PROTOCOL for the RESEARCHER PROJECT:

Long-term outcome in cervical dystonia patients treated with chronic pallidal deep brain stimulation compared to repeated botulinum toxin injections – a cross-sectional observational study

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1. BACKGROUND AND STATUS OF KNOWLEDGE.

Cervical dystonia (CD) is the most common isolated dystonia in adults, with a prevalence of 9-13/100000. CD has a mean age at onset of 40 years, and is almost twice as common in women than in men. Cervical dystonia symptoms can in most patients be managed well by botulinum toxin (BTX) injections, and supporting treatment measures. However, one-fifth to one-third of patients do not obtain sufficient relief from long-term BTX therapy, resulting in reduced quality of life (1, 2, 3).

Deep brain stimulation in the postero-ventral part of the internal globus pallidus (GPi-DBS) has been established as an effective treatment of primary generalized dystonia, through the pioneer open study (4), the first single-blinded study (5), and the randomized sham-stimulation controlled study, in which our center participated (6). The latter study also included 24 segmental dystonia patients who all had a cervical component. Both in those and the generalized dystonia patients it was noted that the cervical component responded particularly well to GPi-DBS.

The first case series indicated that focal or segmental CD could be a good indication for GPi-DBS (7,8). A multi-centre, randomized sham-stimulation study of GPi-DBS in CD performed in Germany, Austria and Norway showed a 26% improvement in the Severity score of the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) after 3 months in the stimulated group versus a 6 % improvement in the sham-stimulated group (p=0,0024). After another 3 months active stimulation in both group the improvements were 29% and 26%, respectively (9). Up to 5 years outcome data of this study has been collected, but has not yet been published.

Long-term outcome of pallidal DBS in cervical dystonia has only been published in some smaller series. The first study with blinded, long-term outcome (1 year, n=10) (ref.10), showed an average improvement of 43 % in the Severity score of the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS). In our own prospective, single-center study of eight CD patients with blinded outcome assessments, we found an average improvement of 70% in the Severity score of the TWSTRS (11), and 91% and 92% improvement, respectively, in the Disability and Pain scores, at median 30 months follow-up. The two largest unblinded series showed average improvements of 55 % and 58 %, at mean follow-up 32 months (n=10), and 2 years (n=6), respectively (12,13).

Although the above studies are promising, there is a lack of documentation of outcome of GPi-DBS in CD beyond 3 years of treatment and in larger patient materials. We will therefore perform a long-term follow-up study of patients who were operated at Oslo University Hospital with a DBS-device targeting the GPi bilaterally, and who have been treated with chronic GPi-DBS for a minimum of 3 years. The patients will be investigated with the TWSTRS score at the time of long-term follow-up which will be compared to the TWSTRS score obtained prior preoperatively as part of the routine work-up. In addition, cross-sectional evaluations will be performed of disease-specific quality of life, using the Cervical Dystonia Impact Profile-58 (CDIP-58), Visual Analog Scale of Global Burden of Disease, and Hospital Anxiety and Depression scale, to evaluate frequency of associated symptoms of anxiety and/or depression.

We will compare this DBS-treated cohort with an age- and gender matched group of CD patients who are receiving treatment with botulinum neurotoxin (BoNT) injections and have been treated for at least 3 years as well. We hypothesize that the DBS-treated group will have a significantly lower mean TWSTRS total score at long-term follow-up than the BoNT treated group.

2. HYPOTHESES, STUDY OVERVIEW AND METHODS

The group treated with long-term GPi-DBS have all been implanted with a Medtronic DBS-device, between June 2004 and December 2017, thus with a follow-up period of 3-13 years at the time of evaluation (2020), and include around 30 patients. Our main objective is to assess remaining CD severity and CD-related Quality of Life (QoL) in the DBS-treated group and compare this with an age- and gender matched group of CD-patients treated with BoNT-injections for a minimum of 3 years (BoNT-group), using the TWSTRS Total score as the primary outcome variable/endpoint. The BoNT-group will be assessed both before and 4-6 weeks after the last injection, but the score 4-6 weeks after injection will be used for comparison with the DBS-group. Secondary outcomes are TWSTRS Severity, Disability and Pain score, and CDIP-58 Total scores. Exploratory variables are the eight Symptom/Domain scores of the CDIP-58 and Visual Analog Scale for Global Burden of Disease (VAS-GBD). Other outcome variables are complications and severe adverse events of the two treatment types, and the Anxiety and Depression scores of the Hospital Anxiety and Depression Scale (HADS).

I. Study overview.

- Study design: Single- center, cross-sectional observational study, comparing two groups.
- Number of patients to be included: 50 patients, 25 in each group.
- Inclusion criteria: DBS-group: Patients with isolated cervical dystonia (focal or part of segmental dystonia) who have been operated at Oslo University between June 2004 and June 2017 and treated with bilateral GPi-DBS for a minimum of 3 years, and who give their informed consent to participate in this follow-up study. BoNT-group: Patients who are receiving regular BoNT-injections at Oslo University Hospital for isolated cervical dystonia (focal or part of segmental dystonia), who are gender-and age-matched to the operated patients, and who give their informed consent to participate in this follow-up study.
- Exclusion criteria: Dementia/inability to respond to the CDIP-58.
- Primary endpoint: Difference of TWSTRS Total score at long-term evaluation between the DBS-group and BoNT-group.

- Secondary endpoints: Difference of TWSTRS Severity, Disability and Pain-scores, CDIP-58 Total scores.
- Exploratory endpoints: Differences in CDIP-58 Domain scores and VAS-GBD at long-term evaluation between the DBS-group and BoNT-group. In the DBS-group: Difference of TWSTRS Total, Severity, Disability and Pain from preoperative to time of long-term evaluation of GPi-DBS.
- Other outcomes: Treatment complications and serious adverse events for the two treatment groups. HAD scores for Depression and Anxiety. Neck Disability Index (NDI) and EuroQoL-5D (only as part of validation study of the Norwegian translation of the CDIP-58).

II. Methods.

i) Epidemiological and clinical characteristics of the study population

Epidemiological: Gender, age, education, civil status, work status, smoking, alcohol consumption.

Clinical: Age at onset of CD symptoms (;involuntary head movements), age at diagnosis, age at onset of BoNT-treatment, duration of treatment(s) at evaluation. Neurological and other comorbidities. Medication use, current (and previous since onset of CD) (type, dose).

ii) Clinical evaluations and scoring.

- Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS). This scale consists of three subscales: Severity, Disability and Pain. The Severity subscale is scored by a physician or physiotherapist and assesses objectively maximum head deviation in three planes, presence of lateral or sagittal shift, duration of symptoms, response to sensory tricks, presence of shoulder elevation, range of head movements, and time with head in midline. It does not contain a score for head tremor. Both the Disability and Pain subscales are scored by the examiner, based on interview with the patient. The Disability subscale assesses the limitations due to cervical dystonia that is experienced by the patient in activities such as work/housework, activities of daily living, driving, reading, watching television, and activities

outside home such as shopping, hiking/sports, attending performances, etc. High scores indicate more symptoms/disability/pain. It is the most used scale in research papers on cervical dystonia for the last 20 years.

- Fahn Tolosa Marin tremor rating scale. This scale is a validated and much used scale for quantification of tremor, and will be used to score head tremor (at rest and in posture), and if present tremor in other locations. Higher scores indicate more symptoms.

- Unified Parkinson´s Disease Rating Scale (UPDRS) motor score (part III). This scale is a validated and well-established scale for the quantification of parkinsonian symptoms such as bradykinesia, rigidity, tremor, dysarthria, hypomimia, and alterations of gait, balance and posture. Higher scores indicate more symptoms. It will be used to investigate eventual parkinsonian side effects of GPi-DBS.

- Standard neurological examination.

iii) Patient rated outcomes:

Cervical Dystonia Impact Profile-58. The Cervical Dystonia Impact Scale (CDIP-58) is a disease-specific patient-rated questionnaire that assess quality of life in patients with cervical dystonia. It includes 58 items grouped into eight dimensions: head and neck symptoms, pain and discomfort in neck and shoulders, sleep disturbance, upper limb activities and walking, and psychosocial features (annoyance, mood, psychosocial functioning). Eight summary scale scores are generated by summing items and are then transformed to a 0 to100 scale. High scores indicate worse health (14,15).

CDIP-58 has been translated into Norwegian following international guidelines for translation and cross-cultural adaption of patient-reported outcome measures (16).

Hospital Anxiety and Depression Scale. Hospital Anxiety and Depression Scale is a validated and much used self-rated questionnaire, developed especially for persons with somatic disease, and contains seven items for symptoms of anxiety and seven items for symptoms of depression, each scored 0-4 Higher scores indicate more severe symptoms (17,18).

In addition to the patient-rated outcomes of the main study presented above, we want to test the psychometric properties of the Norwegian translation of the questionnaire The Cervical Dystonia Impact Scale (CDIP-58). This methodological study has already been approved by REK (2019/342) in an earlier application. For this purpose we will also include the following questionnaires:

EQ-5D. The EuroQol-5D (EQ-5D) is a brief self-reported generic measure of current health-related quality of life (HRQL). The EQ-5D-5L evaluates five dimensions: mobility, self-care, activities of daily life, pain and anxiety/depression, each with five levels of functioning (no problems, slight problems, moderate problems, severe problems, and unable to/extreme problems for all dimensions). The EQ-5D includes an EQ-VAS where own health ‘‘today’’ is rated on a scale from 0 (worst imaginable health) to 100 (best imaginable health) (19,20). The EQ-5D is translated into Norwegian.

Neck Disability Index (NDI). Neck Disability Index (NDI) is a strongly validated instrument for assessing self-rated disability in patients with neck pain, scoring items concerning pain intensity, reading, headache, concentration, work, driving, sleeping, and recreation. Each item is scored from 0 (no disability) to 5 (greatest disability) (ref.21). The questionnaire is translated into Norwegian.

Table 1. Overview of investigations and patient-rated outcomes:

Main study			
	DBS	BoNT	
		Before injection (Time 1)	4-6 weeks after inj. (Time 2)
TWSTRS	X	X	X

CDIP-58	X	X	X
FTMTRS (head tremor, tremor in other tremor localizations)	X	X	X
VAS Global burden of disase	X	X	X
UPDRS III	X	N.a.	N.a.
HAD	X	X	X
In addition: Only for the validation study of the Norwegian translation of CDIP-58			
CDIP-58	1 week after X	-	1 week after X
NDI	X	-	X
EQ-5D	X	-	X

iv) Treatment characteristics.

DBS-group: Deep Brain Stimulation of the Globus Pallidus internus bilaterally (GPi-DBS)

- details of operation procedure, duration of treatment, stimulation parameters at 3 years of treatment and at long-term evaluation, concomitant medication preoperatively and at long-term evaluation, such as anti-cholinergics, levodopa, benzodiazepines, analgesics, or supplementary BoNT-injections (if no medication, when stopped?). Early (first 6 months) or late surgical complications.

BoNT-group: Botulinum Toxin injections.

- duration of treatment, number of treatment sessions, mean total dose last year, total dose at last session, median number of muscles injected last year and number of muscles injected last session, whether EMG- or Ultrasound-guidance used.

v) Sample size and power calculation, and plan for statistical analyses.

The null hypothesis is no difference between the DBS-group and the BoNT-group in TWSTRS total scores at long-term evaluation. A sample size of 50 (25 in each group) would power the study at 80% with a 5% probability of type I error, and would allow for a detection

of a difference in mean TWSTRS total score of 8 points between the two treatment groups, assuming a mean of 25 points in the group with the highest score and a standard deviation of 10 points.

The null hypothesis will be tested using independent samples t-test, or Mann-Whitney U-test (if the distribution of the TWSTRS total score in one or both groups is highly skewed). Secondary endpoints will be tested used the same tests.

3. Project plan, project management, organization and collaboration.

The project is carried out at the Department of Neurology, Oslo University Hospital (OUH). The project leader is Inger Marie Skogseid, senior consultant neurologist and researcher, who has extensive experience in treatment studies of DBS in dystonia (and other movement disorders) and from a former long-term evaluation study in cervical dystonia treated with botulinum toxin treatment. She will be the daily scientific leader of the project and coordinate the activities of the other participants. She has seen the majority of the DBS-treated patients both at their preoperative evaluations and at longitudinal evaluation postoperatively, and has extensive experience in botulinum toxin treatment in cervical dystonia patients.

A Postdoctoral fellow, neurologist Iselin Marie Wedding, will perform the long-term follow-up evaluations of the DBS-treated patients at OUH, location Rikshospitalet.

An experienced neurological physiotherapist, Vibeke Siewers, will be the main collaborator to perform the evaluations of the botulinum toxin treated patient cohort, supported by Dr Wedding and Dr Skogseid. She has long-standing clinical experience with cervical dystonia patients, and in using TWSTRS and CDIP-58 in these patients. She has been a major contributor to the work done at OUH to translate and culturally adapt the CDIP-58 into Norwegian. Her main work location will be at OUH location Ullevål, but patients treated with BoNT may be recruited both from Rikshospitalet and Ullevål.

The project is financed through a private donation given to the Department of Neurology from a former patient´s testament, who wished to contribute to research on the impact of treatment of on quality of life in cervical dystonia patients. This donation provides a 40 %

salary to Inger Marie Skogseid, a 33% salary to Iselin Marie Wedding and a 20 % salary to Vibeke Siewers.

4. Relevance and benefit to society

Cervical dystonia affects adults in the middle of their working life, and the disease has a huge impact on quality of life and work ability if treatment is not successful. On the other hand, we and others have shown that it is possible to obtain good symptom relief and good quality of life both in the majority of botulinum toxin treated cases, leading to increased employment rate, and with DBS-treatment. The question is whether DBS should be offered to a larger number of patients instead of continued chronic BoNT-treatment, at least in patients with suboptimal relief from this treatment. The answer to this question is of major relevance to the patient group and to the society.

5. Environmental impact

To our knowledge there are no significant environmental impacts associated with the project.

6. Ethical perspectives

Adult patients (aged 18 years or older, of both genders) will be included only upon written informed consent, and after approval is obtained from the Regional Committee for Medical Research Ethics (RCMRE), and by the Privacy Ombudsman (Personvernombudet, PO) at OUH. Data will be stored in a secure research server at OUH.

Study participants are free to withdraw at any point. If patients do not wish to participate, this will not affect their treatment.

The study will be registrated in ClinicalTrials.gov before inclusion of patients is started.

7. Dissemination and communication of results

7.1. Dissemination plan

Publication of results in peer-reviewed medical journals. Media, popular science magazines.

7.2. Communication with users

The Project Leader has had close communication with one of the most relevant patient groups (Norwegian Dystonia Association) for many years, and has been a frequent speaker at their annual meetings. Popular lectures and scientific articles will be provided to this patient organizations and their magazine. Relevant clinicians (neurologists, neuroradiologists, neurosurgeons, as well as general practitioners) will be informed of project progress through presentations in specific clinical fora, and through the Oslo University Hospital website.

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