



Original Article

Hallucinations in narcolepsy with and without cataplexy: Contrasts with Parkinson's disease

Smaranda Leu-Semenescu^{a,b}, Valerie Cochen De Cock^c, Valerie Dauriac Le Masson^d, Rachel Debs^e, Sophie Lavault^a, Emmanuel Roze^f, Marie Vidailhet^{b,f}, Isabelle Arnulf^{a,b,*}

^a Sleep Disorders Unit, Pitié-Salpêtrière Hospital, AP-HP, Paris 6 University, Paris, France

^b INSERM UMRS 975, Paris, France

^c Department of Neurology, Gui de Chauliac Hospital, Montpellier, France

^d Department of Medical Information, Sainte-Anne Hospital, Paris, France

^e Department of Neurology, Purpan Hospital, Toulouse, France

^f Department of Neurology, Pitié-Salpêtrière Hospital, AP-HP, Paris 6 University, Paris, France

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ABSTRACT

Background: Narcolepsy and Parkinson's disease (PD) are associated with hallucinations, excessive daytime sleepiness, REM sleep behavior disorder (RBD), as well as complete (narcolepsy with cataplexy) vs. partial (PD, narcolepsy without cataplexy) hypocretin-1 deficiency.

Objective: To compare the hallucinations associated with narcolepsy to those of PD.

Methods: One hundred patients with narcolepsy (with and without cataplexy) and 100 patients with PD were consecutively interviewed about their hallucinations (frequency, phenomenology, insight into unreality and association with sleep) as well as their risk factors.

Results: Hallucinations occurred more frequently and with more motor and multimodal aspects in narcolepsy with cataplexy (59%) than in narcolepsy without cataplexy (28%) and PD (26%). Compared to PD, the hallucinations in narcolepsy were less frequently of the passage/presence type (passage: brief visions of a person or animal passing sideways; presence: perception that a living character or an animal is behind or near the subject, without the subject actually seeing, hearing or touching it), more frequently auditory and more often associated with sleep. However, in 40% of the patients with narcolepsy and 54% of the patients with PD, the hallucinations occurred while the patients were wide awake. Patients with cataplexy had reduced immediate insight into the unreality of their hallucinations compared to patients with PD, but the delusions were exceptional (2%), transient and based on hallucinations in both groups. The risk factors for hallucinations were sleep paralysis and RBD in narcolepsy and motor disability and sleepiness in PD.

Conclusions: The multimodal, dreamlike aspect of hallucinations in narcolepsy with cataplexy could transiently impair the patients' insight. The high frequency of these hallucinations (compared to those in narcolepsy without cataplexy or PD) suggests that complete (more than partial) hypocretin-1 deficiency promotes hallucinations.

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1. Introduction

Because of their possible link to the dreaming process, hallucinations remain some of the most intriguing phenomena in neurology. Narcolepsy with cataplexy is a model for studying hallucinations in a neurological disease because of the following characteristics: high frequency (45–80%), occurrence in young subjects

without major cognitive impairment, occurrence at sleep onset (especially REM sleep) and offset (sleep-related hallucinations), and possible relationship to dreaming phenomena [1–4]. However, the respective influences of cataplexy and REM sleep behavior disorder (RBD) on hallucinations have not been studied [5]. Narcoleptic hallucinations differ from schizophrenic hallucinations because they are particularly associated with sleep are more frequently visual and multimodal and include exceptional delusional thinking [3,4,6].

These hallucinations do not resemble hallucinations in psychiatric diseases and may share similarities with those reported in other neurological diseases, such as Guillain-Barré Syndrome [7], Charles-Bonnet syndrome and Parkinson's disease (PD). One-third

* Corresponding author at: Unité des Pathologies du Sommeil, Hôpital Pitié-Salpêtrière, 47-83 Boulevard de l'Hôpital, 75651 Paris Cedex 13, France. Tel.: +33 142167702; fax: +33 14216 77 00.

E-mail addresses: isabelle.arnulf@psl.aphp.fr, isabelle.arnulf@psl.ap-hop-paris.fr (I. Arnulf).

of patients with PD experience hallucinations, which are mostly visual, while 4% have delusional thinking [8,9]. PD hallucinations are more frequent in patients with old age, cognitive impairment, visual defects and in those who are using dopamine agonists [10]. Several pieces of evidence point to a link between the hallucinations in PD and the disturbances of REM sleep and dreaming. Hallucinations are more frequent in patients with excessive sleepiness [8]. They may occur at the end of REM sleep episodes both at night and during the day, suggesting that they are REM-sleep-related [11]. Some patients with PD experience severe sleepiness and sleep onset in REM periods that resemble a secondary narcolepsy without cataplexy [12]. In addition, RBD affects 30–60% of patients with PD [13,14], suggesting that the executive systems of REM sleep are damaged in PD brains. Of interest, the hypocretin-1 neurons in the hypothalamus, which are completely lost in primary narcolepsy/cataplexy [15], are partially damaged in narcolepsy without cataplexy [16] and in PD [17,18]. However, hallucinations may also occur in wide-awake patients with PD [19]. Therefore, the objective of this study was to determine, in a large cross-sectional cohort, if hallucinations are as frequent in PD as they are in narcolepsy with or without cataplexy. We also investigated whether there were phenomenological similarities between the hallucinations in PD and those in narcolepsy, which could support a common mechanism. The association between clinical RBD and hallucinations was particularly studied.

2. Methods

2.1. Subjects

All patients provided written informed consent for the protocol, which was approved by the local ethics committee. One hundred consecutive patients who met the criteria for narcolepsy with or without cataplexy were recruited [20]. The patients were treated and regularly followed up in the Sleep Disorders Unit of the Pitié-Salpêtrière University Hospital. The 100 patients underwent a classical polysomnography followed by five multiple sleep latency tests. Narcoleptics without cataplexy had an undisturbed nocturnal sleep lasting 6 h or more, mean daytime sleep latencies lower than 8 min and two or more sleep onset in REM periods. Plus, long term sleep recordings during 48 h were performed [21] as soon as idiopathic hypersomnia with long sleep time was suspected by interview. Unrecognized chronic sleep restriction was also ruled out using interview, sleep agenda and test of extending sleep. One hundred consecutive patients, who met the criteria for idiopathic PD [22], were recruited from the Movement Disorders Unit of the same hospital. The patients were treated and their cognitive status (i.e., a Mini-Mental State Examination [MMSE] score above 24) allowed them to participate in the study [23]. The characteristics of RBD in this cohort have already been published [14].

2.2. Interviews

The same neurologists conducted in-person interviews of the patients with PD and those with narcolepsy. They collected the following information about the patients: demographics; medical history; disease progression; treatment; and the presence of clinical RBD (confirmed by the bed-partner) [14,24], restless legs syndrome [25], daytime sleepiness using the Epworth sleepiness scale [26] and depression using the Beck depression inventory [27]. In patients with narcolepsy, the presence of cataplexy, sleep paralysis and the genotype DQB1*0602 of the human leukocyte antigen were assessed. The demographic and clinical characteristics of patients with narcolepsy (with and without cataplexy) are shown in Supplementary Table A. In patients with PD, the Frontal

Assessment Battery [28], MMSE [23] and Unified Parkinson's Disease Rating Scale (UPDRS)-Part III [29] were assessed. The total daily levodopa-equivalent dose was calculated [30].

2.3. Phenomenology of hallucinations

Patients were interviewed using a semi-structured questionnaire that gathered information regarding the frequency, type, content and course of the hallucinations over their lifetime. If they relabeled the hallucinations as pathological while they were in progress or just after experiencing them, we concluded that there was insight related to the hallucination; otherwise, the patient was scored as having a lack of insight. We classified the mental experiences as vivid dreams (qualitatively vivid, seemingly real, temporally condensed, internally organized and coherent dreams) [31], illusions (perception of real objects or persons in a distorted manner, or the external stimulus is perceived but then misinterpreted) or as the following types of hallucinations (perceptions without any real objects to be perceived): minor (presence and passage hallucinations), formed with a single sensory modality (visual, auditory, tactile, motor, olfactory), multimodal (with at least two sensory types involved in the same hallucination), or elaborate (a brief scenario) [8]. Presence hallucinations were defined as the perception that a living character or an animal is behind or near to the subject, without the subject actually seeing, hearing or touching it [8]. Passage hallucinations were the brief visions of a person or animal passing sideways [8].

2.4. Statistical analysis

Groups were compared by univariate analyses using the chi-square test for categorical variables and the Mann-Whitney two-tailed U-test for continuous variables. The *p* value for significance was set below 0.05. The multivariate analysis used a stepwise logistic regression and introduced all covariates that showed significance lower than 0.15. The levodopa-equivalent dose was dichotomized by using the median as a cut-off. Cognitive disorders were defined as an MMSE score lower than 24 and depression was defined as a Beck depression inventory score greater than 13 [32]. Sleepiness and UPDRS scores were entered as continuous variables in the models. Odds ratios (OR) are presented with their 95% confidence intervals in parentheses. Statistical analyses were performed using STATA-8-SE software (StataCorp LP, College Station, TX, USA).

3. Results

3.1. Hallucinations in narcolepsy

3.1.1. Vivid dreams

Eight (8%) patients with narcolepsy reported some recurrent vivid dreams. The dreams were mostly bloody. A patient dreamed he accidentally killed his wife. Another dreamt he ran on his bloody, amputated stumps (knees and elbows). He also was tortured (he felt this pain) while a prisoner of war and was crushed under the wheels of a tank in his nightmare. Of note, the patient was not a soldier and had no traumatic war experience. Two patients reported vivid dreams involving their participation in a dramatic car accident. One patient reported that the content of the vivid dream occasionally leaked into wakefulness (i.e., it continued for a few seconds once awake). For example, after he dreamed of dead bodies, images of decapitated heads (or his wife covered by the blood) persisted for five seconds on the sheets of his bed while the lights were on. Pleasant vivid dreams were rarer and included a sense of well being while flying in the blue sky or the feeling of a

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