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CASE REPORT

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Menstruation-Related Hypersomnia (MRH): Three Adolescent Cases Responding to Treatment with the Oral Contraceptive Pill (OCP)

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Abstract

Menstrual-Related Hypersomnia (MRH) is a disorder characterized by recurrent episodes of excessive daytime sleepiness (EDS) with a cyclical relationship to the menstrual cycle and that last from a few days up to a few weeks. Such episodes often begin during adolescence. Other concomitant associated clinical features may include eating disorders, mental and behavioral disturbances. Menstrual-Related Hypersomnia (MRH) is classified as a subtype of Kleine-Levin syndrome (KLS).

In this report, we describe three adolescent cases presenting with recurrent episodes of MRH, for whom investigations excluded a specific organic cause. After receiving hormonal treatment, the episodes of somnolence ceased or were isolated with few remaining symptoms.

Cases of MRH episodes prevented by the oral contraceptive pill (OCP) have rarely been described in the literature. Since sex hormones play an important role in sleep regulation, the option of hormonal treatment should be further explored.

Keywords: Menstrual-Related Hypersomnia; Sleep Disorders; Kleine-Levin Syndrome; Oral Contraceptives; Hormonal Treatment

List of abbreviations: BD: Bipolar Disorder; EDS: Excessive Daytime Sleepiness; FSH: Follicle Stimulating Hormone International Classification of Sleep Diseases; KLS: Kleine-Levin Syndrome; LH: Luteinizing Hormone; MRH: Menstrual Related Hypersomnia ; OCP: Oral Contraceptive Pill; PMDD: Premenstrual Dysphoric Disorder

Introduction

Menstrual-Related Hypersomnia (MRH) is a rare disorder defined by cyclical episodes of hypersomnolence recurring in association with menses together with various symptoms, such as dysautonomic features, weight gain and mood disturbances [1].

The onset generally takes place during adolescence and the prevalence nor the duration of MRH are known. The diagnosis of MRH is essentially based on clinical features and on the recurrence of symptoms but no biological markers is yet available.

MRH seems closely related to Kleine-Levin syndrome (KLS), a central hypersomnia disorder, mostly characterized by recurrent episodes of hypersomnolence. Since the 1970s, whether MRH constitutes a separate clinical entity or a variant of KLS has been questioned [2].

The second edition of the International Classification of Sleep Disorders (ICSD-2, 2005) described KLS and MRH as two separate types of recurrent hypersomnia (RH); however, the ICSD-3, (2013) tends to consider MRH as a simple subtype of KLS [3,4].

Despite being well described, KLS is an extremely rare disorder affecting 1-5 individuals per million [5]. KLS affects mostly male adolescents and is characterized by episodes of hypersomnolence, lasting from a few days to a few weeks, in association with cognitive

impairment, altered perception, either hyperphagia or anorexia, and behavioral disturbances such as hypersexuality. Patients usually present with clinophilia, spend more time in bed, and often report headaches in association with the episodes. It is noteworthy that affected people are entirely asymptomatic between episodes. The etiology of KLS remains largely unexplained. Autoimmune and genetic factors may be involved, but evidence for these associations is lacking [6].

Various pharmacological options have been proposed to reduce symptoms during the episodes, including stimulants (methyl phenidate, D-amphetamine, modafinil), anti-epileptics (valproic acid, carbamazepine), anti-depressants (imi-pramine, sertraline, monoamine oxidase inhibitors), anti-psychotics (clozapine, risperidone), antivirals (acyclovir) and benzodiazepines, but without significant results [7]. Although the benefit of symptomatic treatment has not been established, prophylactic medications such as lithium appear to reduce the frequency of relapses in KLS [8].

MRH treatment is poorly described in the literature. The most successful treatments reported so far in preventing re-lapses are carbamazepine and combined birth control pills [9-14]. Both approaches showed a significant reduction in the severity and number of episodes. However, no clinical trials, guided by treatment responsive cases, have yet been conducted to evaluate pharmacological treatments in recurrent hypersomnia.

As an alternative to lithium therapy, hormonal treatment has been proposed to prevent recurrent episodes of hyper-somnolence in MRH patients. The Oral Contraceptive Pill (OCP) combines an estrogen and a progestogen that suppress FSH and LH throughout the cycle, thus preventing ovulation. The aim of the present work is to report on the potential therapeutic effect of the OCP among three adolescent females presenting with de novo recurrent episodes of hypersomnia with a close cyclical relationship to menstruation. The clinical outcome of these patients was compared to published data.

Report of Cases

All three patients being under 18 years old at the time of the assessment, both parents provided their consent for their child to be involved in the present clinical report.

Patient 1

We report a 15-year-old Caucasian girl of Ashkenazi origin with MRH beginning at 13 years of age. The diagnosis was based on recurrent episodes of severe sleepiness, hyperphagia, behavioral and cognitive disturbances, which were thus consistent with ICSD-3 criteria [4]. The patient showed seven periodic episodes of hypersomnia over eighteen months, lasting each around seven to ten days. Excessive daytime somnolence usually started during, or few days after menstruation. Table 1 shows the occurrence of the episodes of somnolence along with the dates of menstruation and medication intake. (Data unavailable for Patient 2 and Patient 3 due to the retrospective nature of the study).

Most of the episodes started with headaches and variable symptoms such as compulsive eating, derealization, depersonalization, anxiety, and apathy, visual and olfactory hallucinations. Weight gain occurred throughout the episodes. The patient's weight was 69 kg for 158 cm at the time of the first assessment in December 2015 (BMI: 27,6 kg/m^2). However, she had already gained eight kilos in a few weeks, after experiencing the first symptoms of sleepiness. At the peak of the disease in February 2016, the patient reached 71 kg for 159 cm (BMI: 28,1 kg/m^2).

There was no prior psychiatric or medical history except a surgical intervention for strabismus during childhood.

Aggressive behavior towards her family members that was out of character was also reported. Furthermore, this student with an excellent academic record missed over a month of school in total due to the occurrence of multiple episodes. In between episodes, based on parental reports and clinical observations, the patient was completely asymptomatic, with the exception of a constitutive anxious temperament. None of her first-degree relatives exhibited the same phenotype.

Regarding investigations performed, no abnormality was found on cerebral magnetic resonance imaging (MRI), or on standard electro-encephalogram (EEG). A careful physical examination failed to show any clinical abnormality. No comorbid illness was reported, and no regular medications were noted. The patient contracted viral meningitis in 2008 and underwent surgery in 2015 for a vertical strabismus. Routine blood tests, including complete blood count, TSH, CRP, metabolic lipid and liver panels showed no abnormality. Comorbid psychiatric disorders had been ruled out by means of a standardized interview with a senior psychiatrist.

No specific medication had previously been proposed to prevent the recurrence of the attacks. Due to the diagnosis of MRH, and the link between menses and the timing of the episodes, the patient started treatment with a discontinuous OCP (Minidril®, combining ethinylestradiol [30 µg] and levonorgestrel [150 µg], one pill every day for 21 days then a pause of seven days) from mid-February 2016, at the beginning of her menstrual cycle. One episode of hypersomnia occurred during menses at the very beginning of the treatment and the patient remained free of any episode over the following three months (Table 1). Unfortunately, the OCP medication was interrupted because of heavy bleeding and replaced by Seasonique®*, also an estro-progesterone, which was initiated and taken continuously for 91 days thus reducing the frequency of withdrawal bleeding to only four times per year. *84 days of combined ethinylestradiol (30µg) and levonorgestrel (150µg), then 7 days of ethinylestradiol (10µg).

During the first three months of treatment, the patient did not experience any typical or atypical (minor) episodes (Table 1). The last episode, which was reported in May 2017, had remarkably few symptoms, which did not prevent the patient from going to school. No link with menses was observed. The patient felt exhausted but managed to resist the urge to sleep. She mostly experienced depersonalization and barely spoke. The symptoms resolved by the end of the day.

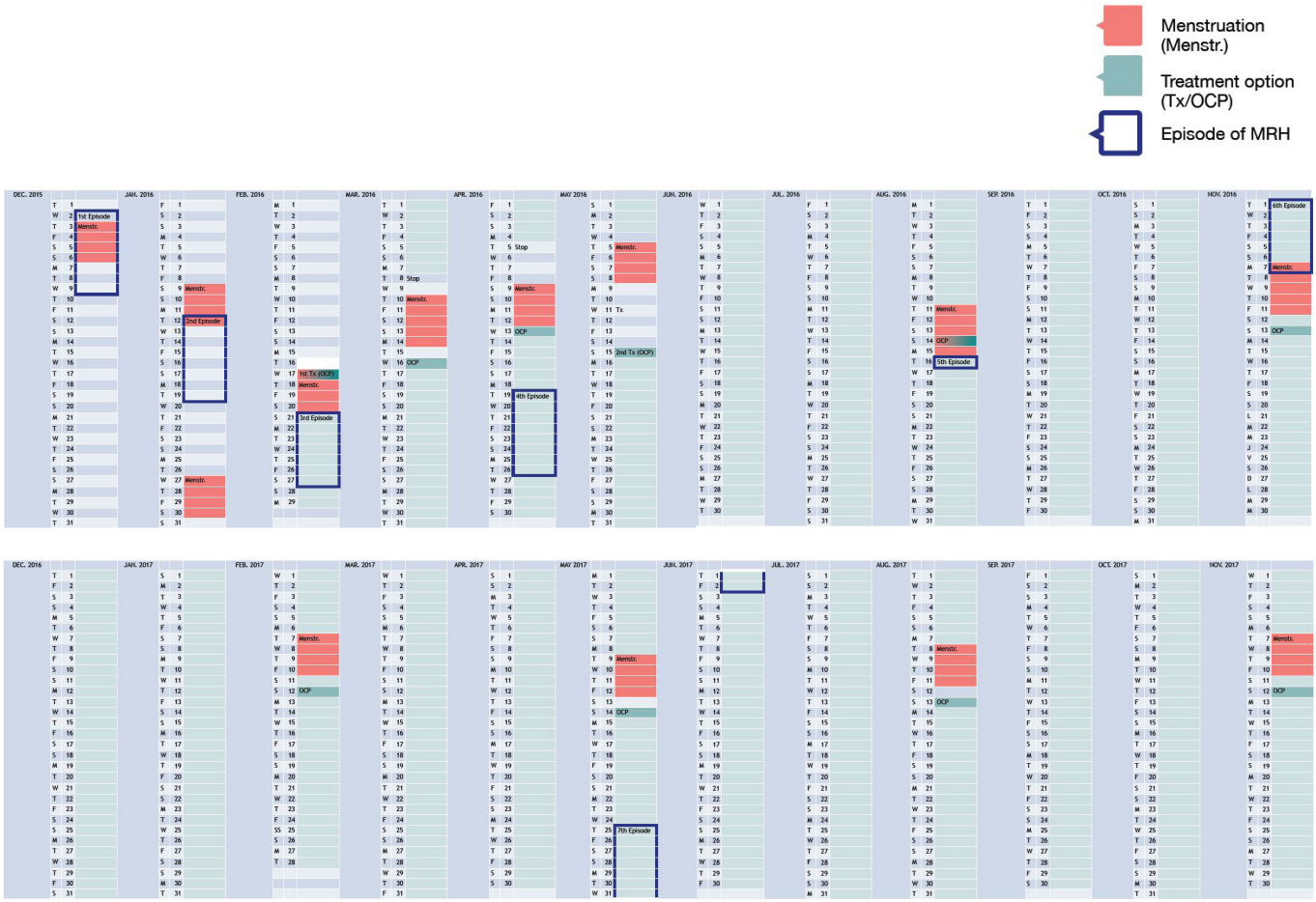

Table 1: Calendar of events for the 1st patient, including episodes of MRH, menstruation, and OCP intake

Patient 2

Patient 2 was first seen at the age of 15 years and originated Republic of Benin (Africa). She suffered from recurrent episodes of hypersomnia since the age of 13 years. At the time of the assessment, the patient had experienced 11 well identified episodes of hypersomnia, each one lasting around four to ten days. There was no prior psychiatric or medical history during childhood as reported by her father who is a pediatrician.

The first episode occurred in July 2014 following a high fever of unidentified cause, which started in March 2014, lasted over a month and required antibiotics medication. A lumbar puncture was performed during the febrile episode showing no abnormality. The patient was pale, asthenic and developed abrupt and unusual daytime sleepiness. Her appetite was not modified and she did not gain weight. Weight was stable over time, 53 kg for 157 cm (BMI: 21,5 kg/m^2). The first episode lasted two weeks with gradual improvement over time. One month later, a very similar episode occurred, marked by an even more extensive period of daytime sleep.

From January 2015, when her first menstruation started at the age of 13 (Jan 2015), until July 2015, the patient presented with seven episodes of hypersomnia. A clear link was established between the menstrual cycle and the sleeping episodes, occurring during or few days after menses. During the subsequent episodes, the patient presented mostly with sleepiness, clinophilia, and fatigue, which was accentuated compared to the first episodes. The patient did not report any confusion, derealization, hallucination or hyperphagia. She also had elevated mood, characterized by singing during the episodes. Besides headaches, the patient did not present any other prodromal symptom. Her two sisters never experienced any sleepiness or episodes of hyper somnolence in relation to their hormonal cycles.

The patient underwent many investigations including routine biological tests EEG, cerebral MRI and computerized tomography (CT) which revealed no abnormalities. Unfortunately CSF analysis did not measure hypocretin levels. Follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol and progesterone levels were measured before initiation of the oral contraceptive and were normal.

Prophylactic treatment was initiated in July 2015 using Optidril®, an oral contraceptive combining ethinylestradiol (30 µg) and levonorgestrel (150 µg), taken for 28 days (21 days of active pills then 7 days of placebo). Over a period of five months, only one episode was reported in December 2015, which lasted four days without any documented link with menses. During this shorter episode, the patient did not complain of headache but experienced deeper sleep than usual. She did not present with any further episodes of somnolence for more than two years afterwards. The last episode occurred in January 2018, but was minor and unrelated to menstruation. Currently, the patient is still taking the OCP and has remained completely symptom-free for more than a year, enabling her to achieve to a high academic level.

Patient 3

We report the case of a 16-year-old Caucasian girl presenting with episodes of somnolence lasting two to three weeks and recurring approximately every three months during the last four years prior to her visit at the Sleep Center. At the time of the assessment the patient presented with moderate obesity, 79 kg for 161 cm (BMI: 30.5 kg/m^2). The patient was free of any psychiatric symptoms or medical history prior to the onset of disease. The symptoms were defined by severe fatigue and clinophilia, with excessive sleep duration of up to 16 hours per day. The first menstruation started at the age of 11 years (June 2012), which was contemporaneous with the emergence of the recurrent somnolence that began three days prior to her menstrual cycle. In June 2016, the patient started a discontinuous progesterone-containing treatment with Lutéran® 10 mg (chlormadinone acetate) for 15 days out of 28. After four months of treatment, the episodes became very rare with mild symptoms and reduced daytime sleep. One last episode was described under medication in March 2016 which duration was one week. No major cognitive impairment was reported during the episode. The patient was able to achieve her homework, but unable to attend school for a few days due to excessive sleepiness. Her appetite varied from having very low to increased hunger, and she developed significant weight gain under treatment. The patient also reported nausea and headaches in association with the episode. At the time of the current report, the patient was still medicated with chlormadinone acetate.

Discussion

The three cases reported above demonstrated characteristics consistent with the clinical diagnosis of MRH and com-plement the several cases already described in the literature.

Among these, Rocamora *et al.*, reported a case where a male adolescent was diagnosed with KLS when his sister re-ceived a diagnosis of MRH and responded to oral contraceptive [11]. Rare other descriptions, which point to similar responses to hormonal treatment in patients with MRH, are listed in Table 2.

Published literature	Population	Age	Diagnosis	Treatment	Associated treatment	Outcome
Billiard *et al.* [2]	N = 1 1 female	13	**MRH**	**Hormonal treatment**	None	**Remission** (succesfull)
Sachs *et al.* [12]	N = 1 1 female	16	**MRH**	**Oral contraceptive** Ethinyl Estradiol 0,05 mg + Lynestrenol 2,5 mg	None	**Remission** (cessation of hypersomnia)
Papy *et al.*[13]	N = 1 1 female	21	**MRH**	**Oral contraceptive**	None	**Remission** (the attacks disappeared completely)
Price *et al.* [29]	N = 1 1 female	35	**BD**	**Oral contraceptive** Ethinyl Estadiol + Norethrindone (Ortho- Novum)	Imipramine	**Remission** (no further episodes of depression or mania)
Chouinard *et al.* [22]	N = 2 2 females 1 post-menopausal	49; 56	**BD**	**Hormonal Replacement Therapy**	Lithium (resistant)	**Remission (antodepressant and mood stabilizing properties)**
Rasgon *et al.* [18]	N = 6 females (OCP users out of 17 subjects with BD)	18-45	**BD**	**Oral contraceptive**	Mood stabilizers + Antidepressants	**Response** (less mood fluctuation across the menstrual cycle in OC users)
Huang *et al.* [30]	N =1 1 female	31	**BD** (post-partum mania)	**Hormonal Replacement Therapy** Estrogen 0,625 mg + Medroxyprogesterone 2,5 mg	Lithium + Valproate (resistant)	**Remission**
Rocamora *et al.* [11]	N =1 1 female	15	**MRH**	**Oral contraceptive**	None	**Remission** (free of symptoms)
Robakis *et al.* [20]	N = 20 females (OCP users among 91 subjects with BD)	18-45	**BD**	**Oral contraceptive**	GABAA R modulators ± Lamotrigine	**Response** (improved mood ratings)

Suau *et al.* [14]	N = 1 1 female	18	**MRH**	**Oral contraceptive** Ethinyl Estradiol 0,035 mg + Norgestimate 0,25 mg (without placebo)	None	**Remission** (asymptomatic)

Table 2: Summary review of literature reporting effects of hormonal treatment in patients with MRH and BD

All three cases described here support the use of an OCP to improve the condition of MRH. A clear amelioration was clinically observed, corroborating these previous findings.

In fact, the symptoms were very similar to those of Kleine-Levin syndrome, except that their timing was related to the menstrual cycle.

Symptoms during an episode including those of KLS (DSM-5)	Patient 1	Patient 2	Patient 3
Excessive sleepiness	☑	☑	☑
Cognitive dysfunction	☑	☐	☐
Altered perception	☑	☐	☐
Hyperphagia	☑	☐	☑
Anorexia	☐	☑	☑
Disinhibited behavior	☐	☐	☐
Asthenia	☑	☑	☑
Irritability	☑	☐	☑
Headaches	☑	☑	☑
Nausea	☐	☐	☑
Apathy	☑	☐	☑
Weight gain	☑	☐	☑

Table 3: Symptoms during an episode of MRH (before treatment)

Table 3 shows symptoms that overlap with the diagnostic criteria for Kleine-Levin syndrome according to the DSM-5 criteria and, additional symptoms reported by the MRH patients such as headaches and fatigue.

To prevent episodes of hypersomnolence, the OCP has been proposed as an alternative to lithium, to ensure regular periods and to avoid potential side effects of lithium. However, more data are required to reach a consensus regarding the use of long-term OCP versus lithium therapy in patients with MRH. Moreover, MRH may resolve spontaneously and differently than KLS [15].

After initiation of hormonal treatment, all three patients were largely free of relapses after a few months of treatment, which allowed them to return to their previous life-styles. The isolated episodes that occurred were markedly attenuated, especially decreased somnolence with mild residual symptoms without any link with menses in most cases. No significant weight gain occurred over the period of follow up in two of these cases. However, there were insufficient grounds to conclude a potential impact of treatment on weight control during episodes.

Interestingly, the third patient was treated with progesterone-containing treatment only 15 days per month, and we presume that this treatment was neither antigonatropic nor prevented ovulation. Besides, the third patient's symptoms and frequency of episodes improved with this particular treatment indicating that hormonal treatment may have a therapeutic effect through progesterone replacement, rather than through a central blockade of ovulation.

It is known that the first years following menarche are frequently marked by dysovulatory or even anovulatory cycles [16]. In this context, adolescents frequently have irregular menses associated with a relative progesterone deficiency in the luteal phase of the menstrual cycle.

To our knowledge, no other studies to date have described cases of patients with MRH whose symptoms have been by progesterone-only treatment at non-antigonadotropic doses. Thus, the combined estro-progesterone pills, as well as the discontinuous progesterone pills, could restore this progesterone deficiency specific to the pubertal period.

Sex hormones have a role in the regulation of daily sleep-wake rhythm in women, and orexin/ hypocretin neurons involved in regulation of arousal, sleep-wake cycles and appetite are known to have a regulatory role on catecholaminergic neurons, including dopamine neurons at the level of the lateral hypothalamus [17].

Interestingly, the second case presented a first episode almost a year before onset of menstruation. Although the first episode of hypersomnia for the second case was premenarchal, it started at a time when the synthesis of estradiol would have been highly variable. It is therefore tempting to propose that hypersomnolence observed in MRH does not directly result from a defect in gonadotropic axis function but may be due to abnormal pubertal maturation of the neuronal circuits governing sleep, which are influenced by estradiol and/or progesterone levels. Thus, improvement of hypersomnolence during and subsequent to treatment could be attributed to maturation of this system.

Several elements described above suggest some parallels with bipolar disorders (BD), particularly the possible cyclicality of periods characterized by mood and/or sleep disturbances, observed in both MRH and BD. We confirm that none of the three cases reported here had BD according to current diagnostic criteria, and no case of BD was reported among their respective families. However, some similarities are discernible between MRH and early onset bipolar disorders. In fact, both entities may share similar features such as age of onset during puberty, symptoms related to menses, response to similar classes of treatment, and a similar mechanism of action originating in the hypothalamic area.

Concerning the age of onset, most cases reported in the literature have shown an onset during adolescence and not during childhood, supporting the role of hormone fluctuation found both in BD and MRH [18].

In a large study, it was reported that MRH patients developed symptoms of depression and mood lability, which was not the case in ourr patients [1]. Furthermore, mood changes are related to the menstrual cycle in women with bipolar disorder, and among those taking OCPs, mood fluctuations are lessened [19].

Table 2 shows data from a literature search regarding response to hormonal treatment in women presenting with BD or MRH.

OCPs have also enabled significant improvements in the treatment of women with BD when used in association with lamotrigine or other medications with GABAa receptor modulating effects [20]. Interestingly, OCP cessation has also been noted as a triggering factor for onset of rapid cycling BD, in the same way it has led to recurrence of hypersomnolence in MRH cases [21].

A possible mood stabilizer effect of OCPs has been suggested, and high doses of estrogen have been equally effective to antidepressants in treating patients with chronic relapsing depression [22,23]. Premenstrual Dysphoric Disorder characterized by mood swings, fatigue, depression and insomnia, has also been attenuated by the use of OCPs and shows similar symptoms and therapeutic responses as MRH and BD [24,25].

In fact, hormonal changes have been implicated as influential for the onset or evolution of many neurological and psychiatric diseases, including catamenial epilepsy, catamenial migraines, and multiple sclerosis [26-28]. In most cases, these disorders are alleviated by the prescription of a progesterone-containing pill, estro-progesterone pill, or during pregnancy. Thus, among patients with MRH, improvement of a putative estrogen/progesterone imbalance could have a beneficial effect on the neuronal defects responsible for hypersomnolence. Further studies are needed to support the effectiveness and the tolerability of OCPs for the treatment of MRH among adolescent patients, which may also lead to a better understanding of the pathophysiology of the disorder and of its relationship with KLS [29-30].

Conflict of Interest

All authors contributed to the writing of this report and approved the final version.
Institution where work was performed: AP-HP, Pediatric Sleep Center, Hospital Robert-Debré, Paris, France

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