Two cases of Smith–Magenis syndrome

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= Abstract =

Smith–Magenis syndrome (SMS) is a rare disorder with multiple congenital anomalies caused by a heterozygous interstitial deletion involving chromosome 17p11.2, where the retinoic acid–induced 1 (RAI1) gene is located, or by a mutation of RAI1. Approximately 90% of the patients with SMS have a detectable 17p11.2 microdeletion on fluorescence in-situ hybridization (FISH). SMS is characterized by mental retardation, distinctive behavioral features, craniofacial and skeletal anomalies, speech and developmental delay, and sleep disturbances. Although there are some intervention strategies that help individuals with SMS, there are no reported specific interventions for improving the outcome in children with SMS. Here, we report two cases of Smith–Magenis syndrome. (Korean J Pediatr 2009;52:701-704)

Key Words: Smith–Magenis syndrome, Chromosomal study, Fluorescence in-situ hybridization

Introduction

The Smith–Magenis syndrome (SMS) is a rare disorder associated with multiple congenital anomalies: it is caused by heterozygous interstitial deletion involving chromosome 17p11.2 that contains the retinoic acid–induced 1 (RAI1) gene or a mutation of RAI1. Approximately 90% of patients with the SMS have a detectable 17p11.2 microdeletion by fluorescence in situ hybridization (FISH), while the remaining 10% have a mutation of RAI1. The SMS is characterized by mental retardation, distinctive behavioral features, craniofacial and skeletal anomalies, speech and developmental delay, and sleep disturbance. Occasionally, systemic features such as cardiac and renal defects, cleft lip and/or palate have been observed. There are no specific treatment strategies available to improve the outcome of children with the SMS: the interventions are primarily supportive. Here we report two cases of SMS.

Case Report

Case 1

A 9-year-old girl with mental retardation presented to our hospital. The patient was born at 38 weeks gestation; the birth weight was 2,600 g. Development delay was diagnosed by 11 months of age; she could not sit, had a flat, broad nasal bridge, slanting palpebral fissures, protruding forehead, opened mouth, and slanted hands on physical examination. The laboratory findings including the CBC, electrolytes, biochemistry, and thyroid function tests were normal. The patient was reported to have a normal conventional karyotype. The brain MRI showed no specific findings except for a mild ventriculomegaly, and the EEG was normal. At four years of age, the receptive language was at the 24 month level and the expressive language was at the 25 month level. With time the features of the SMS became more apparent. The patient had severe mental retardation, distinctive behavioral features, craniofacial and skeletal anomalies (including brachydactyly), speech and developmental delay, and sleep disturbance (Fig. 1A–1D). On the second cytogenetic study, an interstitial deletion of 17p11.2 was detected by conventional banding and deletion of the FL1 gene was confirmed by FISH using the Cytocell SMS probe (Fig 2A, 2B).
Fig. 1. A) The patient had flattened mid-face with a broad nasal bridge, underdeveloped cheekbones, opened mouth. B, C) A protruding forehead, slanting palpebral fissures, prognathia were showed. D) Slanted hands and brachydactyly were showed.

Fig. 2. A) Karyotype of peripheral blood cells from case 1: 46,XX,del(17)(p11.2p11.2) at the 550 band resolution. The arrow indicates the deleted homologue. B) The two interphase and one metaphase cells were showed by FISH. The deletion of the FL1 gene was confirmed by FISH using the Smith–Magenis/Miller–Dieker probe (Cytocell, 17p11.2 FL1 gene/ 17p13.3 LIS1 gene).
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Because the patient sleeps for only four hours per day, melatonin was provided for the restoration of the circadian rhythm. In addition, early childhood intervention programs, special speech and language education, and multidisciplinary evaluations as well as care for the behavioral and systemic manifestations were provided.

Case 2

A 20-year-old man presented to our hospital for the evaluation of seizures. The patient was born at full term; the birth weight was 2,700 g. When he was six months old, he was found to have microcephaly on physical examination. The patient was diagnosed with mental retardation and had his first seizure at 11 years of age; his EEG showed focal epilepsy. The laboratory findings including the CBC, electrolytes, biochemistry, and thyroid function tests were normal. Valproate and topiramate were used to treat the epilepsy.

The patient had an osteochondroma of the fourth toe of the right foot and had orthopedic surgery to remove it. The patient had recurrent seizures and was admitted to the hospital for treatment. On admission, the patient was noted to have microcephaly, speech and developmental delay, as well as the epilepsy. The chromosome study and FISH showed an interstitial deletion of 17p11.2 on conventional banding and deletion of the FL1 gene by FISH using the Cytocell SMS probe.

Discussion

First identified in 1982, the Smith–Magenis syndrome (SMS) is a multisystem, neurodevelopmental, genetic disorder typically caused by a sporadic deletion on chromosome 17 (del 17p11.2)\(^2\). This disorder is rare in the general population. Prevalence estimates suggest an occurrence rate of 1:25,000 live births, with males and females affected equally\(^3\).

The importance of a high index of clinical suspicion and skilled laboratory evaluation is needed to make this easily missed diagnosis\(^5\).

Several physical anomalies are usually present including a broad head, prominent forehead, eye and vision abnormalities, flattened mid-face with a broad nasal bridge, underdeveloped cheekbones, down-turned mouth, a prominent jaw, short stature, small toes, inwardly bent fingers, and hypotonia\(^10\). Approximately three quarters of the individuals with the SMS show clinical signs of nerve damage in the extremities, including muscle weakness, walking difficulties, decreased deep tendon reflexes, and decreased sensitivity to temperature and pain\(^7\). In addition, developmental and behavioral concerns may be present such as, hyperactivity, impulsiveness, restlessness, distractibility, temper outbursts, and difficulty with sleep as well as progressive hearing loss\(^8, 13\). The treatment of affected individuals is supportive. There are no specific interventions available for children with the SMS.

In the first case, the patient showed the typical SMS clinical manifestations when she initially presented to the hospital. However, the karyotype was reported as normal by standard techniques, 46, XX. As the patient matured the features of the SMS became more obvious. Therefore, we repeated the chromosome study and included FISH, and an interstitial deletion of 17p11.2 was detected. The chromosome diagnosis can usually be made by either high-resolution cytogenetic studies or FISH. Some studies have reported that approximately 90% of cases with the SMS have a FISH-detectable deletion, and about 70% have the common, approximately 3.5 Mb deletion, while the remaining 30% have smaller or larger deletions\(^13, 14\). A typical SMS patient is predicted to have about a \(-5\) Mb deletion. However, patients harboring a deletion of <2 Mb and showing subtle or variant phenotypes may go undetected unless molecular studies are performed\(^1, 9\).

The patient was treated with melatonin for the sleep disturbance. The circadian rhythm associated with melatonin is closely associated with the sleep–wake cycle; administration of melatonin affects the latency to sleep onset, sleep consolidation, slow waves, sleep spindles, and REM sleep\(^10\). The melatonin resulted in a dramatic improvement in sleep quality. Rosario et al\(^11\) reported on the treatment of sleep disorders, in children with the SMS, with a selective β₁-adrenergic antagonist plus melatonin.

In the second case, the clinical findings were not characteristic for the SMS, except for the presence of microcephaly and mental retardation. The patient was being treated for a seizure disorder. The cytogenetic study revealed an interstitial deletion of 17p11.2 and the diagnosis of the SMS was confirmed. The SMS may have features of both central and peripheral nervous system abnormalities. Central nervous
system anomalies include seizures in about one quarter of the cases, mental retardation and central hypotonia\(^{12}\).

Both patients participated in childhood intervention programs, special speech and language education and vocational training. The importance of a high index of clinical suspicion and skilled laboratory evaluation is needed for the diagnosis of the SMS. The melatonin therapy was useful for the sleep disturbance present in one of the patients, and anti-epileptic drugs for seizure control in the other patient: special speech and language education as well as vocational training for mental retardation were provided for both patients.

References


