Mismatch between electrophysiologically defined and ventriculography based theoretical targets for posteroventral pallidotomy in Parkinson’s disease

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Abstract

Objectives—Over the past few years many reports have shown that posteroventral pallidotomy is an effective method for treating advanced cases of Parkinson’s disease. The main differences with earlier descriptions were the use of standardised evaluation with new high resolution MRI studies and of single cell microrecording which can electrophysiologically define the sensorimotor portion of the internal globus pallidus (GPi). The present study was performed on a consecutive series of 40 patients with Parkinson’s disease who underwent posteroventral pallidotomy to determine localisation discrepancies between the ventriculography based theoretical and the electrophysiologically defined target for posteroventral pallidotomy.

Methods—The tentative location of the posteroventral GPi portion was defined according to the proportional Talairach system. Single cell recording was performed in all patients. The definitive target was chosen according to the feasibility of recording single cells with GPi cell features, including the presence of motor drive and correct identification of the internal capsule and of the optic tract by activity recording and microstimulation.

Results—In all 40 patients the electrophysiologically defined sensorimotor portion of the GPi was lesioned, with significantly improved cardinal Parkinson’s disease symptoms as well as levodopa induced dyskinesias, without damage to the internal capsule or optic tract. Significant differences between the localisation of the ventriculography based theoretical versus electrophysiological target were found in depth (p<0.0008) and posteriority (p<0.04). No significant differences were found in laterality between both approaches. Difference ranges were 8 mm for laterality, 6.5 mm for depth, and 10 mm for posteriority.

Conclusions—Electrophysiologically defined lesion of GPi for posteroventral pallidotomy, shown to be effective for treating Parkinson’s disease, is located at a significantly different site from the ventriculography based theoretical target.

Keywords: pallidotomy; Parkinson’s disease; microrecording; globus pallidus

Over the past few years many reports have shown that posteroventral pallidotomy is an effective method for treating advanced cases of Parkinson’s disease. The main differences with earlier descriptions are the use of standardised evaluation methods such as the core assessment program for intracerebral transplantation (CAPIT), high resolution MRI targeting, and single cell microrecording within the striatum, which can electrophysiologically define the sensorimotor portion of the internal globus pallidus (GPi).

Commonly, GPi localisation has been performed indirectly, using the anterior commissure-anterior comissure (AC-PC) line as reference, whether determined by ventriculography, CT, or MRI. However, due to substantial individual AC-PC line variation, target coordinates are expressed as a range, rather than as exact values. In a survey of current practice of pallidotomy within the United States, Favre et al reported the results of a questionnaire sent to different centres, of which 50% performed the procedure with microrecording and 50% without, but neither data on the outcome nor on complications of the procedure were presented. Even though no conclusion can be drawn from such a study, it provoked the controversy over the usefulness and safety of microrecording. Those who perform microrecording argue that it is no better than the use of macrostimulation to obtain a correctly located pallidotomy and that if it increases the risk of side effects then it should only be used for research purposes.

The present study was carried out to determine localisation discrepancies between the ventriculography based theoretical and the electrophysiologically defined target within the sensorimotor portion of the GPi in a prospective series of patients who underwent posteroventral pallidotomy.

Methods

A consecutive series of 40 patients who underwent microguided posteroventral pallidotomy was included in the analysis. All patients met UKPDS-BB clinical criteria for idiopathic Parkinson’s disease, had a positive response to levodopa, and presented motor fluctuations and marked dyskinesias.

Inclusion criteria for the posteroventral pallidotomy programme were basically as
Mean (SD) UPDRS motor section and dyskinesia score values

<table>
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<th></th>
<th>State</th>
<th>Preoperative</th>
<th>Postoperative</th>
<th>ANOVA</th>
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<tr>
<td></td>
<td>On</td>
<td>14.8</td>
<td>11.3</td>
<td></td>
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<td></td>
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<td>0.8</td>
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<td></td>
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<tr>
<td>Bradykinesia Off</td>
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<td>0.1</td>
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<td>On</td>
<td>0.1</td>
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<tr>
<td>PIGD</td>
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<td>5.1</td>
<td>1.4</td>
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<tr>
<td></td>
<td>On</td>
<td>2.7</td>
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<td>On</td>
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<td>(operated side) limb dyskinesia</td>
<td>0.38</td>
<td>0.53</td>
<td></td>
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</tbody>
</table>

Differences in depth (mm)

-3  -2  -1  0  1  2  3  4  5

Differences in posteriority (mm)

-3  -2  -1  0  1  2  3  4  5

Differences in laterality (mm)

-3  -2  -1  0  1  2  3  4  5

Case number

Figure 1 Bars indicate differences (mm) between the ventriculography based theoretical and electrophysiological target for each patient. (A) Laterality from midline (x), (B) posteriority to AC line (y), and (C) depth from AC-PC line (z). In order not to underestimate the differences because of negative and positive values, Sqr were calculated as in the text. Differences in depth show a tendency of theoretical target estimation to be deeper, whereas differences in anteroposterior locality are highly variable, representing target variability rather than theoretical targeting error.

TENTATIVE TARGET PLANNING (VENTRICULOGRAPHY BASED THEORETICAL TARGET)
Under local anaesthesia a Talairach frame was affixed at four points. Ventriculography was used to identify the AC and PC, the AC-PC line, and thalamic height. The proportional Talairach lines were established according to these parameters. The tentative target for the initial track was calculated 2–3 mm ahead of the midpoint on the AC-PC line, at a depth equivalent to one quarter of the thalamic height below the AC-PC line (4 to 6 mm) and 18–21 mm lateral to the midline.

MICRORECORDING DEFINITION OF TARGET (ELECTROPHYSIOLOGICAL TARGET)

Microrecording was made by means of a platinum/iridium (80%/20%) microelectrode with an impedance of 0.8–1.2 Megohms measured at 1000 Hz with glass insulation, sheathed inside a 26 gauge stainless steel tube which was itself insulated with polyamide tubing with an outer diameter of 0.625 mm (FHC 14 TDS KM). A preamplifier (ARS-3D-1 remote probe, Atlanta, USA) was connected to a differential amplifier, impedance meter, and biphasic pulse generator (ARS-MDA41, Atlanta, USA). The signal was amplified, isolated, and led to oscilloscopes, to a window discriminator, and to an audio equaliser. The window discriminator had different voltage levels to allow triggering pulses and to count and display firing frequencies. The signal was recorded in a high fidelity videocassette using an analog video/audio recording system (ARS-DC1, Atlanta, USA) for postprocessing analysis. On line recording and raster display were monitored together with an EMG and an accelerometer signal. The number of recording tracks performed at each operation depended on: (1) the ability to identify unequivocally the putamen, GPs, and GPi; (2) the presence of motor drive (enhanced phase response to proprioceptive stimuli in Gpi neurons); (3) correct identification of the internal capsule by microstimulation; and (4) correct identification of the optic tract by microstimulation and activity recording after visual stimulation.

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Differences evaluated by multivariate analysis of variance (MANOVA) with post-hoc paired t test. All p values are two tailed. The threshold for significance was p<0.05. In order not to underestimate the range of differences between the ventriculography based theoretical and electrophysiological targets due to the presence of negative and positive gaps, an Sqr (theoretical-electrophysiological)^2 was applied to all differences and mean SD range of differences calculated on this value. Difference mode was also calculated to disclose a tendency for a positive or negative value.

Results

CLINICAL OUTCOME
In all 40 patients the electrophysiologically defined sensorimotor portion of the GPi was lesioned, with significant improvement in cardinal Parkinson’s disease symptoms as well as in levodopa induced involuntary movements. Forty patients, 25 men and 15 women, completed 1 year postsurgical follow-up after posteroventral pallidotomy treatment for Parkinson’s disease. Mean age was 57.94 (SD 11.65) years, with a mean disease duration of 13.87 (SD 4.83) years. Mean Hoehn and Yahr score was 3.78 (SD 1.07) in the off state and 3.29 (SD 0.96) in the on state. Mean ADL score was 37.69 (SD 27.8) in off versus 50.25 (SD 24.3) in on. Preoperative and postoperative clinical evaluation scores are displayed in the table. No damage to the optic tract was seen in any patient. Morbidity included transient facial palsy in one patient, transient crural paresis in two, transient dysarthria in one, postoperative delirium in two, seizures in one at 2 months after surgery, postoperative pneumonia in one, subdural haematoma in one, and wound infection in one. Therefore, overall morbidity of the procedure was 14.81%. Although not reported in this series, only one patient out of 75 died from an intracerebral haematoma (1.3%).

DIFFERENCES IN VENTRICULOGRAPHY BASED THEORETICAL VERSUS ELECTROPHYSIOLOGICAL TARGET
Significant differences between the localisation of the ventriculography based theoretical versus electrophysiological target were found in depth (y; F(1,39)=26.5; p<0.0008) and anteroposterior locality (z; F(1,38)=4.11; p<0.04). No significant differences were found in laterality (x; F(1,38)=0.25; p<0.6) between both approaches. Difference ranges were 8 mm for laterality, 6.5 mm for depth, and 10 mm for posteriority. Modes for differences in z, y, and x were –2, 1, and 0 respectively (fig 1 A, B, and C).

In 30 patients (70%), none of the theoretical x, y, or z coordinates matched the electrophysiological coordinates. In five patients (12.5%), one theoretical coordinate matched the electrophysiological coordinate, and in four patients (10%), two coordinates. In only one patient did the theoretical target match the electrophysiological target (fig 2 A, B, and C).

Discussion

This study highlights three main findings: (1) There is a significant individual variability in the spatial position of an atlas defined GPi target. (2) The electrophysiologically defined localisation for posteroventral pallidotomy, shown to be effective for treating Parkinson’s disease, is located at a significantly different site than the ventriculography based theoretical target. (3) Differences in anteroposterior locality were highly variable, whereas in depth the theoretical target was commonly located deeper than the electrophysiological target. This may be interpreted as follows: whereas differences in anteroposterior locality are due to target variability, differences in depth are mainly attributable to a limitation of our theoretical calculation of the target according to the proportional Talairach system. These findings confirm the need for electrophysiological recording not only to improve...
On reviewing MRI studies of patients not included in the present series but referred to our centre with previously unsuccessful operations we saw that patients with lesions that only partially involved GPi, or lesions spreading to the GPe, sustained less benefit than those in whom the lesion had been properly situated and this is in agreement with other previous reports.23 Vitek et al published their results on microrecording guided pallidotomy in a series of patients followed up for 18 months that showed no beneficial effect wearing off.1 This is in agreement with the results published by Lang et al,1 but at variance with those presented by Samii et al in a 2 year follow up of posteroventral pallidotomy not guided by microrecording, who reported that the beneficial effects of surgery were maintained.24 This suggests that performance of the lesion under microelectrode guidance could also have a beneficial effect on the long term effect of surgery. Unfortunately, the only way to resolve the usefulness of microrecording in posteroventral pallidotomy is by means of a prospective randomised double blind evaluation, which has not yet been carried out.

The demonstration of degenerative processes of the myelin sheath was of course a crucial tool with which to reveal degenerative pathology.

Augustus Volney Waller (1816–70) developed a vital technique in the study of the nervous system. He was born on a Kent farm, but spent his childhood in France, and qualified in Paris in 1840. He then practised in Kensington (1842–51) and later went to Europe to become an outstanding experimental physiologist. In 1850, Waller reported his findings to the Royal Society. He showed that if the glossohypoglossal and hypoglossal nerves are cut, the distal segment containing axis cylinders cut off from the nerve cell undergoes degeneration. Since the cell body and proximal stump remained intact for a long period, Waller inferred that the nerve cells nourish nerve fibres. His studies made it possible to trace nerve fibres and their diseases. Combined with Forel’s seminal studies, Waller’s work was a necessary foundation for the neuron theory:

"It is my intention at present to describe various alterations, as seen under the microscope, which take place in the structure of the same nerves after their continuity with the brain has been interrupted...at the end of the third or fourth day, we detect the first alteration...about five or six days after section, the alteration of the nerve-tube...has become much more distinct by a kind of coagulation or curdling of the white substance and axis cylinder...the disjointed condition...is greater toward the extremities...as we ascend toward the brain the disorganisation appears to decrease...On the 7th, 8th and 9th days...the curdled particles of medulla become still more disconnected, and in parts are removed by absorption. The tubular sheath is also ruptured and disorganised...collected into oval or circular coagulated masses..."

Wallerian degeneration was born and has been inculcated into medical students ever since. Copious references and extracts of these investigations are contained in McHenry’s, and in Clarke and O’Malley. Waller ceased clinical practice in 1851, returning to Bonn where he worked with Budge on pupillary innervation that he showed derived from the T1-T2 segments (ciliospinal centre) and the sympathetic trunk that exerted a vasoconstrictor action. He travelled to Paris in 1856 and fell sick, probably with rheumatic fever. He recovered and took the chair of physiology in Birmingham, but further illness hastened retirement. He died with severe angina in 1870.

His son Augustus D Waller became a distinguished physiologist, who on mention of father’s name, remarked: “I am the Wallerian degeneration.”

The varied terminations of axons was studied by Willy Kuhnle, and Nissl had advanced descriptions of the cell body constituents by using aniline dyes as cell stains. Rudolf Virchow in 1846 first observed the neuroglia, as an elevated membrane of what he realised was connective tissue, beneath the ventricular ependyma. In 1870, Bernhard Aloys von Gudden (1824–1886), professor of psychiatry at Zurich and later Munich, produced secondary atrophy of the central nervous systems by the removal of sensory organs or cranial nerves in young animals. In 1889, he showed the crossed and uncrossed fibres of the optic nerve and the occurrence of secondary atrophy in the thalamic after removal of specific cortical areas—transneuronal degeneration.

This vast field of work culminated in the work of Camillo Golgi who used silver stains and demonstrated structures previously invisible, which were to be the basis of his axonal net theory that displaced Gerlach’s notion of a neural plexus.