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Efficacy of Modafinil on Excessive Daytime Sleepiness in Prader–Willi Syndrome

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Excessive daytime sleepiness is a frequent and a highly disruptive symptom to the daily routine of children with Prader–Willi Syndrome (PWS) and their families. The objective of the study was to evaluate the efficacy of modafinil, a central stimulant, on excessive daytime sleepiness in children and adolescents with PWS. The efficacy of modafinil was evaluated in this open label pilot study comparing the Epworth sleepiness scale before and after treatment. Ten patients with molecularly confirmed PWS and a complaint of excessive daytime sleepiness underwent a night-time sleep recording and multiple sleep latency tests. One patient was excluded because of severe obstructive sleep apnea syndrome. Nine patients (4 males) with median age of 16 years (8–21) received modafinil at a starting dose of 100 mg/day. We found that all patients had excessive daytime sleepiness with an Epworth sleepiness scale at 14 (11–20) and mean sleep latency on multiple sleep latency tests at 5 (3–6) minutes. Moreover, six patients had at least two sleep-onset rapid eye movement periods showing a narcolepsy-like phenotype. Modafinil significantly improved sleepiness in all patients on the Epworth sleepiness scale from 14 (11–20) to 4 (3–12), ($P = 0.007$). Body mass index of the patients did not change significantly under treatment. No side effects were reported, and the drug was well-tolerated. We posit that this open label case series shows good efficacy of modafinil in nine children and adolescents with PWS.

Key words: Prader–Willi syndrome; daytime sleepiness; modafinil

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INTRODUCTION

Prader–Willi Syndrome (PWS) is a complex genetic rare disorder characterized by short stature, hypotonia, hyperphagia, early onset childhood obesity, impaired sexual development and impaired cognitive ability [Waters et al., 1990; Holm et al., 1993]. The last 10 years have been marked by a decrease of age at diagnosis, improvement in comprehensive description of both symptoms and natural history of the condition, particularly regarding sleep and respiratory disorders. In addition, excessive daytime sleepiness (EDS), a highly disruptive symptom to the daily routine of children with PWS and their families has been identified as an important issue affecting clinical care and learning [Cotton and Richdale, 2006]. Sleep-disordered breathing and hypothalamic dysfunction seem to contribute to EDS [Nixon and Brouillette, 2002], but sleepiness persists in patients with PWS after weight loss and reduction of pre-existing sleep disordered breathing by nocturnal continuous positive airway pressure treatment [Harris and Allen, 1996]. Growth hormone (GH) treatment, widely used in these children for their short stature and their abnormal body composition, does not improve this symptom.

In addition, some patients have a narcolepsy-like pattern of hypersomnia with sleep onset REM periods that can be detected by Multiple Sleep Latency Tests (MSLT) and nocturnal polysomnography [Aldrich et al., 1997; Manni et al., 2001] and can develop cataplexia [Cassidy et al., 1990]. Others have hypersomnia without REM sleep abnormalities [Manni et al., 2001]. In these patients, hypersomnia may be an expression of the hypothalamic

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dysfunction, which is characteristic of PWS rather than a symptom of narcolepsy [Vgontzas et al., 1996; Parkes, 1999; Manni et al., 2001]. A recent study confirmed this hypothesis showing hypocretin deficiency in PWS [Nevsimalova et al., 2005]. This hypothalamic neurohormone, which is deficient in narcolepsy/cataplexy, is secreted by the lateral hypothalamus and regulated by peripheral hormones.

Modafinil is a central stimulant of post-synaptic alpha-1 adrenergic receptors [Ferraro et al., 1996] that promotes alertness in a selective way. Treatment with modafinil is not associated with the development of either dependence or tolerance [Beusterien et al., 1999]. The use of modafinil is currently established for narcolepsy and idiopathic hypersomnia in adults, but is not approved for children and adolescents less than 16 years [Group, 2000]. Studies involving patients with neurological, psychiatric and other disorders associated with fatigue and hypersomnia demonstrated benefits of modafinil treatment [Talbot et al., 2003]. Modafinil increased in vigilance without changes in the sleep pattern [Group, 2000]. This study was an open label case series pilot study on the effect of modafinil in children and adolescents with PWS who have EDS.

METHODS

The care of rare disorders in France is organized around reference centers labeled by the French ministry of Health and coordinated by a recognized team in a university hospital linked with a patient association. The reference centers coordinate and organize the care of patients with rare diseases in the country by providing information on the diseases to the general population (www.chu-toulouse.fr/-centre-de-reference-du-syndrome-de,892-) and by teaching and training health professionals. They also write and/or broadcast clinical practice guidelines. Epidemiological, clinical and basic researches are also mandatory. For PWS, the coordination team (Coordinator Pr M. Tauber) is located in the Endocrinology Unit of the Children's Hospital in Toulouse who is in charge of the patients living in the area (2 million inhabitants) and admitted patients referred by physicians from all over the country. Seventy-seven patients were regularly followed in our unit. From December 2004 to June 2008, 10 patients with PWS who complain of excessive daytime sleepiness were recruited for this open label case series.

This observational study was performed according to French regulations. Data were collected in the database of the reference center [Molinas et al., 2008] as part of the routine follow-up which does not require an IRB review in France [Public Health Law, 2004]. Parents and children were given information prior to beginning data entry into the database. The database was authorized by the Commission Nationale de l'Informatique et des Libertés (CNIL).

The polysomnography and latency tests were done in the reference center for sleep studies in our hospital. Reference centers for sleep studies are determined by the French Ministry of Health throughout the country.

All the patients, and parents if applicable, agreed to undergo testing and to receive modafinil treatment if needed. All patients had molecularly confirmed diagnoses. Sleepiness in these patients was not secondary to sleep restriction according to parents and/or caregivers who observe sleep duration of the patients. One patient was excluded from the study because of severe obstructive sleep apnea syndrome on the sleep recording. Her sleepiness disappeared under nocturnal continuous positive airway pressure (CPAP).

Data about demographic characteristics, medical history, PWS course and treatment were collected from the database completed in the reference center [Molinas et al., 2008].

EDS was evaluated using a modified Epworth sleepiness scale (ESS) administered to the child's caregiver. The ESS is a measure of person's general level of daytime sleepiness [Johns, 1991]. It is an 8-item questionnaire detailing an individual propensity to fall asleep during commonly encountered situations. Scores can range 0–24. In adults, an ESS score >10 indicates increased daytime sleepiness [Johns, 1991]. The ESS was slightly modified to be more applicable to children: storytelling was added to reading in question one, the mention of alcohol was deleted in question seven and question eight was taken to indicate that the subject was dozing during class [Melendres et al., 2004; Williams et al., 2008]. Obesity was diagnosed according to International Obesity Task Force Charts using body mass index (BMI) charts [Cole et al., 2000]. BMI was expressed in *Z*-score for patients under 18 years old and in kg/m^2 in older patient. Overweight was confirmed when *Z*-score BMI was above 2 in children and above $25\,kg/m^2$ after 18 years.

All patients underwent a full night video polysomnography and a multiple sleep latency test (MSLT) to characterize their sleep disorders and their excessive daytime sleepiness in the sleep laboratory of Toulouse Hospital. The monitoring included Fp1-Cz, O2-Cz, C3-A2 electroencephalography (EEG) according to the international system of classification IS1020 for electrodes positioning, right and left electro-oculogram, nasal pressure via cannula, mouth airflow by thermistors, tracheal sounds via microphone, thoracic and abdominal belts to assess respiratory efforts, electrocardiography, pulse oxymetry, submental and tibialis anterior electromyography, EEG-synchronized infra-red video-monitoring, and ambiance microphone. The day after nocturnal polysomnography, each patient underwent a MSLT at 08:00 AM, 10:00 AM, 12:00 PM, 2:00 PM, and 4:00 PM. EDS was confirmed when the mean sleep latency was shorter than 8 min. In addition, the presence of EDS and at least two REM sleep episodes on the five tests confirmed a narcolepsy-like phenotype.

The sleep stages [Rechstchaffen and Kales, 1968], arousals [American Sleep Disorders Association, 1992], and respiratory events [American Thoracic Society, 1996] for children until 18 were scored by visual inspection according to standard criteria. Obstructive Sleep Apnea Syndrome was defined as an obstructive apnea index (OAI) $\geq$1/hr until the age of 18. Severity of OSAS was classified on the bases of the obstructive apnea index (OAI). In addition an apnea hypopnea index (AHI) >1.5/hr was considered abnormal in patients less than 18 years of age [Melendres et al., 2004]. For the only patient over 18 years (aged 21), we used the adult standard criteria for respiratory events and OSAS defined as an obstructive sleep apnea index over 5/hr [American Academy of Sleep Medicine Task Force, 1999].

Nine patients received modafinil with a starting dose of 100 mg. It was subsequently increased if there was not clinical improvement. The efficacy of modafinil was evaluated by comparing the ESS before and after treatment. PSG and MSLT were not performed

TABLE I. Clinical Characteristics of the Patients at Time of Enrollment

Patient	Sex	Age (years)	BMI (kg/m^2)	BMI (Z-score)	Genetic diagnosis	Intelligence quotient	Treatment with GH	ESS (/24)	Modafinil (mg)	Duration of modafinil treatment (months)
1	M	17	25.5	+3.0	Deletion	75	Stopped for 2 years	16	200	11
2	F	16	31.3	+5.0	Deletion	75	Stopped for 3 years	13	200	5.5
3	M	15	24.6	+2.6	UPD	69	Under treatment	17	100	5.7
4	M	8	19.8	+2.9	Deletion	64	Under treatment	14	100	12
5	F	17	37.1	+7.5	UPD	—	No	14	200	4.2
6	F	17	39.4	+8.5	Deletion	—	Stopped for 2 years	13	200	14.7
7	M	21	31.6	NA	AMP	—	Under treatment	17	300	1.7
8	F	12	21.1	+1.8	UPD	95	Under treatment	11	200	7.3
9	F	10	17.8	+1.0	Deletion	72	Under treatment	20	100	4.2

BMI, body mass index; ESS, Epworth sleepiness scale; UPD, uniparental disomy; AMP, abnormal methylation profile; NA, nonapplicable.

after the treatment if significant clinical improvement was reported by patient and/or caregiver.

Results are reported as median and range. Correlation analysis used the Spearman test. Wilcoxon signed-rank test was used for comparisons.

RESULTS

Nine patients (4 males, median-aged 16 years ranging from 8 to 21 years (1 patient older than 18 years) were included (Table I). Five patients had paternal 15q11–q13 microdeletion, three had maternal uniparental disomy of chromosome 15, and one had an abnormal methylation profile without mutation detection. One patient had never received growth hormone (GH), three had stopped it 1 year before the study as they had reached adult height, and five were still under GH treatment with treatment median duration of 4.5 years ranging from 3 to 9 years. Seven patients were obese, two patients were prepubertal, one just started puberty, and six were pubertal and under substitutive treatment (two boys received testosterone and four girls received estrogen).

The median intelligence quotient of the patients was 73.5 (ranging from 64 to 95). The patients were not receiving antidepressant or antipsychotic medications. All nine patients complained about sleepiness, in the absence of shortened sleep, as confirmed by a median ESS at 14 (11–20). Two patients had experienced symptoms suggestive of cataplexy with muscle tone following laughter. None complained about sleep paralysis or hypnagogic hallucinations. We found no correlation between intelligence quotient and ESS ($P = 0.24$) or MSL ($P = 0.59$). There was no correlation between ESS and MSL. In addition, clinical investigation of respiratory variables during sleep demonstrated that six patients were habitual snorers.

Night-time sleep characteristics in terms of total sleep time, sleep efficacy, sleep fragmentation and sleep stages duration did not show major disturbances (Table II). Six patients had at least two sleep onset REM periods (SOREMPs) during the night showing a narcolepsy-like phenotype. Mean oxygen saturation was 96 (95–99)%. Two patients had minimum oxygen saturations below 89% associated with rare obstructive episodes. Only one patient had mild OSAS with an OAI at 1.3/hr and AHI at 4.3/hr.

Mean sleep latency on MSLT was 5 (3–6) minutes, confirming objective EDS in all patients who complained for sleepiness. Moreover, six patients had at least two sleep onset REM periods showing a narcolepsy-like phenotype.

There was no correlation between Body Mass Index (BMI) and ESS ($P = 0.4$) or mean sleep latency ($P = 0.2$). There was no correlation between age and ESS ($P = 0.9$) or mean sleep latency ($P = 0.2$).

We observed no difference in ESS and mean sleep latency on MSLT in patients with paternal 15q11–q13 deletion or maternal uniparental disomy of chromosome 15. The prevalence of narcolepsy-like phenotype on MSLT was not different in patients with deletion (3/5) versus disomy (2/3).

Modafinil was ingested at 100 mg a day in three patients, 200 mg a day in 5, and 300 mg per day in one. All showed significantly improved sleepiness in all patients, according caregivers and patients. The median ESS score decreased from 14 (ranging from 11 to 20) to 4 (ranging from 3 to12) ($P = 0.007$), with a median duration of modafinil of 7 months (ranging from 4 to 20 months). There was a median reduction of the ESS score of 8 points (ranging from 5 to 17; Fig. 1). BMI of the patients did not change significantly on treatment (Fig. 1).

None of the patients reported side effects such as headache, insomnia, anxiety, or nausea, which are sometimes reported by patients ingesting modafinil.

DISCUSSION

Patients with PWS receiving modafinil treatment for confirmed EDS without sleep disordered breathing improved their sleepiness. We confirmed that hypersomnolence complaints in PWS are associated with confirmed objective EDS on MSLT. EDS in this population is commonly attributed to sleep-disordered breathing, but in this study only one patient had mild OSAS, even though three were overweight and four were obese.

Given that modafinil has been linked to decreased food consumption [Makris et al., 2004], its efficacy could have been linked to a weight loss. Nevertheless, EDS was not linked to obesity and BMI did not change significantly on treatment in our patients. The improvement of sleepiness is not the result of a weight loss in our

TABLE II. Sleep Characteristics and Multiple Sleep Latency Tests Results Before Treatment

	Night-time sleep									Respiratory parameters				Multiple sleep latency test	
	Sleep characteristics														
Patient	TST (min)	SE (%)	Arousal index (no./hr)	Stage 1%	Stage 2%	Stage 3 + 4%	REM sleep%	Sleep latency	REM sleep latency	OAI	AHI	Mean SaO_2	Min SaO_2	Time with $HbSaO_2 < 90\%$ (%TST)	MSL (min)	SOREMPs
1	432	92	4.6	11.5	47.0	13.5	27.9	4.0	14.0	1.3	4.3	96	89	0.9	6.0	3
2	491	97	4.7	7.9	45.4	24.3	22.2	33.0	5.0	0	0.4	97	86	2.8	5.5	4
3	416	96	3.7	4.6	47.6	27.7	19.7	29.5	86.2	0	0.1	95	92	0	4.2	2
4	490	95	0.0	13.3	38.4	30.8	17.0	5.5	102.5	0	0	96	93	0	3.2	1
5	447	94	2.3	4.5	60.3	16.3	19.0	11.5	85.0	0.5	0.3	96	84	0.7	5.2	0
6	395	98	1.1	4.0	56.1	25.9	13.0	89.5	197.0	0	0	95	89	4.35	5.6	2
7	396	83	9.7	7.4	57.2	16.6	18.7	14.5	105.5	0.2	0.8	97	89	4.3	4.4	3
8	483	97	2.9	3.2	48.2	22.2	26.3	12.2	15.7	0	0	99	89	0.9	2.9	4
9	454	95	2.4	5.6	38.2	34.1	21.9	13.5	73.0	0	0.4	97	93	0.4	5.4	1

TST, total sleep time; SE, sleep efficacy; REM, rapid eye movement; OAI, obstructive apnoea index; IAH, apnoea hypopnoea index; MSL, multiple sleep latency; SOREMPs, sleep onset rapid eye movement periods.

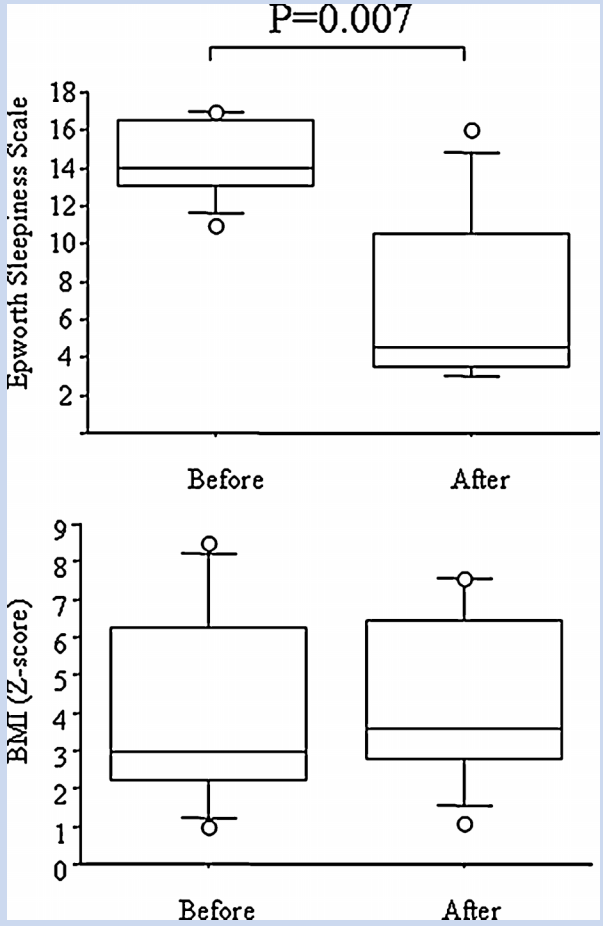

FIG. 1. A: Improvement of sleepiness measured on the Epworth sleepiness scale (ESS) of the nine children and adolescents with PWS before and after treatment with modafinil. B: Evolution of BMI before and after treatment with modafinil.

patients. We found no correlation between BMI and ESS or mean sleep latency on MSLT. Two studies [Harris and Allen, 1996; Priano et al., 2006] reported no correlation between EDS and obesity, whereas other studies showed that obese patients with PWS had more sleepiness [Vgontzas et al., 1996; Butler et al., 2002; O-'Donoghue et al., 2005]. In this study, patients with sleep disordered breathing likely associated with obesity were excluded. This raises the hypothesis that sleepiness and obesity are not caused by the same central (hypothalamic?) dysfunction.

We found a high prevalence (6/9) of narcolepsy-like phenotype on the MSLT of our patients, which has been described by other groups [Manni et al., 2001]. Two patients had cataplexy. None had hypnagogic hallucinations or sleep paralysis. These narcoleptic-type symptoms had rarely been reported [Cassidy et al., 1990; Clift et al., 1994].

One limit of this study is that patients did not undergo HLA DQB1*0602 typing which is a subtype associated with narcolepsy. But other studies have shown that patients with PWS with narcoleptic-like phenotype on MSLT did not have the peculiar immunogenetic narcoleptic-phenotype [Manni et al., 2001]. A

central cause for somnolence is suspected in PWS since hypothalamic dysfunction is present in these patients [Harris and Allen, 1996]. Recent studies supported this hypothesis showing a hypocretin deficiency in PWS [Nevsimalova et al., 2005]. This neurohormone, which is deficient in narcolepsy/cataplexy, is secreted by the hypothalamus, and hypocretin deficiency observed in PWS has been shown to correlate with the severity of EDS [Nevsimalova et al., 2005]. In addition, a new animal model of PWS, the Magel2 null mouse that reproduces most of the features of PWS such as neonatal growth retardation, excessive weight gain and increased adiposity has reduced levels of hypocretin 1 and 2 and fewer neurons expressing hypocretin in the lateral hypothalamus [Bischof et al., 2007; Kozlov et al., 2007]. The narcolepsy phenotype observed in PWS might be the consequence of the inactivation of *MAGEL2* that induces a reduction of hypocretin levels.

Another limitation of the study was the lack of validation of the modified ESS for children although it has been used in some publications [Melendres et al., 2004; Williams et al., 2008].

We found no correlation between age and EDS, but we noted that in our series among the three patients without narcoleptic-like phenotype on the MSLT, two were the youngest of the group, as if the narcoleptic-like phenotype could be the full-blown characteristic of this central hypersomnia.

Heussler et al. [2008] have recently reported the efficacy of modafinil in three children with PWS. Two of them had received it in a placebo-controlled way that confirmed the efficacy compared to placebo. This report was an open label case series. Although a placebo effect of modafinil cannot be excluded, its observed efficacy for over 2 years in most patients with sustained pharmacological effect indicates otherwise. ESS is a subjective scale to evaluate sleepiness. Repeated MSLT after treatment, acknowledging the fact that it is the gold standard for proving the efficacy of modafinil [Annane et al., 2006], would have been a more objective way to measure sleepiness, but it was difficult to ask children and adolescents with PWS to stay another long day of testing, after treatment, given the fact that these patients had already a heavy follow-up for routine clinical care.

The fact that the patients continued to take the drug also indicates useful efficacy as judged by the patient and the family and care givers. The improvement in lifestyle issues, as reported by the patient/family/care givers is dramatic. Given the positive results of this pilot study, additional studies are needed to confirm the efficacy of modafinil. Cognitive impairment and behavioral difficulties are one of the most disabling symptoms of PWS; therefore EDS in patients with PWS may worsen these symptoms. Further studies are needed to determine if modafinil, improve cognition and behavior in PWS patients [Vela-Bueno et al., 1984] by effectively treating excessive daytime sleepiness.

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