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Mapping stimulation-induced beneficial and adverse effects in the subthalamic area of essential tremor patients

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ABSTRACT

Background: Stimulation of the subthalamic area (STA) is an effective treatment in essential tremor patients, but limited by stimulation induced adverse effects. The aim of this study was to determine the spatial distribution of stimulus related tremor suppression, ataxia induction and paresthesia of the upper limb in the subthalamic area (STA) of essential tremor patients.

Methods: We recruited eight patients with essential tremor in a stable postoperative condition (> 3 months after surgery). Stimulation-induced effects were assessed with suprathreshold stimulation. Tremor severity was assessed with the Fahn-Tolosa-Marin tremor rating scale (TRS) and cerebellar impairment was evaluated using the international cooperative ataxia rating scale (ICARS). Patients rated paresthesia intensity with a visual analog scale. Linear regression analysis was performed to associate stereotactic coordinates with tremor, ataxia and paresthesia.

Results: Suprathreshold stimulation significantly decreased tremor and elicited ataxia and paresthesia in all patients ($P < 0.001$). Tremor rating scale (TRS) total score was positively correlated with y-coordinates ($r = 0.44$, $P < 0.05$), i.e. anterior stimulation sites were more effective to suppress tremor. Concerning adverse effects, ataxia induction was positively correlated with z-coordinates almost reaching statistical significance ($r = 0.50$, $P = 0.07$), i.e. inferior stimulation sites elicit stronger ataxia. Furthermore, paresthesia was positively correlated with y-coordinates ($r = 0.66$; $P < 0.01$) and to a lesser degree with x-coordinates ($r = 0.32$; $P = 0.08$), i.e. posterior and lateral stimulation sites within the STA caused more paresthesia.

Conclusion: Antero-dorso-medial stimulation site in the STA were associated with less tremor and adverse effects in our small single-center cohort of ET patients with thalamic DBS.

1. Introduction

Essential tremor is one of the most common movement disorders. Deep brain stimulation (DBS) in the ventral intermediate thalamic nucleus (VIM) and subthalamic area (STA) can improve tremor symptoms and quality of life in cases of insufficient medical treatment [1,2]. Precise localization of DBS electrodes lays the ground to accurately target nuclei and fibers. However, the optimal implantation site to maximize tremor suppression and minimize adverse effects is still a matter of debate [3]. Stimulation-induced tremor improvement suggested a clustering of the most effective contacts within the STA [3,4]. Retrospective and a recent well-designed prospective trial also revealed that STA-DBS is at least equally effective and probably more efficient to reduce tremor than VIM-DBS [5]. In view of these studies, stimulation in the STA might be favored over stimulation in the VIM. Although DBS treatment is very effective, the therapeutic window is often limited by adverse effects comprising ataxia, paresthesia and dysarthria [1,6,7]. Previous studies were unable to attribute stimulation-induced effects and side effects to certain anatomical areas in the subthalamic area [8]. Therefore, it remains unclear if there is a potential optimal subtarget within the STA.

In this study, we aimed to evaluate the contribution and effect of stereotactic contact localizations according to tremor suppression, ataxia induction and paresthesia. Given that the STA is an effective and efficient implantation site, the spatial distribution of beneficial and adverse effects within the STA was the focus of this study. For this

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Abbreviations

DBS	deep brain stimulation
ICARS	International Cooperative Ataxia Rating Scale
ICL	intercommissural line
MCP	mid-commissural point
STA	subthalamic area
TRS	Fahn-Tolosa-Marin Tremor Rating Scale
VIM	ventral intermediate thalamic nucleus

reason, eight patients with essential tremor were recruited who were implanted in the STA with a second-generation DBS system. In a systematic double-blind single center exploratory study, we assessed the extent of upper limb tremor, ataxia and paresthesia according with stereotactic coordinates of the two lowest contacts.

2. Methods

2.1. Ethical approval and informed consent

The study protocol was approved by the Ethics Committee of the Hamburg Board of Physicians (PV5281). The investigation was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

2.2. Study design

From January 2017 to October 2017, eight patients with essential tremor were recruited in the Clinic of Neurology at the University Medical Center Hamburg-Eppendorf. The baseline characteristics were described previously [9]. Data analysis was performed in April and May 2018. The inclusion criteria were as follows: age > 18 years, diagnosis of essential tremor, implantation with the Infinity DBS system (St. Jude Medical Neuromodulation Division, Plano, TX, USA) in the VIM/STA and > 12 weeks after DBS implantation. Eight patients (one female) were included in this study. Tremor medication was discontinued at least 6 weeks before the study except of one patient who was under a stable dosage of primidone since DBS implantation.Written informed consent was obtained from all participants.

2.3. Surgical procedure

All patients were implanted with the Infinity DBS system (St. Jude Medical Neuromodulation Division, Plano, TX, USA) according to standard surgical procedures at our center as previously described in detail [10,11]. Briefly, surgery involved microelectrode recordings from two trajectories as well as test stimulation to determine thresholds for tremor suppression and typical adverse effects, such as tingling or tetanic muscle contractions. In order to cover the subthalamic area we attempted to position the spacing between the two middle contacts of a quadrupolar electrode at the intercommissural level, which was distant less than 1 mm from the electrophysiologically mapped floor of the thalamus. Contacts located below the intercommissural plance were supposed to cover the subthalamic area. The localization of the implanted electrode contacts was determined by co-registration of the preoperative T1-MRI-scans and post-operative CT-scans using commercially available software (iPlan stereotaxy; Brainlab, Feldkirchen, Germany). Mean coordinates of the distal contact (1 and 9) of the DBS electrode (n = 16) were x: 10.7 ± 1.3 mm lateral to midline, y: 8.5 ± 1.6 mm posterior to mid-commissural point (MCP), z: 4.1 ± 1.3 mm below the plane between anterior and posterior commissure, whereas the mean coordinates of the second distal contact (2ABC and 10ABC) of the DBS electrode (n = 16) were x: 11.7 ± 1.2 mm lateral to midline, y: 7.0 ± 1.6 mm posterior to mid-commissural point (MCP), z: 2.0 ± 1.3 mm below the plane between anterior and posterior commissure (Supplementary Table 1). Each lead consisted of four contact levels (interelectrode distance, 0.5 mm) with a conventional ring at the highest (most dorsal) and lowest (most ventral) position.

2.4. Clinical evaluation

Clinical evaluation of tremor, ataxia and paresthesia was performed as previously described [9]. Severity of limb tremor was evaluated using the Fahn-Tolosa-Marin Tremor Rating Scale (TRS) using items 5 or 6 (postural tremor of right or left upper extremity), 11 (drawing large Archimedes spiral), 12 (drawing small Archimedes spiral) and 13 (drawing straight lines). Resting tremor was observed only in 5/18 cases in the OFF state and was therefore omitted in further analysis. Afterwards a FTMTRS composite score was calculated by summing up items 5/6, 11, 12 and 13 (maximum score 16 with higher scores indicating more tremor) [7,12]. Severity of limb ataxia was evaluated using item 10 and 14 of the International Cooperative Ataxia Rating Scale (ICARS) [13]. An ICARS composite score was calculated by summing up items 10 and 14 (maximum score 10 with higher scores indicating more severe dysmetria and ataxia). Paresthesia was evaluated using a visual analog scale (0 – none, 10 – strongest imaginable).

2.5. Stimulation parameters

Patients were assessed on the lowest (i.e. contact 1 and 9) and second lowest contacts (i.e. contact 2ABC and 10ABC) in the following two stimulation conditions: (1) no stimulation (off stimulation) and (2) suprathreshold stimulation, i.e. clinical signs of dysmetria and ataxia. The required stimulation amplitude was determined by incremental amplitude increases of 0.5 mA until the onset of ataxia and subsequent reduction in 0.1 mA steps. Suprathreshold stimulation was defined as stimulation amplitude 0.5 mA above the threshold for inducing ataxia. To avoid any interhemispheric interference we deactivated stimulation contralateral to the active side. The stimulation device was controlled by an independent clinician. The patient and the examiner were both blinded to the stimulation condition and chosen contact.

2.6. Statistical analysis

A sample size calculation using α (p-value) of 0.05, β-coefficient of 0.2 and an expected correlation coefficient r of 0.5 rendered a number of 29 contacts. Relationships between stereotactic coordinates and clinical scores were assessed by Spearman correlation analyses (correlation coefficient ρ) or linear regression analyses (beta coefficient and 95% confidence interval, CI). Statistical analysis was performed with IBM SPSS Statistics (version 22, IBM Corp., Armonk, NY) and GraphPad Prism (version 5 for Windows, La Jolla, USA).

2.7. Data statement

Individual de-identified participant data, related documents such as study protocol and statistical analysis will be shared by request from any qualified investigator for 3 years after the date of publication.

3. Results

3.1. Patient characteristics and stimulation parameters

Eight ET patients (1 female) were included in this study. Mean age was 66 ± 3.5 years, disease duration was 33.4 ± 6.1 years and mean duration of DBS treatment was 21.8 ± 2.3 weeks (Supplementary Table 1). All patients were treated with bilateral DBS. Parameters for assessment of lowest contacts were 3.12 ± 0.21 mA, 60 ± 0 µs, 130 ± 0 Hz and of second lowest contacts were 3.44 ± 0.13 V,

60 ± 0 µs, 130 ± 0 Hz (Supplementary Table 2).

3.2. Tremor and electrode position

Tremor severity in the OFF state was 13.1 ± 2.4 using the TRS composite score with a maximum score of 16 (n = 32 contacts in 8 patients). Tremor with supramaximal stimulation was suppressed by 55 ± 21% (P < 0.001; Fig. 1A). To facilitate comparison of tremor suppression, TRS composite score with stimulation were normalized to the OFF state. Relative tremor suppression of the upper limb did not correlate with x- and z-coordinates (Fig. 1B and D). But we observed a strong and significant correlation of relative tremor suppression with y-coordinates in the range of 5.2–11.8 mm posterior to MCP (r = 0.44, P < 0.05) (Fig. 1C). Therefore, anterior stimulation sites elicited better tremor suppression than posterior stimulation sites in our single center cohort.

3.3. Ataxia and electrode position

In the OFF state only slight ataxia (i.e. ICARS score: 1 point) was present in one patient. Therefore, we used absolute ICARS score without normalization to OFF state. Supramaximal stimulation induced ataxia in almost all patients (P < 0.001; Fig. 2A). Ataxia induction did not correlate with x-, y- and z-coordinates (Fig. 2B and C). Using second lowest contacts only, which were in the range of −0.2–3.7 mm below the plane between anterior and posterior commissure, we observed a positive correlation between ICARS score with z-coordinates, which almost reached statistical significance (r = 0.50, P = 0.07) (Fig. 2D). But ICARS score did not correlate with z-coordinates of the lowest contacts, which were localized in the range between 1.5 and 6.1 mm below MCP.

3.4. Paresthesia and electrode position

No paresthesia was present in the OFF state. Therefore, absolute values without normalization were used. Supramaximal stimulation strongly and significantly induced paresthesia in almost all patients (P < 0.001; Fig. 3A). For the second lowest and lowest contacts, a positive correlation was observed between paresthesia intensity and x-coordinates, which nearly reached statistical significance (r = 0.31, P = 0.08) (Fig. 3B). A strong and positive correlation between paresthesia and y-coordinates was observed for the lowest and second lowest contacts (r = 0.57, P = 0.001) (Fig. 3C). We did not observe any correlation of paresthesia with z-coordinates for the lowest and second lowest contacts (Fig. 3D).

4. Discussion

The optimal target for tremor suppression in essential tremor patients is still a matter of debate. VIM is a well-established target for DBS in ET patients [14,15]. But small prospective studies, a large retrospective analysis and a well-designed prospective randomized double-blind crossover trial suggest that STA is at least equally effective and probably more efficient than traditional VIM-DBS [5,16–18]. Although these studies favor the STA as optimal target, the most favorable subtarget within the STA remains unclear [5]. The STA is bordered superiorly by the ventrolateral thalamus, inferiorly by the substantia nigra, medially by the red nucleus, laterally by the internal capsule, posteriorly by the medial lemniscus and anteriorly by the STN and fields of Forel (thalamic and lenticular fascicles). The STA consists of the caudal zona incerta (cZi) and prelemniscal radiation (RAPRL). The Zi is a cellular nucleus, which reveals numerous connections with the cerebellum, brainstem, reticular formation, pedunculopontine nucleus, substantia nigra, globus pallidus, superior colliculi, thalamus, cerebral cortex and spinal cord, whereas the RAPRL is a fiber bundle with projections to the mesencephalon, cerebellum and thalamus [19]. Given the various and diverse afferent and efferent pathways, it is not surprising that no neuroanatomical area in the STA could be attributed to specific stimulation-induced effects and side effects [8]. Now, our study suggests that within the STA (1) an anterior stimulation is more effective to suppress tremor, (2) an inferior stimulation is more likely to elicit upper limb ataxia, and (3) paresthesia is more severe with posterior and lateral stimulation.

Concerning tremor suppression, we observed the best effect around 5 mm posterior of MCP in the subthalamic area below intercommissural line (ICL), which most likely corresponds to the caudal zona incerta and prelemniscal radiation [20]. Using the tremor rating scale, our group and others have shown a relative tremor suppression of > 50% in the

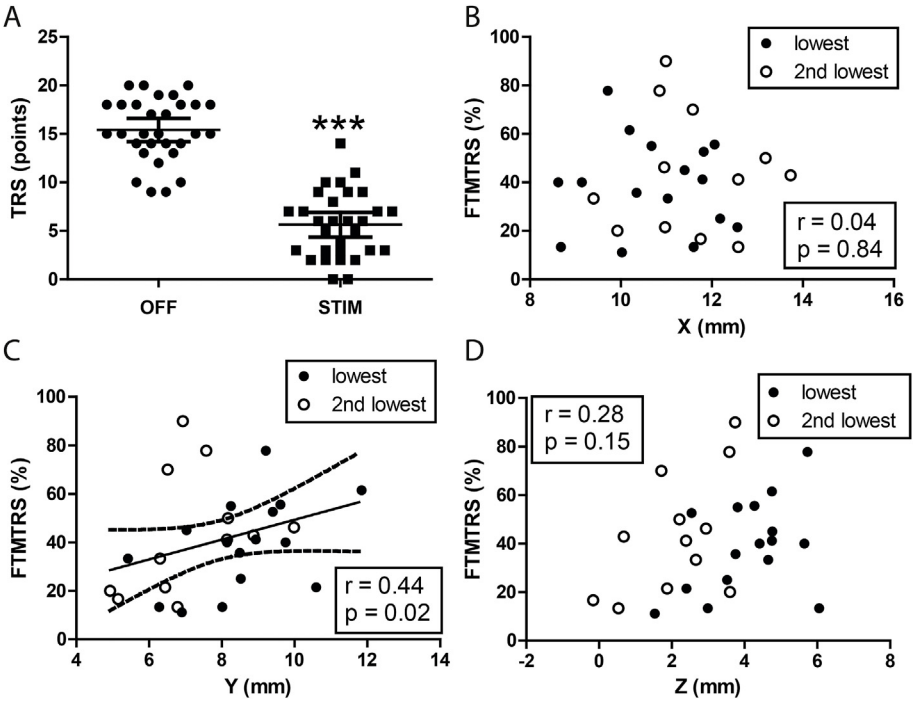

Fig. 1. Correlation of tremor-suppressing effects with stereotactic coordinates.
(A) Stimulation (STIM) reduced tremor compared without stimulation (OFF). Correlation analysis of normalized FTMTRS score (tremor) with x-coordinates (B), y-coordinates (C) and z-coordinates (D) with lowest contacts 1/9 (●) and 2nd lowest contacts 2ABC/10ABC (○). For the significant correlation with x-coordinates, regression line with 95% confidence interval is shown. (n = 28 contacts in 8 patients, ***P < 0.001).

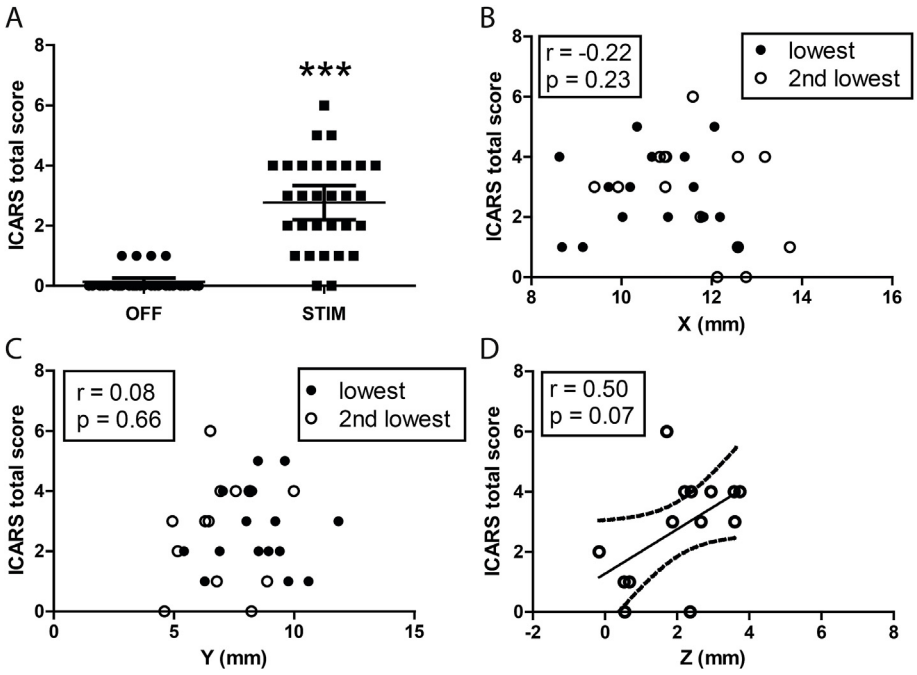

Fig. 2. Correlation of ataxia-inducing effects with stereotactic coordinates.
(A) Stimulation (STIM) induced ataxia compared without stimulation (OFF). (B–D) Correlation analysis of ICARS score (ataxia) with x-coordinates (B) and y-coordinates (C) with lowest contacts 1/9 (●) and 2nd lowest contacts 2ABC/10ABC (○). (D) Correlation analysis of ICARS score (ataxia) with 2nd lowest contacts 2ABC/10ABC (○). For the almost significant correlation with z-coordinates, regression line with 95% confidence interval is shown. (n = 30 contacts in 8 patients for x- and y-coordinates; n = 14 contacts in 8 patients for z-coordinates; ***$P < 0.001$).

STA using active contacts at 11–13 mm lateral, 6–7 mm posterior and 2–4 mm inferior to MCP [3,17,21,22]. In general, stimulation sites below the ICL have proven more efficient for tremor suppression [5,17]. Our data reveal that anterior electrode localizations within STA (i.e. below the ICL) are more effective to suppress tremor. This is line with a recent study, which revealed that a more anterior electrode placement is a predictor of long-term benefit, whereas x- and z-coordinates did not [23]. Interestingly, tractography-based targeting using cerebellar inputs and motor cortical output fibers revealed a more anterior optimal implantation site compared with conventional targeting (8.5 mm vs 6.7 mm anterior to posterior commissure) [24]. Our work adds to these recent findings that anterior electrode localizations within the STA are also associated with short-term benefits and that the extent of tremor suppression is linearly distributed along the y-axis below the ICL.

Adverse effects of thalamic DBS, including dysarthria, paresthesia and ataxia, define the upper border of the therapeutic window [1,2,25]. Especially gait and limb ataxia are severe adverse effects, which limit thalamic DBS treatment. Ataxia-inducing cerebello-rubro-spinal fiber tracts have a more ventral localization in the STA, because the lowest contacts elicit the strongest ataxia [7,12]. In our study, we also observed a linear correlation of ataxia with more ventral electrode positions in the range of 0–4 mm below MCP. However, more ventral electrode positions (i.e. 4–6 mm) did not further increase ataxia. Inferior stimulation sites are more effective to suppress tremor [5], but induce more ataxia [7,12]. In addition to electrode position, optimization of stimulation parameters (e.g. 30 or 40 μs) can attenuate side effects with preserved tremor suppression [9,26].

Besides ataxia, paresthesia is the most common and acute stimulation-induced side effect. Especially posterior electrode positions elicited

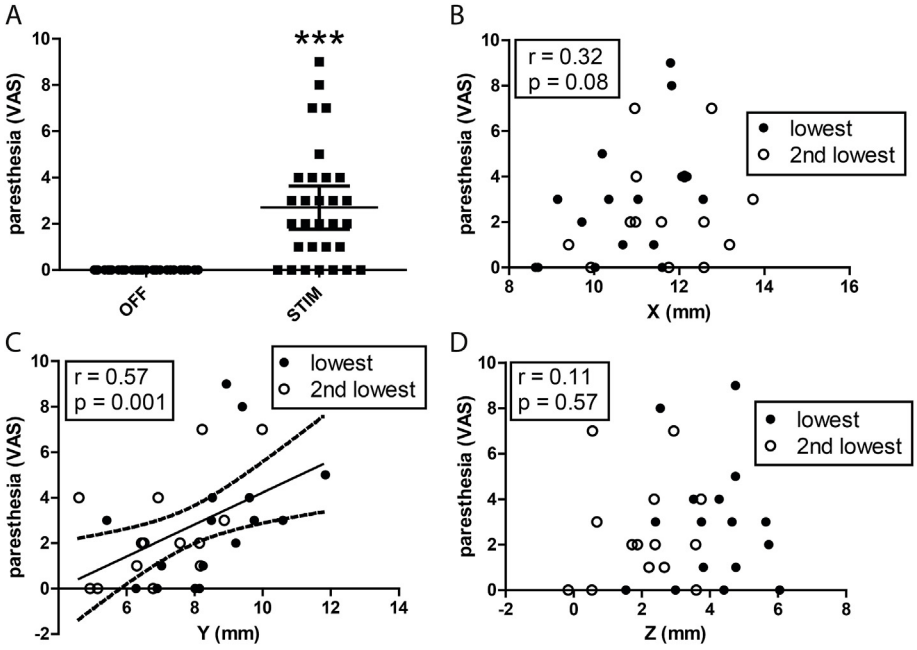

Fig. 3. Correlation of paresthesia with stereotactic coordinates.
(A) Stimulation (STIM) induced paresthesia compared without stimulation (OFF). (B–D) Correlation analysis of parestheisa with x-coordinates (B), y-coordinates (C) and z-coordinates (D) with lowest contacts 1/9 (●) and 2nd lowest contacts 2ABC/10ABC (○). For the significant correlation with y-coordinates, regression line with 95% confidence interval is shown. (n = 30 contacts in 8 patients, ***$P < 0.001$).

unacceptably strong paresthesia requiring repositioning in some cases [4,27]. This is not surprising, because the posterior STA receives sensory inputs from the medial lemniscus and trigeminal pathway. Conversely, anterior active contacts predicted a better long-term success possibly allowing higher stimulation intensities without limiting paresthesia [23]. In correspondence with these reports, we observed a strong linear correlation of paresthesia induction with more posterior electrode positions in the range between 4 and 12 mm on the y-axis. Our results suggest a continuum of stimulation-induced paresthesia, rather than a circumscribed focus in this wide range. This is in line with a previous report, which was unable to attribute paresthesia to specific anatomical areas in the STA [8]. In addition to posterior localizations, we observed a nearly significant correlation of paresthesia with lateral electrode positions, which is explained by stimulation of the posterior limb of the internal capsule – the lateral border of the STA.

Limitations of our study are the single-center study design, the small number of patients and the assessment of acute effects in an experimental setting. Especially, the small number could possibly result in a selection bias indicated by differences of mean stereotactic coordinates compared with other STA studies [12,22,28]. Therefore, larger long-term trials are required to verify our findings and should also evaluate quality of life and clinical relevance of our data.

In summary, an antero-dorso-medial stimulation site in the STA was associated with reduced adverse effects and increased tremor suppression in our small single-center cohort implicating a potential optimal subtarget.

Author contributions

UH acquired, analyzed, interpreted the data and drafted the article. MS acquired, analyzed and interpreted the data and revised the article critically for important intellectual content. CKEM conceived the study, analyzed and interpreted the data and revised the article critically for important intellectual content. AG, JK, CB, CG and MPN analyzed and interpreted the data and revised the article critically for important intellectual content. WH analyzed and interpreted the data and drafted the manuscript. CUC conceived and designed the study, acquired, analyzed and interpreted the data and drafted the manuscript. All authors approved the final version of the article to be submitted.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2019.03.028.

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