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DAYTIME SLEEPINESS AND REM ABNORMALITIES IN PRADER-WILLI SYNDROME: EVIDENCE OF GENERALIZED HYPOAROUSAL

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The aim of this study was to clarify the nature of the sleep abnormalities (excessive daytime sleepiness [EDS] and rapid eye movement [REM] sleep alterations) in Prader-Willi Syndrome (PWS). Eight PWS patients, 15 normal, 16 narcoleptic, and 16 obese subjects were recorded in the sleep laboratory, both during daytime and nighttime. A principal-finding was that EDS in PWS was associated with an increased amount and depth of sleep. In PWS patients with EDS, compared to those PWS patients without EDS or the narcoleptic, obese, and normal groups, there were significant

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decreases in wakefulness and increases in percentage of sleep time (ST) and slow-wave sleep (SWS) both during daytime and nighttime testing. Also, in the adult PWS subjects ($n = 6$), in contrast to normal and narcoleptic subjects, intensity of EDS was correlated with increased nocturnal percentage of ST and SWS and % SWS was positively correlated with % ST (both during daytime and nighttime testing). Another principal finding was that in PWS there is a unique alteration of the distribution of REM sleep in relation to controls. PWS patients with EDS or shortened nocturnal REM latencies showed a significantly increased number of REM periods, and a decreased average REM interval between REM periods compared to PWS patients with nonshortened nocturnal REM latencies or to the three control groups. Our data suggest that EDS and REM abnormalities in PWS are not manifestations of a narcoleptic-type syndrome or consequences of obesity. We propose that generalized 24-hour hypoarousal is the primary mechanism underlying the sleep abnormalities in PWS patients.

Keywords: Daytime sleepiness; narcolepsy; obesity; PWS; REM sleep.

Prader-Willi Syndrome (PWS) is reported to be associated frequently with excessive daytime sleepiness (EDS) and REM abnormalities (Vela-Bueno, Kales, Soldatos, Dobladez-Blanco, Campos-Castello, Espino-Hurtado, Olivan-Palacios, 1984; Hertz, Cataletto, Feinsilver & Angulo, 1993; Helbing-Zwanenburg, Kamphuisen & Mourtazaev, 1993). Several studies of patients with PWS have shown that REM abnormalities are independent of respiratory disturbances (Vela-Bueno *et al.*, 1984; Kaplan, Frederickson & Richardson, 1991; Hertz *et al.*, 1993; Helbing-Zwanenburg *et al.*, 1993; Vgontzas, Bixler, Kales & Vela-Bueno, 1995; Vgontzas, Kales, Seip, Mascari, Bixler, Myers, Vela-Bueno, Rogan in press). Also, excessive daytime sleepiness as assessed objectively in the sleep laboratory, appears to be to a large extent, independent of sleep disordered breathing, although sleep apnea and obesity may increase sleepiness (Hertz *et al.*, 1993; Helbing-Zwanenburg *et al.*, 1993; Clift, Dahlitz & Parkes JD, 1994; Vgontzas *et al.*, 1995; Vgontzas *et al.* in press).

The relationship between EDS and REM abnormalities and sleep structure in PWS has not been systematically assessed. Also, it has been speculated that EDS and sleep onset REM (SOREM) in PWS are likely manifestations of a narcoleptic-like syndrome (Helbing-Zwanenburg *et al.*, 1993). However, no study has systematically compared the sleep/wakefulness patterns of PWS patients with those of other patients with EDS, for example narcoleptics or obese persons without sleep apnea.

In order to clarify the nature of the sleep abnormalities in PWS, we: (1) evaluated the relationship of EDS and SOREM to daytime and nighttime sleep patterns in PWS patients; and (2) assessed whether sleep/wakefulness profiles of these patients differ from those of normal, narcoleptic and obese subjects without sleep apnea. The obese group was included because obesity is a characteristic feature of PWS and obese patients without sleep apnea frequently experience EDS while their nighttime sleep organization is significantly altered (Vgontzas, Tan, Bixler, Martin, Shubert & Kales, 1994).

PATIENTS AND METHODS

Subjects

Eight subjects (seven females, one male) ranging from 6 to 40 years of age (two children, six adults), whose diagnosis was confirmed with molecular genetic techniques (Vgontzas *et al.* in press), participated in our study (Table I). Two of them were referred by a Prader-Willi home for evaluation of EDS. The other six were recruited from a list of eight PWS patients (two patients refused to participate) who had been previously diagnosed with molecular techniques by the Division of Genetics, Department of Pediatrics (PKR and MM). There were no a priori selection criteria of these patients except their geographic proximity (no more than two hours distant from our facility) and their willingness to participate in the study. None of the subjects participating in this study was on stimulant or antidepressant medication for at least two weeks prior to the polysomnographic studies.

In order to assess the effects of PWS on sleep, we contrasted the sleep/wakefulness profile of PWS subjects to those of normal, narcoleptic, and obese subjects. In analyses involving these control groups we included only the adult PWS subjects ($n = 6$) as young control data were unavailable. The normal and narcoleptic groups were selected from a larger group of normals and narcoleptics so that their mean age was similar to the adult PWS patients. Also, the obese group was selected from a larger sample so that their mean body-mass-index (BMI) and age were similar to those of the adult PWS patients. Our comparison groups consisted of 15 normals (mean age ± SE 28.4 ± 1.4), 16 narcoleptics (mean age ± SE 29.4 ± 1.6), and 16 obese subjects (mean age ± SE 29.1 ± 1.4).

TABLE I Clinical and Sleep Profile of PWS Subjects

Patient	*PW2*	*PW8*	*PW16*	*PW25*	*PW27*	*PW31*	*PW32*	*PW33*
Age Years	6	25	12	22	24	19	21	40
Sex	F	F	F	F	F	F	F	M
Height								
Centimeters	103	141	119	146	146	150	141	151
(%)*	<5	<5	<5	<5	<5	<5	<5	<5
Weight								
Kilometers	24.09	87.73	38.18	69.09	65.45	78.18	53.64	52.27
(%)*	78	95	21	78	72	91	31	5
SOREM	–	–	+	–	+	+	+	–
EDS	None	Severe	Moderate	None	Moderate	Severe	Severe	None

*Indicates percentiles of anthropometric measurements of PWS compared to normative data controlled for age and sex (National Center for Health Statistics, 1977; Butler & Meaney, 1987)
SOREM: Defined by a REM latency ≤ 10 minutes
EDS: Defined by a sleep latency of ≤ 5 minutes (severe) or ≤ 10 minutes (moderate)

Sleep Lab Procedures

All the patients and controls were evaluated in the sleep laboratory for at least one night in sound-attenuated, light- and temperature-controlled rooms and were monitored continuously for 8 hours using 16-channel polygraphs (model 78c, Grass Instrument Co., Quincy, Mass). In addition, following nocturnal polysomnographs, the patients (with the exception of the obese group) were recorded for two, 1-hour each, daytime naps as previously described (Kales, Bixler, Soldatos, Cadieux, Manfredi & Vela-Bueno, 1987; Roth, Nevšímalová, Šonka & Dočekal, 1986). Electroencephalographic, electro-oculographic, and electromyographic recordings were obtained in accordance with standard methods (Rechtschaffen & Kales, 1968). Subsequently, sleep records were scored, independent of any knowledge of the experimental conditions, according to standardized criteria (Rechtschaffen & Kales, 1968).

Respiration was monitored throughout the night by thermocouples at the nose and mouth (model TCT 1R, Grass Instrument Co.) and by thoracic strain gauges, which are based on a Wheatstone bridge. All-night recordings of hemoglobin oxygen saturation were obtained using an oximeter (model 47201A, Hewlett-Packard Co., Palo Alto, Calif., or model Biox ILA, Biox Technology Inc., Boulder, Colo., or Pulse Ox, Nonin, Plymouth, Minn.) attached to an earlobe.

Data from the scoring of the records were processed through several special purpose computer programs designed to reduce the data to mean values for each recording period (naps and nocturnal period). The following values were employed in this study: sleep latency (SL), wake time after sleep onset (WTASO), total wake time (TWT), number of awakenings, percentage sleep time, percentage of each sleep stage, REM latency, REM duration, REM interval and number of REM periods.

Sleep onset and REM latency were determined for each recording. The onset of sleep was established by the presence of any sleep stage for a duration of one minute or longer. However, if the initial stage of sleep was Stage 1, it had to be followed, without any intervening wakefulness, by at least 60 s of Stages 2, 3, 4, or REM. Sleep latency was defined as the time elapsed from lights out to sleep onset. A sleep latency of 5 minutes or less was considered as objective evidence of severe EDS while a sleep latency of more than 5 minutes, but less than 10 minutes, was evidence of moderate EDS (Richardson, Carskadon, Flagg, Van den Hoed, Dement & Mitler, 1978; Kales *et al.*, 1987). REM latency was defined as the total amount of time from sleep onset to the first appearance of REM sleep. SOREM was determined as the occurrence of REM sleep within the first 10 minutes following sleep onset (Mitler, Van den Hoed, Carskadon, Richardson, Park, Guilleminault & Dement, 1979). Finally, shortened REM latency was defined as the occurrence of REM sleep in less than 70 minutes following sleep onset.

An apneic event was considered present if breathing ceased for 10 seconds or more. An hypopneic event was defined as at least a 50% decrease in thermocouple output with associated oxygen desaturation of at least 4%. Oxygen desaturation was evaluated in terms of minimum oxygen saturation during wakefulness, NREM sleep and REM sleep.

Statistical Analysis

Comparisons between PWS subjects and each of the control groups were performed using a two-tailed student *t*-test. Correlations between nocturnal and daytime sleep variables were calculated by the Pearson product-moment correlation. The statistical confidence level was set at $p < .05$. Also, because of the small sample sizes, trends ($p < .1$) are reported.

RESULTS

None of our subjects demonstrated significant sleep disordered breathing or hypoventilation (Vgontzas *et al.* in press).

EDS and Daytime Sleep Characteristics

Five of the eight patients demonstrated either severe ($n = 3$) daytime sleepiness (SL ≤ 5 minutes in at least one of the naps) or moderate ($n = 2$) daytime sleepiness (SL ≤ 10 minutes but > 5 minutes) (Table I).

All patients had some sleep during either of the two naps. Five of them had some sleep during both naps. In general, the daytime sleep of PWS subjects with EDS compared to that of narcoleptics was characterized by less intensity (longer sleep latencies), but increased amount (less WTASO) and greater depth (more SWS) (Table II).

Specifically, during both naps, the four adults with EDS demonstrated a relatively high % ST (76.8% and 81.2%, respectively for each nap), similar to the % ST of narcoleptics (85.0% and 81.1%, both NS), and higher than the % ST of normals (66.4%, NS and 55.5%, $p = .1$). PWS patients demonstrated higher amounts of sleep during the second nap, while narcoleptics and normals demonstrated higher amounts of sleep during the first nap (Table II).

PWS subjects with EDS demonstrated longer sleep latencies than narcoleptics, but shorter than normals (7.6 min vs 5.2 min and 12.2 min, respectively for the first nap and 9.0 min vs 3.9 min and 20.3 min, respectively for the second nap, all NS). In contrast, PWS subjects with EDS, during the second nap,

TABLE II Daytime Sleep of PWS Subjects with EDS in Comparison to Control Groups

	Nap #1		
	Prader Willi (n = 4)	*Narcoleptics (n = 13)*	*Normals (n = 15)*
Sleep Latency	7.6 ± 3.0	5.2 ± 1.5	12.2 ± 2.6
WTASO	6.2 ± 2.7	3.8 ± 1.7	8.0 ± 2.0
TWT	13.8 ± 4.4	9.0 ± 2.8	20.2 ± 3.2
% ST	76.8 ± 7.4	85.0 ± 4.7	66.4 ± 5.3
% SWS	0.0 ± 0.0	0.9 ± 0.5[a]	2.3 ± 1.9
% REM	8.6 ± 5.1	37.1 ± 5.2[b]	11.7 ± 6.3

[a] - greater than PWS $p < .1$
[b] - greater than PWS $p < .01$

	Nap #2		
	Prader Willi (n = 4)	*Narcoleptics (n = 13)*	*Normals (n = 15)*
Sleep Latency	9.0 ± 4.5	3.9 ± 1.1	20.3 ± 3.4
WTASO	2.1 ± 1.1	7.4 ± 3.6	6.4 ± 2.3[a]
TWT	10.8 ± 4.9	11.3 ± 4.1	26.7 ± 4.4[a]
% ST	81.2 ± 8.7	81.1 ± 6.9	55.5 ± 7.4[b]
% SWS	9.9 ± 8.5	5.0 ± 3.2	5.4 ± 3.4
% REM	17.2 ± 8.0	31.7 ± 7.0	5.1 ± 3.1

Data represent mean values ± SE
[a] - greater than PWS $p = .1$
[b] - less than PWS $p = .1$

demonstrated considerably lower amounts of WTASO (2.1 min) compared to narcoleptics (7.4 min, NS) and normals (6.4 min, $p = .1$) (Table II).

In terms of sleep stages, an interesting finding was the presence of significant amounts of SWS during the second nap of those PWS subjects with objective evidence of EDS. The average SWS of the four adults with severe or moderate EDS was approximately 10.0% which is about twice the average for the SWS demonstrated by narcoleptics or controls for the same testing period (5.0% and 5.4%, respectively, both NS).

EDS and Nocturnal Sleep Characteristics

In general, the nocturnal sleep of PWS with EDS was characterized with more % ST, less wakefulness, and more SWS compared to those PWS patients without EDS or the narcoleptic, obese, and normal groups (Table III). Specifically, the five PWS subjects (including four adults) that showed severe to moderate EDS had markedly lower TWT compared to the three PWS subjects with no objective signs of EDS (65.4 min vs 121.0 min, $p = .1$).

TABLE III Nighttime Sleep of PWS Subjects with EDS in Comparison to Control Groups

	Prader Willi (*n* = 4)	*Narcoleptics* (*n* = 16)	*Obese* (*n* = 16)	*Normals* (*n* = 15)
Sleep Latency	14.9 ± 6.1	10.4 ± 2.2	20.4 ± 3.6	24.6 ± 7.1
WTASO	49.4 ± 7.6	72.8 ± 15.1	83.0 ± 12.5[a]	54.0 ± 15.9
TWT	64.4 ± 9.0	83.2 ± 15.4	103.5 ± 14.1[a]	78.6 ± 19.3
% ST	86.6 ± 1.9	82.2 ± 3.4	78.4 ± 2.9[b]	83.6 ± 4.0
% SWS	13.9 ± 4.7	7.5 ± 1.8	6.5 ± 1.6[c]	6.5 ± 1.7[c]
% Sleep Stage 4	10.2 ± 3.7	2.2 ± 1.1[d]	0.6 ± 0.3[c]	0.5 ± 0.2[c]

Data represent mean values ± SE
[a] - greater than PWS $p < .05$
[b] - less than PWS $p < .05$
[c] - less than PWS $p < .1$
[d] - less than PWS $p < .01$

Percentage ST of the four adult PWS subjects with EDS was also higher compared to narcoleptic, normal, and obese subjects (86.6% vs 82.2% and 83.6% and 78.4% [the last comparison was significant at $p < .05$]). In terms of sleep latency, the four PWS adults with EDS showed higher sleep latencies than narcoleptic (14.9 min vs 10.4 min, NS), but lower than normal or obese subjects (24.6 min and 20.4 min, respectively, both NS). Also, these PWS subjects had nonsignificantly lower WTASO compared to both narcoleptic and normal subjects (49.4 min vs 72.8 min and 54.0 min, respectively, both NS) and significantly less WTASO when compared to obese subjects (49.4 min vs 83.0 min, $p < .05$). Also, the same pattern of differences seen with WTASO was observed for TWT (64.4 min vs 83.2 min and 78.6 min and 103.5 min, respectively [the last comparison was significant at $p < .05$]).

In terms of sleep stages, the three adult subjects with severe EDS showed large amounts of SWS (average of 18.5%). Also, the average SWS of the four adults with severe or moderate EDS was 13.9% which is about two times the level of SWS demonstrated by the age-controlled narcoleptic (7.5%, NS), normal (6.5%, $p = .08$) or obese subjects (6.5%, $p = .08$). Further, PWS subjects had a significantly higher % stage 4 compared to narcoleptic (10.2% vs 2.2%, $p < .01$), normal (0.5%, $p = .08$) or obese subjects (0.6%, $p = .08$).

Relationship Between Daytime and Nocturnal Sleep in Terms of Intensity, Amount and Depth

We also assessed in adult PWS subjects ($n = 6$) the relationship between intensity of EDS (daytime sleep latency) and length (% ST) and depth (% SWS) of sleep and then, whether this relationship was different from that of narcoleptics and normals. In general, intensity of EDS in PWS, in contrast to narcoleptics and normals, was associated with greater amounts of sleep (% ST) and deeper sleep (% SWS).

Specifically, in adult PWS subjects there was a strong correlation between intensity of daytime sleepiness (as defined by the shortest SL during either nap) and % ST at night ($r_{xy} = -.58$, NS) and SWS ($r_{xy} = -.73$, $p = .1$). In contrast, the intensity of daytime sleepiness in narcoleptics was associated with lower nocturnal % SWS ($r_{xy} = .63$, $p < .05$) while there was no correlation with % ST. Also, in normals there was no correlation between intensity of daytime sleepiness and % ST or SWS.

In addition, because depth, and to a lesser extent amount of sleep, depend on prior wakefulness/sleep (Webb & Agnew Jr., 1965; Borbely, Baumann, Brandeis, Strauch & Lehmann, 1981; Feinberg, Floyd & March, 1987), we assessed the relationship between amount of nocturnal sleep with amount and depth of daytime sleep. The correlation of nocturnal amount of sleep (% ST) with daytime amount of sleep (% ST) was strong for PWS ($r_{xy} = .72$, $p = .1$), intermediate for narcoleptic ($r_{xy} = .45$, NS) and nonexistent for normal subjects. Similarly, the correlation of nocturnal amount of sleep (% ST) with daytime depth of sleep (% SWS) was positive for PWS ($r_{xy} = .51$, NS), nonexistent for narcoleptic and negative for normal subjects, ($r_{xy} = -.46$, $p = .08$).

Furthermore, because % SWS is independent of duration of sleep (Horne, 1988), we examined the relationship between depth of nocturnal sleep and amount of sleep, both during the daytime and nighttime. In PWS subjects % SWS during the nighttime testing was positively correlated with % ST during the daytime period ($r_{xy} = .84$, $p < .05$), while the same correlation was negative for narcoleptics ($r_{xy} = -.45$, $p = .1$) or nonexistent for normals. Finally, in PWS subjects % SWS at night was positively correlated with nighttime % ST ($r_{xy} = .55$, NS), while this relationship was negative in normals ($r_{xy} = -.43$, $p = .1$), and nonexistent in narcoleptics.

Daytime and Nocturnal REM Sleep Characteristics

Four of the eight PWS patients presented SOREM during at least one of the naps, while two of them demonstrated SOREM during both naps. These four subjects also met the criteria for EDS (Table I). The amount of REM sleep of PWS subjects with severe or moderate EDS was higher than the amount of REM sleep of normals during the second nap (17.2% vs 5.1%, respectively NS), but lower than the amount of REM sleep of the narcoleptics for both naps (8.6% vs 37.1%, $p < .01$ in the first nap and 17.2% vs 31.7%, in the second nap, NS) (Table II). PWS subjects had higher amounts of REM sleep during the second nap in contrast to narcoleptics and normals who had a higher amount of REM sleep during the first nap.

There was a great variability for the percentage of nocturnal REM sleep in PWS, ranging from 6.6% to 27.1%. In general, PWS with EDS or shortened REM latencies had a higher number of REM periods and decreased average REM

interval compared to PWS with nonshortened REM latencies and to the three control groups.

Specifically, three subjects had REM latencies below 70 minutes. The group with shortened REM latencies, compared to those with REML > 70, had a significantly higher mean number of REM periods (5.0 vs 3.6, $p < .05$) and a significantly shorter mean interval between REM periods (82.9 min vs 110.6 min, $p < .05$). There was no difference in terms of % REM and mean duration of REM period between those with shortened REM latencies (REML < 70 minutes) and those with REML > 70 minutes. The number of REM periods of those with shortened REM latency tended to be significantly higher than the number of REM periods of narcoleptic (5.0 vs 3.8, $p = .06$), normal (3.4, $p = .08$), and obese subjects (3.1, $p < .05$) (Table IV). Also, the mean interval between REM periods of those with shortened REM latency tended to be significantly shorter than that of narcoleptic (82.9 vs 108.3 min, $p = .1$), normal (116.2 min, $p < .05$), and obese subjects (119.1 min, NS).

The same type of differences tended to exist when we compared adult PWS subjects with EDS and the three control groups in terms of the same REM variables. Specifically, PWS subjects had the highest number of REM periods [4.5 vs 3.8 for narcoleptic, and 3.4 for normal, and 3.1 for obese subjects (last comparison significant at $p = .06$)]. Also, PWS subjects with EDS had the shortest REM interval (94.6 min vs 110.5 min for narcoleptic, and 116.2 min for normal, and 119.1 min for obese subjects all NS).

DISCUSSION

The findings of our study show that the sleep/wakefulness profiles in PWS are distinctly different from those in narcolepsy or obesity. The major finding is that EDS in PWS is associated with an increased amount and depth of sleep, both during the

TABLE IV Nighttime REM Characteristics of PWS Subjects with a Shortened REM Latency (≤70 min) in Comparison to Control Groups

	Prader Willi (*n* = 3)	*Narcoleptics* (*n* = 16)	*Obese* (*n* = 16)	*Normals* (*n* = 15)
% REM	19.3 ± 3.7	19.8 ± 1.5	17.0 ± 1.6	18.3 ± 2.0
REM Interval	82.9 ± 8.3	110.5 ± 7.4	119.1 ± 10.7	116.2 ± 6.3[a]
# REM Periods	5.0 ± 0.6	3.8 ± 0.3[b]	3.1 ± 0.3[c]	3.4 ± 0.4[b]

Data represent mean values ± SE
[a] - greater than PWS $p < .05$
[b] - less than PWS $p < .1$
[c] - less than PWS $p < .05$

day as well as at night. In addition, the circadian and ultradian distribution of REM sleep in PWS subjects differs from that of narcoleptic, obese and normal subjects.

First, the intensity of sleepiness in PWS subjects as measured by nocturnal or daytime sleep latencies was much less than that of narcolepsy. Also, the frequency of severe sleepiness (as determined by sleep latency criteria) in the randomly selected PWS was rather low (16.7%) compared to the frequency of severe EDS in narcolepsy (71%) (Kales *et al.*, 1987). These objective findings confirm clinical observations that sleepiness in the form of sleep attacks is not common in PWS patients.

Second, EDS in PWS was associated with decreased amounts of wakefulness during both the nocturnal and daytime sleep testing. This contrasts with the nocturnal sleep of narcoleptics which was disturbed as indicated by increases in both wake time after sleep onset and total wake time. Also in PWS, EDS was associated with increased amounts of SWS during both the nocturnal and daytime sleep. In contrast, in narcoleptics SWS was not increased, compared to normals, either at night or during the daytime, and was not correlated with the degree of daytime sleepiness. These results are consistent with the findings of a larger study that reported that narcoleptics, compared to controls, have an increased number of awakenings, wake time after sleep onset, total wake time, and percentage of stage 1 sleep (Bixler, Kales, Vela-Bueno, Drozdiak, Jacoby & Manfredi, 1986). The same differences, albeit to a larger extent, were noted between the sleep structure of PWS and obese subjects. Obese subjects demonstrated significantly higher WTASO and TWT and lower SWS indicating that obesity cannot account for the sleep organization of PWS.

Third, SWS sleep in PWS appeared to be positively associated with the amount of sleep. This contrasted with the findings in our normal group that showed a negative correlation between amount of sleep and SWS. Also these results in our PWS group contrast with well-established findings in normals that amount of SWS depends on prior wakefulness (Webb *et al.*, 1965; Borbely *et al.*, 1981; Feinberg *et al.*, 1987) while prolonged sleep does not affect the absolute amount of SWS (Horne, 1988). These results indicate that the mechanism of sleep satiation (sleep pressure or relief as a result of prior amount of wakefulness or sleep) in PWS is impaired.

Fourth, EDS or shortened REM latencies in PWS subjects were associated with an increased number of REM periods and a decreased average interval between REM periods, compared to PWS subjects without shortened REM latencies, narcoleptic, normal, and obese subjects. In narcolepsy, the disturbance of REM sleep is one of timing of the first REM period while the distribution of REM sleep across the night, including number of REM periods, is very similar to that of normals (Bixler *et al.*, 1986). In obesity, the disturbances of REM sleep were in the

opposite direction of PWS REM abnormalities (increased REM latency, suppressed amount of REM and decreased number of REM periods) indicating again that obesity is not the underlying factor of REM disturbances in PWS. Finally, in PWS subjects, the amount of REM sleep was higher in the afternoon nap than in the morning which is opposite to the finding that "REM propensity" is greater in the morning than later in the day (Webb & Agnew Jr., 1967). The REM disturbances described in PWS subjects indicate an abnormality, both of the ultradian (shortened REM interval) and circadian rhythms (SOREM and greater amount of REM sleep later in the day). Although circadian abnormalities of REM sleep have been described in other disorders, such as narcolepsy (Schulz, Lund, Cording & Dirlich, 1979; Mosko, Shampain & Sassin, 1984) or depression (Kupfer, 1976), ultradian abnormalities appear to be unique in PWS.

Our findings on the characteristics of sleep and REM disturbances in PWS are consistent with those reported by Hertz, *et al.* (1993) who showed a positive association between intensity of daytime sleepiness and % ST and an increased number of REM periods in PWS patients. Our results do not support the notion that SOREM and EDS are likely to be manifestations of a narcoleptic-type syndrome (Helbing-Zwanenburg *et al.*, 1993) and add further to the clinical and genetic evidence that the sleep abnormalities in the two disorders are of a different nature (Vela-Bueno *et al.*, 1984; Hertz, Cataletto, Feinsilver & Angulo, 1994).

Based on these characteristics, we propose that PWS is associated with a generalized hypoarousal which is the primary underlying mechanism of the sleep/wakefulness abnormalities of this disorder. This is in contrast to narcolepsy where the primary abnormality is a circadian dysrhythmia consistent with hypoarousal during the day and hyperarousal at night (Schulz *et al.*, 1979; Mosko *et al.*, 1984).

We speculate that in PWS patients, the increased frequency of REM periods which represent periods of heightened physiological arousal, serves a homeostatic function by counterbalancing the physiologic and metabolic effects of the generalized hypoarousal associated with the disorder. This hypothesis is supported by our findings that the more severe REM disturbances, i.e., SOREM, were present in those PWS patients with severe EDS, and that REM sleep during the day was increased during periods of increased sleepiness (noon vs early morning period). Our speculation about the role of REM abnormalities in PWS patients is consistent with the hypothesis of other investigators that REM sleep prevents sleep from becoming too "deep" (homeostatic theory) (Ephron & Carrington, 1966; Snyder, 1984). Finally, the proposed neurophysiologic model of generalized hypoarousal in PWS is supported by findings on the neurochemistry of PWS. Specifically, it has been shown that plasma GABA levels (a primary inhibitory neurotransmitter in the brain) are elevated 4 to 5 times above normal in PWS (Cassidy, 1984; Ladda & Rogan, 1992).

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