

# Inverted rhythm of melatonin secretion in Smith–Magenis syndrome: from symptoms to treatment

Hélène De Leersnyder

Department of Genetics, Robert Debré Hospital, 48 boulevard Sérurier, 75019 Paris, France

**Smith–Magenis syndrome (SMS) is a mental retardation syndrome with distinctive behavioral characteristics, dysmorphic features and congenital anomalies ascribed to an interstitial deletion of chromosome 17p11.2. Severe sleep disturbances and maladaptive daytime behavior have been linked to an abnormal circadian secretion pattern of melatonin, with a diurnal instead of nocturnal secretion of this hormone. SMS provides a demonstration of a biological basis for sleep disorder in a genetic disease. Considering that clock genes mediate the generation of the circadian rhythm, haploinsufficiency for a circadian system gene, mapping to chromosome 17p11.2 might cause the inversion of the melatonin circadian rhythm in SMS. The disorder of circadian timing in SMS might also affect the entrainment pathway (retinohypothalamic tract), pacemaker functions (suprachiasmatic nucleus) or synthesis and release of melatonin by the pineal gland. Elucidating pathophysiological mechanisms of behavioral phenotypes in genetic disease can provide an original therapeutic approach in SMS: blockade of endogenous melatonin production during the day combined with exogenous melatonin administration in the evening.**

## Introduction

First described by Smith *et al.* [1,2], Smith–Magenis syndrome (SMS) is a severe neurodevelopmental disorder ascribed to an interstitial deletion of chromosome 17 (17p11.2) [3,4]. The diagnosis is based on clinical features and confirmed on high-resolution karyotype with detectable deletion of 17p11.2 and by the fluorescence *in situ* hybridization (FISH) probe specific for SMS [5,6]. Most patients have a common deletion interval of 3.5–5.0 megabases. However, deletions have ranged from <2 to >9 megabases, and mutations in the retinoic acid-induced gene (*RAI1*) were shown [7] in individuals who had phenotypic features consistent with SMS but did not have 17p11.2 deletions detectable by FISH. The prevalence of the syndrome is estimated to be one in 25,000 live births. All cases occur *de novo*, there is no parental imprinting.

Several distinctive features characterize the phenotype of SMS [8,9] (Box 1), including brachycephaly with a typical craniofacial appearance (midface hypoplasia, characteristic mouth with a ‘cupid’s bow’ shape, prognathism);

ocular abnormalities (myopia and strabismus, iris anomalies); speech delay with or without hearing loss; hoarse, deep voice; short stature with a history of failure to thrive; brachydactyly; peripheral neuropathy (*pes cavus* or *pes planus*, depressed deep tendon reflexes) and scoliosis. All patients have some degree of developmental delay and mental retardation; intelligence quotient scores range between 35 and 78, most falling in the moderate range of 45–55. Behavioral problems consistently include aggression, self-injurious behaviors, low sensitivity to pain, temper tantrums, impulsivity, repetitive behavior and hyperactivity with attention deficit [10]. Two stereotypical behaviors – spasmodic upper-body squeeze or ‘self-hug’, and hand licking and page flipping (‘lick and flip’) – seem to be specific to this disease. Severe sleep disturbances [11] and an unusual circadian rhythm are almost constant features of the syndrome. Other variable features include cardiac defects, renal abnormalities, seizures, cleft palate, low immunoglobulin levels and thyroid function defect.

SMS is an emblematic model of microdeletion syndromes. Indeed, elucidating behavioral phenotypes in mental retardation syndromes was a first step for the medical care of these patients who were mainly children. Listening to clinical particularities and studying sleep disorders in SMS led us to describe one of the few genetically determined defects affecting the known human circadian rhythm: the inversion of the rhythm of melatonin synthesis in SMS patients. This finding, which suggests a skewed biological clock in SMS, ‘opened the door’ to the genetic study of circadian rhythms and to the treatment of sleep disturbances. Indeed, in SMS, where the circadian rhythm of melatonin secretion is shifted,  $\beta_1$ -adrenergic antagonists combined with evening melatonin administration restore a circadian rhythm of melatonin secretion, suppress inappropriate diurnal melatonin secretion, and improve sleep and behavioral disorders.

## Sleep disturbances in SMS

Significant symptoms of sleep disturbance are seen in 65–100% of SMS patients and have a major impact on both the patient and other family members, many of whom become sleep deprived themselves [11]. Prominent sleep problems include early sleep onset (19.30–20.30 h), repeated and prolonged awakening during the night and early sleep offset (04.00–05.00 h), regardless of age and sex [12,13]. The duration of night sleep averages 7.50 h,

Corresponding author: De Leersnyder, H. (deleers@club-internet.fr). Available online 4 August 2006.

### Box 1. Distinctive features of the phenotype of SMS

SMS is a clinically recognizable syndrome caused by interstitial deletion of chromosome 17p11.2. The clinical phenotype includes: midface hypoplasia, downturned mouth with a 'cupid's bow' shape, ear anomalies, relative prognathism and brachydactyly (Figure 1). Mental retardation with speech delay, hyperactivity and attention deficit, outbursts and self-aggression are characteristic of the disease. The children have major sleep disturbances and behavioral problems ascribed to a phase shift in their circadian rhythm of melatonin secretion, with paradoxical diurnal secretion of this hormone. Elucidating the pathophysiological mechanisms of the behavioral phenotype is important for developing a therapeutic approach.



Figure 1.

declines with age and is slightly shorter than that of age-matched patients. Because patients are mentally retarded and hyperactive, this behavior forces parents or care givers to look after them constantly and to devise ways of keeping them in the bedroom by night (e.g. lock the door, switch off light and remove furniture and objects to avoid accident). During the day, behavioral problems correlate with night sleep insufficiency: most patients exhibit morning tiredness when their circadian vigilance should be high; they have temper tantrums when tired, and nap (for more than 30 min) during the day. Most interestingly, they consistently have 'sleep attacks' at the end of the day, suddenly falling asleep during evening meals, even with a full mouth.

Twenty-four-hour polysomnography, correlated with actimetric recordings and sleep diaries, reveal a reduced total sleep time in 57% of patients [12]. All sleep stages are present but stage 3–4 nonrapid eye movement sleep is reduced. Rapid eye movement sleep is disrupted, and arousals with increased tonic electromyogram activity are frequent. Awakenings (more than 15 min) occur in 75% of cases.

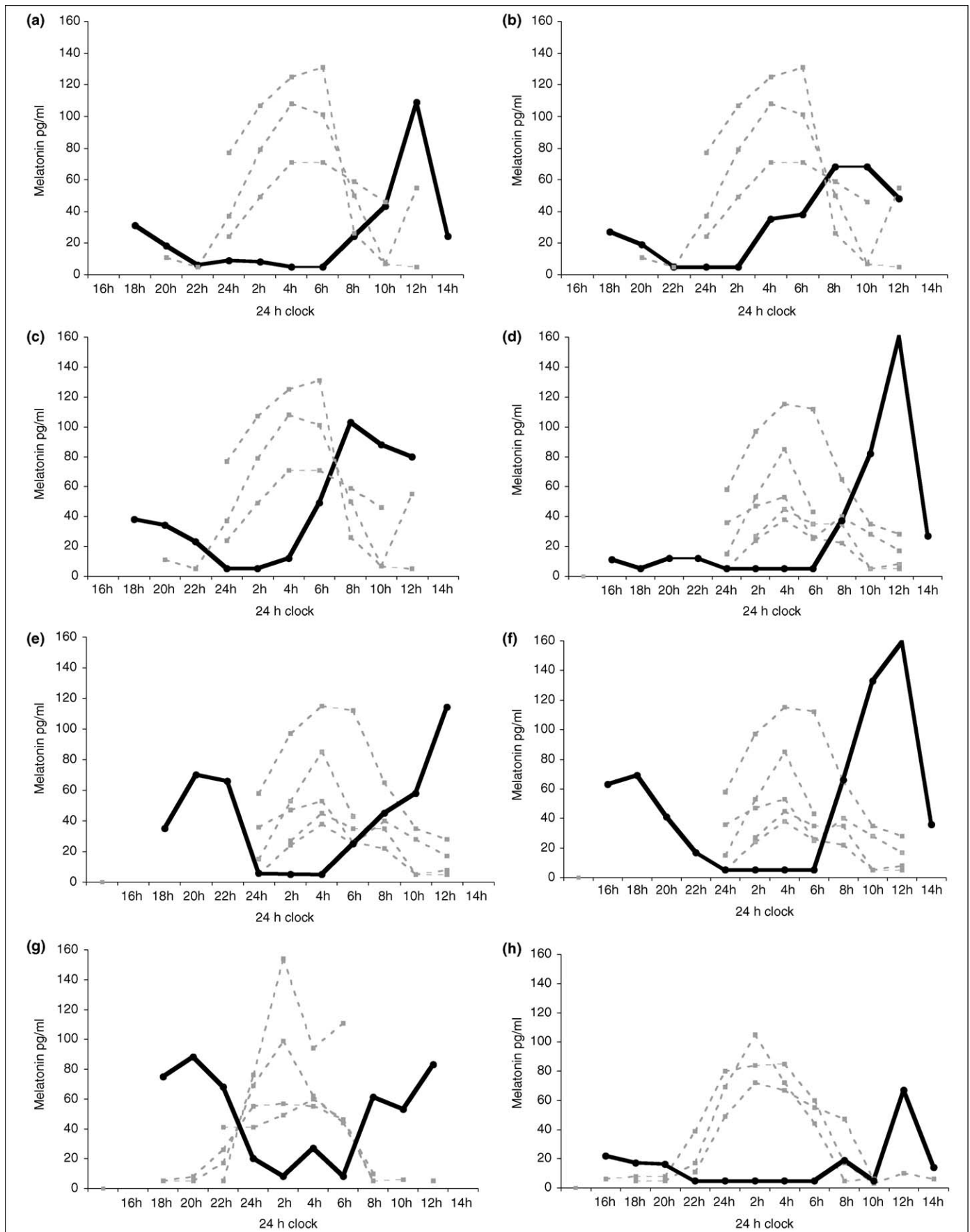
Interestingly, all SMS patients display a phase shift in their circadian rhythm of melatonin secretion [12–14] (Figure 1). Indeed, the time of onset of melatonin secretion in SMS is 06.00 h  $\pm$  2 h (controls: 21.00 h  $\pm$  2 h), peak time is at 12.00 h  $\pm$  1 h (controls: 03.30 h  $\pm$  1.30 h) and melatonin offset is at 20.00 h  $\pm$  1 h (controls: 06.00 h  $\pm$  1 h). Melatonin peak value rises to 94  $\pm$  12 pg/ml (controls: 76 pg/ml). Irregular levels of melatonin are noted during the day, with a second peak between 18.00 h and 20.00 h

(45  $\pm$  32 pg/ml), and the total duration of melatonin secretion is protracted in SMS, 15.5  $\pm$  3.5 h (controls: 8.0  $\pm$  1.0 h). Similarly, urinary melatonin and 6-sulfatoxymelatonin (the major metabolite of melatonin secreted in the urine) assays revealed an inverted night–day ratio. Patients with SMS undergo a constant shift in phase of the melatonin rhythm of 9.6  $\pm$  0.9 h but not a full reversal of the circadian melatonin rhythm [15]. This anomaly was reproductive day after day, with melatonin following a regular 24 h period secretion. This disorder cannot be considered as a comprehensive rhythm disorder because it does not affect the phase position of other endocrine functions generated and regulated by a circadian timing system. Cortisol, growth hormone (GH) and prolactin follow their usual pattern of circadian secretion in SMS patients and are in the normal range (Figure 2). The core body temperature rhythm does not seem to have significant inverted timing, although this has not yet been studied for long periods in basal conditions. The abnormal circadian rhythm of melatonin secretion parallels sleep disturbances and abnormal daytime behavior in SMS (Figure 3). During the night, when melatonin levels are low, 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 might represent the endogenous sleep onset of the patient and could therefore be regarded as being 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 levels rise. Nap and sleep attacks occur when melatonin peaks at midday and in the evening, respectively. It is thus tempting to hypothesize that at least part of the hyperactivity and attention deficit occur because the patients struggle against the sleepiness resulting from the physiological effects of high daytime melatonin levels. This is particularly relevant for child behavior. For ethical reasons, there have been no studies investigating sleep patterns in SMS patients allowed to choose their sleep times freely. We would expect that SMS patients would sleep during the day and remain awake during the night. Interestingly, there are anecdotal reports of SMS patients traveling across time zones, who then sleep well for a few nights.

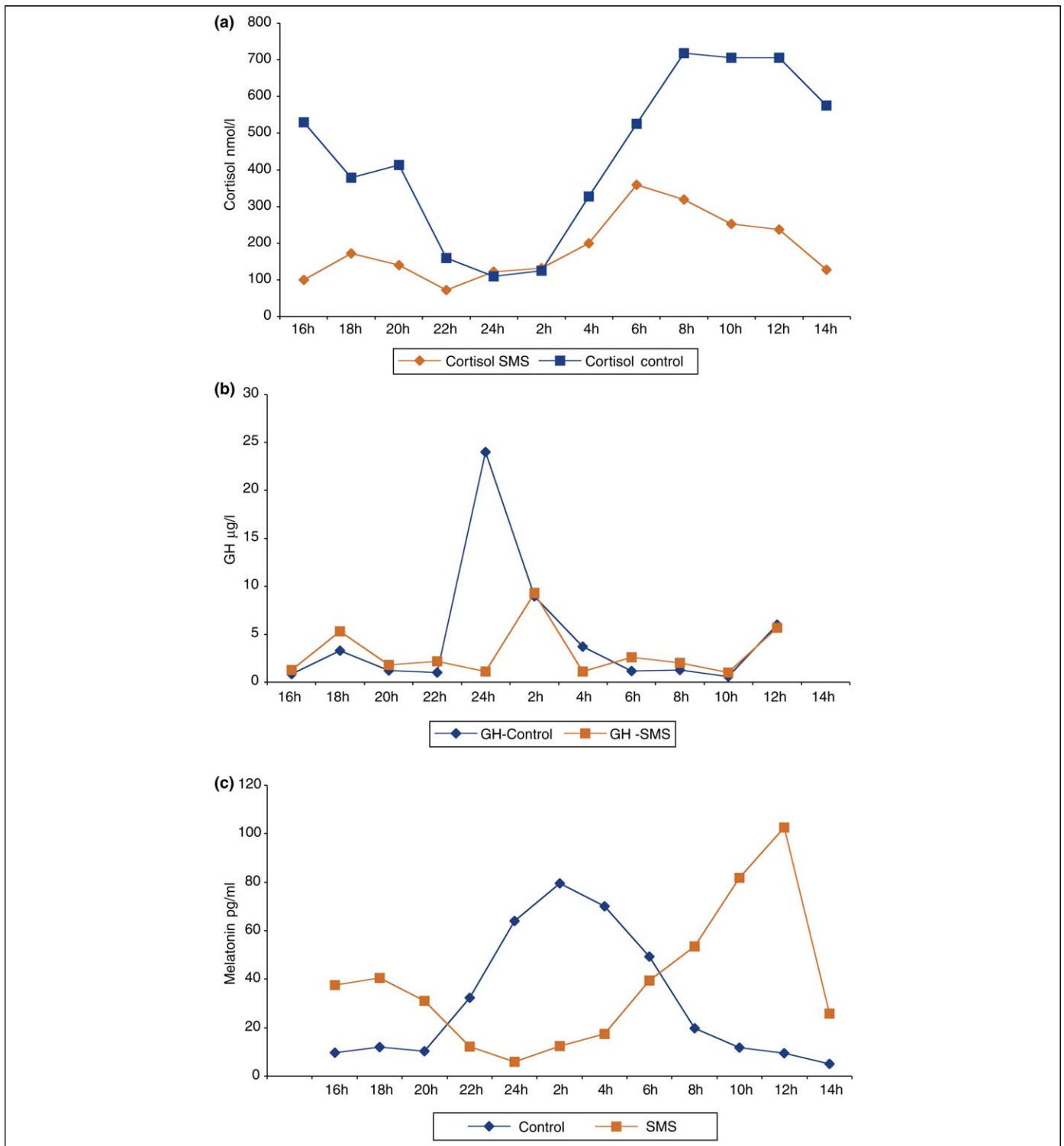
Heterozygous frameshift and nonsense mutations leading to protein truncation in *RAI1*, a gene that lies in the SMS critical region (1.1 Mb region), were identified in nine patients, with phenotypic features consistent with SMS, including developmental delay, craniofacial and behavioral anomalies, and sleep disorder [16]. Standard FISH techniques did not detect the 17p11.2 deletion in these patients. These authors did not provide accurate descriptions of sleep disturbances, including sleep phase advance, and melatonin secretion was not studied [16].

#### Hypothesis concerning melatonin dysfunction

Melatonin, the main hormone secreted from the pineal gland, is synthesized from 5-hydroxytryptamine (5-HT). Its synthesis and release are stimulated by darkness and inhibited by light (Box 2). Light entrainment proceeds



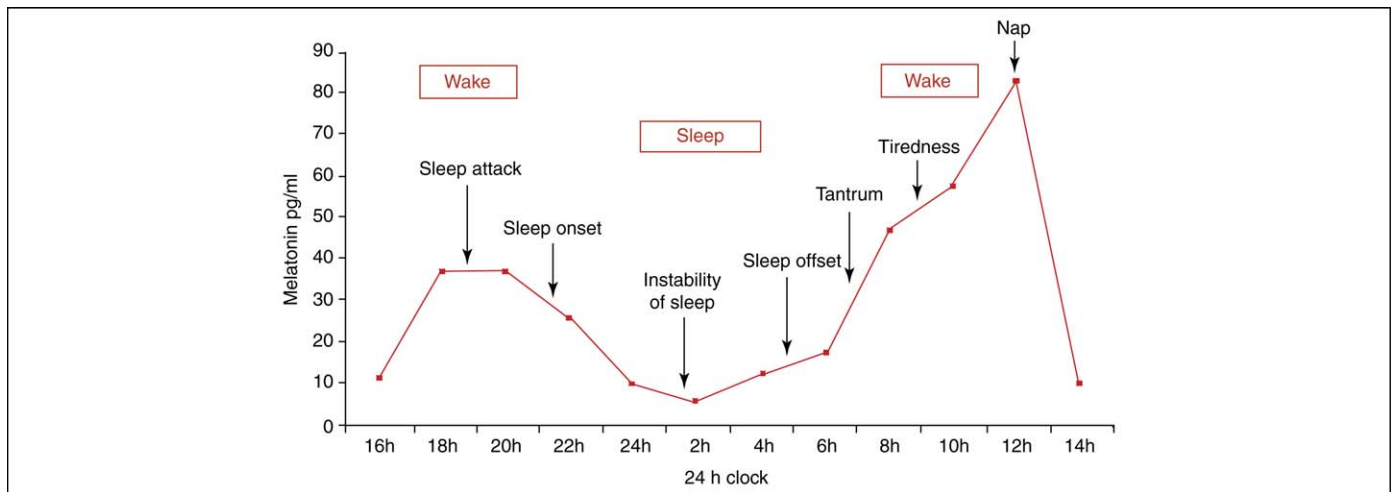
**Figure 1.** Circadian variation of plasma melatonin levels in eight SMS children and controls. Solid lines refer to SMS children aged 5–6 years (a–c), 7–8 years (d–f), 12 years (g) and 17 years (h). Dotted lines refer to age-matched controls. Aged-matched controls were healthy children or adolescents hospitalized for small stature. Note the inverted rhythm of melatonin in SMS patients, regardless of age and sex. Reproduced, with permission, from Ref. [12].



**Figure 2.** Circadian variation of cortisol (a), GH (b) and melatonin (c) levels in a 9-year-old SMS child and a control. Cortisol and GH have a normal circadian rhythm whereas the melatonin rhythm is inverted. GH values are lower than those of the control group but secretion is prolonged and the total amount of secreted GH falls within the normal range. These results were similar for all SMS patients studied. Modified, with permission, from Ref. [12].

through the retinohypothalamic tract (RHT) to reach the suprachiasmatic nucleus (SCN) of the anterior hypothalamus [17,18]. The SCN is the site of the central circadian pacemaker, which generates all other circadian rhythms that are entrained by environmental stimuli. Several clock genes controlling circadian rhythms have recently been identified in higher eukaryotes [19]. Their expression shares common features across species [20,21], in that they

oscillate with a 24 h rhythm which persists in the absence of environmental cues. The rhythm is reset by changes in the light–dark cycle and undergoes negative feedback that downregulates its own activity [22]. Considering that clock genes are expressed in a circadian pattern in the SCN, one can hypothesize that haploinsufficiency for a clock gene could account for sleep disturbance in SMS. Some genes are candidates by virtue of both function and position. The



**Figure 3.** Sleep–wake patterns correlated with melatonin secretion in SMS. The melatonin curve was obtained from the mean values of blood samples of melatonin in eight SMS patients. Reproduced, with permission, from Ref. [12].

*Per1* gene, a circadian regulator gene crucial for circadian rhythmicity, is expressed in a 24 h rhythm in the SCN and maps to chromosome 17p12. This region is not deleted in SMS. However, subunit 3 of the COP9 signal transduction complex (*COPS3*) maps within the SMS critical region on chromosome 17p11.2. COP9 is essential for the light control of gene expression during plant development and is conserved across species [23]. However, haploinsufficiency in one gene might not be enough to explain the melatonin phase shift in SMS; an age-dependent penetrance, especially during embryonic development, might explain part of the expression of the phenotype. Recent studies investigated *RAI1* function in mice and suggested that *RAI1*

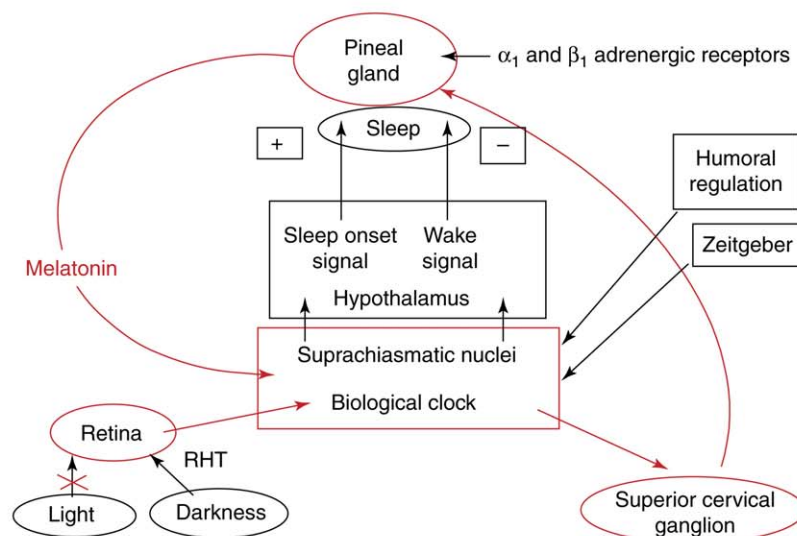
is functioning as a transcriptional regulator, is required during developmental stages and is crucial in embryonic development [24].

Circadian rhythmicity not only involves clock genes, but also requires an input signaling pathway for detection of exogenous signals (zeitgeber or time-giving) [25] and their transmission to the SCN via the RHT. An output signaling pathway of postganglionic fibers ascending to the pineal gland is required to maintain melatonin secretion under the control of the SCN. Melatonin is the circadian signal that prepares the body for sleep by initiating vasodilatation in the hands and feet, which leads to sleepiness. The inversion of the circadian rhythm of melatonin secretion in SMS might

## Box 2. Physiology of melatonin secretion

Melatonin is the main hormone secreted by the pineal gland. Photic information is transmitted to the pineal gland through multisynaptic routes (Figure II). The synthesis and release of melatonin are stimulated by darkness and inhibited by light. Light or dark entrainment proceed through the RHT to reach the SCN of the anterior hypothalamus (the biological clock), then to the superior

cervical ganglion and finally to the pineal gland. The activation of  $\alpha_1$  and  $\beta_1$  adrenergic receptors in the pineal gland raises cyclic AMP and activates arylalkylamine *N*-acetyltransferase, initiating the synthesis and release of melatonin. The daily rhythm of melatonin secretion is controlled by a free-running pacemaker located in the SCN.



**Figure II.**

also result from an alteration in the input–output signaling pathway (e.g. photic entrainment in the retina via the RHT,  $\beta_1$ -adrenergic signal transduction to the pineal gland, or activity of arylalkylamine *N*-acetyltransferase, the enzyme that regulates melatonin synthesis). The mechanism of this quantitatively normal but rhythmically abnormal melatonin secretion is, as yet, unknown. One possibility is that it might modify brain levels of monoamine transmitters, thereby initiating a cascade of events culminating in the activation of sleep.

The link between melatonin and neurodevelopment in infants has recently been discussed elsewhere [26]. A significant bilateral decrease in gray matter concentration and hypoperfusion was detected in the insula and lenticular nucleus in SMS children using anatomical magnetic resonance imaging (MRI) analyzed using optimized voxel-based morphometry, correlated with positron emission tomography (PET) and the water-labeled method [27]. This anatomo-functional evidence of bilateral insulo-lenticular anomalies could be consistent with neurobehavioral symptoms and attention deficit hyperactivity disorder (ADHD). Indeed, functional MRI studies have shown a bilaterally reduced perfusion of the lenticular nucleus in ADHD [28]. Antidopaminergic activity has been demonstrated in the striatum, and the interaction of melatonin with the dopaminergic system might have a significant role in the non-photic and photic entrainment of the biological clock [29]. Future neurotransmitter PET studies will hopefully determine the role of dopaminergic activity in SMS.

### Treatment of the inverted rhythm of melatonin secretion in SMS

Maladaptive behavior and sleep disturbances are extremely severe and difficult to manage. Most patients have been tried on several medications to control behavior and sleep, with only mild responses being observed. All treatments (neuroleptics, antipsychotics, hypnotics, antiepileptic drugs, serotonin reuptake inhibitors and stimulants) help for a short time but manifest side effects, habituation or adverse events.

If we consider that the inversion of the circadian rhythm of melatonin secretion in SMS is a biological rhythm anomaly, we should be able to develop a therapeutic approach to correct it. Melatonin is useful for sleep disorders in children with multiple disabilities [30]. In SMS, melatonin administration alone is not necessarily warranted because the amount of secreted hormone is usually normal but its kinetics are erratic, in that melatonin receptors are fully activated at the end of the day. An original therapeutic approach for SMS patients would involve blocking endogenous melatonin signaling pathways, combined with timed exogenous melatonin administration [31,32].

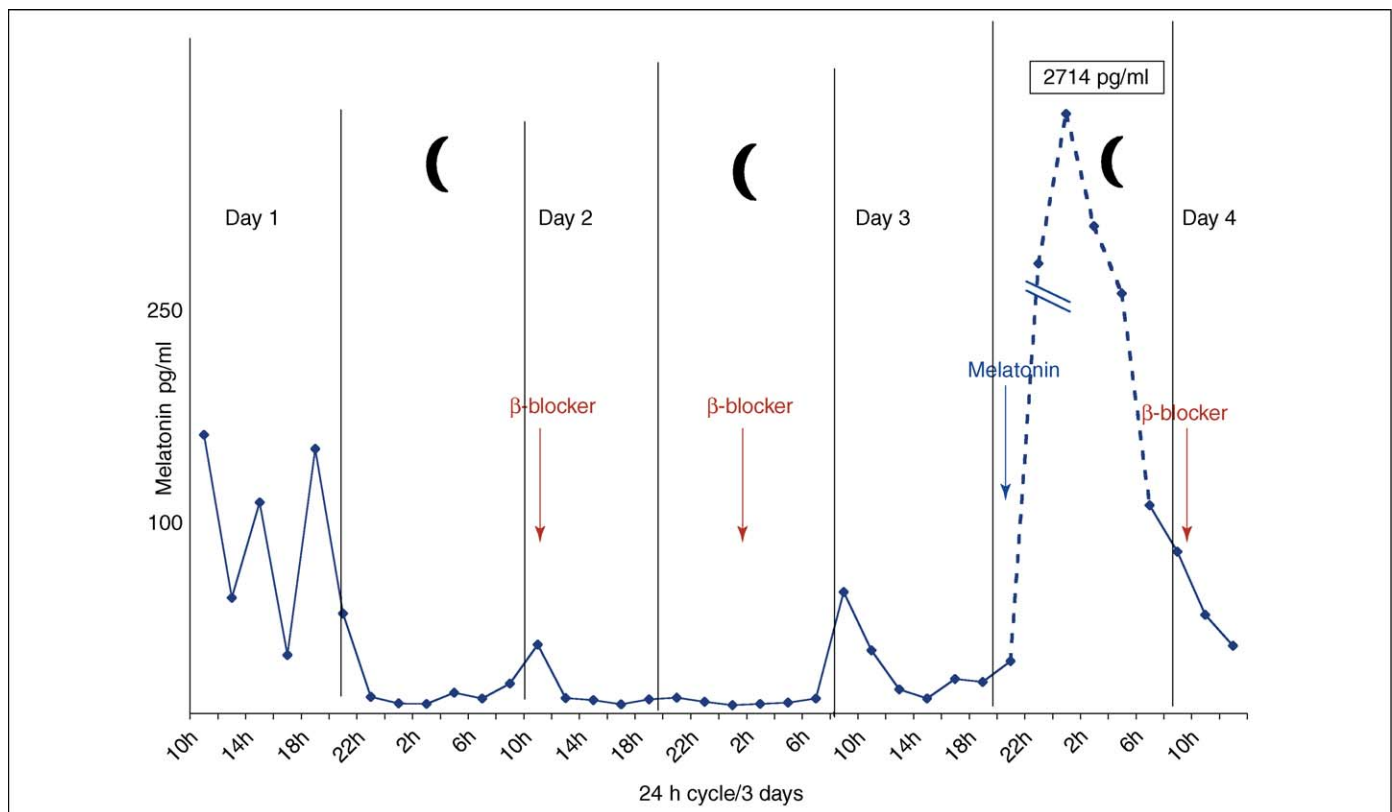
To eliminate any possible contraindications, a complete review of physiological systems, including cardiac and pulmonary examinations, were performed before treatment [33]. Asthma is one such contraindication. The treatment is started six months after the initial diagnosis. Treatment helps to manage behavioral problems but does not cure the syndrome, nor does it have any effect on developmental delay or inherited malformations. Indeed,

behavioral management and special education strategies are the most important features to develop in an individualized educational plan, and should be organized before any medication is prescribed.

Because the circadian rhythm of melatonin secretion is controlled by the sympathetic nervous system [34], SMS patients were given a  $\beta_1$ -adrenergic antagonist to reduce the production of this hormone [31]. After morning  $\beta_1$ -adrenergic antagonist administration (acebutolol: 10 mg/kg in a single morning dose), plasma melatonin levels rapidly decreased in all SMS patients. Mean melatonin levels fell from 68 pg/ml to 8 pg/ml after drug administration. Individual melatonin levels decreased by three- to 20-fold, remained low from 08.00 h to 06.00 h the following day and rose again from 06.00 h to 08.00 h before the next drug administration (Figure 4). With this treatment, daytime behavior markedly improved. Whereas untreated patients had 1–3 naps daily and frequent sleep attacks at the end of the day,  $\beta$ -adrenoceptor antagonist administration resulted in the disappearance of naps and sleep attacks. The explosive tantrums (1–2 each day) were less frequent (one or two per week) and could be easily managed. Parents, teachers, friends and uninformed neighbors noted a more appropriate behavior. Before treatment, SMS patients had a poor ability to concentrate (less than 10 min, even for the oldest members of the group); when given  $\beta$ -adrenoceptor antagonists, they were able to concentrate for periods of 30–60 min or more for parlor games, computer activity, watching television, gardening or small jobs around the house. Teachers acknowledged improved levels of concentration during school hours, and children were reported to be quieter and less hyperactive. Home and social behavior improved but remained problematic. No significant increase in cognitive performance was observed.

The combination of morning  $\beta_1$ -adrenergic antagonist and evening melatonin administration [32] restored circadian plasma melatonin rhythmicity, improved behavioral disturbances and enhanced sleep in SMS patients. Studies were conducted using a controlled-release formulation of melatonin. After a single dose of exogenous melatonin, plasma melatonin levels rapidly peaked and then slowly decreased, thus mimicking the effects of endogenous melatonin on circadian rhythm. Mean melatonin levels rose from  $12.7 \pm 10.6$  pg/ml to  $2189 \pm 1800$  pg/ml two hours after drug administration. Individual melatonin levels increased by 170-fold, compared with levels after  $\beta_1$ -adrenergic antagonist administration, remained high from 22.00 h to 02.00 h and slowly decreased until 06.00 h (Figure 4). 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 longer 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 desensitization was observed over a four-year period of drug administration.

Currently, most French SMS patients receive this treatment strategy of  $\beta$ -blockers  $\pm$  melatonin. This treatment has been tested for SMS patients in the UK, Germany, USA, Israel, Italy, Spain, Canada, The Netherlands and



**Figure 4.** Circadian variation of plasma melatonin levels before treatment (day 1), after morning  $\beta$ -blocker administration alone (day 2) and after morning  $\beta$ -blocker and evening melatonin administration (day 3) of an 8-year-old child. These results were similar for all SMS patients studied. Note the inverted melatonin secretion before treatment at day 1, the suppression of melatonin secretion after  $\beta$ -blocker treatment at day 2 and the reset of normal plasma melatonin levels after  $\beta$ -blocker treatment in the morning and melatonin treatment in the evening. Mean melatonin levels increased by 170-fold two hours after drug administration, remained high from 22.00 h to 02.00 h and slowly decreased until 06.00 h. Reproduced, with permission, from Ref. [32].

Switzerland, with similar results. The children, adolescents and young adults attending their first consultation are aged 3–28 years. There have been no adverse events related to this treatment, nor any side effects, and a consistent improvement in sleep disorders, with no habituation, is seen.

## Conclusion

SMS is a rare genetic disorder ascribed to interstitial deletion of chromosome 17 (17p11.2). SMS is also a circadian disorder with an extreme phase shift of melatonin secretion. This is the first biological model of sleep and behavioral disorders in a genetic disease. This anomaly opens up the field of transverse studies affecting different research subjects: which among the 20 genes present in the SMS critical region causes the melatonin secretion anomaly in SMS, and thereby modifies its circadian timing? Is a single gene (*RAI1*) responsible for most of the features of SMS? Is magnetic resonance spectroscopy able to detect changes in brain metabolism (5-HT, melatonin), in a non-invasive way? Greater understanding of the cellular and molecular control of both the circadian clock and pineal functioning will provide options for pharmacological interventions that could reset the biological clock, not only in SMS, but also in common disorders such as jet lag, sleep disorders or neuropsychiatric illnesses. Until a precise genetic approach to this biological anomaly is provided in SMS, treatment with conventional drugs can improve aberrant sleep patterns and behavior in SMS patients and therefore ease the burden on patients and their families.

## Acknowledgements

We are grateful to the individuals, parents and the ASM 17 family support group of France for participating in the studies. We thank Arnold Munnich and Marie Christine de Blois for their assistance with the studies in the Necker-Enfants Malades Hospital, Paris, France; and Bruno Claustrat at the Neurologic Hospital, Lyon, France; Alain Verloes and Marion Gérard at the Robert Debré Hospital, Paris, France; and Ann Smith and Wallace Duncan at the NIH SMS Research Unit for helpful cooperation.

## References

- Smith, A.C.M. *et al.* (1982) Deletion of the 17 short arm in two patients with facial clefts. *Am. J. Med. Genet.* 34 (Suppl. A), 410
- Smith, A.C.M. *et al.* (1986) Interstitial deletion of (17)(p11.2p11.2) in nine patients. *Am. J. Med. Genet.* 24, 393–414
- Greenberg, F. *et al.* (1991) Molecular analysis of the Smith–Magenis syndrome: a possible contiguous-gene syndrome associated with del(17)(p11.2). *Am. J. Hum. Genet.* 49, 1207–1218
- Juyal, R.C. *et al.* (1996) Molecular analysis of 17p11.2 deletion in 62 Smith–Magenis syndrome patients. *Am. J. Hum. Genet.* 58, 998–1007
- Lucas, R.E. *et al.* (2001) Genomic organization of the ~1.5 Mb Smith–Magenis syndrome critical interval: transcription map, genomic contig, and candidate gene analysis. *Eur. J. Hum. Genet.* 9, 892–902
- Shaw, C.J. *et al.* (2004) Uncommon deletions of the Smith–Magenis region can be recurrent when alternance low copy repeats act as homologous recombination substrates. *Am. J. Hum. Genet.* 75, 75–81
- Slager, R.E. *et al.* (2003) Mutations in *RAI1* associated with Smith–Magenis syndrome. *Nat. Genet.* 33, 466–468
- Greenberg, F. *et al.* (1996) Multi-disciplinary clinical study of Smith–Magenis syndrome (deletion 17p11.2). *Am. J. Med. Genet.* 62, 247–254
- Smith, A.C.M. *et al.* (1998) Behavioral phenotype of Smith–Magenis syndrome (del 17p11.2). *Am. J. Med. Genet.* 81, 179–185
- Shelley, B.P. and Robertson, M.M. (2005) The neuropsychiatry and multisystem features of the SmithMagenis syndrome: a review. *J. Neuropsychiatry Clin. Neurosci.* 17, 91–97

- 11 Smith, A.C.M. *et al.* (1998) Sleep disturbance in Smith–Magenis syndrome (del 17p11.2). *Am. J. Med. Genet.* 81, 186–191
- 12 De Leersnyder, H. *et al.* (2001) Inversion of the circadian rhythm of melatonin in the Smith–Magenis syndrome. *J. Pediatr.* 139, 111–116
- 13 De Leersnyder, H. (2006) Sleep and circadian rhythm of melatonin in Smith–Magenis syndrome. In *Neuroendocrine Correlates of Sleep/Wakefulness* (Cardinali, P.C. and Pandi-Perumal, S.R., eds), pp. 259–267, Springer
- 14 Potocki, L. *et al.* (2000) Circadian rhythm abnormalities of melatonin in Smith–Magenis syndrome. *J. Med. Genet.* 37, 428–433
- 15 Cornelissen, G. *et al.* (2003) Point and interval estimations of circadian melatonin ephasia in Smith–Magenis syndrome. *Biomed.Pharmacother.* 57 (Suppl. 1), 39s–44s
- 16 Girirajan, S. *et al.* (2005) *RAI1* variations in Smith–Magenis syndrome patients without 17p11.2 deletions. *J. Med. Genet.* 42, 820–828
- 17 Arendt, J. (2005) Melatonin: characteristics, concerns, and prospects. *J. Biol. Rhythms* 20, 291–303
- 18 Van Esseveldt, K.E. *et al.* (2000) The suprachiasmatic nucleus and the circadian time-keeping system revisited. *Brain Res. Brain Res. Rev.* 33, 34–77
- 19 Piggins, H.D. and Loudon, A. (2005) Circadian biology: clocks within clocks. *Curr Biol.* 15, R455–R457
- 20 Wager-Smith, K. and Kay, S.A. (2000) Circadian rhythms genetics: from flies to mice to humans. *Nat. Genet.* 26, 23–27
- 21 Bell-Pedersen, D. *et al.* (2005) Circadian rhythms from multiple oscillators: lessons from diverse organisms. *Nat. Rev. Genet.* 6, 544–556
- 22 Von Gall, C. *et al.* (2005) Melatonin plays a crucial role in the regulation of rhythmic clock gene expression in the mouse pars tuberalis. *Ann. N. Y. Acad. Sci.* 1040, 508–511
- 23 Potocki, L. *et al.* (1999) Subunit 3 of the COP9 signal transduction complex is conserved from plants to humans and maps within the Smith–Magenis syndrome critical region in 17p11.2. *Genomics* 57, 180–182
- 24 Bi, W. *et al.* (2005) Inactivation of *RAI1* in mice recapitulates phenotypes observed in chromosome engineered mouse models for Smith–Magenis syndrome. *Hum. Mol. Genet.* 14, 983–995
- 25 Mistlberger, R.E. and Skene, D.J. (2005) Non photic entrainment in humans? *J. Biol. Rhythms* 20, 339–352
- 26 Tauman, R. *et al.* (2002) Melatonin production in infants. *Pediatr. Neurol.* 26, 379–382
- 27 Boddarta, N. *et al.* (2004) Anatomical and functional brain imaging evidence of lenticulo-insular anomalies in Smith–Magenis syndrome. *Neuroimage* 21, 1021–1025
- 28 Teicher, M.H. *et al.* (2000) Functional deficits in basal ganglia of children with attention-deficit/hyperactivity disorder shown with functional magnetic resonance imaging relaxometry. *Nat. Med.* 6, 470–473
- 29 Zisapel, N. (2001) Melatonin-dopamine interactions: from basic neurochemistry to a clinical setting. *Cell. Mol. Neurobiol.* 21, 605–616
- 30 Jan, J.E. and Freeman, R.D. (2004) Melatonin therapy for circadian rhythm sleep disorders in children with multiple disabilities: what have we learned in the last decade? *Dev. Med. Child Neurol.* 46, 776–782
- 31 De Leersnyder, H. *et al.* (2001) Beta-1-adrenergic antagonists improve sleep and behavioral disturbances in a circadian disorder, Smith–Magenis syndrome. *J. Med. Genet.* 38, 586–590
- 32 De Leersnyder, H. *et al.* (2003) Beta-1-adrenergic antagonists and melatonin reset the clock and restore sleep in a circadian disorder, Smith–Magenis syndrome. *J. Med. Genet.* 40, 74–78
- 33 Waldron, D.L. *et al.* (2005) Melatonin: prescribing practice and adverse events. *Arch. Dis. Child.* 90, 1206–1207
- 34 Stoschitzky, K. *et al.* (1999) Influence of beta blockers on melatonin release. *Eur. J. Clin. Pharmacol.* 55, 111–115

## Elsevier celebrates two anniversaries with a gift to university libraries in the developing world

In 1580, the Elzevir family began their printing and bookselling business in the Netherlands, publishing works by scholars such as John Locke, Galileo Galilei and Hugo Grotius. On 4 March 1880, Jacobus George Robbers founded the modern Elsevier company intending, just like the original Elzevir family, to reproduce fine editions of literary classics for the edification of others who shared his passion, other ‘Elzevirians’. Robbers co-opted the Elzevir family printer’s mark, stamping the new Elsevier products with a classic symbol of the symbiotic relationship between publisher and scholar. Elsevier has since become a leader in the dissemination of scientific, technical and medical (STM) information, building a reputation for excellence in publishing, new product innovation and commitment to its STM communities.

In celebration of the House of Elzevir’s 425th anniversary and the 125th anniversary of the modern Elsevier company, Elsevier donated books to ten university libraries in the developing world. Entitled ‘A Book in Your Name’, each of the 6700 Elsevier employees worldwide was invited to select one of the chosen libraries to receive a book donated by Elsevier. The core gift collection contains the company’s most important and widely used STM publications, including *Gray’s Anatomy*, *Dorland’s Illustrated Medical Dictionary*, *Essential Medical Physiology*, *Cecil Essentials of Medicine*, *Mosby’s Medical, Nursing and Allied Health Dictionary*, *The Vaccine Book*, *Fundamentals of Neuroscience*, and *Myles Textbook for Midwives*.

The ten beneficiary libraries are located in Africa, South America and Asia. They include the Library of the Sciences of the University of Sierra Leone; the library of the Muhimbili University College of Health Sciences of the University of Dar es Salaam, Tanzania; the library of the College of Medicine of the University of Malawi; and the University of Zambia; Universite du Mali; Universidade Eduardo Mondlane, Mozambique; Makerere University, Uganda; Universidad San Francisco de Quito, Ecuador; Universidad Francisco Marroquin, Guatemala; and the National Centre for Scientific and Technological Information (NACESTI), Vietnam.

Through ‘A Book in Your Name’, these libraries received books with a total retail value of approximately one million US dollars.

**For more information, visit [www.elsevier.com](http://www.elsevier.com)**