The long-term results of stereotaxic surgery and L-dopa therapy in patients with Parkinson's disease

A 10-year follow-up study

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Sixty patients with Parkinson's disease underwent stereotaxic surgery in Edinburgh between 1965 and 1967, and were examined every 2 years for a total follow-up period of 10 years. Although stereotaxic surgery had been extremely effective in treating tremor and rigidity, the other manifestations of Parkinson's disease were noted to progressively affect more patients at each follow-up examination. L-dopa therapy was instituted in 36 patients after 1968. The effect of L-dopa on bradykinesia was remarkable, but the long-term benefit on the other manifestations of Parkinson's disease was negligible. Furthermore, in most cases L-dopa became progressively ineffective for bradykinesia after 3 to 5 years. L-dopa-induced tremor and involuntary movements were less frequently noted in limbs contralateral to the side of a previous stereotaxic procedure. It was concluded that in patients presenting with tremor and rigidity as the major problem in their parkinsonian syndrome, the most effective form of palliative therapy is stereotaxic surgery, and that L-dopa should be reserved for the management of bradykinesia.

Key Words • Parkinson's disease • stereotaxic technique • L-dopa • tremor • rigidity • bradykinesia

Most patients with Parkinson's disease who present with tremor and rigidity unilaterally develop bilateral symptoms and bradykinesia after a few years.²,¹² In spite of initial optimism that L-dopa could permanently control Parkinson's disease, it is now clear that the progression of the disease is unaltered by L-dopa or any other form of therapy.¹,²,¹⁴ Furthermore, in most patients, L-dopa is initially effective in the management of bradykinesia but becomes progressively ineffective after a few years.¹⁸

Certainly, the goal of therapy in these patients is to postpone disability, which is initially caused by tremor and rigidity and later by bradykinesia. Although current literature indicates that L-dopa is effective in the management of bradykinesia, but less effective in the control of rigidity and tremor, the practice of many neurologists and primary care physicians is to begin L-dopa or carbidopa in patients presenting with tremor and rigidity, but without bradykinesia. Because of certain severe side-effects of long-term L-dopa therapy, such as dyskinesia and psychosis, it is important to review the situation objectively as regards the most effective form of management.

Since the therapeutic effect of L-dopa compounds may be limited to a few years, it would seem more logical to withhold L-dopa, or Sinemet, in these patients until they develop bradykinesia, provided that an effective means for the palliation of tremor and rigidity resistant to first-line anti-parkinsonian drugs were available.

Before L-dopa achieved widespread acceptance for the treatment of Parkinson's disease, stereotaxic surgery was a major form of therapy, and it had notable success in the treatment of tremor and rigidity.³,⁸,¹⁷ Improvement in methodology and stereotaxic localization, particularly at European centers, has resulted in greater accuracy for lesion placement and improved results.⁶,⁹,¹⁴ The following study will demonstrate that modern stereotaxic surgery can give good long-term palliation in the subgroup of patients whose disability is due to tremor and rigidity, and that...
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L-dopa may be advantageously instituted when bradykinesia develops later in the course of the disease.

Clinical Material and Methods

Sixty patients with Parkinson's disease underwent stereotaxic surgical procedures between 1965 and 1967 at the Western General Hospital in Edinburgh, Scotland. The surgical procedure and its electrophysiological control by microelectrode recording, as practiced in the Department of Surgical Neurology, have been described elsewhere.6

The patients were examined preoperatively and every 2 years postoperatively for a total of 10 years to determine the presence or absence of tremor, rigidity, bradykinesia, gait disturbance, speech disturbance, and mental deterioration. A speech pathologist's evaluation was included in the studies of patients exhibiting signs of speech disturbance, including a reduction of voice volume, dysarthria, or dysphasia. In patients with signs of mental deterioration, usually manifested by reduction of recent memory, the neuropsychological evaluation was more complete.

The patients were also examined in the Department of Occupational Therapy. They were evaluated as to their speed and ability to perform routine tasks and were assigned to one of five categories based upon their Activities of Daily Living (ADL) score:

Class I: no significant slowing or difficulty produced by the symptoms of the disease
Class II: some difficulty and slowing of function produced by the disease (but the patient is still totally independent)
Class III: moderate amount of difficulty produced by the disease (these patients require some part-time help to accomplish their ADL tasks)
Class IV: the patient requires help with all tasks
Class V: the patient is bedridden.

In the period 1968 to 1970, 42 of the 60 patients began to take L-dopa as additional therapy. A low dose 0.5 to 1 gm daily, was used initially and was increased until satisfactory benefit was derived or side-effects occurred. In most of these patients, carbidopa was substituted for L-dopa when carbidopa became available. Similarly, patients were evaluated every 2 years after beginning L-dopa therapy, and were assessed by the presence or absence of the same six symptoms that were used to judge the efficacy of surgical treatment, as well as the ADL score.

Results

The mean age of the patients in this study was 54.4 years with a standard deviation of 7.6 years. The average duration of symptoms at the time that the patients received surgical treatment was 7.7 years, with a standard deviation of 7.5 years. Of the 60 patients admitted to this study, 50 survived 10 years.

Surgical Results for Tremor and Rigidity

A total of 87 procedures were performed on the 60 patients: 36 unilateral, 24 bilateral, and three repeat surgical procedures. There were no operative deaths. Fifty-seven patients had a surgical procedure for tremor and 58 for rigidity. The results of the first surgical procedure on tremor are given in Fig. 1 left, which displays the percentage of patients free of tremor in the contralateral limbs at 2, 4, 6, 8, and 10 years after a stereotaxic lesion. Tremor was found to have been abolished at the first postoperative evaluation in 90%. At 4 years, 4% of the patients (that is, three patients) had recurrence of the tremor; 86% remained tremor-free. At 6 years, 73% of the patients remained free of tremor, and at 10 years, only 57% of the surviving patients (28 of 50) were still free of tremor.

At the first postoperative evaluation, 51 of the 58 patients (88%) who were operated on for rigidity were found to have had rigidity abolished (Fig. 1 right). The control of rigidity decreased with time; after 10 years, only 27 of the surviving patients (55%) remained free of rigidity. However, in most of these cases with late recurrence of tremor and/or rigidity, the recurrence was minor and not of disabling significance.
Bilateral Procedures

Twenty-four patients underwent a contralateral surgical procedure within 4 years after the first operation. Four years after the second procedure for the abolition of tremor and rigidity, the success rate was 78% for tremor and 80% for rigidity. For tremor, the surgical success rate was not significantly less on the second side than that from the original procedure when comparing the results 4 years postoperatively.

Bilateral procedures, however, were not infrequently associated with speech problems, especially if the patient had preoperative speech difficulty as a manifestation of his or her disease. Twenty-one of the 24 patients were noted to have reduced voice volume before the second surgical procedure. Nine of these patients had a significant further reduction of voice volume following the second operation.

Other Parkinsonian Manifestations

There was no beneficial effect of surgery on any of the other manifestations of Parkinson's disease, as shown by Fig. 2. The other disease manifestations progressively affected more patients at each follow-up evaluation postoperatively in terms of bradykinesia, gait disturbance, speech disorders, and mental symptoms. A relative plateau in the number of patients with each of these symptoms was attained at 6, 8, and 10 years postoperatively due to the institution of L-dopa therapy and the death of the more severely affected individuals.

Evaluation by Activities of Daily Living

At the preoperative evaluation, as shown by the ADL score, parkinsonian symptoms caused difficulty and slowing in the performance of the activities of daily living in 41 of the 60 patients (Fig. 3). After the
first stereotaxic procedure, only 10 patients were observed to have difficulty in the activities of daily living, so that 50 patients were then designated as Class I. Four years postoperatively, 23 patients still remained in Class I, 25 patients were in Class II, and the remainder were in Classes III or IV. The major cause of this deterioration was the onset of bradykinesia. The ADL distribution remained relatively the same, however, at the 6-year evaluation because 16 patients were then receiving L-dopa. At the 10-year follow-up evaluation, only 10 patients remained in ADL Class I, 10 had died, and 24 were in various stages of dependency in spite of contralateral surgical procedures in 34 patients and L-dopa therapy in 36.

Results of L-Dopa Therapy

During the period of 1968–1970, 42 patients were treated with L-dopa. The medication was discontinued in five patients because of side-effects (gastrointestinal symptoms in two, dyskinesia in two, and aggravation of symptoms in one) and in one patient because of ineffectiveness. The result of L-dopa therapy on the various manifestations of Parkinson’s disease in the remaining 36 patients is given in Fig. 4.

The greatest response to L-dopa occurred with bradykinesia. Thirty-four of the 36 patients (94%) were observed to have some degree of bradykinesia before treatment with L-dopa. Two years after L-dopa therapy was begun, only seven of the 36 patients (19%) were observed to have bradykinesia. After 4 years, however, the number of patients with bradykinesia increased to 54%. The final reduction in the percentage of bradykinetic patients occurred because the more severely affected patients had died. A transient improvement was also observed in the gait disturbances of parkinsonian patients (Fig. 4), but the number of patients thus affected increased to pretreatment levels within 4 years after therapy with L-dopa had been started.

The effect of L-dopa on rigidity was not significant when all cases were considered as a group. In individual patients, however, a reduction in rigidity was observed. This is not reflected in the group results, because these improvements were offset by other patients whose rigidity progressed. This was also the case with speech disturbances in patients treated with L-dopa. No significant consistent improvement could be documented when all cases were considered as a group.

Only one of the four patients who presented symptoms of mental deterioration before L-dopa therapy had a transient improvement in recent memory. The decrease in patients with mental symptoms from 18% to 15% (Fig. 4) reflects the fact that three patients in the group died.

Before L-dopa therapy was started, 17 of 36 patients were observed to have some degree of tremor. Two years after L-dopa was begun, 27 of the 36 patients (75%) were observed to have some degree of either tremor or other involuntary movement. Between 2 and 4 years, this number decreased slightly, because five patients had further stereotaxic surgery during that period.

Although in certain cases L-dopa was observed to reduce tremor, it was directly related to the appearance of involuntary movement in 14 cases. The side on which L-dopa-induced tremor or involuntary movements appeared depended, in part, on the prior surgical procedure. Of these 14 patients, four had recurrence of tremor on the treated side, whereas eight developed tremor on the untreated side, that is, ipsilateral to the side of the previous stereotaxic surgery. In two patients, the tremor began bilaterally after L-dopa was started.

Fig. 4. The results of 36 patients treated with L-dopa as reflected in the percentage of patients noted to have each of the symptoms or signs represented in the figure.
Surgical procedures on the basal ganglia and thalamus have had notable short-term success in the ablation of tremor and rigidity due to Parkinson's disease. Gillingham and colleagues reported 70% postoperative ablation of tremor and rigidity in a study of 60 patients with Parkinson's disease treated with thalamic and pallidal lesions. Later, the technique of microelectrode recording was incorporated into the operative procedure. The postoperative results in the present series reflect the improved accuracy afforded by microelectrode recording. The short-term rate of ablation for tremor and rigidity reported here (90% and 88%, respectively) is consistent with that reported in other series for unilateral lesions.

In this study, the surgical results for the contralateral procedures in patients with bilateral parkinsonism were only slightly worse than those for the first procedure for tremor and about the same as for the first procedure for rigidity. Similar findings were also reported by Cooper and colleagues in 1968.

Admittedly, the surgical ablation of either tremor or rigidity is of only minor benefit to the patient if its function is not improved. In our experience, and that of others, patients with tremor and rigidity are not gravely disabled by these symptoms. Most of them, on objective evaluation, demonstrate only some slowing and minimal difficulty in performing the fine tasks of daily living. However, following a stereotaxic lesion, most of these patients returned to ADL Class I. Although a small percentage of patients remained in this classification for 10 years, most deteriorated after 2 to 5 years because of bradykinesia, which was the truly disabling symptom. In our experience, bradykinesia was not improved by stereotaxic surgery, which is in agreement with the findings of others.

In this study, the effect of L-dopa on bradykinesia was pronounced for 3 to 5 years, except in patients with rapidly progressive parkinsonism, for whom its effect, even on a short-term basis, was minimal. After 3 to 5 years, most of these patients who had an initially good response to L-dopa gradually worsened. In a 5-year study of 70 parkinsonian patients treated with L-dopa, 37 maintained some degree of improvement from pretreatment levels, and the rest experienced progressive debilitation. Sweet and McDowell also found that after 5 years of L-dopa therapy, half of 47 patients remained at least 25% better than their pretreatment evaluation. Although other factors may contribute to the progressive ineffectiveness of L-dopa, one postulated explanation is that a progressive loss of dopamine receptors occurs in the basal ganglia concurrent with the advancing disease process. Yahrt, however, believed that L-dopa possesses a peculiar pharmacodynamic property that results in a finite period of usefulness.

We were unable to document any consistent improvement in parkinsonian tremor in patients treated with L-dopa. Frequently, tremor or other involuntary movements were associated with the addition of L-dopa to the therapeutic regimen. Furthermore, in many cases dyskinesia was traded for tremor between doses of L-dopa. In a study of 37 parkinsonian patients, lower urinary levels of dopamine and its metabolites were observed in bradykinetic patients than in those with tremor. This suggested that the tremor of Parkinson's disease has a different neurochemical concomitant from bradykinesia, and may explain the inconsistent response of parkinsonian tremor to L-dopa.

Although it is believed by some neurologists that the response to L-dopa is better in patients who have not undergone previous thalamic or basal ganglia surgery, we were unable to find any study in the literature to support this. On the contrary, two studies have shown that the therapeutic response to L-dopa is equally good, regardless of previous surgical therapy. Furthermore, L-dopa can be used advantageously in patients developing bradykinesia after stereotaxic surgery has been performed for tremor, since a previously performed stereotaxic procedure appears to "protect" the patient from involuntary limb movements that occur with L-dopa, as noted in this study and by others.

Even though the longevity of patients with Parkinson's disease cannot be improved at the present time, their eventual disability can be delayed with appropriate treatment. A carefully performed stereotaxic procedure can control tremor and rigidity for a number of years, and reduce the incidence of L-dopa-related involuntary movements once this drug is instituted to treat bradykinesia. Modern stereotaxy with the precision afforded by microelectrode recording allows precise subcortical localization so that smaller more specific lesions may be made to treat a particular patient's symptoms without the speech, gait, and mental complications that were not infrequently noted following larger stereotaxic lesions. Therefore, patients with disabling tremor and rigidity resistant to first-line anti-parkinsonian drugs can be safely treated by stereotaxic surgery. Since the therapeutic effect of L-dopa and carbidopa may be limited to 3 to 5 years in many cases, it would seem best to withhold these drugs until the patient develops bradykinesia, at which time the maximum therapeutic benefit may be derived from these medications.

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