In the second case, the patient developed focal seizures and PLEDs on the EEG. The initial recordings were suggestive of complex partial status, with asymmetric discharges abolished by diazepam but without any observable clinical change. Subsequent recordings were more characteristic of Creutzfeldt-Jakob disease, particularly as the patient had developed myoclonus. Although the electrographic changes were abolished by diazepam, suggesting seizure activity, the modification of both clinical and EEG activity in Creutzfeldt-Jakob disease by benzodiazepines has been reported giving rise to further confusion with epileptiform sharp wave activity. The focal nature of the patient’s signs and the laterisation on the EEG is well recognised in Creutzfeldt-Jakob disease as are...
periodic PLEDs, which are often associated with contralateral myoclonic jerks. 1 2

The two cases described here illustrate that a diagnosis of Creutzfeldt-Jakob disease should be considered where a rapid decrease in consciousness is accompanied by EEG changes apparently compatible with complex partial status. When there is a clinical suspicion of Creutzfeldt-Jakob disease, the ideal method of monitoring such patients is with continuous EEG recording, allowing documentation of rapid fluctuations. The present cases are atypical in that the progression from presentation to death was rapid, but they underline the fact that minute to minute changes in EEG rhythm, asymmetry, and electrographic responsiveness to benzodiazepines can all be seen in Creutzfeldt-Jakob disease.

Letter J H Rees, National Hospital for Neurology and Neurosurgery, Queen Square, London, UK

Correspondence to: Dr J H Rees, National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG, UK

Childhood demyelinating diseases with a prolonged remitting course and their relation to Schilder's disease: report of two cases

Schilder's disease or myelinoclastic diffuse sclerosis is a rare acute or subacute demyelinating disorder which primarily affects children and young adults. 1 2 We report the clinical and neuroradiological follow-up of two boys affected by a demyelinating disease with a prolonged relapsing-remitting course, response to corticosteroids, and relatively good long term prognosis. The first patient presented at the age of 12 with a 2 month history of repeated episodes of headache and blurring vision followed by weakness of the left leg, lasting a few hours. Head CT and bilateral carotid angiography were normal. Two weeks later the left hemiparesis and headache recurred. T2 weighted images on brain MRI disclosed a hypointense signal in the right parieto-occipital white matter, involving the right centrum semiovale, with mass effect. The second patient was admitted at the age of 4 because of the sudden onset of headache and vomiting with ataxia and drowsiness followed by generalised clonic seizures. Clinical examination on admission showed left hemiparesis, anisocoria (left>right), and dysarthria. Ocular fundoscopy was normal. Head CT disclosed a reduced right lateral ventricle and subarachnoid spaces and, 1 week later, a small hypodense area in the right periventricular white matter. A carotid angiogram was normal at age 5. The child had a second episode characterised by high fever, vomiting, sixth nerve bilateral paresis, dysarthria, truncal ataxia, and stupor. Treatment with corticortrophin (35 units daily for 5 days, then every 48 hours for 20 days) induced a rapid clinical improvement. From the ages of 5 to 14 the child had yearly relapses characterised by the sudden onset of left hemiparesis with variable involvement of the cranial nerves and impairment of consciousness associated with inconsistent alteration of white matter on brain CT (widespread hypodensity in the right centrum semiovale with a mass effect on the right ventricle). These attacks regressed spontaneously or after corticosteroid treatment. The last episode, at the age of 14, consisted of right sided paraparesis of the face and hand, right hemiparesis, dysarthria, and drowsiness. T2 weighted sequences on MRI disclosed multi focal abnormalities in supratentorial white matter. Corticosteroid treatment induced marked clinical improvement. Follow up at the age of 18 detected only a bilateral parietal myostagnus and hypometric saccades. Mental development was normal. Brain MRI showed that the white matter lesions had partially regressed.

In both patients the following investigations during and between attacks yielded normal findings: CSF examination (absence of oligoclonal bands), CSF lactate and pyruvate; extensive serological and CSF immune screen; extensive viral, bacterial, and parasitic serological and CSF tests; blood lactate, blood ammonia, amino acids in plasma, urine, CSF, gas chromatography-mass spectrometer analysis of organic acid in urine, adrenal function, plasma C26/C22 fatty acid ratio, serum copper, plasma ceruloplasmin, pyruvate dehydrogenase complex and cytochrome c oxidase activity in skin fibroblasts; arylsulphotase A, β-galactosidase, β-glucosidase, and galactocerebroside-β-galactosidase activities in leucocytes.

In both cases the overdoses also raised the question of myelinoclastic diffuse sclerosis. 1 2 A prerequisite for the diagnosis is a normal very long chain fatty acid plasma concentration. Clinical signs include an intracranial hypertension syndrome, mental deterioration, hemiplegia, and visual field defects. The disease has either a monophasic course, rarely rapid and fatal, or a relapsing-remitting course. 3 Most patients have neurological sequelae during follow up, and few patients recover fully. 4 Histological studies typically show a demyelinating process similar to that of multiple sclerosis, with an inflammatory perivascular infiltrate, and in severe cases, cystic lesions. Neurological findings include temporal lobe epilepsy and parietal sequelae during follow up and few patients recover fully. 4

In both the patients described the association of headache, signs of diffuse and focal brain dysfunction, a relapsing course, and the response to corticosteroid therapy raises the possibility of an isolated CNS angiitis, a condition primarily affecting middle aged and elderly people. But neither cerebral angiography nor histological examination disclosed a primary vascular disorder. In addition, the early onset and the sporadic occurrence of the disorder rule out another recently described vasculopathy often associated with familial hemiplegic migraine. 5

In conclusion, although demyelinating diseases that do not fulfill the classical definition of multiple sclerosis or encephalomyelitis remain difficult to label in children, the two cases we report here seem to fit Schilder's description of myelinoclastic diffuse sclerosis. Owing to the current lack of knowledge on the causes of this disease strict diagnostic criteria cannot be applied. Some presentations may warrant brain biopsy. The differing clinical and neuroimaging features seen in these patients may help in delineating Schilder's disease subtypes.

VINCENZO LEZZUZI
Dipartimento di Scienze Neurologiche e Psichiatriche dell’Età Evolutiva, Università La Sapienza, Roma, Italy

GILLES LYON
Maria Roberta Cilio
Servizio di Neuropediatria, Università Catholique de Louvain, Bruxelles, Belgium

JEAN MICHEL PEDENSPAT
DANIEL FONTAN
Unité de Neurologie Infantile
JEAN-FRANCOIS CHATEIL
Unité de Neurologie

ANNE VITAL
Unité de Neuropathologie, Centre Hospitalier Pigeiron, Béziers, France
Correspondence to: Dr Vincenzo Leuzzi, Istituto di Neurologia Vall d’Hebron, M. Fimiani, Via del Sabelli 108, 00185 Roma, Italy. Telephone 0039 6 44712221; fax 0039 6 4957857; email leuzzi@shareware.it


Guillain-Barré syndrome after heat stroke

Heat stroke is usually not listed among the events triggering Guillain-Barré syndrome. Two cases of a Guillain-Barré syndrome-like polyneuropathy after heat stroke are on record, although without reference to electrolyte disturbances.1 We report on a patient, who developed Guillain-Barré syndrome 10 days after severe heat stroke. He had electrophysiological evidence of demyelination, increased CSF protein, and high anti-GM1 antibodies. It cannot be excluded that the course of Guillain-Barré syndrome was precipitated by the heat stroke itself, but probably did not cause it. The patient had all characteristics and course of 28 patients with Guillain-Barré syndrome examined in the same laboratory. They generally did not have Guillain-Barré syndrome. In our patient who proved clinically electrolyte disturbances, including high anti-GM1 IgM antibodies and thus may induce Guillain-Barré syndrome. In our patient with Guillain-Barré syndrome as well. Weakness of proximal arm muscles had MRC grades 3/5, and sural nerve conduction was normal and sural nerve conduction was moderately slowed (36 m/s) at day 2. Needle EMG disclosed abundant fibrillations and positive sharp waves in proximal and distal limb muscles at day 95. Decreasing sweat due to anticholinergic medication, cocaine induced increased heat production, and high ambient temperature precipitated heat stroke in our patient. Ten days after withdrawal the patient had an acute neuropathy that met clinical and neurophysio-

omicologic criteria for Guillain-Barré syndrome. Similar time delays have been seen in two other patients with Guillain-Barré syndrome-like neuropathies after heat stroke1 and in the second of two patients reported as critical illness neuropathy after extreme hyperpyrexia.1 This patient had increased CSF protein and fasciculations which are unusual in critical illness neuropathy. He may have had Guillain-Barré syndrome as well. Weakness evolved with delay in these four patients with Guillain-Barré syndrome-like neuropathies, whereas it was present immediately after hyperpyrexia in five more patients, who probably had not Guillain-Barré syndrome. One patient with heat stroke was tetraparetic when he regained consciousness.1 He had pyramidal and cerebellar signs and persistent atrophic weakness due to axonal or motor neuron loss and no neurophysiological evidence for demyelination. Four of 14 patients with cancer exposed to whole body hyperthermia and chemotherapy complained of weakness immediately after hyperthermia.1 Their nerve conduction abnormalities are reported as “compatible with scattered demyelination”.1 Our patient had chronic HCV infection which may be associated with vasculitic neuropathy and cryoglobulinaemia, both absent in our patient. A connection between Guillain-Barré syndrome and non-A non-B hepatitis has been suggested,1 but the close temporal relation makes heat stroke a more probable cause of the disease in our patient. His high anti-GM1 antibodies suggested immune mediation. Anti-GM1 IgA is increased after Campylobacter jejuni infection. Heat stroke disrupts the gastrointestinal mucosal wall. Endotoxins enter circulation and stimulate macrophages, which release TFN-γ, IL-1, IL-6, and IFN-γ. All these cytokines are raised after heat stroke2 and the blood-nerve barrier. This may have exposed the GM1 epitope in our patient. IFN-γ induces Schwann cells to express MHC class II gene product, inviting T cell attack. TNF-α is proinflammatory-cytokine and toxic, and increased in Guillain-Barré syndrome. Guillain-Barré syndrome-like neuropathies have been reported from Asia,1 where heat stroke is common, but they were not noted in connection with epidemic heat stroke in North America.1 Our patient had all features associated with fatal heat stroke: long lasting coma, shock requiring vasopressor catecholamines, metabolic acidosis, and disseminated intravascular coagulation.1 Guillain-Barré syndrome may occur more often after heat stroke, if more patients survive extreme hyperthermia thanks to intensive care.1

Hydrodynamic performance of a new siphon preventing device: the SiphonGuard

Around 10% to 30% of shunt revisions may be attributed to posture related overdrainage. Of the various siphon preventing devices available at present, two construction types are the most prominent: those using a gravitational mechanism and those using a subcutaneous membrane. Gravitational devices, such as the Elekta-Cordis Horizontal Vertical Valve, Chhabra Valve, Fuji Valve, or Miethe Dual-Switch Valve are widely used.1 Their main drawback is susceptibility to malfunction when the shunt becomes displaced from its vertical axis after implantation and unpredictable operation during persistent bodily movements. The membrane devices: the Anti-Siphon Device (ASD), Heyer Siphon (HSD) or Siphon Control Device (SCD), Medtronic PS, Micra Valve, and SiphonGuard proved clinically effective,2 although in some cases these devices may obstruct the CSF drainage when the subcutaneous pressure increases or the scar tissue isolates the device from atmospheric pressure. The flow regulat-
ing Orbis-Sigma Valve (Elekta-Cordis) may also reduce clinical complications related to overdrainage in the upright body position. It prevents excessive CSF drainage by instantaneously increasing its hydrodynamic resistance when the drainage rate rises.

The new Codman SiphonGuard device is intended to reduce the drainage rate when the flow dramatically increases during transition from a horizontal to vertical body position. It consists of two passages for the CSF drainage. In the central, wide channel a ball on spring valve is inserted. The valve, unlike in all hydrocephalus shunts, is normally open and closes when the flow rate exceeds the specific threshold level. Then the drainage of CSF is diverted to a much thinner channel, which constitutes a high hydrodynamic resistance. This action may help to prevent posture related overdrainage.

We tested a sample of three SiphonGuards (kindly provided by Johnson and Johnson) in the United Kingdom Shunt Evaluation Laboratory to characterise the hydrodynamic performance of the device and its ability to reduce posture related overdrainage.

The pressure flow performance curve consisted of two straight lines of different slopes, both crossing the origin. They represent the two possible states of the SiphonGuard—low resistance (mean of 1.5 mm Hg/ml/min) and high resistance (mean of 42 mm Hg/ml/min, figure A). The differential pressures resulting from the above values, providing the CSF flow is on average 0.3 ml/min in the horizontal body position, would be 0.45 mm Hg and 12.6 mm Hg respectively.

Switching between low and high resistance was initiated by a flow rate, the threshold of which varied between 0.7 and 1.8 ml/min (figure B).

Switching from the high to low resistance was initiated by the differential pressure decreasing below the threshold from 4 to 6 mm Hg.

Overall, the mechanism of the SiphonGuard seemed to work according to the designers’ intention. It is supported by the concept that, during rapid transition from horizontal to vertical body position, initial flow rate increases above 2–3 ml/min. This is enough to switch the valve to the high resistance state, limiting overdrainage. However, in practice, it may not always be the case. In patients with small or slit ventricles previously having overdrainage, CSF may not be available to produce the flow at such a high rate. Moreover, because reliable switching occurs above 1.8 ml/min, in shorter persons or in patients resting persistently in a semisitting position (for example, elderly patients watching TV or reading books) the drainage rate of 1 ml-1.5 ml may cause clinical deterioration without initiating the anti-siphon action of the SiphonGuard. Another possible drawback concerns the reverse change—that is, switching back from high to low resistance, to be expected when a patient moves from a vertical to a horizontal position. The device may not return to its state of low resistance. If the resistance switching mechanism is indeed triggered by a differential pressure (with a threshold of around 5 mm Hg) the SiphonGuard may stay in the high resistance state permanently. Its high hydrodynamic resistance may force the differential pressure to persist higher than 9–16 mm Hg, under conditions when the CSF drainage rate should equal its formation rate (0.2–0.4 ml/min). Hence, it is possible that the device may remain “locked” in the high resistance state, causing underdrainage in the horizontal body position.

In vivo, the device may contribute to the significant fluctuations of pressure resulting from the difference between the operating pressures for low and high resistance—similar to that described for the Orbis-Sigma Valve. Moreover, it may not prevent the overdrainage related to nocturnal vasomotor pressure waves, as often reported in paediatric cases. These reservations, based on our short laboratory study, should be taken into consideration both by neurosurgeons and the manufacturer. Whether they cause system malfunction under specific clinical conditions remains to be shown. We advocate a well-controlled multicentre study on this new and interesting device together with in vivo measurements of shunt function using a CSF infusion test during tilting.

ZOFIA CZOSNYKA
MAREK CZOSNYKA
JOHN D PICKARD

The UK Shunt Evaluation Laboratory, Academic Neurosurgical Unit, Addenbrooke’s Hospital, PO Box 167, Cambridge CB2 2QQ, UK

correspondence: The UK Shunt Evaluation Laboratory, Academic Neurosurgical Unit, Addenbrooke’s Hospital, PO Box 167, Cambridge CB2 2QQ, UK

Convulsions induced by donepezil

Donepezil, a centrally acting acetylcholinesterase inhibitor, has been recently introduced for the symptomatic relief of cognitive impairment in patients with mild to moderate Alzheimer’s disease. Several adverse events thought to be related to donepezil have been reported so far, the most common ones being gastrointestinal disturbances due to cholinomimetic effects of donepezil.1 Convulsions have not been reported for donepezil to date. We report on a patient with mild Alzheimer’s disease who presented with convulsions during treatment with donepezil.

The patient was a 72-year-old man, ApoE4 homozygous, who was diagnosed with dementia of probable Alzheimer’s type (NINCDS-ADRND criteria) 14 months previously. His medical history, with the exception of non-familial dementia, was unremarkable and his only medication was 100 mg aspirin daily. His mini mental state examination score was 22 points. He was treated with 5 mg donepezil once daily for 2 weeks, and then 10 mg a day for 23 days, after which he was admitted due to convulsions. The patient was unconscious for 40 minutes with urinary incontinence and bitten tongue. Blood analyses were normal. A contrast brain CT showed a mild degree of cortical atrophy with no structural lesions. EEG showed mild and diffuse neuronal dysfunction with the absence of grafoelements indicative of epilepsy. No further treatment was discontinued and no other therapy was instituted. Six weeks later 5 mg donepezil once daily was restarted. On day 52 of donepezil treatment the patient’s caregiver had reported loss of consciousness and convulsions in our patient. The donepezil was discontinued and 100 mg indomethacin a day was prescribed. For the subsequent 8 months the patient has been convulsion free and his current mini mental state examination score is 15.

Convulsions in Alzheimer’s disease are rare until late in the illness, when up to 5% of patients reportedly have infrequent seizures.2 We think that convulsions reported in our patient could be due to donepezil. It has already reported that some centrally acting cholinesterase inhibitors—that is, tacrine, varenicline, and physostigmine—might induce convulsions in patients with Alzheimer’s disease. The mechanism of convulsive action of acetylcholinesterase inhibitors is not clear. As donepezil seems a useful drug in some of the carefully selected patients with mild to moderate dementia of Alzheimer’s type, we think that this report will extend our knowledge of donepezil’s safety profile.


Severe toxic neuropathy due to fibrates

The main adverse effects of lipid lowering agents in the fibrate family involve the gut, the skin, the liver, the blood, and the muscular system. Some of these complications are more frequent when renal failure exists.3 Here we report a case of neuropathy secondary to long term use of fenofibrate in a patient without renal failure taking recommended doses. A 60 year old man was seen in September 1996 complaining of leg pain for 6 months. His relevant medical history included coronary artery disease treated for 10 years with 6 mg molsidomine/ day and 60 mg isosorbide dinitrate/ day, high blood pressure and hyperlipidaemia treated respectively with 100 mg atenolol/ day and 1000 mg fenofibrate/day for the past 5 years. He complained of parasthesias along the posterior aspect of both thighs, later complicated by progressive muscle weakness. The physical examination disclosed a patient incapable of standing on his toes or heels. No proximal muscle weakness was present. The deep tendon reflexes were reduced in all limbs. There was no sensory loss to light touch, vibratory sense, pain perception, and joint position sense. There was no disturbance of sphincter control or postural fainting and no impairment of potency to suggest dysautonomia. The rest of the physical examination was within normal limits. The EMG suggested an axonal sensory motor neuropathy with reduced amplitude of nerve action potentials without any significant slowing of conduction velocity. There were spontaneous fibrillations in the right tibial anterior muscle. The complete blood cell count, erythrocyte sedimentation rate, fibrinogen, C reactive protein, and serum protein electrophoresis were normal. Muscle enzymes were normal. Immunological studies (antinuclear factor, serum and urinary immunoelectrophoresis, circulating immune complexes, serum complement, ANCA) were non contributive. Antipancreatic polyclonal antibodies and antiglycolipid antibodies were not detected. Two CSF examinations were performed: the CSF contained 1 white cell/mm³, the protein concentration was 65 mg/dl, the glucose concentration was 2.5 mmol/l. Accessory salivary gland biopsy eliminated amyloidosis, sarcoidosis, and Gougerot-Sjögren’s syndrome. Nerve biopsy confirmed axonal disease and disclosed a focal perivascular infiltration of lymphocytes and monocytes infiltrate without vasculitis. No ultrastructural study was performed. An adverse drug effect was suggested in May 1997 and fenofibrate was discontinued. Three months later the patient indicated improvement in the distance he could walk. In December 1997, he no longer complained of myalgia. Improvement in motor function was apparent; the patient could now stand on his toes and heels without help. Axonal sensorimotor neuropathy was confirmed in this case by electrophysiological and histological findings. Other common causes of axonal neuropathy were excluded and a toxic cause was considered.4 Because the patient had been receiving all of his medications well before the beginning of the clinical manifestations, there was no chronologically argument targeting any one drug in particular. However, a review of the literature suggested fenofibrate as the causative agent as neuropathies have been described after treatment with clofibrate and bezafibrate.5–7 In addition, none of the other drugs he was taking have been associated with neuropathy. The role of fenofibrate was confirmed by regression of the symptoms after discontinuation of this drug without the addition of any other treatment. There are no previous reports of histological findings in neuropathy due to fibrates. The delay between initial treatment with fenofibrate and the appearance of the symptoms as well as the time required for them to regress, suggest a cumulative toxic effect but no other predisposing risk factor such as high dosage or renal failure was present.

In conclusion, fibrates can be responsible for neuropathies even when given in approved doses and in the absence of renal failure. 1 Peres Guardiola, 2 boulevard Tonnelle, 37044 Tours Cedex, France
Correspondence to: Dr P Corcia, Clinique Neurologique, CHU Bretonneau, 2 Bd Tonnelle, 37044 Tours Cedex, France. Fax 0033 2 47 47 38 08; email corcia@med.univ-tours.fr

Macs with multiple sclerosis

Rothwell and Charlton8 have suggested that Scottish ancestry is associated with an increased susceptibility to multiple sclerosis. They make the novel observation that a higher than expected proportion of patients with multiple sclerosis had Scottish surnames as defined by the prefix Mc or Mac. They quote that the percentage of patients with multiple sclerosis in the Highlands and Islands with a surname of Mc or Mac is 22.6%. They then suggest that this is the percentage with Mc or Mac in Orkney and Shetland but these islands are not part of the Highlands and Islands. In Orkney and Shetland, in fact, only 3.5% of the population have a surname beginning with Mc or Mac, which is much lower than the percentage in north east Scotland—namely 7.5%.

Rothwell and Charlton do make the point, however, that an increase in the proportion of surnames prefixed with Mc or Mac with latitude within Scotland is not associated with an increase in the prevalence of multiple sclero-

The main adverse effects of lipid lowering agents in the fibrate family involve the gut, the skin, the liver, the blood, and the muscular system. Some of these complications are more frequent when renal failure exists. Here we report a case of neuropathy secondary to long term use of fenofibrate in a patient without renal failure taking recommended doses. A 60 year old man was seen in September 1996 complaining of leg pain for 6 months. His relevant medical history included coronary artery disease treated for 10 years with 6 mg molsidomine/ day and 60 mg isosorbide dinitrate/ day, high blood pressure and hyperlipidaemia treated respectively with 100 mg atenolol/ day and 1000 mg fenofibrate/day for the past 5 years. He complained of parasthesias along the posterior aspect of both thighs, later complicated by progressive muscle weakness. The physical examination disclosed a patient incapable of standing on his toes or heels. No proximal muscle weakness was present. The deep tendon reflexes were reduced in all limbs. There was no sensory loss to light touch, vibratory sense, pain perception, and joint position sense. There was no disturbance of sphincter control or postural fainting and no impairment of potency to suggest dysautonomia. The rest of the physical examination was within normal limits. The EMG suggested an axonal sensory motor neuropathy with reduced amplitude of nerve action potentials without any significant slowing of conduction velocity. There were spontaneous fibrillations in the right tibial anterior muscle. The complete blood cell count, erythrocyte sedimentation rate, fibrinogen, C reactive protein, and serum protein electrophoresis were normal. Muscle enzymes were normal. Immunological studies (antinuclear factor, serum and urinary immunoelectrophoresis, circulating immune complexes, serum complement, ANCA) were non contributive. Antipancreatic polyclonal antibodies and antiglycolipid antibodies were not detected. Two CSF examinations were performed: the CSF contained 1 white cell/mm³, the protein concentration was 65 mg/dl, the glucose concentration was 2.5 mmol/l. Accessory salivary gland biopsy eliminated amyloidosis, sarcoidosis, and Gougerot-Sjögren’s syndrome. Nerve biopsy confirmed axonal disease and disclosed a focal perivascular infiltration of lymphocytes and monocytes infiltrate without vasculitis. No ultrastructural study was performed. An adverse drug effect was suggested in May 1997 and fenofibrate was discontinued. Three months later the patient indicated improvement in the distance he could walk. In December 1997, he no longer complained of myalgia. Improvement in motor function was apparent; the patient could now stand on his toes and heels without help. Axonal sensorimotor neuropathy was confirmed in this case by electrophysiological and histological findings. Other common causes of axonal neuropathy were excluded and a toxic cause was considered. Because the patient had been receiving all of his medications well before the beginning of the clinical manifestations, there was no chronologically argument targeting any one drug in particular. However, a review of the literature suggested fenofibrate as the causative agent as neuropathies have been described after treatment with clofibrate and bezafibrate. In addition, none of the other drugs he was taking have been associated with neuropathy. The role of fenofibrate was confirmed by regression of the symptoms after discontinuation of this drug without the addition of any other treatment. There are no previous reports of histological findings in neuropathy due to fibrates. The delay between initial treatment with fenofibrate and the appearance of the symptoms as well as the time required for them to regress, suggest a cumulative toxic effect but no other predisposing risk factor such as high dosage or renal failure was present.

In conclusion, fibrates can be responsible for neuropathies even when given in approved doses and in the absence of renal failure.
sis. Indeed this is borne out by the prevalence figure for the Western Isles of Scotland of only 81 per 100 000, which is one of the lowest prevalence rates found in the United Kingdom and yet these islands have the highest percentage of Scottish surnames.

DAVID I SHEPHERD
Department of Neurology, North Manchester General Hospital, Crumpsall, Manchester M8 6BZ, UK


High incidence and prevalence of multiple sclerosis in south east Scotland: evidence of a genetic predisposition

We read with interest the results of Rothwell and Charlton regarding the incidence and prevalence of multiple sclerosis in south east Scotland.1 They have identified standardised multiple sclerosis prevalence rates for the Lothian and Border Regions of 203 and 219 per 100 000 respectively, the results challenging the assertion made by Del Brutto that the apparent step in the prevalence rates found in the United Kingdom might come from a prevalence study of multiple sclerosis in Northern Ireland.2 This is evident and indisputable world wide. However, he is correct to point out that the prevalence of multiple sclerosis in south east England are still considerable. This is supported by major differences in the HLA types of the two populations.3 Contrary to Shepherd’s assertion, the Highlands and Islands telephone book does include Orkney. However, he is correct to point out that the prevalence of surnames pre-fixed with Mc or Mac is indeed lower on Orkney than in the region as a whole.

Further insights into the high prevalence of multiple sclerosis in the north of the British Isles might come from a prevalence study which is currently being planned on the Isle of Skye.

P M ROTHWELL
Department of Clinical Neurology, Radcliffe Infirmary, Woodstock Road, Oxford OX2 6HE, UK


Abendazole therapy for subarachnoid cysterci: clinical and neuroimaging analysis of 17 patients

By contrast with the weaknesses of anecdotal observations from case series, the power of randomised clinical trials for deciding the benefit of therapy has become increasingly evident and indisputable world wide. Nowadays, to argue against the validity of this assertion may seem superfluous; however, a recent paper reported by Del Brutto2 regarding treatment in neurocysticercosis ignores basic procedures for well performed clinical trials by using inappropriate and misleading methodology to evaluate medical therapy.

By definition, a clinical trial is a prospective study comparing the effect and value of treatment against a control in human subjects. The main drawback of Del Brutto’s report is that it does not include a control group against which the intervention group is compared; therefore, its results are definitely flawed. Additionally, a basic experimental study design requires at least specification of inclusion and exclusion criteria, randomisation, and definitions of response or outcome variables. This information is not provided by Del Brutto’s report; its design fails to protect against potential bias in patient selection or evaluation of outcome. The definition of subarachnoid cysterci used by Del Brutto was based on “appearance on CT of hypodense cystic lesions located over the cerebral hemispheres, the Sylvian fissure, or the CSF cisterns at the base of the brain”. It is well known that there are many other diagnostic possibilities to be considered in the differential diagnosis of subarachnoid hypodense lesions.2,3 Besides, CT is not a reliable procedure for diagnosing subarachnoid cysterci, as is MRI. In fact, we cannot be completely sure, for example, that the CT image shown in the report really corresponds to subarachnoid cysterci. If we were to use MRI on this patient, they might correspond to a parenchymal cyst which resolved as a reflection of the natural history of the condition. Therefore, Del Brutto objectively confirms or rejects this assertion.

Del Brutto’s report1 maintains that evaluation of the therapeutic response to albendazole included comparison of the size of the cysts, as well as clinical parameters, before and after treatment. To consider the size of cysts as a response variable is certainly useless because of the obvious difficulties in measuring cyst size in the subsequent follow up CT. It is also widely accepted that the clinical manifestations of neurocysticercosis are polymorphic, and their clinical course is unpredictable; therefore, the clinical manifestations as an outcome variable is entirely biased. Another personal appreciation of Del Brutto is that albendazole reaches high concentrations in CSF, and has been used with success in some patients with subarachnoid cysterci; nevertheless, studies used “support of the presumption” as is MRI. In fact, we cannot be randomised or blinded, having historical control groups or patients who served as their own control, and regarding clinical evaluation as an outcome variable. Whereas it is generally assumed that albendazole is effective treatment for neurocysticercosis, a critical review of the literature4 suggests that the studies on which these assumptions are based are defective in terms of patient selection, assignment to treatment, and selection and measurement of outcome variables. Many authors have warned that this therapy in some patients might sometimes be harmful, particularly in the initial localisation, because some patients have developed arteritis and hydrocephalus after the administration of antihelminthic drugs.5 According to these authors a parasite may be easily removed surgically before an inflammatory reaction develops.6 A randomised clinical trial of treatment of neurocysticercosis7 considers the question of to what extent and in which patients treatment with either praziquantel or albendazole is effective. The improvement attributed to these drugs in several studies may be related to the lack of appropriate controls and is likely to be a reflection of the natural history of the condition. The authors point
out the need to conduct a long term, placebo controlled trial with precise end points, proper randomisation, sample size calculations, and predetermined statistical calculations, to evaluate properly the effectiveness and determine the indications of aetiological treatment for neurocysticercosis.

In the era of evidence-based medicine, we neurologists and general practitioners should be demanding regarding use of sound scientific information with methodological rigour for improving our clinical decision making. Medical information from reports that do not conform to the minimal requirements of a clinical trial should be avoided.

A CARPIO
University of Cuenca School of Medicine, PO Box 0101–719, Cuenca, Ecuador.

Correspondence to: Professor A Carpio, University of Cuenca School of Medicine, PO Box 0101–719, Cuenca, Ecuador.


The author’s reply:
I celebrate the rigid academic standards of Carpio’s medical practice, but wish there were matched with knowledge on the available literature on albendazole therapy for neurocysticercosis. That albendazole actually has a cysticidal effect is beyond all doubt.1 The drug has been used to treat patients with neurocysticercosis since 1987, and physicians who are familiar with the disease know that it is effective. Moreover, the single study in which albendazole has not been useful for adults, the cortical parenchymal brain cysticerci—published by Carpio et al—has been questioned due to inaccurate recollection of data.2 In our study, we did not attempt to verify the cysticidal effect of the drug (it has already been demonstrated) but to document if albendazole could also be useful in a severe form of neurocysticercosis that has been associated with a grim prognosis.3 Under these circumstances, it is not ethical to deprive a group of patients of a safe and inexpensive treatment just for the sake of science. In addition, Carpio’s concerns about the criteria we used for the diagnosis of subarachnoidal cysticerci are more typical of those who are not familiar with the disease. The problem with CT is that this imaging method may overestimate the number of cysticerci detected. This work has gathered pace and over the past 10 years, peripheral neuropathies have been described in association with specific antiganglioside and antiprotein antibodies.4

Alongside this expansion of interest in the immunology of peripheral nerve disorders, new infective neuropathies have emerged such as those due to HIV and Lyme disease, first recognised in 1993.5 It is an appropriate time then for this authoritative text on immune mediated neuropathies. The scope of the book is wide, including scientific overviews of immune interactions in the peripheral nervous system as well as pragmatic accounts of the use of immunosuppressant drugs and the management of neuropathic pain. The inflammatory demyelinating and axonal neuropathies are comprehensively surveyed, as well as more difficult entities such as the post-polio syndrome and the rare toxic inflammatory neuropathies. The dry review of silicone neuropathies and myeloma was noted in the 1930s and that with an IgM monoclonal gammapathy was reported in the 1960s.6 Twenty years later IgM antibodies were found that were directed against myelin associated glycoprotein. This work has gathered pace and over the past 10 years, peripheral neuropathies have been described in association with specific antiganglioside and antiprotein antibodies.7

BOOK REVIEWS


Ever since the landmark overview “Do stroke units save lives?”9 the momentum behind the organisation of stroke sevices has inexorably increased. Within this concise paperback of seven chapters and 112 pages, written in the main by Langhorne and Dennis on behalf of the Stroke Unit Trialists Collaboration, lies a detailed, evidence-based, and critical summary of the arguments for stroke units. The authors lead the reader in a logical fashion through the steps necessary to critically appraise and assimilate available evidence into a systematic review. Basic but often overlooked general principles such as sources of bias are discussed in detail as well as matters relating more specifically to stroke such as outcome measurement.

Particularly helpful are the chapters on the economics of stroke units and the implications for service planning in which the available evidence has been used to suggest a model for how and at what cost (in fact an overall saving) stroke units might be developed. This comprehensively referenced book will be read by members of all disciplines involved in stroke care. If I was about to ask for fund-

This is a handsome and liberally illustrated guide to the success and frozen section diagnosis in neuropathology. This aspect of practice remains a central part of a clinical neuropathologist’s role and this book can be recommended to trainees and practitioners for its wealth of illusional and pedagogically oriented text. It is particularly useful to see a wide range of appearances for each tumour illustrated—for example, 20 figures illustrating metastatic tumours, 13 illustrating pituitary adenomas, and 38 illustrating various grades of astrocytic tumours. This enables the less readily diagnosed examples to be considered as well as more typical varieties. Typical varieties tend to be the only ones illustrated in a less specialised text. There are 18 chapters that cover each of the main types of tumour encountered as well as providing advice on making and interpreting smears and dealing with lesions that do not smear well. The emphasis is on using smears as standard preparations with frozen sections as back up when required—a procedure that is probably adopted in most neuropathology departments.

The success of a book like this depends crucially on the quality of the photographs. These are, appropriately, all in colour. Many are of excellent quality. Some are intentionally obscure—for example, to make the point that desmoplastic carcinomas may be too tough to examine in smears (fig 18.1). A few have rather poorly defined features and these tend to be illustrations of frozen sections which inevitably lack the crispness of smears. However, even these illustrate the points intended. The legends to the figures are full enough to avoid the need for arrows that might otherwise have obscured the images. There is a useful index, but the book would have benefited from more references—I found only six. Smear diagnosis is best learnt by doing it, with a sympathetic, experienced colleague at one’s elbow. Often this condition cannot be fulfilled and I would strongly recommend this book as a very valuable alternative or adjunct.

MARGARET ESIRI


Tethered spinal cord comprises a group of dysraphic conditions in which the conus medullaris is located in an abnormally low position. Tethered cord syndrome is stretch induced symptoms manifested by motor and sensory deficits in the lower limbs and incontinence, and is often associated with musculoskeletal deforming bones. This book draws together all aspects of the embryology, pathophysiology, diagnosis, and treatment of this rare but important condition in a detailed but readable format. Inevitably there is repetition but this is unavoidable in a multi-author text in which each chapter can be read as a whole. The text is well illustrated with diagrams, clear radiological images, and selected clinical photographs.

The chapter on pathophysiology of the tethered spinal cord is a fascinating summary of the various experimental studies that have been undertaken in this condition. Although the relevance of some of the models to the condition may be questioned one cannot help but admire the ingenuity and inventiveness of the investigators. Acute traction on the spinal cord has been shown to be associated with impairment of evoked potentials, reduction in spinal cord blood flow, and changes in glucose metabolism. Chronic experiments have shown recovery in neurological deficits after 9 months.

There are well written chapters on diagnosis, investigation, and surgical treatment with plenty of intraoperative details. The final chapter considers controversies associated with the treatment of the tethered cord syndrome. Most neurosurgeons would now agree that surgical treatment is definitely indicated in patients with progressive neurological deficits and most are increasingly prepared to consider prophylactic surgery in patients with tethering but in whom neurological deficits are absent or established. Although urodynamical testing helps to identify patients with neurogenic bladders, urinary dysfunction may be intermittent and symtomatic tethering may not always be disclosed. A tethered spinal cord is prone to produce problems during periods of rapid growth in childhood, but even when growth is complete patients with an undiagnosed tethered cord may undergo serious deterioration if subjected to sudden flexion movements associated with trauma. A selection process is outlined to help decide treatment in four main categories of presentation. Unfortunately the algorithm can be difficult to interpret—for example, “fluctuating signs and symptoms noted in a patient with stable neurological deficits must be followed closely for detection of minor progression”.

A useful book which I would recommend to all doctors who treat patients with spinal dysraphism and I suspect that many will wish to have a copy in their personal collection.

R LAING


Do you find conference dinners a dull ordeal? Fear no longer! You can sparkle with amusing clinical anecdotes taken from this comprehensive collection. Amaze your colleagues with tales of seizure induced religious conversion or of the patient who ate lunch at his work canteen, had an amnestic seizure, and went to eat another one. He obviously didn’t work in the NHS. Tickle them with the patient for whom safety pins triggered a pleasurable aura that he favoured over sexual intercourse. At last I understand the punk movement.

But what if you want a detailed evaluation of the diagnosis and management of partial seizures and the psychiatric disorders associated with epilepsy? You can find brief chapters adequately covering these issues, but you can read about them in any one of several previous volumes on the subject or in the big, bulky text of epilepsy you use on hot summer days to hold the door open. In this book you can learn about the patient who sang rap music during her seizure—no doubt now residing on Sunshine Boulevard. Or the woman who experienced sexual arousal during her seizures and made excessive demands of her husband until a parietal tumour was removed (from her).

The cases in this book are collected from a wide search of the literature and start with the famous Dr Z. They include ictal and interictal manifestations and are totally delightful. They make this book a good read. These bizarre mental manifestations of epilepsy provide an opportunity to explore mind-brain relations that is sadly missed by the author. Some controversial issues are covered, such as ictal violence, but if you want a detailed clinical manual, look elsewhere. As a source of anecdotal cases for lectures, this book is ideal.

MARK MANFORD


