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Incidence of RBD and hallucination in patients affected by Parkinson's disease: 8-year follow-up

M. Onofrj[1] (✉) · A. Thomas[1] · G. D'Andreamatteo[1]
D. Iacono[1] · A.L. Luciano[1] · A. Di Rollo[1]
R. Di Mascio[2] · E. Ballone[2] · A. Di Iorio[3]

[1] Department of Oncology and Neuroscience; Neurophysiopathology, G. D'Annunzio University, Ospedale Civile di Pescara, Via Fonte Romana, I-65124 Pescara, Italy
[2] Institute of Statistics, G. D'Annunzio University, Chieti, Italy
[3] Department of Medicine and Ageing, Geriatric Unit, Via dei Vestini, Chieti, Italy;

Abstract We describe the 8-years follow-up of 80 patients affected by idiopathic, L-dopa-responsive Parkinson's disease. All patients were evaluated at baseline and during the follow-up with visual evoked potential, P300 event related potentials and polysomnography. The patients and their relatives compiled sleep and hallucination questionnaires. Statistical analysis was performed to evaluate if visual abnormalities, abnormal P300 recordings or sleep disturbances were linked to the development and hallucinations. Our results show that abnormal vision and abnormal P300 did not correlate with the incidence of hallucinations. However, the presence of REM sleep behavioral disorder (RBD) was significantly related to the development of hallucinations, independently of age, gender or duration of disease but dependent on the amount of dopaminoagonist treatment.

Many studies have reported visual abnormalities with electroretinogram and visual evoked potential (VEP) alterations in Parkinson's disease (PD) [1–3], showing that visual abnormalities are due to dopamine deficiency and related to the perception of the spatial frequency of stimuli [4]. Oddly enough, with the exception of one study based on color and contrast perception [5], visual abnormalities were not studied in relation to the occurrence of the well known "visual" complication of PD, i.e. visual hallucinations. Visual hallucinations are attributed to abnormalities of the ascending cholinergic and serotoninergic brainstem (and thalamic) pathways involved in the control of sleep-waking state, or to the defective visual processing accompanied by abnormal cortical release phenomenon [6].

The renovated approach to sleep studies in PD and parkinsonism has evidenced that a peculiar disturbance of rapid eye movement (REM) sleep phase, consisting of the loss of normal muscle inhibition during REM sleep and enacting of dreams, i.e. REM sleep behavior disorder (RBD), is present in idiopathic PD [7], in some parkinsonism states and in Lewy body disease (LBD). The presence of RBD has been associated with the occurrence of daytime hallucinations [8]. In order to understand whether hallucinations in PD are related to visual or sleep disturbances, we performed an 8-year follow-up of 80 patients affected by idiopathic, L-dopa responsive PD. All patients were evaluated for VEP alterations and contrast sensitivity, underwent visual P3 event related potential (ERP) recordings and polysomnography, and responded to sleep and hallucinations questionnaires, in order to assess the possible correlation with the onset or severity of hallucinations.

Consecutive patients with probable PD and their caregivers who were followed in the movement disorders outpatients offices were invited to participate in the study. Initial selections included 166 patients. At the end of the study, eight years after admission, 80 patients were considered to be affected by idiopathic PD because, despite occurrence of wearing-off or similar phenomenon, they were (1) still experiencing a benefit from dopaminomimetic therapies that had been increased by 1.5- to 3-times the amount administered at admission, (2) cognitive and behavioral functions were not altered during dopaminomimetic treatment, and (3) tremor was a consistent, although variable, feature in off periods.

Electroretinography (ERG) and polysomnography were performed, and VEPs, contrast sensitivity and visual P300 ERPs were recorded according to methods described in detail elsewhere [4, 9–11]. All electrophysiological recordings were performed at admission, before any treatment regimen was initiated in 52 patients, and 24 hours after the last L-dopa, dopaminoagonist or anticholinergic treatment in the other patients. Recordings were repeated with the same method at the end of the study. Criteria for VEP abnormality were set by the mean latency + 2 standard deviations (SD), for contrast sensitivity abnormality on 2 dB loss of 2–5 cycles per degree (cpd) spatial frequency, for ERG abnormality on the ratio below 50% of 1 vs 3 cpd evoked ERG, for visual P3 ERP abnormality on the mean latency + 1.5 SD. At admission, patients and family members were interviewed on their sleep behavior and sleep history using a simple sleep questionnaire, respecting the minimal ICSD (1997) criteria for RBD in agreement with the spouse's report [8], developed in our center: the questionnaire is proposed to patients and family members and investigates items such as quality of sleep, medication, vocalization, movements during sleep, nightmares, dream enactment, hallucinations when awaking from nightmares and frequency of movements during sleep. Patients and family members were asked with a questionnaire, part of the present state examination [12], about hallucinations and, if present, about the kind of hallucinations.

Questionnaires were administered once every year until the end of the study. Polysomnography in night sleep was performed whenever the sleep questionnaire suggested RBD and at the end of the study. All patients were evaluated at the beginning of the study with the Hoehn/Yahr scale [13], UPDRS [14] and MMSE [15].

Total daily intakes of L-dopa and dopaminoagonist were

compared with the other parameters; for dopaminoagonists an equivalent bromocriptine dose was calculated as 10 mg bromocriptine = 1 mg pergolide, 1 mg pramipexolo, 5 mg ropinirole or 1.5 mg cabergoline.

Systematic differences between hallucinating and non-hallucinating patients were evaluated using χ^2 test, Mantel-Haenzel tests for linear associations and Fisher's exact test. Factors independently associated with hallucinatory status were identified using logistic regression models (CATMOD procedure).

We forced in the logistic model two variables (visual abnormalities and P300), also if the univariated analysis reached a *p* value greater than 0.10. Our intention was to demonstrate the role that both visual abnormalities and P300 play on hallucinatory status development. The saturated logistic model also contained the variables age and sex. Adjusted odds ratio (OR) and 95% confidence interval (CI) were calculated from the estimated coefficients in the model. To evaluate the hierarchically best model, the conditional maximum likelihood ratio (CMLR) was performed, with or without interactions between main predictors. The Hosmer-Lemeshow test χ^2 (8 df), goodness of fit, was also performed. All analyses were performed using SAS package [16].

The RBD questionnaire was validated in comparison with polysomnography recordings: all patients classified as having RBD by questionnaire had polysomnographic evidence of RBD, only 2 patients classified as non-RBD by the questionnaire had 1 or 2 episodes of RBD evidenced by polysomnography (sensitivity, 100%; specificity, 96.3%).

According to the Hoehn/Yahr scale at baseline, 44 patients were at stage 1, 14 patients at stage 1.5, 10 patients at stage 2, and 12 patients at stage 2.5. After 8 years, the staging of the same study population was as follows: 20 patients at stage 2, 14 patients at stage 2.5, 39 patients at stage 3, and 7 patients at stage 4.

At baseline, visual abnormalities were found in 28 PD patients (Table 1). The chronic dopaminergic treatment in "on" state reduced visual abnormalities to normal limits in the majority of patients and at the end of the study visual abnormalities were observed in "off" and "on" state in only 27 patients. Linear regressions of VEP latencies and amplitudes vs. duration and stage of Parkinson's disease did not reach statistical significance. The prevalence of hallucinations was below 40% both in patients with and without visual abnormalities (not significant at χ^2). A delay of P300 was recorded in 2 patients at baseline and in 15 patients during "on" state and 27 patients during "off" state at the 8-year fol-

Table 1 Prevalence of visual and P300 abnormalities, RBD and hallucinations in 80 patients with idiopathic L-dopa-responsive Parkinson's disease. Values are number of patients

	Baseline	3 years	6 years		8 years	
			On	Off	On	Off
Vision						
Normal	52	66	67	59	58	53
Abnormal	28	14	13	21	22	27
P300						
Normal	78	71	69	59	65	53
Abnormal	2	9	11	21	15	27
RBD	5	9	23	–	27	–
Hallucinations	5	8	19	–	31	–

RBD, REM sleep behavioral disorder

Table 2 Prevalence of visual and P300 abnormalities and RBD in patients with hallucinations, identified from 80 patients with idiopathic Parkinson's disease and followed for 8 years. Value are number of patients

	Baseline (n=5)	3 years (n=8)	6 years (n=19)	8 years (n=31)
Vision				
Normal	3	6	11	19
Abnormal	2	2	7	12
P300				
Normal	5	7	13	24
Abnormal	0	1	5	7
RBD	3	8	19	27

RBD, REM sleep behavior disorder

low-up. P300 delay was distributed equally in patients with and without hallucinations, (NS at χ^2). CMLR excluded P300 as a main predictor.

Throughout the follow-up observation, 27 patients were classified to be clinically affected by RBD (questionnaire plus PSG).

At the last visit, only 4 patients describing hallucinations were classified among the normal sleepers (n=53), while 27 PD patients had RBD and experienced hallucinations independently of age or gender. There was a higher incidence of hallucinations in stages 3 and 4 PD patients, not reaching statistical significance ($p<0.6$). CMLR showed that the presence of RBD was significantly related and predictive of the development of hallucinations ($p<0.001$), independently of MMSE score, Hoehn/Yahr stage or UPDRS evaluation. RBD was not correlated with visual abnormalities ($p<0.7$), just as hallucinations were not correlated with visual abnormalities ($p<0.2$). RBD and hallucinations were related to the amount of dopaminoagonist drugs administered: patients who experienced both RBD and hallucinations assumed 32±6 mg/day bromocriptine equivalent, while those with neither RBD nor hallucinations assumed 11±6 mg/day bromocriptine equivalent ($p<0.001$). Table 2 shows the prevalence of visual P300 abnormalities and RBD in patients with hallucinations throughout the 8-year follow-up.

Discussion

Visual abnormalities or abnormalities of cognitive ERPs do not correlate with the presence of visual hallucinations, and do not correlate with the presence of RBD. RBD is significantly correlated with hallucinations independently of duration, gender, age, stage of disease and is correlated with the administered amount of dopaminoagonist therapy. This finding is not surprising as visual abnormalities are corrected by L-dopa or dopaminoagonist therapy, while hallucinations and RBD are precipitated by dopaminoagonist therapy and L-dopa [8].

Many authors have suggested that sleep disruptions, vivid dreams and hallucinations may have a common anatomical locus [17, 18], but only a few studies reported visual hallucinations that occur early in the course of PD. In the nineteenth century, some authors reported hallucinosis in untreated parkinsonian patients [19, 20]. McKee et al. [21] suggested that the hallucinations should be attributed to midbrain alterations, at one time, disturbing sleep or giving rise to visual hallucinations, as the connections of the substantia nigra pars reticulata to brain stem nuclei regulating REM sleep and to the limbic structures may provide an anatomical explanation for both clinical manifestations.

The relationship between hallucinations and sleep disturbances has recently been undergoing a controversial debate. Some authors have suggested that hallucinations, together with sleep disturbances and psychosis, are part of a kindling phenomenon [22], while others stressed the early occurrence of hallucinations, independently of major mental disturbances [23]. The debate has also recently been focused on the hypothesis that hallucinations might be dependent on an alteration of cholinergic pathways [24]. Our study does not address the origin of the disturbances, but undoubtedly shows that the visual abnormalities of PD are not linked to hallucinations. This lack of correlation suggests that the visual abnormalities are not linked to the receptorial neurotrasmitter abnormalities that generate hallucinations and RBD.

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