

this condition. Moreover, in the later stages of Parkinson's disease, a debilitating confusional state with psychotic features is common. Although in some cases this parkinsonian dementia overlaps SDAT, there is presumably a high incidence of pure Lewy body dementia in parkinsonian patients with dementia. As anticholinergic drugs have mild antiparkinsonian effects, however, it is likely that many neurologists will instinctively think that a procholinergic drug will worsen the rigidity.

We report here the results of a pilot study on the use of tacrine in patients with parkinsonian dementia. Seven patients were selected for the study (five men and two women, age range 66 to 82, mean 73.9 years). Patients were selected according to the following criteria: (a) diagnosis of Parkinson's disease before the onset of dementia; (b) rigidity that had initially responded to levodopa; (c) a confusional state incorporating visual hallucinations and exacerbated by dopaminergic drugs; (d) a normal brain MRI or CT within two months of the study, to exclude multi-infarct dementia and reduce the possibility of concurrent SDAT.

All patients had carried the diagnosis of Parkinson's disease for several years before the onset of dementia (mean 7.6 (range 3-18) years). The diagnosis was made in each case on the basis of a syndrome of progressive rigidity and bradykinesia. Four patients also had a mild resting tremor at the time of diagnosis. In each case these presenting symptoms had initially responded well to levodopa, and all patients were taking levodopa at the time of entry into the study. No patient had exhibited dyskinesias as a result of treatment with levodopa. None was currently using dopamine agonists, although four had previously used such drugs but had discontinued them because of worsening confusion. Selegiline had also been used in all patients before the study, and in all patients this drug had been discontinued for the same reason. None had used selegiline within four months of the start of the study. Four subjects had severe motor disability (Hoehn and Yahr stage 5) and were confined to a wheelchair or bedridden. Two were stage 4, and could walk with assistance, and one was stage 3, but had had a recent series of falls. Patients had baseline serum glutamic oxaloacetic transaminase and glutamic pyruvic transaminase studies and were started on tacrine at 10 mg four times daily. Liver function tests were obtained on a weekly basis. After two weeks, if transaminase concentrations remained stable, the dose was increased to 20 mg three times daily and maintained at that level for at least two months. All patients underwent Folstein (mini mental state) testing immedi-

ately before treatment, and again after two months of treatment. Unified Parkinson's disability rating scale (UPDRS) scores were also obtained before and after treatment, the motor categories by direct examination, and the daily activity scores by interview of the spouse or care giver. All patients were maintained on levodopa without change during the trial.

In all cases the frequency of hallucinations was greatly reduced after treatment, and in five cases hallucinations were essentially eliminated. All seven patients showed much improvement in both Folstein scores (mean improvement 7.1, range 3 to 13,  $P < 0.0001$ ) and UPDRS scores (items 1-31: mean score before treatment 79.3, mean score after treatment 29.6,  $P < 0.0001$ ). The table shows these results. Although there was no characteristic pattern of mental change, improvements were seen mainly in the categories of orientation, attention (serial 7s), and visuospatial awareness (copying a geometric figure). In addition, all patients were able to walk independently, improvements in gait corresponding roughly to improvements in mentation. There was no characteristic pattern of motor improvement, and in most patients improvements were seen in most categories of the UPDRS.

One patient (No 2) showed further improvements, according to her family, and underwent repeat Folstein and UPDRS testing seven months after initiation of treatment. At this time the Folstein score had risen to 28/30 (compared with 15/30 before treatment), and the UPDRS had shown a further reduction from 25 to 8. No further improvements were noted in any other patient by their families, and no other patient was retested. On the other hand patient No 4, who had the longest history of Parkinson's disease (15 years), started to decline after six months of treatment with tacrine, indicating possible limits to the duration of benefit in some patients.

In this pilot study of the use of tacrine in parkinsonian dementia, considerable improvements were seen in all patients. The finding of motor improvement was unexpected. Before starting this investigation it was thought that even if the dementia ameliorated patients might become more rigid, as anticholinergic drugs have slight antiparkinsonian motor effects. Indeed there is at least one reported case in which rigidity is said to have developed in a patient with Alzheimer's disease treated with tacrine.<sup>6</sup> In our study, on the contrary, patients became less rigid. This finding may perhaps be understood if the degenerating cholinergic neurons in Parkinson's disease are not striatal interneurons but cortical projections, at least some of which are involved (directly or indirectly) in the generation of movements.

Definitive conclusions regarding the pathogenesis of this effect, however, must await confirmation and further study.

The psychotic confusional state seen in the later stages of Parkinson's disease is a common and significant source of morbidity. Our results suggest that low dose tacrine is efficacious in its treatment. In our study population tacrine dispensed with the need for conventional antipsychotic medications, and was associated with motor improvements. Although these preliminary findings are highly suggestive, caution should be exercised in their interpretation until confirmed by a blinded placebo controlled study, preparations for which are underway.

MICHAEL HUTCHINSON  
ENRICO FAZZINI  
Department of Neurology,  
New York University Medical Center,  
550 First Avenue,  
New York NY 10016, USA

Correspondence to: Dr M Hutchinson.

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#### Central diabetes insipidus: a complication of herpes simplex encephalitis

Secondary diabetes insipidus occurs as a result of damage to the hypothalamic-neurohypophyseal system due to opportunistic infections in AIDS, in neonates, and in children with acute bacterial meningitis. Diabetes insipidus after herpes encephalitis in adults is rare.

Five days before admission, a 42 year old woman developed a prodromal influenza-like illness with rapid onset of headache, behaviour disorder, and clouding of consciousness and became increasingly disoriented and lethargic. She was admitted to hospital because of a tonic-clonic seizure. Her temperature was 38.5°. The Glasgow coma scale score was 12 and she had neck stiffness and bilateral Babinski's sign. The CSF showed mononuclear pleocytosis (600 white cells/ml), 131mg/dl protein, and 80 mg/dl glucose. The EEG suggested encephalitis. Head CT showed an area of low attenuation in the left temporal region. Treatment with acyclovir was started and also amikacin for a urinary infection. Brain MRI showed hyperintensive lesions in the left temporal and frontal lobes and insular cortex, a midline shift to the right, and involvement of the right temporal and frontal lobes highly suggestive of herpes simplex virus encephalitis. There was a significant rise in the titre of serum antibodies

Dementia and motor disability scores in patients with Parkinson's disease before and two months after treatment with tacrine

Patient No	Age (y)	PD (y)	Dementia (y)	MMS pre-Rx	MMS post-Rx	UPDRS pre-Rx	UPDRS post-Rx
1	82	4	1	21	24	34	17
2	72	2	0.5	15	24 (28)*	89	25 (8)*
3	77	6	1	15	23	91	31
4	69	15	2	15	21	86	28
5	78	4	1	15	26	87	44
6	66	5	0.5	16†	24†	65	21
7	74	4	0.25	19	24	103	41

PD = Parkinson's disease duration; MMS = mini mental state score (Folstein) out of 30; UPDRS = unified Parkinson's disability rating scale (items 1-31); pre/post Rx = before/after treatment; \*at 7 months after initiation of treatment; †scored out of 29.

## Water deprivation test

Time	U osmolality mmol/kg	S osmolality mmol/kg	U volume (ml)	Treatment
9.00 am	280	281	165	—
10.00 am	291	—	140	—
11.00 am	308	—	142	—
12.00 am	320	288	126	2 µg ADH
13.00 am	445	—	52	—

S = serum; U = urinary.

against herpes simplex virus. Antibodies against HIV and CSF cultures were negative. Three weeks later, she developed polydipsia and polyuria with a daily urinary output of up to 7 l. Anterior pituitary hormone function was normal. A water deprivation test by the method of Miller and colleagues<sup>1</sup> was performed and the table shows the results. Intravenous infusion of hypertonic saline (5% saline for two hours at a rate of 0.06 ml/kg/min) was performed. Plasma vasopressin concentrations were 3.0, 3.5, 3.3, 3.7, and 3.9 pg/ml at 0, 30, 60, 90, and 120 minutes respectively, in relation to a progressive increment in serum osmolality of 277, 289, 302, 308, and 315 mmol/kg. A diagnosis of partial central diabetes insipidus was made and she was given a course of subcutaneous 1-diamino-8-D-arginine vasopressin (DDAVP). Brain MRI showed the absence of the posterior pituitary "bright spot" in sagittal T1 weighted images. Six months later there was still considerable polyuria, which improved with nasal DDAVP treatment.

Hypothalamic-pituitary dysfunction after acute meningoencephalitis is very rare. A case of central diabetes insipidus was described as a complication of herpes simplex encephalitis in a patient with AIDS.<sup>2</sup> We report here the first case of herpes simplex encephalitis associated with diabetes insipidus in a previously healthy subject. Polyuria and polydipsia can also result from

nephrogenic diabetes insipidus with insensitivity to the antidiuretic actions of vasopressin, which can be caused by several drugs such as aminoglycosides. Although our patient had been treated with amikacin, the persistence of the clinical manifestations after drug withdrawal makes this an unlikely cause. Furthermore, both the water deprivation and hypertonic saline infusion tests clearly indicated a partial central diabetes insipidus. The absence of the posterior pituitary "bright spot" on T1 weighted MRI images, although reported in neurogenic diabetes insipidus, occurs in a large proportion of healthy people.

ANA CANTON  
RAFAEL SIMO  
JORDI MESA

Department of Endocrinology  
CARLOS MOLINA

ALEX ROVIRA  
XAVIER MONTALBAN  
Department of Neurology, Hospital General  
Universitari Vall d'Hebron, Psg Vall d'Hebron  
119-129, 08035 Barcelona, Spain

Correspondence to: Dr Ana Canton, Servicio de Endocrinología, 7ª Planta Impares, Hospital Vall D'Hebron 119-129, 08035 Barcelona, Spain.

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## BOOK REVIEWS

All titles reviewed here are available from the BMJ Bookshop, PO Box 295, London WC1H 9TE. Prices include postage in the United Kingdom and for members of the British Forces Overseas, but overseas customers should add £2 per item for postage and packing. Payment can be made by cheque in sterling drawn on a United Kingdom bank, or by credit card (Mastercard, Visa or American Express) stating card number, expiry date, and your full name.

**The Management of Pituitary Tumours.** Edited by MICHAEL POWELL and STAFFORD L LIGHTMAN. (Pp 238; £49.50.) Published by Churchill Livingstone, Edinburgh 1996. ISBN 0-4430-5214-X.

This is a concise guide to the diagnosis and treatment of pituitary tumours aimed at neurosurgeons, endocrinologists, neurolo-

gists, and ophthalmologists. It aims to give the clinician an overview of pituitary tumour management and achieves this in a compact and well presented style.

The overall approach is that of the joint pituitary clinic at the National Hospital, Queen Square. Following an introduction, separate chapters cover the pathophysiology, medical management, visual manifestations, radiology, surgery, anaesthesia and radiotherapy of pituitary tumours. However, the book emphasises a joint specialist approach which is described in the second chapter.

Of the individual chapters, that on pathophysiology and pathogenesis comprehensively covers the theories of pathogenesis of pituitary adenomas, but does not clearly describe the classifications used in clinical practice. The chapter on medical management is comprehensive and includes protocol for pituitary function tests. The imaging chapter is well illustrated with clear reproductions of Magnetic Resonance and Computed Tomography Scans. The surgery of pituitary tumours has sections on surgical anatomy, classifications, pre-operative work-up, transsphenoidal hypophysectomy and transcranial surgery. It mentions the four main transsphenoidal approaches to the pituitary and then concentrates on the septal

endomucosal approach, which is clearly described. Post-operative management does not advocate neurological observations for all patients undergoing transsphenoidal surgery, which differs from the practice of other units. The penultimate chapter gives an excellent description of other parasellar lesions and the final chapter by the editors concentrates on controversial issues, including a balanced opinion of the treatment of craniopharyngiomas.

My only major criticism is that in a text of handbook style, summaries and key points would have been a useful addition for each chapter. Overall, I think that the book is a useful and readable guide to the management of pituitary tumours and I would recommend it to trainees and consultants, particularly in neurosurgery and endocrinology.

PETER HUTCHINSON

**Pathogenesis and Therapy of Amyotrophic Lateral Sclerosis.** (Advances in Neurology, Volume 68). Edited by GEORGES T SERRATRICE and THEODORE L MUNSAT. (Pp 312; £88.00.) Published by Lippincott-Raven Publishers, Philadelphia, PA 1995. ISBN 0-7817-0333-6.

Although Charcot described amyotrophic lateral sclerosis almost 130 years ago, we have been little the wiser as to its aetiology until very recently. This book, which accompanied the 1994 Marseilles neuromuscular conference, exudes the optimism which followed the discovery of superoxide dismutase mutations in familial ALS, and the results of the Riluzole study.

The book opens with 16 chapters addressing pathogenesis, with a stress on excitotoxic mechanisms, in particular the role of glutamate. SOD1 defects have only been detected in 20% of familial ALS cases, suggesting that glutamate may only play a part in a cascade of processes leading to cell death. The evidence for glutamate transporters, post synaptic receptor changes, and autoimmunity against calcium channels or gangliosides is discussed, together with the evidence from animal models implicating abnormalities of neurofilament genes, and neurotrophins.

The issues of causation having been set out, the niceties of differential diagnosis and natural history are discussed in relation to clinical trial design. In the final section, various therapeutic modalities are discussed, including neurotrophins, glutamate receptor antagonists, and mechanisms of inhibiting excitotoxins. Inevitably, many of the management approaches are based on animal models of diseases which do differ from ALS/MND, and which are reminiscent of the logic by which selegiline was considered a possible neuroprotective agent in idiopathic Parkinson's disease. Nevertheless, the biological principles which are being uncovered may have a role in neurodegenerative diseases other than ALS.

The many short chapters (34 in 277 pages) offer a "bite sized" approach to the subject matter, allowing an easy acquaintance with many of the issues. Whereas some of the chapters are extremely informative, the overall effect of the text is reminiscent of a bowl of Shreddies placed before a Shredded Wheat eater—arguably everything appears to be present, yet something is still missing.

JON SUSSMAN