Parkinson's disease-related non-motor symptoms and risk of post-operative delirium after spinal surgery

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ABSTRACT

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Background: Delirium is an acute confusional state characterized by disturbed attention and fluctuating cognition. Postoperative delirium is well known as the most frequent complication that is strongly associated with poor surgical outcomes and prolonged hospitalization of elderly patients. The clinical features of postoperative delirium are similar to the core features of alpha synuclein-related cognitive disorders, such as Parkinson's disease dementia (PDD) or dementia with Lewy bodies (DLB). Further, previous studies suggest that underlying alpha synuclein pathologies are associated with postoperative delirium. Therefore, we hypothesized that the non-motor symptoms (NMSs) in Parkinson's disease (PD), which precede the cardinal motor features of PD, are likely to be risk factors for developing postoperative delirium. We investigated the association between PD-related NMSs and postoperative delirium in patients aged 65 years and older undergoing elective spinal surgery.

Methods:

This study was a prospective observational study at the Severance Hospital Neurosurgery Department. Participants were enrolled between September 2015 and July 2016. Eligible participants were aged 65 years and older and

scheduled to undergo elective spinal surgery at the Severance Neurosurgical Department. Exclusion criteria included evidence of current or previous delirium before surgery, chemotherapy or radiotherapy for underlying cancer within the previous year, or hepatic or renal dysfunction. During the enrollment period 338 individuals were screened, of whom 42 (12.4%) did not meet the enrollment criteria. One hundred and six (31.4%) patients agreed to participate in this study. Two patients` elective operations were cancelled, leaving 104 participants.

We assessed PD-related NMSs 1 day before the scheduled surgery using tests or questionnaires for each symptom. We chose eight easily-assessed PD-related NMSs: olfactory disturbance, constipation, orthostatic hypotension, insomnia, excessive daytime somnolence, rapid eye movement sleep behavior disorder (RBD), depression, and anxiety. We counted the number of positive findings for these eight PD-related NMSs to produce the prodromal symptoms score (ranging from 0 to 8) in order to analyze the predictability of postoperative delirium.

We assessed the presence of delirium using the short version of the Confusion Assessment Method (Short CAM). A trained neurologist performed the delirium evaluation between 9 am and 12 midday on days 1, 2, and 3 after surgery.

Results: Fifteen (14.4%) of the 104 participants, met the Short CAM criteria for delirium at least once during the three postoperative days. Male sex and a low Mini-mental state examination (MMSE) score in the baseline measures were significantly associated with postoperative delirium ($p=0.029$ and $p=0.023$, respectively); preoperative hyposmia ($p=0.021$), depression ($p=0.027$), and RBD ($p=0.002$) were independent predictors of postoperative

delirium. A higher prodromal symptoms score was associated with a greater risk of postoperative delirium.

Conclusion: Among PD-related NMS, RBD, hyposmia, and depression were independent risk factors for predicting postoperative delirium, and RBD was the strongest predictive factor. Furthermore, our results show that a greater number of NMSs, which may reflect the burden of alpha synuclein deposit, correlates with a higher risk of postoperative delirium. These findings suggest that postoperative delirium may be a preclinical stage of alpha synucleinopathy, and non-motor symptoms may help us to estimate the likelihood of postoperative delirium.

Key words: postoperative delirium, non-motor symptoms of Parkinson's disease, alpha synucleinopathy

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I. INTRODUCTION

Delirium is an acute confusional state or encephalopathy characterized by disturbed attention and fluctuating cognition. It causes serious, often fatal, outcomes and significant medical costs, and has occurrence rates from 10% to 60% of the elderly hospitalized population.[1-3] Moreover, postoperative delirium is well known as the most frequent complication strongly associated with poor surgical outcomes and a prolonged hospitalized period for elderly patients.[4] The reported rates in the literature of postoperative delirium following spinal surgery range from 2.0% to 30% in elderly patients.[5-8] Predisposing and precipitating factors are known to be related to postoperative delirium including age, cognitive decline, depression, medical comorbidity, psychotropic drug use, admittance to an intensive care unit, and type of surgical procedure. Current research suggests that blood-brain barrier breakdown, deranged neurotransmitters and inflammatory process such as interleukin-1b (IL-1b), tumor necrosis factor-a (TNF-a), and interleukin-6 are the primary pathophysiologies of postoperative delirium, although there are insufficient human data to allow a firm conclusion to be reached.[9] In particular, the decreased cholinergic levels that can be

seen in the pathology of dementia with Lewy bodies play an important role in delirium.[10]

The clinical features of postoperative delirium are similar to the core features of alpha synuclein-related cognitive disorders, such as Parkinson's disease dementia (PDD) or dementia with Lewy bodies (DLB): fluctuating attention, visual hallucination, and disorganized thoughts.[11] In terms of clinical similarity, delirium may be a series of cognitive disorders. Alpha synuclein related disorders and postoperative delirium may share an underlying neurochemical change in their pathogenesis. A previous study proposed that underlying alpha synuclein pathologies are associated with postoperative delirium.[12] Therefore, we hypothesized that postoperative delirium could be a preclinical stage of alpha synucleinopathy.

Further, several non-motor symptoms (NMS) in Parkinson's disease (PD), including rapid eye movement sleep behavior disorder (RBD), olfactory loss, constipation, daytime sleepiness, insomnia, depression, anxiety, and orthostatic hypotension have been identified preceding cardinal motor features and being related to alpha synuclein pathology.[13]

We hypothesized that PD-related NMSs are likely to be risk factors for post-operative delirium in elderly people undergoing spinal surgery. We investigated the association between PD-related NMSs and postoperative delirium in patients aged 65 years and above.

II. MATERIALS AND METHODS

1. Participants

This study was a prospective observational study conducted in the neurology and neurosurgery departments of Yonsei University Severance Hospital (Registration: www.clinicaltrial.gov NCT 02550626). Participants were enrolled between October 2015 and July 2016. Eligible participants were age 65 years and older, scheduled to have elective spinal surgery at the neurosurgery department of Yonsei University Severance Hospital, and expected to be hospitalized for at least 3 days. Exclusion criteria included evidence of current or previous delirium before surgery, chemotherapy or radiotherapy within one year due to underlying malignancy, renal or hepatic insufficiency (estimated glomerular filtration rate < 50mL/min or pre-operative hepato-biliary department consultation due to liver enzyme elevation, respectively), severe quadriplegia patients who could not evaluate NMSs, and emergency surgery.

Eligible individuals who were scheduled to have spinal surgery the next day were screened for previous or current delirium using the Confusion Assessment Method(CAM).[14] The Mini-Mental State Examination (MMSE) and neurologic examinations were used for the baseline evaluation. After identifying no current or previous delirium, we used tests and questionnaires for eight easily assessed PD-related NMSs: olfactory disturbance, constipation, orthostatic hypotension, insomnia, excessive daytime somnolence, rapid eye movement sleep behavior disorder (RBD), depression, and anxiety. A neurologist trained for this purpose carried out the interviews and neurological examinations. A trained physician used the Short CAM to assess the patients for post-operative delirium on each of the three days after surgery, with the first assessment carried out within 24 hours of the operation.

The study protocol was approved by the ethics committee of Yonsei University Severance Hospital for experiments using human participants and written informed

consent was obtained from all the participants.

2. Perioperative care

All participants underwent general endotracheal anesthesia with propofol, remifentanil, and pancuronium or vecuronium as muscle relaxants and anesthesia was maintained with desflurane and nitrous oxide inhalation. Participants received vital sign monitoring during the operation, including radial arterial blood pressure and applied warming devices such as forced-air warming devices and warm circuit for maintaining body temperature. All patients received appropriate tracheal extubation before being transported to the ward or the intensive care unit. Surgical procedures in this study included cervical or lumbar decompression, fusion, and tumor removal.

3. Assessment of Parkinson's disease-related non-motor symptoms (NMSs)

Parkinson's disease-related NMSs were evaluated 1 day before scheduled surgery. Many NMSs were well known and their frequency is increasing. [13] We chose easily-assessed eight NMSs: olfactory disturbance, constipation, orthostatic hypotension, insomnia, excessive daytime somnolence, rapid eye movement sleep behavior disorder (RBD), depression, and anxiety. Previous studies have identified that the incidence of all these NMSs is greater among people with Parkinson's disease than among the general population.[15, 16]

We counted the number of positive findings for these eight PD-related NMSs to produce the prodromal symptoms score (randing from 0 to 8). Because the number of NMSs is strongly correlated with advancing Parkinson's disease,[17] this score may reflect the burden and progress of alpha synucleinopathy in accordance with Braak's hypothesis.[13, 18]

3.1 Olfactory disturbance

The 12-item Cross-Cultural Smell Identification Test (CCSIT) was used to measure olfactory function.[19] This comprises a small booklet containing multicultural microencapsulated odorants, which are released by scratching with a pencil. The participants were required to choose one of the 4 alternatives. We define normal olfactory function as 9 points or higher of the total of 12 points, and decreased olfactory function as 8 points or less, based on previous studies.[19, 20]

3.2 Insomnia and daytime somnolence

We used the Insomnia Severity Index (ISI) to measure insomnia. The ISI is a brief screening instrument that measures sleep maintenance difficulties, satisfaction with current sleep patterns, interference with daily functioning, noticeability of quality of life, and the degree of distress or concern expressed by the participant about each item. The total score ranges from 0 to 28 and, based on previous validation research,[21] a score of 8 or higher indicated the possibility of insomnia.

We employed the most frequently used method for measuring daytime sleepiness, the Epworth Sleepiness Scale (ESS)[22] to assess daytime somnolence. We defined excessive daytime sleepiness as an ESS score > 10, in line with previous Asian validation research.[23].

3.3 Rapid eye movement sleep behavior disorder (RBD)

Polysomnography (PSG) evaluation is essential for establishing a definite diagnosis of RBD. However, it is difficult to perform PSG due to accessibility. Instead, we used an easily-assessed questionnaire for screening RBD, a validated Korean version of the RBD screening questionnaire (RBDSQ-K).[24-26] We classified our patients as exhibiting RBD if their total RBDSQ-K score was 5 or higher, in line with an original study.[24]

3.4 Depression

We assessed depression using the Beck Depression Inventory (BDI),[27] which is a

reliable and validated instrument for detecting depressive states in clinical settings. We used the Korean version of the BDI, which has been validated in a previous study.[28] We diagnosed depression in patients who scored ≥ 17.[29]

3.5 Anxiety

We assessed all patients against the Parkinson Anxiety Scale (PAS), a recently developed instrument that has been validated for PD patients.[30] This scale consists of a 12-item observer- or patient-rated scale and three subscales: persisting anxiety (five items), episodic anxiety (four items), and avoidance behavior (three items). We employed the same observer-rated cut-offs as in the original article for totals and subscales to diagnose anxiety disorders (generalized anxiety disorder, panic disorder, and avoidant anxiety disorder).[30] We made a positive diagnosis in the following circumstances: PAS total score for generalized anxiety of 13 or higher; PAS subscale score for persistent anxiety of 9 or higher; PAS subscale score for episodic anxiety 3 or higher; and PAS subscale score for avoidance of 3 or higher.

3.6 Orthostatic hypotension

We investigated participants' orthostatic hypotension using a questionnaire and administering the orthostatic blood pressure test. The Orthostatic Hypotension Questionnaire (OHQ)[31] has a 6-item symptom assessment scale (the Orthostatic Hypotension Symptom Assessment, (OHSA)) and a 4-item daily activity scale (the Orthostatic Hypotension Daily Activity Scale, (OHDAS)). Each item is scored from 0 to 10, with increasing scores reflecting increasing symptom severity; overall OHQ scores range from 0 to 100. Participants also undertook the orthostatic blood pressure test, except for 4 participants who were unable to take the test due to severe pain. After resting in supine position for least 5 minutes, a physician measured blood pressure and heart rate serially after change of posture from supine to standing. Blood pressure and heart rate were obtained in the supine position and immediately after standing, 2 minutes after standing, 5 minutes after standing. We classified our

participants as exhibiting orthostatic hypotension if we confirmed a sustained blood pressure reduction (SBP ≥ 20 mmHg or DBP ≥ 10 mmHg) at any time within 5 minutes of standing. This is a modification of the traditional definition.[32] We conducted the orthostatic blood pressure only once, although several confounding variables existed. Therefore, we also categorized participants who had difficulties with daily activities due to orthostatic hypotension (as assessed by OHDAS) as exhibiting orthostatic hypotension.

3.7 Constipation

Constipation is defined generally as fewer than 3 bowel movements per week.[33, 34] Several studies of NMSs in Parkinson's disease[35, 36] use frequency of bowel movement as a method of assessing constipation. There are various constipation diagnostic methods. However, to avoid diagnostic complexity, we focused simply on the frequency of defecation and the use of laxatives. We classified as constipated participants with ≤ 2 bowel movements per week or taking laxatives for at least 3 months. Further, we employed the constipation scoring system[37] to measure the severity of constipation.

4. Detecting post-operative delirium and neurological evaluation

Each patient was interviewed and evaluated by the same trained researcher pre- and post-operatively within 72 hours of surgery. The preoperative evaluation took place on the day before the operation. During the preoperative evaluation, the researcher recorded the participants' medical history and medication use, carried out a baseline neurological examination, and conducted the Mini-Mental State Examination (MMSE). Because various questionnaires and tests were required for evaluation, we confirmed that all participants were alert and able to communicate. The presence of delirium was assessed using the Short CAM.[14] Because the Short CAM is highly sensitive (sensitivity 94 – 100%), rapid, and simple, it is widely used for assessing

delirium in high-risk settings. The Short CAM consists of 4 clinical features: acute onset (i.e change in mental status) and fluctuating course (feature 1), inattention (feature 2), disorganized thinking (feature 3), and altered level of consciousness (feature 4). A diagnosis of postoperative delirium requires the presence of features 1 and 2 and either feature 3 or 4. We ignored any symptoms or signs of delirium on the day of operation because of the immediate impacts of preoperative medication and anesthetic agents. Delirium assessments took place between 9am and 12 midday on days 1, 2, and 3 after surgery using the Short CAM diagnostic tool for interviews with participants and their caretakers. A trained neurologist identified the presence of delirium based on the Short CAM, and a second investigator validated any assessments of delirium. In the present study, we define postoperative delirium as the presence on any postoperative day of an acute confusional state that meets the Short CAM criteria.

5. Statistical analysis

We compared participants with and without delirium across all the clinical data. The Pearson $\chi 2$ test or Fisher`s exact test for categorical variables was used to compare frequencies. For continuous variables, we examined the normality of their distribution using the Kolmogorov- Smirnov test. Provided the data did not deviate from a normal distribution, we calculated the mean and standard deviation and used independent sample t-tests for comparisons. In the case of data that were not normally distributed, we recorded the median and interquartile range (IQR) and compared them using the Mann-Whitney U test. The optimal cutoff prodromal symptoms score for predicting postoperative delirium was determined with a receiver operating characteristic (ROC) curve. The sum of the sensitivity and specificity values is highest at the optimal cutoff point.

We performed logistic regression analysis to assess the association between postoperative delirium and outcome variables. For univariate logistic regression

analysis, we compared post-operative delirium and possible confounding factors including age, sex, hypertension, diabetes, old cerebrovascular accident, cardiovascular comorbidity, previously diagnosed psychiatric or cognitive disorder, intensive care unit use after operation, perioperative factors such as blood loss and operation time, each PD-related NMS and prodromal symptoms scores. Variables with $P<0.1$ in the univariate analyses were entered into the multivariate model to identify independent predictors of postoperative delirium. The logistic regression analyses results are reported as crude and adjusted hazard ratios with 95% confidence interval (95% CI). SPSS for Windows (version 20.0; SPSS, Chicago, IL) was used as statistical software. *p* values <0.05 were regarded as significant.

III. RESULTS

1. Participants' characteristics

A. Patient enrollments

During the period of the study, 338 individuals were aged 65 years or older and scheduled to undergo elective spinal surgery with general anesthesia at the neurosurgery department of Yonsei University Severance Hospital. After screening out 42 (12.4%) individuals who did not meet the enrollment criteria, 106 (31.4%) patients agreed to participate. Two participants' operations were cancelled abruptly on the day of operation due to patient refusal. Therefore, 104 participants were included in the analysis (Figure 1). Participants` mean age was 71.7 ± 4.7 years, and ranged from 65 to 82 years. Sixty-eight participants (65.4%) were women. Fifteen of these 104 participants (14.4%) met the Short CAM criteria for delirium at least once during three postoperative days.

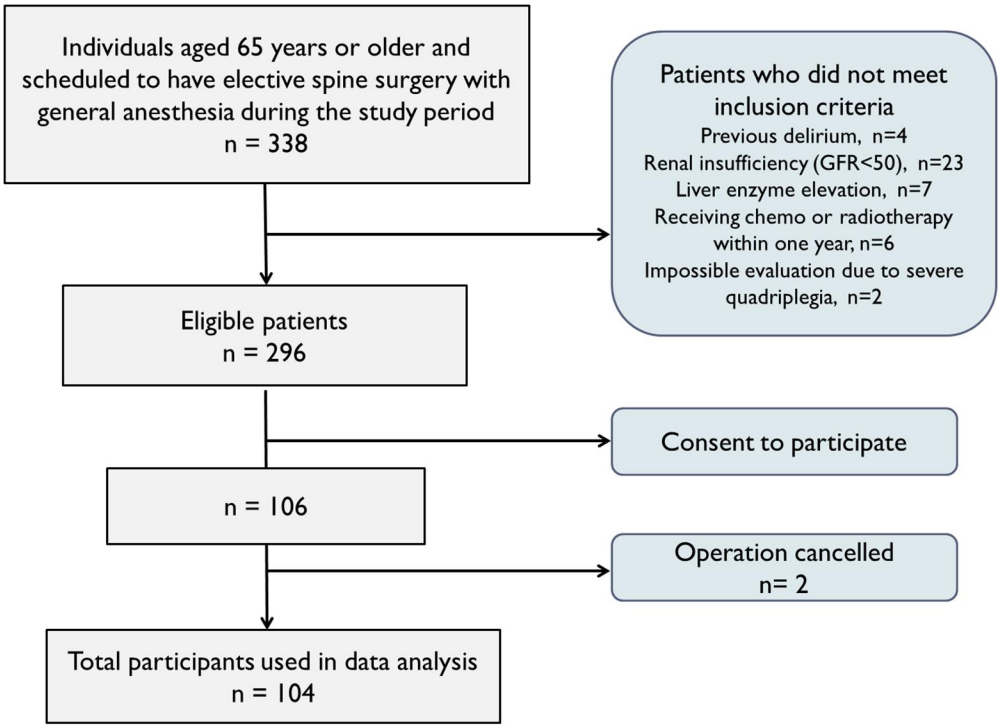

Figure 1. Patient enrollment. 104 participants of 296 eligible patients were included in the study analysis.

B. Baseline clinical characteristics

As noted above, 15 participants (14.4%) met the Short CAM criteria for delirium at least once during three postoperative days. Those with postoperative delirium were more likely to be men. There were no statistically significant differences between the with-delirium and without-delirium groups for any of the other baseline characteristics or preoperative laboratory findings. The baseline clinical characteristics and preoperative laboratory findings are summarized in Table 1.

Table 1. Participants' baseline characteristics and pre-operation laboratory findings

	Total	Postoperative delirium		p-value
		Yes	No	
	(n=104)	(n=15)	(n=89)	
Age (years), mean ± SD	71.7±4.7	73.2±4.7	71.5±4.6	0.185a
Male	36 (34.6)	9 (60.0)	27 (30.3)	0.039d
Education (years)	7.5 [6-12]	6 [6-12]	8 [6-12]	0.817b
Hypertension	67 (64.4)	10 (66.7)	57 (64.0)	0.844c
Diabetes mellitus	24 (23.1)	5 (33.3)	19 (21.3)	0.308c
Psychiatric disorder	13 (12.5)	3 (20.0)	10 (11.2)	0.395d
Previous diagnosis of dementia or MCI	9 (8.7)	3 (20.0)	6 (6.7)	0.12d
old CVA or TIA history	8 (7.7)	3 (20.0)	5 (5.6)	0.088d
Cardiovascular comorbidity	23 (22.1)	5 (33.3)	18 (20.2)	0.258c
Number of drugs before operation	5 [3-7]	5 [2-7]	5[3-7]	0.755b
Statin	50 (48.1)	6 (40.0)	44 (49.4)	0.499c
ARB	39 (37.5)	5 (33.3)	34 (38.2)	0.719c
Anti-thrombotics	30 (28.8)	5 (33.3)	25 (28.1)	0.678c
Psychoactive drugs*	33 (31.7)	6 (40.0)	27 (30.3)	0.457c
Preoperative laboratory findings				
Albumine (g/dL)	4.12 ± 0.33	4.07 ± 0.30	4.12 ± 0.33	0.595a
BUN (mg/dL)	16.9 ± 4.96	15.7 ± 4.50	17.1 ± 5.03	0.331a
Creatinine (mg/dL)	0.77 ± 0.20	0.81 ± 0.19	0.76 ± 0.20	0.343a
Hemoglobin (g/dL)	13.6 ± 1.38	13.5 ± 1.25	13.6 ± 1.40	0.809a
WBC (10^3/μL)	7.064 ± 1.71	6.834 ± 1.15	7.103 ± 1.79	0.452a
Platelet (10^3/μL)	232 ± 57.1	230 ± 47.7	233 ± 58.8	0.84a

Abbreviations: SD, standard deviation; MCI, mild cognitive impairment; CVA, cerebrovascular accident; TIA, transient ischemic attack; ARB, angiotensin II receptor blocker.
Data are expressed as the median [interquartile range] or number (%).
a T-test with equal variance / b Mann-whitney test / c Chi-square test / d Fisher exact test
*Psychoactive drugs included prescribed anti-psychotics, sedative hypnotics, benzodiazepins, opioids, anti-histamine or anti-cholinergic agent and dopanergic substances.[9]

C. Baseline cognitive evaluation and peri-operative factors

As shown in Table 2a, baseline MMSE scores before operation were significantly lower in the postoperative delirium group (p = 0.023). There was no other significant difference between the two groups for the other peri-operative factors. Further, neither surgical lesion nor operation method differed between the two groups. Table 2b summarizes the operation method.

Table 2a. Baseline cognitive evaluation and peri-operative covariates

	Total	Postoperative delirium		p-value*
		Yes	No	
	(n=104)	(n=15)	(n=89)	
MMSE score (0-30)	27 [25-28]	25 [23-27]	27 [25-29]	0.023b
Surgical lesion (cervical)	19 (18.3)	2 (13.3)	17 (19.1)	0.733d
Surgical method				0.729d
Spinal fusion	77 (74.0)	12 (80.0)	65 (73.0)	
Decompression	22 (21.2)	2 (13.3)	20 (22.5)	
Admission to ICU	13 (12.5)	3 (20.0)	10 (11.2)	0.395d
Blood loss during operation (cc)	350 [200-937]	250 [100-800]	400 [200-975]	0.127b
Operation time (min)	183 [142-234]	157 [120-202]	184 [142-239]	0.197b
Presence of postoperative fever (>37.8)	50 (48.1)	7 (46.7)	43 (48.3)	0.906c

Abbreviations: ICU, intensive care unit

Data are expressed as mean ± SD or the median [interquartile range] or number (%).

a T-test with equal variance / b Mann-whitney test / c Chi-square test / d Fisher exact test

Table 2b. Operation method

Type of operation	Total (n=104)
Cervical spinal fusion	13 (12.5%)
Lumbar spinal fusion	64 (61.5%)
Cervical decompression	4 (3.8%)
Lumbar decompression	18 (17.3%)
Removal of spinal tumor	5 (4.8%)

2. Comparison of Parkinson's disease-related NMSs

We collected results for all participants for the eight PD-related NMSs, except the BDI score. Four participants refused to answer the BDI questionnaire; results were available for 100 participants. CCSIT and RBDSQ-K scores were significantly different between the 2 groups (p<0.001 and p<0.001, respectively), while other variables such as ESS, ISI, CSS, OHQ, and BDI scores were similar. PAS total score were higher for the postoperative delirium group, this result was not statistically significant (p=0.057) (Table 3a). Further, hyposmia and RBD, which were determined by CCSIT and RBDSQ-K scores, were significantly associated with postoperative delirium (p<0.001 and p<0.001, respectively). The Prodromal symptoms scores, which are the sum of positive findings on each of the PD-related NMSs, were significantly higher in the postoperative delirium group (p=0.002; Mann-Whitney test) (Table 3b). The Receiver operating characteristic (ROC) curve for predicting postoperative delirium from prodromal symptoms score is provided on Figure 2. The area under the ROC curve (AUC) ± standard error was 0.751 ± 0.059 (p=0.002), indicating fair accuracy. Optimal cut-off value of prodromal symptoms score was 1.5 from the ROC curve. The sensitivity and specificity for predicting postoperative delirium at this score were 86.7, and 52.8% respectively. When 2 point on prodromal symptoms score was used as a cut-off value, a statistically significantly greater proportion of participants with postoperative delirium were included in the group with higher prodromal symptoms scores (odds ratio 7.27) (Table 3b).

Table 3a. Comparison of Parkinson's disease-related non-motor symptoms (NMSs) between subjects with and without post-operative delirium measured by raw scores of each test or questionnaire

	Postoperative delirium		
	Yes	No	p-value
Test or questionnaire	(n=15)	(n=89)	
CCSIT score	6.5 [4-8.25]	9 [8-11]	<0.001
ESS score	2.5 [2-4.5]	3 [2-3.25]	0.596
ISI score	0 [0-8]	0 [0-9.5]	0.798
RBDSQ-K score	1.5 [0-5.5]	0 [0-8]	<0.001
CSS score	0 [0-7.25]	0 [0-0]	0.207
PAS total score	8.5 [0-11.5]	0 [0-9]	0.057
OHQ total score	0 [0-0]	0 [0-0.25]	0.390
OH by 2-positional BP test	1 (6.7)	14 (16.1)	0.685
BDI score	17 [10-28]	11.5 [9-18]	0.159

Abbreviations: CCSIT, Cross-Cultural Smell Identification Test; ESS, Epworth Sleepiness Scale; ISI, Insomnia Severity Scale; RBDSQ-K, Korean version of RBD screening questionnaire; CSS, Constipation Scoring system; PAS, Parkinson Anxiety Scale; OHQ, Orthostatic Hypotension Questionnaire; OH, Orthostatic Hypotension; BDI, Beck Depression Inventory

Data are expressed as the median [interquartile range] or number (%).

Table 3b. Comparison of Parkinson's disease-related NMSs between subjects with and without post-operative delirium measured by each instrument

Test	Postoperative delirium		p-value	Odds ratio (95% CI)
	Yes (n=15)	No (n=89)		
Hyposmia (CCSIT score< 9)	12 (80.0)	30 (33.7)	<0.001	7.87 (2.06, 30.02)
Daytime sleepiness (ESS >10)	1 (6.7)	2 (2.2)	0.376	
Insomnia (ISI >7)	5 (33.3)	22 (24.7)	0.481	
RBD (RBDSQ-K >4)	6 (40.0)	2 (2.2)	<0.001	29.00 (5.08, 165.43)
Constipation	3 (15.8)	16 (18.0)	1.000	
Any anxiety disorder	6 (40.0)	21 (23.6)	0.180	
Orthostatic hypotension	2 (13.3)	19 (21.3)	0.730	
Depression (BDI > 16)	7 (50.0)	27 (31.4)	0.173	
Prodromal symptoms score	3 [2-4]	1 [0.5-2]	0.002	
≥ 2	13 (86.7)	42 (47.2)	0.005	7.27 (1.55, 34.13)

Data are expressed as the median [interquartile range] or number (%).

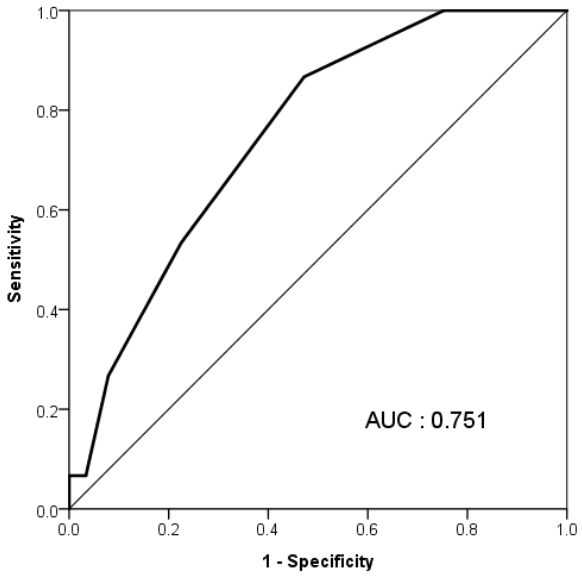

Figure 2 Receiver operating characteristic (ROC) curve for predicting postoperative delirium from prodromal symptoms score

The area under the ROC curve (AUC) ± standard error was 0.751 ± 0.059 (p=0.002).

3. Univariate and multivariate logistic regression analyses for predicting postoperative delirium

When we analyze various confounding factors affecting delirium using univariate logistic regression, postoperative delirium occurred more frequently occurred in male sex and those with high prodromal symptoms scores (≥2). In multivariate analyses using variables with *p*-value <0.1 in the univariate analyses, male sex, low MMSE score, and high prodromal symptoms score (≥2) (odds ratio [OR] 7.34, confidence interval 1.46-36.86, *p*=0.016) were independently associated with postoperative delirium. Elderly patients with high prodromal symptoms score had a greater possibility of postoperative delirium after spinal surgery.

We conducted multivariate analyses for each PD-related NMS with other predisposing covariates that had p-value <0.1 in the univariate analyses except prodromal symptoms score. Multivariate logistic regression demonstrated that RBD (OR=20.36), hyposmia (OR=5.28), and depression (OR=4.74) were independent risk factors for post-operative delirium. The results of logistic regression analyses are summarized in Tables 4a and 4b.

Table 4a. Univariate and multivariate logistic analyses for predicting postoperative delirium using prodromal symptoms score

	Univariate		Multivariate*	
	OR (95% CI)	p value	OR (95% CI)	p value
Age	1.08 (0.96-1.22)	0.187		
Male	3.44 (1.12-10.64)	0.032	4.76 (1.27-17.80)	0.020
Hypertension	1.12 (0.35-3.57)	0.845		
Diabetes mellitus	1.84 (0.56-6.04)	0.313		
Cardiovascular comorbidity	1.97 (0.60-6.49)	0.264		
Psychiatric disease	1.98 (0.48-8.22)	0.35		
Previous dementia or MCI	3.46 (0.76-15.69)	0.108		
Previous old CVA or TIA	4.20 (0.89-19.87)	0.07	2.54 (0.40-15.95)	0.320
MMSE score	0.85 (0.71-1.03)	0.094	0.77 (0.61-0.99)	0.041
admission to ICU	1.98 (0.48-8.22)	0.35		
Blood loss during operation (cc)	0.999 (0.998-1.001)	0.234		
Operation time (min)	0.994 (0.986-1.002)	0.154		
Prodromal symptoms score ≥2	7.27 (1.55-34.13)	0.012	7.34 (1.46-36.86)	0.016

Abbreviations: OR, odds ratio; CI, confidence interval

*Variables (Sex, Previous old CVA or TIA, MMSE score, Prodromal symptoms score≥2), which showed P<0.1 in the univariate analysis, were included in the multivariate analysis.

Table 4b. Multivariate logistic analysis for predicting postoperative delirium using each Parkinson's disease-related NMS

	Univariate		Multivariate*	
Parkinson`s disease-related NMS	OR (95% CI)	p value	OR (95% CI)	p value
Hyposmia	7.87 (2.06-30.02)	0.003	5.28 (1.29-21.57)	0.021
Daytime sleepiness	3.11 (0.26-36.58)	0.368		
Insomnia	1.52 (0.47-4.94)	0.484		
RBD	29.00 (5.08-165.43)	<0.001	20.36 (3.16-130.97)	0.002
Constipation	1.14 (0.29-4.52)	0.851		
Anxiety disorder	2.16 (0.69-6.77)	0.187	2.44 (0.69-8.56)	0.165
Orthostatic hypotension	0.57 (0.12-2.73)	0.479		
Depression	2.19 (0.70-6.85)	0.18	4.74 (1.20-18.78)	0.027

Abbreviations: OR, odds ratio; CI, confidence interval

*Variables (Hyposmia, RBD, Anxiety disorder, Depression), which showed P<0.2 in the univariate analyses, were taken into the multivariate analyses. About each NMS, multivariate analyses were separately performed with sex, Previous old CVA or TIA, and MMSE score, which previously showed P<0.1 in the univariate analyses (Table 4a).

IV. DISCUSSION

To our knowledge, this is the first reported prospective study to analysis the correlation between PD-related NMSs and postoperative delirium. The incidence of postoperative delirium in this study is 14.4%, which is similar to earlier studies of patients undergoing spinal surgery.[6, 7] We found that hyposmia, RBD, and depression are independent risk factors for developing postoperative delirium, even after adjusting for other risk factors (Odds ratio 5.28; 20.36; 4.74 respectively). Our results suggest that RBD is the most powerful risk factor for postoperative delirium of the eight PD-related NMSs that we investigated. The prodromal symptoms score, the number of PD-related NMSs, is also higher in patients with postoperative delirium. Although a simple sum of NMSs cannot represent directly the burden of alpha synucleinopathy, this result supports the hypothesis that preexisting PD-related NMSs may contribute to the development of postoperative delirium. The preexisting PD-related NMSs suggest an underlying pathology that may also predispose the patient to postoperative delirium.

Previous studies about postoperative delirium report many predisposing and precipitating factors.[9] In our study, among the baseline characteristics and perioperative factors, sex and MMSE scores were significantly different between the with-delirium and without-delirium groups (p=0.039, p=0.023, respectively). Cognitive impairment and low MMSE scores are well known as predisposing factors for postoperative delirium, and this is supported by our results.[38] Further, this study suggests that men are at higher risk of postoperative delirium after spinal surgery. Several studies suggest that sex differences affect the likelihood of developing postoperative delirium, although there are many conflicting views.[39, 40] These differences are hypothesized as resulting from differences between the immune systems of males and females,[41] and this hypothesis may explain our results.

However, age, medical comorbidities, number of drugs before operation, and psychotropic drug use, which are well-known predisposing factors,[9] did not differ significantly between the two groups. The proportion of patients having preoperative old CVA or TIA was higher for those with postoperative delirium than those without, although this trend was not statistically significant (p = 0.088). These statistical uncertainties may be explained by the relatively small number of participants (n=104). An earlier analysis of a large retrospective database (n=578457), lumbar fusion was associated with a greater risk of postoperative delirium than lumbar decompression,[5] but our results did not show an association between surgical method and postoperative delirium.

We classified the eight (7.7%) participants in the study who obtained a score of 5 or higher for the RBDSQ-K as exhibiting RBD. There may be an argument that this is a greater rate than previous studies of the general population.[42, 43] However, these studies have some limitations. One study by Ohayon did not perform PSG, and another study by Chiu may have underestimated RBD prevalence by using a screening question about the presence of sleep-related injuries. A recent study of the Korean elderly population aged 60 years or above has suggested that the prevalence of RBD and subclinical RBD confirmed by PSG is approximately 2% and 5% respectively.[44] This is similar to our results, once subclinical RBD is included. Therefore, the proportion of RBD patients assessed by RBDSQ-K in our study was reasonable.

Earlier studies have identified depression was as a risk factor for postoperative delirium, and our study supports this finding.[10,44] The adjusted OR for depressive symptoms among postoperative delirium patients in comparison with the control group is 4.74. The production of small messenger molecules or pro-inflammatory cytokines from psychological stress may depress the immune system, which could make depressive patients vulnerable to postoperative delirium.[45] Several studies have demonstrated that depression is associated with longer duration of delirium

and incomplete recovery to independent daily life. However, we were unable to measure delirium duration and clinical long-term outcomes. We employed the Beck Depression Inventory (BDI), a widely used and verified instrument, to assess depressive symptoms. The questionnaire can be completed in approximately 5 minutes. Therefore, a preoperative evaluation of depressive symptoms using BDI may be helpful in predicting postoperative delirium.

Hyposmia, as measured by CCSIT, is also associated with postoperative delirium. Olfactory dysfunction precedes motor symptoms by several years, and affects up to 90% of PD patients over time; it is considered a preclinical marker of PD.[13] Given the association between hyposmia and postoperative delirium, we may hypothesize that postoperative delirium is the preclinical stage of alpha synucleinopathy such as PD. A recent study has shown that preexisting decreased olfactory function is associated with postoperative delirium in cardiac surgery.[46] Because associations between olfactory dysfunction and preclinical neurodegenerative disease such as PD have already been demonstrated, this may explain the vulnerability of patients with olfactory dysfunction to postoperative delirium.[47]

Our multivariate logistic regression demonstrates that RBD (OR = 20.36) is the most powerful risk factor for postoperative delirium of those we investigated. However, there has been little investigation of associations between RBD and postoperative delirium in the past. Most idiopathic RBD patients in previous cohort studies developed disorders such as PD and DLB over decades.[26, 48] Further, postmortem pathologies in idiopathic RBD patients have identified widespread Lewy bodies pathology.[48] This suggests that RBD may be the prodromal stage of neurodegenerative disease, especially Lewy body disorder. Delirium is a series of cognitive disorders and shares many clinical features with Lewy body disorder. Therefore, these three PD-related NMSs may play an important role in predicting postoperative delirium as well as acting as clinical markers for Lewy body diseases.

We defined the prodromal symptoms score as the sum of the positive findings for

the eight selected PD-related NMSs (range 0-8). We classified the results into two groups by the cutoff value from ROC curve: low (0-1) and high (≥ 2) prodromal symptoms score. If the number of PD-related NMSs represents the burden of alpha synuclein deposit, we are able to analysis the association between the burden of alpha synuclein deposit and postoperative delirium by using prodromal symptom scores. The evidence of prodromal NMSs in PD is based on extranigral alpha-synuclein deposition patterns, suggested by Braak et al.[18] The olfactory bulb and lower brain stem involvement before substantia nigra pars compacta may explain NMS. Further, an earlier study that uses the NMSQuest questionnaire[17] showed that the number of NMSs correlates with disease duration and severity in PD. Thus, in pathological and clinical aspects, NMSs may be useful clinical markers for detecting alpha synucleinopathy and the combination of NMSs may open the possibility of predicting PD in the future.[49, 50] Therefore, we assume that the number of NMSs may reflect the burden of alpha synuclein deposit. In our study, the prodromal symptoms scores are significantly higher in the postoperative delirium group (p=0.002). High prodromal symptoms score (≥2) correlates significantly with higher risk of postoperative delirium in the multivariate regression analyses; OR = 7.34 for high prodromal symptoms score compared with low score. These results suggest that the burden of alpha synuclein deposit correlates with a greater risk of postoperative delirium. With further investigation, the prodromal symptoms scores may be useful as predictive factors for postoperative delirium. In a planned and non-emergency surgical procedure, screening NMSs using this score may assist surgeons in making a decision about undertaking surgery.

Of course, using non-motor features to assume alpha synuclein deposit has several limitations. First, many non-motor features in elderly patients have low sensitivity or specificity for predicting alpha synuclein deposit. The frequency of constipation, hyposmia, orthostatic symptoms, depression, and anxiety tend to be greater than 10% in the elderly population in general.[16] On the other hand, some NMSs such as RBD have low prevalence in the general population, and this makes it difficult to use

these NMSs as predictive factors due to their low sensitivity. Thus, a simple sum of these non-motor features cannot predict exactly the presence of alpha synucleinopathy in the general population.[51] Second, other Lewy body diseases in addition to PD require more evidence than exists at present to prove the correlation between non-motor features and the subsequent development of the disease.[52]
However, direct measurement of alpha synuclein deposit is currently not easy for the general population. Other alpha synuclein markers such as lower cerebrospinal fluid alpha synuclein level or alpha synuclein Positron emission tomography (PET) scan are difficult to use for the general population due to low accessibility. Therefore, we used these non-motor features as an indirect method of measuring the burden of alpha synuclein.

This study used individual tests or questionnaires, which are applicable to general population, to evaluate each non-motor symptom. The Nonmotor Symptom Questionnaire (NMS Quest) for evaluating the frequency and severity of these symptoms in people with PD has been developed and validated.[16, 17, 53] NMS Quest is a 30-item self-administered questionnaire that is useful as a screening tool to detect non-motor features of PD. However, this questionnaire has been validated for people with PD and not for general population, so it may be difficult to apply this questionnaire to the general population. We chose widely used instruments for measuring non-motor features as much as possible and analyzed the associations between each non-motor symptom and postoperative delirium separately. This study concerned patients undergoing elective spinal surgery, rather than other major operations such as cardiac surgery. By selecting spinal surgery and excluding preoperative metabolic derangement, this study tried to focus purely on PD-related NMSs and postoperative delirium.

The major finding of our study is the significant correlation between PD-related NMSs and postoperative delirium. Among PD-related NMS, RBD, hyposmia, and

depression were independent risk factors for predicting postoperative delirium, and RBD was the strongest predictive factor. And, our results show that high prodromal symptoms score, which may reflect the burden of alpha synuclein deposit, correlates with a higher risk of postoperative delirium. These findings suggest that postoperative delirium may be a preclinical stage of alpha synucleinopathy. Postoperative delirium is independently associated with increased mortality, length of hospital stay, and surgical outcomes.[54] Due to the difficulty of treatment, prediction of postoperative delirium is more important. In combination with other predictive factors, these PD-related NMSs may be useful as screening tools for predicting postoperative delirium.

Our study has several limitations. First, not all eligible patients agreed to take part in this study: only one third of all eligible patients were enrolled. Evaluating PD-related NMSs took more an hour, and it was clear that participation in this study distressed participants to some degree. Therefore, it is possible that the eligible patients who declined to participate may have had a greater burden of alpha synuclein deposit. Second, the number of participants is too small to come to more definite conclusions. In this study, several well-known predisposing factors for postoperative delirium did not produce statistically significant results due to the limited number of participants. A larger sample is needed to solidify the correlations between non-motor features and postoperative delirium. Third, we used indirect questionnaires to measure non-motor features rather than specific diagnostic methods. NMS assessments using these questionnaires are dependent on subjects' recall, which may be affected by cognitive function or reporting bias. Fourth, the baseline evaluating of NMSs was performed once only the one day before the operation. NMSs that are assessed by questionnaires or tests may change over time. If NMSs are evaluated repetitively, more exact and reliable results may be obtained. Uneasiness before the operation may influence some non-motor features such as anxiety or insomnia.

V. CONCLUSION

In conclusion, our study demonstrated the association between preoperative PD-related NMS and postoperative delirium in elderly patients who underwent spine surgery with general anesthesia. Among PD-related NMSs, RBD, hyposmia, and depression were independent risk factors for predicting postoperative delirium, and RBD was the strongest predictive factor. Furthermore, we found that number of NMS, which may represent burden of alpha synuclein deposit, correlated with higher risk of postoperative delirium. These findings suggest that postoperative delirium would be a preclinical stage of alpha synucleinopathy, and utilization of NMS as predictive factors could improve predictability of postoperative delirium.

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ABSTRACT(IN KOREAN)

척추수술 환자에서 파킨슨병의 비운동증상과 수술 후 섬망발생과의 연관성 연구

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목적: 섬망은 주의력 손상 및 증상의 변동을 특징으로 하는 급성 혼동 상태를 말하며, 특히 수술 후 섬망은 수술의 불량한 예후와 긴 재원 기간과 직접적인 연관이 있는 흔한 수술 후 합병증이다. 수술 후 섬망의 임상양상은 파킨슨병 치매와 루이소체 치매로 대표되는 알파 시뉴클레인 (alpha synuclein) 연관 인지 장애와 비슷하다. 그리고, 최근 연구에서 기저의 알파 시뉴클레인 병리 소견이 수술 후 섬망과 연관성이 있음이 보고 되었다. 따라서 파킨슨병에서 보이는 비운동 증상이 수술 후 섬망 발생과 연관성이 있음을 가설로 세우고, 본 저자들은 65세 이상 고령의 척추 수술 환자에서 파킨슨병의 비운동 증상과 수술 후 섬망 증상과의 연관성을 알아보고자 하였다.

방법: 본 연구는 기대 관찰 연구로 10개월 (2015년 9월-2016년 7월)동안 세브란스병원 신경외과에서 예정된 65세이상의 척추 수술 환자를 대상으로 하였다. 이전 또는 현재 섬망증상이 있거나, 1년이내에 종양으로 항암, 방사선 치료를 받았거나, 신장 및 간 기능 장애를 보이는 경우는 대상 환자에서 제외하였다. 해당 기간에 총 338명의 대상 환자 중, 등록 기준을 만족시키고 연구 참여에 동의한 환자는 106명이었으며, 이 중 2명의 환자는 예정된 수술을 거부하여 총 104명의 환자를 대상으로 분석을 진행하였다. 파킨슨병의 비운동 증상은 수술 전일 평가하였으며, 비교적 쉽게

접근할 수 있는 8가지 비운동 증상인 후각 저하, 변비, 기립성 저혈압, 불면증, 주간 과다 졸음, 급속 눈운동 수면 행동 장애, 우울증, 불안 장애를 평가하였다. 또한, 8가지 비운동 증상 중 양성 소견을 보이는 항목을 합하여 전조 증상 점수(Prodromal symptoms score)를 새롭게 설정하였으며, 이 점수를 통해 수술 후 섬망을 예측할 수 있는지 알아보았다. 섬망의 평가는 “의식장애 평가법 (short version of the Confusion Assessment Method)”을 사용하였으며, 수술 후 1~3일 째 오전 9시에서 12시 사이에 평가하였다.

결과: 총 104명의 대상자 중 15명 (14.4%)에서 수술 후 섬망이 진단되었다. 남성과 수술 전 낮은 간이정신상태검사 (Mini-mental state examination)가 수술 후 섬망과 유의미하게 연관성을 보였다. 수술 전 평가한 비운동 증상 중에서는 후각 저하 (p=0.021), 우울증 (p=0.027), 급속 눈운동 수면 행동 장애 (p=0.002)가 수술 후 섬망의 독립적인 예측 변수였다. 이 중 급속 눈운동 수면 행동 장애가 가장 강력한 예측인자로 대조군에 비해 20.36배 (95% CI, 3.16-130.97) 높은 수술 후 섬망 증상을 보였다. 또한, 높은 전조 증상 점수 (Prodromal symptoms score)도 수술 후 섬망 발생과 유의미한 연관성을 보였다.

결론: 이 연구에서 저자들은 파킨슨병의 비운동 증상 중 급속 눈운동 수면 행동 장애, 후각 저하 및 우울증이 수술 후 섬망의 독립적인 예측 인자 임을 입증하였다. 그리고 알파 시뉴클레인 (alpha synuclein)의 침착을 반영할 수 있는 비운동 증상의 합도 수술 후 섬망과 연관이 있음을 증명하였다. 본 연구를 통해 수술 후 섬망이 알파 시뉴클레이노증 (alpha synucleinopathy)의 임상전 단계일 수 있으며, 파킨슨병의 비운동 증상이 수술 후 섬망을 예측할 수 있는 인자임을 알 수 있다.

핵심되는 말: 수술 후 섬망, 파킨슨병의 비운동 증상, 알파 시뉴클레이노증 (alpha synucleinopathy)