Neuroleptic Sensitivity in Parkinson's Disease and Parkinsonian Dementias

Dag Aarsland, M.D., Ph.D.; Robert Perry, F.R.C.Path.; Jan P. Larsen, M.D., Ph.D.; Ian G. McKeith, F.R.C.Psych.; John T. O'Brien, M.R.C.Psych.; Elaine K. Perry, Ph.D.; David Burn, M.D.; and Clive G. Ballard, M.R.C.Psych., M.D.

Background: Severe sensitivity to neuroleptic agents is a major clinical problem in dementia with Lewy bodies (DLB), but has not been determined in Parkinson's disease (PD) and PD with dementia (PDD).

Method: Severe neuroleptic sensitivity reactions (NSRs) were evaluated according to an operationalized definition blind to clinical and neuropathologic diagnoses in prospectively studied patients exposed to neuroleptics from 2 centers. The study was conducted from June 1995 to May 2003.

Results: Ninety-four patients were included (15 with DLB, 36 with PDD, 26 with PD, 17 with Alzheimer's disease, all diagnosed with various operational criteria). Severe NSR only occurred in patients with Lewy body disease: DLB (8 [53%]), PDD (14 [39%]), and PD (7 [27%]), but did not occur in Alzheimer's disease ($p = .006$). Severe NSR was not associated with other clinical or demographic features. In DLB, severe NSR was not associated with neuropathologic indices (Consortium to Establish a Registry for Alzheimer's Disease staging, Braak staging, or cortical distribution of Lewy bodies).

Conclusions: An operationalized evaluation of severe NSR blind to diagnosis confirmed the high prevalence in DLB and identified high frequencies in Parkinson's disease and PDD with important implications for clinical practice.

(J Clin Psychiatry 2005;66:633–637)

Received Feb. 16, 2004; accepted Nov. 16, 2004. *From the Section of Geriatric Psychiatry (Dr. Aarsland) and the Department of Neurology (Dr. Larsen), Central Hospital, Rogaland, Stavanger, Norway; the Department of Neuropathology (Dr. Perry) and the Department of Old Age Psychiatry (Drs. McKeith, O'Brien, Perry, and Burn), Newcastle General Hospital, Newcastle Upon Tyne, U.K.; and Wolfson Centre for Age-Related Diseases, King's College London, London, Great Britain (Dr. Ballard).*

The authors report no conflicts of interest, financial disclosures, or other relationships relevant to the subject matter of this article.

The authors would like to thank the Medical Research Council, U.K., for supporting this study.

Corresponding author and reprints: Clive Ballard, M.R.C.Psych., M.D., Wolfson Centre for Age-Related Diseases, School of Biomedical Sciences, King's College London, Guy's Campus, London, Great Britain, SE1 1UL (e-mail: clive.ballard@kcl.ac.uk).

Patients with dementia in the context of parkinsonism, either Parkinson's disease with dementia (PDD) or dementia with Lewy bodies (DLB), frequently experience intrusive and persistent neuropsychiatric symptoms, in particular, visual hallucinations.[1,2] These symptoms are distressing for the patient, present major difficulties for caregivers, and increase the risk for nursing home placement. As a consequence, antipsychotic drugs are commonly prescribed as part of the clinical management of these patients. Of major concern, previous studies have indicated that patients with DLB, who represent 15% to 20% of patients with late-onset dementia,[3] are particularly vulnerable to severe neuroleptic sensitivity reactions (NSRs), which occur in 30% to 50% of DLB patients exposed to these agents, even using low doses or newer neuroleptics such as sulpiride, risperidone, and clozapine.[4–7] These reactions are characterized by a sudden onset of sedation, increased confusion, rigidity, and immobility, with substantial reductions in survival, often leading to a fatal outcome within a few days or weeks.[4] None of the reported case series[4–7] have been large enough to describe whether the frequency of severe NSR appears to be different for individual neuroleptic drugs. Preliminary mechanistic studies[8] have indicated that in DLB patients, these reactions may be associated with dysfunctional dopamine D_2 receptors.

The frequency of severe NSR has not been described in Parkinson's disease (PD) or PDD patients, although these patients are at increased risk of exacerbation of extrapyramidal symptoms with neuroleptics due to nigrostriatal dopaminergic deficiency. Low doses of atypical antipsychotics such as clozapine and quetiapine may be reasonably well tolerated from the perspective of extrapyramidal symptoms,[9] but the issue of severe sensitivity reactions has not been addressed. Reports[10] of neuroleptic malignant syndrome in Parkinson's disease patients after withdrawal of antiparkinsonian agents suggest potential vulnerability of these patients to severe NSRs following the administration of dopaminergic receptor blocking agents. Determining whether these individuals are vulnerable to NSRs is essential in order to be able to effectively weigh the appropriateness of instigating neu-

roleptic therapy and hence provide optimal treatment for these individuals.

There is increasing evidence suggesting that the majority of Parkinson's disease patients develop dementia,[11] and the psychiatric symptoms in Parkinson's disease and DLB are similar.[12] The structural and chemical brain changes are also similar in the 2 conditions.[13,14] One would therefore hypothesize that PDD patients will also be at risk for severe NSR.

There is pathologic heterogeneity within patients with DLB. Patients with more neurofibrillary tangles have a clinical and neurochemical profile more similar to Alzheimer's disease (AD) than DLB.[15] It is therefore possible that these patients, who could be considered as having a "Lewy body variant" of AD, may have a lower propensity for severe NSR.

The aim of the current study was to determine the frequency of severe NSR in DLB and Parkinson's disease with and without dementia and to assess the relationship of severe NSR with concurrent Alzheimer pathology in DLB.

METHOD

Selection and Diagnosis of Patients

Patients with DLB, AD, and Parkinson's disease with and without dementia were recruited from 2 centers: a dementia case register of consecutive referrals to old-age psychiatry services in Newcastle Upon Tyne, U.K., (N = 338) and Stavanger, Norway (epidemiologic cohort study of PD: N = 238; consecutive PD referrals to old-age psychiatry services: N = 9). All patients at both centers were assessed prospectively with a standardized physical examination that incorporated an operationalized evaluation of parkinsonism and psychotic symptoms. The diagnostic evaluation has been described previously and is only briefly reviewed here.[16] The study was conducted from June 1995 to May 2003.

For a diagnosis of Parkinson's disease, at least 2 of the following signs had to be present: resting tremor, rigidity, akinesia, and postural instability. The response to a dopaminergic agent had to be at least moderate. Patients with other neurologic diagnoses or presence of radiologic structural brain abnormalities compatible with diagnoses other than Parkinson's disease were excluded.[16] Parkinsonism prior to neuroleptic treatment was staged using the Hoehn and Yahr scale.[17]

Delusions were defined as a false unshakable belief, which could not be understood in terms of the person's culture or peer group, with the additional stipulation that the delusions should occur over a period longer than 1 week to distinguish them from confabulations. Visual hallucinations were defined as a visual percept in the absence of a stimulus. It was stipulated that these hallucinations must have been directly reported to the assessor or reported to the informant by the patient and could not be inferred from behavior.[1]

Postmortem diagnosis was made according to operationalized pathologic criteria.[18,19] If autopsy tissue was available, the neuropathologic diagnosis took primacy. If no autopsy tissue was available, patients were clinically diagnosed according to validated operationalized criteria.[18,20,21] As stipulated in the consensus criteria used at both centers, a diagnosis of DLB was made only if the onset of parkinsonism occurred less than 1 year prior to the onset of dementia. If onset of dementia occurred more than 1 year after onset of parkinsonism, the diagnosis was PDD. Patients receiving neuroleptic treatment before the onset of Parkinson's disease were excluded. A high degree of clinical diagnostic accuracy has been achieved in Newcastle for the operationalized clinical diagnosis in the first 50 patients coming to postmortem from the overall sample of 338 individuals within the overall case register (DLB: sensitivity = 0.83, specificity = 0.91; AD: sensitivity = 0.87, specificity = 0.83).[18]

The criteria to diagnose dementia in people with longstanding Parkinson's disease in Stavanger was based on a semistructured interview based on the DSM-III-R dementia criteria,[22] the Mini-Mental State Examination (MMSE),[23] and the Dementia Rating Scale,[24] using population-based, age- and education-corrected normative data.[24,25] Further details of the assessment and diagnostic procedures are reported elsewhere.[11,16,27] The Stavanger Parkinson's disease patients were assessed at baseline and 4 and 8 years later, while the Newcastle cohort was assessed annually and recruited for brain donation.

The Joint Ethics Committee of Newcastle and North Tyneside Health Authority, University of Newcastle Upon Tyne (Newcastle Upon Tyne, U.K.) and The Committee for Ethics in Medical Research, University of Bergen (Bergen, Norway) granted ethical approval. Following full explanation and discussion of the study, patients and healthy volunteers gave their consent to the test, with additional assent from the next of kin for all cognitively impaired patients.

Assessment of Neuroleptic Sensitivity

All patients who received a neuroleptic agent during a period of prospective evaluation were identified and included in the study. The following symptoms were quantified using a standardized pro forma rating of mild, moderate, or severe: cognitive worsening, impairment of consciousness/drowsiness, delirium, agitation, worsening of parkinsonism (tremor, akinesia, loss of balance, and rigidity), orthostatic hypotension, falls, dizziness, impairment of activities of daily living, and other physical symptoms. If such symptoms emerged or worsened after administration of an antipsychotic agent, and no other adequate cause was apparent, the symptom was considered as indicating sensitivity to neuroleptic treatment.

Mild to moderate sensitivity reaction was defined as having 1 symptom of not more than moderate severity, or more than 1 symptom of mild severity. Severe sensitivity reaction was defined as present if there was (1) documented worsening of parkinsonism and at least 1 other severe symptom; (2) documented worsening of parkinsonism and a minimum of 2 symptoms, one of at least moderate severity; and (3) in the absence of worsening of parkinsonism, 2 symptoms of at least moderate severity.

The clinical ratings were made by one of the authors (D.A.) blind to neuropathologic and as far as possible clinical diagnosis, although the presence of the target symptoms would have given information pertaining to the likely diagnostic assignment.

Neuropathologic Evaluation

Formalin-fixed right cerebral hemispheres were sliced in the coronal plane and blocks were embedded in paraffin for immunochemistry analysis. The quantitative assessment of Lewy body density followed the consensus protocol,[28] but used α-synuclein rather than ubiquitin immunohistochemical methods to detect and distinguish cortical Lewy bodies. Quantification of Alzheimer pathology (senile plaques and neurofibrillary tangles) was performed according to standard protocols (Consortium to Establish a Registry for Alzheimer's Disease and Braak staging).[19,29]

Statistics

The main focus for the current article is severe NSR, as this is clinically both distinct from and more serious than the mild reactions, which are predominantly worsening of parkinsonism. Therefore, for the majority of evaluations, the groups of patients with no NSR or mild to moderate NSR are grouped together and compared with individuals who experienced severe NSR. Mean values and proportions were compared using 1-way analysis of variance and χ^2 tests as appropriate. p Values below .05 were considered statistically significant.

RESULTS

One hundred seven patients taking neuroleptics were identified. Eight Stavanger patients and 5 Newcastle patients were excluded due to diagnoses other than DLB, AD, PD, or PDD or missing data. Ninety-four patients were included (DLB = 15, PDD = 36, PD = 26, AD = 17). In 80% (N = 12) of DLB and 71% (N = 12) of AD patients, the diagnosis was autopsy confirmed.

The mean observation period was 2.7 years in Newcastle and 5.2 years in Stavanger. At first assessment, DLB patients who had received neuroleptic treatment were older than those who had not received treatment (mean age = 81.3 vs. 76.1 years, p = .013), whereas sex distribution was similar. In the AD and PD groups, there were no differences in age or sex between those with or without neuroleptic treatment.

Table 1. Frequency of Neuroleptic Sensitivity Reactions (NSRs) According to Diagnosis in 94 Patients[a,b]

Frequency	DLB (N = 15)	PDD (N = 36)	PD (N = 26)	AD (N = 17)
No NSR	2 (13)	16 (44)	15 (58)	10 (59)
Mild to moderate NSR	5 (33)	6 (17)	4 (15)	7 (41)
Severe NSR	8 (53)	14 (39)	7 (27)	0

[a]All values are shown as N (%).
[b]$\chi^2 = 12.4$, df = 3, p = .006.
Abbreviations: AD = Alzheimer's disease, DLB = dementia with Lewy bodies, PD = Parkinson's disease, PDD = Parkinson's disease with dementia.

Twenty-nine patients (31%) experienced severe NSR, 22 (23%) had mild NSR, and 43 (46%) did not have NSR. The distribution of patients with NSR in the different diagnostic groups is shown in Table 1. The proportion of patients with severe NSR was 53% in DLB and 39% in PDD, compared with 27% in PD and none in AD ($\chi^2 = 12.4$, df = 3, p = .006).

There were no significant differences between patients with and without severe NSR with regard to age (p = .8), duration of disease (p = .4), MMSE score (p = .7), Hoehn and Yahr scale stage (p = .4), or sex distribution (Table 2). There were no associations between AD pathology (senile plaques, neurofibrillary tangles) or Lewy body distribution and the occurrences of NSR in the patients (DLB = 13, PDD = 3) examined at autopsy (Table 3).

The most frequent symptoms reported were emergence or worsening of parkinsonism. Worsening of at least 1 extrapyramidal symptom occurred in 27 (93%) of those with severe NSR. Of those patients with severe NSR, drowsiness or impaired consciousness was reported in 18 (62%), worsening of cognition in 10 (35%), and decrease in activities of daily living in 9 (31%). Of the 8 DLB patients with severe NSR, 2 (25%) died within 4 weeks of neuroleptic exposure, and 2 (14%) of the 14 PDD patients with severe NSR died within 1 year of exposure. Worsening of parkinsonism was not seen in any of the patients without NSR, but was evident in 21 (96%) of those patients with mild to moderate NSR.

Sixty-one percent (N = 57) of patients received 1 period of treatment with neuroleptics, 30% (N = 28) received 2 treatment periods, and 9% (N = 8) received more than 2 treatment periods. Forty-two percent (N = 39) received typical neuroleptic agents, and 58% (N = 55) received atypical neuroleptic agents. The proportion receiving typical antipsychotic drugs was higher in the DLB (73% [N = 11]) and AD (88% [N = 15]) patients compared with the PDD (25% [N = 9]) and PD (15% [N = 4]) patients ($\chi^2 = 32.9$, df = 3, p < .001). However, the proportion with severe NSR was 31% (N = 29) both among subjects receiving typical and atypical antipsychotics. Overall, there was a significant difference in the fre-

Table 2. Characteristics of 94 Patients With and Without Neuroleptic Sensitivity Reactions (NSRs)

	Dementia With Lewy Bodies			Parkinson's Disease With Dementia			Parkinson's Disease Without Dementia		
Characteristic	No Severe NSR	Severe NSR	p	No Severe NSR	Severe NSR	p	No Severe NSR	Severe NSR	p
Female/male, N	4/3	6/2	.5	11/11	4/10	.8	12/7	4/3	.2
Age, mean (SD), y	81.4 (4.1)	80.1 (6.6)	.2	75.6 (7.4)	75.4 (4.8)	.6	72.4 (6.2)	73.9 (4.7)	.8
Duration of disease, mean (SD), y	2.8 (2.4)	5.1 (4.1)	.7	13.2 (6.2)	12.2 (4.5)	.4	13.2 (4.2)	13.7 (5.5)	.6
Mini-Mental State Examination score, mean (SD)	11.1 (9.9)	13.3 (8.0)	1.0	19.2 (6.3)	17.3 (6.6)	.8	26.2 (4.1)	27.1 (3.5)	.3
Preneuroleptic Hoehn and Yahr scale stage, mean (SD)	1.4 (1.8)	1.4 (1.4)	.7	3.4 (0.8)	3.3 (1.0)	.9	3.2 (0.7)	2.8 (0.8)	.6

Table 3. Characteristics of Patients With Neuropathologically Verified Dementia With Lewy Bodies (N = 12) and Parkinson's Disease With Dementia (N = 3) Examined at Autopsy

		Neuroleptic Sensitivity		
Characteristic	Designation	None (N = 4)	Mild to Moderate (N = 5)	Severe (N = 6)
CERAD plaque severity	None	1	0	0
	Mild	1	0	1
	Moderate	0	2	2
	Severe	2	3	3
Braak stage	0–II	2	2	4
	III/IV	1	3	1
	V/VI	1	0	1
Dementia with Lewy bodies type	Brainstem	0	0	0
	Limbic	2	1	2
	Neocortical	2	4	4

Abbreviation: CERAD = Consortium to Establish a Registry for Alzheimer's Disease.

Table 4. Proportion of Patients With Neuroleptic Sensitivity Reactions (NSRs) and Dosage of the Most Commonly Used Neuroleptic Drugs

Drug	N	Severe NSR	Median Daily Dosage, mg	Interquartile Range (low)	Interquartile Range (high)
Olanzapine	33	19	5	2.5	5
Risperidone	8	2	1	1	1
Clozapine	9	1	25	25	75
Thioridazine	16	1	25	12.5	50

quency of severe NSR with different neuroleptic drugs ($\chi^2 = 9.9$, df = 4, p = .04). The highest frequency was seen in those patients treated with olanzapine (Table 4).

DISCUSSION

Severe NSR was defined according to operationalized criteria applied blind to neuropathologic diagnosis. The main finding in this study was the high frequency of severe NSR across the spectrum of Lewy body diseases, including PD (27%) and PDD (39%) as well as DLB (53%). There were no significant differences in age between people with or without severe NSR. Greater caution would seem appropriate for the use of antipsychotic agents in PD and, in particular, PDD patients. In common with previous reports,[4–7] severe NSR was not identified in patients with AD.

Severe NSRs were reported for patients taking atypical as well as typical neuroleptic drugs. Although comparisons are problematic because agents were not randomly assigned and there were differences in the frequency of use of individual agents in PDD and DLB, there was a significant difference in the frequency of severe NSR with different neuroleptic agents, with potentially important implications for clinical practice. Although a substantial proportion of diagnoses were made neuropathologically, some were made based upon operationalized clinical criteria, and the possibility of some incorrect diagnostic assignment cannot be ignored. The highest frequency occurred in patients receiving olanzapine (58%) and the lowest occurred with thioridazine (6%) and clozapine (11%). Our findings thus add support to a recent consensus recommendation suggesting an acceptable risk from clozapine but an unacceptable safety profile of olanzapine for the treatment of psychosis in Parkinson's disease.[9]

A recent report[30] of the long-term efficacy and tolerability of the atypical antipsychotic quetiapine also identified that PDD patients are more likely to experience worsening of their symptoms than Parkinson's disease patients without dementia. The apparent differential frequencies of severe NSR with different neuroleptic drugs indicated that dysfunctional dopamine D_2 receptors are unlikely to be the sole explanation for these phenomena. Further mechanistic studies are required to enable better prediction of "at-risk" people within the Lewy body disease spectrum, to optimize choices between different neuroleptic agents, and to evaluate the potential role of alternative pharmacologic approaches such as cholinesterase inhibitors.[31]

In DLB patients, there was no association between the frequency of severe NSR and the severity of concurrent Alzheimer pathology, indicating that the "Lewy body variant" cases are all at equally high risk as DLB patients without concurrent AD pathology. This finding is clinically important, as these patients have a symptom profile less typical of DLB and are, hence, more difficult to clinically distinguish from AD, with substantial implications for the use of neuroleptics in AD patients. These findings also emphasize the importance of developing improved criteria

for the Lewy body variant of AD, particularly as less than 50% of these patients meet operationalized clinical criteria for probable DLB.[32] In the Parkinson's disease patients, the presence of dementia indicated a higher risk for severe NSR, but there were no other clinical characteristics associated with elevated risk of severe NSR.

It is a limitation of the current study that only a small number of PDD and no Parkinson's disease patients were examined at autopsy; hence, the relationship of AD pathology and severe NSR could not be determined in these groups. Reports of loss of L-dopa responsiveness in PDD and of significant striatal α-synuclein pathology in DLB[33] are consistent with a hypothesis that neuronal loss or dysfunction within the putamen may be pathophysiologically relevant for the higher frequency of NSR in these groups. Low levels of cerebrospinal fluid dopamine metabolites may be predictive of neuroleptic malignant syndrome reactions in Parkinson's disease patients withdrawn from antiparkinsonian agents.[34] Steroid pulse therapy has been shown to be useful for this syndrome.[10] It will be important to determine whether these approaches can also help in the prediction of at-risk patients and the treatment of severe NSR in patients with DLB, Parkinson's disease, and PDD.

In conclusion, there was a high frequency of severe NSR in patients with Parkinson's disease and PDD as well as DLB independent of clinical and neuropathologic characteristics, with key implications for the use of neuroleptics in these populations.

Drug names: clozapine (Clozaril, FazaClo, and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

REFERENCES

1. Ballard C, Holmes C, McKeith I, et al. Psychiatric morbidity in dementia with Lewy bodies: a prospective clinical and neuropathological comparative study with Alzheimer's disease. Am J Psychiatry 1999;156: 1039–1045
2. Fenelon G, Mahieux F, Huon R, et al. Hallucinations in Parkinson's disease: prevalence, phenomenology and risk factors. Brain 2000;123: 733–745
3. Rahkonen T, Eloniemi-Sulkava U, Rissanen S, et al. Dementia with Lewy bodies according to the consensus criteria in a general population aged 75 years or older. J Neurol Neurosurg Psychiatry 2003;74:720–724
4. McKeith I, Fairbairn A, Perry R, et al. Neuroleptic sensitivity in patients with senile dementia of Lewy body type. BMJ 1992;305:673–678
5. Ballard C, Grace J, McKeith I, et al. Neuroleptic sensitivity in dementia with Lewy bodies and Alzheimer's disease [letter]. Lancet 1998;351: 1032–1033
6. Imamura T, Hirono N, Hashimoto M, et al. Clinical diagnosis of dementia with Lewy bodies in a Japanese dementia registry. Dement Geriatr Cogn Disord 1999;10:210–216
7. Sadek J, Rockwood K. Coma with accidental single dose of an atypical neuroleptic in a patient with Lewy body dementia [letter]. Am J Geriatr Psychiatry 2003;11:112–113
8. Piggott MA, Perry EK, Marshall EF, et al. Nigrostriatal dopaminergic activities in dementia with Lewy bodies in relation to neuroleptic sensitivity: comparisons with Parkinson's disease. Biol Psychiatry 1998;44: 765–774
9. The Movement Disorder Society Task Force. Drugs to treat dementia and psychosis: management of Parkinson's disease. Mov Disord 2002;17 (suppl 4):S120–S127
10. Sato Y, Asoh T, Metoki N, et al. Efficacy of methylprednisolone pulse therapy on neuroleptic malignant syndrome in Parkinson's disease. J Neurol Neurosurg Psychiatry 2003;74:574–576
11. Aarsland D, Andersen K, Larsen JP, et al. Prevalence and characteristics of dementia in Parkinson disease: an 8-year prospective study. Arch Neurol 2003;60:387–392
12. Aarsland D, Ballard C, Larsen JP, et al. A comparative study of psychiatric symptoms in dementia with Lewy bodies and Parkinson's disease with and without dementia. Int J Geriatr Psychiatry 2001;16:528–536
13. Tiraboschi P, Hansen LA, Alford M, et al. Cholinergic dysfunction in diseases with Lewy bodies. Neurology 2000;54:407–411
14. Harding AJ, Broe GA, Halliday GM. Visual hallucinations in Lewy body disease relate to Lewy bodies in the temporal lobe. Brain 2002; 125:391–403
15. Merdes AR, Hansen LA, Jeste DV, et al. Influence of Alzheimer pathology on clinical diagnostic accuracy in dementia with Lewy bodies. Neurology 2003;60:1586–1590
16. Tandberg E, Larsen JP, Nessler EG, et al. The epidemiology of Parkinson's disease in the county of Rogaland, Norway. Mov Disord 1995;10:541–549
17. Hoehn MH, Yahr MD. Parkinsonism: onset, progression, and mortality. Neurology 1967;17:427–442
18. McKeith IG, Ballard CG, Perry RH, et al. Prospective validation of consensus criteria for the diagnosis of dementia with Lewy bodies. Neurology 2000;54:1050–1058
19. Mirra SS, Heyman A, McKeel D, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD), pt 2: standardization of the neuropathologic assessment of Alzheimer's disease. Neurology 1991;41:479–486
20. McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984;34:939–944
21. Larsen JP, Dupont E, Tandberg E. Clinical diagnosis of Parkinson's disease: proposal of diagnostic subgroups classified at different levels of confidence. Acta Neurol Scand 1994;89:242–251
22. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revision. Washington DC: American Psychiatric Association; 1987
23. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–198
24. Mattis S. Dementia Rating Scale. In: Bellak L, Karasu TB, eds. Geriatric Psychiatry: A Handbook for Psychiatrists and Primary Care Physicians. New York, NY: Grune & Stratton; 1976:108–121
25. Crum RM, Anthony JC, Bassett SS, et al. Population-based norms for the Mini-Mental State Examination by age and educational level. JAMA 1993;269:2386–2391
26. Lucas JA, Ivnik RJ, Smith GE, et al. Normative data for the Mattis Dementia Rating Scale. J Clin Exp Neuropsychol 1998;20:536–547
27. Ballard CG, Aarsland D, McKeith I, et al. Fluctuations in attention: PD dementia vs DLB with parkinsonism. Neurology 2002;59:1714–1720
28. McKeith IG, Galasko D, Kosaka K, et al. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. Neurology 1996;47:1113–1124
29. Braak H, Braak E. Neuropathological staging of Alzheimer-related changes. Acta Neuropathol (Berl) 1991;82:239–259
30. Fernandez HH, Trieschmann ME, Burke MA, et al. Long-term outcome of quetiapine use for psychosis among parkinsonian patients. Mov Disord 2003;18:510–514
31. McKeith I, Del Ser T, Spano P, et al. Efficacy of rivastigmine in dementia with Lewy bodies: a randomised, double-blind, placebo-controlled international study. Lancet 2000;356:2031–2036
32. Ballard CG, Jacoby R, Del Ser T, et al. Neuropathological substrates of psychiatric symptoms in autopsy confirmed prospectively studied patients with dementia with Lewy bodies (DLB). Am J Psych 2004;161:843–849
33. Duda JE, Giasson BI, Mabon ME, et al. Novel antibodies to synuclein show abundant striatal pathology in Lewy body diseases. Ann Neurol 2002;52:205–210
34. Ueda M, Hamamoto M, Nagayama H, et al. Biochemical alterations during medication withdrawal in Parkinson's disease with and without neuroleptic malignant-like syndrome. J Neurol Neurosurg Psychiatry 2001;71:111–113