l-Dopa responsiveness in dementia with Lewy bodies, Parkinson disease with and without dementia

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Neurology 2004;63;376
DOI 10.1212/01.WNL.0000130194.84594.96

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Abstract—The authors analyzed whether nondemented (PD) and demented Parkinson patients (PDD) and patients with dementia with Lewy bodies (DLB) respond similarly in the levodopa test (LDT). Percentage of motor improvement was similar in the three groups; the proportion of patients with 10% and more improvement was greater in PD than in PDD and DLB. Positive LDT was predictive for favorable response in chronic levodopa treatment, but also some nonresponsive demented patients profited from chronic levodopa therapy.

NEUROLOGY 2004;63:376–378

Dementia with Lewy bodies (DLB) is clinically characterized by progressive dementia, parkinsonian motor symptoms, fluctuations in cognitive functions and vigilance, and visual hallucinations.[1] An interval of 1 year or less between onset of motor symptoms and dementia is required for diagnosis of DLB, whereas dementia developing later than 1 year after manifestation of L-dopa-responsive parkinsonian motor symptoms is designated PD with dementia (PDD).[1] Previous studies suggest that DLB patients exhibit less resting tremor and asymmetry of symptoms and more posture and gait impairment than do patients with uncomplicated PD.[2,3] Non-quantitative studies observed diminished levodopa responsiveness in some DLB patients.[2]

The levodopa test (LDT) is a generally accepted instrument for the assessment of levodopa responsiveness of parkinsonian motor syndromes.[4] We tested the null hypothesis that DLB, PDD, and PD patients respond similarly in the LDT and to chronic levodopa treatment.

Patients and methods. Patients with probable DLB (including all major criteria, namely dementia, parkinsonian motor syndrome, visual hallucinations, and fluctuations of intellectual functions and alertness), PDD, and PD, who had no history of neuroleptic therapy and no significant concomitant cerebrovascular pathology (CT or MRI), such as vascular dementia,[5] territorial infarcts, or relevant subcortical vascular encephalopathy, were consecutively enrolled until 20 patients per group were available. Because of an age mismatch among the three groups, six PD patients aged under 65 were replaced with six individuals aged 65 and older. Clinical ratings by means of the Unified PD Rating Scale (UPDRS) motor scale[6] were performed by two experienced investigators with good interrater reliability (intraclass correlation coefficient r = 0.9646).

Pretreated patients (16 PD, 20 PDD, and 7 DLB patients) were withdrawn from levodopa for a minimum of 12 and from dopamine agonists (pramipexole and ropinirole) for 36 hours. The LDT was performed in the morning during fasting state. Patients were attentive and not psychotic. They were first rated using the UPDRS motor subscale, then challenged with 200/50 mg oral soluble levodopa/benserazide (Madopar LT) and retested 1 hour later, whereby the UPDRS motor scale On:Off ratio was calculated (primary outcome measure). Moreover, UPDRS subscales I, II, and IV, the Hoehn and Yahr scale,[6] and the Mini-Mental State Examination (MMSE) were performed. Kruskal-Wallis analysis of variance (ANOVA) and the Mann-Whitney U test were chosen, with alpha values ≤ 0.05 considered significant.

Irrespective of LDT results, all patients were put on the optimum (in terms of motor effect and tolerability) chronic levodopa therapy, PD patients also on dopamine agonists, and followed for 0.4 to 3 years. Motor response to chronic L-dopa/dopamine-agonist therapy was evaluated in interviews with patients and caregivers, repeated clinical assessments, by means of patients' diaries and levodopa withdrawals, and rated by consensus (S.B.B., G.R.) as ineffective, mildly, moderately, or markedly effective.

Results. *Demographic and clinical data.* Demographic and clinical data are available in tables 1 and 2. Age was similar in the three groups, age at disease onset significantly higher, and duration of parkinsonian motor symptoms significantly shorter in DLB than in PDD or PD, and also shorter in PD than in PDD. Duration of dementia was insignificantly shorter in DLB than in PDD. The UPDRS I scores (mentation, depression, thought disorder, motivation, and initiative) were significantly higher in DLB than in PDD or PD. MMSE sum scores were comparable in DLB and PDD, and significantly lower than in PD. Prevalence of comorbidities was comparable in the three groups. Despite shorter duration of parkinsonian motor symptoms in DLB, the UPDRS motor sum scores, the sum of the scores for items considered to be independent of cognitive functions (hypomimia, resting and action tremor, rigidity, bradykinesia),[7] and Hoehn and Yahr scores during "practical Off" were comparable in the three groups. DLB patients had higher scores for posture impairment ($p = 0.05$) and lower resting tremor scores ($p = 0.03$; Kruskal-Wallis ANOVA and Mann-Whitney U test; data not shown) than did PD patients. Three patients in the DLB, six in the PDD, and seven in the PD group showed dyskinesia; four

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Received November 25, 2003. Accepted in final form March 12, 2004.

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Table 1 *Demographic and clinical data*

Group	Age, y	M/F	Age at disease onset, y	Duration of parkinsonian motor symptoms, y	Duration of dementia, y	UPDRS I	Hoehn and Yahr stage (OFF)	MMSE	Comorbidities
DLB (n = 20)	75.9 ± 5.0	12/8	[b]73.6 ± 5.8[a]	[b]2.4 ± 1.7[b]	2.3 ± 1.5	[b]8.4 ± 2.7[a]	3.8 ± 1	[b]20.9 ± 4.7	h: 5, c: 7, hc: 3, dm: 0, ob: 2, o: 6
PDD (n = 20)	74.0 ± 5.4	12/8	63.0 ± 9.2[a]	11.0 ± 5.8[b,a]	3.3 ± 3.3	6.3 ± 1.8[a,b]	4.1 ± 0.8	20.6 ± 5.9[b]	h: 5, c: 5, hc: 3, dm: 2, ob: 2, o: 8
PD (n = 20)	73.4 ± 5.3	10/10	[b]65.7 ± 6.2	[b]7.8 ± 4.9[a]	—	[b]2.9 ± 2.4[b]	3.4 ± 1	[b]28.1 ± 1.1[b]	h: 8, c: 5, hc: 2, dm: 3, ob: 0, o: 5
Kruskal-Wallis ANOVA *p* values	0.30		0.0002	0.0001		0.0001	0.11	0.001	

Values are mean ± SD or n. Comparison of the three groups (DLB/PDD, DLB/PD, PDD/PD) by means of the Mann-Whitney *U* test.

[a] $p < 0.05$.
[b] $p < 0.0001$.

UPDRS = Unified Parkinson Disease Rating Scale; MMSE = Mini-Mental State Examination; DLB = dementia with Lewy bodies; h = hypertension; c = coronary heart disease; hc = hypercholesterolemia; dm = diabetes mellitus; ob = obesity; o = "other" (anemia, aortal-coronary bypass, breast cancer, compensated renal dysfunction, M. Bechterew, pulmonary emboli, aortal stenosis, chronic obstructive pulmonary disease); PDD = Parkinson disease with dementia; PD = Parkinson disease; ANOVA = analysis of variance.

patients in the DLB, eight in the PDD, and nine in the PD group showed wearing-off phenomena. Five DLB and six PDD patients were on central cholinesterase inhibitors at time of the LDT.

Levodopa test and chronic levodopa therapy. Levodopa test and chronic levodopa therapy are shown in tables 2 and 3. Global motor improvement (ratio of UPDRS motor sum scores during "On" vs "Off") was similar in PD, PDD, and DLB. The On:Off ratios of the sum scores of motor items considered to be independent of cognitive functions[7] were also similar in the three groups. There were also no group differences for resting and action tremor, rigidity, sum scores of distal limb movements (items 23 to 26) or of axial motor functions (items 27 to 30 of the UPDRS) (data not shown). When differentiating with respect to ≤9.99%, 10% to 19.99%, ≥20%, and ≥30% responders in the LDT, the proportion of good responders was higher in PD than in PDD or DLB (see table 3). There were no differences in age, UPDRS motor scores during Off, or MMSE between ≥10% and ≤9.99% responders in the DLB group (Mann-Whitney *U* test). In all groups and patients 20% or more response on the LDT (PD n = 18; PDD n = 13; DLB n = 10) predicted marked clinical improvement under chronic levodopa therapy, 10% to 19.99% response (PD n = 1; PDD n = 4; DLB n = 5) moderate or marked response. Less than 9.99% response (PD n = 1; PDD n = 3; DLB n = 5) predicted no (PDD n = 1; DLB n = 2) or mild (PD n = 1; PDD n = 1; DLB n = 1) improvement, however, two DLB

Table 2 *Levodopa test*

	UPDRS III motor sum score†		Scores independent of cognitive functions: UPDRS III motor sum score of face, resting tremor, action tremor, rigidity, and bradykinesia†		UPDRS III motor sum score	Scores independent of cognitive functions: UPDRS III motor sum score of face, resting tremor, action tremor, rigidity, and bradykinesia
Group	OFF	ON	OFF	ON*	ON:OFF	ON:OFF
DLB (n = 20)	42.7 ± 18.6[b]	35.8 ± 14.8[b]	17.8 ± 6.6[c]	14.0 ± 5.3[c,a]	0.84 ± 0.2	0.79 ± 0.2
PDD (n = 20)	47.6 ± 11.4[c]	33.9 ± 10.3[c]	19.2 ± 7.0[c]	12.4 ± 5.8[c]	0.71 ± 0.2	0.65 ± 0.3
PD (n = 20)	40.1 ± 17.7[c]	27.1 ± 13.8[c]	15.9 ± 8.3[c]	9.8 ± 5.1[c,a]	0.68 ± 0.2	0.62 ± 0.2
Kruskal-Wallis ANOVA *p* values	0.21	0.76	0.44	0.04	0.09	0.14

Values are mean ± SD.

* Comparison of the three groups (DLB/PDD, DLB/PD, PDD/PD) by means of the Mann-Whitney *U* test.
† Comparison of the motor scores assessed in the three groups during "practical OFF" and "ON," Wilcoxon test.
[a] $p \leq 0.05$.
[b] $p \leq 0.01$.
[c] $p \leq 0.001$.

UPDRS = Unified Parkinson Disease Rating Scale; DLB = dementia with Lewy bodies; PDD = Parkinson disease with dementia; PD = Parkinson disease; ANOVA = analysis of variance.

Table 3 *Improvement in UPDRS III sum score (ON:OFF)*

Group	≤9.99%	10%–19.99%	≥20%	≥30%
DLB (n = 20)	5 (25)	5 (25)	10 (50)	8 (40)
PDD (n = 20)	3 (15)	4 (20)	13 (65)	8 (40)
PD (n = 20)	1 (5)	1 (5)	18 (90)	12 (60)

Values are n (%).

UPDRS = Unified Parkinson Disease Rating Scale; DLB = dementia with Lewy bodies; PDD = Parkinson disease with dementia; PD = Parkinson disease.

and one PDD patient profited moderately to markedly from chronic levodopa therapy.

Discussion. The present study shows that patients with PDD, PD, or DLB with significant parkinsonian symptoms respond similarly on the LDT. In accordance with the literature[2] the proportion of patients with no or little response to levodopa is higher and with good response lower in DLB than in PDD or PD.

To minimize selection bias we enrolled consecutive patients admitted to our institution irrespective of age, insurance status, disease severity, or domicile. Multimorbid, markedly handicapped residents of senior homes, however, might be underrepresented in our samples. Replacement of six PD patients aged under 65 with six patients older than 65 did not alter the results. The patients were carefully examined by experienced specialists including imaging, and comorbidities were similar in the three groups. Moreover, the specificity of the clinical diagnostic criteria for DLB, PDD, and PD approximates 90%.[8]

However, the samples were relatively small, long-term levodopa response in pretreated patients might have modified the motor scores during "practical Off,"[9] and the proportion of pretreated patients was different in the three groups, so that a type II error in the results cannot be ruled out.

Our study demonstrates that in all three groups ≥10% response on the LDT is predictive for effective chronic levodopa therapy. Fifteen (75%) DLB patients improved moderately to markedly under chronic levodopa treatment. On the other hand, patients with less than 10% response (5 DLB, 3 PDD, 1 PD patients) may or may not profit from chronic levodopa therapy. In any case, chronic levodopa therapy should be attempted in every PDD and DLB patient.

In accordance with the literature, DLB patients were characterized by higher age at disease onset, shorter disease duration, but similar motor impairment suggesting more rapid progression of motor symptoms and thus of nigro-striatal, but also non-dopaminergic pathology in DLB as compared to PDD and PD, which has recently been demonstrated.[3,10]

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