Original Article

An Analysis of Long-term L-dopa Therapy in 122 Cases of Parkinson's Disease over 14 Years
—When should L-dopa therapy be initiated?—

Toshikatsu Indo and Akira Takahashi

L-Dopa was administered to 122 patients with Parkinson’s disease over a time period up to 14 years. The results were summarized below. 1) The akinesia and postural instability scores were significantly improved up to the 9th year. 2) The rigidity and static tremor scores and the Parkinson score were significantly improved up to the 11th year. 3) The Yahr stage was significantly improved up to the 8th year. 4) The time course of Parkinson score was investigated in three groups, Yahr stage I/II group, Yahr stage III group, and Yahr stage IV/V group, taking into account the time interval between the onset of the disease and initiation of L-dopa therapy. No significant difference was found among the three groups. The above results suggested that the long-term prognosis of patients on L-dopa therapy in Japan was better than in Western countries. It was also thought that L-dopa therapy should be instituted at the earliest possible stage of the disease.

Key Words: Parkinson’s disease, L-dopa therapy, Long-term L-dopa syndrome

Even today, L-Dopa therapy is undoubtedly the most important therapeutic approach to Parkinson’s disease. It has been pointed out that the effect of L-dopa becomes gradually attenuated as the duration of treatment increases. For example, Rinne et al. reported that a complete reversion to the pretreatment condition occurred 7 years after initiation of treatment and Rajput et al. also reported that the same occurred 5 years after initiation of treatment. In Japan, we know of few published reports on this subject. There are opposite views on the opportune time of initiation of L-dopa therapy from the standpoint of long-term prognosis: one school of thought claims that the initiation of L-dopa therapy should be postponed until the degree of disability is so advanced as to interfere with activities of daily living. The other school says that L-dopa therapy should be initiated at the earliest possible stage. The question remains to be answered yet.

The present study was conducted to investigate the time course of the clinical effect of L-dopa in 122 patients on the therapy for a varying period of time up to 14 years and also to determine which is more appropriate, the early initiation of L-dopa therapy or the postponement of L-dopa therapy up to the time when functional disturbances have progressed so much as to cause difficulties in daily life.

SUBJECTS AND METHODS

The study was conducted in 122 patients with Parkinson’s disease. They were 54 men and 68 women, aged 39 to 78 years (mean ± S.E., 59.3 ± 10.4 years) at the initiation of L-dopa therapy. The Yahr stage before initiation of L-dopa therapy was stage I/II in 25 patients, stage III in 48, and

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Received for publication August 20, 1985.
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stage IV/V in 49. The interval between the first onset of disease and the initiation of L-dopa therapy was 24.58 ± 27.82 months in stage I/II patients, 48.6 ± 33.90 months in stage III patients, 82.39 ± 69.65 months in stage IV/V patients. L-dopa (alone or in combination with a peripheral decarboxylase inhibitor) was administered to the above patients in stepwise-increasing doses, and weighting therapeutic effects with side effects, the daily dose of L-dopa on the single agent basis was set at 3.0 g or less. In combination therapy using L-dopa and a peripheral decarboxylase inhibitor, the actual dose of L-dopa was multiplied by 5 for calculation of the single agent equivalent. Patients treated concurrently with L-threo-DOPS or bromocriptine were excluded from the present study.

In evaluating the therapeutic effect of L-dopa, the four major signs of Parkinson's disease, i.e. muscular rigidity (R), static tremor (S), akinesia (A) and postural instability (P), were used as parameters. The Yahr stage and the Parkinson score (PS) which is a sum total of scores on a 4-point scale for 26 signs of parkinsonism (Table) were also investigated.

Evaluations were made as to the following items.

R (5 items): dropping head, upper extremities (right and left) and lower extremities (right and left); S (5 items): upper extremities (right and left), lower extremities (right and left) and head; A (5 items): poverty of movement (gait), pronation and supination of upper extremities, the same of lower extremities, circling movement on standing, and leaving the bed and standing on feet; and P (3 items): forward, sideway and backward.

As to the evaluation method, PS and four major signs of the disease were all evaluated on the 4-point scale of severe = 3, moderate = 2, mild = 1, and none = 0. Thus, the maximum score was 15

<table>
<thead>
<tr>
<th>Table. Quantitative Scale of Disability of Parkinson's Disease</th>
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<tr>
<td><strong>Items</strong></td>
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<tr>
<td>(1) Abnormal posture</td>
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<td>(2) Masked face</td>
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<td>(3) Speech disturbance</td>
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<td>(4) Dropping head</td>
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<td>(5) Upper extremity (r)</td>
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<td>(6) Upper extremity (l)</td>
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<td>(7) Lower extremity (r)</td>
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<td>(11) Lower extremity (r)</td>
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<td>(12) Lower extremity (l)</td>
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<tr>
<td>(13) Head</td>
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<tr>
<td>(14) Poverty of movement (gait)</td>
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<td>(15) Pronation and supination of upper extremities</td>
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<td>(16) Pronation and supination of lower extremities</td>
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<td>(17) Circling movement on standing</td>
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<td>(18) Leaving the bed and standing on feet</td>
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<td>(19) Anteflexed posture</td>
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<td>(20) Short range between legs on gait</td>
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<td>(21) Absence of arm pendulung</td>
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<td>(22) Start hesitation</td>
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<td>(23) On turning</td>
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<td>(24) Forward</td>
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<td>(25) Sideway</td>
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<td>(26) Backward</td>
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3: Severe, 2: Moderate, 1: Mild, 0: None
for each of R, S and A, 9 for P, and 78 for PS. Using the above evaluation criteria, neurological examination was made for the four major signs, PS and Yahr stage immediately prior to L-dopa therapy and after initiation of L-dopa therapy. As a rule, L-dopa therapy was first given on the inpatient basis and then on the outpatient basis after switching to the maintenance dose. The patient was examined every two weeks to follow the changes in efficacy of L-dopa. It is known that with prolongation of L-dopa therapy, some cases show the wearing-off phenomenon or, though rarely, the on-and-off phenomenon. In both cases, the score midway between the on-phase and the off-phase was adopted as an indicator of the effect of L-dopa therapy. According to the above evaluation method, we investigated the opportune time of initiation of L-dopa therapy as well as the efficacy of long-term L-dopa therapy. In statistical analysis, if the significance level was 5% or less, the

![Fig. 1-A. Time courses of mean neurological sign scores (Rigidity: R, static tremor: S, akinesia: A).](image)

![Fig. 1-B. Time course of mean neurological sign score (postural instability: P).](image)
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difference was considered to be significant.

RESULTS

1) Time courses of mean scores of neurological signs

(1) Time course of R score (Fig. 1-A)

The R score which was 7.25 ± 3.99 immediately before initiation of L-dopa therapy improved to 1.56 ± 2.37 after 6 months, and 1.54 ± 2.41 after 12 months. The score hit the bottom of 1.37 ± 2.32 after 2 years but then tended to increase gradually. However, compared to the pretreatment level the score was still as low as 2.50 ± 2.56 in the 10th year and 1.0 ± 1.73 in the 11th year. In the 12th and subsequent years when the number of cases was 3 or less, too small in number to permit drawing a meaningful conclusion, the R score remained low with the exception that it was 4.0 in one case in the 14th year. The statistical analysis at the stage of 5 cases showed a significant improvement up to the 11th year (R score: 1.0 ± 1.73) as compared with the pretreatment value.

(2) Time course of S score (Fig. 1-A)

While the S score immediately before initiation of L-dopa therapy was 2.48 ± 2.25, the score hit the bottom of 0.34 ± 0.83 at 18 months. Then, it remained low with minor fluctuations and was 0.25 ± 0.47 in the 10th year and 0.1 ± 0.22 in the 11th year. The statistical analysis showed that the S score was significantly improved up to the 11th year of L-dopa therapy (S score: 0.1 ± 0.22) as compared with the pretreatment value.

(3) Time course of A score (Fig. 1-A)

The A score which was 7.13 ± 3.88 immediately before initiation of L-dopa therapy improved gradually to 1.68 ± 2.32 at 6 months. The greatest improvement, 1.63 ± 2.66, was obtained after 2 years but subsequently the score increased gradually and reached 5.06 ± 2.81 in the 10th year. The score of 4.20 ± 2.77 was registered in the 11th year. The statistical analysis showed that a significant improvement in A score was obtained up to the 9th year (A score: 4.25 ± 2.05) as compared with the pretreatment value.

(4) Time course of P score (Fig. 1-B)

The P score which was 4.07 ± 3.24 immediately before initiation of L-dopa therapy improved gradually to 0.87 ± 1.76 at 6 months. Thereafter, the score increased gradually with minor fluctuations and was 3.0 ± 2.88 in the 10th year and 3.1 ± 1.75 in the 11th year. The statistical analysis showed that a significant improvement was obtained up to the 9th year (P score: 2.0 ± 2.30) as compared with the score before treatment.

(5) Time course of Parkinson score (PS) (Fig. 2)

The PS which was 30.89 ± 15.92 immediately before initiation of L-dopa therapy improved remarkably to 6.72 ± 8.75 after 12 months, and 6.27 ± 9.06 after 2 years. However, the score then began to increase progressively and reached 8.86 ± 9.13 after 5 years, 17.50 ± 8.16 after 10 years, and 14.0 ± 8.12 after 11 years. The statistical analysis showed that the score was significantly improved up to the 11th year (PS: 14.0 ± 8.12) as compared with that at the initiation of the treatment.

(6) Time course of Yahr stage (Fig. 3)

The Yahr stage which was 3.23 ± 0.87 immediately before initiation of L-dopa therapy improved steadily to 2.02 ± 1.08 after 3 months, 1.82 ± 1.14 after 6 months, and 1.81 ± 1.19 after 18 months.

![Fig. 2. Time course of mean Parkinson score (PS).](image-url)
However, in the 2nd and subsequent year, the Yahr stage increased gradually to 2.75 ± 0.62 at 9 years after initiation of L-dopa therapy, 2.88 ± 0.64 at 10 years, and 3.0 at 11 years. The statistical analysis showed that a significant improvement in Yahr stage was obtained up to the 8th year (Yahr stage: 2.64 ± 1.22) as compared with the pretreatment value.

2) Study on the opportune time of initiation of L-dopa therapy (Fig. 4)

The chronology of Parkinson's disease shows that unless treated the disease progresses from Yahr stage I/II to Yahr stage III or IV/V in a few years. For an accurate comparison of changes due to L-dopa therapy among these three groups, it is important to take into account the time interval between the onset of the disease and the initiation of L-dopa therapy. Concerning the interval between the onset of the disease and the initiation of L-dopa therapy, it may be assumed that the time...
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period obtainable by subtracting the mean interval of 24.58 (months) in Yahr stage I/II group from the mean interval of 48.60 (months) in Yahr stage III group, i.e. 24.0 (months), is the time period in which the disease if untreated will progress from stage I/II to stage III where L-dopa therapy is to be initiated. The same holds true with the relation between stage III group and stage IV/V group. If, on the basis of this assumption, the duration (years) of L-dopa therapy in the stage I/II group is plotted on the abscissa and the Parkinson score (PS) as a disability score on the ordinate, we find a time course of Parkinson score as shown in Fig. 4. By comparing the values of PS among the groups at each point of the time scale, we may determine whether L-dopa therapy should be initiated in the early stage where the grade of disability is mild (Yahr stage I/II) or the stage where the disability has advanced to moderate grade (Yahr stage III) or whether L-dopa therapy should be withheld till the stage (Yahr stage IV/V) where disability is so advanced as to make activities of daily life difficult.

In the Yahr stage I/II group, whereas PS at initiation of L-dopa therapy was 17.82 ± 9.58, it was 4.52 ± 5.44 after 1 year and 2.78 ± 2.34 the lowest level, after 2 years. The Yahr stage III group in which L-dopa therapy was initiated at this time-point showed a PS of 22.96 ± 8.81. After 3 years (in the Yahr stage III group, at 1 year), however, the Yahr stage III group had a PS of 4.70 ± 4.70, whereas PS in the Yahr stage I/II group was 4.58 ± 4.19. Thus, statistically no significant difference was found between the two groups. After 4 years, PS was 6.75 ± 5.73 in the Yahr stage I/II group and 3.73 ± 5.15 in the Yahr stage III group. Again, no significant difference was found between the groups. At 5 years, PS in the Yahr stage I/II group was 7.63 ± 7.26 and that in the Yahr stage III group was 6.59 ± 7.50. No significant difference was found, either. About 3 months before this time point, L-dopa therapy was initiated in the stage IV/V group at which time PS was 46.51 ± 12.58. At 6 years, the Yahr stage I/II group showed a PS of 9.43 ± 8.56, while PS in the Yahr stage III group was 8.48 ± 11.24 and that in the Yahr stage IV/V group was 9.91 ± 11.66. The statistical analysis showed no significant difference among the three groups. At 7 years, PS in the Yahr stage I/II group was 6.80 ± 8.44. At this time-point, PS in the Yahr stage III group was 5.62 ± 4.61 and that in the Yahr stage IV/V group seemed to be 9.90 ± 11.81. The statistical analysis revealed no significant difference among the three groups. At 8 years, PS in the Yahr stage I/II group was 11.33 ± 8.33, while PS in the Yahr stage III group was 9.30 ± 6.20 and that in the Yahr stage IV/V group was considered to be 9.84 ± 10.59.

Since the number of cases in the Yahr stage I/II group was as small as 3, statistical analysis was made only between the Yahr stage III group and Yahr stage IV/V group. No significant difference was found between the two groups. PS in the Yahr stage I/II group was 11.33 ± 8.33, which was close to that in the Yahr stage III or IV/V group. The PS in the Yahr stage I/II group at 9 years was 16.25 ± 0.35 and at this time, PS in the Yahr stage III group was 11.06 ± 8.23 and that in the Yahr stage IV/V group was 9.11 ± 8.36. In view of the number of cases, statistical analysis was made between the Yahr stage III group and the Yahr stage IV/V group, and no significant difference was found between the two groups. After this time-point, statistical analysis could not be made because of the paucity of cases but it appeared difficult to find a difference among Yahr stage groups in the change of PS due to L-dopa therapy.

DISCUSSION

It has been pointed out that the efficacy of L-dopa in Parkinson's disease declines gradually with prolongation of the therapy1-6). As a cause for this, Marsden et al.11) reported that degeneration of the nigrostriatal dopaminergic tract progresses even during L-dopa therapy. Lieberman et al.12) argued that progression of the disease results in so few remaining nigrostriatal dopaminergic neurons that a sufficient amount of dopamine to stimulate the striatal dopamine receptors cannot be produced. As to the extent of declining efficacy, Rajput et al5) reported that the degree of improvement reaches a peak at 6 months after initiation of the therapy but the effect of the therapy begins to decline in the second year and while a significant
improvement persists up to 3 years and a half, the disability grade at 5 years is the same at initiation of L-dopa therapy. Rinne et al.\(^5\) reported that the disability grade begins to fall 2 or 3 years after initiation of L-dopa therapy and returns to the pretreatment level after 7 years. On the other hand, Yahr\(^13\) reported that the greatest improvement occurred within 3 years and that although the effect then declined gradually, an improvement of 40% was found even after 7 years. The long-term prognosis in his report was somewhat better than that reported by Rajput et al\(^5\) or by Rinne et al\(^4\).

In our present study, PS was significantly improved up to the 11th year. In the 7th year, PS stood at 11.10 and the improvement rate was 64.1% as compared with 30.89 at initiation of L-dopa therapy. This result was better than that reported by Yahr\(^13\). Rinne\(^1\) reported that individual signs of parkinsonism, just like overall improvement, returned virtually to the pretreatment level at 7 years after initiation of L-dopa therapy. In our study, in which the time courses of four major symptoms were investigated, scores for R and S were significantly improved up to the 11th year, scores for A and P were significantly improved up to the 9th year, and PS was significantly improved up to the 11th year. Thus, the same tendency was found as in the report of Rinne\(^1\).

In Japan, Kase et al\(^6\) who studied the long-term prognosis of L-dopa therapy reported that the Yahr stage did not differ significantly after 9 years of L-dopa therapy as compared with the pretreatment level. This result is similar to ours. Moreover, they reported that rigidity and static tremor were significantly improved up to the 12th year; akinesia and postural instability tended to show less and less improvements after several years: akinesia and postural instability ceased to show a significant difference after 12 years and 8 years, respectively, as compared with the pretreatment grades. Therefore, taking into account the report of Kase et al\(^6\) and our results, we may assume that the long-term prognosis of Japanese patients on L-dopa therapy is relatively better than in Western countries. This, however, should be collaborated by further detailed studies.

Referring, now, to the time of initiation of L-dopa therapy, i.e. the question of whether L-dopa therapy should be instituted at the time when the grade of disability is still mild or whether the therapy should be withheld until disability has so advanced as to interfere with activities of daily life, Lesser et al\(^8\) advanced the view that L-dopa therapy itself might induce an attenuation of effects. Rajput et al\(^5\) reported that the attenuation of effects during L-dopa therapy is inevitable and asserted that the use of L-dopa should be withheld as far as possible. On the other hand, Hoehn\(^9\) argued that L-dopa should be initiated as soon as the diagnosis of Parkinson’s disease is made, for in long-term prognosis, disability was milder in cases in which L-dopa therapy was instituted in the early stage than in cases in which the therapy was delayed. Markham et al\(^10\) classified the interval between the onset of the disease and the initiation of L-dopa therapy into three groups, i.e. 1–3 years, 4–6 years, and 7–9 years, and investigated the time courses of their disability scores. They reported that there was no significant difference in the change of the score among the three groups and that the time to initiation of L-dopa therapy was unrelated to therapeutic prognosis, concluding that L-dopa therapy should be instituted at the earliest possible stage. The results of the present study suggest that long-term prognosis does not differ, irrespective of whether L-dopa therapy is instituted at the time when disability is as mild as Yahr stage I/II or at the time when the grade of disability has progressed to Yahr stage III or IV/V. It is concluded that it is unnecessary to delay the initiation of L-dopa therapy. Therefore, L-dopa therapy should be initiated soon once the diagnosis of Parkinson’s disease has been made.

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