

## SHORT REPORT

# Deep brain stimulation of the centre median-parafascicular complex in patients with movement disorders

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The centre median-parafascicular (CM-Pf) complex of the thalamus is considered to be a possible target for deep brain stimulation (DBS) in patients with movement disorders. In a prospective study on the effect of CM-Pf DBS versus somatosensory thalamic DBS on chronic neuropathic pain, three of 12 patients had additional movement disorders. Bifocal quadripolar electrodes were implanted by computed tomography guided stereotactic surgery under local anaesthesia contralaterally to the side of the pain for test stimulation. Two of the three patients with movement disorders had permanent implantation of CM-Pf electrodes. During test stimulation of the left CM-Pf complex for several days, a 67 year old woman received no benefit with respect to the neuropathic pain, but the choreo-athetotic movements of her right foot ceased. As the pain syndrome was not improved, she decided not to have permanent implantation. A 74 year old man with postzoster neuralgia and allodynia enjoyed excellent relief from his pain with chronic CM-Pf DBS. In addition, improvement in the tremor at rest was noted. A 72 year old man had sustained reduction in his stump dyskinesias. Further evaluation of the possible role of the "forgotten" central and medial thalamic nuclei in the treatment of movement disorders may be warranted.

Current targets for deep brain stimulation (DBS) for treatment of movement disorders include the ventro-intermediate thalamic nucleus, the subthalamic nucleus, and the globus pallidus internus. There is interest, however, to expand this technology to other targets in order to increase efficacy and reduce side effects. The centre median-parafascicular (CM-Pf) complex, in particular, is considered to be a candidate target in patients with movement disorders.<sup>1</sup> There is some evidence from earlier reports on DBS and from centres performing medial thalamotomy that targeting the medial thalamus including the CM-Pf complex is efficient in controlling movement disorders.<sup>2,3</sup> Furthermore, a recent study comparing the results between two teams performing thalamic DBS for parkinsonian tremor indicated that CM-Pf stimulation may have a beneficial effect on dyskinesias.<sup>4</sup>

At present, we are conducting an open label prospective study on the effects of CM-Pf versus somatosensory thalamic stimulation for treatment of severe neuropathic pain. Here, we present the findings of CM-Pf stimulation in three patients who had concomitant movement disorders.

## PATIENTS AND METHODS

### Patients

Since December 1997, a total of 12 patients with chronic neuropathic pain have undergone bifocal contralateral stereotactic implantation of quadripolar electrodes in the CM-Pf complex and the somatosensory thalamus after having given informed

consent. Preliminary results on the effect of CM-Pf DBS on neuropathic pain have been published elsewhere in abstract form.<sup>5</sup> The mean age at surgery was 56 years. There were six men and six women. The mean history of pain was nine years. All patients had participated in numerous medical trials with insufficient control of their pain. Pain was limited to one side of the face, body, or extremities in every instance.

Three patients had concomitant movement disorders: patient 1 had mild bilateral tremor at rest; patient 2 had mild choreoathetotic movements of the right foot; and patient 3 had amputation stump dyskinesias of his left thigh. The movement disorders in these patients did not result in additional disability and did not require medical treatment.

### Methods

Bifocal quadripolar electrodes were implanted stereotactically under local anaesthesia in the CM-Pf complex and the ventroposterolateral (VPL) or the ventroposteromedial (VPM) thalamic nucleus contralateral to the side of the pain (Medtronic 3387; Medtronic Inc, Minneapolis, Minnesota, USA). The VPM thalamic nucleus was chosen in patients with hemifacial or hemicranial neuropathic pain. Preliminary coordinates were determined by stereotactic computed tomography including alignment correction.<sup>6,7</sup> The stereotactic coordinates used to approach the targets (related to the intercommissural line) were as follows: CM-Pf complex, x=7–10, y=8 (posterior), z=0; VPL thalamic nucleus, x=13–15, y=9–10 (posterior), z=0; VPM thalamic nucleus, x=12–14, y=9–10 (posterior), z=0. Differences in the x coordinates accounted for variability in the width of the third ventricle. Microelectrode recordings were performed with high impedance electrodes (0.5–1.8 M $\Omega$ ) with tip sizes ranging from 15 to 40  $\mu$ m. Macrostimulation was performed directly via the quadripolar electrodes. Both electrodes were externalised, and test stimulation trials alternating between the two targets were performed for several days to determine the site of optimal pain relief. Patients rated pain relief on visual analogue scales for pain at its maximum, pain at its minimum, pain on average, and allodynia.

### RESULTS

There were no adverse effects during the operation or during the stimulation trials. Microelectrode recordings in the VPL and VPM thalamic nuclei showed spontaneous noisy background activity. Tactile cells responding to light touch or brushing of the contralateral extremities were identified in the VPL thalamic nucleus, and neurones with fields receptive to touching of the face were consistently found in the VPM thalamic nucleus. The ventral border of the somatosensory thalamus could be identified by a decrease in the background

**Abbreviations:** DBS, deep brain stimulation; CM-Pf, centre median-parafascicular; VPL, ventroposterolateral; VPM, ventroposteromedial

activity. Along the trajectory to the CM-Pf complex, various neurones firing in bursts were identified in agreement with previous studies.<sup>3,8</sup> Often, such neurones had the features of low threshold calcium spike bursts. There were clearly fewer bursting neurones when the basis of the target was approached. Postoperative 1 mm computed tomography scans confirmed the position of the implanted electrodes.

Pain scores were significantly improved by CM-Pf stimulation compared with before the operation and with results of somatosensory thalamic stimulation. Eleven patients subsequently had continuous CM-Pf DBS. Test stimulations and chronic DBS were performed continuously at variable amplitudes for pain relief at a frequency of 130 pulses per second and a pulse width of 180–210 microseconds.

### Case histories

Patient 1, a 74 year old man, suffered from postzoster neuralgia and allodynia in the left C2 dermatome. The pain had a burning quality and was refractory to a variety of analgesic drugs. He also had mild bilateral tremor at rest, but no other parkinsonian symptoms were present. He enjoyed excellent improvement in pain from right sided chronic thalamic CM-Pf DBS over a follow up of two years. There was also considerable improvement in the tremor at rest, which was more pronounced on the left side, contralateral to the DBS.

Patient 2, a 67 year old woman, suffered from dysaesthetic pain of the right half of her body after having sustained a haemorrhage to the left posterior thalamus two years earlier. She also developed mild choreoathetotic movements of her right foot, which did not concern her. She experienced no improvement in her dysaesthetic pain with either CM-Pf or somatosensory thalamic test stimulation for a week. The dyskinesias, however, disappeared during CM-Pf stimulation. As the pain was not improved, she opted not to have permanent DBS. After removal of the electrodes, the dyskinesias were the same as before surgery.

Patient 3, a 72 year old man, developed severe aching and burning stump pain and stump dyskinesias after amputation of his left leg at the mid-thigh 21 years earlier. A neuroma was excluded. During the test stimulation, he enjoyed considerable improvement in pain and an 80% reduction in the frequency of the stump dyskinesias during CM-Pf stimulation. One year after surgery, there was a recurrence of the pain, which was still responsive, however, when the amplitude of the voltage was increased. There was a sustained reduction in both the severity and frequency of the stump dyskinesias.

### DISCUSSION

The intralaminar thalamic nuclei, including the CM-Pf complex, have recently been designated by Jones as “the forgotten components of the great loop of connections joining the cerebral cortex via the basal ganglia”.<sup>9</sup> The CM-Pf complex is an integral part of the sensorimotor basal ganglia circuitry.<sup>9,10</sup> The intralaminar thalamic nuclei receive inputs from the striatum, upper brainstem, and cerebellum.<sup>9</sup> The CM is primarily innervated from the globus pallidus internus.<sup>11,12</sup> Pallidal axons projecting into both the lateral region of the thalamus and the central complex have been found in primates.<sup>13</sup> The inputs into the Pf are less well established, but appear to come mainly from the brainstem. The pedunculo-pontine nucleus projects into the Pf through cholinergic pathways.<sup>14,15</sup> There are multiple striatal and cortical projections from the CM-Pf complex.<sup>16–18</sup> It has also been suggested that activity of the subthalamic nucleus is regulated by afferents from the Pf.<sup>19</sup> The striatal CM-Pf projections are glutamatergic.<sup>20</sup>

Our observations provide direct evidence that chronic DBS of the CM-Pf may be useful in patients with movement disorders. Conclusions from these findings are limited, however, for several reasons. The movement disorders were mild and not a

source of disability in the three patients reported here. Furthermore, spread of the current to adjacent structures of the thalamus cannot be excluded. Although stimulation of fibres in the subthalamic area is unlikely from the position of the electrode contacts, inhibition of neighbouring thalamic nuclei is conceivable. Spread of current may involve the centrolateral nucleus, which is another forgotten thalamic nucleus, and also the ventrointermediate or the ventrolateral thalamus. Although it is well known that thalamic stimulation is beneficial for tremor and dyskinesias, there is only limited experience with stump dyskinesias. Control of involuntary stump movements by modulation of thalamic activity has been previously reported by Mazars *et al.*<sup>21</sup>

The effect of stereotactic lesioning of the CM-Pf on movement disorders in earlier studies is difficult to appreciate.<sup>22–24</sup> Usually, additional lesions were placed in other nuclei. Medial thalamotomy for treatment of movement disorders is only rarely performed nowadays. Jeanmonod *et al.*<sup>7</sup> reported 50–100% relief in 43% of patients with motor disorders. Recently, a patient with tardive dystonia was reported to be considerably improved after a thalamotomy, with lesions placed mainly in the VPM thalamus and the CM-Pf complex.<sup>25</sup>

The first attempts at chronic DBS of the CM-Pf complex were pioneered by Andy in 1980.<sup>2</sup> Three patients with pain that was refractory to medical treatment were reported to show improvement with regard to both pain and accompanying movement disorders on chronic intermittent stimulation. The movement disorders that were improved included parkinsonian rigidity, spasticity/dystonia, and cervical dystonia. Another patient with choreoathetosis was also reported to benefit from CM-Pf DBS. No follow up information was provided. Caparros-Lefebvre and colleagues<sup>4</sup> compared the results of thalamic DBS for Parkinson's disease between the teams of Lille and Grenoble. Targeting the ventrointermediate thalamus, both teams achieved suppression of parkinsonian tremor, but a clear improvement in choreic peak dose dyskinesias was found only in the patients from Lille. Retrospective analysis of the electrode position showed that improvement in levodopa induced dyskinesias was associated significantly with a more medial, more posterior, and deeper placement of the electrode—that is, probably closer to the CM-Pf than to the ventrointermediate thalamus.

It remains unclear which patients with movement disorders may be suitable candidates for CM-Pf DBS. As degeneration of the CM-Pf complex has been reported in both patients with Parkinson's disease and those with hyperkinesias, the effect of lesioning or chronic stimulation of the CM-Pf complex is probably not mediated by mere reduction or inhibition of neuronal net activity, but rather by its impact on different neuronal substrates in the CM-Pf complex. Patients with Parkinson's disease have a 30–40% neuronal loss in the CM-Pf complex, which is even more evident in neuronal subpopulations.<sup>26</sup> A 50% loss of parvalbumin positive neurones was observed in the Pf, and a 70% loss of non-parvalbumin positive neurones was noted in the CM. These findings were interpreted to indicate that degeneration of the CM-Pf complex is likely to exacerbate the clinical signs and symptoms of Parkinson's disease. Henderson and colleagues<sup>26</sup> suggested that selective degeneration of neuronal Pf subpopulations is unlikely to be a source of subthalamic nucleus hyperactivity in Parkinson's disease.

Given the dense integration of the CM-Pf complex in the circuitry of basal ganglia structures known to be involved in the pathophysiology of various movement disorders, further evaluation of these structures as targets for surgical treatment of movement disorders may be warranted. Some caution is advisable in patients with Parkinson's disease with regard to the neurodegenerative changes described in the CM-Pf complex and the experience with chronic DBS in a patient in whom an electrode was misplaced in the CM-Pf.<sup>27</sup>

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