Long term follow up of thalamic deep brain stimulation against tremor- patient satisfaction and mortality

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By
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ABSTRACT

Background
Deep brain stimulation (DBS) is used as a symptomatic treatment of tremor in several movement disorders. We report the findings of a retrospective study of all patients with non-Parkinson disease (PD) non dystonic tremor receiving DBS in the ventral intermediate nucleus of thalamus (VIM) at Oslo University hospital- Rikshospitalet from 1996 to 2010 with analysis of survival, mortality, adverse effects, patient satisfaction and self-reported effect of VIM-DBS.

Methods
Retrospective study including 53 patients. Data obtained from patients records and an 18-item questionarie including VAS scale. SPSS used for statistical analysis. P-value < 0.05 considered statistically significant.

Results
Of 53 included patients there were 32 (60.4%) men and 21 (39.6 %) women. 46 patients diagnosed with ET. The other 7 patients had symptomatic tremor conditions: cerebellar tremor (2), cerebellar tremor in MS (1) Holmes tremor (1) and action tremor after vascular ischaemic lesions in the posterior fossa (3). Mean age at operation was 60.9 years. 9 patients (17 %) died during the study period. Mean age at death was 75.3 years and mean time from surgery until death was 7.7 years. There were no significant increase in mortality. The patients reported high satisfaction with VIM-DBS together with a good effect on tremor at long term follow up. Adverse effects were generally well tolerated.

Conclusions
We conclude that VIM-DBS is a safe symptomatic treatment of non-PD non dystonic tremor conditions with a long-term effect on tremor.
Long term follow up of thalamic deep brain stimulation against tremor – patient satisfaction and mortality

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INTRODUCTION

Tremor is a common sign in movement disorders and can in advanced cases lead to severe loss of daily function. Deep brain stimulation (DBS) of the ventral intermediate nucleus (VIM) of the thalamus was introduced by Benabid et al.\textsuperscript{1,2} against tremor in Parkinson’s Disease (PD) in 1987 and against essential tremor (ET) in 1991. Today DBS is commonly used in PD, but other targets are usually preferred since VIM-DBS is not effective against other parkinsonian symptoms.\textsuperscript{3} VIM-DBS has been reported effective in dystonic tremor,\textsuperscript{4} but the internal segment of pallidum is usually the preferred target in dystonic patients.\textsuperscript{5} As concerns other tremors, several studies have confirmed that VIM-DBS is effective in ET,\textsuperscript{6-9} and the method is now well established as a symptomatic treatment for severe medically resistant tremor. For other non-PD non-dystonic tremor conditions such as MS, Holmes tremor and cerebellar tremor, however, documentation is sparse and inconsistent.\textsuperscript{10-12} To our knowledge there are no previous studies of mortality after DBS for ET or other symptomatic tremor conditions.

Here we report the findings of a retrospective study of all patients with non-PD non-dystonic tremor receiving VIM-DBS in our hospital from 1996 to 2010, with analysis of survival, mortality, adverse effects, patient satisfaction and self-reported effect of VIM-DBS.

PATIENTS AND METHODS

Study population
All 53 patients that underwent VIM-DBS surgery for tremor unrelated to PD and dystonia at Oslo University Hospital-Rikshospitalet from 1996-2010 were included in this study. There were 21 (39.6%) women and 32 (60.4%) men. The indication for VIM-DBS was severe and incapacitating tremor with unsatisfactory response to medical treatment. 46 patients had been diagnosed with ET according to the consensus statement of the Movement Disorder Society on tremor.\textsuperscript{13} The other 7 patients had different symptomatic tremor conditions: cerebellar tremor (2), cerebellar tremor in MS (1) Holmes tremor (1) and action tremor after vascular ischaemic lesions in the posterior fossa (3). All patients were followed until November 1, 2012, or death. The date of death was obtained from
the hospital’s electronic patient record system. This system is continuously updated with
information from the National Population Registry of Norway.

The data on medication, stimulation parameters, comorbidity and cause of death were obtained
from medical records, from an 18-item questionnaire sent to all surviving patients, and from the
Norwegian death-registry. Overall patient satisfaction and self-reported treatment effects were
measured by visual analog scales (VAS). Written informed consent was obtained from all
participants. The Regional Committee for Medical and Health Research Ethics in South-East
Norway approved the study.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Epidemiological characteristics of patients treated with VMDBS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
</tr>
<tr>
<td>See MIF</td>
<td>32/1</td>
</tr>
<tr>
<td>Follow up time</td>
<td>7.0 (5.4) (0.6-16.1)</td>
</tr>
<tr>
<td>Age at follow up</td>
<td>67.9 (13.2) (35.2-80.0)</td>
</tr>
<tr>
<td>Age at operation</td>
<td>60.9 (13.4) (20.5-84.2)</td>
</tr>
<tr>
<td>Placement of electrode</td>
<td></td>
</tr>
<tr>
<td>Left lateral</td>
<td>6</td>
</tr>
<tr>
<td>Right lateral</td>
<td>3</td>
</tr>
<tr>
<td>Bilateral</td>
<td>44</td>
</tr>
<tr>
<td>Earlier unilateral DBS</td>
<td>2</td>
</tr>
<tr>
<td>Earlier thalamotomy</td>
<td>5</td>
</tr>
</tbody>
</table>

F: female  M: male
Data presented as mean values ± standard deviations (range)
Follow up until 01.11.12 or death

Surgical procedure
Preoperative MRI sequences were obtained on the day before the operation. On the day of surgery a
CRW^(TM) stereotactic frame, (Radionics, MA, USA) was mounted, placed parallel to the AC-PC
line, before a stereotactic CT scan was performed. This was done in local anesthesia. The MRI and
CT scans were merged using the iPlan^(TM) (version 3.0) computer-aided neuronavigation system
(BrainLAB, München, Germany), after which the targets and the trajectory of the electrode were
planned using the same software.

During the planning the targeting of the VIM was done using our standard stereotactic coordinates
in relation to the anterior commissure (AC)-posterior commissure (PC) line: approximately 30% of
the AC-PC distance anterior to PC, 50% of the AC-PC distance lateral of the midline and 0-2mm
superior to the AC-PC line. The target was adjusted in some patients with abnormal ventricles and
according to the symptoms, so that the target was 12mm (narrow ventricles and main symptoms in
lower extremity) -- 16mm (wide ventricles and main symptoms in upper extremity) lateral to the
midline. The trajectories were planned so that interference with vessels, sulci and ventricles were
avoided.

After clinical test stimulation in the awake patient, confirming good tremor suppression and no
unacceptable side effects, a permanent quadripolar electrode (model 3387 or 3389, Medtronic, MN,
USA) was inserted. Electrode position was checked using perioperative radiography, and the
electrodes were fixed to the skull using the Stimloc system. With 9 exceptions all patients were
operated bilaterally. Both electrodes were implanted during the same operation. After removal of
the stereotactic frame, the electrodes were connected to a dual pulsegenerator (Activa PC,
Medtronic) implanted in the subclavicular region. This was done under general anesthesia. Of the
44 patients receiving bilateral stimulation, 2 had earlier received unilateral stimulation and 5 had
earlier been treated with unilateral thalamotomy.
Statistical analysis
SPSS were used for statistical analysis. Data presented as mean values ± standard deviations (SD) and range in table 1, 2 and 4. Table 3 and 5 presented as number of patients and percent.
Stimulation parameters compared at postoperative year and 3-8 years follow up, P-value < 0.05 considered statistically significant.
Kaplan-Meier survival curve was constructed using death as outcome. Mortality in ET patients was compared to the general population of Norway using standard mortality ratio (SMR). Death statistics of 2006 obtained from Statistics Norway (SSB).

RESULTS

Outcome
Mean follow up time was 7.0 years (range, 0.6-16.1), and mean age at final evaluation was 67.9 years (range, 35.2-90). 14 patients had a follow up time of less than 3 years, 6 patients of 3-5 years, 16 patients of 5-10 year, and 17 patients of more than 10 years.
As reported in table 2, stimulation parameters 3-8 years after surgery were available in 34 patients in the total operation group. A significant increase was seen both in voltage and frequency. Mean voltage had been increased from 2.4V first postoperative year to 3.3V at follow up, whereas mean frequency had been increased from 150.9Hz to 171.7Hz over the same period. The mean pulse width had been reduced from 90.4 to 85.6 microsec, but this was not significant. The increase in voltage was higher in the group of ET patients than in the symptomatic tremor group. (1.1V and 0.5V).

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Stimulation parameters during long-term VM-DBS treatment</th>
<th>All postoperative year</th>
<th>All 3-8 years follow up</th>
<th>ET postoperative year</th>
<th>ET 3-8 years follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>34</td>
<td>34</td>
<td>30</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Mono/bipolar</td>
<td>4/30</td>
<td>4/30</td>
<td>4/26</td>
<td>4/26</td>
<td></td>
</tr>
<tr>
<td>Voltage</td>
<td>2.4 (0.6)</td>
<td>3.3 (0.8)</td>
<td>2.4 (0.6)</td>
<td>3.4 (0.7)</td>
<td></td>
</tr>
<tr>
<td>Puls width</td>
<td>90.4 (13.4)</td>
<td>85.6 (13.9)</td>
<td>90.5 (14.7)</td>
<td>85.5 (13.5)</td>
<td></td>
</tr>
<tr>
<td>Frequency</td>
<td>150.9 (27)</td>
<td>171.7 (23.9)</td>
<td>151.1 (27.5)</td>
<td>172.2 (24.5)</td>
<td></td>
</tr>
</tbody>
</table>

Data presented as mean values, ± standard deviations

Of 53 possible participants in the patient satisfaction survey, 9 had died and 1 was unable to participate due to cognitive impairment. 31 of the remaining patients (72%) answered the questionnaire. Mean follow up time in the responding patients was 6.3 years (range, 1.9-16.4) Medication against tremor was used preoperative by 45.2%, by 16.1% of the patients during the first postoperative year, and by 35.5% at follow up (table 3). There were no difference between responders with ET and all responders.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients N=31</td>
<td>Yes</td>
</tr>
<tr>
<td>preoperative</td>
<td>14 (45.2)</td>
</tr>
<tr>
<td>postoperative</td>
<td>5 (16.1)</td>
</tr>
<tr>
<td>at follow up</td>
<td>11 (35.5)</td>
</tr>
</tbody>
</table>

Data are given in number of patients = n ( %) with use of medication including betablockers, antiepileptics, benzodiazepines
Mean self-reported VAS-score of the effect of VIM-DBS on tremor was 7.9 (SD, 2.3) at postoperative, and was significantly reduced to 5.9 (SD, 3.1) at follow up in all responders (table 4). The responding patients reported a mean score of 7.6 (SD, 3.3) for overall satisfaction with VIM-DBS treatment. ET responders reported better effect of VIM-DBS on tremor at postoperative than symptomatic tremor responders, with a mean VAS score of 8.2 (SD, 2.4) vs 6.9 (SD 1,6). Both groups reported reduced effect at follow up, but only the ET responders showed a significant reduction from the postoperative score from 8.2 to 6.2 (SD, 3.0) points at follow up.

DBS showed no significant effect on the working situation in our patients.

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Patient selfreport with VAS scale</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All (n)</td>
</tr>
<tr>
<td>DBS effect on tremor after first operation</td>
<td>28</td>
</tr>
<tr>
<td>DBS effect on tremor today</td>
<td>29</td>
</tr>
<tr>
<td>Overall satisfaction with DBS</td>
<td>29</td>
</tr>
</tbody>
</table>

VAS scale 1-10, where 0 is no effect and 10 is maximum effect. Data presented as mean values ± standard deviations

Complications and battery replacements

Table 5 shows reported adverse effects. Dysarthria was the most common adverse effect, reported by 21 patients (67.7 %) with both unilateral and bilateral stimulation. Other common adverse effects were headache reported by 11 patients (35,5 %) and paresthesia reported by 10 patients (32,2%). 8 patients (25,8%) reported abnormal taste. There were no significant increase in reported psychiatric symptoms after surgery.

<table>
<thead>
<tr>
<th>Table 5</th>
<th>Most common adverse effects with VIM-DBS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bilateral</td>
</tr>
<tr>
<td>Number of patients</td>
<td>27</td>
</tr>
<tr>
<td>Dysarthri</td>
<td>18 (66,7)</td>
</tr>
<tr>
<td>Headache</td>
<td>11 (40,7)</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>9 (33,3)</td>
</tr>
<tr>
<td>Taste</td>
<td>8 (29,6)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>7 (25,9)</td>
</tr>
<tr>
<td>Uncomfort tongue</td>
<td>5 (18,5)</td>
</tr>
<tr>
<td>Balance, coordination</td>
<td>4 (14,8)</td>
</tr>
<tr>
<td>Other</td>
<td>8 (29,6)</td>
</tr>
</tbody>
</table>

Data given in number of patients = n (%) experiencing adverse effects

The battery was replaced in 34 patients after a mean time of 4.0 years (range, 2.0-8.5). On November 1, 2012 he original battery was still functioning in 15 patients after a mean time of 3.2 years (range, 1.9-6.4). When replacing the battery 3 patients got an infection and were treated with antibiotics. One of these developed into a meningitis, and the electrodes were removed and replaced later.
Mortality
As reported in table 1, 9 patients (17%) died during the study period (3 women, 6 men). The mean time from surgery to death in the total operation group was 7.7 years (range, 0.6-16.1) and the mean age at death was 75.3 years (range, 48.1-89.2). One patient died within 6 months after surgery. Mean age at surgery were higher among the dead patients compared to the total operation group.

8 of the dead patients were in the ET group (2 women, 6 men). Mean age at death in patients with ET was 78.7 years (range, 70.3-89.2). ET patients were operated in a more advanced age compared to the tremor patients. (62.7 vs 49.4 years).

The mortality in ET patients was calculated using Standard mortality ratio (SMR). Calculated expected deaths in the ET patients were 6.35, while 8 deaths were observed in this group. This gave a standard mortality ratio of 1.26 with a 95 % confidence interval ranging from 0.54 - 2.48. SMR in the total operation group were 1.38 with a 95 % confidence interval ranging from 0.63 - 2.61.

Both in the total operation group and the ET group 10 years survival after DBS operation were above 85 % (figure 1).

Figure 1 - Kaplan Meier curve
DISCUSSION

The present study shows good long-time survival after VIM-DBS both for ET patients and symptomatic tremor patients. Louis et al.\(^{14}\) indicated that the mortality in ET patients not treated with DBS is increased compared with a control group without ET. We did not find any significant increase in mortality in operated ET patients. The calculated SMR in these patients was 1.26 compared to the general Norwegian population. The group of patients included in our study is relatively large compared to most other studies of ET patients. All patients receiving VIM-DBS at our hospital from 1996-2010 were included. However, the total number of patients is still relatively small. Because of this a possible modest increase in mortality would not give a significant increase in SMR, and could therefore escape recognition.

There are several other limitations in this comparison of mortality in ET patients. One factor that might affect our results could be that ET patients selected for surgery have less comorbidity than those excluded. Another limitation is that we have used statistics from the general population of 2006 to compare the mortality in a group studied over a period of time from 1996-2012. By this we have assumed that the mortality in the Norwegian population over this period were near constant, and that possible small changes will not affect the final results.

In spite of these uncertainties, our study shows that the total survival 10 years after VIM-DBS implantation (figure 1) was above 85 % both for ET patients and for the entire operated group. We therefore feel safe to conclude that VIM-DBS is a safe symptomatic treatment for tremor conditions.

The results from the patient questionnaire are hampered by its retrospective design, with both recall- and selection bias. Out of 43 possible participants, 31 answered (72 %). All responders reported a high VAS score for the postoperative effect of VIM-DBS on tremor. The effect reported by the ET responders were somewhat better than that reported by the symptomatic tremor responders (8.2 vs 6.9). At follow up, all responders reported a reduction in the effect of VIM-DBS on tremor compared to the postoperative score (5.9 vs 7.9). Also the ET and symptomatic tremor responders reported reduced effect (6.2 and 5). However, this reduction did not reach significance in the symptomatic tremor responder group. In spite of this, a 5.9 VAS score for the effect of VIM-DBS on tremor in all responders after a mean of 6.3 years follow up, together with a reported medication reduction compared to preoperative use, indicate that VIM-DBS has a good long-term effect on tremor in these patient groups. We found that the overall patient satisfaction with DBS treatment in all responders was 7.6, and there were no differences between the symptomatic tremor and the ET responders (7.8 vs 7.6).

VAS-scale were also used by Zhang et al.\(^{15}\) in their long term study. At 56.9 months follow up they found a 1.43 (± 2.62) score for VIM-DBS effect on tremor in patients with ET. Some other studies have also reported a decrease in activities of daily living (ADL) and an increase in tremor at long-term follow up, indicating a loss of benefit of VIM-DBS over time.\(^{16,17}\) Our results seem to indicate a better long-term effect of DBS on tremor, similar to what described in a few other long-term studies of ET.\(^{6,7,9}\) However, there are in general few studies on the effect of VIM-DBS over time. VIM-DBS showed no significant effect on working situation in our patients. This may at least in part be explained by the high mean age at operation, and by a large proportion of patients already on disability benefit (38.7%).

Dysarthria was the most frequent reported adverse effect. Similar findings have been reported from other DBS studies, especially after bilateral stimulation.\(^{18,9}\) In our study patients with unilateral VIM-DBS reported dysarthria as frequently as patients stimulated bilaterally (table 5). Despite our small number of patients with unilateral stimulation, this finding might suggest that dysarthria in DBS is not related only to bilateral stimulation. Disequilibrium and balance difficulty together with
reported falls have been used as a caution against bilateral stimulation. However, coordination problems and dizziness were not reported as severe problems in our study (table 5).

There are few reports on mean battery depletion time, and the time reported is ranging from 2.5 years to 7 years. In our patients the mean battery depletion time was 4.0 years. This indicates that a follow up time of 5 years, as used by Pawha et al. might not be sufficient to include the longest depletion times. Stimulation parameters were increased both for voltage (2.4V-3.4V) and frequency (151.1hz-172.2hz) from the first postoperative year until follow up in the ET group. These findings are similar to previous reports on ET. A smaller voltage increase was seen in the symptomatic tremor group (2.2V-2.7V). Whether this increase in stimulation parameters for the ET patients is related to disease progression or tolerance to the VIM-DBS treatment, is still unclear.

Psychiatric symptoms as adverse effects to DBS have been reported for other targets than VIM, especially for the STN. There are to our knowledge no reports of psychiatric adverse events in VIM-DBS, but there are few studies on this field. We do not find any overall increase in depressive- or anxiety symptoms in the total operation group. However, 1 patient reported temporary increasing depressive symptoms after surgery, but that had declined until follow up. Another patients with a previous history of depression got an exacerbation of depressive symptoms after surgery, continuing until follow up. Thus, it is possible that also VIM-DBS may be associated with psychiatric side effects.

CONCLUSIONS

We found no significant increase in mortality in ET patients treated with VIM-DBS when compared to the general population of Norway. The estimated overall survival rate after VIM-DBS is high, indicating that VIM-DBS against tremor is a safe symptomatic treatment of non-PD non-dystonic tremor conditions. The adverse effects are generally well tolerated, and the patients report high long-term satisfaction with the treatment, with a continuing effect of VIM-DBS on tremor in both the ET responders and the symptomatic tremor responders. Our results do not reveal unacceptable adverse effects after bilateral stimulation, and bilateral treatment in patients with bilateral tremor thus appears to be safe.
REFERENCES