Should Levodopa Therapy for Parkinson's Disease be Started Early or Late? Clinical Course of the Major Tetrad in 122 Parkinsonian Patients Treated with Levodopa over 14 Years.

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The study was carried out to clarify whether levodopa should be started early or late in the course of Parkinson's disease. In this study, 122 patients treated with levodopa over 14 years were included. The time course of each of the four major signs (rigidity, static tremor, akinesia and postural instability) and Yahr stage was investigated in three groups, Yahr stage I/II group, Yahr stage III group and Yahr stage IV/V group, taking into consideration the time period preceding the initiation of levodopa therapy. When the time periods in years since onset of symptoms were matched, no significant differences were recognized among the three groups. There seemed to be no benefit in delaying levodopa therapy but, rather, levodopa therapy should be started as early as possible. The declining efficacy often recognized during levodopa therapy was thought probably due to progression of Parkinson's disease itself rather than to levodopa.

Key words: Parkinson's disease, Levodopa

In regard to the limited time in which levodopa therapy is effective for Parkinson's disease, there are two schools of thought, one proclaiming that levodopa therapy should be delayed until the disease has progressed to interfere with the patient's daily activity (1-5), while the other taking the diametrically opposite position that it is more rewarding to initiate levodopa therapy as early as possible from the standpoint of long-term prognosis (6-11).

In our previous investigation (10), we found no significant difference among the 3 Yahr stage groups of I/II, III, and IV/V in the courses of levodopa-induced dyskinesia, psychiatric symptoms and motor fluctuation and the time course of Parkinson disability score and accordingly reported that levodopa therapy should be instituted at the earliest opportunity. However, in order that we may

categorically conclude that early institution of this therapy is truly pertinent, it is essential for us to investigate whether the same conclusion could be reached in regard to the major tetrad of Parkinson's disease. It appears that to this day no pertinent research has been attempted as yet.

The purpose of this paper is to clarify the optimum timing for initiating levodopa therapy for each component sign of the major tetrad.

SUBJECTS AND METHODS

The cases were the same as those used in the previous study (10). Yahr staging before initiation of levodopa therapy disclosed stage I in 10 cases, stage II in 15 cases, stage III in 48 cases, stage IV in 30 cases, and stage V in 19 cases. These cases were grouped into the mild stage I/II group of 25 cases,

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the intermediate stage III group of 48 cases, and the advanced stage IV/V group of 49 cases. The time interval from onset of the disease to initiation of levodopa therapy was 24.58 ± 27.82 months in the stage I/II group, 48.60 ± 33.90 months in the stage III group, and 82.39 ± 69.65 months in the stage IV/V group. The daily dose of levodopa was not over 3.0 g on a single drug basis.

Efficacy evaluation was made in terms of the four major neurological signs (major tetrad) of Parkinson's disease, i.e. muscular rigidity (R), static tremor (S), akinesia (A) and postural instability (P) (10).

The time course of Yahr stage was investigated at the same time. The specific items of evaluation were as follows. In regard to R, 1) head dropping, 2) upper extremities (right and left) and lower extremities (right and left) (5 items); as to S, 1) upper extremities (right and left), 2) lower extremities (right and left), and 3) head (5 items); as to A, 1) poverty of movement (gait), 2) pronation and supination of upper extremities, 3) the same of lower extremities, 4) circling motion on standing, and 5) leaving the bed and standing on feet (5 items), and as to P, 1) forward, 2) sideways, and 3) backward (3 items). Each of the above evaluation items was classified into 4 stages and the severe sign was given the score of 3 points, the moderate sign 2 points, the mild sign 1 point, and no sign 0 point. Therefore, the maximum score was 15 points for each of R, S and A and 9 points for P. Using the above rating scale, the major neurological signs and Yahr stage immediately before initiation of levodopa therapy and those at predetermined intervals during the therapy were scored and evaluated. As the levodopa therapy was prolonged, the wearing-off phenomenon and, rarely, the on-and-off phenomenon were observed in some cases. In these cases, the score midway between the on-phase and the off-phase was adopted. In this manner, the opportune time for initiating levodopa therapy was investigated for each sign of the major tetrad and Yahr stage. Statistical analysis was performed in populations of at least 5 cases, using the 5% level of significance.

RESULTS

(1) Study of the tetrad

In a comparison of the effect of levodopa therapy among several Yahr stage groups, it is important to

take into consideration the time interval from onset of the disease to initiation of the therapy. In the present study, the mean interval was 24.58 months in the Yahr stage I/II group, 48.60 months in the III group, and 82.39 months in the IV-V group. Therefore, each tetrad score in each group was plotted on the ordinate against the number of disease years on the abscissa and the resulting pattern was shifted by the group mean interval between onset of the disease and initiation of levodopa therapy. The resulting correlations are shown in Fig. 1. The motive was that we thought that by thus aligning and comparing the time courses of each neurological sign among the 3 Yahr stage groups, we might resolve the question of whether levodopa therapy should be initiated early after onset of the disease or be postponed until the functional disability has progressed to interfere with the patient's daily activity.

As a result, for any of R, S, A, and P, statistically no significant difference was found between I/II and III groups at each of years 5, 6 and 7 after onset of the disease. There was no significant difference, either, among the three Yahr stage groups at year 8 and subsequently.

(2) Time course of Yahr stage

Fig. 2 shows the time course of Yahr stage in the three groups. Though Yahr stage as a global indicator of ADL generally tends to worsen progressively after several years following initiation of treatment, it also showed no significant difference among the 3 groups.

DISCUSSION

The above investigation generated the following three findings. First, with regard to any of the major neurological signs (muscular rigidity, static tremor, akinesia, postural instability), there was no rationale for postponing levodopa therapy until disability has progressed to interfere with daily activity. Secondly, the same was true of Yahr stage, too. Thirdly, not only from the standpoint of overall disability but also from that of long-term prognosis of the tetrad and Yahr stage, levodopa therapy need not be postponed but ought to be instituted as early as possible.

Fig. 1. Disability scores on major tetrad (R: rigidity, S: static tremor, A: akinesia, P: postural instability). When years since onset of symptoms were matched, scores did not differ between the groups despite the differing durations of levodopa treatment.

Fig. 2. Disability rated on the Yahr scale. Results were the same as Fig. 1.

Markham et al. (8) (1981) who classified cases with Parkinson's disease into 3 groups according to the interval between onset of the disease and initiation of levodopa therapy and weighted them with the duration of illness found no significant difference in the overall disability score among the three groups and proposed an early initiation of levodopa therapy. Against this, Fahn et al. (5) (1984) criticized that the UCLA scoring scale Markham et al. (8) had used did not accurately reflect the disability statuses in Parkinson's disease. However, Markham et al. (7) have recently reported that the use of the Yahr staging system as an indicator led to the same conclusion. The present study revealed no significant difference, either, among Yahr stage groups of I/II, III and IV/V. The question remained unresolved whether the position advocating an early initiation of levodopa therapy could find a rationale for each of the major neurological signs of Parkinson's disease as well. In this respect, it is very important that our present analysis covering the major tetrad also yielded results in favor of early institution of levodopa therapy.

The efficacy of levodopa in Parkinson's disease diminishes gradually after several years of administration (3, 10) and as a cause of this, some advance the view that levodopa itself is a causative factor (1, 2) but our data suggests that the decline of clinical effect of levodopa is less associated with levodopa than it is correlated with the progression of Parkinson's disease.

Guttman et al. (12) (1986) who determined the density of D₂ dopamine receptors in the caudate nucleus and putamen using [³H] spiperone in 36 cases with Parkinson's disease found that the D₂ dopamine receptor density was constant irrespective of the duration of illness, age and duration of levodopa therapy and reported that long-term levodopa therapy would not decrease the density of D₂ receptors, concluding emphatically that the

attenuation of effect in a course of levodopa therapy is not due to levodopa itself.

As a conclusion, the present authors reiterate that levodopa therapy in Parkinson's disease should be initiated as early as possible if only from the standpoint of long-term prognosis of the major tetrad and Yahr stage.

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