The subthalamic nucleus, hemiballismus and Parkinson’s disease: reappraisal of a neurosurgical dogma

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Summary

The subthalamic nucleus (STN) currently is considered to play a key role in the pathophysiological origin of the parkinsonian state and is therefore the main target for surgical treatment of Parkinson’s disease. The authors review the incidence of hemichorea/ballism (HCB) as a complication of thalamotomy, pallidotomy or campotomy procedures before the introduction of levodopa therapy, including the few reported cases accompanied by a neuropathological study. The literature shows that only a small number of parkinsonian patients with HCB had a lesion of the STN. Preliminary data in Parkinson’s disease patients submitted to a subthalamotomy with current functional stereotaxy also indicate that HCB is a very rare complication. To explain this observation, we suggest that the parkinsonian state is characterized by an increased threshold for the induction of dyskinesia following STN lesioning. This arises as a consequence of reduced activity in the ‘direct’ GABA projection to the globus pallidus medialis (GPM) which accompanies dopamine depletion. Lesioning of the STN reduces excitation of the GPM, and theoretically this should induce dyskinesias. However, an STN lesion also, simultaneously, further reduces the hypoactivity in the globus pallidus lateralis (GPl) that is a feature of Parkinson’s disease, and hence may compensate for GPM hypoactivity, thus self-stabilizing basal ganglia output activity and reducing the risk of HCB. We conclude that lesioning of the STN in Parkinson’s disease is a feasible approach in some circumstances.

Keywords: subthalamic nucleus; hemiballismus; Parkinson’s disease; subthalamotomy; stereotaxy; history

Abbreviations: GPl = globus pallidus lateralis; GPM = globus pallidus medialis; HCB = hemichorea/ballism; STN = subthalamic nucleus; VL = ventrolateralis nucleus

Introduction

In 1927, Purdon Martin reported the case of a patient with severe hemiballism in whom post-mortem examination showed a focal lesion of the subthalamic nucleus (STN), or nucleus Luysii (Martin, 1927). In the late 1940s, Whittier and Mettler described how a lesion of the STN in monkeys caused hemiballism (Whittier and Mettler, 1949). Over the next three decades, the STN and hemiballism were directly related. As a result, the STN was believed to exert an inhibitory effect on its projection nuclei, and this belief persisted for years. In the 1990s, the prominent role of the STN in the pathophysiology of parkinsonism was recognized in animal models (Mitchell et al., 1989a) and, at the same time, the excitatory nature of its efferent connections was established (Kitai and Kita, 1987; Smith and Parent, 1988). Experimental work in monkeys rendered parkinsonian by MPTP (1-methyl, 4-phenyl,1,2,3,6-tetrahydropyridine) administration showed that intranuclear lesion, either cytotoxic or thermolytic, of the STN was associated with no or only mild dyskinesia (Bergman et al., 1990; Aziz et al., 1992; Guridi et al., 1996). During the last few years, the STN has become one of the optimal targets for the surgical treatment of Parkinson’s disease. Chronic deep brain
stimulation of the STN is used currently as the preferred approach (Limousin et al., 1995, 1998) due to fears that subthalamotomy may induce hemiballism. We have suggested previously that subthalamotomy may be a possible option for surgical treatment of Parkinson’s disease (Guridi et al., 1993) and that the nature of the pathophysiological changes associated with the parkinsonian state may reduce the likelihood of developing hemiballism (Guridi and Obeso, 1997).

Here we review the literature on the incidence of chorea-ballism in patients with Parkinson’s disease treated by classic surgical techniques. We provide evidence to cast doubt on the surgical dogma that equates a lesion of the STN with hemiballism in Parkinson’s disease.

### Post-surgical hemiballism in Parkinson’s disease: clinical data

In the general population, hemichorea/ballism (HCB) is rare (Klawans et al., 1976; Dewey and Jankovic, 1989; Lee and Marsden, 1991). For instance, it was encountered in only 21 of 3084 patients with movement disorders seen in Baylor College in Houston (Shannon, 1998). Parkinson’s disease is estimated to be 500 times as common as ballism (Meyers et al., 1950). The actual frequency of HCB following surgery for Parkinson’s disease is not known precisely, with variations between 0.2 and 10% depending on the authors (Table 1) (Bravo and Cooper, 1959; Rand and Markham, 1960; Gillingham et al., 1964; Gioino et al., 1966; Cooper, 1969; Hassler et al., 1979).

The occurrence of hemiballism or HCB as a complication of surgery has been known since the early pre-levodopa era of stereotactic surgery for Parkinson’s disease in the 1950s and 1960s, called classic surgery in this review. The onset of the dyskinesia could be during surgery or delayed for hours or weeks after the surgical procedure. The intensity was variable, so the terms chorea and ballism were used interchangeably by different authors (Martin and McCaul; 1959; Dierssen and Gioino, 1961). In most patients, the dyskinesia abated spontaneously within days or months after surgery. However, in a small proportion, it was marked and persistent, and a second surgical procedure was needed to try to control the hyperkinesia. Nevertheless, in a few patients, the severity and ceaseless character of HCB were such that patients died of exhaustion and systemic complications (Smith, 1962).

### Thalamotomy and pallidotomy

In the experience of the Freiburg group, the incidence of HCB was 0.3% in >5,000 operations. (Mundinger and Reichert, 1963; Krauss et al., 1996). Krauss reported persistent postoperative HCB in only three cases (0.06%) out of 5,430 functional stereotactic operations; interestingly, none of these affected cases had Parkinson’s disease (J. K. Krauss, personal communication). Similarly, in the large series of 3,500 patients described by Hassler, the incidence of HCB was 0.2% (Hassler et al., 1979, p. 190), and Speelman, in his doctoral thesis, reviewed the surgical results of Van Nanem and found persistent HCB in only 1% of 2,873 operated patients (Speelman, 1991). Gillingham and colleagues also rarely encountered HCB, which developed in only one of 344 unilaterally lesioned parkinsonian patients. However, the frequency rose to 3.6% (three cases in 83) in their cases with bilateral procedures (Gillingham et al., 1964), and a similar experience was reported by other surgical groups (Markham et al., 1966) (Table 1). Dierssen and colleagues indicated that HCB could appear on the ipsilateral side to the lesion even years after the initial (unilateral) lesion (Dierssen et al., 1961a). Cooper was the first to realize that HCB was more often a complication of thalamic rather than pallidal surgery. He reported only one case of HCB in 500 patients treated by pallidal surgery, but 33 cases after 1,000 consecutive chemothalamectomies (lesions of the thalamus induced with alcohol or other chemical substances). He concluded that this complication after thalamic surgery was 17 times more frequent than in pallidal surgery (Cooper, 1981).

Hughes described seven cases of HCB in 200 surgical interventions (3.5%). In the discussion, he indicated that the anatomical site of the lesions that induced hemiballism, though usually located in the basal ganglia, was so widespread that it was difficult to relate its appearance to ‘damage of a single neural circuit’ (Hughes, 1965). Bravo and colleagues published an interesting paper analysing factors determining the occurrence of HCB in 650 surgical patients. They found transient HCB in 26 patients (4%). In patients with a lesion well below the intercommissural line, probably reaching the STN, the incidence of HCB was 50%. When the lesion was at the level of, or above, the intercommissural line, the incidence of HCB was similar to that in the other series, but the most important factors were age at the time of the surgery and disease duration. Thus, the average age of the patients who developed HCB was 30.5 years versus 48 years for

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**Table 1 Incidence of postoperative ballism in patients with Parkinson’s disease treated surgically (1960–70)**

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of cases</th>
<th>%</th>
<th>Target location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gillingham</td>
<td>344/83*</td>
<td>0.3/3.6*</td>
<td>Pallidum/thalamus</td>
</tr>
<tr>
<td>Hassler</td>
<td>3500</td>
<td>0.2</td>
<td>Pallidum/thalamus</td>
</tr>
<tr>
<td>Andy</td>
<td>58</td>
<td>8.4</td>
<td>Campotomy</td>
</tr>
<tr>
<td>Fager</td>
<td>13</td>
<td>10</td>
<td>Campotomy</td>
</tr>
<tr>
<td>Brion</td>
<td>850</td>
<td>1.4</td>
<td>Thalamo-capsulo-pallidal</td>
</tr>
<tr>
<td>Bravo</td>
<td>650</td>
<td>4</td>
<td>Thalamus</td>
</tr>
<tr>
<td>Speelman</td>
<td>2873</td>
<td>1</td>
<td>Pallidum/thalamus</td>
</tr>
<tr>
<td>Cooper</td>
<td>1000/1000</td>
<td>3.3/1.4</td>
<td>Chemo/cryothalamectomy</td>
</tr>
<tr>
<td>Hughes</td>
<td>200</td>
<td>3</td>
<td>Thalamus</td>
</tr>
<tr>
<td>Woringer</td>
<td>63/23</td>
<td>4.6/3.8</td>
<td>Thalamus</td>
</tr>
<tr>
<td>Gros</td>
<td>337</td>
<td>5.6</td>
<td>Thalamus</td>
</tr>
<tr>
<td>Houdart</td>
<td>47</td>
<td>4</td>
<td>Campotomy</td>
</tr>
<tr>
<td>Selby</td>
<td>225/84*</td>
<td>3.1/2.4*</td>
<td>Thalamus</td>
</tr>
<tr>
<td>Lapras</td>
<td>188/12</td>
<td>2.5</td>
<td>Thalamus/pallidum</td>
</tr>
<tr>
<td>LaFia</td>
<td>85</td>
<td>2.3</td>
<td>Thalamus</td>
</tr>
</tbody>
</table>

*Bilateral lesions.
those without this complication. No patient with less than 10 years of evolution of the disease developed HCB (Bravo et al., 1966) (Table 1).

**Campotomy**
During the 1960s, surgery of the subthalamic region, called campotomy or subthalamotomy, was used as an alternative to thalamic surgery for alleviation of tremor and rigidity (Andy et al., 1963; Fager, 1963; Spiegel et al., 1963; Mundinger, 1965). Indeed, some surgeons preferred this approach in spite of the proximity of the STN and the fear of inducing a dyskinetic complication. The intended target for the lesion was the Forel’s field, the zona incerta and the prerubral field. Andy and colleagues reported five instances of HCB postoperatively in 58 parkinsonian patients submitted to a subthalamotomy. In all cases, the dyskinesias disappeared spontaneously within 2 months (Andy et al., 1963). Fager described one patient with HCB persisting for 18 months out of 13 cases treated with a small thermolytic subthalamic lesion (Fager, 1963) (Table 1), and others such as Mundinger reported a 1.1% incidence of transient HCB in 90 cases subjected to lesions in the zona incerta (Mundinger, 1965). A slightly different lesion site was tried by other surgeons, who believed that partial destruction of the cerebellorubrothalamic pathway with a lesion placed medially to the STN and lateral to the red nucleus below the ventrolateralis nucleus (VL) of the thalamus could suppress rigidity and parkinsonian tremor. Out of 47 parkinsonian patients submitted to this type of surgery, one developed athetoid movements that appeared 1 month after surgery and persisted for 10 months. Another patient had an HCB that disappeared with medical treatment. The onset of the dyskinesia was thought to be related to lesions of the internal part of the Luys nucleus (Houdart et al., 1965) (Table 1).

**Summary of clinical findings**
The above data indicate that the development of HCB in patients with Parkinson’s disease treated surgically is difficult to ascertain with accuracy, but all large series reported have shown a low incidence (Table 1). The size and placement of the lesions could not be assessed properly at that time, and the lack of recently developed diagnostic criteria and pharmacological treatments for Parkinson’s disease made the analysis more difficult. The general conclusion was that thalamic lesions were more often associated with HCB than were pallidotomy or campotomy (Schachter et al., 1960; Cooper, 1981). Other factors apparently related to a higher incidence of HCB were: (i) age: more frequent in younger parkinsonian patients and usually they were under 55 years old (Bravo et al., 1966; Cooper, 1981); (ii) aetiology: more frequently seen in patients with post-encephalitic rather than idiopathic parkinsonism (Lapras et al., 1964; Brion et al., 1965; Hughes, 1965; Waltz et al., 1966; Woringer et al., 1968; Modesti and Van Buren, 1979); and (iii) in bilateral stereotactic surgery, the HCB appeared more often after the second operation (Gillingham et al., 1964; Markham et al., 1966).

**Pathological data**
The accuracy of stereotactic procedures in the early years of surgery for Parkinson’s disease was far from what is currently being achieved mainly because modern imaging procedures were not available at that time (Smith, 1962, 1966). In order to carry out a more accurate assessment of the relationship between the STN lesion and the occurrence of HCB following surgery for alleviation of Parkinson’s disease, we have analysed the few cases described in the literature that included a pathological study. The data from these clinicopathological studies have been critical in achieving an understanding of the relationship between lesion location and production of HCB. In this section, we summarize the few (Cases 1–9) well-documented reports available in the literature (Table 2) with HCB after basal ganglia surgery in which a pathological study was included.

**HCB with involvement of the STN**
**Capsulopallidal lesion and partial involvement of the anterior thalamus and STN**
Brion and colleagues described two clinicopathology studies in a series of 12 parkinsonian patients with post-surgical hemiballism out of 850 surgical procedures (Brion et al., 1965). **Case 1.** This 39-year-old man with idiopathic Parkinson’s disease developed left-sided HCB and mild hemiparesis associated with confusion and hyperthermia postoperatively, and died 70 days later. The thermolytic lesion was located in the dorsomedial region of the globus pallidus medialis (GPm), the anterior portion of the posterior arm of the internal capsule and the ventral anterior thalamic region. The STN was partially lesioned in its anterior and dorsal region.

**Lesion of the STN**
**Case 2.** Woringer and colleagues reported a 55-year-old patient with left-sided tremor and rigidity, bilateral akinesia and some axial problems (Woringer et al., 1968). A right thalamotomy was attempted but, due to a technical error (recognized subsequently), the lesion probe was placed 15 mm behind the anterior commissure, 9 mm below the intercommissural line and 12 mm lateral to the third ventricle (this stereotactic point may correspond theoretically to the STN). The first lesion did not stop the tremor but caused nausea (indicative of a ventrocaudal placement). The probe was withdrawn 5 mm dorsally and a second lesion was made. This led to tremor abolition and a left facial paralysis. A few hours later, the patient developed HCB that persisted despite medical treatment. Four days later, a successful pallidotomy
resulted in the reduction of the hyperkinesia but the movements recurred 48 h later. The patient developed phlebitis in the left leg and died of a pulmonary embolism. Post-mortem study showed that the first coagulation had destroyed ~80% of the STN (Hopf et al., 1968), and also showed the GPm lesion resulting from the second coagulation (Woringer et al., 1968).

**Ventralis oralis anterior thalamus, zona incerta and partial lesion of STN**

Hassler, in his classic book on stereotactic surgery, described 17 parkinsonian patients submitted to surgery and included post-mortem studies (Hassler, 1979). One patient had suffered HCB postoperatively.

*Case 3.* This patient was a 63-year-old man with an 11-year history of Parkinson’s disease which had started on the left side and later extended to the right side. A right pallidotomy was performed with improvement in the tremor and rigidity of the contralateral limbs. Ten months later, rigidity was absent and a slight tremor was present on the left side, while the signs had become more severe in the right limbs. A second stereotactic operation was performed 19 months after the first. The target was the ventralis oralis anterior thalamus. In Hassler’s terminology, this is the anterior portion of the VL. In the immediate postoperative period, there was a slight improvement of rigidity and diminution of the tremor in the right arm, and the patient showed frequent ‘strike out’ movements of the right hand. The patient developed bronchopneumonia and died 27 days after the second surgical operation. The post-mortem study showed that the centre of coagulation was in the left dlencephalon, 11.5 mm from the wall of the third ventricle. The lesion destroyed the peduncle at its transition into the internal capsule and the fasciculus H1. The zona incerta and the ventralis oralis anterior thalamus were severely damaged. The subthalamic lesion affected only 15% of the nucleus and was confined to the rostromedial region (Hassler et al., 1979, pp. 75–83) (Table 2).

**Lateral thalamus, zona incerta, segmental area and partial STN lesion**

Marion Smith analysed the site of stereotactic lesion in 15 parkinsonian patients who had died after a surgical procedure (Smith, 1962). In 10 patients, the surgical target was the pallidum, and in five the thalamus. In five patients from the first group, the lesion involved the STN to differing degrees, but none had HCB. In the second group, the lesion involved the STN in three patients with no clinical consequences, except for one (Case 4) who developed HCB.

*Case 4.* This 43-year-old man with post-encephalitic parkinsonism underwent a right thalamotomy with an immediate good result. Tremor and rigidity were relieved, but HCB ensued the next day on the left side and he died 11 days after the operation from pneumonia and exhaustion. The lesion was placed lateral to the thalamus, above the red nucleus and reaching the zona incerta, the segmental area and the most dorsal pole of the STN.

**HCB without involvement of the STN**

**HCB with a capsulopalidal lesion and partial involvement of the thalamus**

*Case 5.* The second patient of Brion et al. (1965) was a 50-year-old man with post-encephalitic parkinsonism predominantly on the left side. Surgery of the right GPm was undertaken first, resulting in some improvement of the parkinsonian signs, but HCB developed 5 days post-operatively. A few weeks later, a second lesion was targeted with a laterality of 22 mm from the midline. The patient developed a massive hemiplegia as a result of the surgical procedure. The dyskinesia stopped completely, but his general condition deteriorated until his death a few days later. The pathological study revealed a lesion of the medial region of the GPm, and large-scale destruction of the posterior arm of the internal capsule and of a small region of the VL. The STN was not affected, but retrograde degeneration was observed (Table 2) (Brion et al., 1965).

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**Table 2 Summary of patients with post-surgical hemiballism in Parkinson’s disease and their pathological findings**

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (years)</th>
<th>Latency</th>
<th>Risk factors</th>
<th>Target</th>
<th>Anatomical lesion</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>39</td>
<td>2 days</td>
<td></td>
<td>Palli/thal</td>
<td>GPm/ansa/STN/ic</td>
<td>Brion et al. (1965)</td>
</tr>
<tr>
<td>2</td>
<td>55</td>
<td>OT</td>
<td></td>
<td>VL</td>
<td>STN</td>
<td>Woringer (1968)</td>
</tr>
<tr>
<td>3</td>
<td>63</td>
<td>OT</td>
<td>Bilat surg</td>
<td>Voa</td>
<td>H1/STN/Voa/GPm</td>
<td>Hassler (1979)</td>
</tr>
<tr>
<td>4</td>
<td>43</td>
<td>1 day</td>
<td>Post-encephal</td>
<td>Thalamus</td>
<td>STN/ZI/Vop/RN</td>
<td>Smith (1962)</td>
</tr>
<tr>
<td>5</td>
<td>50</td>
<td>5 days</td>
<td>Post-encephal</td>
<td>Palli/thal</td>
<td>GPM/IC/VL</td>
<td>Brion et al. (1965)</td>
</tr>
<tr>
<td>6</td>
<td>50</td>
<td>1 month</td>
<td>Bilat surg</td>
<td>VL</td>
<td>Vim/intralami</td>
<td>Modesti et al. (1979)</td>
</tr>
<tr>
<td>7</td>
<td>35</td>
<td>3–4 h.</td>
<td>Post-encephal</td>
<td>VL</td>
<td>V/L/fasc/ZI/RN</td>
<td>Dierssen et al. (1961)</td>
</tr>
<tr>
<td>8</td>
<td>48</td>
<td>1 week</td>
<td>Bilat surg</td>
<td>VL</td>
<td>Voa/Vop</td>
<td>Markham et al. (1966)</td>
</tr>
<tr>
<td>9</td>
<td>40</td>
<td>OT</td>
<td></td>
<td>VL</td>
<td>V/L/fasc</td>
<td>Cooper et al. (1963)</td>
</tr>
</tbody>
</table>

OT = operating theatre; ansa = ansa lenticularis; IC = internal capsule; ZI = zona incerta; H1 = Forel field H1; fasc = fasciculus lenticularis; Voa/Vop = ventralis anterior and posterior thalamus; Vim = ventralis intermedius; RN = red nucleus; intralami = intralaminaris nuclei thalamus; Bilat surg = bilateral surgery; Post-encephal = post-encephalitis.
Focal thalamic (ventralis intermedius, VL and centromedianum) lesion

Case 6. A 50-year-old patient with idiopathic Parkinson’s disease reported by Modesti and Van Buren (Modesti and Van Buren, 1979) had a left thalamotomy 2 years after diagnosis. A left-sided tremor appeared 2 years later, and surgery aimed at producing a lesion 18 mm from the midline and 4 mm behind the midpoint of the intercommissural line was carried out. This resulted in left facial weakness, a Babinski sign and ataxic gait. One month later, left arm ballistic dyskinesias ensued. The HCB could not be controlled despite various drug treatments. Six months after the beginning of the hemiballism, a right pallidotomy was performed but the patient did not wake from the anaesthesia, remained comatose and died 2 months later. The lesion was some 4 mm in diameter and involved the ventralis intermedius, the ventralis oralis anterior and lateral nucleus, as well as the centromedianum nucleus; the STN was intact.

Lesion of the ventrolateral thalamus, zona incerta and fasciculus thalamicus

Case 7. Dierssen and colleagues reported a 35-year-old patient with severe tremor and rigidity submitted to a right thalamotomy (Dierssen et al., 1961b). The patient had a bad attack of influenza 4 years after the onset of the symptoms and the parkinsonism worsened. Chorea-ballism developed 4 h after surgery and persisted for days. Surgery was undertaken a second time to alleviate the hyperkinesia, moving the cannula deeper, but the patient showed no change. On the sixth postoperative day, the patient suffered a pulmonary embolism but recovered after a tracheostomy. The further course of the disease was a slow deterioration until his death 5 months after the surgical procedure. The pathological study showed that the first lesion was placed in the ventro-inferior portion of the VL thalamus, also involving the fasciculus thalamicus and the zona incerta, and the STN was intact. The second lesion, which did not improve the HCB, was in the dorsal portion of the red nucleus and rubral radiations (Dierssen et al., 1961b) (Fig. 1). This case was also reported by Gioino and colleagues as case number 6 (Gioino et al., 1966) and by Cooper as case number 1 (Cooper, 1981) (Table 2).

Lesion in the ventrolateral thalamic nucleus

Case 8. Markham and colleagues also described four post-mortem studies after surgical procedures. Their case number 4, a 48-year-old parkinsonian patient with no history of encephalitis, underwent a right thalamotomy which alleviated contralateral tremor and rigidity, but the right-sided symptoms continued to progress. A left thalamotomy was done a year later with abolition of tremor and rigidity. For a week after the operation, the patient developed mild ballistic and rotatory movements of the right arm, but then became stuporous and later hypertensive. The patient died a few weeks later following a systemic metabolic decompensation. The HCB persisted unchanged until death. The description of the pathological study indicated that the first lesion had been placed in the ventralis oralis anterior/ventralis oralis posterior. The centre of the lesion was 5 mm above the intercommissural line and 1 mm dorsal to the H1 field of Forel. The STN was not affected (Markham et al., 1966).

Lesion in the VL thalamic nucleus and fasciculus thalamicus

Case 9. Cooper and colleagues also described pathological studies of a number of patients treated with thalamic surgery resulting in abolition of tremor and rigidity who died suddenly from systemic complications (Cooper et al., 1963). Their case 4 was a 40-year-old patient who after a left thalamotomy
had an immediate tremor arrest and rigidity but exhibited a choreiform hyperkinesia that increased to HCB during the following day. The movement persisted during the follow-up, and a left chemopallidotomy was performed a year later with complete alleviation of the right upper limb dyskinesia. The patient died 6 months later of a presumed viral pneumonia. The anatomical study showed that the first lesion was placed in the VL, involving the thalamic fasciculus and sparing the STN. The second lesion hit the ‘junction of the pallidum and putamen’. This case was also reported by Cooper in his book The Vital Probe as case number 2 (Cooper, 1981) and by Gioino and colleagues as case number 7 (Gioino et al., 1966).

**Subthalamic lesion without HCB**

Taking the same authors as references, we have encountered a few pathological reports of Parkinson’s disease patients who had had a STN lesion induced during surgery, but in whom HCB never developed. Hassler and colleagues described several patients (cases 2, 13 and 16 in Hassler et al., 1979) in whom the anatomical study showed a thermolytic STN lesion involving >20% of the nucleus, which is greater than the ‘minimal volume’ of the lesion needed to provoke hemiballism in the normal monkey according to Whittier and Mettler (Whittier and Mettler, 1949). Hassler suggested that such an effect could be due to an additional lesion of Forel’s field H2 or the fasciculus lenticularis, perhaps mimicking the effect of pallidotomy (Hassler et al., 1979, p. 224). This surgical concept was based on Balthasar’s previous experience (Balthasar, 1930). Another example of an STN lesion without HCB was described by Cooper and colleagues as case 1 in their paper on pathological studies in parkinsonian patients who died from systemic complications after surgery (Cooper et al., 1963). Smith described a patient with Parkinson’s disease who died of a pulmonary embolism 8 days after a thalamotomy. The lesion was placed in the thalamus and the zona incerta dorsal to the red nucleus, and partially affected the STN. It is noteworthy that the STN lesion in this patient had an anatomical distribution very similar to that of Case 4 who developed HCB (Fig. 2). There were two clinical differences between these two cases. The patient who developed HCB was young (43 years old) and had postencephalitic parkinsonism, while the patient without HCB was older (56 years old) and had idiopathic Parkinson’s disease (Smith, 1962).

In summary, the clinicopathological reports indicate that HCB was associated with STN involvement in four patients, two with a large lesion (Cases 1 and 2) and two with partial lesions (Cases 3 and 4). In all the other patients with postoperative HCB encountered in the review (Cases 5–9), the STN appeared to be intact (Table 2). These reports also showed that post-surgical HCB in Parkinson’s disease may be suppressed by lesions placed in the GPM, as was the case in patients 2, 5, 6 and 9 described here. This observation is in keeping with monkey data from Carpenter and colleagues (Carpenter et al., 1950), and also recent surgical experience in patients (Suarez et al., 1997; Vitek et al., 1999). The incidence of HCB as a surgical complication was considered higher when lesions were below the intercommissural line, and this was, and still is today, taken as a dogma in stereotactic surgery. However, the data summarized in this section clearly indicate that the origin of HCB is not determined only by the lesion location. Thus identically situated lesions of the STN may or may not have been accompanied by HCB. Moreover, HCB was encountered in patients with lesions which spared the STN but involved other basal ganglia nuclei. Altogether, this information indicates that other pathophysiological factors besides lesion of the STN determine the occurrence of HCB in Parkinson’s disease (Dierssen and Gioino, 1961a; Hughes, 1965; Bravo et al., 1966).

**Effect of lesioning the STN in parkinsonian monkeys and in Parkinson’s disease**

**Experiments in monkeys**

The injection of an excitotoxic agent such as ibotenic or kainic acid provokes selective cell damage while sparing the surrounding fibres (Olney et al., 1974; Hammond et al., 1979). Local administration of any of these agents into the STN allows the effect of intranuclear damage to be studied without lesioning the adjacent pathways. Using the model of parkinsonism induced by MPTP in monkeys, the groups of Crossman and of DeLong showed independently that neuronal hyperactivity of the STN plays a key role in the origin of parkinsonian motor features (Mitchell et al., 1989b; DeLong, 1990). These findings led researchers to undertake excitotoxic and thermolytic lesioning of the STN in MPTP monkeys (Table 3) which produced a dramatic improvement of parkinsonian signs mainly contralateral to the lesioned side. Guridi and colleagues showed that the motor improvement induced by subthalamotomy was accompanied by a marked reduction of GABAergic activity in both the GPM and substantia nigra pars reticulata (Guridi et al., 1996). These experiences and observations provide us with a very appropriate model for analysing the impact of lesioning the STN in the parkinsonian state within fairly controlled conditions.

A total of 13 monkeys are available for review of the effect of lesioning the STN in the parkinsonian state (Table 3). Bergman and colleagues first reported a dramatic improvement in contralateral limb akinesia, rigidity and postural tremor after unilateral injection of ibotenic acid into the STN in two MPTP monkeys. Both monkeys developed a transient hemichorea after the lesion. The dyskinesia disappeared within a week after surgery in one animal and persisted in the other with mild intensity until sacrifice (Bergman et al., 1990). The ibotenic acid lesion had resulted in 70 and 51% destruction of the nucleus in these two
Subthalamotomy in Parkinson’s disease

Fig. 2 Two patients with similarly placed lesions (cases 8 and 9 reported by Smith, 1962). In both patients, only the most cranial pole of the STN was involved within the lesion. Patient 8 improved after surgery, but the next day he developed HCB and died 11 days post-surgery. The second patient (no. 9) showed a similarly placed lesion but had no dyskinesia. GP = globus pallidus; IC = internal capsule; OT = optic tract; P = putamen; RN = red nucleus; SN = substantia nigra; STN = subthalamic nucleus; Th = thalamus.

Table 3 HCB following lesion of the STN in parkinsonian monkeys

<table>
<thead>
<tr>
<th>Authors</th>
<th>No. of monkeys</th>
<th>Procedure</th>
<th>Dyskinesia</th>
<th>% volume of STN lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bergman et al.</td>
<td>2</td>
<td>Ibotenic acid</td>
<td>Microrecording</td>
<td>2 hemichorea</td>
</tr>
<tr>
<td>Aziz et al.</td>
<td>6</td>
<td>Thermolesion</td>
<td>Ventriculography</td>
<td>3 hemichorea</td>
</tr>
<tr>
<td>Guridi et al.</td>
<td>5</td>
<td>Kainic acid</td>
<td>Ventriculography</td>
<td>4 hemichorea</td>
</tr>
</tbody>
</table>

Animals, respectively (Wichmann et al., 1994a, b). Using a similar methodology, we also found that motor improvement was associated with mild chorea in all but one of the MPTP monkeys (Guridi et al., 1994) which developed a relatively severe dyskinesia mainly affecting the upper limb. Despite dyskinesias, all the animals studied, including the one with the most severe ballistic movements, showed a significant improvement in manual dexterity. In our experience, the dyskinesia persisted in all the animals during a maximum follow-up period of >6 months. The excitotoxic lesion involved at least 80% of the STN (Guridi et al., 1996).

Aziz and colleagues reported the effect of thermo-coagulation lesioning in six MPTP monkeys, including bilateral lesioning in two. Dyskinesias were only mild, and transient, in three animals. The ablative lesion destroyed between 42 and 100% of the STN (Table 3). However, thermolytic lesions are known to destroy both neurones and fibres. Indeed, histological examination of these monkeys’ brains showed extension of the lesion to the internal capsule, ansa lenticularis and GPM in half of the animals (Aziz et al., 1991, 1992).

Vascular lesions of the STN in Parkinson’s disease patients

A few patients with Parkinson’s disease and HCB associated with a vascular basal ganglia lesion have been described in the last few years. Sellal and colleagues reported a 70-year-old patient with Parkinson’s disease who suddenly developed left hemiballism with the disappearance of the parkinsonian signs in the affected side (Sellal et al., 1992). CT of the head showed a haemorrhage in the right STN. The hyperkinesia disappeared within 2 weeks, but clinical alleviation of Parkinson’s disease persisted chronically. Vidakovic and colleagues reported another parkinsonian patient (case 21) who developed hemiballism due to a contralateral infarct of the basal ganglia without selective involvement of the STN, but with a marked improvement of parkinsonian features. As in the former case, the hemichorea disappeared within weeks after onset, but the improvement of parkinsonian signs persisted (Vidakovic et al., 1994). On the other hand, Inzelberg and Korczyn reported a patient with ballism induced by a large haemorrhagic lesion in the STN region that ameliorated parkinsonian motor features in the contralateral limbs, but in this case the hyperkinesia persisted during the 3 months of follow-up (Inzelberg and Korczyn, 1994).

Contemporary subthalamotomy

Alvarez and colleagues reported major clinical benefits in 11 patients with advanced parkinsonism lesioned unilaterally in the STN (Alvarez et al., 1999). The procedure was performed with CT, digitized planification using the Schaltenbrand and
Wahren atlas (Schaltenbrand and Wahren, 1977) and semi-microrecording (Macias et al., 1997). The parkinsonian features of all patients were greatly alleviated, with a marked effect on axial symptoms, freezing and gait, and a significant reduction in daily levodopa requirements. Most patients showed transient dyskinesias during the lesioning procedure, which lasted for up to 72 h in all but one patient. This patient developed hemichorea after a delayed stroke 5 days after surgery which was abolished after a pallidotomy several months later. More recently, the same group has reported a more striking benefit with bilateral lesion of the STN without permanent dyskinesia (Alvarez et al., 2000). Gill and Heywood briefly reported the effect of a small (2–3 mm in diameter) dorsolateral subthalamotomy in 10 patients (Gill and Heywood, 1997, 1998). The procedure was performed bilaterally in five patients and unilaterally in another five patients. They also reported a significant anti-parkinsonian effect, and only one patient had minor dyskinesias. We (Fig. 3) and other experienced surgical groups currently are undertaking subthalamotomy in special patients (A. M. Lozano and J. L. Vitek, personal communication) with uniformly good results, and without dyskinesias as a lasting complication. Cognitive impairment as seen with pallidotomy (York et al., 1999), or the unilateral neglect reported with subthalamotomy in marmosets (Henderson et al., 2000), have not been encountered in patients (McCarter et al., 2000). In fact, this preliminary experience suggests that the intraoperative development of dyskinesias is a good indication of major clinical benefit, a phenomenon already reported for pallidotomy (Lozano et al., 1996; Merello et al., 1997).

### HCB and Parkinson’s disease: current concepts

**Pathophysiology of HCB**

The experimental findings mentioned above should logically have led to proposing therapeutic subthalamotomy for Parkinson’s disease (Guridi et al., 1993). However, the classic neurosurgical view of avoiding lesioning the STN because of fear of inducing HCB proved critical in halting this approach in favour of pallidotomy and, later, STN deep brain stimulation. We have argued, however, that the effect of an STN lesion may be different in the parkinsonian and normal states (Guridi and Obeso, 1997). In other words, a lesion of the STN (or any other structure) cannot necessarily be expected to have the same behavioural and pathophysiological consequences in the normal basal ganglia as in the dopamine-depleted condition.

In 1949, Whittier and Mettler published a classic paper on the characteristics of ‘hyperkinesia choreica’ (hemiballismus) after ablation of the STN in monkeys by electrolytic lesion. They reported that the movements so induced were very severe and did not abate spontaneously. A minimal destruction of 20% of the nucleus was deemed necessary to induce the hemidyskinesia (Whittier and Mettler, 1949). More recently, Hamada and DeLong reported that a single excitotoxic lesion, as small as 4–11% of the total volume of the STN, is sufficient to induce transient dyskinesias in the contralateral limb in normal monkeys (Hamada and DeLong, 1992a). The key point of the latter study is that ibotenic acid was injected specifically into the dorsolateral region of the STN, which corresponds to the sensorimotor zone. In addition, the animals...
were intact, i.e. there was no lesion of the basal ganglia or dopaminergic system, a feature that we believe is a relevant determinant of whether or not hemiballism develops following lesion of the STN (Guridi and Obeso, 1997).

The pathophysiology of HCB has been unravelled in the last few years thanks to a series of studies by Crossman and collaborators. They elicited HCB in monkeys by injecting a GABA antagonist (bicuculline) into the STN, thus inducing a non-specific depolarization blockade leading to functional inactivation of the nucleus (Crossman et al., 1984). They obtained a similar result after indirect inactivation of the STN by blocking the GABAergic striopallidal projection with bicuculline, disinhibiting the globus pallidus lateralalis (GPi) which in turn over-inhibits the STN (Crossman et al., 1988). The dyskinetic movements induced by both procedures, direct and indirect inactivation of the STN, were indistinguishable. The same group applied the 2-deoxyglucose technique marked with $^{14}$C in monkeys to map metabolic changes associated with dyskinesias (Mitchell et al., 1985a, b; 1989b). The procedure permitted the autoradiographic measurement of local glucose uptake, which was used as an indication of regional afferent synaptic activity. The study concluded that the GPI–STN pathway was abnormally overactive on the side contralateral to hemiballism, causing inhibition of STN, and was associated with diminished GPM output to the thalamus. This series of studies established in the 1980s the concept of dyskinesias (i.e. HCB) occurring as the result of reduced neuronal activity in the STN–GPm, with consequent disinhibition of the thalamocortical projection (Crossman et al., 1987, 1988; DeLong, 1990).

The electrophysiological counterpart of dyskinesias has been worked out independently by the groups of DeLong and Filion (Filion and Tremblay, 1991a; Hamada and DeLong, 1992a, b). Hamada and DeLong showed that HCB induced in monkeys by ibotenic acid injections in the sensorimotor region of the STN was associated with a reduction of 31 and 35%, respectively, in the mean firing frequency of GPM and GPI neurones. When Matsumura and colleagues injected the GABA antagonist bicuculline into the GPI of normal monkeys (blocking GABA inhibition from the striatum), they induced dyskinesias identical to those provoked by lesioning of the STN, or by administration of dopaminergic drugs, in MPTP monkeys. The electrophysiological analysis of the changes in neuronal firing showed a complex pattern. Thus, 86% of the units recorded during the dyskinesias in the GPI increased their firing rate and 56% in the GPM showed a reduction. However, the authors stressed the large variability of neuronal discharging in both nuclei. In particular, the frequency of GPM neurones increased (44%), decreased (15%) or both (41%) during dyskinesias. Moreover, these changes were not homogeneous in the temporal domain so that neurones located close by could increase or decrease their activity simultaneously. They suggested that dyskinesia cannot be explained solely as a simple imbalance between both pallidal segments, but also as changes in the pattern of activity (Matsumura et al., 1995). Recording GPM neuronal activity after apomorphine in MPTP monkeys was accompanied by a mean reduction in the firing rate but also changes in the duration of pauses, frequency of bursting activity and in the centre surround inhibition (Filion and Tremblay, 1991b).

More recent studies in MPTP monkeys (Papa et al., 1999) and Parkinson’s disease patients during surgery have confirmed the reductions in firing frequency of GPM neurones following administration of apomorphine or levodopa. However, a current understanding (Lozano et al., 2000; Obeso et al., 2000a) is that reduction in firing rates of GPM neurones is not the only basis for levodopa-induced dyskinesias in Parkinson’s disease. Indeed, metabolic studies undertaken in MPTP monkeys showed that dyskinesias induced by chronic levodopa treatment are associated with a moderate reduction in the expression of glutamic acid decarboxylase mRNA in the GPI and GPM, and of cytochrome oxidase mRNA in the GPI, GPM and STN. These data suggest that the dyskinetic state is associated with a level of neuronal activity which is reduced with respect to the parkinsonian state but still above normal (Herrero et al., 1996; Vila et al., 1996). Suarez and colleagues found a mean firing frequency in the GPM of 30 Hz in one patient with vascular hemiballism (Suarez et al., 1997). This was close to that recorded in parkinsonian patients (52 Hz) when studied under the effect of levodopa, and significantly reduced with respect to the mean firing rate in the parkinsonian (‘off’ drugs) motor state (96 Hz). Vitek and colleagues described another patient with hemiballism in whom neuronal recording in the GPM showed irregularly grouped discharges and intermittent pauses, with a mean firing frequency of 33.7 Hz (Vitek et al., 1999). Thus, the concept that HCB is due to a reduction in GPM activity provoking disinhibition of the thalamocortical projection has given way to the idea of modifications in the firing pattern as one crucial feature underlying dyskinesias (Obeso et al., 2000a). Pallidotomy may act against dyskinesias by interrupting the generation of such abnormal patterns.

In monkeys, the appearance and intensity of dyskinesias following a lesion of the STN seem to vary according to the functional status. Hamada and DeLong induced choreic movements of the lower limbs in normal animals after a small unilateral lesion (Hamada and Delong, 1992b). The same group, using a similar methodology, produced 51 and 70% lesions of the STN in two MPTP-intoxicated monkeys which resulted in transient dyskinesias of mild intensity. Guridi and colleagues lesioned the STN unilaterally (by kainic acid injection) in two groups of animals. In five previously normal Macaca fascicularis, the lesion induced severe hemiballism within the first 24 h which hampered the utilization of that arm for any purpose. In fact, some animals tried to stay quietly in the cage in order to avoid the enhancement of dyskinesias by activity. The second group consisted of five monkeys previously treated with intravenous MPTP. These animals only developed mild to moderate chorea contralateral to the STN lesion. Since the unilateral
Fig. 4 Hypothetical representation of the functional state of the STN and GPm in three different clinical conditions (HCB, normal and parkinsonism). The STN activity in these three different motor states, and consequently the GPm GABAergic output to the thalamus, differs. The threshold for the appearance of the HCB may be correlated with the GPm-GABAergic output activity more than with the volume of the STN lesion. In the normal condition, a lesion of the STN could lead to a more profound reduction of GPm-GABA efferent activity onto the thalamus than in the parkinsonian state. The hyperactivity of the STN-GPm in the parkinsonian state might decrease the probability of reaching the reduction in GPm-GABA activity necessary to produce dyskinesias (left side of the curve).

lesion induced a marked improvement in movement capacity, all the monkeys preferred using the dyskinetic arm rather than the arm on the parkinsonian side that was still parkinsonian (Guridi et al., 1996), thus indicating the minimal disability provoked by the dyskinesias. Histological analysis of the brain in both groups showed a large (>80% of nuclear volume) lesion of the STN and no difference in the magnitude and distribution of cell loss. Overall, these experiments lead us to conclude that the induction of HCB following STN lesion differs in normal and parkinsonian monkeys (Guridi and Obeso, 1997) (Fig. 4). Accordingly, it should be possible to perform a subthalamic lesion in patients with Parkinson’s disease without the threat of dyskinesias as a major complication.

Why don’t STN lesions provoke HCB in Parkinson’s disease patients?

One possible explanation why STN lesions do not provoke HCB in Parkinson’s disease patients is that the thermolytic lesions performed in monkeys (Aziz et al., 1992) and patients involved fibres running dorsally to the STN. These may include the pallidothalamic projection, and may, therefore, have a pallidotomy-like effect. An argument against this explanation being the only basis for the observation is that similar results were encountered in MPTP monkeys with excitotoxic lesions (sparing fibres). Similarly, the above revised evidence indicates that HCB is infrequent after thermolytic lesions of the subthalamic region in parkinsonian animals (Aziz et al., 1991, 1992). Accordingly, we would like to suggest that the functional modifications occurring in

Fig. 5 (A) Schematic diagram of the basal ganglia in the parkinsonian state highlighting the hyperactivity of the STN and increased activity of the GABA efferent projections to the thalamus and brainstem. (B) Main modifications in basal ganglia output activity following lesion of the STN in Parkinson’s disease. The reduction in GPm and substantia nigra reticulata neuronal activity has been demonstrated in MPTP monkeys. Restoration of thalamocortical activation is deduced indirectly from PET studies showing increased cortical activity after surgery. CM/Pf = centrum medianum and parafascicular nucleus; SNr = substantia nigra reticulata; SNC = substantia nigra compacta; VL/VA = ventralis lateralis and ventralis anterior.
the basal ganglia in Parkinson’s disease reduce the likelihood of developing HCB after an STN lesion. In other words, the threshold for dyskinesias associated with an STN lesion seems to be increased in the parkinsonian state. The crucial point is what is different in the parkinsonian brain which seemingly modifies the threshold necessary to induce the HCB following lesion of the STN. To explain this, one may propose several putative mechanisms. First, the reduction in GPm neuronal activity provoked by a lesion of the STN may remain above or within normal levels but in any case above the level associated with dyskinesia. In keeping with this idea is the fact that in MPTP monkeys, subthalamotomy reduced the expression of glutamic acid decarboxylase mRNA in the GPm but the levels of activity were still above control values (Guridi et al., 1996). A second possible explanation concerns the functional state of the GPl in the parkinsonian state. Thus, the GPl is supposed to be underactive as a result of increased inhibition from the striatum following dopamine depletion (Fig. 5A) (DeLong, 1990).

Recent studies in the MPTP monkey and in patients with Parkinson’s disease have confirmed the existence of reduced firing rate in the GPl with respect to the GPm (Filion et al., 1991a; Boraud et al., 1998; Lozano et al., 2000). Similarly, the GPl/GPm index of metabolic activity, as measured by in situ hybridization of cytochrome oxidase mRNA expression (Vila et al., 1997), indicates that the GPl is hypoactive compared with the GPm (Obeso et al., 2000a). Subthalamotomy also induces a reduction in GPl activity by withdrawing its excitatory input from the STN (Hamada and DeLong, 1992b; Vitek et al., 1999). The net result could be that GPl neuronal activity may be quite reduced in patients treated with lesion of the STN due to such a dual mechanism, i.e. increased striatopallidal inhibition and reduced glutamatergic excitation. This could lead to decreased GABAergic inhibition over the GPl (Fig. 5B), thus potentially compensating for the direct loss of glutamatergic excitation in the STN–GPm projection.

The GPl would play, in this regard, a fundamental role in both the parkinsonism and the dyskinetic states, a view which has gained increased popularity (Parent and Hazrati; 1995; Obeso et al., 1997, 2000a, b; Smith et al., 1998). Thus, functional changes in neuronal activity leading to increased GPl activity are prodyskinetic (Mitchell et al., 1985a, b, 1989b; Crossman, 1987, 1988) and, vice versa, the hypoactivity of the GPl acts to increase the dyskinesia threshold for HCB following lesion of the STN. This may be one important mechanism in explaining the observations in Parkinson’s disease patients treated with subthalamotomy. The onset of dyskinesia may be viewed as the net result of the activity of two reciprocally linked systems (Smith et al., 1998). These are, on the one hand, the reduction in neuronal activity secondary to lesion of the glutamate projection onto the GPm and, on the other hand, the opposite effect provoked by the decreased excitation of GPl neurons leading to reduced inhibitory tone over the GPm. Whether or not HCB appears will be determined ultimately by the degree of GABAergic activity from the GPm onto the thalamus. The presence of a lesion of the STN is an important triggering factor in the origin of HCB, but not the only determinant of GPl effenter activity. Indeed, the STN–GPl–GPm (Fig. 5) microcircuitry may have a self-stabilizing property which would tend to reduce the intensity and duration of HCB following an STN lesion (Obeso et al., 2000b). This would account for the well-known self-limiting evolution of HCB in many patients following vascular lesion of the basal ganglia.

Conclusions

The evidence reviewed above indicates that there are very few cases of STN involvement and of hemiballism after surgery in parkinsonian patients. Most of the cases described with HCB were associated with lesions elsewhere in basal ganglia. The analysis of all the work published on parkinsonian monkeys with an STN lesion, as well as the patients described above, leads us to conclude that, in most cases, the hemichorea was very mild or non-existent, but that improvement in parkinsonism persisted. The threshold for HCB seems to be higher in the parkinsonian condition than in the normal state, possibly due to reduced GABAergic pallidal transmission onto the GPm. Thus, STN inactivation is less likely to induce HCB in the parkinsonian state. The fear of provoking permanent and severe hemiballism following subthalamotomy should be abandoned in view of current information. This in turn should lead to a revision of the prevailing pathophysiological model of the basal ganglia.

The STN nucleus is contemplated as a main target for Parkinson’s disease after the revitalization of stereotaxy for Parkinson’s disease based on the pathophysiological model of the basal ganglia. In practice, the procedure of choice currently is chronic electrical stimulation of the STN, which has been shown to produce a significant improvement in the parkinsonian condition and a reduction in daily levodopa requirements (Limousin et al., 1995, 1999; Krack et al., 1998, 1999; Kumar et al., 1998; Houeto et al., 2000; Molinuevo et al., 2000). STN stimulation is a safe and effective treatment for Parkinson’s disease. However, chronic stimulation is an expensive treatment and requires several adjustments in order to remain effective throughout evolution. From this point of view, subthalamic lesioning is a surgical procedure that may be performed in candidates who are not suitable for electrode implantation. A randomized comparative study of the effect of bilateral subthalamotomy and deep brain stimulation of the STN in Parkinson’s disease is warranted (Quinn, 1999).

References


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