LETTERS TO THE EDITOR

Risperidone in levodopa induced dyskinesiae

Levodopa induced dyskinesiae represent a common complication of the chronic treatment of patients with Parkinson's disease.¹ Refining the schedule of levodopa administration and adding controlled release preparations of levodopa, or dopamine agonists, or both often prove insufficient to control these problems. Pharmacological agents which exert a mild antagonism on striatal dopamine receptors or modulate the dopamine systems by interacting with serotonergic pathways have recently shown beneficial effects in levodopa induced dyskinesiae.^{2,3}

Risperidone is a new, atypical neuroleptic drug with potent serotonin-5₂ and secondary dopamine-D₂ antagonist properties.⁴ It has antipsychotic effects with a low incidence of extrapyramidal side effects, a feature which makes this drug a candidate for the treatment of levodopa induced psychosis and dyskinesia in patients with Parkinson's disease. We have previously obtained beneficial effects with low dosages of risperidone in levodopa induced psychosis in patients with Parkinson's disease.⁵ Here we report our open experience with low dosages of risperidone in levodopa induced dyskinesiae.

Eight patients (five women, three men) with advanced Parkinson's disease, motor fluctuations, and levodopa induced dyskinesiae took part in the study. All gave informed consent. Clinical details were as follows: mean age 67.3 (range 57-81) years; mean Parkinson's disease duration 12.7 (8-20) years; Hoehn-Yahr stage in "off" phase: IV in five patients, III in three patients; mean duration of levodopa therapy 9.6 (range 6-14) years; duration of levodopa induced dyskinesiae 4.3 (range 2-7) years. All but one had peak dose dyskinesiae. The remaining patient had diphasic (beginning and end of dose) dyskinesiae. The risperidone dosages ranged from 0.125 to 0.25 mg once a day, at bedtime. The chronic antiparkinsonian treatment (levodopa/dopa decarboxylase inhibitors monotherapy in four patients; levodopa plus bromocriptine or pergolide in four patients) remained unchanged during the trial. The severity of parkinsonism and dyskinesiae was assessed at regular intervals during the trial using the unified Parkinson's disease rating scale (UPDRS; part III-motor scale)

and the abnormal involuntary movement scale (AIMS). All patients but one were evaluated during the period of maximum benefit from therapy ("best on" condition); the remaining patient, with diphasic dyskinesiae, was evaluated during the beginning of the levodopa effects. Patients were asked to fill in diaries at home with the number of hours spent in "on" and "off" conditions, but data were available only in a few cases and were not reported.

The table summarises the results. After risperidone therapy all the patients had moderate to pronounced reduction in dyskinesiae. These effects have been maintained during the follow up (mean 11 (range 6-21) months). The final AIMS score of the group was significantly lower compared to the baseline score ($P < 0.01$, Wilcoxon test). Three patients (2, 4, 6) took 0.25 mg risperidone/day with no modification of their parkinsonism. Three other patients (1, 3, 5) were unable to tolerate the initial 0.25 mg dosage owing to a worsening of parkinsonism (increase of number of hours spent in "off" conditions or worsening of "on" conditions) and their dosage was therefore reduced to 0.125 mg/day after some weeks. This produced a smaller improvement in the dyskinesiae with no great worsening of parkinsonism (table). One patient (7) received 0.125 mg risperidone/day from the beginning of the trial. The last patient (8), with diphasic dyskinesiae, received 0.25 mg risperidone/day for about one year, with considerable improvement in the dyskinesiae. Subsequently, owing to a worsening of parkinsonism, the risperidone dosage of this patient was reduced to 0.25 mg twice a week, although some improvement in dyskinesiae was maintained. The final UPDRS score of the group showed no significant changes when compared with the baseline score (Wilcoxon test) (table). No serious side effects were encountered during this risperidone trial.

The results of this open experience suggest that in some patients with Parkinson's disease low dosages of risperidone might have beneficial effects on levodopa induced dyskinesiae, without causing significant worsening of parkinsonism. In the light of the pharmacological properties of risperidone, both dopamine and serotonin antagonism might play a part in the effects we found on levodopa induced dyskinesiae. It has to be stressed that, owing to the extreme sensitivity of patients with Parkinson's disease to both the beneficial and undesirable effects of neuroleptic drugs, treatment with risperidone must be started with very low dosages (0.125 mg daily) and continued with caution. In conclusion, these results warrant larger, controlled studies to

test the therapeutic potential of risperidone in levodopa induced dyskinesiae.

GIUSEPPE MECO
EDITO FABRIZIO
ANDREA ALESSANDRI
NICOLA VANACORE
VINCENZO BONIFATI

Department of Neurological Sciences, Viale dell'Università 30, 00185 Roma, Italy.

Correspondence to: Dr G Meco, Department of Neurological Sciences, Viale dell'Università 30, 00185 Roma, Italy. Telephone 0039 6 49914706; fax 0039 6 49914840.

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Lack of association of a Taq 1 polymorphism of the human myelin oligodendrocyte glycoprotein gene with multiple sclerosis in a population of patients from the Southampton area

The lesions of multiple sclerosis are most often held to be caused by an immune attack on CNS myelin.¹ The nature of the antigens involved remains obscure, but peptides from at least two major myelin proteins—myelin basic protein and proteolipid protein—are known to cause cell mediated demyelination in animals (experimental allergic encephalomyelitis) which in some ways resembles human multiple sclerosis.¹ Minor myelin components may presumably also act as autoantigens. Myelin oligodendrocyte glycoprotein (MOG) is a quantitatively minor myelin protein localised to oligodendrocyte cell bodies and processes and to the outer layer of CNS myelin sheaths. Originally detected by a mouse monoclonal antibody to rat cerebellar glycoproteins, the amino acid sequence of MOG has been deduced from cDNAs of rat, mouse, human, and bovine species and shows a high degree of evolutionary conservation and sequence motifs identifying it as a member of the immunoglobulin superfamily. In common with several other members of this family, MOG has a membrane spanning domain and an extracellular glycosylated N-terminus and its presence on the outermost surface of myelin and the oligodendrocyte plasma membrane may make MOG accessible to the immune system. The evidence that MOG may act as an autoantigen in multiple sclerosis includes reports that anti-MOG antibodies cause extensive CNS demyelination both in vivo and in vitro, that peptides from the primary sequence of MOG can produce experimental allergic encephalomyelitis, that the predominant T cell response in a population of patients with multiple sclerosis is to MOG and that antibodies to MOG can be demonstrated in the CSF and serum of patients with multiple sclerosis. Additionally the human MOG gene has been localised to a region of the major histocompatibility complex on chromosome 6, the significance of this in immune theories of the causation of multiple sclerosis being unclear.² Against this

Patient No	Levodopa dosage (mg/day)	Risperidone dosage (mg/day)	Duration*	UPDRS score		AIMS score	
				Baseline	Final	Baseline	Final
1	1450	0.125	12	48	48	14	6
2	1100	0.25	21	23	23	18	2
3	500	0.125	9	14	14	16	1
4	800	0.25	12	32	32	9	5
5	1025	0.125	7	6	13	16	9
6	875	0.25	9	22	25	26	12
7	925	0.125	6	44	44	22	14
8	675	0.25	12	23	29	12	5
Mean	919	0.187	11	26.5	28.5	16.6	6.75
SD	287	0.067	4.66	14.2	12.7	5.4	4.6
p Value†				NS		<0.01	

* Months of duration of risperidone treatment.

† Comparison of final v baseline scores (Wilcoxon test).

Table 1 Distribution of *Taq* 1 digest polymorphic bands in patients with multiple sclerosis and controls

Band size (kb)	n (%) showing polymorphic bands	
	Patients (n = 40)	Matched controls (n = 80)
4.9	11 (27.5)	23 (28.8)
4.4	39 (97.5)	78 (97.5)
3.25	38 (95)	76 (95)
2.4	14 (35)	32 (40)
1.9	5 (12.5)	7 (8.8)
1.65	15 (37.5)	27 (33.8)

background, analysis of the human MOG gene has defined its intron/exon structure and provided evidence that a 1.9 kb *Taq* 1 restriction fragment length polymorphism (RFLP) of the human MOG gene could be linked to multiple sclerosis in a significant fashion in a population of Australian patients with multiple sclerosis.³ We have examined this *Taq* 1 polymorphism in a population of patients with multiple sclerosis and controls from the Southampton area.

Venous blood samples were obtained from 40 patients with multiple sclerosis in the Southampton area and from 80 age and sex matched controls. The patients were 29 women and 11 men diagnosed as having clinically definite multiple sclerosis by the Poser criteria.⁴ The age range was 23–43 years with a mean of 33.9 years. DNA was extracted by standard procedures,⁵ digested with *Taq* 1, electrophoresed, and subjected to Southern blotting using the same human MOG cDNA as previously.³ Six polymorphic bands of 4.9, 4.4, 3.25, 2.4, 1.9, and 1.65 kb were found, plus three invariant bands of 1.75, 1.25, and 1.05 kb. This contrasts with the Australian study, in which *Taq* 1 digestion of human genomic DNA and hybridisation with the same MOG cDNA probe showed five polymorphic bands of 5.25, 4.65, 2.4, 1.9, and 1.05 kb and only one invariant band of 1.7 kb. In that study the 1.9 kb band was present in 12.2% of patients with multiple sclerosis and 3.7% of controls, a difference which was significant ($p < 0.05$). The table shows the distribution of the *Taq* 1 digest polymorphic bands between patients with multiple sclerosis and controls in the present study; none of these distribution differences were statistically significant. We assume that the 1.9 kb band found here is the same as in the previous study, in which case the incidence in the two sets of patients with multiple sclerosis is very similar—12.5% and 12.2%. However the incidence of this RFLP in the control group in the present study was much higher than in the previous study—8.8% *v* 3.7%—thus denying significance. We assume our finding of extra invariant bands in *Taq* 1 digests of the human MOG gene and largely different sized RFLPs are due to genetic differences in the two populations. This illustrates the difficulties of extrapolating between two geographically widely separated cohorts. It is also important to have comparable groups in terms of clinical types of multiple sclerosis, age and sex structures, and nature of the control populations used.

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JOANNA BROWN
LESLEY HINKS
R J THOMPSON

Wessex Human Genetics Institute, Duthie Building,
Mailpoint 808, Southampton General Hospital,
Tremona Road, Southampton SO16 6YD, UK

Correspondence to: Professor R J Thompson, Wessex Human Genetics Institute, Duthie Building, Mailpoint 808, Southampton General Hospital, Tremona Road, Southampton SO16 6YD, UK.

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Pneumocephalus as a complication of metastases and eroding infection in the sacral region

Pneumocephalus is a well known and rare disease that denotes a pathological presence of intracranial air. Below, we describe an extremely rare case of the development of pneumocephalus.

A 66 year old woman was admitted to our clinic with headache persisting for the previous two months. The headache had become particularly severe and had been accompanied by vomiting during the previous week. One year before being admitted to our clinic, the patient had undergone brain CT along with other tests and the results were normal. Medical records indicated that 10 years ago the patient had undergone surgical treatment of an adenocarcinoma of the rectum. Since then she had been under an oncologist's observation. Seven years after surgery, metastases developed in the L5

vertebral body and the sacrum. This was confirmed by radiography of the lumbosacral spine and the sacrum, by radioisotope bone scans, by sacrum CT, and by pathohistological analysis of the biopsy of the sacral region. Despite implemented radiation therapy the general condition of the patient deteriorated. She lost weight and finally became paralysed. Skin and subcutaneous tissue defects appeared in the sacral region and did not heal. Repeated cultures isolated *Enterococcus*, *Enterobacter* species, and *Hafnia alvei*. The patient refused the proposed necrotomy; instead she received antibiotic treatment. At admission the patient was extremely thin, subfebrile 37°C; cardiocirculatory and respiratory systems were stable. Findings of the anus praeter naturalis in the abdominal region were normal. In the sacral region a deep seated ulcerative lesion 12×9 cm in size was visible, covered by brown strata, which secreted purulent and bloody substance. A neurological examination indicated that the patient was conscious, that her speech was normal, and that there were no signs of meningeal irritation. Flaccid paraplegia was present together with sensory modalities impaired in the right L4 and S1 dermatome and the left L5, S1, S2, and S3 dermatome and she was incontinent for faeces and urine. Routine laboratory blood tests showed the following increases: erythrocyte sedimentation rate 56 mm/h, ALP 105 U/l, ALT 59 U/l, AST 28 U/l and reduced values of: HGB 113, HCT 0.345, MCHC 26.4 g/l. The findings from other laboratory tests were normal. The fundus oculi examination was normal. Findings from radiography of the paranasal sinuses and the skull were normal except for the presence of air in the third and in the lateral ventricles. The brain CT indicated that the size of the ventricular system was normal and the ventricular system was for the most part filled with very hypodense zones which, according to absorptivity, corresponded to the air. Some air was visible around the brainstem. Such a finding indicates a pneumocephalus (fig 1). The sacrum CT showed a large skin and subcutaneous defect. The sacrum was mostly destroyed and filled with

Figure 1 Brain CT showing intraventricular air.