SMITH-MAGENIS SYNDROME INFORMATION

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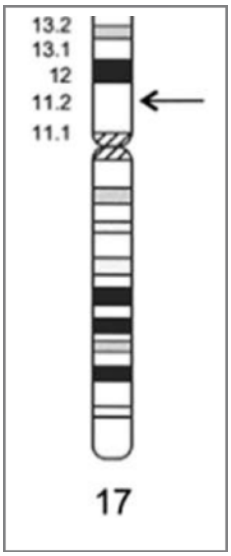

Smith-Magenis Syndrome (SMS) is an established genetic disorder, known since 1986 when Ann Smith and her colleagues showed that deletion in the 17p11.2 segment causes a complex but recognizable phenotype. In most cases, the patients have a 3.5-3.7 Mb deletion involving ~80 genes.

With Smith-Magenis Syndrome, patients with point mutations in the RAI1 gene reveal similar clinical manifestations, and presence of mutation in the RAI1 gene is sufficient for diagnosis of SMS (even if there is no deletion in 17p11.2). Currently, ~15% of known patients with SMS are patients with RAI1 mutations but this may be an underestimation. Cytogenetic examination shows all patients with deletions (even when the diagnosis was not suspected) but diagnostics of mutation requires or whole exome sequencing or specific examination of the RAI1 gene (and clinical suspicion of the SMS).

SMS is present in about 1:15,000-1:25,000 births[1]. The diagnosis itself is often delayed and does not occur until a mean age of 4.6. This is in part due to most patients having birth parameters within a normal range. Parents first begin to express concerns around 10 months of age and the first genetic screens are performed at a mean age of 2.8 years[2].

Key clinical manifestations of SMS include unique patterns of physical development, cardiac defects, neurodevelopment, behavior, and disrupted circadian sleep-wake patterns.

There are several distinctive craniofacial and skeletal features of those with SMS. This consists of a broad, square-shaped face with brachycephaly, midface hypoplasia, tented upper lip, micrognathia, up-slanting palpebral fissures, deep-set eyes, short full-tipped nose, and downturned corners of the mouth[3]. Although patients typically have normal growth parameters at birth, this changes as the patient ages. After the age of 9, 47.8% of patients will be >95

percentile for weight[4]. Other physical attributes include a short stature, scoliosis in 43% of patients, dental abnormalities in 56%, ophthalmological problems in 89%, and deafness or hearing impairment in at least one ear in 32% of patients[2].

Various cardiac defects may be found in ~25% of patients. This includes ventricular septal defects, atrial septal defects, tricuspid stenosis, mitral stenosis, tricuspid and mitral regurgitation, aortic stenosis, pulmonary stenosis, mitral valve prolapses, tetralogy of Fallot, and total anomalous pulmonary venous connection[5]. In the vast majority of patients, however, these defects are not life-threatening and do not require surgical correction.

Almost all SMS patients exhibit some degree of intellectual disability. The range of intellectual disability varies widely. Severe or profound intellectual disability occurs in less than 10% of patients. Many will have a delayed age of walking, with an average age of 25 months. Only 68% have their first words by age 3 and only 18% have their first sentence before 3 years of age[2].

SMS has several unique behavioral patterns. Most patients (88%) will have behavioral disorders to some extent. One such behavior is self-injurious behavior. This includes self-biting, self-hitting, inserting of foreign objects into orifices of their body, skin pricking, and tearing off nails[6]. Many patients will also have temper tantrums (84%), attention seeking, and aggressive behaviors[2].

Patients almost always have abnormalities in their circadian sleep-wake patterns. This includes fragmented and shortened sleep cycles, reduced or absent eye movement (REM) sleep, frequent nocturnal and early morning awakenings, and excessive daytime sleepiness. This is largely due to both an imbalance in melatonin levels throughout the cycle as well as body temperature[4]. This is thought to be so prevalent due to the role RAI1 has in regulating circadian rhythm genes. Sleep deficits are thought to contribute to the severity of behavioral and learning problems of patients. Those with increasingly adverse sleep patterns often have higher levels of depression and anxiety[7].

Patients who have a RAI1 mutation will have different expression of SMS in comparison to those who have the 3.5-3.7 Mb deletion within 17p11.2. Those with the deletion often have more severe phenotypes than those with just a RAI1 mutation. This includes speech and motor delay, short stature, hearing loss, hypotonia, and cardiovascular anomalies. The overall size of the mutation will affect the phenotype as well. Patients with mutations smaller than the typical 3.5-3.7 Mb may reveal phenotypes similar to those with a RAI1 mutation. It is thought that mutations in RAI1 results in a truncated and/or a nonfunctional protein product resulting in haploinsufficiency[3].

There are no current cures for SMS. Rather, patients and their families focus on treatments that address the patient's behavioral problems and sleep disturbances. Some strategies families have developed to combat behavioral problems include being proactive, providing predictability, and aiming at

prevention[1]. Many patients can follow adapted schooling (55%), some with a personal classroom assistant, and others attend out-of-school outpatient centers[2]. However, a key feature in managing behavioral problems is managing sleep disturbances. Patients with less sleep disturbances will have fewer behavioral problems. The sleep disturbances are often treated with melatonin at night and beta-blockers in the morning to help restabilize a traditional circadian rhythm[8].

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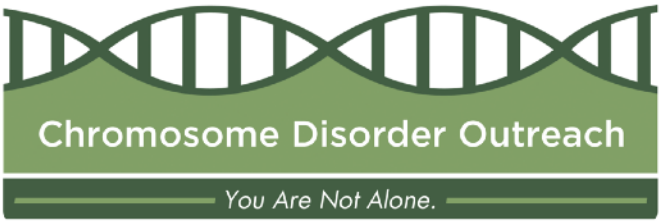

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