Levodopa-induced dyskinesia and thalamotomy

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SUMMARY Levodopa-induced dyskinesia of the limbs in thirteen cases of Parkinsonism, which was choreic, ballistic or dystonic in type, was alleviated almost completely by stereotaxic surgery using a microelectrode technique for the ventralis oralis anterior and posterior nuclei of the thalamus, but much less by the ventralis intermedius nucleus. Control of levodopa-induced dyskinesias by thalamic lesions in the course of routine treatment of Parkinsonism is discussed.

Levodopa-induced dyskinesia, a phenomenon not recognised in the early years of levodopa treatment, has emerged as one of the major limiting factors to long-term use of levodopa, or of levodopa in conjunction with a peripheral decarboxylase inhibitor. The long-term use of dopamine agonists may also produce this unfavourable effect. The dyskinesias appear typically in the extremities, trunk and facial-oral area, and are choreic, ballistic, athetotic or even dystonic in quality. In older patients, the dyskinesias affect principally the oral-facial, buccolingual or neck areas; in younger patients with Parkinsonism, the extremities and trunk may be more involved. It is also known that levodopa-induced dyskinesia is particularly prevalent and severe among patients with early onset, that is, the juvenile type of Parkinsonism. Since juvenile Parkinsonism represents 7% to 10% of the Japanese population with Parkinson's disease, control of levodopa-induced dyskinesia has been of considerable importance to the authors.

Levodopa-induced dyskinesia has been viewed as the "reverse" phenomenon of the disturbed physiology in Parkinson's disease. Since Parkinsonian symptoms have been understood as a result of nigrostriatal dopamine deficiency, levodopa-induced dyskinesia has been interpreted as due to overdose of medicine or, possibly, to hypersensitivity of striatal neurons to dopamine.

As reported by Hughes et al., levodopa-induced dyskinesia was observed not to involve extremities contralateral to the side of thalamotomy. On the other hand, Duvoisin reported that a previous thalamotomy seemed to have no influence on the development of dyskinesia. In 25 cases he observed dyskinesia in 20 cases, which showed no difference between operated and unoperated sides. However, in all of these studies, exact identification of the operated thalamic subnuclei were not analysed accurately, since the surgical techniques then used for targeting depended mostly on neuroradiological measurements with some observations of the effects by high frequency electrical stimulation of the structures. Radiological measurement is not exact enough, especially in the antero-posterior view, when atrophy of brain exists. Effects of high frequency stimulation are also varied when the size of electrode is not small enough. The present study aims to analyse the association of levodopa-induced dyskinesia and thalamotomy, identification of the targeted structures being based on the microelectrode technique to be described. It considers the role of specific subnuclei of the thalamus in producing levodopa-induced dyskinesia as well as the physiology of dyskinesias in relationship to those of Parkinson's disease—rigidity, akinesia and tremor.

Patients and methods

Cases Thirteen cases were studied (table). Twelve belonged to the group of juvenile Parkinsonism as defined by Yokochi and Narabayashi. Symptoms of the disorder appeared at age 42 in case 13; this case is included because of its similarity to more typical examples of juvenile Parkinsonism. The cases were placed in three subgroups according to the date of surgery, that is, (1) before 1973, (2) 1974 to 1979, and (3) 1980 to the present. Structures ablated for alleviation of rigidity and/or tremor differed somewhat during these three intervals.
Table 1 *List of cases with levodopa-induced dyskinesia*

<table>
<thead>
<tr>
<th>Case</th>
<th>Age at surgery (ys)</th>
<th>Diagnosis</th>
<th>Age of onset (ys)</th>
<th>Thalamotomy on</th>
<th>Levodopa-induced dyskinesia</th>
<th>Dose of levodopa</th>
<th>Present status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>36</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>37</td>
<td>JP</td>
<td>34</td>
<td>L-Vo compl. (1968)</td>
<td>In these 3 cases, surgery was done before introduction of levodopa</td>
<td>Levodopa 1-2 g</td>
<td>bedridden, died for accident</td>
</tr>
<tr>
<td>3</td>
<td>37</td>
<td>JP</td>
<td>30</td>
<td>L-Vo compl. (1969)</td>
<td></td>
<td>Sinemet 4T (10/100)</td>
<td>back to job</td>
</tr>
<tr>
<td>4</td>
<td>44</td>
<td>JP</td>
<td>38</td>
<td>L-Vim (1975) (micro)</td>
<td>Levodopa was not used before surgery</td>
<td>Levodopa 1-2 (almost normalized ADL)</td>
<td>back to job</td>
</tr>
<tr>
<td>5</td>
<td>16</td>
<td>JP</td>
<td>12</td>
<td>L-Vim (1976) (micro)</td>
<td>severely dystonic and ballistic (+++)</td>
<td>Levodopa 0-6 g</td>
<td>bedridden</td>
</tr>
<tr>
<td>6</td>
<td>55</td>
<td>JP</td>
<td>37</td>
<td>L-Vim (1979) (micro)</td>
<td>slight levodopa-induced dyskinesia on both sides (+)</td>
<td>Sinemet 6T</td>
<td>bedridden</td>
</tr>
<tr>
<td>7</td>
<td>32</td>
<td>JP</td>
<td>25</td>
<td>R-Vim (1980) (micro)</td>
<td>L: severely dystonic &amp; choreoathetoid (+++)</td>
<td>Levodopa 0-6 g</td>
<td>back to job</td>
</tr>
<tr>
<td></td>
<td>33</td>
<td></td>
<td></td>
<td>L-Vim &amp; Vo compl. (micro) (1981)</td>
<td>Levodopa was not used before surgery</td>
<td>Levodopa 1-2 (almost normalized ADL)</td>
<td>Sinemet 3T</td>
</tr>
<tr>
<td>11</td>
<td>46</td>
<td>JP</td>
<td>31</td>
<td>R-Vo compl. &amp; Vim (micro) (1982)</td>
<td>bilat. athetoid (+) (L &gt; R)</td>
<td>Sinemet 4T</td>
<td>back to job</td>
</tr>
<tr>
<td>13</td>
<td>46</td>
<td>PA(?) or JP</td>
<td>42</td>
<td>L-Vim &amp; Vo compl. (micro) (1982)</td>
<td>R: dystonic (+)</td>
<td>Sinemet 3T</td>
<td>Sinemet 7T</td>
</tr>
</tbody>
</table>

**Change of extent of stereotaxic lesion** The authors' surgical theatre was equipped for microstereoelectrode surgery in 1973. Recording of neuronal activities through the depth microelectrode during thalamotomy was first introduced by Albe-Fessard et al. in 1963 and then developed in several centers. This method is especially useful for determining the important tremor-locked neurons in the ventralis intermediate nucleus (Vim) of the thalamus and then to demarcate and map the anteriorly lying nuclei such as the ventralis oralis posterior (Vop) and anterior (VoA)*. The details of the microelectrode recording in human thalamus are described in previous papers by Narabayashi and his co-workers, and Ohye. *VoA plus Vop are almost equivalent to the ventral lateral nucleus (VL) in American terminology. In this paper, we tried to use German terminology and the term VoA complex is used to describe both VoA and Vop together.
The first group was of cases operated prior to 1973. Stereotactic lesion placement was based upon 3-dimensional radiological measurements, analysis of thalamocortical evoked potentials at the premotor scalp area, and high-frequency electrical stimulation effects on tremor or rigidity. Relatively large lesions, approximately 7–8 mm in diameter, were produced by oil-wax injections before 1965 and by controlled hyperthermia using high-frequency electrical current after 1966. These relieved both rigidity and tremor. The lesions included both the Vo complex and the Vim. Cases 1 to 3 belong to this first group.

The second group, cases 4 to 7, was those patients operated principally to abolish tremor. It was expected that rigidity would better be treated pharmacologically. During this period, single or paired lesions of approximately 3 mm diameter were made within the Vim where the tremor-locked unitary burst discharges were recorded. These small lesions were presumed not to involve the major part of the Vo complex.

The third group, cases 8 to 13, were operated with the objective of controlling both rigidity and tremor. Paired lesions were made in each of the subnuclei. One was placed in the Vim to abolish tremor and the second in the Vo complex, anterior to the Vim lesion on the same needle track penetrating both structures in order to control rigidity.

The role of these subnuclei of the thalamus in the generation of rigidity or of tremor has been discussed by the authors in previous publications. The location and size of lesions in each group are illustrated in fig 1a, b, c and c'.

Recording of levodopa-induced dyskinesia. Levodopa-induced dyskinesia was described and characterised clinically, and surface EMG recordings were used to evaluate the severity, pattern and distribution of levodopa-induced dyskinesia in all cases. The dosage of levodopa associated with the appearance of levodopa-induced dyskinesia for each case is shown in the table. Abnormal movements in each studied case were characterised as dystonic, choreic, athetoid or ballistic. Severity was ordered according to grades ++ (severe abnormal movements), + (moderate abnormal movements), + (slight abnormal movements) and − (zero, no abnormal movements).

Results

The severity of levodopa-induced dyskinesia improved after thalamic surgery in all thirteen cases. However, relatively clear differences were observed in the degree of effect of thalamotomy upon levodopa-induced dyskinesia between each group depending upon the site of surgical lesion that was employed. Differences in lesion position, with respect to specific thalamic structures, had been readily substantiated by using the microelectrode techniques which clearly localised the position of proprioceptive neurons within the Vim and its anterior border with the Vo complex. By means of such a neurophysiological device the location of lesions with respect to the Vim and Vo complex has been unambiguous.

Thalamotomy was undertaken prior to the availability of levodopa therapy for the patients in group 1. When the drug was administered subsequently, severe dyskinesias were provoked on the unoperated side even by small doses while the operated side was not at all involved with levodopa-induced dyskinesia. This response was associated with lesions involving both Vo complex and Vim (fig 1a). In the second group of patients, where limited lesions were undertaken only for the relief of tremor, small lesions were confined within the zone of tremor-locked rhythmically discharging neurons in Vim. Subsequent to surgery, levodopa-induced dyskinesia diminished only partially (fig 1b). Typical surface EMG recordings obtained in case 6 are illustrated in fig 2.

In the third group of patients, a lesion aimed to relieve both rigidity and levodopa-induced dyskinesia was located within Vo complex. An additional lesion for the relief of tremor was localised in Vim. Such lesions were achieved by two different approaches. In one they were made in series along a single needle track which penetrated both Vo complex and Vim; in others the two loci were entered by separate needle penetrations (fig 1c and c'). Alleviation of levodopa-induced dyskinesia in the extremities contralateral to thalamotomy was virtually complete in the third group. Typical surface EMG recording of the dyskinesias in case 11 are illustrated in fig 3.

The marked reduction of levodopa-induced dyskinesia achieved by surgery in cases, 1, 7, 9, 10 and 12, allowed greater tolerance of levodopa. Administration of the drug in higher doses became possible, and this resulted in better movement ability in the activities of daily living. On the other hand, in case 13, where symptoms were markedly asymmetric, symptomatic improvement of the severer side allowed marked postoperative reduction of Sinemet (10/100) from 7 to 3 tablets per day. Both the symptoms of Parkinson's disease as well as the levodopa-induced dyskinesia disappeared on the operated side and the much slighter symptoms on the non-operated side were satisfactorily controlled with reduced dosage of the drug.

No side-effects with respect to motor, psychological or speech functions were observed in any patient. Six of the thirteen are currently working at their customary occupation at a near normal level of proficiency. Prior to surgery their professional activities had been severely limited. Two other patients, though not employed, continue an independent existence at home. A single patient (case 1) has died three years after the second surgery, death having been attributed to ileus by a local physician.
Fig 1 Location of surgical lesions in the thirteen cases. The position and size of each lesion is estimated during the stereotaxic procedure. The method depends upon careful radiologic measurements of electrically coagulated points with respect to the third ventricle and upon firstly identifying the target within the Vim as an area containing proprioceptive or kinaesthetic neurons as determined by physiologic recordings. The distance between the anterior (CA) and the posterior (CP) commissures is 24 millimeters. (a) Lesion in Group 1: dense dot: Case 1, left side, thin stripe: Case 1, right side, thick stripe: Case 2, left side, sparse dot: Case 3, left side. *large-sized left thalamic lesion in Case 1 operated on 1965 is also shown for pathology in fig 4. (b) Lesion in Group 2: cross: Case 4, left side, thick stripe: Case 5, left side, sparse dot: Case 6, left side, dense dot: Case 7, left side, thin stripe: Case 7, right side. (c) Lesion in Group 3: dense dot: Case 8, left and right sides, sparse dot: Case 9, right side, stripe: Case 10, left side. (c') Lesion in Group 3: stripe: Case 11, right side, sparse dot: Case 12, left side, dense dot: Case 13, left side.
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L-SCM  L-Triceps  L-Biceps  L-Ext  L-Flex  L-Tib. ant.
R-SCM  R-Triceps  R-Biceps  R-Ext  R-Flex  R-Tib. ant.

Case 11  46y Woman (after r. thalamotomy)

L-Biceps
L-Triceps
L-Flex
L-Ext
L-Tib. ant.
L-Gastro
R-Biceps
R-Triceps
R-Flex
R-Ext
R-Tib. ant.
R-Gastro

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200μV

Fig 2  Levodopa-induced dyskinesia in Case 6 after the left Vim thalamotomy. Surface EMG recording in supine position at rest. Levodopa-induced dyskinesia on the right side of the body is less than the left, but still exists SCM: sternocleidomastoid muscle, Triceps: triceps brachii muscle, Biceps: biceps brachii muscle, Ext.: forearm extensor muscle, Flex.: forearm flexor muscle, Tib. ant.: tibialis anterior muscle, L: left-sided, R: right-sided.

Fig 3  Levodopa-induced dyskinesia in Case 11 after the right Vo complex + Vim thalamotomy. No levodopa-induced dyskinesia is observable on the left side of the body. Abbreviation of muscle is same as in fig 2. Gastro.: gastrocnemius muscle.

For three years prior to this complication, the patient, a lady poet by profession, had enjoyed virtually normal mental and physical activity, requiring less than 1-6 grams of levodopa. She was not troubled by levodopa-induced dyskinesia. Two additional patients died of causes unrelated to the thalamotomy, one and six years after surgery.

Discussion

The three groups differed substantially with respect to the response of levodopa-induced dyskinesia to thalamotomy. In groups 1 and 3, levodopa-induced dyskinesia was virtually abolished in the extremities contralateral to thalamotomy. Severe choreoballistic movements persisted on the unoperated side, however. In group 2, levodopa-induced dyskinesia, though substantially attenuated, still persisted subsequent to surgery.

Differences in the effect of surgery upon levodopa-induced dyskinesia appear to reflect differential involvement of thalamic subnuclei by the lesion, especially of Vo complex. In group 1,
relatively large lesions positioned by classical techniques of stereotaxis based both upon radiologic measurement and electrical stimulation, involved both Vo complex and Vim. Among all three patients of this group (four operations), tremor and marked rigidity with cogwheeling were satisfactorily alleviated on the side contralateral to the lesion. Levodopa-induced dyskinesia was also almost completely suppressed. The lesions made in the patients of group 2 were deliberately much reduced in size and confined strictly to Vim where they were located in the domain of tremor-locked neurons. Whereas these lesions improved tremor, they had little or no effect upon rigidity or levodopa-induced dyskinesia. For this reason, the operative strategy was revised for patients of group 3 to include a second lesion placed in the ventral part of Vo complex, anterior to the site of the Vim lesion. Uniformly, this third surgical approach led to complete and sustained control of levodopa-induced dyskinesia for the patients of group 3 and as a benefit of a second operation undertaken in case 1 and case 7.

These observations taken together suggest that control of levodopa-induced dyskinesia depends upon whether the lesion involves Vo complex, specially of Vop as will be seen from fig 1. This assumes that the locus of the lesion is correctly understood; this has been verified pathologically with case 1. The location of the surgical lesion which involved both Vo complex and Vim in the left side is illustrated in fig 4, the right hemisphere having been frozen for biochemical study.

Vim has been viewed by Narabayashi and Ohye\textsuperscript{17,21} and by Narabayashi\textsuperscript{22,23} as playing a key role in generating tremor. Rhythmic neuronal discharges, synchronous with extremity oscillation, may be recorded from Vim. Further, high frequency electrical stimulation of Vim produces immediate inhibition of tremor, while limited electrical coagulation within this structure results in immediate and complete abolition of tremor. Rigidity, by contrast, is only slightly modified by small lesions of Vim.\textsuperscript{16,22} This subnucleus, which corresponds to the oral part of the ventral posterior nucleus (VP) of experimental animals, does not receive pallidal afferents; these project mainly to the ventral anterior and lateral
Lesions in the Vo complex alleviate rigidity. They have only a temporary effect upon tremor, and this is presumed to be secondary to the more primary effect upon rigidity. Stereotaxic lesions in the ventromedial part of the pallidum internum (Pi) abolish rigidity almost completely, and the effect is an enduring one. Such lesions influence tremor only transiently, perhaps for one to two weeks. Such observations suggest that rigidity but not tremor is conveyed by the pallidal-thalamic projection which flows into Vo complex. The rigidity of Parkinsonism is considered to result from dopamine deficiency in the striatum, which may produce the pallidal pathophysiology, although the neuronal network and physiologic mechanisms involved are still not well understood in detail.

Because levodopa-induced dyskinesia is almost completely abolished by lesions in the Vo complex and Vim but not satisfactorily controlled by lesions of Vim alone, it is probable that this "reverse" phenomenon of Parkinsonian rigidity reflects supersensitivity of striatal neurons to dopamine. Both levodopa-induced dyskinesia and rigidity are diminished by lesions located in the Vo complex plus Vim but not when the lesion is confined to Vim. Thus, these two opposite symptomatic states may reflect disordered function of the same, (the pallidothalamic), pathway and may be due either to an excessive or diminished level of dopamine drive of the system as it arises in the striatum. In this regard, levodopa-induced dyskinesia is not considered a "reverse" phenomenon of tremor.

Consistently, levodopa-induced dyskinesia appears to have a relatively differential distribution depending upon age. In the aged, it involves more the buccolingual or neck area than extremities while in younger patients it effects predominantly the extremities. Unilateral Vo complex lesions, appropriate for satisfactory control of levodopa-induced dyskinesia involving the extremities, has often little or no effect upon levodopa-induced dyskinesia when it involves the rostral part of the body such as with buccolingual dyskinesia. Although the levodopa-induced dyskinesia as expressed in both patterns is choreic, athetoid or dystonic, the effect of lesions of Vo complex upon the movements is clearly different in these two parts of the body, the rostral area and extremities. The reason for this difference has not been explained. Perhaps it relates to the fact that the neck and tongue receive bilateral innervation from the forebrain. In this regard, bilateral operation did lead to satisfactory control of buccolingual and truncal dyskinesia in case 1. Operation on the two sides were separated by an interval of 13 years. The typical neck and tongue dyskinesias were still present to a moderate degree before the second operation. In two other cases where bilateral operations were performed, levodopa-induced dyskinesia was largely limited to the extremities even before surgery. Generally, the aged patients with only the perioral or neck distribution of levodopa-induced dyskinesia have not been considered for surgery.

Levodopa-induced dyskinesia is sometimes a substantial limitation to long-term levodopa therapy of Parkinsonian symptoms. Pharmacologic means of control are difficult and may be hazardous. Bromocriptine or dopamine-agonists may suppress this side-effect to some extent, but later on they may, instead, augment levodopa-induced dyskinesia. When levodopa-induced dyskinesia is not satisfactorily controlled by currently available pharmacologic agents, microstereoecephalotomy directed to Vo complex or to this nucleus plus Vim should be considered as an alternative therapy. This mode of treatment is particularly to be considered among patients of younger age of onset of symptoms.

As a rule, the severity of levodopa-induced dyskinesia is often experienced more on the side of the severer rigidity and tremor. These latter symptoms as well as the dyskinesia typically effect more severely the side of the body where symptoms first started. Among those patients where symptoms of Parkinson's disease and levodopa-induced dyskinesia are asymmetric, thalamic surgery directed to control of symptoms on the severer side is an effective and practical approach. Provided the lesions are located accurately in Vo complex and Vim with application of the microelectrode technique, effective control of Parkinsonian symptoms of rigidity and tremor as well as the drug induced dyskinesia are to be expected. Where symptoms are bilaterally severe and disabling, bilateral operations might be considered but only in younger age patients and with great caution. Our experience with this approach on the cases with levodopa-induced dyskinesia is limited to three cases; in each a substantial interval (13, 1 and 1 years) separated the two procedures. With none of the three was there evidence of mental, language, or motor deterioration as a consequence of the second surgical intervention. In younger patients, bilateral procedures may be undertaken safely. Even in this selected group, it would seem prudent to observe the precautions which we have taken in the older patient population: the lesions should be delivered by microelectrode technique and should be controlled in size and accurately positioned with respect to Vo complex and Vim. The two procedures should be separated by an interval of not less than one year.
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References