Circadian rhythm disorder in a rare disease: Smith–Magenis syndrome

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Abstract
Smith–Magenis syndrome (SMS) is a clinically recognizable contiguous gene syndrome, caused by interstitial deletion of chromosome 17p11.2. The SMS phenotype include distinctive facial features, developmental delay and neurobehavioral abnormalities. The patients present major sleep disturbances ascribed to a phase shift of their circadian rhythm of melatonin with a paradoxical diurnal secretion of the hormone. Treatment with morning beta-blockers and evening melatonin reinstated a normally timed melatonin circadian rhythm, improved daytime behavior and restored normal sleep habits, resulting in a greatly improved quality of life for both SMS patients and their family. SMS is the demonstration of biological basis for sleep disorder in a genetic disease. Considering that clock genes mediate generation of circadian rhythms, we suggest that haploinsufficiency for a circadian system gene mapping to chromosome 17p11.2 may cause the inversion of circadian rhythm in SMS.

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1. Introduction
Smith–Magenis syndrome (SMS) is a rare genetic disease emblematic of neurodevelopmental disorder. The SMS phenotype includes mild dysmorphism, developmental delay and abnormal behavior. Severe sleep disturbances and maladaptive daytime behavior were linked to abnormal circadian rhythm of melatonin. SMS is the demonstration of biological basis for sleep disorder in a genetic disease. Considering that clock genes mediate generation of circadian rhythms, we suggest that haploinsufficiency for a circadian system gene mapping to chromosome 17p11.2 may cause the inversion of circadian rhythm in SMS.

First described by Ann Smith et al. in 1982 (Smith et al., 1986; Greenberg et al., 1991), SMS is a contiguous gene deletion syndrome ascribed to interstitial deletion of chromosome 17 (17p11.2) (Juyal et al., 1996). However, deletions have ranged from <2 to >9 megabases and mutations in RAI1 (Retinoic Acid-Induced gene) were shown in individuals who have phenotypic features consistent with SMS (Slager et al., 2003).
The birth incidence is reported at 1/25,000 live births. All cases occur de novo, there is no parental imprinting.

2. Clinical features and diagnosis criteria
Several distinctive features characterize the phenotype of Smith–Magenis syndrome (Smith et al., 1998a), including brachycephaly with midface hypoplasia, mouth characteristic with cupid’s bow, ocular abnormalities, speech delay with or without hearing loss, hoarse deep voice, short stature, brachydactyly. Other variable features include cardiac defects, renal abnormalities, seizures, peripheral neuropathy, scoliosis, cleft palate, low immunoglobulins and thyroxin defect. Decreased sensitivity to pain was ascribed to anatomical and functional brain anomalies (Boddaert et al., 2004) All patients have some degree of developmental delay and mental retardation. IQ scores range between 20 and 78. Behavioral problems include consistently hyperactivity with attention deficit, aggression, self injurious behaviors, temper tantrums. Severe sleep disturbances (Smith et al., 1998b) and unusual circadian rhythms are constant features of the syndrome.
The diagnosis is based on clinical features and confirmed on high resolution karyotype with detectable deletion of 17p11.2 and by fluorescence in situ hybridization (FISH) probe specific for SMS (Lucas et al., 2001).

3. Night and day sleep disturbances in Smith–Magenis syndrome
The behavioral phenotype includes significant sleep disturbance and have a major impact on the child and other family members, many of whom become sleep deprived themselves. Questionnaires, sleep consultations, sleep diaries and actimetric recordings revealed sleep disturbance in most SMS subjects. All
patients go to bed easily after a short bed-time ritual. Bedtime is similar at 8–9 p.m. regardless of age and sex. The duration of night sleep average 7.30 h. All SMS persons consistently wake up one to three times per night and fall back asleep within 30 min or more. Once awaken, they are hyperactive. This behavior force parents or care keeping to constantly look after them and to devise artifices to keep them in the bedroom by night (lock the door, switch light, remove furniture and objects). The mean wake-up time is 5.30 a.m. Behavioral problems correlate with night sleep insufficiency. Most patients exhibit morning tiredness when normally circadian vigilance is high. They have temper tantrums when tired and naps (more than 30 min) during the day, regardless of age. Most interestingly, they consistently have “sleep attacks” at the end of the day.

The 24 h-polysomnography, correlated with actimetry and sleep diaries, reveal a reduced total sleep time in 57% of the patients. All sleep stages are present but stage 3–4 non-rapid eye movement (NREM) sleep is reduced. REM sleep is disrupted and arousals with increased tonic EMG activity are frequent. Prolonged awakenings occur in 75% of cases.

Interestingly, all SMS patients display a phase shift in their circadian rhythm of melatonin (De Leersnyder et al., 2001a,b) (Fig. 1). Indeed, time at onset of melatonin secretion in SMS is 6 a.m. ± 2 (controls: 9 p.m. ± 2), peak time is at 12 p.m. ± 1 (controls: 3:30 a.m. ± 1.30) and melatonin offset is at 8 p.m. ± 1 (controls: 6 a.m. ± 1). Melatonin peak value rises 94 ± pg/ml (controls: 76 pg/ml). Irregular levels of melatonin are noted during the day with a second peak between 6 and 8 p.m. (45 pg/ml ± 32) and the total duration of melatonin secretion is protracted in SMS: 15.5 h ± 3.5 (controls: 8 h ± 1). Similarly urinary melatonin and 6-sulfatoxymelatonin revealed an inverted night/day ratio (Potocki et al., 2000).

Cortisol, growth hormone (GH) and prolactin follow a usual circadian secretion and are in the normal range.

This abnormal circadian rhythm of melatonin parallels sleep disturbances and abnormal day behavior in SMS (Fig. 2). During the night, early sleep onset, frequent awakenings and early sleep offset are consistent features of the disease and are highly specific diagnostic criteria in SMS. The sleep attacks occurring at the end of the day may represent in fact the endogenous sleep onset of the patient that could be regarded therefore as equivalent to a sleep phase advance. According to this hypothesis, the endogenous sleep onset time would be masked by the imposed social activities.

During the day patients are tired in the morning and tantrums appear when melatonin rises. Naps and sleep attacks occur when melatonin peaks at midday and in the evening, respectively. Considering that behavioral problems correlate with the abnormal circadian rhythm of melatonin in SMS, it is tempting to hypothesize that at least part of hyperactivity and attention deficit occur because the patients struggled against sleep when melatonin rise during the day.

4. Hypothesis concerning melatonin dysfunction

Melatonin, the main hormone of the pineal gland, is synthesized from serotonin. Its synthesis and release are stimulated...
by darkness and inhibited by light. Light entrainment pro-
ceeds through the retino-hypothalamic tract (RHT) to reach
the suprachiasmatic nuclei (SCN) of the anterior hypothala-
mus (Moore, 1997). SCN contain biological clocks, which are
endogenous pacemakers generating circadian rhythms entrained
by environmental stimuli. A number of clock genes control-
ing circadian rhythms have been recently identified in higher
eukaryotes (Van Esseveldt et al., 2000). Their expression shares
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ceed through the retino-hypothalamic tract (RHT) to reach
light entrainment pro-
rhythm of melatonin is controlled by the sympathetic nervous
sys
secretion under the control of the SCN. Consequently, the inver-
sion of the circadian rhythm of melatonin in SMS is also re-
result from an alteration of the input/output-signaling pathway (e.g.
photic entrainment in the retina/RHT or output signaling pathway of postganglionic fibers
ascending to the pineal gland is required to maintain melatonin
secretion). Actually, the mechanism of this quantitatively normal but rhythmically abnormal melatonin
secretion in SMS is not known.

5. Treatment of the inverted rhythm of melatonin in
Smith–Magenis syndrome

We hypothesized that behavioral problems and night sleep
insufficiency in SMS may correlate with the inverted circadian
rhythm of melatonin. Sleep disturbances are extremely severe
and difficult to manage. These observations are particularly rel-
vant to therapeutic approaches in SMS. Indeed the circadian
rhythm of melatonin is controlled by the sympathetic nervous
system and it is known that β1-adrenergic antagonists reduce
the production of melatonin (Stoschitzky et al., 1999). An orig-
inal therapeutic approach including blockade of endogenous
melatonin signaling pathways combined with on-time exoge-
nous melatonin administration was studied in patients aged 6–18
years (De Leersnyder et al., 2001a,b, 2003). A cardiac and pneu-
mologic examination was performed before trial. After a morn-
ing β1-adrenergic antagonists administration, plasma melatonin
levels rapidly decreased in all SMS patients. Mean melatonin
levels fell from 68 to 8 pg/ml after drug administration. Individ-
ual melatonin levels decreased 3–20-fold, remained low from
8 a.m. to 6 a.m. the next day and rose again from 6 to 8 a.m.
prior to drug administration (Fig. 3).

With this treatment, day behavior markedly improved. While
untreated patients had 1–3 naps/day and frequent sleep attacks
at the end of the day, beta-blocker administration resulted in the
disappearance of naps and sleep attacks. The explosive tantrums
(1–2 each day) were less frequent (1 or 2 per week) and could
be easily managed. Concentration increased during school time
and children were reported to be quieter and less hyperactive.
No significant increase of cognitive performance was observed.

The combination of morning β1-adrenergic antagonist and
evening melatonin administration restored plasmatic circadian
melatonin rhythmicity, improved behavioral disturbances and
enhanced sleep in SMS. Studies were conducted with a control
release (CR) melatonin (De Leersnyder et al., 2003). After a
single dose of exogenous melatonin, plasmatic melatonin levels
rapidly peaked and slowly decreased thus mimicking the effects
of endogenous melatonin on circadian rhythm. Mean melatonin
levels rose from 12.7 ± 10.6 to 2189 ± 1800 pg/ml 2 h after drug
administration. Individual melatonin levels increased 170-fold
compared to levels after β1-adrenergic antagonists administra-
tion, remained high from 10 p.m. to 2 a.m., and slowly decreased
till 6 a.m. (Fig. 3). Mean sleep onset was delayed by 30 min, sleep
offset by 60 min and the mean gain of sleep was 30 min. Sleep
awakenings disappeared in most cases and wake-up time was
delayed. Patients no more woke up during the night and EEG
recordings confirmed a more regular sleep stage organization
and a rapid access to sleep stage 3–4. Sleep was deep and quiet
and day/night life was dramatically improved. No desensitiza-
tion was observed over a 3 years period of drug administration.

As this treatment restored a biological rhythm when it was
inverted, it is proposed for most SMS patients, in respect of con-
traindication. Finally, there were no adverse events related
to the treatment, no side effects or habituation, and children,
parents and care giving were convinced for continuation of the
treatment.
6. Conclusion

Smith-Magenis syndrome is a rare genetic disorder ascribed to interstitial deletion of chromosome 17 (17p11.2). SMS is also a circadian disorder with extreme phase shift of melatonin secretion. This is the first biological model of sleep and behavioral disorders in a genetic disease. Elucidating pathophysiological mechanisms of behavioral phenotypes is particularly relevant to therapeutic approach in genetic diseases. Indeed, in SMS where the circadian rhythm of melatonin is shifted, β₁-adrenergic antagonists combined with evening melatonin administration restore a circadian rhythm of melatonin, suppress inappropriate diurnal melatonin secretion and improve sleep and behavioral disorders.

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