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Characteristics and prognostic factors of Parkinson's disease patients with abnormal postures subjected to subthalamic nucleus deep brain stimulation

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ABSTRACT

Objective: In Parkinson's disease (PD), abnormal postures are often accompanied, which interfere with rehabilitation and subsequent functional recovery. This study investigated the relationship between clinical characteristics and improvement in abnormal postures of PD patients who received subthalamic nucleus deep brain stimulation (STN-DBS).

Methods: Seventy-four PD patients were included in this study. Clinical data were analyzed using the patients' functional status at pre- and post-STN-DBS, including anteflexion vs. non-anteflexion, scoliosis vs. non-scoliosis, improved anteflexion vs. non-improved anteflexion, and improved scoliosis vs. non-improved scoliosis.

Results: In patients with anteflexion, UPDRS III motor score at off medication was worse than that of patients with non-anteflexion. Patients with scoliosis presented with more comorbid spinal deformity and longer disease duration than those without scoliosis. Cobb angle of patients with asymmetrical psoas major and erector spinal muscles was more than that of patients without the asymmetry. Patients with improved anteflexion after STN-DBS had thicker abdominal oblique muscle and transverse abdominal muscle than those of patients without improved anteflexion. Patients with improved scoliosis were significantly younger at PD onset than those without improvement.

Conclusions: There were only a few prognostic factors recognized in patients with improved postures. The thick abdominal muscle for anteflexion and younger PD onset for scoliosis were significant factors for improvement by STN-DBS. Rehabilitation designed to maintain muscle for correct postures may contribute to the amelioration of abnormal postures by STN-DBS, although multicenter trials are needed.

1. Introduction

Parkinson's disease (PD) patients often display sagittal and/or coronal plane deformities [1]. In sagittal plane deformities, the term 'camptocormia' is routinely defined as a thoracolumbar flexion angled over 45° [1]. In coronal plane deformities, scoliosis is a common spine condition. The incidence rate is reported as 3–17.6% for camptocormia, and 8.5–60% for scoliosis [1]. Severe abnormal posture leads to back pain, gait disturbance, tendency to fall and altered physical appearance [2].

The causes of abnormal posture in PD patients may be related to dystonia, rigidity, myopathy, drug-induced adverse effects, failure of sensory integration in the central nervous system, vestibular dysfunction, musculoskeletal degeneration and so on. However, the specific cause is still controversial. Therefore, the treatment for abnormal posture in PD patients varies from adjustment of anti-parkinsonian drug, botulinum toxin, steroid, spinal surgery, rehabilitation, and subthalamic nucleus deep brain stimulation (STN-DBS), depending on the individual patient's condition.

In PD patients, abnormal postures usually persist even after STN-DBS because such stooped posture and gait disturbance interfere with rehabilitation despite the patients' improvement in motor function. Interestingly, there are some PD cases with subsequent amelioration in abnormal postures following STN-DBS. That STN-DBS may correct abnormal postures in some PD patients, but not in others warrants a closer examination. In this study, we sought to analyze the abnormal postures

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of PD patients in an effort to reveal critical factors that influence the clinical outcomes of STN-DBS.

2. Methods

2.1. Patients

In this study, PD patients who received STN-DBS in Okayama University Hospital between September 2011 and December 2015 were included. Patients included in this study satisfied the conditions as stated below.

1. First STN-DBS performed in Okayama University Hospital, 2. Preoperative and postoperative clinical data were available at 1 day, 3 months, and 6 or 12 months after surgery, 3. No severe psychiatric symptoms, 4. Definite PD diagnoses. STN-DBS was approved for reasons of wearing-off, no severe cognitive dysfunction, no severe depression and dyskinesia. This study was approved by Okayama University ethical committee (Protocol number: 1705-015). All patients agreed and signed informed consent forms.

2.2. Outcome measures

In this study, characteristics of patients were assessed, such as, sex, age, body mass index (BMI: kg/m^2), past history, disease duration, preoperative UPDRS III total score, preoperative levodopa equivalent daily dose (LEDD). For neuroradiological endpoints, Cobb angle (Fig. 1A), C7 sagittal vertical axis (C7SVA, Fig. 1B) [3], T12-S1 lumbar lordosis (LL), iliac crest tilt [4], paraspinal muscle volume, and paraspinal muscle thickness (Fig. 1C) were evaluated. All measurement was done by the first author to avoid inter-examiner error of measurement.

2.3. Definition of abnormal postures and improvement by STN-DBS

Abnormal postures, which refer to anteflexion and scoliosis of PD patients were evaluated in terms of the improvement by STN-DBS. In this study, X-ray images of whole spine were taken at dopaminergic off-medication with standing state. Patients were divided into anteflexion group (C7SVA more than 5 cm) and non-anteflexion group (C7SVA less than 5 cm) [3]. The improvement of anteflexion was defined as over 5 cm improvement. Scoliosis was defined as Cobb angle over 15° at coronal plane X-ray image with standing state. The improvement of scoliosis was defined as Cobb angle over 5° improvement at 3–6 months after surgery. In patients with scoliosis, the side of curve convexity, defined as the convex side, was evaluated. Percentage of asymmetry in cross-section area (CSA) was calculated as [(non-convex side – convex side)/non-convex side] [5]. In a previous report, the cut-off value of 10% was used in % CSA asymmetry. They reported that at L3-L4 level, % CSA asymmetry of multifidus muscle was 8.44 ± 5.92 and erector spinae's % CSA asymmetry was 5.24 ± 4.03 [5]. In this study, the cut off value of 20% asymmetry was used as criterion for inclusion and exclusion of cases.

2.4. Quantitative evaluation of paraspinal muscle

The assessment tissue included muscle cross-sectional area (psoas major muscle, quadrate muscle, and erector spinae muscle) [6] and muscle thickness (rectus abdominal muscle, abdominal oblique muscle, and transverse abdominal muscle) (Fig. 1C). The thickness and area of muscles were measured at L3 level axial muscle CT scan [7]. The difference in muscle area and thickness between convex and non-convex side was assessed at L3 level in CT scan (Aquilion One, Toshiba, Japan) with subsequent evaluation of % CSA asymmetry.

2.5. Statistical analysis

Data were assessed by the software SPSS 15.0 for Windows. Mann-Whitney's *U* test and Chi-square test were used to assess the differences and tendency (age, BMI, LEDD, UPDRS III score, UPDRS postural score, X-ray image assessment items, and muscle CT assessment items) between two preselected matched groups (anteflexion group vs. non-anteflexion group, scoliosis group vs. non-scoliosis group, % CSA asymmetry > 20% group vs. %CSA asymmetry < 20% group, improved anteflexion group vs. non-improvement group, and improved scoliosis group vs. non-improvement group). The significant value was set at $p < 0.05$. Data are shown mean ± standard error (SE).

3. Results

3.1. Patient characteristics

A total of 74 patients were included in this study to meet the inclusion criteria. Of the 74 patients, 37 patients were male and 37 patients were female. The mean age was 62 ± 0.9 years. The mean BMI was 22.7 ± 0.4 kg/m^2. The mean LEDD was 667 ± 31 mg. The mean scores of UPDRS III (on/off) were 17.7 ± 1.1/33.5 ± 1.7. The mean C7SVA was 53.9 ± 7.9 mm and the mean Cobb angle was 8 ± 1.1°.

3.2. Anteflexion

Evaluation of anteflexion was based on data from 62 patients. Six patients could not stand by themselves at off-medication. S1 vertebral body was out of range or could not be detected clearly in the X-ray images of the other 6 patients. Thirty patients (male/female: 15/15) were classified in anteflexion group and 32 patients (male/female: 15/17) were in non-anteflexion group. In 30 anteflexion patients, 11 patients (36.7%) had spinal morphological change notably compression fracture as detected in X-ray, 1 patient (3.3%) had history of spinal surgery, and 1 patient (3.3%) had history of hip joint surgery. In 32 non-anteflexion patients, 7 patients (21.9%) had spinal morphological change visualized in X-ray, 1 patient (3.1%) had history of spinal surgery and no patient had history of hip joint surgery. Table 1 shows the comparison of the two groups. UPDRS III motor score at off medication and with the response to levodopa of anteflexion group (37.5 ± 2.7 and 20.2 ± 2.6) was significantly worse than those of non-anteflexion group, respectively (29.3 ± 2.5 ($p = 0.008$) and 13 ± 1.9 ($p = 0.034$)). Moreover, in anteflexion patients, 'posture' score in UPDRS III score was worse (3.4 ± 0.6, $p = 0.005$) and lumbar lordosis was less (29.4 ± 3.4°, $p = 0.001$) than those in non-anteflexion patients (0.6 ± 0.5 and 45.5 ± 1.9°).

3.3. Factors related to improvement of anteflexion by STN-DBS

One of 30 patients with anteflexion was completely followed postoperatively by another hospital, therefore data analyses were limited to 29 patients, which were divided into two groups, namely improved C7SVA group and non-improved group. In 17 patients (male/females: 8/9), C7SVA was improved by more than 5 cm and in 12 patients (male/female:6/6), C7SVA improvement was less than 5 cm. In improved C7SVA group, 5 patients (29.4%) had spinal morphological change, 1 patient had history of spine surgery, and no patient had history of hip joint surgery. In non-improved group, 5 patients (41.7%) had spinal morphological change, no patient had history of spine surgery, and one patient had history of hip joint surgery. There were no significant differences in age, UPDRS III score and UPDRS postural score between the two groups (esupp 1). About the abdominal muscle, the thickness of abdominal oblique muscle and transverse abdominal muscle of improved C7SVA group (4.0 ± 0.8 mm) was significantly more than that of non-improved group (1.3 ± 0.3 mm, $p = 0.014$).

3.4. Scoliosis

Evaluation of scoliosis was based on available data from 68 patients.

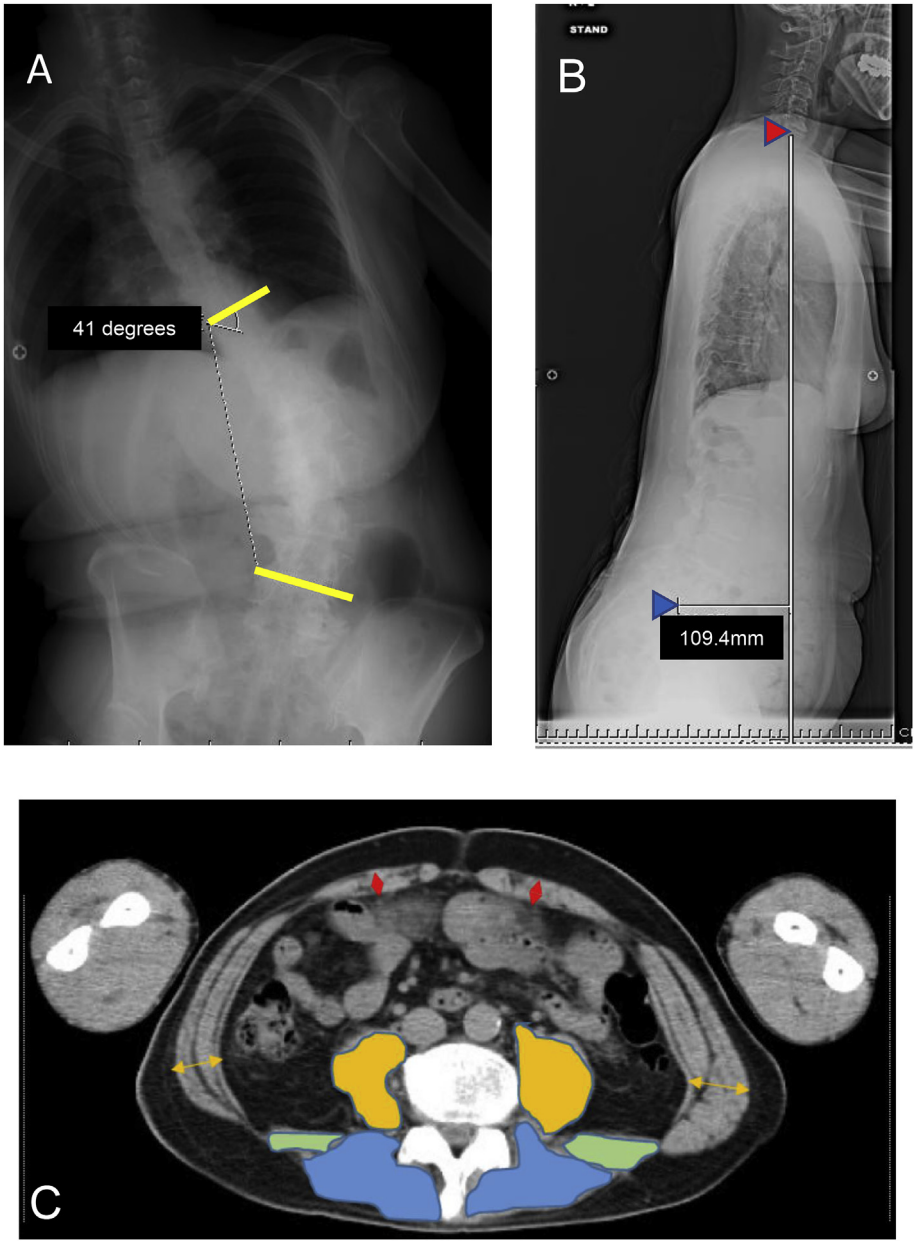

Fig. 1. A: Cobb angle of a representative patient with scoliosis. B: C7SVA of a representative patient with anteflexion. C: Measurement of muscle thickness and area. Red arrow: thickness of rectus abdominal muscle, yellow arrow: thickness of transverse abdominal muscle + abdominal oblique muscle, yellow area: psoas major muscle, green area: quadrate muscle, blue area: erector spinae muscle.(For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Six patients could not stand by themselves at off-medication. Sixteen patients (male/female: 6/10) presented with scoliosis defined in this study as Cobb angle over 15° and 52 patients (male/female: 27/25) did not present with scoliosis. Table 2 shows the comparison of the two groups. Sixteen patients had scoliosis preoperatively. Of 16 scoliosis patients, 9 patients (7 females, 77.8%) had left convex curve and 7 patients (3 females, 42.3%) had right convex curve. From this cohort of 16 scoliosis patients, 9 patients (56.3%) had spinal morphological change, no patient had history of spine surgery, and one patient had history of hip joint surgery. In 52 non-scoliosis patients, 11 patients (21.2%) had spinal morphological change, 1 patient had history of spine surgery, and 1 patient had history of hip joint surgery. The comorbid spinal deformity was significantly recognized in scoliosis patients ($p = 0.007$, Chi square). There were no significant differences in age, UPDRS III score and UPDRS postural score between the two groups. The disease duration of scoliosis group (13.4 ± 1.4 years) was longer than non-scoliosis group (10.3 ± 0.7 years, $p = 0.045$). Assessment of psoas major and erector spinal muscle revealed a significant difference in Cobb angle between % CSA asymmetry > 20% group and CSA % asymmetry < 20% group (esupp 2). There was no significant difference in each muscle volume between non-convex and convex side (esupp 3) in 16 patients with scoliosis, although there appeared a tendency of superiority of non-convex side muscle to convex side muscle. In this study, concomitance of anteflexion and scoliosis was recognized in 9 patients. Only 2 patients improved their posture, but both C7SVA and Cobb angle were improved in those 2 patients by STN-DBS.

3.5. Potential factors mediating improvement of scoliosis by STN-DBS

Three scoliosis patients in 16 patients were completely followed postoperatively by other hospitals thus data analyses were limited to 13

Table 1
Comparison of data between PD patients with and without anteflexion.

	Non-Anteflexion	Anteflexion	p value
Total number of patients	32	30	
Number of Females	17	15	
Body mass index in kg/m^2	22.9 ± 0.6	22.2 ± 0.6	.449
Age at onset PD in years	50.1 ± 1.5	52.7 ± 1.4	.225
Age at DBS in years	60.2 ± 1.6	64.5 ± 1.2	.065
Duration of disease in years	10.1 ± 0.8	11.8 ± 0.9	.078
LEDD in mg	649 ± 45	686 ± 445	.561
Number of spinal morphological change (%)	7 (22)	11 (37)	
Number of history of spine surgery (%)	1 (3.1)	1 (3.3)	
Number of history of hip joint surgery (%)	0 (0)	1 (3.3)	
UPDRS III Motor Score			
On Meds	16.3 ± 1.5	18.2 ± 1.7	.352
Off Meds	29.3 ± 2.5	37.5 ± 2.7	.013*
Off-On Score gap (response to levodopa)	13 ± 1.9	20.2 ± 2.6	.034*
Sagittal plane X-ray			
C7SVA in mm	6.0 ± 5.7	105.1 ± 7.5	.00
Kyphosis T5-12 in degrees	31.8 ± 2.8	24.8 ± 3.6	.128
Kyphosis T10-L2 angle in degrees	18.4 ± 1.8	15.7 ± 3.0	.078
Lordosis T12-S1 in degrees	45.5 ± 1.9	29.4 ± 3.4	.001*

* indicates significant difference.

Table 2
Comparison of data between PD patients with and without scoliosis.

	Non-scoliosis	Scoliosis	p value
Total number of patients	52	16	
Number of Females	25	10	
Body mass index in kg/m2	22.8 ± 0.5	22.1 ± 0.9	.805
Age at onset PD in years	51.2 ± 1.2	51.7 ± 2.5	.373
Age at DBS in years	61.6 ± 1.1	65.1 ± 1.7	.069
Duration of disease in years	10.3 ± 0.7	13.4 ± 1.4	.045*
LEDD in mg	642 ± 31	703 ± 83	.376
Number of spinal morphological change (%)	11 (21)	9 (56)	.012*
Number of history of spine surgery	1	0	
Number of history of hip joint surgery	1	1	
UPDRS III Motor Score			
On Meds	18.3 ± 1.3	16.4 ± 2.1	.457
Off Meds	33.0 ± 2.1	36.7 ± 3.2	.263
Off-On Score gap (response to levodopa)	15.2 ± 1.5	20.3 ± 3.8	.160
Coronal plane			
Cobb angle in degree	4.1 ± 0.7	20.9 ± 1.6	.000*
Leaning angle of pelvis	0.3 ± 0.3	2.4 ± 1.1	.057
Absolute value of leaning pelvis angle	1.9 ± 0.2	3.9 ± 0.8	.015*

* indicates significant difference.

patients which were divided into two groups, namely improved-scoliosis showing more than 5° (5 patients) and non-improved group (8 patients). Five patients (male/female: 3/2) presented with improvement of scoliosis over 5° and 8 patients (male/females: 1:7) presented without improvement of scoliosis. Male dominancy is not significant, but seemed to be more inclined towards improvement of scoliosis ($p = 0.071$, Chi square). In 5 patients in improved-scoliosis group, 3 patients (60%) had spinal morphological change, and no patient had history of spine or hip joint surgery. In 8 non-improved group, 6 patients (75%) had spinal morphological change, no patient had history of spine surgery, and one patient had history of hip joint surgery. There were no significant differences in disease duration, UPDRS III, UPDRS postural score. Age at PD onset of improved-scoliosis group (45.0 ± 6.8 years) was younger than that of non-improved group (57.1 ± 0.9 years, $p = 0.045$, Table 3).

Table 3
Comparative data of PD patients with and without improved scoliosis by STN-DBS.

	Non-improvement	Improved scoliosis	p value
Total number of patients	8	5	
Number of Females	7	2	
Body mass index in kg/m^2	21.4 ± 1.3	23.2 ± 2.1	.724
Age at onset PD in years	57.1 ± 0.9	45 ± 6.8	.045*
Age at DBS in years	67.9 ± 1.7	62.6 ± 4.1	.622
Duration of disease in years	10.8 ± 1.3	17.6 ± 3.2	.065
LEDD in mg	850 ± 114	509 ± 143	.127
Number of spinal bone deformity	6	3	
Number of history of spine surgery	0	0	
Number of history of hip joint surgery	1	0	
UPDRS III Motor Score			
On Meds	15.4 ± 3.9	18.6 ± 2.7	.268
Off Meds	34 ± 5.9	35.6 ± 4.1	.876
Off-On Score gap (response to levodopa)	18.6 ± 6.7	17 ± 4.8	.876
Scoliosis postural abnormality in UPDRS score			
On Meds	0.6 ± 0.4	1.6 ± 0.7	.343
Off Meds	0.8 ± 0.6	1.8 ± 0.7	.310
Off-On Score gap (response to levodopa)	0 ± 0.3	0.2 ± 0.4	.690
Anteflexion in UPDRS score			
On Meds	1 ± 0.4	1.6 ± 0.5	.432
Off Meds	2.4 ± 0.2	2.8 ± 0.2	.310
Off-On Score gap (response to levodopa)	1 ± 0.3	1.2 ± 0.5	1.00
Coronal plane			
Cobb angle in degree	22 ± 2.8	22.4 ± 2.1	.435
Leaning angle of pelvis	2.5 ± 1.5	2.6 ± 2.4	.833
Absolute value of leaning pelvis angle	3.3 ± 1.3	5.0 ± 1.1	.222
Sagittal plane			
C7SVA in mm	59.5 ± 16.6	41.3 ± 36.7	.914
Kyphosis T5-12 in degrees	34 ± 9.9	29.5 ± 10.7	1.00
Kyphosis T10-L2 angle in degrees	16 ± 3.5	17.3 ± 8.8	1.00
Lordosis T12-S1 in degrees	41 ± 4.1	45 ± 5.7	.548

* indicates significant difference.

4. Discussion

4.1. Anteflexion vs. non-anteflexion

In this study, lumbar lordosis angle in anteflexion group was below normal values. Indeed, patients with high C7 SVA (> 5 cm) present with significantly lower lumbar lordosis angle (29.3 vs. 43.5°, $p < 0.001$) [3] and that C7SVA negatively correlates with lumbar lordosis angle [8]. Loss of lumbar lordosis in PD patients may accompany anteflexion, suggesting that rehabilitation designed to maintain muscles associated lumbar lordosis can attenuate anteflexion of PD patients. In general, compression fracture due to osteoporosis and disc degeneration may lead to decreased lumbar lordosis in the elderly. However, in our study, the rate of compression fracture was not different between the two groups. These results imply that anteflexion of PD patients is caused not only by the breakdown of the anterior column, but also by other factors, such as disproportionate muscle tension of body trunk or spinal column. Degeneration of psoas major muscle and quadrate muscle may manifest with anteflexion in PD patients [6,9,10]. In our study, there were no significant differences in the area and thickness of muscle of body trunk or spinal column. These negative data might be due to the small number of patients and the method of measurement using single section of abdominal CT image. On the other hand, there was no significant difference in preoperative LEDD between the two groups.

4.2. Improvement of anteflexion after STN-DBS

In our study, abdominal oblique muscle and transverse abdominal muscle in improved C7SVA group were thicker than those in non-improved group. Camptocormia may be improved by the combination of lidocaine injection into external oblique muscle and rehabilitation [10,11]. Maintenance of the thickness of abdominal oblique muscle and transverse abdominal muscle by exercise may contribute to positive outcomes for PD patients with anteflexion receiving STN-DBS. In parallel, because PD patients have risk of malnutrition [12], a nutrition support team may be helpful to avoid muscular atrophy.

4.3. Scoliosis vs. non-scoliosis

A close interaction exists between abnormal posture and PD progression. PD patients with scoliosis tend to be older [13]. The rate of abnormal posture increases during PD progression [14]. Disease duration of PD in patients with scoliosis was longer than that without scoliosis. Our study showed that the absolute value of pelvis leaning angle at coronal plane in scoliosis group was larger than in non-scoliosis group. Pelvis leaning may also affect scoliosis, as well as curve of the spine. To this end, rehabilitation to maintain muscles related to pelvis leaning may be important for treating scoliosis in PD patients. The need for such muscle maintaining rehabilitation becomes more apparent for PD patients with Pisa syndrome, as evidenced by their electromyogram-detected abnormal tonic hyperactivity on the side of the deviation in the abdominal oblique muscles and the paravertebral muscles. Additionally, these patients may also display lumbar paraspinal muscular atrophy on the side of the deviation based on CT images [15,16]. Interestingly, resolution of performance status after botulinum toxin injection in the quadratus lumborum muscle provides further impetus for muscle rehabilitation [17], altogether suggesting that various muscles are closely involved in the abnormal posture in coronal plane of PD patients.

4.4. Improvement of scoliosis after STN-DBS

We observed here that improvement of scoliosis in PD patients was related to young age at PD onset and male. Other than these mitigating factors, there were no significant values to predict the prognosis on scoliosis of PD patients by STN-DBS. We recognize the small number of patients enrolled here, especially when evaluating scoliosis. Further evaluation by multicenter trials are warranted to reveal true prognostic factors of STN-DBS in ameliorating the abnormal postures of PD patients.

4.5. STN-DBS and postural abnormality

Although DBS has been reported to affect postural abnormality of PD patients [18], only a few studies reveal the treatment's prognostic factors [19–22]. STN-DBS may be effective in patients with early spinal deformity [19], but treatment initiation should be considered before irreversible skeletal deformity develops. In PD patients with severe camptocormia at off-medication thoracolumbar angle over 45°, duration and severity of camptocormia and the levodopa responsiveness of the thoracolumbar angle are suggested as prognostic factors of STN-DBS [21]. However, short duration of camptocormia, but not the degree of camptocormia, may represent as the only prognostic factor for improving abnormal posture with STN-DBS [20]. Until now, few studies have analyzed separately anteflexion and scoliosis. Here, we demonstrated that systematic analyses of anteflexion and scoliosis of PD patients receiving STN-DBS revealed that the single prognostic factor identified that closely approximated an improvement in scoliosis by STN-DBS was the young onset age of PD. However, there was no significant prognostic factor detected in the improvement of anteflexion in PD patients treated with STN-DBS. With the small number of patients included in our study, a large multicenter trial may reveal true prognostic factors of STN-DBS in the treatment of abnormal postures in PD.

4.6. Study limitation

As we described several times in the text, the largest limitation is the number of patients in our study. Additionally, there were some patients without serial follow-up, because they were enrolled from distant areas and followed-up at regional hospitals. Another limitation is that the available data were obtained mainly preoperatively. Moreover, the measurement of muscle area and thickness was based on single slice at L3 level, preventing us to conduct analyses of whole muscle volume which be a critical contributing factor to abnormal postures. Despite these limitations, our study provided valuable characteristics of PD patients with anteflexion and scoliosis and determined that age of PD onset was a crucial prognostic factor for improving scoliosis.

5. Conclusion

We retrospectively reviewed data from PD patients with abnormal postures to determine prognostic factors of STN-DBS. PD patients with anteflexion displayed low motor and posture score. Prognostic factors for ameliorated anteflexion was thick abdominal oblique muscle and transverse abdominal muscle. PD patients with scoliosis exhibited more comorbid spinal deformity and long disease duration. High %CSA asymmetry of psoas major and erector spinal muscles was significantly correlated with scoliosis. Prognostic factor of ameliorated scoliosis was young age at PD onset. A multicenter study is warranted to reveal further prognostic factors of STN-DBS.

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Appendix A. Supplementary data

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