Quality of life in patients with an idiopathic rapid eye movement sleep behaviour disorder in Korea

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SUMMARY

There have been few quality of life studies in patients with idiopathic rapid eye movement sleep behaviour disorder. We compared the quality of life in idiopathic rapid eye movement sleep behaviour disorder patients to healthy controls, patients with hypertension, type 2 diabetes mellitus without complication and idiopathic restless legs syndrome. Sixty patients with idiopathic rapid eye movement sleep behaviour disorder (24 female; mean age: 61.43 ± 8.99) were enrolled retrospectively. The diagnosis was established based on sleep history, overnight polysomnography, neurological examination and Mini-Mental State Examination to exclude secondary rapid eye movement sleep behavior disorder. All subjects completed questionnaires, including the Short Form 36-item Health Survey for quality of life. The total quality of life score in idiopathic rapid eye movement sleep behaviour disorder (70.63 ± 20.83) was lower than in the healthy control group (83.38 ± 7.96) but higher than in the hypertension (60.55 ± 24.82), diabetes mellitus (62.42 ± 19.37) and restless legs syndrome (61.77 ± 19.25) groups. The total score of idiopathic rapid eye movement sleep behaviour disorder patients had a negative correlation with the Pittsburg Sleep Quality Index ($r = -0.498$, $P < 0.001$), Insomnia Severity Index ($r = -0.645$, $P < 0.001$) and the Beck Depression Inventory-2 ($r = -0.694$, $P < 0.001$). Multiple regression showed a negative correlation between the Short Form 36-item Health Survey score and the Insomnia Severity Index ($\beta = -1.100$, $P = 0.001$) and Beck Depression Inventory-2 ($\beta = -1.038$, $P < 0.001$). idiopathic rapid eye movement sleep behaviour disorder had a significant negative impact on quality of life, although this effect was less than that of other chronic disorders. This negative effect might be related to a depressive mood associated with the disease.

INTRODUCTION

Rapid eye movement (REM) sleep behaviour disorder (RBD) is a type of parasomnia characterized by dream-enacting and prominent motor activity during REM sleep (Schenck *et al.*, 1986). In addition, as an alpha-synucleinopathy, its association with neurodegenerative diseases including Parkinson's disease (PD), multiple systemic atrophy and dementia with Lewy bodies have been studied (Boeve *et al.*, 2007; Iranzo *et al.*, 2009). Large clinical series have reported that the idiopathic form of RBD (iRBD) accounts for up to 60% of the cases, although some of these patients may eventually develop a degenerative disorder in the long term (Fantini *et al.*, 2005). RBD *per se* can lead to sleep disturbance or physical injury to the patient or bed partner. As a result, it may impact the patient's quality of life (QOL) negatively. There have been few studies on the association between RBD and QOL, in particular for patients with iRBD. In a study evaluating 36 PD patients for the presence of RBD (Postuma *et al.*, 2008), emotional functioning and general health QOL measured by the Parkinson Disease Questionnaire-39 (PDQ-39) and the Short Form-36 health survey (SF-36) were lower in those with RBD, but there were no differences in overall physical QOL. In a study of probable RBD in 93 PD patients (Suzuki *et al.*, 2013) evaluated with the PDQ-39, cognition and emotional wellbeing had a significant impact on QOL. In

a study of probable RBD in 475 patients with PD using the EuroQol five dimensions questionnaire (EQ-5D) questionnaire (Rolinski *et al*., 2014), probable RBD was shown to be associated with greater sleepiness, depression and cognitive impairment. Additionally, patients with concomitant probable RBD more often reported a lower QOL. However, the available data pertain to patients with PD or subjects with a probable diagnosis of RBD based on a questionnaire. Thus, these studies have evaluated the impact of concomitant symptoms of Parkinsonism, rather than RBD *per se*, on QOL. As a result, the exact factors affecting QOL in iRBD remain debatable. In this study, we have investigated the QOL of patients with iRBD, as well as the factors that may influence it, compared to age- and gender-matched healthy controls (HC) and patients with other chronic medical conditions, such as hypertension (HTN) and type 2 diabetes mellitus without complication (DM).

METHODS

This study was approved by the institutional ethics committee as a retrospective study. We selected 116 adult patients with RBD who had presented to a tertiary care sleep centre in South Korea between April 2013 and July 2015. The diagnosis of RBD was based on history and an overnight polysomnography (PSG) following the guidelines of the Third International Classification of Sleep Disorders (American Academy of Sleep Medicine, 2014): (a) repeated episodes of sleep-related vocalization and/or complex motor behaviours; (b) these behaviours, documented by PSG, occur during REM sleep, or based on clinical history of dream enactment, are presumed to occur during REM sleep; (c) PSG recording demonstrates REM sleep without atonia; and (d) the disturbance is not explained more clearly by another sleep disorder, mental disorder, medication or substance use. Criteria (a) to (d) must be met.

Further studies were performed to differentiate secondary RBD from iRBD. To exclude secondary RBD, patients with the following conditions were excluded from the study: HTN, DM, stroke, dementia, psychiatric disorders including major depression, other clinical sleep disorders (e.g. primary insomnia, narcolepsy, restless legs syndrome, obstructive sleep apnea) and medications that might influence sleep and could not be withheld (e.g. benzodiazepines, anti-psychotics, alprazolam, clonazepam, quetiapine, tricyclic antidepressants, selective serotonin re-uptake inhibitors, serotonin–norepinephrine reuptake inhibitors). In addition, all patients underwent a baseline neurological examination and a Mini-Mental State Examination to exclude secondary RBD associated with neurodegenerative diseases. During the survey, trained research coordinators were available to help subjects having difficulty completing the questionnaires. We chose HTN and DM as common chronic medical diseases and restless legs syndrome (RLS) as a comparable sleep disorder for controls. Age- and gender-matched patients with HTN, RLS and DM were screened using face-to-face interviews along with their hospital charts. They were selected from the cardiology, endocrinology and sleep centre clinics at the same university hospital.

The measure of QOL was based on the Korean version of the SF-36 (Han *et al*., 2004), including eight domains: physical function, role limitations due to physical problems, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems and mental health. The score ranges from 0 to 100 points, with the higher score representing better QOL. The SF-36 is a widely used standardized tool to assess health-related QOL. As there is no questionnaire measuring RBD symptom severity, we used various questionnaires which can evaluate sleep and mood status. The patients completed all the Korean versions of the Pittsburg Sleep Quality Index (PSQI) (Sohn *et al*., 2012), Insomnia Severity Index (ISI) (Cho *et al*., 2014), Hospital Anxiety Scale (HAS) (Oh *et al*., 1999), Epworth Sleepiness Scale (ESS) (Cho *et al*., 2011), Beck Depression Inventory-2 (BDI-2) (Jo *et al*., 2007) and Hospital Depression Scale (HDS) (Oh *et al*., 1999). These results were compared to the scores from HC, patients with HTN, DM and idiopathic drug-naive RLS. The sleep- and mood-related questionnaires were not performed in the disease groups (HTN, DM). The HC were selected from individuals undergoing regular check-ups who were found to be healthy.

Statistical analysis

The analysis was performed using statistical software SPSS version 18.0 for Windows. The clinical characteristics and QOL were compared using the χ^2 test, independent *t*-test or analysis of variance (ANOVA). The parameters associated with QOL were analysed using Pearson's correlation. Stepwise multiple regression analysis was used to select the significant predictors for the QOL in the iRBD patients and, at each step, independent variables were entered if factors correlated significantly with QOL were present. Analysis of covariance (ANCOVA) was used for covariance for depression (BDI-2). The level of significance was $P \leq 0.05$ for all comparisons.

RESULTS

After careful screening of 116 PSG-confirmed RBD patients, a total of 56 patients were excluded, as nine were diagnosed with secondary RBD associated with neurodegenerative diseases (6 PD; 3 dementia), 17 with a comorbid sleep disorder (14 obstructive sleep apnea; one narcolepsy; two insomnia) and 36 with a comorbid medical disorder (20 HTN; 16 DM), and six were on medications that might influence sleep. Twelve had more than one exclusion criterion; eight obstructive sleep apnea and HTN, two obstructive sleep apnea and PD, one obstructive sleep apnea and DM and one obstructive sleep apnea, HTN and DM. We finally enrolled 60 (52.7%) confirmed iRBD patients, 36 of whom (60%) were male (mean age: 61.43 $\pm$ 8.99). Thirty-five (58.3%) iRBD patients were aware of their vigorous, violent and injurious

oneiric behaviour. The mean duration of the self-awareness was 4.53 ± 4.55 years, and the mean frequency of the oneiric behaviour was 3.62 ± 2.40 times per week. Twenty-eight (38.3%) patients experienced some form of injury during sleep. There were 240 controls, including 60 normal HC, 60 subjects with HTN, 60 subjects with DM and 60 subjects with idiopathic drug-naive RLS. The comparison of demographic characteristics between the HC and patients with other medical diseases is shown in Table 1. There were no significant differences in age, gender, body mass index, alcohol consumption or smoking between the groups. Depressive symptoms (13.78 ± 9.67), which were evaluated by BDI-2, were higher in the iRBD group than HC (8.22 ± 3.56), and showed a lower trend than those of the RLS group (17.52 ± 10.51). The onset age, frequency, sleep-related injury, self-awareness and duration of oneiric behaviours did not show any significant association with the total SF-36 score.

The QOL based on the total SF-36 score of each group was 70.63 ± 20.83 for iRBD, 83.38 ± 7.96 for HC, 60.55 ± 24.82 for HTN, 62.42 ± 19.37 for DM and 61.77 ± 19.25 for RLS. The total SF-36 score of iRBD patients was lower than that of the HC, but higher than those of HTN, DM and RLS. The iRBD group showed lower SF-36 scores than the HC in all domains except for social functioning. The iRBD patients had higher scores than those of RLS patients on the total SF-36, bodily pain, vitality, social functioning, mental health, physical component summary (PCS) and mental component summary (MCS), whereas they had lower scores on the ISI, ESS, PSQI, HAS and BDI-2. When we controlled for depressive mood in iRBD, RLS and HC, the total SF-36 score of iRBD patients was still lower than that of the HC, but it did not show a significant difference when compared to the RLS patients. The iRBD group had higher scores than those with HTN on the total SF-36, general health perceptions, vitality, social functioning, mental health, PCS and MCS. They also showed higher scores than DM patients on the total SF-36, general health perceptions, social functioning, mental health, and MCS (Table 2, Fig. 1).

The total SF-36 scores for iRBD patients showed a significant inverse correlation with the scores of the ISI ($r = -0.645$, $P < 0.001$), PSQI ($r = -0.498$, $P < 0.001$), HAS ($r = -0.497$, $P < 0.001$), HDS ($r = -0.435$, $P = 0.001$) and BDI-2 ($r = -0.694$, $P < 0.001$), as presented in Table 3. Multiple regression analysis showed that the total SF-36 score was correlated significantly with the ISI ($\beta = -1.100$, $P = 0.001$) and BDI-2 ($\beta = -1.038$, $P < 0.001$) (Table 4).

DISCUSSION

Studies in western countries have demonstrated the negative impact of RBD *per se* and its common co-existent disorders on QOL. However, these studies included patients with probable RBD and RBD associated with neurodegenerative diseases (Postuma *et al.*, 2008; Rolinski *et al.*, 2014; Suzuki *et al.*, 2013). We sought to investigate QOL in patients with idiopathic RBD and characterize any risk factors involved. Therefore, we recruited only iRBD patients with no neurodegenerative diseases or medications such as benzodiazepines, anti-psychotics or antidepressants involved. We also included PSG as an extra measure to confirm the diagnosis of RBD.

Based on the SF-36 scores reflecting QOL, iRBD has a negative impact on QOL. Although the results of this study

Table 1 Clinical and demographic characteristics of patients with iRBD, HC and other disease controls

	iRBD	*HTN*	*DM*	*RLS*	*HC*	P	*Post-hoc Scheffé*
Sample size	60	60	60	60	60		
Age (years)	61.43 ± 8.99	61.40 ± 13.09	60.03 ± 7.80	57.88 ± 8.06	58.68 ± 6.66	0.222	
Gender (M/F)	36/24	29/31	26/34	23/37	22/38	0.132	
(%)	60/40	48.3/51.7	43.3/56.7	38.3/61.7	36.7/63.3		
BMI	23.42 ± 2.63	23.87 ± 3.14	23.74 ± 2.40	22.90 ± 2.76	23.10 ± 2.43	0.211	
Smoking (%)	18 (30.0)	10 (16.7)	12 (20.0)	8 (17.8)	9 (15.8)	0.056	
Alcohol (%)	18 (38.3)	18 (30.0)	16 (26.7)	18 (30.0)	22 (36.7)	0.510	
Self-awareness (%)	35 (58.3%)						
Injury (%)	28 (38.3%)						
Duration (years)	4.53 ± 4.55						
Frequency (/week)	3.62 ± 2.40						
ISI	8.93 ± 6.92			15.77 ± 6.91	4.13 ± 3.10	<0.001	b > a > c
ESS	4.43 ± 2.58			7.12 ± 4.74	5.17 ± 3.35	<0.001	b > a, c
PSQI	7.55 ± 4.15			11.17 ± 4.75	4.03 ± 1.33	<0.001	b > a > c
HAS	4.95 ± 3.82			7.32 ± 4.31	3.35 ± 2.42	<0.001	b > a, c
HDS	7.50 ± 4.02			8.85 ± 4.31	5.60 ± 3.06	<0.001	a, b > c
BDI-2	13.78 ± 9.67			17.52 ± 10.51	8.22 ± 3.56	<0.001	a, b > c

iRBD, idiopathic rapid eye movement sleep disorder; HC, healthy controls; HTN, hypertension; DM, type 2 diabetes mellitus without complication; RLS, restless legs syndrome; M/F, male/female; BMI, body mass index; ISI, Insomnia Severity Index; ESS, Epworth Sleepiness Scale; PSQI, Pittsburg Sleep Quality Index; HAS, Hospital Anxiety Scale; HDS, Hospital Depression Scale; BDI-2, Beck Depression Inventory-2. a: iRBD; b: RLS; c: HC.

Table 2 Comparisons of the disease groups for total score and subdomains of the SF-36

		HC	*BDI-2 controlled*	*HTN*	*DM*	*RLS*	*BDI-2 controlled*
	iRBD	*iRBD versus HC* t (*P*)	*iRBD versus HC* F (*P*)	*iRBD versus HTN* t (*P*)	*iRBD versus DM* t (*P*)	*iRBD versus RLS* t (*P*)	*iRBD versus RLS* F (*P*)
Total	70.63 ± 20.83	83.38 ± 7.96 −4.430 (< 0.001)	4.237 (0.042)	60.55 ± 24.82 2.410 (0.018)	62.42 ± 19.37 2.238 (0.027)	61.77 ± 19.25 2.422 (0.017)	1.925 (0.168)
Physical function	75.25 ± 22.24	86.25 ± 12.71 −3.327 (0.001)	2.520 (0.115)	67.17 ± 31.28 1.632 (0.106)	75.08 ± 22.99 0.040 (0.968)	72.83 ± 25.35 0.555 (0.580)	0.084 (0.773)
Physical role	71.67 ± 36.67	97.50 ± 15.74 −5.014 (< 0.001)	9.931 (0.002)	59.58 ± 44.17 1.630 (0.106)	62.08 ± 41.55 1.339 (0.183)	65.42 ± 38.81 0.907 (0.366)	0.003 (0.955)
Body pain	72.88 ± 28.66	84.75 ± 15.39 −2.825 (0.006)	0.549 (0.460)	71.63 ± ±25.47 0.253 (0.801)	70.72 ± 23.56 0.452 (0.652)	52.57 ± 26.88 4.005 (< 0.001)	11.443 (0.001)
General health	57.38 ± 22.74	71.08 ± 10.99 −4.202 (< 0.001)	5.282 (0.023)	48.50 ± 22.96 2.129 (0.035)	42.78 ± 20.86 3.665 (< 0.001)	49.45 ± 21.32 1.972 (0.051)	0.995 (0.321)
Vitality	58.83 ± 18.85	68.33 ± 13.86 −3.145 (0.002)	2.564 (0.112)	47.50 ± 19.23 3.260 (0.001)	53.17 ± 17.83 1.692 (0.093)	50.58 ± 21.10 2.259 (0.026)	1.987 (0.161)
Social function	86.57 ± 20.67	86.40 ± 13.87 0.052 (0.959)	8.545 (0.004)	69.33 ± 25.73 4.045 (< 0.001)	73.48 ± 21.62 3.389 (0.001)	70.58 ± 25.79 3.747 (< 0.001)	9.525 (0.003)
Role emotion	71.67 ± 40.19	95.60 ± 11.31 −4.440 (< 0.001)	5.989 (0.016)	60.55 ± 45.74 1.414 (0.160)	61.67 ± 41.59 1.339 (0.183)	70.02 ± 38.70 0.229 (0.819)	1.019 (0.315)
Mental health	70.53 ± 19.93	77.33 ± 11.21 −2.304 (0.023)	0.005 (0.942)	59.60 ± 17.33 3.207 (0.002)	59.80 ± 15.58 3.287 (0.001)	62.13 ± 19.64 2.325 (0.022)	1.726 (0.192)
PCS	67.05 ± 21.01	81.35 ± 8.56 −4.883 (< 0.001)	7.592 (0.007)	58.68 ± 24.76 1.996 (0.048)	60.63 ± 20.62 1.688 (0.094)	58.12 ± 18.97 2.445 (0.016)	2.133 (0.147)
MCS	68.83 ± 19.91	79.70 ± 8.09 −3.916 (< 0.001)	2.008 (0.159)	57.11 ± 22.29 3.038 (0.003)	58.15 ± 18.09 3.076 (0.003)	60.52 ± 19.34 2.321 (0.022)	1.530 (0.219)

SF-36, Short Form-36 health survey; iRBD, idiopathic rapid eye movement sleep disorder; HTN, hypertension; DM, type 2 diabetes mellitus without complication; RLS, restless legs syndrome; PCS, physical component summary; MCS, mental component summary.

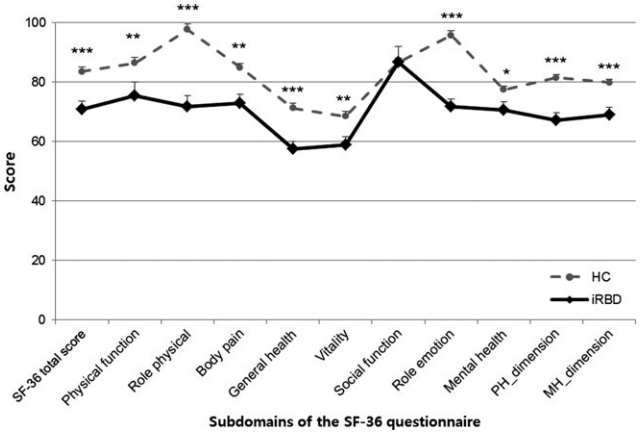

Figure 1. SF-36 scores for iRBD patients ($n = 60$) compared with HC ($n = 60$). SF-36, Short Form-36 health survey; iRBD, idiopathic rapid eye movement sleep disorder; HC, healthy controls. $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.

indicate a significantly lower QOL in iRBD patients than the HC, there was no significant influence on social functioning, which might lead the patients to dismiss their oneiric behaviour as neither serious nor medically important. When we controlled for depressive mood in iRBD, RLS and HC, the iRBD patients showed lower total SF-36 scores and higher social function scores than the HC. In contrast, the iRBD patients showed no difference compared to the RLS patients after controlling for depressive mood. Therefore, depressive mood seems to have a considerable effect on both the iRBD and RLS patients. The lower QOL in patients with iRBD could be caused by their awareness of the diagnosis, as they might search and learn about 'RBD' and feel depressed about the risk of neurodegenerative diseases in the future (Boeve, 2010). Nevertheless, in this study, as the subjects completed the series of questionnaires during the initial interview, the depressive mood seems to be an independent contributor to the QOL of iRBD patients.

Comparing the iRBD and RLS groups, our findings suggest less impact on QOL, sleep and mood in iRBD than RLS patients. Other studies have shown considerably lower QOL in RLS patients compared to those with HTN, DM or the HC (Cho *et al.*, 2012; Kushida *et al.*, 2007). As a sensory neurological disorder, RLS symptoms affect QOL due to uncomfortable feelings in the legs, sleep disturbance and social consequences, including work performance during daytime (Cho *et al.*, 2012). Also, an anxious or depressive mood is common in RLS (Kushida *et al.*, 2007). The lower QOL in RLS could be explained by higher scores in sleep and mood-related questionnaires, indicating lower sleep quality as well as a more anxious or depressive mood. Comparing

Table 3 Correlation analysis of total SF-36 scores in the iRBD group

	Age	*BMI*	*ISI*	*ESS*	*PSQI*	*HAS*	*HDS*	*BDI_2*
Variables				r*(P)*				
Total SF-36	−0.248 (0.056)	0.150 (0.260)	−0.645 (<0.001)	−0.088 (0.506)	−0.498 (<0.001)	−0.497 (<0.001)	−0.435 (0.001)	−0.694 (<0.001)

BMI, body mass index; ISI, Insomnia Severity Index; ESS, Epworth Sleepiness Scale; PSQI, Pittsburg Sleep Quality Index; HAS, Hospital Anxiety Scale; HDS, Hospital Depression Scale; BDI-2, Beck Depression Inventory-2.

Table 4 Multiple regression analysis of total SF-36 scores in the iRBD group

				95% Confidence interval	
Regression	β	*Standardized* β	*P-value*	*Low*	*Upper*
Constant	94.768		<0.001	88.155	101.381
ISI	−1.100	−0.366	0.001	−1.742	−0.457
BDI-2	−1.038	−0.482	<0.001	−1.498	−0.578

Adjusted $R^2 = 0.556$, S.E. = 13.88, $P < 0.001$, ISI, PSQI, HAS, HDS, BDI-2. SF-36, Short Form-36 health survey; BMI, body mass inde; ISI, Insomnia Severity Index; ESS, Epworth Sleepiness Scale; PSQI, Pittsburg Sleep Quality Index; HAS, Hospital Anxiety Scale; HDS, Hospital Depression Scale; BDI-2, Beck Depression Inventory-2.

the groups, we found less impact on QOL by iRBD than HTN and DM. Studies on QOL in patients with HTN or DM have attributed the lower QOL to the awareness of the diagnosis and the need for lifetime treatment (Korhonen *et al.*, 2011; Marrero *et al.*, 2014; Trevisol *et al.*, 2011; Venkataraman *et al.*, 2014).

The age of onset in iRBD varies widely from 40 to 70 years (61.43 ± 8.99 in our study), and the frequency varies from nightly to monthly (3.62 ± 2.40 times per a week in our study). In a previous study, 53.9% of patients with iRBD had self-awareness of the behaviour with a mean disease duration of 7.2 ± 7.2 years; 55.9% experienced sleep related self-injury and 23.5% hurt their spouses (Iranzo *et al.*, 2009). Another study demonstrated a diagnostic delay of 8.7 ± 11 years, often due to the belief that symptoms were not serious enough to seek medical attention (White *et al.*, 2012). Our findings confirm these reports, as RBD tends be regarded as insignificant despite its impact on QOL. In fact, despite our assumption that age of onset, frequency, sleep-related injury, self-awareness or disease duration may be associated with QOL, we did not find such an association. The possibility of depression and other conditions, such as insomnia being an early premotor symptom of iRBD, has been studied. A putative association between depression and iRBD has been suggested, i.e. depression possibly being an early sign of a neurodegenerative process (Aguirre-Mardones *et al.*, 2015; Frauscher *et al.*, 2014), but QOL was not evaluated in these studies. In our study, regression analysis showed that the BDI-2 and ISI were correlated with the SF-36. Although the depressive mood and insomnia were mild, they were also shown to be contributing factors to QOL in iRBD. As insomnia can be regarded as a comorbid symptom of depression, rather than iRBD, it is supposed that the QOL in RBD is related to a depressive mood, although the direction of causality is unclear. Recently, a study with transcranial sonography showed that hyperechogenicity of the substantia nigra and hypoechogenicity of the brain stem raphe nucleus are frequent in iRBD with depression, suggesting that dysfunction of the serotonergic system in the brain stem may explain the depression in iRBD (Vilas *et al.*, 2015). From this viewpoint, depression and insomnia in this study can be considered as early premotor symptoms of neurodegenerative disease. Thereby, QOL may be related to such symptoms of iRBD.

We identified a significant negative impact on QOL in iRBD, although it was less significant compared to other chronic disorders. This might be related to an associated depressive mood. It is interesting that, despite reasonable scores on the QOL questionnaire for mental health and role emotion subdomains, the BDI score was still high for iRBD patients. Therefore, given its potential effect on QOL, managing depression should be considered as part of treatment of iRBD.

To the best of our knowledge, this is the first study to investigate the QOL in iRBD using the SF-36. Secondly, in addition to careful neurological examination and history-taking by experienced neurologists, we recruited only PSG-confirmed iRBD patients, as using RBD screening questionnaires alone would have limited sensitivity and specificity. There are, however, limitations to our study; as recent studies have suggested, iRBD is linked to asymptomatic autonomic dysfunctions (Lee *et al.*, 2015; Postuma *et al.*, 2010) and 'asymptomatic' signs, i.e. those not recognized by patients, would hardly affect QOL. We did not assess depression and

insomnia in the HTN or DM control groups. The retrospective nature of this study, based in a single centre with possible selection bias, may be another limitation. Further prospective multi-centre studies using a disease-specified QOL assessment tool for RBD would be needed to address these limitations.

AUTHOR CONTRIBUTIONS

For contributions to the research project: conception, KTK and YWC; for organization, YWC; for execution, KTK and YWC. For statistical analysis, design and execution, review and critique, YWC; for execution, GKM. For manuscript preparation, writing the first draft and review and critique, KTK; for review and critique, GKM.

CONFLICT OF INTEREST

This is not an industry-supported study. The authors have no financial conflicts of interest.

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