

Smith Magenis Syndrome: A syndrome with intellectual disability and neurobehavioral problems

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ABSTRACT

Smith Magenis syndrome is a rare, complex neurobehavioral genetic disorder caused by an interstitial deletion of chromosome 17p11.2. This region includes retinoic acid induced-1 (RAI-1), gene, which is responsible for most clinical features of Smith Magenis syndrome. Some patients may have a point mutation of RAI1. An 11-year-old girl with intellectual disability was referred to the pediatric genetics department. She had a history of seizures and neurobehavioral problems including impulsivity, aggressiveness, self-injury and sleep disturbance. Ophthalmologic and cardiac examinations were normal. Neurobehavioral pattern and intellectual disability was suggestive for Smith Magenis syndrome, and this was confirmed by fluorescence *in situ* hybridization (FISH), which revealed del (17) (p11.2p11.2) (RAI1-). This patient shows that facial and ophthalmological features may be absent in patients and neurobehavioral phenotype may be the prominent finding.

Key words: Smith Magenis syndrome, RAI1, 17p11.2 deletion, neurobehavioral problems

Introduction

Smith Magenis syndrome is a rare genetic syndrome with a prevalence estimated to be 1/25000 [1]. Smith Magenis syndrome is characterized by neurobehavioral problems including infantile hypotonia, delay in expressive speech and language, hoarse voice, self-injurious behavior—(head banging, wrist biting, onychotillomania, polyembolokoilomania), sleep disorders and autism spectrum disorders. Craniofacial pattern abnormalities include brachycephaly with midface hypoplasia, prominent forehead, broad nasal bridge, synophrys, downturned corners of the mouth, prognathism and low-set ears. Congenital heart defects, structural renal anomalies, scoliosis, brain abnormalities; eye abnormalities including strabismus, myopia, microcornea, iris dysplasia; hearing loss; extremity abnormalities (brachydactyly, pes planus/varus) may also be present in patients [1,3]. This syndrome should be considered in patients with intellectual disability, behavioral abnormalities and certain dysmorphic features.

Case Presentation

An 11-year-old girl was referred to our center due to neurobehavioral findings. The personal history revealed that she was born at term after an uncomplicated pregnancy with spontaneous vaginal delivery, with a birth weight of 3300 g. The parents were both healthy. She was the first child of a non-consanguineous couple.

Motor delay was present in the infancy period. She was able to sit with support at 6 months, without any support at 10 months and walked at 18 months of age. She spoke her first word at 9 months but she was only able to speak 5 words by 3 years of age. Neurobehavioral features became increasingly obvious with age.

On physical examination, her height was 148 cm (50th centile), weight 33 kg (10th-25th centile), and head circumference 51 cm (10th-25th centile). She had neurobehavioral phenotype with self-injurious attitudes, sleep disturbance, hoarse deep voice and severe intellectual disability. She had no significant

facial dysmorphic features and her cardiac, ophthalmologic, auditory examinations were normal.

Developmental, physical and neurobehavioral features with sleep disturbance were clinically suggestive of Smith Magenis syndrome. Chromosomal study was performed on phytohaemagglutinin stimulated lymphocytes and revealed 46,XX. Fluorescence *in situ* hybridization (FISH) was performed with specific probes for 17p11.2 region (Cytocell CPU019 Smith Magenis RAI1 Probes). FISH revealed interstitial deletion of chromosome 17p11.2 region. Final karyotype was 46,XX,ish del (17) (p11.2p11.2) (RAI1-). Fragile X syndrome was also ruled out, with an indication of coexistent intellectual disability and behavioral problems.

Genetic counseling was given to this family regarding Smith Magenis syndrome and afterwards the patient was consulted to both the pediatric neurology, and child psychiatry and was provided with special needs education.

Discussion

Smith Magenis syndrome is a rare, complex neurobehavioral genetic disorder caused by an interstitial deletion of chromosome 17p11.2. The prevalence may be as high as 1/25000 [1]. The clinical phenotype is rarely evident before late childhood or early adolescence (1). The diagnosis of Smith Magenis syndrome is based upon clinical recognition of a unique phenotype involving physical, developmental and behavioral aspects [2].

Smith Magenis syndrome patients have a recognizable craniofacial appearance including brachycephaly, midface hypoplasia, a prominent forehead, broad nasal bridge, down-turned corners of the mouth, upslanting palpebral fissures, synophrys, prognathism, epicantal folds and low-set ears [1-2]. Other abnormalities of this syndrome include broad hands with brachydactyly, short stature, hearing loss, renal anomalies, cardiac defects, scoliosis, eye abnormalities (myopia, microcornea, strabismus), peripheral neuropathy, seizures, low immunoglobulin and thyroxine levels [1,3].

Most Smith Magenis syndrome patients (%96.6) present with neurobehavioral problems [3]. These problems include intellectual disability, impulsiveness, disobedience, attention seeking, temper tantrums, aggression, distractibility, self injurious behavior (head banging, wrist biting, onychotillomania, polyembolokoilamania). Stereotypic behaviors such as mouthing objects and putting hand in

mouth, teeth grinding, lick-and flip behavior spasmodic upper-body squeeze (self hugging), body are rocking present in many patients [2,3].

Sleep disturbance is present in almost all patients with Smith Magenis syndrome and is one of the signs of the disease [4]. Short sleep cycles, difficulties in falling asleep, diminished REM sleep, decreased nocturnal sleep, early awakenings and daytime sleepiness can be observed due to inverted or shifted circadian rhythm of melatonin [2,4].

Speech/language delay with or without hearing loss occurs in most Smith Magenis Syndrome patients [2]. Besides, autism spectrum disorders, peripheral neuropathy and seizures may occur in some of the patients with Smith Magenis syndrome.

Almost all patients with Smith Magenis syndrome have mild to moderate intellectual disability with an IQ ranging from 20 to 78 [5].

Smith Magenis syndrome is caused by an interstitial deletion of the short arm of chromosome 17 [7]. This region (17p11.2) consist of approximately 25 genes, including retinoic acid-induced gene 1 (*RAI1*) which is responsible for most of the features of patients with Smith Magenis syndrome [1]. Approximately 90% of the patients have 17 p 11.2 deletion and 10% of the patients have a mutation in the *RAI1* gene [4]. Most patients have a common deletion interval of 4-5 megabases ranging from 2 to 9 megabases [7]. The mechanism of Smith Magenis syndrome is due to homologous recombination of a flanking repeat gene cluster, which leads to mismatch pairing [4].

G-banded cytogenetic analysis (550 band or higher) and FISH with *RAI1* gene probes are classically used for diagnosis and detects the deletion in 90% of the patients. MLPA (Multiplex Ligation-dependent Probe Amplification), qPCR and whole genome chromosome microarray studies can also be used for diagnosis [4]. The deletion usually occurs sporadically. Patients who were found to have no deletion in 17p11.2 region should have the *RAI1* gene sequencing to detect a mutation and parental samples should be evaluated to confirm that the mutation is *de novo* [4].

Management of a patient with Smith Magenis syndrome is difficult because of cognitive, developmental, behavioral deficits and speech delay. Assessment for speech and language delays and treating feeding difficulties is important to consider [2,4]. Organic causes of behavior problems (gastroesophageal reflux, acute otitis media, joint and

organ pain) should be treated appropriately, as some drugs such as beta-blockers, mood stabilizers (serotonin reuptake inhibitors, lithium, antipsychotics) may be added to the treatment [2,4]. A careful neurologic evaluation such as electroencephalography should be performed in all individuals to assess for subclinical seizures [2]. Nowell-controlled treatment plan has been reported concerning management of sleep disturbance. Treatment with acebutolol and melatonin have been reported to improve the behavioral problems [4].

Our patient is interesting she indicates that there are patients with less prominent facial and ophthalmological features and more prominent neurobehavioral phenotype. Smith Magenis syndrome should be kept in mind as a possible diagnosis in patients with intellectual disabilities and behavioral problems as described above. Facial features are helpful in establishing a clinical diagnosis, however, they may be absent as in the present patient. Patients must be directed for supportive therapies and the family should be given appropriate genetic counseling on this usually sporadic disorder.

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