conscious but appeared unable to move or co-ordinate her limbs. Severe rigidity and increased muscle tone was observed in all four limbs, predominantly the extensor muscle groups. Myoclonic jerks, twitching of all muscle groups and profound diaphoresis were observed. The patient was hyperpyrexial (40.6°C) and had a tachycardia (110 to 130 beats per minute). The rest of the examination was entirely normal. Specifically, the blood pressure was recorded as 100/70 mm Hg throughout the examination and there was no evidence of cardiac failure. Laboratory investigations, chest radiograph, electrocardiography and blood tests (full blood count, glucose, hepatic enzymes, urea, electrolytes, calcium and magnesium levels) were all within normal limits. A toxicology screen confirmed the presence of tricyclic antidepressants (TCA) and benzodiazepines in the blood.

The patient was paralysed with 4 mg pancuronium and was sedated with 10 mg diazepam both administered intravenously. Immediately following relaxation of the musculature the temperature decreased. Dantrolene sodium, at a dosage of 20 mg was administered 15 minutes later but by this time the temperature had already decreased to 39°C and became normal within 2 hours. Within 3 hours the patient was able to move all limbs and the following morning she was extubated. She had no residual neurological deficits after 16 hours.

The clinical presentation in this case report was not typical of the neuroleptic malignant syndrome which develops over 24–72 hours and resolves only 5 to 7 days after discontinuing the offending neuroleptic agents.¹ In addition, hyperthermia, hyper-tonicity and fluctuating levels of consciousness are invariably accompanied by instability of the autonomic nervous system, specifically blood pressure fluctuations. The rapid onset and recovery of symptoms in our patient and the stable blood pressure that she manifested made this diagnosis unlikely.

The more commonly recognised side effects of MAOI include severe hypertension, orthostatic hypotension, mania, anxiety and convulsions in patients with epileptic foci.^{1,2} Increased neuromuscular activity, muscle twitching and gross involuntary movements can occur when large doses of MAOI are administered.² Other symptoms which may take up to 12 hours to develop consist of agitation, rigidity and hyperpyrexia.^{1–3} Less well known are the rare hyperthermic reactions occasionally seen when synthetic narcotic drugs or tricyclic antidepressants are given with MAOI.² Guzé and Baxter¹ also described

drug interactions with MAOI inhibitors as causing a syndrome with some similarities to the neuroleptic malignant syndrome. The administration of tricyclic antidepressants in therapeutic doses in combination with MAOI in therapeutic doses may cause seizures, hyperpyrexia and death. These severe reactions including death are usually associated with drug overdosages but have been described when MAOI and small doses of imipramine,^{4–6} clomipramine,⁷ desipramine,⁸ or amitriptyline⁸ have been combined.

Our patient may have manifested her symptoms as a result of the MAOI tranylcypromine alone. However, only a small dose (40 mg) of tranylcypromine was ingested. The symptoms are more likely to have been caused by drug interactions. The hyperpyrexia in this patient appeared to be caused by muscle hyperactivity and responded promptly to paralysis and ventilation. It is obviously difficult to be certain which drug interacted with the MAOI but it appears most likely to have been clomipramine (a tricyclic antidepressant) or possibly trazadone.

When drug combinations of MAOI and tricyclic antidepressants are required for refractory depressions, it appears preferable to limit these combinations to those tricyclic antidepressants which have not been associated with adverse reactions. These drug combinations have been employed with very good results⁵ but, because of the potentially lethal side effects, they should only be used in exceptional circumstances when all else has failed.

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Carbamazepine induced vasculitis

Sir: Adverse effects due to carbamazepine occur in up to 25% of treated patients.^{1,2} Hypersensitivity reaction comprise about 5% and include skin rashes, agranulocytosis, fever and abnormal liver function tests.³ Skin involvement complicating carbamazepine therapy is usually manifested by a variety of dermatoses including maculopapular, urticarial, erythematous and pruritic rashes.¹ Lupus erythematosus-like diseases,⁴ exfoliative dermatitis⁵ and Stevens-Johnson syndrome⁶ have been reported rarely. Carbamazepine, as a cause of cutaneous vasculitis, is extremely uncommon.⁷ We describe a patient who developed hypersensitivity leukocytoclastic vasculitis, following the administration of carbamazepine.

A 66 year old man had suffered from trigeminal neuralgia for several months. Carbamazepine, 200 mg three times daily, was prescribed. Three weeks after initiation of therapy, he noticed a pruritic rash over the left leg which spread rapidly and was associated with a high grade fever. The patient had mild hypertension, treated by α -methyl dopa 250 mg bd for the previous 5 years.

On admission he appeared very ill and had peripheral cyanosis. The temperature was 39.8°C, pulse rate 104 min, blood pressure 140/90 mm Hg. A confluent purpuric rash was observed on the trunk and limbs without involvement of the mucous membranes (fig 1). The heart and lungs were normal. The liver was not palpable and the spleen was palpable 1 cm below the costal margin. Relevant laboratory findings were: erythrocyte sedimentation rate 38 mm after one hour (Westergren), urinalysis 2+ protein and 20–25 red blood cells per high power

Fig 1 Lower extremities of the patient showing multiple confluent purpuric lesions.

Fig 2 Skin biopsy showing typical leukocytoclastic vasculitis. The walls of the small blood vessels are infiltrated by polymorphonuclear leukocytes and nuclear debris. (Haematoxylin and eosin $\times 380$.)

field, white blood count 10900mm^3 with eosinophilia of 1760mm^3 , haemoglobin 16g/dl and platelets 167000mm^3 . Blood coagulation tests and liver function tests were normal. Blood urea was 8.6mmol/l , creatinine $141\mu\text{mol/l}$ and creatinine clearance 41ml/min . Rheumatoid factor, antinuclear antibodies, cold agglutinins, hepatitis B surface antigen and antibodies were not detected. Heterophil antibodies, Weil-Felix, Widal reactions as well as antibodies to brucella, rickettsia, cryoglobulin and cryofibrinogen, serum complement (C_3) and immunoelectrophoresis were all normal or negative. IgG antibodies to Epstein-Barr virus, cytomegalovirus and antistreptolysin 0 were positive in low titres without clinical evidence of recent infection. Urine, throat and blood cultures were sterile. Electrocardiogram, chest radiography and a bone marrow aspiration were normal. Skin biopsy (fig 2) revealed the classical picture of leukocytoclastic vasculitis with massive infiltration of polymorphonuclear cells around the small blood vessels of the dermis, haemorrhages and karyorrhexis. Direct immunofluorescence microscopy demonstrated deposits of C_3 and IgG in the small dermal vessels. Carbamazepine was discontinued and the patient was treated with

hydrocortisone 300mg/day intravenously which resulted in a gradual improvement of his general condition. The purpura resolved within 3 months. Rechallenge was not performed because of the severity of the reaction associated with the drug.

McCoombs⁸ reviewed 72 cases of systemic allergic vasculitis of whom 26 were related to drugs; none of the patients had received carbamazepine. Cluff⁹ and Gammon¹⁰ did not include carbamazepine in the list of drugs causing vasculitis. Mullick *et al*⁷ described one case of carbamazepine vasculitis which was fatal and involved the skin, heart, liver, kidneys, lungs and the central nervous system.

The patient described above developed non-thrombocytopenic purpura with histological features of leukocytoclastic vasculitis during treatment with carbamazepine. The skin lesions appeared 3 weeks after initiation of treatment and disappeared after its cessation. Although the patient received α -methyl dopa as well, it is highly unlikely that it played any aetiological role in this disease since the drug had been taken for more than 5 years and was continued in spite of the appearance of the purpura.

The most common drugs incriminated in the aetiology of leukocytoclastic vasculitis

are: penicillin, sulfonamides, phenothiazine, propylthiouracil, allopurinol, procainamide and iodides.⁹

It is suggested that drug induced vasculitis results from depositions of immune complexes in the vessel walls with the drug or its metabolites acting as the antigenic stimulus.¹¹ Our patient, as well as patients reported by others,^{7 12 13} had deposits of C and IgG in the blood vessel walls, which may play a role in the production of vascular damage. Other manifestations presented by this patient including fever, hematuria, eosinophilia, and a good response to steroid therapy, support the immunological aetiology of the disease.

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Matters arising

Visual evoked potentials and pattern electroretinograms in Parkinson's disease and control subjects

Sir: We read with interest the report by Nightingale *et al*¹ on visual evoked potentials (VEPs) and electroretinograms in Parkinson's disease. In that study two checkerboard stimuli, respectively with checks of 25' and 50' angular subtense, over a central field (17° × 14° in size) were presented to 36 patients with idiopathic Parkinson's disease. Inter alia, it was found that "the latency of the P100 and N150 components were not significantly different between the Parkinson's disease patients and control subjects at either check size".

This result contributes to the controversy on the existence of VEP latency abnormalities in Parkinson's disease. In fact, while some authors refer to the occurrence of significantly delayed P100 to sine-wave gratings,²⁻⁴ depending on spatial frequency,⁴ others did not find changes in the latency of P100, generally to checkerboard presentation.⁵⁻⁷

Nightingale *et al*¹ quoting our suggestion⁸ that checkerboard might be less effective than grating to identify visual changes due to Parkinson's disease, pointed out that our two stimuli differed not only in pattern form but also in angular subtense and retinal field stimulated. In particular, they argued that under these conditions it would be very difficult to establish whether the two pattern forms have a different diagnostic yield per se.

It should be noted that our goal was to demonstrate that the possibility of obtaining a delayed P100 in a Parkinsonian patient is contingent upon the stimulus employed. We were so aware of the experimental limitations indicated by Nightingale *et al*¹ as to state that our data did not "presume to

answer the general question as to whether gratings are more effective than checkerboard".⁸ Accordingly, the effectiveness of the two pattern forms was investigated in a further study⁹ of which a brief account may be useful here.

Checkerboard (with checks of 55' angular subtense) and grating (with a spatial frequency of 2c/deg) were presented over different retinal areas, that is: (a) central area 10° wide; (b) central area 4° wide; (c) ring area with outer and inner diameters respectively of 10° and 4°. The average luminance was identical in all the stimuli, the dark elements presenting a luminance of 0.6 cd/m² and the light ones 30 cd/m². Stimuli had no light surround. VEPs were evoked monocularly by pattern reversal at a temporal frequency of 2 Hz. The investigation was carried out in nine patients with Parkinson's syndrome and in nine age matched controls; visual acuity was never less than 20/25. All the Parkinsonian patients were on medication with variable combinations of drugs. Individual latencies of P100 obtained for each stimulus condition were entered into a mixed design of analysis of variance. VEP latencies of Parkinsonians to checkerboard stimuli (55') did not differ from those of controls, although a tendency for the central 4° stimulus to yield a longer latency in the former group was noted. On the contrary, sine-wave grating yielded significantly delayed P100 in Parkinsonians in all the stimulus conditions. In order to assess the incidence of abnormal P100 latencies in Parkinsonian patients as a function of stimulus, the original data⁹ have been re-examined. Latencies were considered abnormal if they outweighed the cut-off value for each stimulus condition, expressed by the mean +1.83 times the SD (that is 95% of control population determined by using a one tailed *t* distribution). Abnormal P100 latencies to checkerboard (55') occurred in one out of 18 eyes (5.5%) with either 10° or 4° stimuli and in no instance with the ring stimulus. Abnormal

P100 latencies to sine-wave grating were found respectively in three eyes (16.7%) with the 10° stimulus, in nine eyes (50%) with the 4° stimulus and in seven (38.9%) with the ring.

Summing up, in Parkinsonian patients the grating has a greater diagnostic yield than checkerboard, no matter what the angular subtense and the retinal projection of the stimulus. However, foveal stimulation seems to be more efficient in identifying the presence of functional damage, irrespective of the stimulus used.

We feel that the low sensitivity of checkerboard in identifying visual changes occurring in Parkinson's disease should be considered when evaluating the results obtained by Nightingale *et al*.¹ This applies to the 50' element and probably also to 25' element checkerboard, although in this regard, the presence of a significant interaction of retinal field calls for further analysis.⁹

As to the main problem whether Parkinson's disease is associated with electrophysiological signs of visual dysfunction, it should be recalled that in multiple sclerosis the occurrence of VEP changes depend on the pattern employed^{10,11} so that only the use of different types of stimuli in the same patient enables a satisfactory assessment of visual function. We believe that such approach should be applied also to Parkinson's disease, particularly if one considers that the disorder seems to involve selectively some aspects of visual function, as processing of spatial,^{4,12} and temporal¹³ frequencies and foveo-perifoveal relationships.⁹ This would allow a better understanding of the visual impairment in Parkinsonians.

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