Sleep Medicine 58 (2019) 102–106

Contents lists available at ScienceDirect

Sleep Medicine

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

Original Article

Clinical features of isolated sleep paralysis

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ARTICLE INFO

Article history:
Received 15 October 2018
Received in revised form
22 February 2019
Accepted 12 March 2019
Available online 23 March 2019

Keywords:
Sleep paralysis
Isolated sleep paralysis
Sleep-wake disorder
Anomalous experiences
Parasomnia
Hallucinations

ABSTRACT

Objective: Isolated sleep paralysis (ISP) is a relatively common parasomnia often accompanied by fear and distress. However, little is known about the range and relative severities of typical ISP symptoms and accompanying hallucinations. Furthermore, there have been inconsistent findings with regard to demographic differences in ISP.
Patients/Method: In sum, 185 individuals with ISP (and 322 controls) were assessed for 27 symptoms and hallucinations using a clinical interview and trained diagnosticians. Insomnia symptoms were also assessed.
Results: Rates of ISP did not differ according to gender or ethnic minority status, but higher levels of insomnia were associated with episodes. The participants with ISP reported a mean of 7.73 symptoms beyond atonia. Hallucinations of the presence of others were relatively common. Specifically, 57.84% of the sample sensed a presence in the room with them during ISP, and the majority believed it to be a non-human presence. In addition, 21.62% of the sample experienced visual hallucinations of others, with the majority perceiving strangers as opposed to known individuals. A panoply of supernatural/paranormal entities were reported by the 24.32% of participants who hallucinated non-human beings. A minority of individuals with ISP experienced clinically-significant distress (10.27%) and/or impairment (7.57%) as a result of episodes.
Conclusion: ISP episodes were complex and often multisensorial experiences, and the majority of assessed symptoms were associated with clinically-significant levels of fear/distress. Vivid hallucinations of other people and entities were common as well, and it is recommended that ISP be assessed when patients report seemingly anomalous experiences.

1. Introduction

Sleep paralysis[1] (SP) is a transient, dissociated sleep state during which REM sleep atonia continues into wakeful consciousness. It is a fairly common experience found in 7.6% of the general population, 28.3% of students, and 31.9% of psychiatric patients [1]. Reasons for higher rates in the latter two populations are somewhat unclear (see Ref. [2]), but could be due to factors such as a higher frequency of sleep disruptions, substance use, and more variable sleep schedules. When SP occurs independently of conditions such as narcolepsy, it is termed isolated sleep paralysis (ISP) [3].

Research over the past decade has made important gains in terms of understanding certain aspects of ISP. For instance, Brooks & Peever [4] identified the neurotransmitters involved in general REM sleep atonia whereas Denis et al. [5], using a sample of twins, found a possible genetic predisposition to ISP (ie, a polymorphism on the PER2 gene). However, when compared to other, more well-studied disorders, many gaps in the literature remain.

1.1. Variables associated with ISP

Recent reviews [6,7] cataloged many of the potential risk factors and/or variables associated for SP. Unfortunately, a heterogeneity of sample compositions and non-standardized methods of assessment (eg, brief self-report questionnaires vs. clinical interviews; inability to establish ISP as opposed to SP) appear to have led to inconsistent results.

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[1] SP = sleep paralysis, ISP = isolated sleep paralysis, REM = rapid eye movement.

https://doi.org/10.1016/j.sleep.2019.03.007
1389-9457/

The impacts of demographic differences have been particularly variable. In terms of gender, studies can be found which report higher rates of ISP in males [8,9], higher rates in females [10], and some revealing no significant differences [9]. In terms of ethnicity, higher rates of ISP have been found in non-Whites [11], however, this is not always the case [12].

The association of ISP with sleep difficulties appear to be more consistent. For example, sleep deprivation [13,14] and shorter sleep durations [15] are both correlated with ISP. Poorer subjective sleep quality was a significant predictor of SP in at least two multiple predictor models [5,16]. However, one study [17] found that the presence of insomnia disorder did not remain a significant and independent predictor in a logistic regression model.

1.2. Accompanying symptoms and hallucinations

Although atonia in the context of a clear sensorium is the only diagnostic requirement for ISP episodes, hallucinatory experiences and other symptoms are frequent accompaniments [3,18]. These range from pleasant kinesthetic sensations (eg, floating) to catastrophic cognitive appraisals (eg, "I am going to die") and terrifying hallucinations (eg, sensing a presence in the room, perceiving malevolent beings, and/or suffering an assault).

Though SP and ISP have often been associated with significant fear and, in certain cases, even impairment (eg, Refs. [19,20]), much remains to be learned about the full range of accompanying symptoms and corresponding levels of distress. The few studies that assessed these phenomena were somewhat limited in that they only assessed a small number of symptoms [21], relied exclusively on internet-based self-report measures [19], or suffered from a small sample size [11].

More specifically, much remains to be learned about the clinical importance of hallucinations accompanying ISP. Given their vivid nature, often involving multiple sensory faculties, it is perhaps not surprising that several researchers documented cases in which patients misconstrued SP episodes as actual physical assaults [22,23] or "visitations" from entities such as ghosts [24], witches [25], or extraterrestrials [26]. Further, patient descriptions of hallucinatory phenomena may lead to misdiagnosis (eg, a psychotic disorder as described in Ref. [27]). Therefore, gaining a better understanding of the full range of typical ISP experiences may have important clinical implications.

2. Study goals

The main purposes of this study are: (a) to explore the impact of demographic variables (eg, gender, race) and insomnia symptoms on rates of ISP, (b) to catalog the frequency, relative severities, and specific manifestations of 27 ISP symptoms and accompanying hallucinations, and (c) to assess the overall levels of distress and interference associated with ISP.

3. Method

3.1. Participants

As elevated rates of ISP are found in undergraduate students [1], participants were recruited from two universities in the US (Washington State University, $N = 325$; Pennsylvania State University, $N = 188$). All institutional approvals were obtained and the study was carried out in accordance with the Code of Ethics of the World Medical Association. All participants completed oral and written informed consent procedures. Those endorsing ISP during a mass screening and a group of ISP-negative controls were invited for in-person diagnostic interviews conducted by a licensed clinical psychologist ($N = 1$), doctoral student in clinical psychology ($N = 3$), or advanced undergraduate lab manager ($N = 1$). All were trained in general semi-structured diagnostic interviewing and ISP assessment. Students were supervised by a licensed clinical psychologist, all interviews were audiotaped, and any diagnostic disagreements were resolved during weekly consensus meetings.

A total of 513 participants completed the diagnostic interview. The sample was young ($M = 19.65$ years old) and included 347 female, 163 male, and 2 transgender individuals (1 declined to answer). It was ethnically diverse with 308 Whites, 50 Asians, 43 Hispanics, 36 African Americans, 5 Native American, and 67 of mixed ethnically or "other" participants. Of these, four participants declined to respond to this question.

A subsample of 191 participants met criteria for at least one SP episode. Six of these were excluded due to the presence of medical conditions such as narcolepsy, lupus, or hypokalemic periodic paralysis that complicated the assessment of ISP. The majority (88.6%) of individuals with ISP reported more than one lifetime occurrence, with 32.97% experiencing at least one episode ($M = 0.84$, $SD = 1.80$, median $= 0$) in the past month. The age of onset for first episode was early adolescence ($M = 13.47$, $SD = 4.66$, median $= 15.00$).

3.2. Measures

3.2.1. Isolated sleep paralysis

Participants were assessed for ISP using the expanded version of the Fearful Isolated Sleep Paralysis Interview (FISPI) [11,28]. The FISPI is a reliable, clinician-administered, semi-structured diagnostic interview that assesses ISP episodes and diagnosis based on International Classification of Sleep Disorders-3 (ICSD-3) criteria [3]. It also assesses the fear/distress levels associated with paralysis and 27 other specific symptoms/hallucinations using 0–8 Likert-type severity scales (ie, 0 = none, 2 = mild, 4 = moderate, 6 = severe, 8 = very severe; 4 and above = clinically-significant). Questions relevant for differential diagnosis (eg, alcohol/substance use, symptoms of narcolepsy, hypokalemic periodic paralysis), are included as well.

3.2.2. Insomnia

Symptoms of insomnia were assessed using the Insomnia Severity Index (ISI) [10]. The ISI is brief, valid, and reliable self-report screening measure that assesses the presence, nature, and severity of insomnia symptoms. The seven items of the ISI are rated on a 5-point Likert scale and yield a total score with established clinical cut-offs [29].

3.3. Notes on analyses

As Levene's test for equality of variances was significant for all ISI score distributions according to ISP status and study site, only descriptive statistics and non-parametric analyses are reported below.

The total samples for each site did not differ in terms of male-female distribution or ISI total scores (p's > 0.43). However, the age difference between the Washington state sample ($M = 19.80$) and the Pennsylvania sample ($M = 19.40$) reached statistical significance (F (1, 508) $= 3.99$, $p = 0.046$, partial $\eta^2 = 0.008$). The Washington sample also included significantly more minority participants (x^2 (1, $N = 507$) $= 10.23$, $p = 0.002$, $\varphi_c = 0.14$). As the effect sizes for both of these analyses were relatively small, a decision was made to pool both samples for all analyses.

4. Results

4.1. Demographic differences in the lifetime prevalence of ISP episodes

In terms of ISP prevalence rates, non-White participants did not significantly differ from Whites ($p > 0.07$) and males did not significantly differ from females ($p > 0.13$). Both transgender participants (not included in the chi square analysis) reported lifetime episodes of ISP.

4.2. Symptoms of insomnia and ISP

A Mann–Whitney U test ($U = 22{,}586.50$, $p < 0.001$, $r = 0.18$) indicated that those with ISP ($M = 10.07$) reported significantly higher insomnia symptoms than those without ($M = 7.74$).

4.3. Locus of fear during ISP episodes

Data were mixed in terms of whether individuals with ISP experienced the paralysis (46.7%) or other accompanying symptoms (45.1%) as more distressing, with 8.2% describing them as equal. Both the paralysis ($M = 4.31$, $SD = 2.23$) and other symptoms ($M = 4.46$, $SD = 2.39$) were rated as moderately distressing.

4.4. Characteristic symptoms and hallucinations

Table 1 displays the distribution of specific symptoms, hallucinations, and their relative severities. The majority of participants (93.0%) endorsed symptomatology beyond minimal ICSD-3 episode criteria with a mean of 7.73 ($SD = 4.97$) symptoms experienced during a typical ISP episode.

4.5. The sensed presence and visual hallucinations of presence of others

As shown in Table 1, a sensed presence and visual hallucinations of presence of others were the symptoms associated with the highest levels of fear. Those experiencing a sensed presence during ISP were more likely to attribute it to a non-human source.

In terms of visual hallucinations of others, perceptions of non-human entities were more frequent than of other people. The most common of these non-human entities were shadow people, ghosts/spirits, and animals. Notably, many of the entities summarized from the earlier literatures (eg, vampires, extraterrestrials) were infrequently reported in this sample.

Of those participants who hallucinated human beings, the majority perceived strangers, but 16 reported seeing various known individuals (eg, a neighbor, a romantic partner). Five of these participants perceived a recently-deceased loved one (eg, grandparent) during their first experience of ISP. Though reporting positive relationships with the loved ones when they were alive, all of these participants experienced fear during these ISP episodes.

4.6. Overall distress and interference associated with ISP

Diagnosticians rated the overall levels of distress and interference caused by ISP episodes using the same 0–8 severity scales. These data were both positively skewed. Overall distress levels ($M = 1.38$, $SD = 1.60$, Median = 1.00) fell below mild, with only 10.27% of the ISP sample reaching clinical significance (ie, 4 or above). Interference ($M = 0.71$, $SD = 1.28$, Median = 0) also fell below "mild", with 7.57% reaching clinical significance.

Table 1
Symptoms and Hallucinations Accompanying Isolated Sleep Paralysis and their Relative Severities.

Symptom	% of Sample	Mean (0–8) Fear/Severity (SD)
Paralysis[a]	100.00%	4.58 (2.01)
Try to speak/call out, but feel unable to do so[b]	58.69%	5.02 (2.07)
Feel like you might die	37.30%	5.09 (2.18)
Erotic/sexual feelings	4.86%	1.89 (1.17)
Kinetic Hallucination		
Feel that you got out of bed/moved a part of your body, only to discover that you had not actually moved	52.97%	4.16 (2.02)
Feel body falling	34.59%	3.91 (1.98)
Feel like you temporarily leave your body	33.51%	4.13 (1.96)
Feel body floating	26.49%	3.14 (1.67)
Feel body spinning	12.97%	4.02 (1.60)
Feel body turning	11.89%	3.23 (2.00)
Feel body flying	9.19%	2.65 (1.73)
Tactile Hallucination		
Numbness	58.38%	3.93 (1.89)
Pressure on chest or other body part	51.89%	4.42 (2.01)
Tingling sensations	41.08%	3.18 (1.74)
Smothering sensations	38.92%	4.72 (2.23)
Feel cold	25.95%	3.69 (1.64)
Feel like you're being physically touched[b]	22.28%	4.38 (2.22)
Vibrating sensations	19.46%	3.47 (2.15)
Feel pain	16.76%	3.66 (2.05)
Feel like you're being strangled	15.68%	4.22 (2.22)
Auditory Hallucination		
Hear unusual sounds[b]	32.61%	4.08 (1.94)
Hear unclear speech or gibbering	24.32%	4.87 (2.03)
Hear footsteps[c]	15.30%	4.34 (2.25)
Visual Hallucination		
See a being in the room[c,d]	24.59%	5.97 (1.72)
"Shadow person"/shadowy figure (N = 17)		
Ghost/spirit (N = 8)		
Indistinct creature/face (N = 7)		
Animal (N = 6)		
Hooded humanoid figure (N = 5)		
Demon/devil (N = 2)		
Alien (N = 1)		
Vampire (N = 1)		
See a person in the room	21.62%	5.71 (2.20)
Unknown person/stranger (N = 24)		
Known person/relative (N = 16)		
See a shape/inanimate object in the room[c]	16.94%	4.15 (2.10)
Autoscopy	16.76%	4.53 (1.92)
Sensed Presence		
Sense a Presence in the Room	57.84%	5.60 (2.07)
Nonhuman (N = 57)		
Human (N = 39)		
Not sure (N = 11)		

Note: 0 = "none", 2 = "mild", 4 = "moderate", 6 = "severe", and 8 = "very severe"; total *N* of ISP sample = 185.

[a] Although all 185 participants reported paralysis, only those reporting fear at a level above 0 were included in this calculation.

[b] Percentage calculated from a total *N* of 184.

[c] Percentage calculated from a total *N* of 183.

[d] In cases where multiple, different hallucinations were reported, these were included in the individual sums.

5. Discussion

In the largest ISP study to date where individuals were assessed using a clinical interview, group differences in ISP prevalence and insomnia symptoms were cataloged. In contrast to some previous findings, gender and a non-White ethnicity were not associated with a higher risk of ISP. However, group differences were found in insomnia severity, with the ISP group falling within the "sub-threshold" range (ie, 8–14) and the control group scoring in the "no insomnia" range (ie, 0–7) [29].

With regard to the subsample of ISP individuals, both the atonia and other symptoms were rated as moderately distressing, and these results are consistent with the overall episode distress ratings reported by Ramsawh et al. [30], (M = 4.5/8.0). The majority of participants experienced complex, and often multisensorial ISP experiences, with 17 of the 27 individual symptoms associated with clinically-significant levels of distress. However, in spite of the uncomfortable nature of ISP, only a small percentage of participants experienced clinically-significant distress or impairment as a result of the episodes.

Over half of the sample sensed a presence in the room with them during ISP, but fewer than 25% experienced corresponding visual hallucinations of human or non-human beings (see Table 1). It is noteworthy that akin to normal dreaming, persons known to the individual were occasionally incorporated into accompanying hallucinations (see also [24]). It is possible that this may be more common in the wake of traumatic events [7], but this awaits additional research. In contrast to normal dreaming, though, the hallucinations accompanying ISP were far more likely to be negatively-valenced [31]. Taken together, these findings lend additional credence to the idea that ISP assessment may have a role in certain forensic situations (eg, Ref. [23]). Similarly, the multiple reports of hallucinated, fantastical non-human entities were consistent with ISP's hypothesized role as a naturalistic explanation for putative paranormal experiences [25].

In summary, ISP can be a frightening event that is associated – at least in some cases – with clinically-significant distress and impairment. It may also be linked with unhelpful beliefs (eg, see Ref. [26]). However, in spite of these clinical implications, there are currently few treatment options available. Psychopharmacological agents such as antidepressants [32] or sodium oxybate [33] may be effective. Moreover, two psychotherapy protocols (ie, meditation combined with relaxation [34] and cognitive-behavioral therapy for ISP [28]) are currently available. However, the authors are not aware of any large scale or randomized controlled trials for ISP. Therefore, at present there are no well-established treatment options available to help ISP sufferers [35].

5.1. Clinical implications

- When assessing for the clinical impact of ISP episodes, it may be important to ask supplemental questions beyond minimal ICSD-3 criteria.
- ISP should be considered as a diagnostic possibility when patients report seemingly anomalous events that appear to lack real-world veracity.
- ISP without hallucinations may still be a distressing event for sufferers.
- Treatments which reduce insomnia and/or general sleep disruption may be helpful for alleviating ISP.
- Though ISP is usually a frightening experience for individuals, only a minority experienced clinically-significant levels of distress or impairment as a result of episodes.

5.2. Limitations

Although ISP episodes and phenomena were assessed by trained raters, no polysomnographic or other laboratory assessments were conducted to more definitively rule out other conditions (eg, narcolepsy). Further, the sample consisted exclusively of undergraduate students; thus, it is unclear if these results will generalize to other populations.

Funding

The second author received funding for this research from the Grant Agency of Charles University (GAUK Nr. 1786218) and by the project Nr. LO1611 with financial support from the MEYS under the NPU I program.

Acknowledgments

The authors would like to thank Jessica Grom, Dakota Mauzay, Joseph Tse, and Jacob Zimmerman for their assistance on this project.

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2019.03.007.

References

[1] Sharpless BA, Barber JP. Lifetime prevalence rates of sleep paralysis: a systematic review. Sleep Med Rev 2011;15:311–5.
[2] Lišková M, Janečková D, Kráčmarová LK, et al. The occurrence and predictive factors of sleep paralysis in university students. Neuropsychiatr Dis Treat 2016;12:2957–62.
[3] Medicine AAoS. International classification of sleep disorders—third edition (ICSD-3). Darien, Illinois. 2014.
[4] Brooks PL, Peever JH. Identification of the transmitter and receptor mechanisms responsible for REM sleep paralysis. J Neurosci 2012;32:9785–95.
[5] Denis D, French CC, Rowe R, et al. A twin and molecular genetics study of sleep paralysis and associated factors. J Sleep Res 2015;24:438–46.
[6] Denis D, French CC, Gregory AM. A systematic review of variables associated with sleep paralysis. Sleep Med Rev 2018;38:141–57.
[7] Sharpless B, Denis D. Isolated sleep paralysis. In: Unusual and rare psychological disorders: a handbook for clinical practice and research. Oxford University Press; 2017.
[8] Young E, Xiong S, Finn L, et al. Unique sleep disorders profile of a population-based sample of 747 Hmong immigrants in Wisconsin. Soc Sci Med 2013;79:57–65.
[9] Wing Y-K, Lee ST, Chen C-N. Sleep paralysis in Chinese: ghost oppression phenomenon in Hong Kong. Sleep 1994;17:609–13.
[10] Bastien CH, Vallières A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. Sleep Med 2001;2:297–307.
[11] Sharpless BA, McCarthy KS, Chambless DL, et al. Isolated sleep paralysis and fearful isolated sleep paralysis in outpatients with panic attacks. J Clin Psychol 2010;66:1292–306.
[12] Paradis CM, Friedman S, Hatch M. Isolated sleep paralysis in African Americans with panic disorder. Cultur Divers Ethn Minor Psychol 1997;3:69–76.
[13] Takeuchi T, Miyasita A, Sasaki Y, et al. Isolated sleep paralysis elicited by sleep interruption. Sleep 1992;15:217–25.
[14] Takeuchi T, Fukuda K, Sasaki Y, et al. Factors related to the occurrence of isolated sleep paralysis elicited during a multi-phasic sleep-wake schedule. Sleep 2002;25:89–96.
[15] Munezawa T, Kaneita Y, Osaki Y, et al. Nightmare and sleep paralysis among Japanese adolescents: a nationwide representative survey. Sleep Med 2011;12:56–64.
[16] Hsieh S-W, Lai C-L, Liu C-K, et al. Isolated sleep paralysis linked to impaired nocturnal sleep quality and health-related quality of life in Chinese-Taiwanese patients with obstructive sleep apnea. Qual Life Res 2010;19:1265–72.
[17] Ohayon MM, Zulley J, Guilleminault C, et al. Prevalence and pathologic associations of sleep paralysis in the general population. Neurology 1999;52:1194–200.
[18] ICSD A. International classification of sleep disorders, revised: diagnostic and coding manual. Darien, IL. American Academy of Sleep Medicine; 2005. p. 298.
[19] Cheyne JA, Newby-Clark IR, Rueffer SD. Relations among hypnagogic and hypnopompic experiences associated with sleep paralysis. J Sleep Res 1999;8:313–7.
[20] Sharpless BA, Grom JL. Isolated sleep paralysis: fear, prevention, and disruption. Behav Sleep Med 2016;14:134–9.
[21] Solomonova E, Nielsen T, Stenstrom P, et al. Sensed presence as a correlate of sleep paralysis distress, social anxiety and waking state social imagery. Conscious Cogn 2008;17:49–63.
[22] Douglass AB, Hays P, Pazderka F, et al. Florid refractory schizophrenias that turn out to be treatable variants of HLA-associated narcolepsy. J Nerv Ment Dis 1991:12–7.

[23] Hays P. False but sincere accusations of sexual assault made by narcotic patients. Med Leg J 1992;60:265–71.
[24] Hinton DE, Pich V, Chhean D, et al. 'The ghost pushes you down': sleep paralysis-type panic attacks in a Khmer refugee population. Transcultur Psychiatry 2005;42:46–77.
[25] Hufford D. The terror that comes in the night. Philadelphia: University of Pennsylvania Press; 1982.
[26] McNally RJ, Clancy SA. Sleep paralysis, sexual abuse, and space alien abduction. Transcult Psychiatry 2005;42:113–22.
[27] Gangdev P. Relevance of sleep paralysis and hypnic hallucinations to psychiatry. Australas Psychiatry 2004;12:77–80.
[28] Sharpless B, Doghramji K. Sleep paralysis: historical, psychological, and medical perspectives. Oxford University Press; 2015.
[29] Morin CM, Belleville G, Bélanger L, et al. The Insomnia Severity Index: psychometric indicators to detect insomnia cases and evaluate treatment response. Sleep 2011;34:601–8.
[30] Ramsawh HJ, Raffa SD, White KS, et al. Risk factors for isolated sleep paralysis in an African American sample: a preliminary study. Behav Ther 2008;39:386–97.
[31] Cheyne JA, Rueffer SD, Newby-Clark IR. Hypnagogic and hypnopompic hallucinations during sleep paralysis: neurological and cultural construction of the night-mare. Conscious Cogn 1999;8:319–37.
[32] Koran LM, Raghavan S. Fluoxetine for isolated sleep paralysis. Psychosomatics 1993:184–7.
[33] Mamelak M, Black J, Montplaisir J, et al. A pilot study on the effects of sodium oxybate on sleep architecture and daytime alertness in narcolepsy. Sleep 2004;27:1327–34.
[34] Jalal B. How to make the ghosts in my bedroom disappear? Focused-attention meditation combined with muscle relaxation (MR therapy)—a direct treatment intervention for sleep paralysis. Front Psychol 2016;7.
[35] Sharpless BA. A clinician's guide to recurrent isolated sleep paralysis. Neuropsychiatr Dis Treat 2016;12:1761–7.