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 highly educated, ApoE4 homozygous, 72 year old man, who was diagnosed with dementia of probable Alzheimer's type (NINCDS-ADRND criteria) 14 months previously. His medical history, with the exemption 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 when 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. Donepezil 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 19.

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, velnacrine, and physostigmine³⁻⁵ 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.

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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.¹ Here we report a case of neuropathy secondary to long term treatment with 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 200 mg fenofibrate/day for the past 5 years. He complained of paresthesias 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, vibration 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 sensorimotor 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 and immunological studies (antinuclear factor, serum and urinary immunoelectrophoresis, circulating immune complexes, serum complement, ANCA) were negative. Antiparaneoplastic 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 inflammatory lymphocytic 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 an 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.² Because

the patient had been receiving all of his medications well before the beginning of the clinical manifestations, there was no chronological 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.³⁻⁵ 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.

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CORRESPONDENCE

Macs with multiple sclerosis

Rothwell and Charlton¹ 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 the population 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 sclerosis.

sis. Indeed this is borne out by the prevalence figure for the Western Isles of Scotland² 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.

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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 theory that the high prevalence rates previously reported in Scotland are peculiar to the north east and its offshore islands. The authors postulate that the apparent step in prevalence rates between England and Scotland may be due to the distinctive Celtic ancestry of the Scottish population as can be crudely measured by surnames prefixed with Mc or Mac.

In Northern Ireland we have also identified a much higher prevalence rate for the disease than exists in England and Wales and have speculated that the similar rate to that in Scotland is at least partly a function of the common ethnic origins of the two populations.² The contiguous region of Coleraine, Moyle, Ballymena, and Ballymoney lies less than 20 miles from Scotland at its closest point and has a standardised prevalence rate for all multiple sclerosis, based on the 1961 census population for Northern Ireland,³ of 230 (95% confidence interval (95% CI) 207-256) per 100 000. Using a similar method to Rothwell and Charlton (British Telecom phone book of the area), 17% of the study population had a surname prefixed with Mc or Mac and it is of note that 22.9% of prevalent cases had such a surname prefix (odds ratio = 1.46, 95% CI 1.09-1.93, $\chi^2=6.82$, $p=0.009$).

Our results support the conclusion of Rothwell and Charlton that Celtic ancestry is a risk factor for multiple sclerosis and confirm the existence of a step in multiple sclerosis prevalence in the British Isles between England/Wales and Scotland/Northern Ireland.

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The author's reply:

The study of the prevalence of multiple sclerosis in Northern Ireland by McDonnell and Hawkins is interesting.¹ The findings are similar to those of the recent study in south east Scotland.² Both studies suggest that there is an increased prevalence of multiple sclerosis in the north of the British Isles compared with the south. It seems likely, as McDonnell and Hawkins suggest, that this at least partly reflects differences in the genetic susceptibility of the respective populations.

The south east Scotland study did, as Shepherd suggests, attempt to link the high prevalence of multiple sclerosis to Scottish ancestry. However, the study used a standard text of several hundred surnames which are considered to have originated in Scotland,³ rather than just those prefixed with Mc or Mac. This is obviously still a very crude approach to the problem, but any bias is likely to have weakened rather than strengthened the association. The proportion of cases in the telephone book with a surname pre-fixed with Mc or Mac was simply used as a crude illustration of the fact that the differences in apparent ancestry between the Scotland and England are still considerable. This is supported by major differences in the HLA types of the two populations.⁴ 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.

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Albendazole therapy for subarachnoid cysticerci: 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 Brutto¹ 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 treat-

ment 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 minimal information regarding 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 cysticerci used by Del Brutto was based on "appearance on CT of hypodense cystic lesions located over the convexity of 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 cysticerci, as is MRI. In fact, we cannot be completely sure, for example, that the CT images shown in the report of Del Brutto correspond to subarachnoid cysticerci. 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. There is no evidence that 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 evaluation of patients 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 Brutto¹ is that albendazole reaches high concentrations in CSF, and has been used with success in some patients with subarachnoid cysts; nevertheless, studies used as support¹ of this presumption are similarly flawed in that they are not 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 literature^{3,4} 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 subarachnoidal localisation, because some patients have developed arteritis and hydrocephalus after the administration of antihelminthic drugs.³ According to these authors a parasite may be easily removed surgically at a cystic stage before an inflammatory reaction develops.³ A randomised clinical trial of treatment of neurocysticercosis⁴ 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