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CASE REPORTS

Melatonin-Responsive Complex Nocturnal Visual Hallucinations

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Complex nocturnal visual hallucinations are vivid, dramatic, intricate visual hallucinations occurring during sleep onset or awakenings at night, generally lasting for a few minutes at most and disappearing with increased levels of light. They may occur in a number of neurological conditions, as well as in normal individuals. The optimal treatment for this condition remains unclear. We describe three patients with complex nocturnal visual hallucinations in whom melatonin brought about a dramatic improvement in symptoms. Our report suggests that melatonin may be a safe, effective treatment for this rare but often distressing and anxiety-provoking condition.

Keywords: complex nocturnal visual hallucinations, hallucinations, melatonin, parasomnias

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INTRODUCTION

The term "complex nocturnal visual hallucinations" has been used to describe the phenomenon of vivid, dramatic, detailed, and often intricate visual hallucinations occurring during sleep onset or awakenings at night, generally lasting for a few minutes at most and disappearing with increased levels of light.[1] Most patients have insight into the fact that these hallucinations are not real, but they may nevertheless cause anxiety and distress. However, optimal treatment of this condition remains unclear. We describe three cases of complex nocturnal visual hallucinations that responded to melatonin therapy.

REPORT OF CASES

Case 1

The first case involves a 59-year-old woman who worked as a police employee. She had no significant neurological impairments, and had a history of anxiety and sleepwalking as a child (that resolved spontaneously in adolescence), as well as a very abusive childhood.

In her 20s, she began experiencing visual hallucinations in the middle of the night upon awakening, usually after 2 to 3 hours of sleep. These included seeing people in her room, bugs in her bed, and tarantulas on the ceiling. At times, she saw similar images, as well as a paisley pattern (akin to looking through sheer lace), while going to the bathroom at night in low lighting. She stated that she was fully awake when she saw these images, which persisted for seconds to minutes and vanished upon turning on the light. Some of these images appeared to move, for example, a wedding dress floating under the ceiling, whereas others remained immobile.

These hallucinations appeared very real and had no auditory or tactile accompaniment, although early in the course she experienced very rare auditory hallucinations at sleep onset, such as hearing a word in her head, which occurred separately from the visual hallucinations. The hallucinations were not associated with dreams. The frequency of these hallucinations waxed and waned throughout her life, and worsening with stress; they were almost daily at the time of presentation.

Initially she would respond with fright to these images, screaming and bolting out of bed fully awake, occasionally injuring herself as a result; later she "got used to them." She had a history of heavy weekend alcohol use when they began, and subsequently quit drinking, but the hallucinations persisted. She was not on a beta blocker when her hallucinations initially appeared, although propranolol 40 mg twice a day was added for palpitations approximately 2.5 years prior. She was also on venlafaxine 37.5 mg a day for her anxiety. She had no significant visual complaints, and in 2014 she underwent an optometric evaluation that showed full visual fields, bilateral best corrected visual acuity of 20/30, keratitis sicca, and bilateral nuclear sclerosis, but no retinal disease or glaucoma.

In 2015, she underwent polysomnography (PSG) for complaints of snoring, choking/gasping during sleep, and daytime sleepiness, and was found to have mild obstructive sleep apnea (OSA), with an apnea-hypopnea index (AHI) of 5.9 events/h. She was started on treatment with an auto-adjusting continuous positive airway pressure device, with which she had trouble remaining adherent; she abandoned its use, and it did not affect the frequency or nature of her hallucinations. A few months later she was started on melatonin 10 mg a night; this improved her self-reported sleep duration from 6.5 hours to about 7.25 hours and reduced her nocturnal awakenings from four to five per night to zero to once per night. Within 1 week of initiating melatonin, she noticed a dramatic improvement in the frequency ("decreased by 95%") and intensity (would now only occasionally see immobile unformed patterns on the ceiling) of her hallucinations. She subsequently combined 5 mg immediate-release (to treat the hallucinations) and 5 mg timed-release (to improve sleep continuity) forms of melatonin

with near-resolution of hallucinations; this benefit is currently sustained.

Case 2

The second case involves a 45-year-old woman with diabetes and no significant neurological impairments, in whom moderate OSA (AHI 26.6 events/h) was diagnosed by PSG in 2009, and whose snoring and daytime sleepiness were effectively controlled on continuous positive airway pressure (CPAP). In 2013, she was started on bisoprolol for high blood pressure. She had no visual complaints, and optometric examination earlier this year showed a visual acuity of 20/20 and full visual fields bilaterally, with no retinal disease or glaucoma.

She also had a history of sleepwalking and sleeptalking/sleepscreaming since childhood, now occurring two to five times per month, usually in the first half of the night, and often triggered by periods of stress. Her bedpartners also noted occasional kicking in her sleep, and there were rare episodes of possible dream enacting behavior (she recalled two episodes in the remote past when she punched and kicked in her sleep and had been dreaming of fighting and trying to "keep the offenders down"); however, for the most part there was no dream recall with her abnormal sleep behaviors.

She had a history of occasional bouts of anxiety/depression, although a mood disorder was not formally diagnosed nor was the patient taking mood stabilizers. In 2015, while still adherent to CPAP and with a residual AHI that was consistently normal on multiple compliance downloads, she started to experience visual hallucinations two to three times per week, distinct from her sleeptalking/sleepscreaming episodes, generally occurring on awakening from sleep in the middle of the night (usually around 2:00–3:00 AM), consisting mainly of spiders climbing from the floor to the walls onto the ceiling fan, near her fax machine, and in her bed; she occasionally had accompanying tactile hallucinations (could "feel the spiders falling"). The hallucinations lasted several seconds to up to 1 minute ("once a spider crawls too close or falls, the image is gone"), and were not affected by light. She was not sure if she was always fully awake, but the hallucinations seemed very real.

She was then started on nightly melatonin 5 mg taken 20 to 30 minutes before bedtime, which improved her self-reported sleep duration from 5.5 hours to 6.5 hours, and reduced her nocturnal awakenings from two to three time a night to zero to one time a night. Within a week of initiating melatonin, she reported a significant reduction in the frequency of these hallucinations (to about once or twice a week). When she switched to the 10-mg timed-release form, both the hallucinations and sleeptalking/sleepscreaming completely resolved; this benefit is currently sustained.

Case 3

The third case involves a 65-year-old woman who was a social drinker with no history of neurodegenerative disease, who was started on metoprolol 100 mg twice a day in 2012 for hypertension, and with a history of left nephrectomy secondary to nephrosclerosis, arteriolar hyalinosis and near-complete renal artery stenosis who had no significant psychiatric history and was not taking any psychotropic medications. She had a history of bilateral laser vision correction and cataract surgeries, and optometric evaluation in 2017 showed visual acuities of 20/50 in the right eye and 20/70 in the left eye, but no retinal disease or glaucoma.

In 2014, she presented with a 3-year history of insomnia due to frightening hallucinations that occurred on awakening from sleep in the middle of the night. They occurred nearly every night and were complex (seeing a dog or a cat in the corner of her room, spiders and bugs moving on the floor and in her bed, a shower hovering over her head), and were not part of preceding dreams. They lasted for up to 1 minute and disappeared with increased levels of illumination or when the patient became fully awake. There was no auditory or tactile component to these hallucinations. These hallucinations were anxiety provoking and frequently caused her leap out of bed fully awake. She denied sleep paralysis or excessive daytime sleepiness.

There was also a history of sleepwalking and dream enactment; for example, she would dream of moving a painting, and the painting was actually moved in the morning. Sometimes she would wake up in a random corner of the house or in the kitchen with a knife in her hand, stabbing the wall, and remembering that she was dreaming of trying to "kill bugs." On another occasion, she dismantled a lamp in her sleep, and recalled dreaming of there being a mouse in the lamp. Because she lived alone, she could not provide further details of her parasomnias, although on a couple of occasions visiting family members witnessed her getting out of bed confused. She could only recall one episode of sleepwalking in childhood.

Bran magnetic resonance imaging was performed without contrast in early 2016, with normal results. She did not have any visual complaints, and underwent optometric evaluation in August 2017 that showed a visual acuity of 20/50 in the right eye and 20/70 in the left eye with bilateral nuclear sclerosis, but no retinal disease or glaucoma.

She underwent PSG in 2014 at initial presentation and obtained a diagnosis of moderate OSA (AHI 20 events/h); no dream-enacting behavior was captured and rapid eye movement (REM) atonia was well preserved, although occasional periodic limb movements of sleep were seen in REM sleep. For her OSA, she elected to use an oral appliance, which she subsequently abandoned due to lack of perceived benefit (and which did not improve hallucinations or parasomnias).

For her hallucinations and insomnia, she was started on melatonin 3 mg a night in 2014, which did not provide a benefit. She was instructed on sleep hygiene; she stopped watching TV in bed, avoided caffeine, and regulated her sleep schedule. This, in combination with an increase in melatonin dosage to 5 mg nightly, resulted in a significant improvement in the hallucinations (decreased to once or twice per month) and dream enactment. Her self-reported sleep duration remained the same at 9 h/night, but she stated that her nocturnal awakenings, which had previously been occurring three to four times a night, were eliminated. Because of initial complaints of morning sleepiness, the dose of melatonin was decreased back to 3 mg, but both hallucinations and sleepwalking recurred, so she went back to taking melatonin 5 mg in combination with a 5-mg timed-release form. Despite this higher total dose of melatonin, her side effect of morning sleepiness did not recur,

and the hallucinations do not occur more than three times a month on this regimen.

DISCUSSION

Complex visual hallucinations have been described in a number of conditions, including visual impairment (Charles-Bonnet syndrome, seen with macular degeneration, cataracts, diabetic retinopathy, glaucoma, etc.),[2,3] brainstem disorders (peduncular hallucinosis), parietal[4] and occipital lobe lesions,[5] neurodegenerative conditions such as treated Parkinson and untreated Lewy body dementia,[1] epilepsy,[6] psychiatric conditions such as schizophrenia,[7] with medication use (especially beta blockers and dopaminergic agents), and with alcohol and hallucinogen use.[7,8] Although hallucinations in most of these conditions occur during both day and night (with a tendency to occur during situations of low illumination in Charles Bonnet syndrome), the term "complex nocturnal visual hallucinations" generally refers to hallucinations occurring exclusively or predominantly at night, usually during periods of abrupt awakening from sleep; the third edition of the International Classification of Sleep Disorders classifies them as a parasomnia.[9] The hypnagogic and hypnopompic hallucinations that occur in narcolepsy-cataplexy syndrome due to REM sleep intrusion may represent a variant of this phenomenon, but unlike complex nocturnal visual hallucinations, they are usually accompanied by complaints of excessive daytime sleepiness, cataplexy and sleep paralysis. In addition to the aforementioned conditions, complex nocturnal visual hallucinations may be seen in normal individuals. Prior attempts to treat complex nocturnal visual hallucinations with benzodiazepines and tricyclic antidepressants have been unsuccessful.[1]

Given the rarity of complex nocturnal visual hallucinations, there is a paucity of descriptions in the literature; in a small study of 12 patients, Silber et al.[1] noted a mean age of onset in the fifth decade, with a mean event frequency of four times a week. As with our cases, they found that hallucinations were primarily visual (sometimes accompanied by unrelated auditory hallucinations) and included highly detailed, at times bizarre people and animals, with a striking stereotypy within individuals. They also noted a female preponderance; 11 of their patients were women. All of our patients were women as well; however, both the case series by Silber et al. and our case series are too small to draw definite conclusions about sex-based prevalence. As with our patients, they noted frequent coexisting independent parasomnias (sleepwalking, sleeptalking, and dream enactment due to REM sleep behavior disorder [RBD]; our patient in case 2 had sleeptalking, sleepscreaming, and sleepwalking and possible dream enacting behavior). It is unclear whether our patient in case 3 truly had RBD; although she described sleepwalking and dream enactment, she did not meet criteria for REM without atonia based on PSG findings, and therefore may have actually had a non-rapid eye movement sleep parasomnia (getting out of bed while apparently enacting a dream would suggest this). However, in both our case series as well as those of Silber et al., patients usually were fully awake and had complete recall of the hallucinations themselves, as opposed to their parasomnias where recall was variable. This suggests that although they may coexist with other parasomnias, complex nocturnal visual hallucinations are a distinct parasomnia in their own right.

The etiology of complex nocturnal visual hallucinations in our patients is unclear. Although none of our patients exhibited extrapyramidal signs on neurological examination (such as axial or appendicular cogwheel rigidity, resting tremor, or autonomic or gait instability), hallucinations may be the presenting symptom for neurodegenerative conditions such as Lewy body disease[10]; it is possible that this may be true of our cases as well, and that they may go on to develop overt signs of such a disorder. Therefore, serial neurological examinations are recommended for all patients presenting with hallucinations, whether nocturnal or diurnal. Similarly, although all our patients had nonfocal neurological examinations, consideration should be given to performing appropriate neuroimaging in patients with hallucinations and clinical findings suggestive of cortical or brainstem disease. Electroencephalography (EEG) should be obtained in patients in whom seizures are being considered; all three of our patients had EEG channels as part of their standard PSG tests (C3, C4, O1, O2) as well as EMG channels in the bilateral tibialis anterior muscles; in two patients (the patients in case 1 and case 3), the montage included temporal EEG leads (T3 and T4) and an additional EMG electrode in each upper extremity; epileptiform activity was not recorded in any of our patients. Patients with occipital lobe epilepsy generally experience simple hallucinations (unformed images), unlike our patients, and while there have been rare cases of complex visual hallucinations occurring with temporal lobe epilepsy,[6] these tend to be limited to the relevant visual field,[11] and occur during the day in addition to being nocturnal. Indeed, the occurrence of hallucinations purely at night in our patients, associated with sleep onset or awakenings from sleep and related to low levels of illumination, sets them apart from those seen in the aforementioned neurological conditions. As mentioned, this pattern may be seen with visual impairment, where it is thought to occur as a release phenomenon[2,3]; however, visual impairment-related complex nocturnal hallucinations tend to be much more prolonged than those experienced by our patients.[8] Nevertheless, visual field and acuity testing, as well as ophthalmological/optometric referral as appropriate, is important in those patients in whom visual impairment is considered a potential cause of complex nocturnal visual hallucinations. All our patients did undergo optometric evaluation; although the patient in case 3 had relatively poor visual acuity, the patients in case 1 and case 2 demonstrated full visual fields and good visual acuity (after correction of refractory errors). One cautionary note is the existence of reports in the literature of Charles Bonnet-type hallucinations in patients with relatively preserved visual acuity and lesions in other parts of the visual pathway resulting in defective visual fields.[12,13]

None of our patients complained of cataplexy or sleep paralysis, and although our patients in case 1 and case 2 did complain of excessive daytime sleepiness, this was attributed to underlying OSA. Nevertheless, we cannot completely rule out that our patients may have been suffering from narcolepsy without cataplexy (or narcolepsy with cataplexy suppressed by

a REM-suppressing antidepressant, venlafaxine, in case 1). Because our patients did not have significant complaints beyond the hallucinations themselves, which responded to melatonin, we did not perform Multiple Sleep Latency Testing to evaluate for the possibility of narcolepsy, but in patients in whom this is a significant clinical concern, such an evaluation should be considered.

Both of our patients with additional nonhallucination parasomnias had OSA (adequately treated with CPAP in case 2 and untreated in case 3), which may have been triggers for these events, especially in view of an absence of childhood history of parasomnias; however, it is unclear what role, if any, OSA played in the hallucinations of these patients. To the best of our knowledge, there have not been any reports of nocturnal visual hallucinations associated with OSA, but in case 1 and case 3, the patients were unable to remain adherent to treatment for their OSA, and this may have disrupted their sleep architecture and caused frequent awakenings, contributing in some way to increased frequency of hallucinations.

Nightmares were also considered an unlikely explanation for the hallucinations, as our patients experienced them while fully awake and had no dream recall associated with them. Although our patient in case 1 had a diagnosis of anxiety and our patient in case 2 complained of episodes of mood dysfunction, they had no other symptoms of schizophrenia or psychosis and had no daytime hallucinations; one of the patients in the case series by Silber at al.[1] also carried a diagnosis of anxiety, but the nature of the relationship between anxiety and complex nocturnal visual hallucinations, if any, remains unclear.

The mechanism by which melatonin treats complex nocturnal visual hallucinations remains speculative. Exogenous melatonin is a well-known soporific and sleep phase-altering agent, and meta-analyses suggest that, compared to placebo, it modestly reduces sleep onset latency, increases sleep efficiency, and increases total sleep duration in healthy adults.[14] Additionally, one study found a tendency for prolonged stage N2 sleep and shorter stage N3 sleep after the consumption of physiological doses of melatonin, whereas stage N1 and stage R sleep were unaffected.[15] This may be the mechanism behind the effectiveness of melatonin in treating parasomnias caused by partial arousals, such as sleep terrors and sleepwalking, as reported in the literature,[16,17] and similar to our observations of patients in case 2 and case 3. However, it is to be noted that the literature regarding changes in sleep architecture produced by melatonin are scant and contradictory.[12] Along the same lines, it is possible that increased sleep duration and an alteration of sleep architecture is responsible for the response of complex nocturnal visual hallucinations to melatonin. After starting melatonin, all three of our patients had fewer nocturnal awakenings, and patients in case 1 and case 2 reported modestly longer sleep duration. Randomized controlled trials, with baseline and posttreatment PSG and actigraphy evaluation in patients with complex nocturnal hallucinations on melatonin therapy, may help to elucidate these relationships. An intriguing question is the relationship between beta-blocker use and hallucinations; all three of our patients were started on beta blockers at some point in the course of their history. Beta blockers are known to suppress melatonin production[18]; in the case series described by Silber et al.,[1] three patients who were on beta blockers noted complete resolution of hallucinations when the beta blockers were discontinued, raising the possibility that blunting of endogenous melatonin production may be a cause of complex nocturnal visual hallucinations. In our case 1, hallucinations preceded beta-blocker use by many years, suggesting that they were unrelated, but in case 2 and case 3 the patients experienced onset of hallucinations after initiation of beta blockers, with hallucinations responding to melatonin despite continuing the beta blocker. A recent study showed that, compared to placebo, a short course of nightly melatonin supplementation improved total sleep time, sleep efficiency, and sleep onset latency in hypertensive patients taking beta blockers.[19] It is therefore possible that, at least in patients on beta blockers, nocturnal hallucinations occur as a result of adverse effects on sleep architecture caused by melatonin suppression, and either withdrawing the beta blocker or supplementing melatonin may reduce the hallucinations

In summary, our case series describes the novel observation that melatonin may be a relatively safe, inexpensive, and easily available treatment option for patients with nocturnal visual hallucinations. However, large randomized trials to validate our empirical observations are needed.

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DISCLOSURE STATEMENT

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