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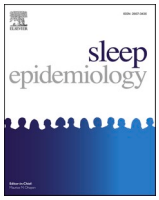

Listening to patients: Incidence and distribution of sleep disorders in Prader-Willi syndrome

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ABSTRACT

While the medical community continues to recognize the contributions of disordered sleep to the burden of Prader-Willi syndrome (PWS), the medical literature lacks characterization of the patient burden of sleep disorders by people living with PWS and their caregivers. We developed and fielded a 72-question survey to the online PWS community, to query caregivers about their experiences with sleep symptoms. Respondents for all age groups reported sleep-disordered breathing (40 %), cataplexy-like symptoms (28.4 %), and insomnia (43.5 %). The presentation of cataplexy-like symptoms tended to change as children aged, presenting initially (ages 0–4 years) as head bobbing while eating, then transitioning to knee buckling between the ages of 5–12 years. Finally, loss of generalized tone associated with extreme emotions became more common in the teenage years. Frequent screening for potentially treatable sleep disorders should be considered the standard of care for individuals with PWS.

Introduction

Prader-Willi Syndrome (PWS), a rare genetic neuroendocrine disorder, occurs in 1/10,000 to 30,000 live births [1]. Most descriptions of PWS describe it as presenting first with failure to thrive, then, later in life, with a strong food drive referred to as hyperphagia. While sleep issues have been documented, most reports focus on sleep-disordered breathing related to hypotonia, obesity, airway muscular insufficiency, and facial dysmorphic features [2–6]. The importance of sleep disturbances in the PWS community has only been recently recognized, and descriptors of the epidemiology of sleep problems in this patient population are largely lacking [7–9]. Recently, we and others have published clinical recommendations that call for further research into sleep problems in PWS [10].

Social listening identified a rising trend in discussions surrounding sleep issues in online PWS-focused communities and that topics related to sleep were discussed more often than issues related to hunger and weight, the latter of which is the classical focus of clinical management [11]. Social media analysis is an accessible source of real-world, patient-centered information that can characterize caregiver and

Abbreviations: BMI, body mass index; BPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; EDS, excessive daytime sleepiness; EEG, electroencephalogram; hGH, human growth hormone; PDSS, pediatric daytime sleepiness scale; PWS, Prader-Willi syndrome.

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patient perspectives on the impacts of disease symptoms, therapeutic efficacy, and side effects [11–16]. Such data may become particularly useful in generating hypotheses related to identifying therapies for sleep-related conditions, such as narcolepsy, which may relieve substantial PWS disease burden, including cognitive disability [17].

For the current study, we conducted an online survey based on observations made during social listening to describe caregiver experiences of sleep disturbances in individuals with PWS.

Methods

The 72-question survey was advertised at the PWS Association 35th National Convention (2019), widely fielded to the entire online PWS community (caregivers of adult and pediatric patients), widely posted on the internet (including PWS-related Facebook groups), and administered through the TREND online platform. Cataplexy-like symptoms were identified with three questions that included the following descriptions of symptoms: (1) muscle weakness while eating, (2) muscle weakness while experiencing a strong emotion, and (3) unresponsiveness while awake. The latter was used in recognition of the fact that parents did not understand the phrase "loss of generalized tone with intact consciousness" or could not recognize or grasp all the symptoms due to the suddenness of the loss of generalized tone. Sleep-disordered breathing and apnea-related issues were measured with four symptoms: (1) snoring, (2) pauses in breathing while sleeping, (3) breathing through the mouth while sleeping, and (4) use of either a continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BPAP) machine during sleep. Insomnia was measured by asking questions referencing difficulty falling asleep, difficulty staying asleep, and early morning awakenings. Data were cleaned to remove duplicates and reviewed to remove any identifiers. The study received IRB approval from WCG IRB on October 22, 2022. Respondents provided informed consent and were offered a $10 gift card to complete the survey.

Results

A total of 195 caregivers of people with PWS completed the 72-question survey, which covered three major sleep issues (sleep-disordered breathing, cataplexy-like symptoms, and insomnia). Not all respondents answered all the questions. Approximately half (52 %) of the individuals with PWS were female, 43 were 0–4 years old, 77 were 5–12 years old, 40 were 13–18 years old, and 35 were 19–40 years old. While most respondents were from the US ($n = 152$), other respondents came from the United Kingdom ($n = 14$), Canada ($n = 10$), Israel ($n = 2$) and elsewhere in Europe and Asia. The survey indicated that 94.7 % were taking human growth hormone (hGH) therapy, and 97 % had taken it at some point (data not shown). Respondents reported that 20.3 % of individuals with PWS had been classified by a doctor as overweight, including 12.5 % of 0- to 4-year-olds, 22.4 % of 5- to 12-year-olds, and 24.3 % of 13- to 18-year-olds (Table 1).

Two-thirds of individuals with PWS took one or more naps daily (Table 1), suggesting that daytime sleepiness is pervasive in this population. In many cases, individuals took two or more naps daily (32.6 % of individuals 0–4 years, 14.3 % of individuals 5–12 years, 20 % of individuals 13–18 years, and 40 % of individuals ≥19 years). Overall, many respondents answered yes to questions indicative of sleep problems: 40 % for sleep-disordered breathing, 25.3 % for cataplexy-like symptoms, and 30.6 % for insomnia (Table 1).

The incidence of sleep-disordered breathing was highest in very young children, 0–4 years (47.6 %), and in adults, 19+ (50 %). Snoring was more common in individuals aged 0–4 years (38 %) than in individuals aged 5–12 years (31.1 %), individuals aged 13–18 years (25.6 %) and adults (20.6 %). One-third (38.2 %) of adults reported using a CPAP or BPAP machine.

The presentation of cataplexy-like symptoms changed as children aged (Fig. 1). While children ≤ 4 years experienced knee buckling and loss of generalized tone, head bobbing (muscle weakness while eating) was more common in children ≤4 years than any other age group. In contrast, children aged 5–12 years tended to present with muscle weakness while experiencing a strong emotion, and caregivers of teenagers reported their children experiencing loss of generalized tone much more commonly than head bobbing or knees buckling. Adult patients were the most likely to present with loss of generalized tone, with 23.5 % of respondents indicating that this had happened more than once. However, the survey did not specify if the loss of tone in the adult patients occurred in adulthood or during childhood.

Table 1
Sleep survey results.

Age (years)	Survey response "yes"	n[a]	
Overweight			
0–4	5	40	12.5 %
5–12	17	76	22.4 %
13–18	9	37	24.3 %
19+	21	34	61.8 %
All	**52**	**187**	**27.8 %**
One or more naps per day			
0–4	36	43	84 %
5–12	47	77	61 %
13–18	23	40	58 %
19+	24	35	68.6 %
All	**130**	**195**	**67 %**
Sleep-disordered breathing			
0–4	20	42	47.6 %
5–12	24	77	31.2 %
13–18	10	39	25.6 %
19+	17	34	50.0 %
All	**71**	**192**	**40.0 %**
Cataplexy-like symptoms			
0–4	9	41	22 %
5–12	16	76	21.1 %
13–18	14	39	35.9 %
19+	9	34	26.5 %
All	**48**	**190**	**25.3 %**
Insomnia			
0–4	15	43	34.9 %
5–12	39	77	50.6 %
13–18	13	40	32.5 %
19+	17	33	51.5 %
All	**84**	**193**	**43.5 %**

[a] Number of respondents answering related questions in each age range out of 195 total respondents to the survey.

Discussion

Narcolepsy involves five characteristic symptoms: excessive daytime sleepiness (which may include "sleep attacks" or rapid onset of sleep), cataplexy, hallucinations while falling asleep or while waking up from sleep, sleep paralysis, and fragmented sleep. The findings reported here support the evidence from online conversations among caregivers of people living with PWS that sleep problems are of concern in this population [10]. The variations in the presentation of symptoms from classical narcolepsy may be due to a different underlying pathophysiology in patients with PWS versus the general population.

Growing evidence suggests that the differences in the presentation of cataplexy in children as compared to adults means that cataplexy is underdiagnosed in the pediatric population [18]. In adults, cataplexy is typically characterized by a generalized loss of tone in which the individual experiences a collapse while maintaining consciousness. In contrast, cataplexy can be subtle in children, presenting with eye or facial twitching in the setting of extreme excitement, such as laughter, anger, or hunger. During the cataplexy episode, the individual can hear but cannot move. Cataplexy in children may also have variable presentations that can mimic seizures. The primary difference between cataplexy and seizures is that cataplexy occurs when the patient is awake and is not associated with abnormalities on the

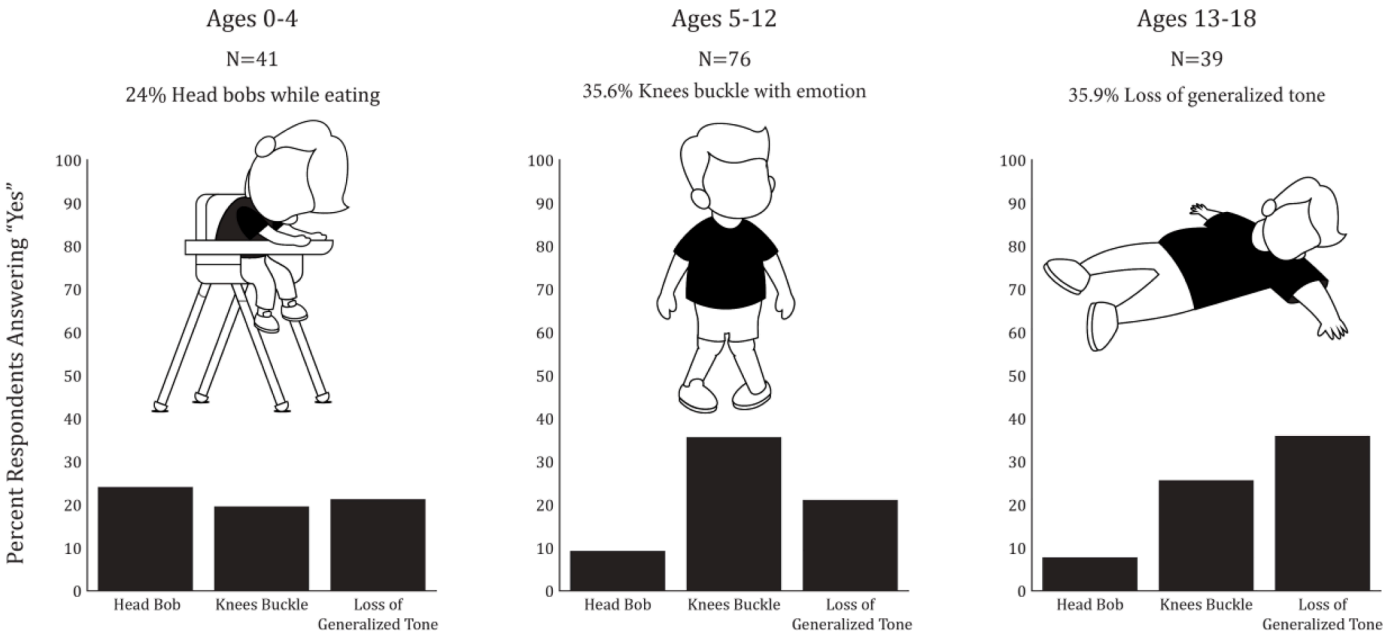

Fig. 1. Presentation of cataplexy like symptoms in different age groups.

electroencephalogram (EEG). Patients experiencing cataplexy remain aware as they experience a generalized loss of tone. The survey probed this issue with a question describing a period of "unresponsiveness while awake."

In particular, the survey responses reinforce the descriptions of loss of tone captured in online conversations. The results suggest that approximately one-third of children with PWS have cataplexy-like symptoms, a finding consistent with the discussions held online on social media. These conversations reveal that parents of very young children frequently describe their child's head bobbing while eating; parents of young children often describe their child's knees buckling while running in play; and parents of teenagers report concerns about their child's refusal to move or acknowledge external stimuli despite the use of severe measures.

The survey responses indicated that food appears to trigger narcolepsy/cataplexy-like symptoms in individuals with PWS. One-third (35.8 %) of respondents indicated that individuals with PWS sometimes, often, or "all the time" became sleepy or fell asleep while eating. Falling asleep while eating was most common in children aged 0–4 years (56 %), and 26 % of adults also presented with this symptom. These results suggest that perhaps food is an emotional trigger in the PWS population.

We recognize that our survey has multiple limitations and that our findings are more hypothesis-generating than conclusive and do not lend themselves to statistical analysis. Not only are caregiver survey responses an inherently subjective assessment of sleep disorders, but individuals who participate in online support groups and surveys are likely biased toward having the means and the time to participate. Such individuals are likely to be more attuned to symptoms of PWS and are more rigorously managing PWS than individuals in the larger PWS population. The questions were worded with non-technical language and did not probe into the diagnosis of cataplexy versus epilepsy, sleep-related movement disorders, parasomnias, and the adherence or efficacy of PAP for those on PAP.

Despite these limitations, we believe that the survey data support the recommendation that patients with PWS should be made aware of the possibility of sleep problems and be screened for sleep disorders at regular healthcare visits. In addition, recognizing symptoms in a rare condition such as PWS may lead to interventions that aim to improve the overall quality of life. Pharmacological solutions that have demonstrated efficacy in this population include modafinil and pitolisant [6, 17]. In particular, a phase 3 clinical trial is underway to investigate the safety and efficacy of pitolisant in patients with PWS [19].

CRediT authorship contribution statement

Amee Revana: Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Methodology, Formal analysis, Conceptualization. **E. Robert Wassman:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Niva Haber:** Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration, Formal analysis, Data curation. **Lara C. Pullen:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Conceptualization. **Terry Jo Bichell:** Writing – review & editing, Writing – original draft, Conceptualization. **Jessica Duis:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Randy Bartlett:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Formal analysis, Data curation, Conceptualization. **Christopher DeFelice:** Writing – review & editing, Writing – original draft, Software, Resources, Methodology, Conceptualization. **Maria Picone:** Writing – review & editing, Writing – original draft, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

A.R is the primary investigator in the Phase II clinical trial for Pitolisant in PWS in collaboration with Harmony Biosciences (sponsor). M.P. and C.D. are co-owners of TREND Community, and E.R.W. holds stock options in the company. L.P. has no conflicts to disclose. ERW. NH. TJB. JD. RB—no conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in

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References

[1] Bohonowych J, Miller J, McCandless SE, Strong TV. The global Prader-Willi syndrome registry: development, launch, and early demographics. Genes 2019;10(9):713. https://doi.org/10.3390/genes10090713 (Basel).

[2] Butler MG, Miller JL, Forster JL. Prader-Willi syndrome - clinical genetics, diagnosis and treatment approaches: an update. Curr Pediatr Rev 2019;15(4):207–44. https://doi.org/10.2174/1573396315666190716120925.

[3] Canora A, Franzese A, Mozzillo E, Fattorusso V, Bocchino M, Sanduzzi A. Severe obstructive sleep disorders in Prader-Willi syndrome patients in southern Italy. Eur J Pediatr 2018;177(9):1367–70. https://doi.org/10.1007/s00431-017-3083-9.

[4] Pavone M, Caldarelli V, Khirani S, et al. Sleep disordered breathing in patients with Prader-Willi syndrome: a multicenter study. Pediatr Pulmonol 2015;50(12):1354–9. https://doi.org/10.1002/ppul.23177.

[5] Sedky K, Bennett DS, Pumariega A. Prader Willi syndrome and obstructive sleep apnea: co-occurrence in the pediatric population. J Clin Sleep Med 2014;10(4):403–9. https://doi.org/10.5664/jcsm.3616.

[6] Weselake SV, Foulds JL, Couch R, et al. Prader-Willi syndrome, excessive daytime sleepiness, and narcoleptic symptoms: a case report. J Med Case Rep 2014;8:127. https://doi.org/10.1186/1752-1947-8-127.

[7] Agar G, Brown C, Sutherland D, et al. Sleep disorders in rare genetic syndromes: a meta-analysis of prevalence and profile. Mol Autism 2021;12(1):18. https://doi.org/10.1186/s13229-021-00426-w.

[8] Patel VP, Patroneva A, Glaze DG, et al. Establishing the content validity of the Epworth sleepiness scale for children and adolescents in Prader-Willi syndrome. J Clin Sleep Med 2022;18(2):485–96. https://doi.org/10.5664/jcsm.9632.

[9] Duis J. Prader-Willi syndrome: an update. Curr Opin Pulm Med 2023;29(6):539–42. https://doi.org/10.1097/MCP.0000000000001018.

[10] Duis J, Pullen LC, Picone M, et al. Diagnosis and management of sleep disorders in Prader-Willi syndrome. J Clin Sleep Med 2022;18(6):1687–96. https://doi.org/10.5664/jcsm.9938.

[11] Patel A, Glaze D, Picone M, DeFelice C, Pullen L. The utilization of social media to identify sleep problems associated with Prader Willi syndrome. Sleep 2019;42(suppl_1):A309. https://doi.org/10.1093/sleep/zsz067.767.

[12] Convertino I, Ferraro S, Blandizzi C, Tuccori M. The usefulness of listening social media for pharmacovigilance purposes: a systematic review. Expert Opin Drug Saf 2018;17(11):1081–93. https://doi.org/10.1080/14740338.2018.1531847.

[13] Singh D, Miller JL, Wassman ER, et al. The arduous path to drug approval for the management of Prader-Willi syndrome: a historical perspective and call to action. Int J Mol Sci 2023;24(14):11574. https://doi.org/10.3390/ijms241411574.

[14] Goodspeed K, Mosca LR, Weitzel NC, et al. A draft conceptual model of SLC6A1 neurodevelopmental disorder. Front Neurosci 2023;16:1026065. https://doi.org/10.3389/fnins.2022.1026065.

[15] Eggermann T, Monk M, Perez de Nanclares G, et al. Imprinting disorders. Nat Rev Dis Prim 2023;9(1):33. https://doi.org/10.1038/s41572-023-00443-4.

[16] McDonald L, Malcolm B, Ramagopalan S, et al. Real-world data and the patient perspective: the PROmise of social media? BMC Med 2019;17(1):11. https://doi.org/10.1186/s12916-018-1247-8.

[17] Pullen LC, Picone M, Tan L, Johnston C, Stark H. Cognitive improvements in children with Prader-Willi syndrome following pitolisant treatment—patient reports. J Pediatr Pharmacol Ther 2019;24(2):166–71. https://doi.org/10.5863/1551-6776-24.2.166.

[18] Droogleever Fortuyn HA, Swinkels S, Buitelaar J, et al. High prevalence of eating disorders in narcolepsy with cataplexy: a case-control study. Sleep 2008;31(3):335–41. https://doi.org/10.1093/sleep.31.3.335.

[19] A phase 2 study to evaluate the safety and efficacy of pitolisant in patients with Prader-Willi syndrome, followed by an open label extension. ClinicalTrials.gov identifier: NCT04257929. Updated May 6, 2023. Accessed October 4, 2023. https://clinicaltrials.gov/ct2/show/NCT04257929.