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Apraxia of Lid Opening in Subthalamic Nucleus Deep Brain Stimulation for Parkinson's Disease—Frequency, Risk Factors and Response to Treatment

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ABSTRACT: Background: New-onset apraxia of lid opening (ALO) is reported to occur in Parkinson's disease (PD) patients following Deep Brain Stimulation (DBS). There are only few systematic studies on this uncommon disorder of eyelid movements.

Objectives: We aimed to examine the frequency, temporal evolution, predisposing factors and response to treatment, of new-onset ALO in PD patients who underwent bilateral subthalamic nucleus (STN) DBS.

Methods: We retrospectively reviewed the data of patients who underwent STN DBS at our centre between 1999 and 2017, with a minimum of 2 years of follow up after surgery.

Results: New-onset ALO was seen in 17 (9.1%) of the 187 patients after an average of 16.9 months (Range - 6–36 months). Comparison of the groups with and without ALO revealed that ALO occurred more often in older patients, both at the onset of PD symptoms and at surgery and in those with non-tremor dominant subtypes of PD and freezing of gait at baseline. The extent of levodopa dose reduction after surgery and the pre-operative severity of motor symptoms were not risk factors. Response to adjustments of dopaminergic medications and stimulation parameters was ill-sustained or nil. Botulinum toxin therapy resulted in satisfactory improvement in the majority.

Conclusions: New-onset ALO is an uncommon phenomenon that manifests months after STN DBS. Development of ALO is likely to be due to the effects of chronic stimulation of basal ganglia-thalamo-cortical or brain stem circuits controlling lid movements in susceptible patients. Botulinum toxin therapy offers relatively better relief of symptoms than other strategies.

Deep Brain Stimulation (DBS) is an effective treatment option for Parkinson's disease (PD) patients with motor complications of treatment. Subthalamic nucleus (STN) is the preferred target for DBS in PD in most centers. STN DBS improves the cardinal motor signs and the motor complications of levodopa treatment and enables reduction in dopaminergic drug doses. DBS is not free of adverse effects which are related to the neurosurgical procedure or effects of electrical stimulation. The long-term effects of chronic stimulation are not well characterized. New-onset dyskinesia, gait disturbances and apraxia of lid opening (ALO) are known to occur following DBS in PD at variable intervals from surgery.[1] ALO is an intermittent, non-paralytic inability to open the eye lids or keep the lids elevated.[2–4] ALO has been reported as an adverse effect of STN stimulation[5–8] and can be a source of significant visual disability in some patients. As the literature on ALO following STN DBS is limited, we examined its frequency, temporal evolution, predisposing factors and outcome of treatment.

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Methods

We reviewed the medical records of all PD patients who underwent bilateral STN DBS at our center and had systematic follow-up of at least 2 years after surgery. Patients who had ALO at baseline (pre-operative) evaluation were excluded.

Patients were selected for surgery after a careful evaluation by movement disorder specialists to confirm the diagnosis of PD, objective assessment of levodopa response and motor complications by evaluation in OFF and ON states, psychiatry and neuropsychology evaluation and final discussion in a patient-management conference attended by the surgical team including movement disorder specialists, functional neurosurgeon, neuroradiologist and clinical psychologist. Bilateral stereotactic implantation of quadriploar DBS leads (Model 3387 in 9 cases and model 3389 in 178; Medtronic, MN, USA) was done in all patients. STN was located by MRI (1.5 T MR Scanner, Signa, GE Healthcare, MW, USA [for surgeries done from 1999–2006]; 1.5 T MR Scanner, Avanto, Siemens Healthineers, Germany [for surgeries done from 2007–2014] and 3 T MR Scanner, Discovery MR750w, GE Healthcare, MW, USA [for surgeries done after 2014]), 5-channel microelectrode recordings (Leadpoint 4 / Leadpoint 5, Medtronic, MN, USA) with Bengun / Star Drive microelectrode array and macro stimulation in selected tracks. The programmable pulse generator (Kinetra [Surgeries done till 2012]; Activa-PC or Activa-RC [surgeries done after 2012]; Medtronic, MN, USA) was implanted in the left sub-clavicular area and connected to the leads using extension wires (Model 3708660, Medtronic, MN, USA). Electrical parameters (voltage, pulse width, and frequency) were programmed using the physician programmer (N'vision, Medtronic, MN, USA) Post-operative imaging was done to look for surgical complications and to rule out lead malposition. Re-positioning of leads was done (was needed in five cases) when lead malposition was detected.

The motor and cognitive outcomes of our cohort had been reported in our earlier publications.[9–11] All assessments were done in all visits by movement disorder specialists and new onset symptoms and side effects of stimulation were recorded in each visit. The diagnosis of new onset ALO was made from history and clinical examination.[2,3] Based on the severity and functional disability documented in case files, ALO was graded as mild (no significant functional disability and no treatment sought), moderate (some functional disability and interference with daily activities) or severe (marked functional disability limiting daily activities) (Video 1). The interval between surgery and onset of symptoms of ALO, its temporal evolution and the response to treatment were collected. The baseline (pre-operative) demographic data, clinical details including UPDRS part III scores in drug OFF and ON states, treatment details, response of motor symptoms to optimal stimulation and the extent of reduction of dopaminergic drugs following surgery at the time of 1-year follow-up were noted. PD was subtyped as tremor dominant or non-tremor dominant (including both akinetic-rigid and mixed phenotypes) using Unified Parkinson's Disease Rating Scale (UPDRS) sub-scores in baseline OFF.[12] The study protocol was reviewed and approved by the Institutional Ethics Committee (IEC). The requirement for informed consent from study participants was waived off by the IEC as the study was retrospective in nature, data for study was extracted from case files and identity of all participating subjects was masked.

Two sample t test and Fisher's exact test were used for statistical analysis of continuous and categorical variables respectively. The statistical analysis was performed using IBM SPSS Statistics 21 (IBM Corp., Armonk, NY, USA). P value of <0.05 was considered statistically significant.

Results

187 patients with PD (including 64 women) who underwent STN DBS at our centre from 1999 to 2017 were found eligible

Video 1. Video showing development of ALO in two patients who underwent bilateral STN DBS for PD. The pre-operative video segments show no features of ALO in both patients. The first patient who developed severe ALO is a gentleman with akinetic-rigid form of PD who underwent DBS at the age of 62 years, 12 years after the onset of motor symptoms. The first video segment of this patient shows the OFF state with severe freezing of gait pre-operatively and the second segment, ON state with excellent L Dopa response and peak-dose dyskinesia. The third (one-year follow up, in OFF state) segment shows the improvement of motor signs which he had, with DBS. The patient developed ALO 3 years after DBS and the last video segment of this patient was taken during his 5-year follow up visit. The segment shows severe inability to open the eyes once they are closed. The second patient is a gentleman with young onset PD of a mixed phenotype, who underwent bilateral STN DBS at the age of 48, when the disease duration was around 13 years. He also had prominent akinesia and freezing of gait, along with modest degree of rest tremor (First video segment of patient 2, showing pre-operative drug-OFF state), which were levodopa responsive (Second video segment of patient- 2). His third segment shows drug-OFF state, one-year after DBS, with improved freezing of gait. He developed ALO one more year later, which was moderately severe. His last video segment showing ALO was taken during 4-year follow up visit after DBS. In both patients, the ALO did not improve with DBS programming or brief periods of switching off of DBS during programming sessions. Both the patients are getting modest improvement with periodical Botulinum Toxin Injections.

TABLE 1 *Demographic and clinical features at baseline (pre-DBS) assessment*

Characteristic	Patients who did not develop ALO (N = 170)	Patients who developed ALO (N = 17)	*P* value
Age at onset of PD (years)	45.2 (±9.7)	49.8 (±6.6)	0.02
Age at surgery (years)	56.0 (±9.9)	61.1 (±5.7)	0.003
Duration of PD at the time of surgery (years)	11.0 (±4.3)	11.2 (±3.0)	0.79
LEDD (milligrams)	792.0 (±225.1)	802.4 (±170.4)	0.85
UPDRS III (OFF)	47.4 (±12.1)	48.8 (±12.8)	0.64
UPDRS III (ON)	14.9 (± 7.3)	16.7 (± 6.2)	0.32
Levodopa response in UPDRS III (%)	68.4 (±13.5)	63.5 (±17.3)	0.17
MMSE	28.2 (±1.4)	28.7 (±1.1)	0.13
ACE	84.0 (±6.7)	85.1 (±4.6)	0.50

Abbreviations: ACE, Addenbrooke's cognitive examination; ALO, Apraxia of lid opening; LEDD, Levodopa equivalent daily dosage; Levodopa response – (UPDRS III OFF –UPDRS ON)/UPDRS III OFF × 100; MMSE, mini mental status examination; PD, Parkinson's disease; UPDRS, unified Parkinson's disease rating scale.

and were included in the analysis. A single patient had mild ALO at baseline assessment which worsened 6 months after surgery and had been excluded. The mean duration of follow-up was 5.6 (±3.3) years (Range- 2- 16 years). Seventeen (9.1%) patients developed new-onset ALO during the follow-up period. The average interval between DBS surgery and the development of ALO was 16.9 (± 9.8) months [Range: 6–36 months]. The maximum severity of ALO documented during the follow-up period was "mild" in two patients, "moderate" in 11 and "severe" in four. None of the patients achieved complete and persisting remission of ALO.

Table 1 shows the baseline demographic and clinical features of patients who developed ALO ("the ALO group") compared to those who did not ("non-ALO group"). At baseline, the duration and severity of motor symptoms in OFF, drug dosages, percentage of levodopa responsiveness in UPDRS III scores and cognitive scores were similar between the two groups. The ALO group were older, both at symptom onset and at surgery. At baseline, ALO group had a higher frequency of freezing of gait in OFF but not OFF-dystonia. ALO occurred more frequently in the non- tremor dominant subtype of PD (Table 2). At 1-year follow up after DBS and following optimal programming (Table 3), the ALO group had higher UPDRS III scores in Stimulation ON- Drug -OFF and lesser improvement in UPDRS III score from base line. There was no significant difference either in the Levodopa Equivalent Daily Dosage (LEDD) or the percentage reduction in LEDD following DBS, though the ALO group tended to be on a higher LEDD, with lower percentage reductions.

TABLE 2 *Relationship of ALO with freezing of gait, off dystonia and type of PD at baseline assessment*

	Patients who did not develop ALO (N = 170)	Patients who developed ALO (N = 17)	*P* value*
Freezing of gait	99 (58.2%)	16 (94.1%)	0.003
Off dystonia	77 (45.2%)	12 (70.6%)	0.07
Non-tremor dominant PD subtype	123 (72.4%)	17 (100%)	0.008

Abbreviations: ALO, Apraxia of lid opening; DBS, deep brain stimulation.
*Fisher's exact test.

Six patients reported worsening of ALO during historical wearing off of medication effects (four with moderate and two with severe ALO). However, trial of increasing levodopa dose did not yield sustained benefit in any of them. Similarly, three patients reported worsening of ALO in ON but these patients did not show any persistent improvement with reduction in levodopa dose tried. The remaining patients did not notice any relation of symptoms with levodopa and did not respond to changes in doses.

DBS programming was attempted with an intention to relieve ALO in all patients with moderate or severe symptoms. Switching OFF of the stimulator for short periods (a few minutes) during programming sessions was not found to relieve ALO in any; more prolonged withdrawal of DBS was not attempted. Changes in the active contact and amplitude and frequency of stimulation were tried. Contact change (moving to a more dorsal contact on one or both sides – in three), increase in the stimulation amplitude (in four), reduction in stimulation amplitude (in two) or frequency (in two) led to only short-term improvement lasting hours to a few days and not sustained benefits.

Botulinum toxin treatment was tried in all patients with moderate or severe symptoms who agreed for the treatment. Orbicularis oculi and its pre-tarsal portion were injected bilaterally. Eight (three severe and five moderate) among the 14 patients who were injected reported satisfactory improvement and continued treatment while the remaining six discontinued treatment after one or two sessions because of lack of benefit.

TABLE 3 *Improvement with STN DBS at 1-year follow up, and DBS settings*

	Patients who did not develop ALO (N = 170)	Patients who developed ALO (N = 17)	*P* value
UPDRS 3 (OFF)	18.1 (± 5.3)	21.2 (3.9)	0.02
Percentage improvement in UPDRS III (OFF) with DBS	61.5 (±8.1)	55.7 (±7.1)	0.004
LEDD (mg)	435.0 (±133.0)	494.1 (±129.8)	0.08
LEDD reduction (%)	44.1 (±12.2)	38.4 (±11.3)	0.07
DBS settings:			
Amplitude (Right STN)	3.0 (±0.3)	3.1(±0.3)	
Amplitude (Left STN)	3.0 (±0.4)	3.1 (±0.3)	
Pulse width (Right STN)	63.2 (±9.3)	63.5 (±10.0)	
Pulse width (Left STN)	62.1 (±7.7)	61.8 (±7.3)	
Frequency	131.7 (±21.9)	130.9 (±28.1)	

Abbreviations: ALO, Apraxia of lid opening; LEDD, Levodopa equivalent daily dosage; STN, subthalamic nucleus; UPDRS, unified Parkinson's disease rating scale.

Discussion

In this retrospective study of 187 PD patients who underwent bilateral STN DBS, 17 (9.1%) developed new-onset ALO after an average interval of around 17 months; a similar (around 6%) frequency of ALO has been reported by Umemura et al.[6] while higher frequencies (19–30%) have been reported by others.[7,8] These estimates are much higher than the frequency of ALO reported in medically treated PD patients (less than 1%),[4,13] suggesting that STN stimulation can by itself cause ALO or unravel a risk to develop ALO in PD. The predisposing factors were older age both at disease-onset and at surgery, freezing of gait in OFF state before surgery and the non-tremor dominant subtypes of PD. Though there was only a trend towards statistical significance, OFF dystonia at baseline evaluation was seen more in the ALO group. The overall improvement of UPDRS III scores achieved with surgery was lesser in the ALO group. Though the differences did not reach statistical significance, the ALO group tended to be on higher dose of dopaminergic medications and achieved lesser reduction in medication doses following programming.

The pathophysiology of ALO is largely unclear.[14] It is generally agreed that the term "apraxia" in ALO is a misnomer as it does not result from a disturbance of praxis mechanisms.[15] Its consistent association with blepharospasm has led to the suggestion that it may be a dystonia-related phenomenon.[13–15] Involuntary spasms of the pretarsal orbicularis oculi hindering lid elevation has been implicated; demonstration of abnormal persistence of electromyographic activity in the orbicularis oculi muscle during attempted lid elevation and the response to botulinum toxin injections in some of the patients support this theory.[15–17] Thus, ALO may share the pathophysiology of blepharospasm in which blink reflex abnormalities including decreased inhibition of the R2 response by electrical stimulation of supra-orbital nerve, and abnormal plasticity of the blink reflex circuit have been shown.[18–21] Inhibition of the levator palpebrae superioris (LPS) may be the mechanism in some cases of ALO.[22] Such cases may not show the abnormality in R2 recovery index, demonstrable in those with blepharospasm.[23] A pathophysiological relation with freezing or 'motor blocks' has also been proposed.[3,22] Similar to freezing of gait, ALO occurs more frequently in patients with atypical parkinsonism than PD.[4,13,22] It is likely that ALO has a heterogenous pathophysiological basis.[23,24]

It was previously reported that levodopa dose reduction after STN DBS could cause ALO.[25] Though levodopa dose reduction was invariable in all our patients following surgery to alleviate dyskinesias, ALO did not occur in the majority of them. STN DBS allows early levodopa dose reduction within days to few weeks but in this study ALO occurred after an average interval of 17 months from surgery. Besides, the ALO group showed a trend to have only lesser reduction of levodopa after optimal DBS programming, than the non ALO group. Though some of the patients reported worsening of ALO during their wearing off state, there was no persisting improvement in ALO when levodopa dosages were increased in them. It is therefore more likely that ALO is a complication of chronic neurostimulation and occurs in patients who are more vulnerable on account of factors such as age, disease phenotype or the location of the electrode within the target nucleus. Marked worsening of blepharospasm and new-onset ALO following DBS of the Globus Pallidus interna (GPi) has been reported in cranio-cervical dystonia and related to stimulation intensity, suggesting the potential for neurostimulation of the nodes in the basal ganglia circuits to precipitate ALO.[26]

Blinking occurs voluntarily or as a reflex phenomenon and results from an abrupt cessation of activity of the LPS muscle followed by active contractions of the orbital part of orbicularis oculi. Once eye lids close, the activity in the orbicularis oculi ceases and resumes in the LPS, resulting in eye lid opening.[27] The superior colliculus plays a central coordinating role in

blinking. It receives afferent inputs from the dorsal midbrain and trigeminal sensory nucleus and sends efferents to the facial motor and oculomotor nuclei.[28,29] The influence of central dopaminergic activity on blinking is clinically evident from the occurrence of increased blinking in hyper-dopaminergic conditions and vice versa.[30] The dopaminergic influence on blinking is thought to be mediated through two pathways- the direct nigro-collicular inputs and the descending cortical control which is modulated by the cortico-basal ganglio-cortical circuits.[29,31,32] The latter is supported by the occurrence of ALO in focal lesions of the basal ganglia.[33]

Neurostimulation of STN could cause ALO through different mechanisms. Sub-optimal placement of electrodes within the STN can lead to undesirable current spread. The dorsal trigemino-thalamic tract passes caudal and medial to the STN border. A non-physiological stimulation of the afferent inputs conveyed by the tract to the centers controlling lid movements may then lead to ALO. Previous reports of improvement of ALO by more proximal re-positioning of leads support the genesis of ALO by such current spread.[34] We also observed improvement of ALO with stimulation of more proximal lead contacts in a few patients, though it was short-lived in all. Current spread to corticobulbar tracts has also been implicated in the genesis of ALO after DBS.[5] We did not have quantitatively estimated data on the deviation of final electrode position from the planned target, for most patients in our retrospective study and hence we could not examine whether development of ALO has a relation to DBS lead malposition. STN stimulation itself could also potentially change the excitability of brainstem centers controlling blink through its influence on the descending pathways from the cortical motor areas.[35] Voluntary blinking is mediated by descending projections from the motor and supplementary motor areas,[31,32] whose activity can be modulated by DBS through changes in pallidal firing patterns.[36,37] Bologna et al have demonstrated prolongation of the inter-phase (closing-opening) pause duration of blink in STN-stimulated PD patients. This could be the potential mechanism of ALO, mediated by STN DBS through its influence on descending pathways controlling voluntary blinking.[35] The heterogeneity of pathophysiological mechanisms underlying ALO[23,24] explains its improvement in some patients undergoing STN and GPi DBS and the improvement of ALO from increasing the frequency of stimulation in others, reported with STN DBS.[5,38–40]

The association with factors like older age, freezing of gait and non-tremor dominant PD subtypes indicates that ALO is unlikely to be solely related to current spread outside STN and disease-related factors operate. A relation between ALO and freezing of gait has been proposed earlier[22]; ALO is seen frequently in atypical parkinsonian disorders like progressive supranuclear palsy in which freezing of gait is more common.[4,13] Our patients had mean disease duration of around 11 years at the time of surgery, diagnosis of PD confirmed by experienced movement disorder specialists, objectively documented good levodopa response and good response to STN DBS, ruling out the possibility of any atypical parkinsonian disorder. Non-tremor dominant subtypes of PD have been shown to have more extensive neuropathology compared to the tremor-dominant subtype.[41] It could be hypothesized that more extensive neuropathology as seen in older patients and those with non-tremulous forms of PD result in dysfunction of the brainstem and descending cortical-basal ganglionic mechanisms controlling eye lid movements and predispose to ALO. Neurostimulation in some of these patients precipitate ALO either by the deleterious effects of STN stimulation on blinking[35] or through current spread to near-by white matter tracts involved in the control of blinking.

The improvement of motor signs with DBS (UPDRS part III in drug OFF state after optimal programming of DBS) in the ALO group was slightly lower compared to the non-ALO group. This could be explained by the difference in PD subtypes. Nearly one-third of the non-ALO group had tremor-dominant PD, while all the patients who developed ALO had akinetic-rigid or mixed subtypes. Tremor is known to have a better response to STN DBS than other cardinal motor manifestations.[9] The ALO group tended to be on higher LEDD after surgery though the difference did not reach statistical significance; this is naturally expected with the lower motor improvement with DBS in these patients. An alternative explanation for these observations would be lesser-than-optimal placement of DBS leads in the ALO group leading to both lesser motor improvement and spread of stimulation outside STN resulting in ALO. Though slightly lower than the non-ALO group, our ALO group also had more than 55% improvement of UPDRS part III scores in drug-OFF state following DBS indicating that lead malposition was unlikely. Post-operative imaging studies were done in our patients to assess surgical complications including lead malposition; however, the images underwent only visual inspection. Merging of post-operative images with pre-operative planning images to quantitatively assess deviation of final lead position from the planned surgical target, was not routinely performed. Our study, therefore could not address the question whether lead malposition has a role in the pathogenesis of ALO; this is a limitation.

The improvement in ALO achieved with levodopa dose adjustments or changes in neurostimulation parameters was short-lived in all patients. Previous reports also showed that ALO after STN DBS is persistent and generally does not respond to neurostimulation adjustments.[6–8] Switching off of DBS for short periods (a few minutes) during programming sessions was not found to have any effects on ALO; however, it is known that such brief withdrawals are insufficient to washout DBS effects.[42] Whether ALO would be relieved by prolonged cessation of stimulation is unclear. We did not try it to establish causal relationship in our patients during their clinic visits as it is not tolerated by most, and no patient chose to withdraw DBS for relieving ALO, depriving themselves of the motor improvements.

Successful treatment of ALO with botulinum toxin injections has been reported.[16,43] We tried it in 14 patients who were willing and eight reported satisfactory improvement and presented for re-injections. We injected the orbicularis oculi, with pretarsal injections for all the patients.[16,44] The differential response to botulinum toxin injections could be explained by differences in the pathophysiological mechanisms; those with tonic

overactivity of orbicularis oculi are expected to improve.[24] However, data from electromyographic studies of orbicularis oculi were not available in our retrospective study to substantiate this theory and this is another limitation.

In conclusion, new-onset ALO following STN DBS in PD is more common than reported in medically treated PD and occur more often in those who are older and having non-tremor-dominant subtypes of PD. It is more likely to be a side effect of chronic stimulation than levodopa dose reduction. Changes induced by STN stimulation in the supranuclear mechanisms controlling lid movements, is the possible mechanism that leads to ALO in patients who are predisposed to this condition by disease-related factors; undesired stimulation of white matter tracts in STN's proximity could be another. In the small group of patients with ALO in this study, botulinum toxin therapy was found to be more useful than adjustments in levodopa dose or stimulation parameters.

Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the first draft, B. Review and Critique.

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Disclosures

Ethical Compliance Statement: We, the authors, confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines. The study protocol was reviewed and approved by the Institutional Ethics Committee (IEC) of Sree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvananthapuram, India. The requirement for informed consent from study participants was waived off by the IEC as the study was retrospective in nature, data for study was extracted from case files and identity of all participating subjects was masked. Informed, written consent was taken by the corresponding author from both the patients appearing in the video, for publication of the video along with the article.

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