Sleep Medicine 98 (2022) 34–38

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Oculomotor abnormalities and its association with sleep stages in progressive supranuclear palsy

Srikanth Yadav Boini [a], Rohan Mahale [a], Seshagiri Doniparthi Venkata [a], Nitish Kamble [a], Vikram Holla [a], Pramod Kumar Pal [a], Bindu Kutty [b], Ravi Yadav [a, *]

[a] Department of Neurology, National Institute of Mental Health and Neurosciences, Bengaluru, 560029, India
[b] Department of Neurophysiology, National Institute of Mental Health and Neurosciences, Bengaluru, 560029, India

ARTICLE INFO

Article history:
Received 21 December 2021
Received in revised form
8 June 2022
Accepted 11 June 2022
Available online 16 June 2022

Keywords:
Progressive supranuclear palsy
Sleep
Saccades
Oculomotor
Atypical parkinsonism

ABSTRACT

Background: Oculomotor abnormalities are one of the cardinal clinical features of progressive supranuclear palsy (PSP). Vertical saccadic slowing is an early sign of PSP. The association between oculomotor abnormalities and sleep architecture has not been studied so far.
Objectives: To study the association of oculomotor abnormalities of PSP with the sleep stages by using video polysomnography (vPSG).
Methods: This was a cross-sectional single-center study. Twenty-two patients with PSP and 15 age and gender-matched controls were recruited. Saccades, vestibulo-ocular reflex, and optokinetic nystagmus were assessed and graded clinically in all patients and one overnight vPSG was done in all cases.
Results: Vertical saccades, upward more than downwards, were affected in all cases. While horizontal saccades were normal only in 41% of cases. Vertical optokinetic nystagmus (OKN) was affected in all cases. Horizontal OKN was normal in 36% of patients. The vertical upward saccades had a negative correlation with N1% and duration ($r = -0.418$; $p = 0.05$, $r = -0.457$; $p = 0.03$), N3% and duration ($r = -0.486$; $p = 0.02$, $r = -0.510$; $p = 0.01$), REM% ($r = -0.449$; $p = 0.04$), total sleep time ($r = -0.487$; $p = 0.02$) and sleep efficiency ($r = -0.444$; $p = 0.04$). There was a positive correlation between horizontal OKN and sleep onset latency ($r = 0.432$; $p = 0.05$).
Conclusions: Vertical saccadic restriction in PSP has significant negative correlation with total sleep time and sleep efficiency. The oculomotor and sleep abnormalities in PSP are probably interlinked and their assessment is useful in determining the characteristics of the disease.

1. Introduction

Progressive supranuclear palsy (PSP) is a tauopathy characterized by the hyperphosphorylation and subsequent aggregation of the microtubule-associated protein, tau, causing degeneration of cortical and subcortical brain structures, particularly the midbrain. The predominant clinical manifestation of PSP is vertical supranuclear ophthalmoplegia, axial rigidity, bulbar defects, and postural instability causing recurrent falls [1,2]. The eye movement abnormalities in PSP include saccadic fixation, vestibulo-ocular reflex (VOR), pursuits, and vergence abnormalities. Saccadic abnormalities include slowing and restriction of vertical followed by horizontal saccades and impairment of anti-saccades [3,4]. Fixation abnormalities in PSP include the occurrence of square-wave jerks [5,6]. Linear VOR is markedly impaired with relative preservation of angular VOR until the late stages of the disease [7]. Impaired smooth pursuits and saccadic pursuits are due to the involvement of parietal, frontal lobes, dorsolateral pontine nucleus, nucleus reticularis tegmenti ponti and paraflocculus, dorsal vermis of the cerebellum. Reduced amplitude of vergence movements is due to the involvement of the supra-oculomotor area in the mesencephalic reticular formation [8]. The regulation of non-rapid eye movement (NREM) is by anterior hypothalamus, basal forebrain, and REM sleep by sublaterodorsal nucleus (SLD), pedunculopontine

* Corresponding author. Department of Neurology, First floor, Neurosciences Faculty Block, National Institute of Mental Health & Neurosciences (NIMHANS), Hosur Road, Bangalore, 560029, Karnataka, India.
E-mail addresses: srikanthyadav26@yahoo.com (S.Y. Boini), rohanmahale83@gmail.com (R. Mahale), drgiri061@yahoo.com (S. Doniparthi Venkata), nitishlk@gmail.com (N. Kamble), vikramvholla@gmail.com (V. Holla), palpramod@hotmail.com (P.K. Pal), bindu.nimhans@gmail.com (B. Kutty), docravi20@yahoo.com (R. Yadav).

https://doi.org/10.1016/j.sleep.2022.06.008
1389-9457/

and laterodorsal tegmental nuclei (PPT/LDT), and ventromedial medulla (VMM) [9,10]. Literature is scarce on the association of eye movement abnormalities and disturbances in the sleep micro-architecture in patients with PSP. We aimed to study the association of oculomotor abnormalities of PSP with the sleep stages by using video polysomnography (vPSG).

2. Materials and methods

2.1. Study design

The study was a cross-sectional study conducted in the department of neurology of a quaternary care center for neurological disorders in south India.

2.2. Study subjects

Twenty-two patients with PSP diagnosed according to the movement disorder society (MDS) PSP criteria (2017) [11] and 15 age and gender-matched healthy controls were included in the study. The healthy controls were recruited from the study hospital who were hospital employee, out-patient department patient attendants who were voluntarily willing to participate after explaining the objective of the study. Patients and controls with significant medical comorbidities, other neurodegenerative diseases which can affect sleep were excluded. The study period was from December 2018 to December 2020 with a total duration of 24 months. Written informed consent was taken from the patients and the controls seeking their participation. The study was approved by the institutional ethics committee (NO.NIMH/DO/IEC-BS& NS DIV/2018-2019/29-11-2018).

2.3. Data collection

2.3.1. Neurological assessment

The sociodemographic details of the patients included age at presentation, age of onset, gender, duration of illness, educational qualification, socio-economic status, and comorbid illness; clinical data – details about tremors, bradykinesia, rigidity, postural instability, falls, dysarthria, dysphagia, levodopa responsiveness, etc. and neurological examination findings were recorded. The severity of PSP was assessed by progressive supranuclear palsy rating scale (PSPRS) [12]. Unified Parkinson's Disease Rating Scale (UPDRS) part III was used to assess the severity of motor symptoms of parkinsonism [13]. The presence and severity of depression were assesed using Hamilton's depression scales (HAM-D) [14]. The following eye movements assessment was done in all patients and controls. It included: ocular motility and fixation, VOR examination, saccades, and optokinetic nystagmus (OKN) assessment. Ocular motility was assessed in 6 cardinal directions of gaze (both right and left lateral gaze and also up and down gaze in lateral gaze) and also up and downward gaze in primary position. VOR was tested by asking the patient to fixate on target and then passively moving head from side to side (or) up and down. Saccades were assessed in both horizontal and vertical planes by asking the patient to rapidly fixate between two targets. The saccades were graded based on the PSPRS ocular motor score. OKN was assessed in horizontal and vertical planes and graded as 0 as normal, 1 as moderate OKN amplitude but not normal, 2 as minimal OKN amplitude appreciated, and 3 as absent OKN [15].

2.4. Video polysomnographic assessment

A single overnight vPSG was done in all patients and controls in the sleep laboratory of the institute. vPSG was performed as per the guidelines laid down by the American Academy of Sleep Medicine (2017) using SOMNO medics, Germany [16]. The vPSG included eight-channel electroencephalography (EEG) electrodes according to the 10-20 international system, right and left electrooculogram, chin/tibialis anterior electromyogram activity, electrocardiogram, microphone, respiratory effort, and airflow sensor. A sleep lab technician monitored each vPSG recording. The sleep parameters analyzed were total sleep time (TST), wake after sleep onset (WASO), N1, N2, N3, REM sleep duration, latencies and REM density, latency to sleep onset, arousal index and number of awakenings, sleep efficiency, sleep maintenance, number of REM sleep episodes and percent time in N1 sleep, N2 sleep, N3 sleep, and REM sleep. Time in bed (TIB) refers to time from the start of the recording to the end of the recording, TST was the total time spent in NREM or REM sleep after the start of the N1 stage, sleep efficiency was defined as TST/TIB, sleep onset latency was the time from the start of the recording and beginning of the first N1 stage, REM latency was the time from the sleep onset to the first epoch of REM sleep, WASO was the total wake time over the vPSG recording period after the first period of continuous sleep lasting at least 10 min and REM density was number of REMs per each 30-s epoch of REM sleep.

2.5. Sleep data scoring and analysis

The acquired sleep data was converted into European Data Format (EDF) and was analyzed in Polyman software version 1.15. The sleep data were analyzed based on scoring guidelines AASM 2017.

2.6. Statistical analysis

Categorical variables were expressed as frequency, percentage and continuous variables as mean with standard deviation. The normality of data was assessed using the Shapiro-Wilks test. Mann-Whitney *U* test were used for comparison of continuous variables. Categorical variables were analyzed by Pearson's Chi-Square test. Pearson correlation coefficient was used to compare the strength of association between the variables. Data were analyzed with Statistical Package for Social Sciences V20.0 (SPSS Inc, Chicago, IL, USA) and Microsoft Excel sheet. A p-value of <0.05 was considered significant.

3. Results

A total of 22 PSP patients and 15 controls were recruited. However, vPSG was done in 21 cases as one case did not give consent for vPSG and 15 controls. The mean age of patients with PSP was 61.2 ± 7.1 years and controls were 53.9 ± 4.2 years. Nineteen were male patients and 3 were female patients. The mean duration of illness was 19.6 ± 4.8 months (range- 12–24 months). The mean PSPRS score was 30.0 ± 10.7. The mean UPDRS part III score was 29.4 ± 11.1. Nineteen patients belonged to probable PSP-Richardson syndrome and 3 patients to possible PSP-oculomotor subtype. All patients were on levodopa, 8 patients on amantadine and 2 patients on dopamine agonist.

3.1. Eye movements abnormalities (Table 1)

3.1.1. Saccadic abnormalities

Vertical saccades were more affected than horizontal saccades in all cases. Upward saccades were more affected than downward saccades. Grade 4 reduction in the vertical upward saccade amplitude occurred in 36% of patients as compared to vertical

Table 1
Grading of saccadic and OKN abnormalities.

Grading of saccades	Vertical upward-saccades (n/%)	Vertical downward saccades (n/%)	Horizontal saccades (n/%)
Grade 0 or Normal amplitude	0	1/4.5%	9/40.9%
Grade 1 or Slow	2/9%	6/27.2%	10/45.4%
Grade 2 or 51–85% of normal amplitude	4/18%	3/13.6%	0
Grade 3 or 16–50% of normal amplitude	4/18%	6/27.2%	3/13.6%
Grade 4 or 5% of normal amplitude	8/36%	6/27.2%	0
Grading of OKN	Vertical upward OKN (n/%)	Vertical downward OKN (n/%)	Horizontal OKN (n/%)
Grade 0 or Normal	0	0	8/36%
Grade 1 or Mild impairment	1/4.5%	3/13.6%	6/27.2%
Grade 2 or Moderate impairment	12/54%	10/45.4%	8/36%
Grade 3 or Severe impairment	9/40.9%	9/40.9%	0

OKN- optokinetic nystagmus.

downward saccade amplitude in 27% of patients. Horizontal saccades were normal in 41% of patients and grade 1 reduction in amplitude in 45% of patients.

3.2. OKN abnormalities

Vertical OKN was affected in all cases. Severe impairment (grade 3) was similar in both upward and downward vertical OKN. Moderate impairment of vertical OKN (grade 2) was more for upward than downward saccades. Horizontal OKN was impaired in 64% of patients and normal in 36% of patients.

3.3. Correlation of eye movement abnormalities with the sleep architecture

3.3.1. Correlation of OKN with the sleep architecture (Table 2)

There was a positive correlation between horizontal OKN and sleep onset latency ($r = 0.432$; $p = 0.05$) only.

3.3.2. Correlation of saccades with the sleep architecture (Table 3)

A significant negative correlation was noted between the vertical upward saccades and N1% and duration, N3% and duration, REM%, TST and sleep efficiency. There was no significant correlation between the downward saccades and the various sleep parameters. A significant negative correlation was noted between the horizontal saccadic impairment and N3% and duration. There was no significant correlation between the REM density and the saccades.

3.3.3. Correlation of eye movement abnormalities with the PSPRS and duration of illness

There was a positive correlation between the PSPRS and vertical OKN ($r = 0.634$, $p = 0.002$ for up OKN; $r = 0.606$, $p = 0.003$ for down OKN), vertical ($r = 0.710$, $p < 0.001$ for up saccades; $r = 0.655$, $p = 0.001$ for down saccades), and horizontal saccades ($r = 0.400$; $p = 0.06$) suggesting that the severity of the disease was associated with impaired vertical OKN and vertical, horizontal saccades. However, there was no significant correlation between PSPRS and horizontal OKN. A positive correlation was noted between the duration of illness and the severity of impairment of vertical OKN ($r = 0.501$, $p = 0.01$ for up OKN; $r = 0.520$, $p = 0.01$ for down OKN) and horizontal saccades ($r = 0.471$, $p = 0.01$). There was no significant correlation between duration of illness and vertical saccades and horizontal OKN.

3.3.4. Correlation of sleep architecture with the duration of illness

There was no significant correlation between the duration of illness and REM, N1, N2, N3%, latencies and duration, sleep onset latency, sleep efficiency and WASO duration.

Table 2
Correlation of OKN with vPSG parameters.

	Vertical up OKN r	p-value	Benjamini Hochberg adjusted P value	Vertical down OKN r	p-value	Benjamini Hochberg adjusted P value	Horizontal OKN r	p-value	Benjamini Hochberg adjusted P value	Duration of disease r	p-value
WASO duration	0.081	0.74	0.841	0.090	0.71	0.825	0.125	0.61	0.749	−0.194	0.42
WASO%	0.209	0.39	0.639	0.224	0.35	0.630	0.270	0.26	0.530	0.153	0.50
N1%	−0.271	0.23	0.518	−0.306	0.17	0.506	−0.036	0.87	0.914	−0.384	0.08
N2%	−0.035	0.87	0.914	−0.106	0.64	0.777	−0.104	0.65	0.780	0.036	0.87
N3%	−0.324	0.15	0.506	−0.266	0.24	0.529	−0.165	0.47	0.686	−0.130	0.57
REM%	−0.333	0.14	0.506	−0.376	0.09	0.506	−0.211	0.35	0.630	−0.350	0.12
Total sleep time	−0.238	0.29	0.569	−0.302	0.18	0.506	−0.126	0.58	0.728	−0.247	0.28
Sleep onset latency	0.383	0.08	0.506	0.280	0.21	0.506	0.432	**0.05***	0.506	0.196	0.39
Sleep efficiency	−0.285	0.21	0.506	−0.306	0.17	0.506	−0.180	0.43	0.645	−0.119	0.60
N1 latency	0.287	0.22	0.506	0.194	0.41	0.639	0.132	0.18	0.506	0.092	0.69
N2 latency	−0.049	0.84	0.914	−0.049	0.84	0.914	0.139	0.57	0.724	−0.299	0.21
N3 latency	−0.388	0.26	0.530	−0.388	0.26	0.530	−0.315	0.37	0.639	−0.782	0.08
REM latency	−0.169	0.54	0.711	−0.169	0.54	0.711	−0.032	0.90	0.917	−0.112	0.69
N1 duration	−0.287	0.20	0.506	−0.287	0.20	0.506	−0.072	0.75	0.844	−0.384	0.08
N2 duration	−0.034	0.88	0.914	−0.034	0.88	0.914	−0.041	0.86	0.914	−0.153	0.50
N3 duration	−0.350	0.12	0.506	−0.350	0.12	0.506	−0.185	0.42	0.639	−0.286	0.57
REM duration	−0.304	0.18	0.506	−0.304	0.18	0.506	−0.160	0.49	0.696	−0.344	0.12
REM density	−0.023	0.26	0.530	−0.282	0.42	0.639	−0.057	0.19	0.506	−0.362	0.14

WASO- wake after sleep onset; REM-rapid-eye movement; * p-value-<0.05- statistical significance.

Table 3
Correlation of saccades with vPSG parameters.

	Vertical upward saccades r	p-value	Benjamini Hochberg adjusted P value	Vertical downward saccades r	p-value	Benjamini Hochberg adjusted P value	Horizontal saccades r	p-value	Benjamini Hochberg adjusted P value
WASO duration	0.018	0.94	0.949	0.079	0.74	0.841	0.096	0.69	0.810
WASO%	0.256	0.29	0.569	0.163	0.50	0.701	0.325	0.17	0.506
N1%	−0.418	**0.05***	0.506	−0.284	0.21	0.506	−0.144	0.53	0.711
N2%	−0.162	0.48	0.691	−0.218	0.34	0.630	−0.196	0.39	0.639
N3%	−0.486	**0.02***	0.432	−0.344	0.13	0.506	−0.495	**0.02***	0.432
REM%	−0.449	**0.04***	0.506	−0.408	0.06	0.506	−0.337	0.13	0.506
Total sleep time	−0.487	**0.02***	0.432	−0.351	0.11	0.506	−0.353	0.11	0.506
Sleep onset latency	0.343	0.12	0.506	0.328	0.14	0.506	0.276	0.22	0.506
Sleep efficiency	−0.444	**0.04***	0.506	−0.352	0.11	0.506	−0.280	0.21	0.506
N1 latency	0.309	0.18	0.506	0.318	0.17	0.506	0.197	0.40	0.639
N2 latency	0.006	0.98	0.980	0.030	0.90	0.917	0.061	0.80	0.891
N3 latency	−0.200	0.57	0.724	−0.215	0.55	0.716	−0.284	0.42	0.639
REM latency	−0.150	0.59	0.732	−0.297	0.19	0.506	−0.247	0.37	0.639
N1 duration	−0.457	**0.03***	0.506	−0.287	0.20	0.506	−0.215	0.35	0.630
N2 duration	−0.193	0.40	0.639	−0.096	0.67	0.795	−0.144	0.53	0.711
N3 duration	−0.510	**0.01***	0.432	−0.350	0.11	0.506	−0.509	**0.01***	0.432
REM duration	−0.437	0.52	0.711	−0.365	0.38	0.639	−0.348	0.35	0.630
REM density	−0.179	0.45	0.666	−0.367	0.22	0.506	−0.023	0.14	0.506

WASO- wake after sleep onset; REM-rapid-eye movement; * p-value-<0.05- statistical significance.

4. Discussion

Our study was aimed at correlating the sleep architecture with eye movements in PSP. This is necessary to understand whether the disease pathophysiology in the brainstem and cortex is associated with altered sleep architecture in PSP. With the progression of illness, the vertical saccadic velocity is the first to be affected followed by the saccadic amplitude [17]. The slowing of vertical saccades is considered as an early sign of PSP. Vertical saccades are controlled by the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF) in the rostral midbrain reticular formation (RF). Vertical saccades are more affected in PSP due to severe neuronal loss in the midbrain RF [18]. Slowing of saccades in PSP is attributed to the degenerative loss of mesencephalic saccadic burst generators. Shaikh et al. (2017) studied the vertical and horizontal visually guided saccades in PSP and concluded that the PSP saccadic slowing are due to the paucity in burst generation at the excitatory burst neurons and imprecise timing signal from the inhibitory burst neurons. The premature discharge of the inhibitory burst neuron leads to breaks in the saccade trajectory and the maladaptive superior colliculus activity causing aberrant saccades that change the intended trajectory of the ongoing saccade [19]. Terao et al. (2013) reported progressively reduced accuracy of horizontal saccades in PSP suggesting a brainstem oculomotor pathology that includes the superior colliculus and/or paramedian pontine reticular formation [20].

Vertical saccades and OKN were impaired in all the cases in our cohort. Horizontal saccades and OKN were impaired in 64% of patients. The vPSG scoring of REM sleep depends on the presence of the rapid eye movements on the EOG. However, in PSP due to oculomotor abnormalities, REM sleep scoring is known to be difficult. In such a scenario, other markers of REM sleep like sawtooth waves in EEG, phasic EMG activity with low background EMG typical of REM sleep state needs to be looked into for scoring the REM sleep. We considered that the low percentage of REM sleep was due to a decrease of this stage of sleep and not only due to scoring difficulty due to oculomotor abnormalities as other characteristics of REM sleep were assessed during the scoring process.

We found that the severity of vertical upward saccadic restriction had significant negative correlation with NREM, REM sleep and its efficiency. The regulation of NREM sleep is in the anterior hypothalamus and REM sleep in the pons/medulla. The vertical saccades are mediated by the midbrain and horizontal saccades by the pons. Vertical saccadic impairment in PSP had significant negative correlation with REM sleep suggesting degeneration involving midbrain, pons/medulla and NREM sleep suggesting additional degeneration of the hypothalamus. Whether the saccadic impairment and sleep in PSP are closely related needs to be explored.

There is a similarity between the saccades and REMs of REM-sleep. REMs during REM-sleep scan a dream image during sleep like the saccades that scan the external visual world during wakefulness [21]. Three types of brain potentials precede the onset of saccades during wakefulness. The first potential is presaccadic negativity that reflects the voluntary preparatory process initiating saccades appearing about 0.6–3 s before saccade onset. This does not occur during REMs in REM-sleep. The second potential is presaccadic positivity (PrSP) that reflects the oculomotor planning process appearing about 100–250 ms before saccade onset. Frontal eye field, supplementary eye field, and parietal cortex are the generators of PrSP. This does not occur during REMs in REM-sleep. The third potential is the spike potential reflecting the oculomotor execution process appearing almost simultaneously with the onset of saccade and originates from the extra-ocular muscle or oculomotor neurons. The spike potential is also seen during REMs in REM-sleep [22,23]. Abe et al. (2004) reported the appearance of a slow negative potential named as “pre-REM negativity (PRN)” before REMs in REM-sleep. The generators of PRN involve the subcortical network rather than the cortical areas needed for PrSP [24].

We found a very low REM density in PSP patients as compared to REM density in PD patients and healthy controls but REM density had no correlation with voluntary saccades or OKN [25]. REM density is a phasic REM activity which is the frequency of eye movements during REM sleep and is associated with direct activation of the motor cortex during REM sleep [26]. Low REM density in PSP and PD may be due to decreased activation of motor cortex

during REM sleep. There may be independent-generation pathways of phasic REM activities existing which needs to be explored.

The strength of this study was the exploration of the association between the saccadic impairment in PSP and the sleep architecture which has not been done so far. However, the limitations were the relatively small sample size of cases, the impact of lack of adaptation to new sleep environment on the sleep architecture as it was a single night vPSG, sole conduct of clinical assessment of the saccades and OKN, the lack of comparision of sleep architecture with the controls, lack of the assessment of sleep apnoea syndrome, periodic-limb movement index. The Bonferroni correction for the multiple correlation analyses was not done as the sample size was small and we aimed to correlate vPSG sleep parameters with saccadic impairment to find if there is association and the application of the Bonferroni correction would have made the observations of the study non-significant.

5. Conclusion

Vertical saccadic restriction in PSP has a significant negative correlation with the quality and quantity of sleep. There is a need for the recognition and treatment of the sleep disturbances in patients with PSP especially in the presence of vertical saccadic impairment. A future study involving larger cohort of PSP patients to study the association of the oculomotor abnormalities in PSP with the sleep architecture is required to confirm the findings of this study.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Srikanth Yadav Boini: Writing – original draft, Methodology, Investigation, Formal analysis, Resources. **Rohan Mahale:** Investigation, Visualization, Supervision, Project administration, Writing – review & editing. **Seshagiri Doniparthi Venkata:** Visualization, Supervision, Project administration. **Nitish Kamble:** Visualization, Supervision, Resources. **Vikram Holla:** Visualization, Supervision, Formal analysis. **Pramod Kumar Pal:** Visualization, Supervision, Conceptualization. **Bindu Kutty:** Supervision, Conceptualization, Validation. **Ravi Yadav:** Conceptualization, Visualization, Supervision, Formal analysis.

Acknowledgements

Nil.

References

[1] Yousaf T, Pagano G, Wilson H, Politis M. Neuroimaging of sleep disturbances in movement disorders. Front Neurol 2018 Sep 11;9:767. https://doi.org/10.3389/fneur.2018.00767.
[2] Litvan I, Hauw JJ, Bartko JJ, Lantos PL, Daniel SE, Horoupian DS, et al. Validity and reliability of the preliminary NINDS neuropathologic criteria for progressive supranuclear palsy and related disorders. J Neuropathol Exp Neurol 1996;55:97–105.
[3] Chen AL, Riley DE, King SA, Joshi AC, Serra A, Liao K, et al. The disturbance of gaze in progressive supranuclear palsy: implications for pathogenesis. Front Neurol 2010. https://doi.org/10.3389/fneur.2010.00147. DEC. 147.
[4] Leigh RJ, Riley DE. Eye movements in parkinsonism: it's saccadic speed that counts. Neurology 2000;54:1018–9.
[5] Garbutt S, Riley D, Kumar A, Han Y, Harwood M, Leigh R. Abnormalities of optokinetic nystagmus in progressive supranuclear palsy. J Neurol Neurosurg Psychiatry 2004;75:1386–94.
[6] Anagnostou E, Karavasilis E, Potiri I, Constantinides V, Efstathopoulos E, Kapaki E, al rt. A cortical substrate for square-wave jerks in progressive supranuclear palsy. J Clin Neurol 2020;16:37–45.
[7] Joshi AC, Riley DE, Mustari MJ, Cohen ML, Leigh RJ. Selective defects of visual tracking in progressive supranuclear palsy (PSP): implications for mechanisms of motion vision. Vis Res 2010;50:761–71.
[8] Liao K, Wagner J, Joshi A, Estrovich I, Walker MF, Strupp M, et al. Why do patients with PSP fall? Evidence for abnormal otolith responses. Neurology 2008;70(10):802–9.
[9] McCarley RW. Neurobiology of REM and NREM sleep. Sleep Med 2007;8:302–30.
[10] Boissard R, Fort P, Gervasoni D, Barbagli B, Luppi P-H. Localization of the GABAergic and non-GABAergic neurons projecting to the sublaterodorsal nucleus and potentially gating paradoxical sleep onset. Eur J Neurosci 2003;18:1627–39.
[11] Höglinger GU, Respondek G, Stamelou M, Kurz C, Josephs KA, Lang AE, et al. Clinical diagnosis of progressive supranuclear palsy: the movement disorder society criteria: MDS Clinical Diagnostic Criteria for PSP. Mov Disord 2017;32:853–64.
[12] Golbe LI, Ohman-Strickland PA. A clinical rating scale for progressive supranuclear palsy. Brain 2007;130:1552–65.
[13] Movement Disorder Society Task Force on Rating Scales for Parkinson's Disease. The unified Parkinson's disease rating scale (UPDRS): status and recommendations. Mov Disord 2003;18:738–50.
[14] Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62.
[15] Seshagiri DV, Pal PK, Jain S, Yadav R. Optokinetic nystagmus in patients with SCA: a bedside test for oculomotor dysfunction grading. Neurology 2018 Sep 25;91(13):e1255–61.
[16] Berry RB, Brooks R, Gamaldo C, Harding SM, Lloyd RM, Quan SF, et al. AASM scoring manual updates for 2017 (version 2.4). J Clin Sleep Med 2017;13:665–6.
[17] Litvan I, Agid Y, Calne D, Campbell G, Dubois B, Duvoisin RC, et al. Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): report of the NINDS-SPSP International Workshop. Neurology 1996;47:1–9.
[18] Bhidayasiri R, Riley DE, Somers JT, Lerner AJ, Buttner-Ennever JA, Leigh RJ. Pathophysiology of slow vertical saccades in progressive supranuclear palsy. Neurology 2001;57:2070–7.
[19] Shaikh AG, Factor SA, Juncos J. Saccades in progressive supranuclear palsy - maladapted, irregular, curved, and slow. Mov Disord Clin Pract 2017;4:671–81.
[20] Terao Y, Fukuda H, Shirota Y, Yugeta A, Yoshioka M, Suzuki M, et al. Deterioration of horizontal saccades in progressive supranuclear palsy. Clin Neurophysiol 2013;124:354–63.
[21] Dement W, Kleitman N. The relation of eye movements during sleep to dream activity: an objective method for the study of dreaming. J Exp Psychol 1957;53:339–46.
[22] Everling S, Krappmann P, Flohr H. Cortical potentials preceding pro- and antisaccades in man. Electroencephalogr Clin Neurophysiol 1997;102:356–62.
[23] Moster ML, Goldberg G. Topography of scalp potentials preceding self-initiated saccades. Neurology 1990;40:644–8.
[24] Abe T, Ogawa K, Nittono H, Hori T. Lack of presaccadic positivity before rapid eye movements in human REM sleep. Neuroreport 2004;15:735–8.
[25] Schroeder LA, Rufra O, Sauvageot N, Fays F, Pieri V, Diederich NJ. Reduced rapid eye movement density in Parkinson disease: a polysomnography-based case-control study. Sleep 2016;39:2133–9.
[26] De Carli F, Proserpio P, Morrone E, Sartori I, Ferrara M, Gibbs SA, et al. Activation of the motor cortex during phasic rapid eye movement sleep. Ann Neurol 2016;79:326–30.