SMITH-MAGENIS SYNDROME WITH BILATERAL VESICOURETERAL REFLUX: A CASE REPORT

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Abstract: Smith-Magenis syndrome (SMS) is a syndrome of multiple malformations caused by an interstitial deletion of chromosome 17p11.2. We report the case of an 8-year-old boy with SMS. Down syndrome was initially suspected in infancy based on the findings of generalized hypotonia, flat midface, and upslanting palpebral fissures. His sleep had been disturbed since infancy, and self-injurious behavior developed at 2 years. When he was 8 years old, these unusual neurobehavioral features led to suspicion of SMS, and chromosome analysis showed the 17p deletion, which was confirmed by fluorescence *in situ* hybridization of the SMS region. Bilateral vesicoureteral reflux, grade IV, was found at the same time, and he underwent bilateral ureteroplasty. The postoperative course was smooth and he was discharged with antibiotic prophylaxis. His sleep disturbance improved after treatment with melatonin. A high index of suspicion is needed for the timely diagnosis of SMS. Patients should be thoroughly evaluated for associated complications both at the time of diagnosis and at regular follow-up.

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Key words:
Smith-Magenis syndrome
microdeletion syndrome
vesicoureteral reflux

Smith-Magenis syndrome (SMS; MIM 182290) has a clinical presentation characterized by recognizable multiple anomalies and mental retardation caused by an interstitial deletion of chromosome 17p11.2 [1, 2]. Since it was first described in 1982 [3], more than 100 cases have been reported [4]. The most common physical manifestations include brachycephaly, prominent forehead, epicanthal folds, broad nasal bridge, ear anomalies, prognathism and short stature. Behavioral and functional manifestations include mental retardation, hyperactivity, failure to thrive, hoarse and deep voice, peripheral neuropathy, sleep disturbance and self-injurious behavior. Other less common findings include facial clefts, congenital heart defects, seizures, and urinary tract anomalies, especially duplication of the collecting system. This phenotype overlaps with Down syndrome, particularly early in life [5]: brachycephaly, upward slanting palpebral fissures, a short and broad nose, a round face with midface flattening, iris hamartomas, small stature, small hands and feet, and hypotonia. Fluorescence *in situ* hybridization (FISH) of the SMS region is required to diagnose clinically suspected cases in which the deletion is not cytogenetically detectable. We report a case of SMS with a severe complication of bilateral vesicoureteral reflux, grade IV.

Case Report

This patient was first referred to our pediatric clinic at 8 years of age because of mental retardation and behavioral problems. He was an only child and the mother was 26 years old when he was born. There had been no miscarriages and the family history was unremarkable. He was born at term after an uncomplicated pregnancy, and Down syndrome was initially suspected based on findings of developmental delay and characteristic physical features, but was ruled out by cytogenetic study. During infancy, his mother noted abnormally short sleep. At 3 years of age, severe behavioral problems developed, including hyperactivity, unusual onychotillomania (pulling out fingernails and toenails), polyembolokoilamania (object insertion), head banging, wrist biting and skin picking.

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On physical examination, he was in the 10th to 25th percentiles for height (124 cm tall), weight (24 kg) and head circumference (51 cm). He had a characteristic craniofacial appearance, including midface hypoplasia, prominent forehead, upslanting palpebral fissures, epicanthal folds, broad nasal bridge, downturned mouth with Cupid's bow, and relative prognathism (Fig. 1). His voice was hoarse and low pitched. The fingers were short and broad. There were many scars and ecchymoses from hand-biting and decreased sensitivity to pain and temperature was noted. The clinical findings suggested SMS, so chromosome studies were performed. Cytogenetic analysis and FISH using a probe specific for SMS showed an interstitial deletion of chromosome 17p11.2 (Fig. 2). Ophthalmologic and auditory brain stem responses were normal, but polysomnography during sleep revealed markedly reduced rapid-eye-movement (REM) stage sleep with an inadequate sleep time. Multiple sleep latency tests showed excessive daytime sleepiness. Although electroencephalogram showed focal and generalized epileptiform abnormalities with no overt seizures, brain magnetic resonance imaging was normal. Echocardiography demonstrated no cardiac abnormality. Psychomotor testing with the Leiter international performance scale showed moderate mental retardation with an IQ of 51. Renal ultrasound showed a small left kidney with pelvic ectasia. During an episode of hematuria, urine culture grew *Escherichia coli* and impaired renal function was found (blood urea nitrogen, 27 mg/dL; creatinine, 1.1 mg/dL). Voiding cystourethrogram revealed bilateral vesicoureteral reflux, grade IV. Cephalexin was given for 10 days, after which bilateral ureteroplasty was performed. His sleep disturbance and aggressive behavior improved with the administration of melatonin (3–9 mg/day). No side effects of melatonin therapy were noted.

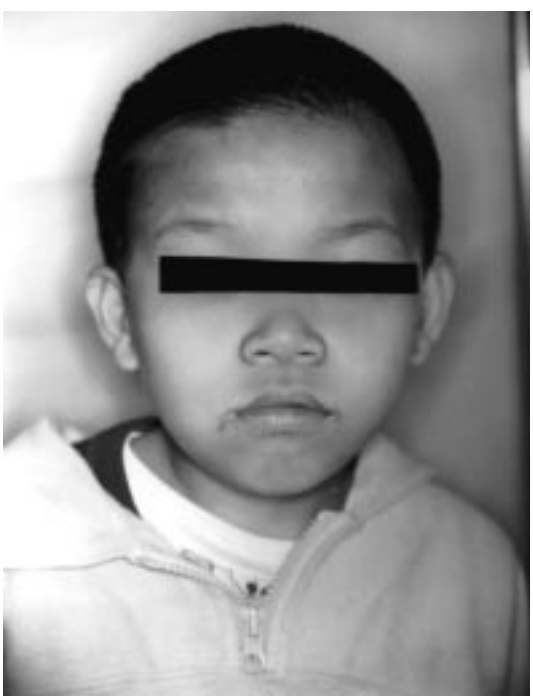

Fig. 1. *Face of a boy with Smith-Magenis syndrome. Note the midface hypoplasia, prominent forehead, broad nasal bridge, downturned mouth with Cupid's bow, and relative prognathism.*

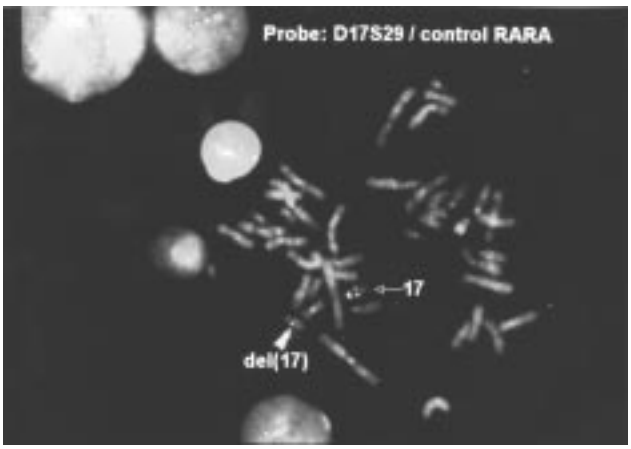

Fig. 2. *Fluorescence* in situ *hybridization on metaphase chromosomes from lymphocytes of a patient with Smith-Magenis syndrome (SMS) using SMS chromosome region (SMCR) probe D17S29 (Oncor) shows the normal pattern of D17S29 (arrow) at the SMCR in the control, but no D17S29 signal (arrowhead) on the patient's chromosome 17, indicating deletion of the probe sequence.*

Discussion

Since its first description in 1982 [3], the clinical phenotype of SMS has been well delineated, and more than 100 reported cases in patients ranging from 1 month to 72 years of age have been identified in a diversity of ethnic groups [4, 6]. The following common clinical features are seen in more than two-thirds of individuals with SMS: brachycephaly with characteristic craniofacial features (midface hypoplasia, broad face and nasal bridge, flat midface, downturned corners of the mouth, frontal bossing, prognathism, telecanthus, upward slanting palpebral fissures, ear and ocular abnormalities), brachydactyly, a hoarse and deep voice, hypotonia and failure to thrive, short stature, speech delay with or without associated hearing loss, signs of peripheral neuropathy, sleep disturbance, mental retardation, hyperactivity and self-injury. Other less common findings include facial clefts, congenital heart defects, seizures, and urinary tract anomalies, especially duplication of the collecting system [6].

The distinctive somatic and behavioral phenotypes appear to be age-dependent, and become most obvious by midchildhood. This phenotype overlaps with Down syndrome, particularly early in life [5]. Lack of awareness of the behavioral features may lead to misclassification. The interstitial deletion of 17p11.2 can be detected by routine cytogenetic analysis or FISH in the SMS region.

Self-injurious behaviors including head banging, wrist biting and skin picking, and two behaviors that may be unique to SMS, onychotillomania and polyembolokoilamania

[4], are problematic. Some of these behaviors appear to be age-related. Head banging and wrist biting often begin early in the second year of life, and onychotillomania is uncommon before the age of 5 or 6 years. In general, SMS patients exhibit relative insensitivity to pain and may cause injury to themselves by persistent picking or biting, or during uncontrolled rages.

This patient had significant symptoms of sleep disturbance, which had a very bad impact on the patient and his family. The mechanism of sleep disturbance in SMS is not fully understood. SMS is a complex disorder caused by a heterozygous deletion of chromosome 17p11.2. Greenberg et al postulated that a gene within the SMS critical region might be involved with REM sleep and hence disturb sleep [5].

Preliminary findings of abnormally elevated urinary 6-sulfatoxymelatonin, the major hepatic metabolite of melatonin, were reported during 24-hour sleep studies of SMS patients [7, 8]. Reversal of the normal pattern of high levels of melatonin in daylight hours versus nighttime hours was also found [7]. Melatonin is the principal hormone of the pineal gland; it acts to induce sleep, and entrain the sleep–awake (circadian) rhythm. Therefore, it may account for the sleep disturbance in SMS. The SMS critical region is hypothesized to be involved in the biologic clock, which might disrupt normal melatonin synthesis and degradation. Reports of a therapeutic benefit from melatonin in SMS are encouraging, but larger studies are needed to clarify these findings [9]. Because our patient had markedly reduced duration of REM sleep, melatonin was administered and improvement in sleep disturbance was evident.

Renal ultrasound identified anomalies in 35% of SMS patients [6]. These anomalies included duplication of the collecting system, unilateral renal agenesis and ectopic kidney. Only one patient had bladder distension with residual urine noted by voiding cystourethrogram. Our patient had severe bilateral vesicoureteral reflux (grade IV), which has not been reported previously. The pathogenesis of vesicoureteral reflux in SMS is still unknown. Because reflux nephropathy accounts for 15 to 20% of all end-stage renal failure in children and young adults, and is an important cause of hypertension in children [10], a high degree of suspicion may lead to a timely diagnosis and treatment, preventing the development of severe complications. Patients with SMS should be thoroughly evaluated for associated complications both at diagnosis and at follow-up, at least annually.

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