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LETTERS TO THE EDITOR

Donepezil for Dementia with Lewy Bodies: A Case Study

Dear Editor

Dementia with Lewy bodies (DLB) has been suggested to be the most common cause of dementia in the elderly after Alzheimer's disease. DLB is characterized clinically by progressive cognitive decline with daily fluctuations, visual hallucinations and parkinsonism (McKeith *et al*., 1996). Little is known regarding treatment of patients with DLB. Atypical neuroleptics may improve hallucinations (Allen *et al*., 1995; Geroldi *et al*., 1997). Subjects with DLB have lower levels of neocortical choline acetyltransferase than those with Alzheimer's disease (Perry *et al*., 1994), and the cholinergic loss is particularly severe in DLB patients with prominent visual hallucinations (Perry *et al*., 1990). Thus, cholinergic agents may be useful and there is some evidence suggesting that DLB patients respond favourably to tacrine (Levy *et al*., 1994). We report a patient with DLB with prominent visual hallucinations who showed a marked response to treatment with donepezil.

CASE PRESENTATION

Presenting history

A 71-year-old woman had experienced visual hallucinations, suspiciousness and mild cognitive impairment for 2 years. She had suffered from mild symptoms of anxiety with vertigo after her husband's death 10 years previously, but a neurological examination and EEG were normal. No other psychiatric or neurologic symptom had previously been reported. She had been treated with amlodipin 5 mg/d, simvastatin 20 mg/d and thyroxin 0.05 mg/d. Two years prior to admission she complained of vertigo and presyncope. A neurological examination was normal, and Doppler ultrasonography of the carotid and vertebralis arteries showed moderate arteriosclerosis but no evidence of stenosis. One month prior to admission, she fell and had a hip fracture. She had lived in her own home until this accident.

Inpatient examinations and investigations

At admission to a psychogeriatric ward she was awake and attentive. No psychiatric symptoms other than visual hallucinations were recorded. Blood pressure was 130/70. Blood tests showed low folates (5 nmol/l), while other blood tests, including vitamin B12, thyroxin and chloresterol, as well as a urine dipstick, were normal. A chest X-ray was normal, and an EEG showed generalized background slowing but no focal abnormalities. A 24-hour Holter registration was normal. CT and MRI scans of the brain were normal. She complained of hip pain, and an X-ray showed some destruction of caput femoris.

A neurological examination including the Unified Parkinson's Disease Rating Scale (Fahn *et al*., 1987) demonstrated mild to moderately severe parkinsonian features, with a motor subscale score of 32/108. The parkinsonian syndrome was dominated by rigidity, bradykinesia and postural instability. Cognitive tests showed mild impairment. She scored 23 on three monthly Mini-Mental State Examinations (MMSE). On two occasions with 5 weeks interval her score on the Mattis Dementia Rating Scale (DRS) was 126 and 120 (maximum score = 144), consistent with mild to moderate cognitive impairment (Mattis, 1976) (Table 1).

The visual hallucinations were recurrent, formed and detailed. Typical themes were men, children and animals intruding into her room. Frequently she would talk to the intruders, sometimes being aware of the unreal nature of the images, usually, however, without insight. Sometimes she would become agitated and angry at the images and throw things at them. The hallucinations occurred several

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Table 1. Performance on MMSE and DRS subtests before and after treatment with donepezil (maximum possible score)

	Before treatment			After treatment 7 weeks	After treatment 19 weeks
Date	10/97	11/97	12/97	6/98	9/98
MMSE (30)	23	23	23	30	28
DRS: attention (37)		37	33	37	37
Initiation and perseveration (37)		26	37	37	37
Construction (6)		6	6	6	6
Categorization (39)		39	29	39	38
Memory (25)		18	15	24	25
Total DRS (144)		126	120	143	143

MMSE, Mini-Mental State Examinations; DRS, Mattis Dementia Rating Scale.

times a day, most often at night. She experienced severe cognitive fluctuations. On some occasions she could be completely disoriented for time, place and situation. Daytime drowsiness was common. She had severe impairment of her personal activities of daily living (ADL) and needed help for most chores.

Treatment and progression

Prior to admittance she had been treated with haloperidol 4 mg/d for 2 weeks without any improvement. She received folates 0.1 mg bid, and amlodipin and simvastatin were discontinued. Treatment with risperidone was initiated, with a gradually increasing dose to 2 mg/d. Chlomethiazole 600 mg was given for insomnia. During the next 10 days, she became severely sedated and developed marked rigidity. Moderate leukocytosis was found, but body temperature and creatinine kinase level were normal. Risperidone and chlomethiazole were discontinued. We hypothesized that pain from the hip could contribute to the condition, and analgetic treatment with dextropropoxyphen 200 mg qid was started. She showed some improvement for 4 weeks and was discharged to a nursing home. However, due to increasing symptoms, she was readmitted 2 months later. She now suffered from daily and disturbing visual and occasional auditive hallucinations and delusions of poisoning, as well as periods of severe mental impairment. She needed assistance for her personal ADL and was occasionally incontinent for urine. Clozapine 12.5 mg/d was started, but after 3 days of treatment she developed severe sedation and rigidity and clozapine was withdrawn. Laboratory tests were normal. A course of risperidone 0.5 mg/d was administered without improvement but with increasing sedation.

After a drug-free period of 5 weeks with marked symptoms, donepezil 5 mg/d was started, increasing to 10 mg/d after 3 weeks. Marked and stable improvements of cognition and visual hallucinations were now observed. The cognitive fluctuations became mild and short-lasting and the hallucinations were less frequent and intense. Her ability to perform personal ADL was much improved and she needed help only with showering and washing her hair. When asked if she felt any improvement in her condition, she answered she was not sure, but she thought things had become a bit boring at the ward lately.

The clinical improvement was verified by rating scales. Orientation was scored on a scale from 0 to 3 by asking the patient what day it was, date and time of day and giving one point for each correct answer. Hallucinations were rated on a scale from 0 to 2, with 0 indicating a complete absence of hallucinations, 1 indicating hallucinations with insight, and 2 if the patient showed hallucinations without insight. The scales were completed every evening by a member of the nursing staff after instruction by one of the authors (KB). The patient was rated for the last 9 days she was without any medication as a baseline. She was then rated every evening for 6 weeks. The data were analysed at four consecutive periods after starting administration of donepezil, each period consisting of 9 days. During the first two post-treatment periods the dose was 5 mg/d and during the last periods it was 10 mg/d.

Remarkable improvements of orientation and hallucinations were observed. A one-way ANOVA showed a significant main-effect of time-period on orientation, $F(4, 40) = 14.7$, $p < 0.001$, and hallucinations, $F(4, 40) = 13.4$, $p < 0.001$ (Fig. 1).

At the end of the four periods, MMSE and DRS were readministered. She now obtained a score of 30/30 on MMSE and 143/144 on DRS.

Three months after discharge, the scores were 28 and 143. (Table 1).

Treatment with donepezil was well tolerated. She reported sialorrhea of moderate severity, periods of mild headache, but no gastrointestinal or other adverse events.

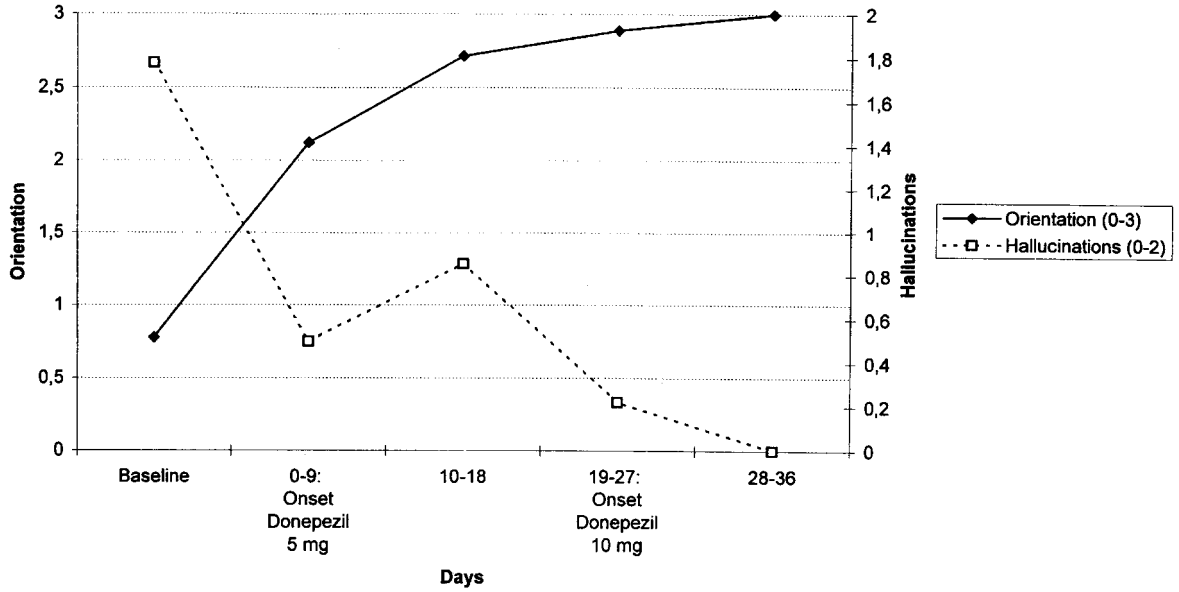

Fig. 1. Severity of visual hallucinations and orientation to time before and after treatment with donepezil

DISCUSSION

To our knowledge, this is the first report of a patient with DLB who showed an early, marked and enduring response after treatment with a cholinesterase inhibitor. She had suffered from severe visual hallucinations, cognitive impairment with marked fluctuations, parkinsonism, repeated falls, syncopes and neuroleptic sensitivity. As reported previously (McKeith *et al.*, 1996; Geroldi *et al.*, 1997; Burke *et al.*, 1998), therapy with neuroleptics, including atypical agents like risperidone and clozapine, induced rigidity and severe sedation with unconsciousness.

We believe that donepezil was the main reason for improvement in this subject. However, other factors might have contributed. A spontaneous remission coinciding with donepezil treatment or improvement induced by expectations concerning a new 'antidementia pill' are possible alternative explanations. However, during the last 18 months prior to treatment with donepezil she had shown rapid deterioration. DLB is a chronic degenerative brain disease with an end-stage of profound dementia, and spontaneous remissions or placebo effects of a magnitude such as that observed in this patient are not likely to occur. Improvements were noted on cognition, visual hallucinations and personal ADL, and were observed on standardized cognitive rating scales, general clinician-based clinical impression and ratings performed by staff members.

Learning may have contributed to the observed improvement, but several factors argue against this. Other agents had been administered with no or only transient improvement. Furthermore, serial testing with MMSE and DRS had been performed prior to donepezil therapy, with no evidence of any learning taking place. Placebo treatment would have been one way to solve this problem and a single-blind placebo period was planned in advance. However, due to the marked improvement on donepezil, it was considered unethical to withdraw this treatment.

Diagnoses other than DLB might be considered for this case. Alzheimer's disease is often accompanied by visual hallucinations (Mega and Cummings, 1996). The clinical course, with marked fluctuations and early parkinsonism, and the pattern of performance on cognitive testing, with only mild impairment of memory and executive functions combined with marked impairment of personal ADL, is not typical for Alzheimer's disease. Parkinson's disease is frequently accompanied by cognitive impairment and visual hallucinations (Aarsland *et al.*, In press). However, parkinsonism was mild and occurred at a later stage than hallucinations and cognitive impairment, which is not consistent with a diagnosis of Parkinson's disease. Finally, delirium has

several features in common with DLB, and a delirium after surgery for hip fracture is another possible diagnosis. However, the symptoms had developed gradually 2 years before this accident and no change was seen for 7 months before treatment with donepezil was introduced, suggesting that delirium was not a major contributing factor in this case.

In summary, this report demonstrates a marked improvement of cognition, ADL functions and visual hallucinations in a patient with clinical probable DLB after treatment with donepezil. Future clinical studies of cholinesterase inhibitors should explore safety and efficacy in patients with DLB.

DAG AARSLAND
KOLBJØRN BRØNNICK
Psychiatric Hospital of Rogaland
Stavanger, Norway

KAREN KARLSEN
Central Hospital of Rogaland
Stavanger, Norway

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'Silent Dependence Syndrome' in Old Age . . .!

Dear Editor

The ICD-10 defines the dependence syndrome as 'a cluster of behavioural, cognitive and physiological phenomena that develop after repeated substance use and that typically include a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal state' (WHO, 1992a). In practice, psychiatric diagnosis of substance dependence is applied only to patients who have been referred to the mental

