Risk stratification for phenoconversion in patients with isolated REM sleep behavior disorder. A follow-up study from Turkey

Gulcin Benbir-Senel, Neris Albayrak, Irem Yanik, Elif Gokcen-Polat, Carlos H. Schenck, Derya Karadeniz

Introduction. Isolated rapid eye movement (REM) sleep behavior disorder (iRBD) is one of the strongest prodromal markers of alpha-synucleinopathies. We aimed to investigate non-invasive clinical and quantitative predictors of phenoconversion from iRBD to parkinsonism.

Patients and methods. We prospectively followed-up a total of 45 patients (57.8% men) for eight years. Clinical assessments, Sniffin' Sticks Odor Identification Test, Farnsworth-Munsell 100 Hue Color Vision test, Beck Depression Inventory and Rome III Criteria for constipation were performed. Polysomnographic parameters, sleep spindles, electroencephalographic (EEG) spectral analysis, heart rate variability (HRV) were analyzed.

Results. Eight patients (17.8%) showed phenoconversion to parkinsonism after a mean duration of 3.2 ± 1 years. *Odds ratio* for predicting phenoconversion was highest for patients ≥60 years of age with anosmia and constipation –44.8 (4.5-445.7); kappa = 4.291–. Duration, frequency or density of sleep spindles failed to demonstrate significant correlations. In EEG spectral analysis, lower alpha power in occipital region during wakefulness and REM sleep was significantly correlated with phenoconversion. Slowing in EEG spectrum power, together with age ≥60 years, anosmia and constipation, resulted in the highest *odds ratio* –122.5 (9.7-1543.8); kappa = 3.051–.

Conclusions. It is of great importance to have a world-wide perspective of phenoconversion rates from iRBD to overt neurodegeneration, since racial and geographical factors may play important modifying roles. Relatively younger age and shorter disease duration may also be confounding factors for lower rate in our study. Neurophysiological biomarkers seem to be important predictors of phenoconversion, though more research is needed to establish subtypes of iRBD with different probabilities of evolution to overt synucleinopathy.

Key words. Anosmia. Electroencephalography. Isolated REM sleep behavior disorder. Parkinsonism. Phenoconversion. Spectral analysis.

Introduction

Idiopathic Rapid eye movement sleep behavior disorder (iRBD) is a rapid eye movement sleep-related parasomnia characterized as abnormal, complex, often aggressive and violent, dream-acting behaviors associated with Rapid eye movement sleep without atonia [1]. It is now well-known that iRBD is a neurodegenerative condition constituting a specific prodromal feature of the alpha-synucleinopathies, such as Parkinson's disease and dementia with Lewy bodies [2,3]. REM sleep without overt rapid eye movement sleep behavior disorder was also shown to be associated with an increasing risk for the emergence of neurodegenerative disorders [4]. Along with the other early non-motor prodromal signs and symptoms, identification of patients with iRBD as prodromal neurodegeneration is of great importance as a biomarker for the conversion to alpha-synucleinopathies.

The predictive risk of hyposmia or anosmia for future phenoconversion was reported to have the second highest hazard ratio following iRBD, being higher than the other known non-motor markers [5]. In addition to olfactory dysfunction, abnormalities in color vision, dysautonomia such as constipation and erectile dysfunction, neuropsychiatric symptoms such as depression, and mild cognitive impairment were described as other relevant biomarkers reflecting the prodromal stage of nigrostriatal dopaminergic denervation [3,6]. Demonstration of pathological α-synuclein in skin, retina, cerebrospinal fluid, along with position emission tomography and single-photon emission computed

Sleep and Disorders Unit. Neurology Department. Medical School. Estanbul Üniversitesi-Cerrahpaşa (G. Benbir-Senel). Hospital Acıbadem in Taksim. Pathology Clinic. Istambul, Turkey (N. Albayrak, I. Yanik). Vivantes Kinikum im Friedrichshain. Cardiology Clinic. Berlin, Germany (N. Albayrak). Neurology Department. Medical School. Harvard University. Boston (E. Gokcen-Polat). Psychiatry Department. Medical School. University of Minnesota. (C.H. Schenck). Minnesota Regional Sleep Disorders Centre. Minneapolis, United States (D. Karandeniz).

Corresponding author:
Dr. Gulcin Benbir Senel. Sleep and Disorders Unit. Neurology Department. Medical School. Estanbul Üniversitesi-Cerrahpaşa. Cerrahpaşa Yerleşkesi Kocamustafapaşa Caddesi No:53. 34098 Istanbul, Turkey.

E-mail:
drgulcinbenbir@yahoo.com

ORCID:
0000-0003-4585-2840 (C.B.S.).

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tomography with ^{123}I-FP-CIT were found as more reliable prognostic markers for phenoconversion [7-11], but these are invasive methods, costly, and require special equipment and techniques. Last, but not least, the role of micro-RNAs in the pathogenesis of non-motor prodromal phase and early Parkinson's disease was introduced as potential non-invasive biomarkers [12].

iRBD is accepted as the most specific and strongest clinical predictive biomarker of alpha-synucleinopathies, as confirmed by the Movement Disorders Society research criteria for Prodromal Parkinson's disease [13]. On the other hand, a better risk stratification for phenoconversion may be aided by using clinical biomarkers besides iRBD alone. In addition to clinical assessments mentioned above, quantitative measurements were performed in iRBD patients demonstrating that electroencephalographic slowing, especially in posterior cortical regions, may reflect cortical dysfunction and increased risk for developing cognitive impairment, dementia with Lewy bodies and Parkinson's disease [14,15]. Alterations in autonomic nervous system shown by the heart rate variability analysis, may suggest cardiac autonomic dysfunction as a pre-motor sign of Parkinson's disease [16,17]. Based on these reported findings, we have conducted a longitudinal prospective study to investigate patients with iRBD for the presence of other non-motor prodromal features, and to build a prognostic model for non-invasive clinical and quantitative predictors of phenoconversion from iRBD to alpha-synucleinopathies.

Patients and methods

During one-year patient-enrollment period, all patients with iRBD were consecutively evaluated. Diagnosis of iRBD was made on the basis of the International Classification of Sleep Disorders 3, revised in 2014, for all patients enrolled into the study [1]. Patients aged 18 years or older, who were newly diagnosed as idiopathic iRBD, were recruited for the study. Motor assessment was performed by the same researcher (G.B.S.) in all patients by means of the Unified Parkinson's Disease Rating Scale part III, and a mini-mental state examination was used for cognitive evaluation. Patients with any parkinsonian symptoms and/or signs of neurodegeneration and/or cognitive impairments, iRBD or REM sleep without atonia related to other sleep disorders (such as narcolepsy, or sleep apnea), or those using drugs, such as serotonin reuptake inhibitors, that interfere with sleep muscle tone were excluded. On the basis of inclusion and exclusion criteria, 45 out of 93 patients were enrolled into the study. Our study was approved by ethics committee and performed in accordance with 1964 Declaration of Helsinki and its later amendments. All persons gave their informed consent prior to their inclusion in the study.

All patients had Sniffin' Sticks Odor identification test [18] for olfactory function, Farnsworth–Munsell 100 Hue color vision test [19] for color discrimination, Beck Depression inventory [20] for depressive symptomatology, and Rome III criteria [21] for constipation. Our initial results defining the prodromal non-motor features of alpha-synucleinopathies in patients with iRBD, were previously presented [22].

Patients were followed for eight years regularly at every six months to a maximum of one-year interval. At each follow-up visit, assessment of eventual phenoconversion to parkinsonism was evaluated by neurological examination with the scorings of Unified Parkinson's Disease Rating Scale III by the same neurologist (G.B.S.) in person, or via telemedicine (due to COVID-19 pandemic). Parkinsonism was defined as bradykinesia plus either resting tremor or rigidity [23]. As discussed among limitations below, global cognitive assessment, or other instrumental and laboratory examinations could not be assessed at follow-up evaluations.

All patients had a full-night video-polysomnography recording in our sleep laboratory, in accordance with the guidelines formed by the American Academy of Sleep Medicine [24]. In the analysis of the absence of atonia during REM sleep, superficial electromyographic recordings from chin and bilateral tibialis anterior muscles were used. Sleep spindle analysis was performed from forebrain regions (C3 and F4) for at least 15 minutes of N2 sleep without artifacts in the first sleep cycle of the night. Duration of the spindles (seconds), frequency (Hz) and density (occurrence per minute) were calculated by using a semi-automated computerized program [25]. Spectral analysis was performed from central and occipital regions separately for wakefulness, NREM and REM sleep. For quantitative electroencephalogram evaluation, artifacts were carefully eliminated, and fast Fourier transform was performed. Heart rate variability analysis was also performed by using whole-night electrocardiograph recordings via a computerized program [26]. Average R-R duration (ms), percentage of NN50 (%), low-frequency power (ms^2), high- frequency power (ms^2), and low frequency/high frequency ratio were

calculated separately for wakefulness, NREM and REM sleep.

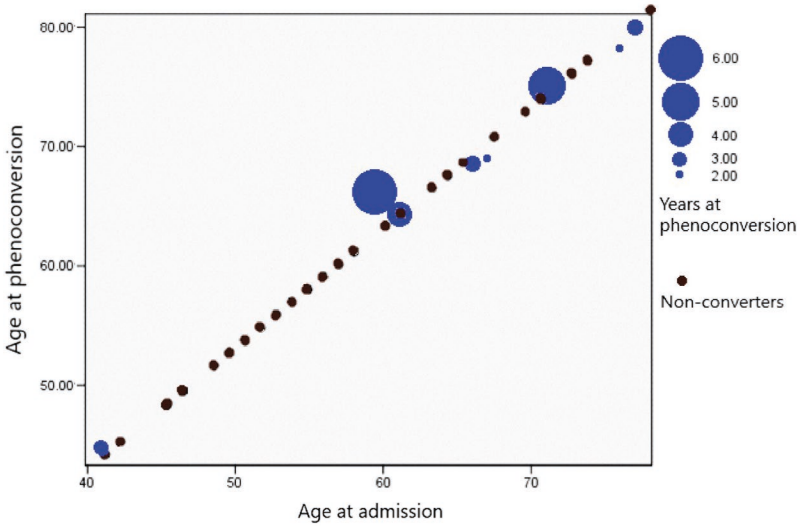
Statistical analysis was performed by using the IBM® statistical package for the social sciences, version 21.0. Data were given as mean ± standard deviation or as percentages. Normal distribution of variables was analyzed by using the Shapiro-Wilk test. Comparisons were analyzed by using chi-square Fisher's exact tests for categorical variables, and by using an unpaired *t* test for normally distributed continuous parameters, and Mann-Whitney U test for numeric variables without normal distribution. *Odds ratio* was calculated for the prognostic models for phenoconversion. Kaplan-Meier survival analyses were performed for the association of demographic parameters, such as age, gender, and clinical non-motor symptoms, alone and in different combinations. Predictive model showing highest performance for overall accuracy, sensitivity and specificity was used and receiver operating characteristic curve was calculated [27]. Univariate Cox proportional hazards regression analyses and partial regression models were performed for parameters showing a significant association with phenoconversion in survival analyses. A *p* value equal to or lower than 0.05 was set as statistically significant threshold.

Results

Forty-five completed the study; average age of the patients was 57,9 ± 10 years, and 26 of them (57,8%) were men. At the end of eight years, eight patients (17,8%) developed parkinsonism following a mean follow-up period of 3,2 ± 1 years. Average age of the patients with phenoconversion (64,8 ± 11,4 years) was significantly higher than those without phenoconversion (56,4 ± 9,2 years, p = 0,034) (Fig. 1). Mean iRBD duration was 5,6 ± 2,2 years in iRBD patients without phenoconversion, and 6,5 ± 3,0 years in those with phenoconversion (p = 0,259).

In prognostic models for predicting phenoconversion in iRBD patients (Table I), *odds ratio* was highest for the patients ≥ 60 years of age with anosmia and constipation –44,8 (4,5-445,7); kappa = 4,291; p < 0,001– (Fig. 2a and b). The model with the second highest *odds ratio* was found in patients with iRBD ≥60 years of age with constipation –36,1 (3,7-350,1); kappa = 4,034; p <0,001–. Male gender was associated with a significant increase in the risk of the development of parkinsonism, though *Odds ratio* was lower compared to other models.

Figure 1. The ages of the subjects participated in the study at the beginning and their ages at the onset of phenoconversion.



Presence of depressive symptomatology was not associated with phenoconversion in any model.

Polysomnography data did not show significant differences between iRBD patients with and without phenoconversion (Table II). REM sleep without atonia was detected in chin electromyography in majority (80%), followed by both chin and anterior tibialis muscles (15,5%), and only in lower extremities (4,5%). REM sleep without atonia type was phasic and tonic in 71,1% of the patients, followed by phasic (17,7%) and tonic (11,2%). While REM sleep without atonia was mostly detected in chin electromyography in mixed type (phasic and tonic) in patients with phenoconversion, neither the localization (p = 0,331) nor the type (p = 0,291) of REM sleep without atonia showed a significant association with phenoconversion. Regression analysis showed that an increase in sleep latency was positively correlated with phenoconversion (r = 0,380, p =0,022; Table III). Sleep spindle analysis did not show significant differences between those patients with and without phenoconversion (Table II). Regression analysis also failed to demonstrate a significant correlation of duration, frequency or density of sleep spindles with phenoconversion (Table III).

In EEG spectral analysis, alpha power in wakefulness and in REM sleep in occipital region was observed to be lower in iRBD patients with pheno-

Table I. Prognostic models for predicting the phenoconversion in idiopathic rapid eye movement sleep behavior disorder patients.

	Odds ratio	Lower-upper (CI 95%)	*t* value	*p* value
Clinical assessments				
Male gender	0.788	0.163-3.794	0.147	0.772
Age ≥60 years	12.923	1.43-116.785	2.887	0.006[a]
Loss of color vision	1.111	0.192-6.44	0.115	0.909
Depressive symptoms	0.203	0.036-1.148	–1.957	0.057
Constipation	0.486	0.349-0.677	2.841	0.007[a]
Loss of smell	0.865	0.761-0.982	1.093	0.281
Male gender + depressive symptoms + constipation + loss of smell	1.619	0.146-17.935	0.388	0.7
Male gender+ constipation + loss of smell	3.1	0.579-16.586	1.362	0.18
Age ≥60 years + loss of color vision	8.1	1.398-46.944	2.72	0.009[a]
Age ≥60 years + loss of smell	14.583	1.607-132.334	3.09	0.004[a]
Age ≥60 years + constipation	36.167	3.735-350.187	4.935	<0.001[a]
EAge ≥60 years + constipation + loss of smell	44.8	4.503-445.734	5.457	<0.001[a]
Constipation + loss of smell	0.378	0.25-0.572	3.544	0.001[a]
Quantitative measures				
Slowing in spectral EEG	0.405	0.274-0.599	3.348	0.002[a]
Age ≥60 years + slowing in spectral EEG	36.167	3.735-350.187	4.935	<0.001[a]
Constipation + slowing in spectral EEG	0.216	0.117-0.399	5.264	<0.001[a]
Loss of smell + slowing in spectral EEG	0.324	0.204-0.516	3.991	<0.001[a]
Age ≥60 years + constipation + loss of smell + llowing in spectral EEG	122.5	9.72-1.543.836	8.3	<0.001[a]

EEG: electroencephalogram; IC 95%:confidence interval at 95%. [a] *p* value < 0,05.

conversion (p = 0,035 and p = 0,044, respectively), while the other parameters were all similar between two groups. Regression analysis demonstrated a significant negative correlation to the development of parkinsonism in lower alpha power in occipital region in both wakefulness (r = –0,327, p = 0,032), and in REM sleep (r = –0,325, p =0,034) (Table III). When slowing in EEG spectrum power is implemented into previous model giving the highest risk stratification for the emergence of alpha-synucleinopathies, the *odds ratio* was found to increase tremendously –122,5 (9,7-1543,8); kappa = 3,051; p < 0,001– (Table I; Fig. 2c and d).

Heart rate variability analysis showed that average R-R duration and percentage of NN50 were lower and hight frequency power was higher in wakefulness, NREM and REM sleep in iRBD patients with phenoconversion in comparison with patients without; none of these was statistically significant. Regression analysis failed to demonstrate significant correlations with the changes in heart rate variability parameters and development of parkinsonism.

Discussion

This is the first study from Turkey investigating the non-invasive predictors of phenoconversion from iRBD to overt parkinsonism. We observed a phenoconversion rate of 17,8% following a mean of about 3,2 ± 1 years. In our previous study investigating patients with iRDB and REM sleep without atonia (iRSWA), we have demonstrated that rates of phenoconversion of 25,8 and 8,9%, respectively, following about 2,6 ± 2,2 years [4]. In a recent meta-analysis of longitudinal studies investigating the risk of neurodegeneration in iRBD, average conversion rate was reported as 31.9% after a mean follow-up of 4.75 ± 2.43 years [28], supporting a significant positive correlation between the rate of phenoconversion and follow-up duration [29,30]. Asian studies from Korea, Japan, China and Hong Kong, on the other hand, found lower phenoconversion rates compared to Caucasian patients in North America and Europe [31-35]. Yoon et al [31] reported conversion rates of 9 and 18% at the 3rd and 5th years from diagnosis of iRBD to development of any neurodegenerative disease. These findings may implicate the presence of racial and geographic factors related to the phenoconversion rates from iRBD to neurodegenerative diseases. Phenoconversion rate in our studies from Turkey seems less than those reported in Europe and United States, but closer to those reported from Asia. Relatively younger age and shorter disease duration of study population may be confounding factors for lower rate of phenoconversion. However, notable low percentage of phenoconversion detected in this selected sample compared to previous works published with larger samples may also result from the lack of evolutionary follow-up neuropsychological tests. Therefore,

not the percentage of total phenoconversion but the percentage of phenoconversion to parkinsonism was reflected herein. A nation-wide multicenter study should be encouraged for the investigation of phenoconversion from iRBD to alpha-synucleinopathies in a sample representative of Turkish population.

Our study showed that the *odds ratio* for predicting phenoconversion in iRBD patients was highest in patients ≥60 years of age with anosmia and constipation. Advanced age has a predictive value in development of neurodegenerative disorders in iRBD, supporting the fundamental role of aging in the pathophysiology of neurodegeneration [36]. In a prospective follow-up study from 24 centers of the International iRBD Study Group [5], risk of phenoconversion was associated with abnormal quantitative motor testing, olfactory deficit, mild cognitive impairment, erectile dysfunction, abnormal DAT imaging, color vision abnormalities, constipation, and age. Among non-motor prodromal features of Parkinson's disease, olfactory dysfunction stands out as the earliest and most specific manifestation predicting the risk for Parkinson's disease and dementia with Lewy bodies conversion, independently from other non-motor symptoms [3,37-40]. Although psychiatric disorders, particularly depression, was suggested as a significant risk factor in predicting the emergence of Parkinson's disease -related pathologies in patients with iRBD [34], contradictory results were also reported [39-41]. We did not find that depressive symptoms were associated with greater phenoconversion to parkinsonism, while this finding should cautiously be evaluated in the absence of follow up cognitive assessments.

As for the electrophysiological biomarkers, we observed a positive correlation between increased sleep latency and phenoconversion in regression analysis, while other polysomnography data failed to show significant association. Although a large prospective study found that the percentage of REM sleep was decreased and REM tonus was increased at the time of diagnosis in iRBD convertors [42], only few studies examined the role of polysomnographic findings for predicting phenoconversion, including quantification of REM sleep without atonia by visual or automated methods [3,43,44], cyclic alternating pattern rate [45], artificial intelligence and machinery learning from EEG spectrograms [46]. Here we demonstrated in EEG spectral analysis that lower alpha power in the occipital region in wakefulness and in REM sleep was significantly correlated with phenoconversion in iRBD patients. Slowing in EEG was previously reported as a promising marker for neurodegeneration in patients with iRBD [15,47]. Higher ratio of slow-to-fast activity was observed in all cortical regions in patients with iRBD developing neurodegenerative diseases [15]. A recent study of iRBD patients found that generalized EEG slowing during phasic REM sleep may be a promising biomarker for phenoconversion [48]. In our prognostic models for risk stratification, slowing in EEG spectrum power, together with age ≥60 years, anosmia and constipation, resulted in the highest *odds ratio*. Although the value of these subtypes of neurophysiological biomarkers currently seems unquestionable, more research including the analyses of sleep spin-

Figure 2. The Kaplan-Meier survival analysis (a) and Hazard function analysis (b) for the model including the age ≥60 years, anosmia and constipation; and the Kaplan-Meier survival analysis (c) and Hazard function analysis (d) for the model including the clinical (age ≥60 years, anosmia, and constipation) and quantitative (slowing in electroencephalogram spectrum) measures.

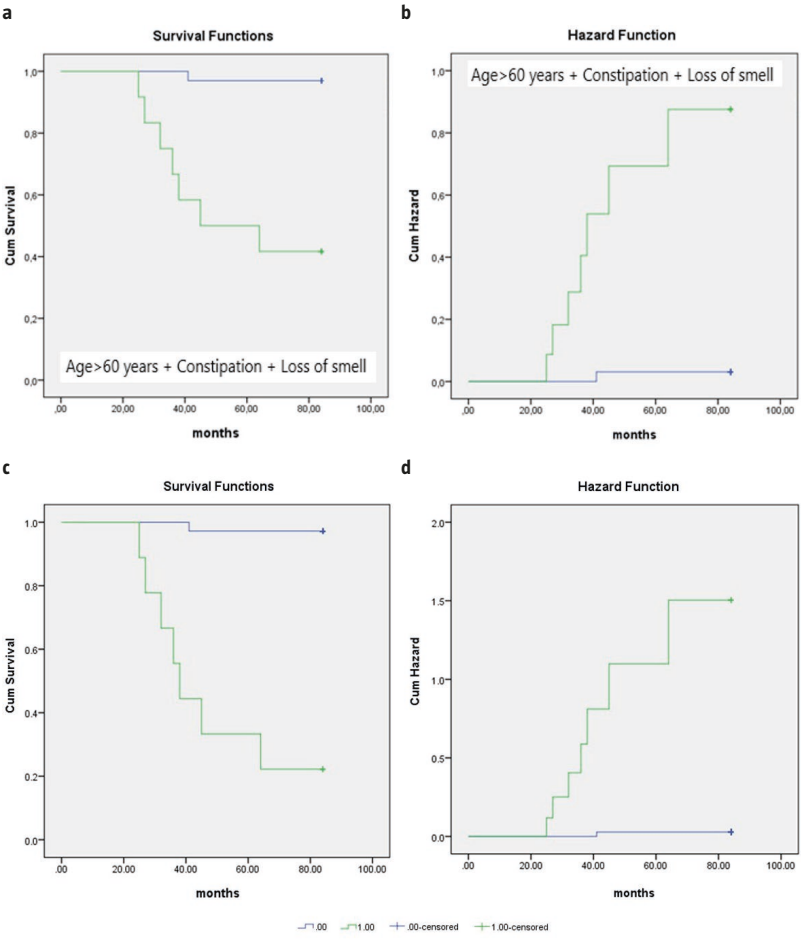


Table II. Sleep spindle analysis in in idiopathic rapid eye movement sleep behavior disorder patients with and without phenoconversion.

	Patients with phenoconversion (*n* = 8)	Patients without phenoconversion (*n* = 37)	*p* value
Polysomnography parameters			
Total sleep time (minutes)	398.6 ± 45.3	376.6 ± 46.2	0.327
Sleep latency (minutes)	35.2 ± 44.6	13.4 ± 12.2	0.597
REM sleep latency (minutes)	149.8 ± 114.4	162.6 ± 103	0.56
Sleep efficiency (%)	85.2 ± 10.1	83.6 ± 9.1	0.59
Wakefulness (%)	11.6 ± 9.6	14.2 ± 9	0.41
N1 sleep stage (%)	5.6 ± 3	6.9 ± 3.4	0.36
N2 sleep stage (%)	49.5 ± 14.6	43.2 ± 10.2	0.2
N3 sleep stage (%)	18.3 ± 11	18.4 ± 9.6	0.893
R sleep stage (%)	14.9 ± 5.8	18 ± 12.2	0.463
Index of periodic leg movements (per hour)	14.2 ± 32.6	11.2 ± 16.1	0.61
Sleep spindle analysis			
Duration (seconds)	0.6 ± 0.07	0.6 ± 0.1	0.673
Frequency (Hz)	12.6 ± 1.2	12.4 ± 0.6	0.716
Density (number per minute)	5.5 ± 2.4	5.4 ± 2.3	0.694

dles, cyclic alternating pattern or macrostructure of sleep is undoubtedly needed. An ongoing Italian database, the risk factors predictive of phenoconversion in iRBD Italian study (FARPRESTO), registered in clinical trials, will harmonize clinical and nigrostriatal functioning data longitudinally to allow better risk characterization [49]. In near future, therapies that slow down or even reverse the functional and cognitive deterioration in neurodegenerative diseases will require the definition of the most sensitive and specific biomarkers of progression from iRBD to overt alpha-synucleopathies, and the ideal moment for the initiation of neuroprotective treatments.

This study has some limitations. Although the phenoconversion from iRBD to parkinsonism was prospectively analyzed, the lack of a longitudinal cognitive evaluation, as discussed above, is the major limitation of our study. Neuroimaging biomark-

Table III. Partial correlation analysis of polysomnography data, sleep spindle and electroencephalogram power spectrum analysis controlled for both age and gender.

	Partial correlation coefficients	*p* value
Polysomnography parameters		
Total sleep time	0.316	0.06
Sleep latency	0.38	0.022[a]
REM sleep latency	–0.162	0.344
Sleep efficiency	0.177	0.3
Wakefulness	–0.209	0.221
N1 sleep stage	–0.194	0.256
N2 sleep stage	0.192	0.263
N3 sleep stage	0.02	0.907
R sleep stage	–0.084	0.626
Index of periodic leg movements	–0.103	0.552
Sleep spindle analysis		
Duration	–0.092	0.559
Frequency	–0.026	0.87
Density	–0.029	0.854
Spectral analysis		
Wakefulness, central region		
Alpha power	–0.228	0.142
Beta power	–0.181	0.247
Theta power	–0.136	0.383
Delta power	–0.117	0.455
Wakefulness, occipital region		
Alpha power	–0.327	0.032[a]
Beta power	–0.143	0.362
Theta power	–0.072	0.647
Delta power	–0.135	0.389

Table III. Partial correlation analysis of polysomnography data, sleep spindle and electroencephalogram power spectrum analysis controlled for both age and gender *(cont)*.

	Partial correlation coefficients	*p* value
NREM sleep, central region		
Alpha power	–0.166	0.287
Beta power	–0.02	0.898
Theta power	–0.136	0.383
Delta power	–0.117	0.455
NREM sleep, occipital region		
Alpha power	–0.272	0.078
Beta power	–0.079	0.614
Theta power	–0.072	0.647
Delta power	–0.135	0.389
REM sleep, central region		
Alpha power	–0.166	0.288
Beta power	–0.183	0.24
Theta power	–0.136	0.383
Delta power	–0.117	0.455
REM sleep, occipital region		
Alpha power	–0.325	0.034[a]
Beta power	–0.076	0.628
Theta power	–0.072	0.647
Delta power	–0.135	0.389

[a] *p* value < 0,05.

ers to show the nigrocaudate dopaminergic deafferentation are also missing. Study population is rather small, and reflects the results of one sleep center only. As the recommendations of SINBAR group were included in later versions of the American Academy of Sleep Medicine manuals (version 2.8, 3.0), they were not applied to the analysis of REM sleep without atonia in our patients. Data regarding socioeconomic factors were not available, and therefore could not be taken into consideration in statistical analysis. Another important limitation may be listed as the lack of healthy control group to compare the percentage of patients who would naturally evolve to parkinsonism and/or synucleinopathy.

Conclusion

In conclusion, our study demonstrated that slowing in EEG spectrum power, especially in lower alpha power in occipital region during wakefulness and REM sleep, together with advanced age (≥60 years), anosmia and constipation, resulted in the highest *odds ratio* for the phenoconversion. This is the first study from Turkey to demonstrate the relative predictive values of prodromal biomarkers of phenoconversion, which provides estimates of patients with iRBD at high risk for developing parkinsonism. It is of great importance to have a world-wide perspective of phenoconversion rates from iRBD to overt neurodegeneration, since racial and geographical factors may play important modifying roles. Neurophysiological biomarkers seem to be important predictors of phenoconversion, though more research is needed to establish subtypes of iRBD with different probabilities of evolution to overt synucleinopathy.

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Estratificación del riesgo de fenoconversión al parkinsonismo en pacientes con trastorno de conducta del sueño REM aislado. Estudio de seguimiento en un centro de Turquía

Introducción. El trastorno aislado de la conducta del sueño con movimientos oculares rápidos (iRBD) es uno de los marcadores prodrómicos más potentes de las alfa-sinucleinopatías. Nuestro objetivo fue investigar los predictores clínicos y cuantitativos no invasivos de la fenoconversión de iRBD a parkinsonismo.

Pacientes y métodos. Se siguió prospectivamente a un total de 45 pacientes (57,8% hombres) durante ocho años del período de estudio. Se realizaron evaluaciones clínicas, la prueba de identificación de olores *Sniffin' Sticks,* la prueba *Farnsworth-Munsell 100 Hue Color Vision,* el inventario de depresión de Beck y los criterios de Roma III para el estreñimiento. Se analizaron parámetros polisomnográficos, husos del sueño, análisis espectral electroencefalográfico (EEG) y variabilidad de la frecuencia cardíaca.

Resultados. Ocho pacientes (17,8%) mostraron fenoconversión a parkinsonismo después de una duración media de seguimiento de 3,2 ± 1 año. La *odds ratio* para predecir la fenoconversión fue más alta para los pacientes ≥60 años con anosmia y estreñimiento –44,8 (4,5-445,7); kappa = 4,291–. La disminución de la potencia del espectro EEG, junto con la edad ≥60 años, la anosmia y el estreñimiento, dio como resultado el índice de *odds* más alto –122,5 (9,7-1543,8); kappa = 3,051–.

Conclusiones. Es de gran importancia tener una perspectiva mundial de las tasas de fenoconversión de iRBD a neurodegeneración manifiesta, ya que los factores raciales y geográficos pueden desempeñar importantes papeles modificadores. Los biomarcadores neurofisiológicos parecen ser predictores importantes de la fenoconversión, aunque se necesita más investigación para establecer subtipos de iRBD con diferentes probabilidades de evolución hacia una sinucleinopatía manifiesta.

Palabras clave. Análisis espectral. Anosmia. Electroencefalografía. Fenoconversión. Parkinsonismo. Trastorno aislado de la conducta del sueño con movimientos oculares rápidos.