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SHORT REPORT

Deep brain stimulation for tremor resulting from acquired brain injury

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ABSTRACT

Objectives To evaluate the efficacy of deep brain stimulation (DBS) in the treatment of tremor resulting from acquired brain injury (ABI).

Methods A series of eight consecutive patients with post-ABI tremor were treated with DBS of the ventro-oralis posterior (VOP)/zona incerta (ZI) region, and subsequently underwent blinded assessments using Bain’s tremor severity scale.

Results VOP/ZI DBS produced a mean reduction in tremor severity of 80.75% based on Bain’s tremor severity scale, with significant reductions in all five component tremor subscores: rest, postural, kinetic, proximal and distal. No adverse neurological complications were reported, although one patient experienced exacerbation of pre-existing gait ataxia.

Conclusion VOP/ZI stimulation is demonstrated here to be an effective and safe approach for the treatment of post-ABI tremor in the largest series published at the time of writing.

INTRODUCTION

Tremor is a debilitating comorbidity which can develop following acquired brain injury (ABI).1,2 There is well-established evidence for the efficacy of thalamic deep brain stimulation (DBS) in the treatment of tremor, particularly in Parkinson’s disease and essential tremor.3 The standard electrode target is the ventralis intermedius (Vim) thalamic nucleus.

DBS is also effective for treating more complex tremor syndromes such as those associated with multiple sclerosis (MS).3,5,6 For complex tremor syndromes, often with proximal and distal components, DBS targeted to the ventro-oralis posterior (Vop)/zona incerta (ZI) has shown good efficacy.6 This is explained by the fact that in Vop/ZI DBS, the electrode is sited in such a way that it traverses both areas, and stimulation can be adjusted to blend the effects of Vop stimulation, which tends to target proximal tremor, and ZI stimulation, which is effective for distal tremor.

Like MS tremor, post-ABI tremor is a highly variable syndrome, with heterogenous patterns of neural damage producing complex movements composed of distal and proximal components. Positron emission tomography has confirmed that after strokes, DBS produces changes in both areas of involvement, as demonstrated by the fact that stimulation of the Vim region can sometimes reduce tremor in the distal hand.7

METHODS

Patients

A consecutive series of eight patients with post-ABI tremor underwent Vop/ZI DBS surgery. All patients provided informed consent for the use of anonymised data in clinical research. Table 1 displays a summary of the clinical characteristics of the patients. Patients had evidence of neural damage to midbrain or cerebellar pathways (n=6), thalamus (n=1) and peri-rolandic cortex (n=1). It is possible that patients had additional neural injury not evident on available imaging. Video assessments were part of the standard clinical assessment and postoperative follow-up. Testing was in accordance with principles of the Declaration of Helsinki and ethical approval obtained from the Oxfordshire REC C: 05/Q1605/47.

Surgery

Surgery was performed by one surgeon between 1999 and 2007 across two centres, Oxford, UK, and Charing Cross, UK. All patients underwent surgery for implantation of DBS electrodes (Medtronic 3387, Medtronic, Minneapolis, Minnesota, USA, each with four 1.5 mm contacts spaced 1.5 mm apart, spanning a total distance of 12 mm) targeting the Vop/ZI contralateral to the side of tremor. Details of surgical technique have previously been published by our group.8 The intended target for Vop was 12, 0, 0 (mm) relative to the MCP in each patient, while ZI was visually targeted, aiming just above the STN. The final electrode position was determined clinically by awake intraoperative testing, producing a possible discrepancy between the original target location and the final positions chosen. Stereotactic coordinates relative to the AC-PC line, electrode configuration and stimulation parameters for each patient are given in table 2. Figure 1 demonstrates the electrode trajectory (A) and the position of the two active contacts (B and C) mapped onto the Schaltenbrand–Wahren atlas for a single patient, illustrating how the electrode can traverse Vop and ZI. The typical anatomical distance between the targets varies between individuals and, if calculated linearly, also depends on the angle of approach. However, based on our subjects and the atlas localisation of the electrode contacts, the distance between ZI and Vop is between 3 and 6 mm. For example, in patient 3, where the angle of the electrode relative to the
AC-PC line was 49°, the centre of contact 10 was within ZI and the centre of contact 11 was within Vop, giving an estimated anatomical separation of 3 mm (see table 2 and figure 1).

Electrode placement was confirmed by postoperative CT scan coregistered to the preoperative MRI. Patient 3 was additionally implanted with a second electrode in the ipsilateral globus pallidus pars interna (GPi) with the intention of suppressing dyskinesias. This lead was turned off throughout testing. Patient 3 had previously undergone a thalamotomy, which produced only transient alleviation of tremor.

No adverse neurological reactions to surgery were reported. One patient suffered two infections at the implantable pulse generator (IPG) site (Medtronic Kinetra Model 7428, Medtronic, Minneapolis, Minnesota, USA) resulting in reposi-

tioning of the IPG with no further complications. One patient suffered an IPG failure resulting in rapid tremor recurrence, which was abolished upon IPG replacement. During follow-up, patients 3, 5 and 6 had replacement of IPG due to end of battery of life.

### Clinical rating scale

The severity of tremor was measured using Bain’s standardised clinical rating scale for tremor. anonymised video clips of clinical assessments were digitised, randomised and rated by two consultant members of the clinical care team blinded to the patient’s operative and stimulation status. Postoperative videos from the longest follow-up period available were selected. Ratings addressed severity of tremor in the affected arm in five categories: rest, postural, kinetic, proximal and distal. Ratings were scored out of 10 for each category with 0 representing the absence of tremor and 10 being the most severe. Ratings were based on the amplitude and intermittency of tremor. Clinical definitions of tremor components have previously been established and described

### Table 1 Summary of clinical characteristics for patients involved in this study

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Tremor side</th>
<th>Age of onset (months)</th>
<th>Age at surgery (months)</th>
<th>Follow-up (months)</th>
<th>Aetiology</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>L</td>
<td>11</td>
<td>30</td>
<td>78</td>
<td>RTA, MRI shows cerebellar atrophy</td>
<td>None noted</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>R</td>
<td>36</td>
<td>40</td>
<td>24</td>
<td>Right vertebral artery occlusion</td>
<td>Worsening of jerk-like movements if amplitude exceeds 3.3 mA</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>R</td>
<td>23</td>
<td>40</td>
<td>46</td>
<td>Right hemisphere peri-rolandic infarction during pregnancy</td>
<td>None noted</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>R</td>
<td>40</td>
<td>43</td>
<td>12</td>
<td>Right midbrain haematomata, involving right cerebellar peduncle</td>
<td>None noted</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>R</td>
<td>11</td>
<td>30</td>
<td>78</td>
<td>RTA, MRI shows cerebellar atrophy</td>
<td>None noted</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>L</td>
<td>14</td>
<td>24</td>
<td>24</td>
<td>RTA, diffuse axonal injury to frontal lobes + left cerebellum</td>
<td>None noted</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>R</td>
<td>64</td>
<td>68</td>
<td>6</td>
<td>Ischaemic CVA, diffuse damage and large left thalamic infarct</td>
<td>Postural tremor well suppressed with arm outstretched but more troublesome with arm bent and on intention. Right leg heaviness and dragging of leg when walking</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>L</td>
<td>20</td>
<td>22</td>
<td>12</td>
<td>RTA, diffuse injury involving brainstem + fluid on cerebellum</td>
<td>Transient pins and needles on changing settings but no other lasting symptoms</td>
</tr>
</tbody>
</table>

### Table 2 Active electrode contacts, stimulation parameters and stereotactic coordinates for each patient where data are available

<table>
<thead>
<tr>
<th>Patient</th>
<th>Electrode side</th>
<th>Electrode configuration</th>
<th>Electrode contacts in the target areas</th>
<th>Stimulation parameters</th>
<th>Angle between electrode and AC-PC line in sagittal plane</th>
<th>Stereotactic coordinates of active contacts relative to AC-PC line</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Left</td>
<td>Case (+), 3 (−) (monopolar)</td>
<td>0 in ZI</td>
<td>2.0 V, 90 μs, 130 Hz</td>
<td>64°</td>
<td>7.3 posterior, 12.2 left, 2.5 inferior</td>
</tr>
<tr>
<td>2</td>
<td>Right</td>
<td>3 (+), 2 (−)</td>
<td>1 in ZI, 2 and 3 in VOP</td>
<td>2.5 V, 90 μs, 130 Hz</td>
<td>68°</td>
<td>0.8 anterior, 10.4 left, 4.6 superior</td>
</tr>
<tr>
<td>3</td>
<td>Right</td>
<td>9 (−), 10 (+)</td>
<td>10 in ZI, 11 in VOP</td>
<td>3.0 V, 210 μs, 100 Hz</td>
<td>49°</td>
<td>3.2 posterior, 12.0 right, 1.6 inferior</td>
</tr>
<tr>
<td>4</td>
<td>Right</td>
<td>4 (−), 6 (+)</td>
<td>4 in ZI, 6 and 7 adjacent to VOP</td>
<td>1.5 V, 90 μs, 130 Hz</td>
<td>80°</td>
<td>5.1 posterior, 13.1 right, 2.5 inferior</td>
</tr>
<tr>
<td>5</td>
<td>Right</td>
<td>5 (−), 7 (+)</td>
<td>–</td>
<td>2.3 V, 210 μs, 180 Hz</td>
<td>–</td>
<td>3.7 posterior, 14.7 right, 2.9 superior</td>
</tr>
<tr>
<td>6</td>
<td>Left</td>
<td>3 (+), 2 (−)</td>
<td>–</td>
<td>3.6 V, 360 μs, 130 Hz</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td>Right</td>
<td>0 (−), 2 (+)</td>
<td>–</td>
<td>2.6 V, 300 μs, 130 Hz</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>8</td>
<td>Left</td>
<td>1 (+), 3 (−)</td>
<td>1 in ZI, 2 and 3 in VOP</td>
<td>3.3 V, 156 μs, 130 Hz</td>
<td>60°</td>
<td>3.1 posterior, 10.8 right, 3.2 inferior</td>
</tr>
</tbody>
</table>

A dash indicates unavailable data due to missing scans. Numbering of contacts is based on two different systems; older devices have contacts numbered 0–3 and 4–7 while newer devices have contacts numbered 0–3 and 8–11. Column 4 shows which contacts fall within the target area based on the Schaltenbrand–Wahren atlas. VOP, ventro-oralis posterior; ZI, zona incerta.
in detail. The mean score from the two observers was used for statistical testing.

RESULTS

All patients were assessed and videoed ON stimulation (n=8) at a mean length of follow-up of 26 months. ON stimulation tremor scores were compared with either OFF stimulation scoring of videos made at the time of follow-up assessment or scores from preoperative videos. Six patients had preoperative video assessments for comparison and five patients had follow-up OFF stimulation video assessments taken after a sufficient wash-out period. Preoperative videos were used in preference over follow-up videos in the six patients where these were available. In the patient with a GPi lead, this was turned OFF throughout all assessments. For the six patients with preoperative and ON stimulation assessments, all showed reductions in tremor severity across the five components of the Bain scale (mean reduction 69.13%, SD 38.69%). Similar results were obtained for the two patients in which ON and OFF stimulation conditions were instead compared (patient 7: mean reduction 77.78% and patient 5: mean reduction 87%). Taken together, there was an overall reduction of tremor severity by 80.75% following stimulation. Figure 2 displays the mean component scores across conditions (preoperative, ON stimulation, OFF stimulation) and table 3 gives individual scores for patients 1–7 (scores for patient 8 are unavailable at the time of writing). The scores from the two observers showed a highly significant correlation (n=95, p < 0.001, r = 0.838, Pearson correlation).

All five tremor elements showed significant reduction in the ON stimulation condition, compared with preoperative levels (n=6, rest p = 0.046, Z = −1.997; postural p = 0.003, Z = −2.943; kinetic p = 0.003, Z = −2.940; proximal p = 0.018, Z = −2.371;...
usually minimised by altering stimulation parameters. A significant reduction in tremor symptoms in eight consecutive patients treated for post-ABI tremor.

**DISCUSSION**

The results of this study provide strong evidence for the efficacy of Vop/ZI DBS in reducing the severity of unilateral post-ABI tremor. Statistically significant improvements following DBS were demonstrated across all five components of the Bain tremor score, evaluated in a blinded fashion by two consultants considered to be expert in the assessment of tremor. The strong benefits of DBS demonstrated in this study are underlined by the report of rapid tremor recurrence following IPG failure in one patient.

Tremor can be a debilitating outcome following severe head injury or stroke,1 2 remaining chronic and refractory to medical therapy in some patients. Damage to the cerebellothalamic pathway may result in kinetic and proximal tremors, and if damage encompasses both cerebellothalamic and nigrostriatal regions, a Holmes tremor may result.13 All patients in our cohort experienced a kinetic or postural tremor, and Holmes’ tremor was diagnosed in six patients (patients 1, 2, 4, 6, 7 and 8). Damage to the cerebellum or cerebellar pathways may also result in ataxia (patients 2 and 5), which is unaffected by DBS and may be a source of remaining functional disability.

One of the remarkable features of our study is that benefit was achieved for all patients despite heterogeneity within the cohort in terms of the neuroanatomical locus of injury (table 1). We suggest that this may be due to the selection of Vop/ZI as the target for surgical intervention in contrast to the more widely targeted Vim nucleus. The choice is borne of clinical experience regarding the efficacy of Vop/ZI in the treatment of complex tremors with heterogenous patterns of underlying neural damage, such as those associated with MS.4 14 A recent DTI study from our group has demonstrated that Vop and Vim have different patterns of connectivity, which may account for the difference in clinical effect of stimulating the two regions.15 However, as with all forms of DBS, a detailed understanding of the mechanistic principles underlying the mechanism of action of Vop/ZI stimulation is still lacking. Nevertheless, the clinical benefit demonstrated in the present cohort is compelling.

We note some limitations of our data, including different lengths of follow-up and the presence of a pre-existing thalamotomy in one patient (however, this had failed to provide lasting clinical benefit which is why the patient was considered for DBS surgery). Our assessment was limited to tremor evaluation in the experimental setting and we did not assess the effect of DBS on coexisting symptoms such as ataxia nor did we assess chronic effects of stimulation. Future studies would also benefit from more comprehensive symptom evaluation, testing over longer durations of stimulation and more extensive quality of life and activities of daily living outcomes. Future studies would also benefit from detailed anatomical mapping of both the lesion site and electrode targets, combined with DTI analysis, to gain deeper mechanistic understanding of the stimulation effects.

**SUMMARY**

Vop/ZI DBS produced a significant reduction in tremor symptoms in eight consecutive patients treated for post-ABI tremor.
despite apparent heterogeneity in the underlying anatomical lesion. Our results confirm earlier reports in small case series and case reports that DBS may be an effective treatment option for post-ABI tremor.\textsuperscript{7–10}

**Contributors**

HS revised and prepared the final manuscript for publication, collected clinical data, analysed electrode locations and produced the figure; PH was involved in project design, data collection, statistical analysis and writing the paper; ZO contributed to experimental design and execution, review of the statistics and paper; NdP was involved in project conception, critique of the statistics and the draft; J-SB was involved in carrying out the testing, reviewing statistics and reviewing a draft; NJ contributed to experiment design, design and critique of the statistics and review of the paper; CJ provided expert advice on stimulation settings, symptoms and side effects for each patient; TZA contributed to experiment conception, statistical review and critique of a draft; ALG contributed to experiment conception, statistical review and critique of drafts.

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**Competing interests** None.

**Patient consent** Obtained.

**Ethics approval**

Oxfordshire REC C: 05/Q1605/47.

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