SMITH-MAGENIS SYNDROME: A CASE REPORT OF IMPROVED SLEEP AFTER TREATMENT WITH β_1-ADRENERGIC ANTAGONISTS AND MELATONIN

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This report describes the case of a 4-year-old boy diagnosed with Smith-Magenis syndrome in whom treatment with a β_1-adrenergic antagonist in the morning (to suppress the diurnal melatonin secretion) and melatonin in the evening (to generate a nocturnal peak of melatonin) improved his sleep quality, evaluated by polysomnographic studies. *(J Pediatr 2006;149:409-11)*

The Smith-Magenis Syndrome (SMS)[1] is a contiguous gene syndrome associated with a deletion within band p11.2 of chromosome 17, with a prevalence estimated at 1/25000. Patients with SMS have a distinctive somatic and behavioral phenotype that has been extensively studied.[1-4] All patients with SMS show sleep disorders[4] with early sleep onset, difficulty in falling asleep, difficulty in staying asleep, frequent awakening, early waking, reduced rapid eye movement (REM) sleep, and decreased sleep time.[2,5] EEG alterations consist of reduced or missing REM sleep. These children go to bed early, have frequent arousals during the night, and wake up early in the morning. During the daytime they feel tired in the morning, have frequent naps, and then have heavy drowsiness in the evening.

Sleep troubles in patients with SMS could be related to a disturbance of the circadian system. Melatonin is a pineal hormone secreted at night, with a circadian rhythm dependent on adrenergic signals from the suprachiasmatic hypothalamic nucleus. This hormone has been found to play a part in regulation of the sleep/activity rhythm. One interesting finding common to all the patients with SMS is the inversion of the circadian rhythm of melatonin.[6,7] Their melatonin secretion is higher during the day than at night, showing an average phase advance shift of 9.6 $\pm$ 0.9 hours with respect to control subjects.[8] The diurnal secretion of melatonin of patients with SMS could be a symptom of the alteration of their circadian cycle as well as the possible cause of their sleep troubles. On this basis, Leersnyder et al[9,10] hypothesized that suppression of the diurnal melatonin rhythm in conjunction with an increase of the nocturnal levels could improve the sleep quality in these patients. Because the circadian rhythm of melatonin is controlled by the sympathetic nervous system, patients with SMS were treated with β_1-adrenergic antagonist in the morning and melatonin in the late evening, thus managing to improve their sleep quality, evaluated by actimetric and subjective methods.[10] Our objective was to assess the efficiency of this treatment by measuring sleep objectively through polysomnographic studies.

METHODS

The patient was a 4-year-old boy, diagnosed with SMS by clinical evaluation and high-resolution karyotype. He showed most somatic and behavioral characteristics of this syndrome. At the time of referral, the boy's parents reported serious sleep disturbances: early onset of sleep, instability with frequent nocturnal waking, and daytime sleepiness.

The treatment consisted of acebutolol, a selective β_1-adrenergic antagonist (10 mg at 10:00 AM to noon daily), and a slow-release melatonin (3 mg in the evening, approximately 1 hour before bedtime).

Polysomnographic studies were carried out before and after 2 weeks of treatment. Variables recorded included electroencephalogram, recorded from central (C3 and C4) against ear reference (A1 and A2) electrodes, electro-oculogram, and electromyogram. Sleep staging was determined by standard criteria.

The boy's spontaneouslyvoided urine was collected during a 24-hour period. Immediately before getting up in the morning (lights on) and before going to bed in the

REM	Rapid eye movement	TST	Total sleep time
SMS	Smith-Magenis Syndrome		

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Submitted for publication Jan 11, 2006; last revision received Mar 15, 2006; accepted Apr 25, 2006.

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0022-3476/$ - see front matter

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10.1016/j.jpeds.2006.04.055

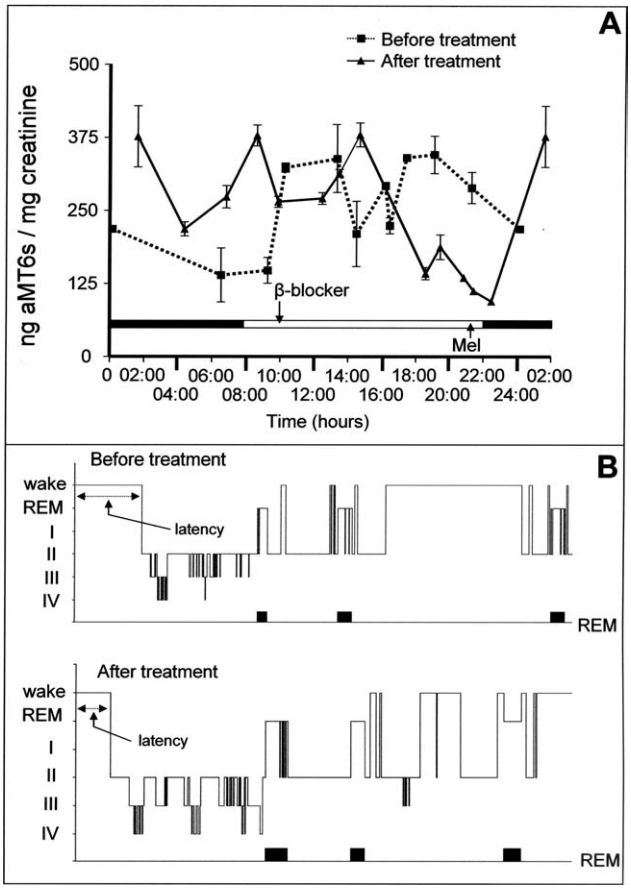

Figure. **A,** Urinary concentration of aMT6s (mean ± SD of triplicate samples) in a 4-year-old boy with SMS, before *(dotted line)* and after *(continuous line)* 2 weeks of treatment with a selective β_1-adrenergic antagonist (acebutolol, 10 mg in the morning) and melatonin (3 mg in the evening). Time of treatments are indicated by *arrows*. Differences between the day/night proportion of melatonin excretion before and after treatment: $P < .01$. **B,** Summary of the polysomnographic records carried out before and after 2 weeks of treatment.

evening (lights off), the child was invited to urinate to empty his bladder and allow us to separate the urine produced during the day from that at night. In all cases, both the volume of the sample and the time of collection were recorded. Urinary concentrations of 6-sulphatoxymelatonin (aMT6s), the major metabolite of melatonin, were measured by radioimmunoassay (Stockgrand LTD, Guildford, UK) and adjusted for creatinine. Results are indicated as mean ± SEM for triplicates of each sample.

RESULTS

The Figure, A, shows the 24-hour profile of the urinary excretion of aMT6s. The area under the curve for the diurnal period was 8.9% lower than it was before treatment. However, for the nocturnal period, the area under the curve was 43% higher than it was before treatment. The differences in the day/night proportions of total urinary excretion before and after treatment are significant (Fisher exact test, $P < .01$).

Before treatment, the patient showed a sleep pattern that was well structured during the first half of the night but then showed prolonged nocturnal awakening in the second half (Figure, B). Findings during nocturnal sleep (Table) include (a) decreased slow deep sleep (especially IV phase), (b) decreased percentage of REM sleep, (c) increased slow light sleep, (d) multiple and spontaneous awakenings in the second half of the night, (d) decreased total sleep time (TST), (e) decreased Sleep Efficiency Index, and (f) prolonged latency for sleep onset. After treatment, we observed (a) an increase of TST (from 290 to 311 minutes) with a better Sleep Efficiency Index (from 55.7% to 73.5% of bedtime), (b) a decrease of slow light sleep (from 77.5 to 66.2% of non-REM sleep time), (c) an increase of slow deep sleep (from 10.5% to 27.7% of non-REM sleep time), (d) a slight increase of REM sleep, (e) a less prolonged sleep latency (from 69 to 29 minutes), and (f) a decrease of spontaneous awakenings in the last half of the night (from 162 to 83 minutes).

Table. Polysomnographic parameters before and after treatment with a selective β_1-adrenergic antagonist (acebutolol, 10 mg in the morning) and melatonin (3 mg in the evening)

Sleep parameters	Basal recording	Post-treatment recording
Bedtime	521	423
Sleep latency	69	29
Total sleep time	290	311
Sleep Efficiency Index	55.7%	73.5%
Wake time	231 (44.0%)	112 (26.5%)
Wake after sleep onset	162	83
REM sleep latency	120	131
REM sleep time	36 (12%)	43 (14%)
Non-REM sleep time	254	268
I	0 (0%)	0 (0%)
II	225 (77.5%)	206 (66.2%)
III	24 (8.4%)	50 (16.1%)
IV	6 (2.1%)	11 (3.7%)
Slow light sleep (I + II)	225 (77.5%)	206 (66.2%)
Slow deep sleep (III + IV)	30 (10.5%)	60 (19.8%)

DISCUSSION

The circadian rhythm of melatonin is closely associated with the sleep-wake cycle and administration of melatonin affects latency to sleep onset, sleep consolidation, slow waves, sleep spindles, and REM sleep.[11] The characteristic inversion of melatonin rhythm in patients with SMS can be reversed by treatment with a β_1-adrenergic antagonist administered early in the morning and single doses of melatonin in the evening.[10] This treatment induced a dramatic improvement in sleep quality, evaluated by actigraphy and sleep diaries.[10] Our patient showed a typical clinical history of SMS. His diurnal excretion of melatonin was higher than the nocturnal one, and the polysomnographic study showed a sleep pattern of reduced TST, frequent awakenings, and early sleep off-

set.[5,7] After treatment with the above-mentioned combination of β_1-blockers (10 mg) and melatonin (3 mg), we observed an objective improvement in sleep quality characterized by a notable decrease in sleep latency, a reduction of the wakefulness periods, better sleep efficiency, and an increase in slow deep sleep. These results provide, for the first time, objective evidence of the advantage of the treatment of sleep disorders in children with SMS with a selective β_1-adrenergic antagonist plus melatonin.

We are grateful to the boy's parents for participating in this study.

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