Neuroleptic Sensitivity to Clozapine in Dementia With Lewy Bodies

William J. Burke, M.D.
Ronald F. Pfeiffer, M.D.
Rodney D. McComb, M.D.

Dementia with Lewy bodies (DLB) may be one of the most common causes of dementia. It should be of particular interest to psychiatrists because hallucinations are common presenting symptoms and because patients with DLB may be particularly sensitive to neuroleptics with respect to developing extrapyramidal symptoms. The authors describe 2 patients with DLB who were intolerant of clozapine, showing not extrapyramidal side effects, but an increase in confusion and behavioral symptoms.

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Recent years have seen the development of an increasing interest in dementia with Lewy bodies (DLB), and consensus criteria have recently been proposed.[1] Although it is still unclear whether DLB represents a unique disorder or a variant of Alzheimer's disease, it is increasingly diagnosed, and it may be the second most common pathological correlate of cognitive impairment in elderly persons.[2]

McKeith et al.[1] described clinical features on the basis of retrospective analysis of case notes from 21 autopsy-proven cases of dementia with Lewy bodies.[3] The principal feature was fluctuating cognitive impairment affecting both memory and higher cognitive functioning. Additional criteria included visual and auditory hallucinations (usually accompanied by paranoid delusions), mild spontaneous extrapyramidal symptoms, repeated unexplained falls, and transient clouding or loss of consciousness.

One of the most striking features of these cases was the occurrence in 8 of the 15 neuroleptic-treated patients of neuroleptic sensitivity syndrome, which resulted in increased mortality and morbidity. In some patients, initial sedation or sudden onset of rigidity was accompanied by postural instability and falls. Others showed rapid deterioration, with increased confusion, immobility, rigidity, fixed flexion posture, and decreased food intake. One patient died within a week, 3 died within 4 weeks, and 4 died within 12 weeks after initially receiving a neuroleptic or experiencing a dosage increase. The mean survival of those treated with a neuroleptic was 11.5 months (SD = 4.5 months), compared with 25 months for the 6 who did not receive a neuroleptic. All patients in this series were treated with traditional neuroleptic agents.

McKeith and co-workers[4] followed up the first series of cases with an additional 20 patients who died in the hospital of DLB. Of the 16 patients who received neuroleptics, 13 experienced adverse reactions. In 7 of these patients, the reactions were severe. Two types of neuroleptic sensitivity were proposed. The first is a mild form that includes the extrapyramidal reactions routinely seen in an aging population. This form affected the Lewy body patients more often than the Alzheimer's disease control subjects. The second is a severe form that includes extremes of the milder type of reaction as well as "idiosyncratic reactions similar to the neuroleptic malignant syndrome."

There have been few reports of the treatment of DLB with newer "atypical" neuroleptics. Chacko et al.[5] reported a single case of a clinically diagnosed individual with diffuse DLB who responded favorably to clozapine. Allen and co-workers[6] described 3 patients meeting the McKeith clinical criteria who improved on low doses of risperidone. However, McKeith and colleagues[7] subsequently reported 3 patients on risperidone with severe extrapyramidal symptoms (although 2 of these patients had recently been treated with standard neuroleptics.)

In this report, we describe the case of a patient treated with clozapine for autopsy-proven Lewy body dementia and a second patient who meets the clinical criteria for DLB. These individuals demonstrated extreme sensitivity to clozapine.

Received January 28, 1997; revised May 23, 1997; accepted May 30, 1997. From the Departments of Psychiatry, Neurology, and Pathology/Microbiology, University of Nebraska Medical Center, Omaha, Nebraska. Address correspondence to Dr. Burke, 600 South 42nd Street, Omaha, NE 68198-5575; e-mail: wjburke@mail.unmc.edu

CASE REPORTS

Case 1. A 71-year-old white man was referred by his neurologist, who had treated him for a diagnosis of mild Parkinson's disease of approximately 4 years' duration. The initial presenting extrapyramidal symptoms included a slowed gait with decreased arm swing, mild rigidity, and very slight intermittent resting tremor of the left hand. The reason for psychiatric referral was increased hallucinations described as cyclically occurring over the prior 6 months. Hallucinations were first noted at the time of a carbidopa-levodopa dosage increase and persisted despite a gradual dose reduction. A particularly bothersome hallucination for the patient began with him hearing someone pounding on his front door. On answering the door, he saw a thin, tall man and a short, stubby man who did not answer his questions and who then jumped over his porch fence and ran into the woods. The patient responded by walking to his hallway, where he was attempting to put together his shotgun when he "suddenly woke up and realized what I was doing." He noted other episodes of hallucinations that were more pleasant and "like a serial." One involved being in a prisoner of war camp, and another involved being superintendent of a large school under construction. Some hallucinations were associated with sleep; others occurred when the patient was fully awake. He believed someone had repaired his wallpaper and fixed up his house. He recalled seeing faceless people in the room who would not respond when he spoke to them. He described the feeling that somebody was always in the house with him.

He denied dysphoria but admitted to decreased interest in hobbies, which he attributed to Parkinson's disease. He described some mild memory problems and loss of energy. At the initial evaluation, he was taking L-deprenyl 5 mg bid; carbidopa-levodopa 25/100 mg tid; and vitamin E 1,000 IU bid. There was no family history of psychiatric or neurological illness. The patient was a retired administrator living with his wife.

Mental status examination revealed a pleasant, alert, cooperative man with some mild word-finding difficulty as well as blocking. He scored 27 of 30 on the Mini-Mental State Examination as a result of failing to 1) recall one of three objects after a delay, 2) execute one part of the three-part instruction, and 3) copy intersecting pentagons. On neurological exam he had mild to moderate rigidity in his extremities, with little to no tremor. He was bradykinetic with a stooped posture and walked with a shuffling, short-stepped gait. He had occasional freezing while walking. His baseline motor examination score on the Unified Parkinson's Disease Rating Scale (UPDRS),[8] a standardized scale to evaluate severity of Parkinson's disease, was 21.

The initial recommendation was to either discontinue L-deprenyl or consider a trial of clozapine. The patient elected to discontinue both deprenyl and vitamin E, which resulted in almost complete resolution of the hallucinations. About once a week he still would see a "faceless boy" and would "have to satisfy myself that he doesn't exist." After 3 months, the patient resumed L-deprenyl because of increased Parkinson's symptoms. The hallucinations recurred and the L-deprenyl was again discontinued, but unfortunately, the hallucinations never abated. At this point, the patient and his wife agreed to proceed with a trial of clozapine on an inpatient basis.

The 24 hours following his first dose of clozapine (6.25 mg) were uneventful. The dose was increased to 12.5 mg on the second night. On the next morning, he complained that "a man and wife kidnapped me and put me in a birdcage during the night." Although oriented, he was markedly paranoid and had struck out at the staff. Subsequently, clozapine was reduced to 6.25 mg. On the following evening, he became very agitated, angry, and confused and was given 1 mg of lorazepam, which resulted in marked sedation, poor coordination, and difficulty performing activities of daily living (ADLs). Two mornings later he was not oriented to time and only partially to place. He denied hallucinations or delusions, stating that "real things" happened. For the next 2 evenings, he was hallucinating, delusional, and paranoid. He thought that he was once again kidnapped and that the staff was lying to him. He had no orthostatic hypotension and minimal sedation, but in light of his increasing psychosis, the clozapine was discontinued.

Over the next 2 weeks he took a low dose of molindone, which was poorly tolerated. The patient continued to have fairly dramatic fluctuations in mental state, alternating between being pleasant and cooperative and being confused and paranoid. He described seeing nuts, bolts, and automobiles in the hall and reported that the "colors were so vivid on the cars they can't possibly be hallucinations." He saw people playing basketball and three men sitting next to him who wouldn't include him in their conversation. Throughout this 2-week period, his neurological exam was unchanged. He showed moderate rigidity and no tremor. His gait and posture were mildly parkinsonian. A switch to thioridazine was attempted, with minimal response. After 3 weeks, he was discharged to a nursing home in another city.

While at the nursing home, he continued to display aggressive behavior, at times attacking people. On at least four occasions, he either wandered away or attempted to escape from the nursing home. Thioridazine was discontinued and his combative and agitated behavior stopped. However, at the same time his wife moved into the nursing home. The wife attributed all of the behavioral changes such as the agitation and aggression to the clozapine. She noted that her husband "has never been the same since then." Three months after his exposure to clozapine, his UPDRS motor exam score was 39.

One year later, he was seen by his neurologist. At that point, his cognitive impairment had so progressed that the patient did not consistently recognize his family. He remained belligerent at times, grabbing and pinching nurses, but this behavior was diminishing. His attempts to escape the nursing home had declined. His Parkinson's disease had not changed dramatically. His gait remained reasonably good, and he experienced very little tremor. However, his posture was severely stooped, and his postural stability had diminished. His UPDRS score was 46. He was taking carbidopa-levodopa 25/100, one and a half tablets tid. There were no further clinic visits. After the patient's death 8 months later, an autopsy was performed.

The final diagnosis of Lewy body dementia was based on the presence of Lewy bodies in the neocortex.[1] There were also degenerative changes and Lewy body formation in the substantia nigra and locus ceruleus. Senile plaques were present, and rare neurofibrillary tangles were observed. However, the quantities were consistent with the patient's age and insufficient to establish a diagnosis of Alzheimer's disease.

Case 2. The second case involved a 69-year-old man who, in retrospect, fit clinical criteria for DLB. He had extrapyramidal symptoms accompanied by marked visual hallucinations, periodic confusion, and a progressive dementia. He was taking carbidopa-levodopa 25/250 bid and 25/100 once per day. He additionally was taking pergolide 0.25 mg tid. Attempts at medication reduction were unsuccessful, resulting in no improvement in hallucinations or confusion but an increase in pain and tremor. There was no family history of psychiatric or neurological illness. The patient was a retired supervisor living with his wife. Mental status examination revealed a pleasant, alert, cooperative white male with some mild latency of response and a tendency to lose track of his place while speaking. He scored 16 of 30 on the Mini-Mental State Examination, missing the following: four orientation items, four serial 7's, one delayed recall item, phrase repetition, executing each part of a three-part instruction, and copying intersecting pentagons. He had moderate tremor, mild to moderate rigidity, and mild bradykinesia. His UPDRS score was 32.

After a single dose of clozapine (6.25 mg), he experienced increased confusion and hallucinations accompanied by paranoia and marked apprehension. Clozapine treatment was discontinued at the family's request. The increase in confusion, apprehension, and paranoia persisted after the clozapine was discontinued. The patient was seen by his neurologist 6 weeks later, at which time the patient was described by his family as "not well" because of the lingering increase in confusion and psychosis. His motor function was unchanged from baseline. After another 4 months the family said that the patient had never returned to his pre-clozapine level of mental function, having increased confusion and more prominent hallucinations. His UPDRS score at this time was 29.

DISCUSSION

The recently proposed consensus criteria for DLB state that the central feature of the condition is a progressive cognitive decline accompanied by 2 of 3 additional core features, which include fluctuating cognition, recurrent visual hallucinations, and spontaneous motor features of parkinsonism.[1] Supportive features of the diagnosis include neuroleptic sensitivity, systematized delusions, hallucinations in other modalities, transient loss of consciousness, syncope, and repeated falls. Given this symptom pattern, it is likely that persons afflicted by DLB will be exposed to neuroleptics, perhaps with dire consequences.

Our case echoes the warning of McKeith et al. that patients with DLB may respond poorly to neuroleptics. We have found that using clozapine for treating psychosis in patients with Parkinson's disease is effective and well tolerated.[9] In only the 2 cases described above have we found an unequivocal decrement in patient well-being after starting clozapine.

Patients with DLB may do poorly even when taking atypical neuroleptics. What is unusual in the cases presented here is that the adverse events were not extrapyramidal side effects, but rather an increase in confusion and behavioral symptoms. Based on our experience and that of McKeith et al., it seems prudent to adopt a cautious approach in treating patients fitting the criteria for DLB. They may be more intolerant of neuroleptics than other patients with neurodegenerative dementia. Prospective reports are needed to establish the optimum treatment for these patients. In the meantime, clozapine must be added to the list of medications that may be problematic.

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