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Intellectual and Behavioral Disabilities in Smith – Magenis Syndrome

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1. Introduction

Smith-Magenis syndrome (SMS) is a rare developmental disorder featuring impaired intellectual and behavioral abnormalities. SMS is still not well known because it is characterized by subtle facial dysmorphology that progresses with age, and clinical features that overlap with other intellectual disability syndromes as Prader–Willi, Williams-Beuren, and Down syndromes. Due to their intellectual impairment especially their abnormal and frequently anti-social behavior, most individuals affected with SMS are institutionalized without proper diagnosis and care.

2. Background

Patients with the features of SMS were first described in 1982 by Ann C.M. Smith in an abstract presented at the Annual Meeting of the American Society of Human Genetics [1]. In 1986, Ellen Magenis together with Ann C.M. Smith and their colleagues published a clinical review of nine individuals affected by this nosologic entity. For this reason the syndrome was named after them [2]. A deletion of chromosome 17p11.2 was identified as the cause of this condition in approximately 90% of cases, and thus this disorder belongs to the group of contiguous-gene syndromes, currently referred to as genome diseases [3-5]. SMS patients without deletions 17p11.2 may carry a point mutation in the gene *RAI1* [6-10], which codes a transcription factor acting in several different biological pathways. *RAI1* dosage is crucial for normal regulation of circadian rhythm, lipid metabolism, and melatonin function. SMS affects both sexes equally and has been found in all ethnic groups. The incidence of SMS was initially estimated at 1:25,000 births [11]. However improvements in cytogenetic techniques and molecular analyses have allowed the diagnosis of most cases, leading to a current prevalence estimate of 1:15,000 [12].

3. Clinical characteristics

SMS dysmorphisms change with age. The most common facial characteristics of the syndrome include broad square-shaped face, brachycephaly, prominent forehead, synophrys, deep-set eyes, broad nasal bridge, midface hypoplasia, micrognathia in infancy, relative prognathism with age, and everted, "tented" upper lip [13]. Dental anomalies such as premolar agenesis and taurodontism have also been reported [14].

Individuals with SMS show mild to moderate mental retardation [11, 15], and behavioral abnormalities such as sleep disturbances, stereotypic movement, and self-injurious behavior [16-21].

To date, nearly two hundred cases have been described in the literature. In 2011 Gamba and colleagues presented seven Brazilian cases and a meta-analysis of clinical signs in SMS reported in the literature, which are summarized in the table below [22].

Clinical	Gamba et al., 2011 N = 7	Literature N = 165	Fisher's Exact test	
		%	<i>P value</i>	
Craniofacial				
Brachycephaly	5/7	95/106	89.6	0.1893
Microcephaly	3/7	9/56	16.0	0.1199
Midface Hypoplasia	6/7	87/10	79.8	1.0000
Broad, square-shaped face	7/7	64/82	78.0	0.3367
Broad Nasal Bridge	7/7	41/51	80.39	0.3356
Short Philtrum	7/7	11/11	100.00	1.0000
Everted, "tented" upper lip	6/7	64/83	77.11	1.0000
Cleft lip/palate	0/7	12/47	25.53	0.3275
Relative prognathism with age	6/7	49/62	79.03	1.0000
Micrognathia	1/7	12/28	42.86	0.2197
Skeletal				
Short stature	6/7	35/71	49.30	0.1115
Scoliosis	3/7	23/53	43.40	0.6971
Dental anomalies	7/7	4/11	36.36	0.0128
Short broad hands	7/7	n/a	n/a	
Clinodactyly	6/7	19/30	63.33	0.3891
Brachydactyly	7/7	67/81	82.72	0.5915
Syndactyly	5/7	15/50	30.00	0.0837
Ocular abnormalities				
Deep-set, close-spaced eyes	6/7	47/72	65.28	0.4156
Synophrys	5/7	31/57	54.39	0.4540

Clinical	Gamba et al., 2011 N = 7	Literature N = 165		Fisher's Exact test
Strabismus	7/7	39/67	58.21	0.0400
Iris Abnormalities	5/7	10/23	43.48	0.3898
Otoringological				
Ear Abnormalities	4/6	48/76	63.16	0.6938
Ear infections	2/7	28/36	77.78	0.0190
Hoarse, deep voice	1/7	40/52	76.92	0.0023
Hearing loss	3/7	46/74	62.16	0.4258
Neurological				
Cognitive impairment/developmental delay	7/7	100/100	100.00	1.0000
Speech delay	7/7	101/111	90.99	1.0000
Motor Delay	7/7	92/114	80.70	0.3479
Infantile hypotonia	4/7	49/77	63.64	0.7054
Sleep disturbance	5/6	97/110	88.18	0.5462
Hyporeflexia	1/7	2/4	50.00	0.4909
Behavior				
Self-Hung	7/7	17/20	85.00	1.0000
Onychotillomania	5/7	15/24	62.50	1.0000
Polyembolokoilomania	6/7	14/23	60.87	0.3717
Head Banging/Face Slapping	1/2	36/43	83.72	0.3273
Hand Biting	4/5	19/19	100.00	0.2083
Attention Seeking	5/5	52/54	96.30	1.0000
Aggressive behavior	7/7	62/67	92.54	1.0000
Self-injurious behaviors	7/7	56/61	91.80	1.0000
Hyperactivity	6/7	52/54	96.30	1.0000
Other features				
Cardiac defects	0/7	44/88	50.00	0.0139
Renal/urinary tract abnormalities	1/7	12/49	24.49	1.0000
EEG abnormal/ evident seizures	3/5	23/58	39.66	0.6687
Hypogonadism male	1/7	21/60	35.00	0.4116
Obesity	3/7	12/51	23.53	0.3597

Bold type Statistically significant values of P less than 0.05 (two-tailed Fisher exact test).

(+) positive (-) negative (n/a) not available

Table 1. Clinical features of seven Brazilian Smith-Magenis syndrome cases and meta-analysis of 165 cases from the literature (Gamba et al., *Genet. Mol. Res.* 10 [4]: 2664-2670, 2011, Published with permission from *Genetics and Molecular Research-Online Journal*) [22].

3.1. SMS features in infancy, childhood/adolescence and adulthood

3.1.1. Infancy

The gestation of children with SMS is commonly uneventful. When maternal report is available, a diminution of fetal movements is described in 50% of cases. At birth all parameters (weight, length, OFC) are normal, including time of gestation.

The occurrence of generalized hypotonia and hyporeflexia promotes a marked oral motor dysfunction, with poor sucking and swallowing, and gastroesophageal reflux. Failure to thrive is attributed to feeding difficulties. During the first year of life, parents often describe SMS cases as perfect babies because they sleep very well and cry little.

Behavior disturbances can be observed as early as 4 months. Videotape analysis shows patients' motor repertoire is significantly reduced, and fidgety general movements, which are typical of that age, are missing. Posture is abnormal and overall movements are jerky and monotonous. These findings indicate a severe motor impairment as early as 4 months of age [23]. Beyond 18 months, signs of developmental delay become increasingly obvious, with early stages of intense crying and sleepless nights. Within 2-3 years of age patients have a clear delay in language acquisition, with lallation [24-25]. Dysmorphic signs subsequently begin to become more evident, with facial hypotonia, and relative micrognathia.

3.1.2. Childhood/adolescence

It is at this stage of life that patients with SBS have dysmorphisms, significant cognitive delays and a peculiar behavior and come to the attention of health professionals. Most patients are diagnosed at this stage of life.

Facial dysmorphisms include broad and square-shaped face, mild face hypoplasia, brachicephaly, short nasal philtrum, a tendency toward an everted upper lip, and relative prognathism. Patients may present with short stature, scoliosis, dental abnormalities, and brachydactyly with clinodactyly at 5th and digital syndactyly between the 3th and 4th toe. Ocular abnormalities may be present, such as deep-set eyes and close-spaced, synophrys, strabismus and iris abnormalities. The main otoryngological alterations are recurrent ear infections resulting in hearing loss, middle/inner ear abnormalities and deep hoarse voice.

Cognitive impairment and developmental delay are pronounced, however the most pronounced neurological alteration is sleep modifications. Patients with SMS often exchange nocturnal sleep for daytime naps, with changes of the circadian cycle and alterations in the release of melatonin [26-28].

Alterations of behavior are atypical and draw the most attention, because they are often unique to patients with SMS. Besides hyperactivity and attention seeking, patients with SMS may present aggressive and self-injurious behavior, including hand biting, head banging, face slapping, self-hanging, onychotilomania and polyembolokotonia [16,19, 29-35]. Other signs reported in up to 50% of patients include obesity, cardiac defects, seizures, cleft lip/palate and male hypogonadism [22].

Figures 1-7 are patients diagnosed with SMS in Genetic Counseling Service Dept Genetics. IBB/ UNESP- Botucatu, Brazil, and several of these patients were published (Published with permission from *Genetics and Molecular Research-Online Journal*, Gamba et al., 2011. *Genet. Mol. Res.* 10 [4]: 2664-2670).



Figure 1. Patient 1. – 8.25 years-old



Figure 2. Patient 2 – 18.83 years-old

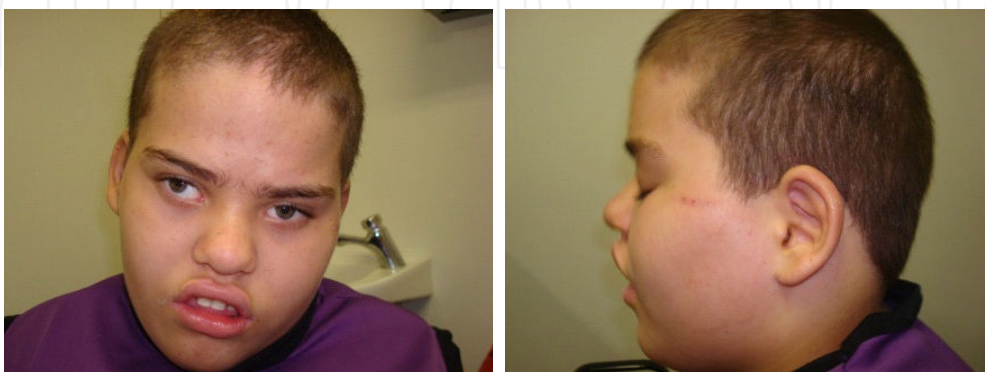


Figure 3. Patient 3. – 12.83 years-old

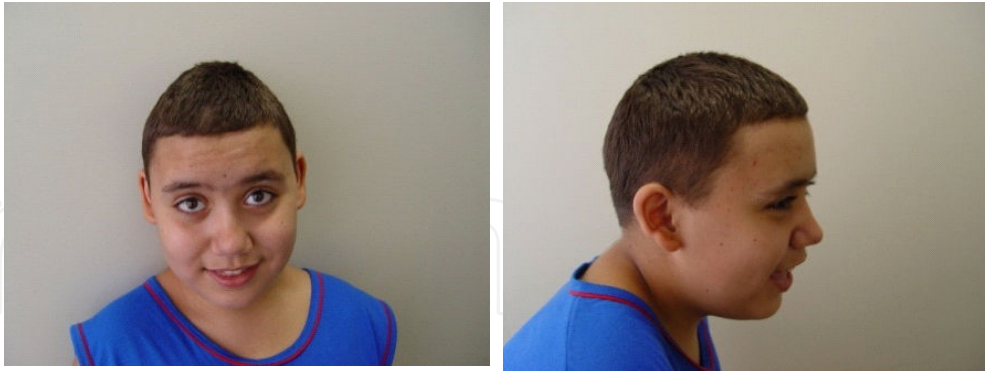


Figure 4. Patient 4 – 12.83 years-old



Figure 5. Patient 5. – 13.33 years-old

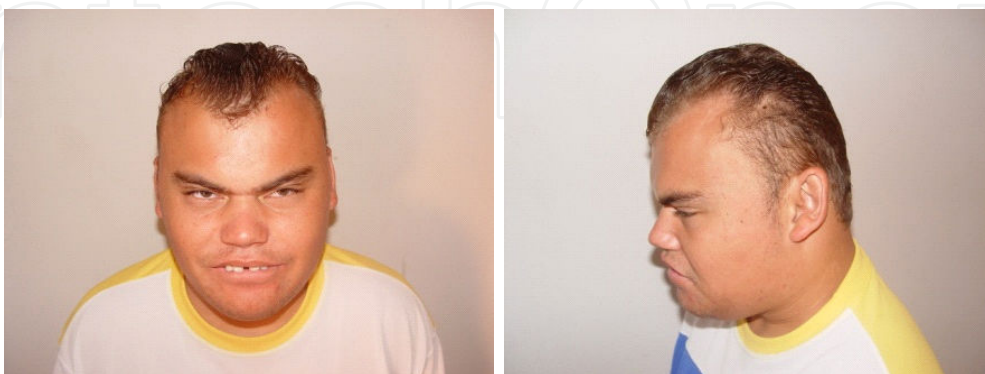


Figure 6. Patient 6 – 19.0 years-old



Figure 7. Patient 7. – 20.58 years-old

3.1.3. Adulthood

Adults with SMS have a diminution of stereotypic movements, but when frustrated, develop aggressive speech, with shouting or profanity at high volume. Little data is published regarding the life expectancy of patients with SMS. However it is believed that life expectancy is normal or similar to that of other individuals with the same level of cognitive dysfunction [36,37].

4. Genetics

Most cases of SMS are caused by a microdeletion on 17p11.2 that encompasses multiple genes, including the retinoic acid-induced 1, *RAI1*, gene. This deletion is observed in 90% of the cases, although in 10% of cases a point mutation in the *RAI1* gene is observed [2, 4, 6, 20, 38]. SMS microdeletions are caused by irregularities in chromosomal recombination mediated by repeat elements referred to as Low copy number repeats (LCR). Already [39] identified three copies of an LCR as being responsible for the deletion on 17p11.2. These repeats (LCRs proximal, middle, and distal - SMS REPs) form substrates for inter- and intrachromosomal recombination. In 70% of SMS cases, unequal meiotic crossovers result in nonallelic homologous recombination between the proximal and distal SMS REPs and a deletion of approximately 3.7Mb. In the remaining 30%, deletions are due to alternate SMS REPs (distal x medial). Moreover, AT-rich repeats and *Alu* elements may act as homologous recombination substrates, and nonhomologous mechanisms can generate deletions of atypical deletions sizes [40-42].

5. Diagnosis

SMS is suspected in individuals presenting distinctive facial features, a behavioral phenotype and sleep disturbance. Initial clinical suspicion of the disorder is confirmed by the presence of a microdeletion in the p11.2 region of chromosome 17 or a mutation in the *RAI1* gene. The

unique SMS behavioral phenotype including sleep disturbance, a hoarse voice, characteristic hands and feet, excellent long-term memory, good ability and focus with computers, self-injury scars and typical facial features are important clues to the diagnosis. Because SMS will rarely be the only possible clinical diagnosis, exams are key to diagnosis.

SMS diagnosis is confirmed by detecting 17p11.2 deletion using classic cytogenetic analysis, molecular cytogenetic analysis, or molecular genetic methods [20].

Cytogenetic analysis by GTG banding at the 550 band level or higher can detect deletions of approximately 4Mb, which account for 70% of the cases. However fluorescent *in situ* hybridization (FISH) using an RAI1-specific probe is the most frequently used technique [20, 22, 43-44] (Fig.8 and Fig. 9).

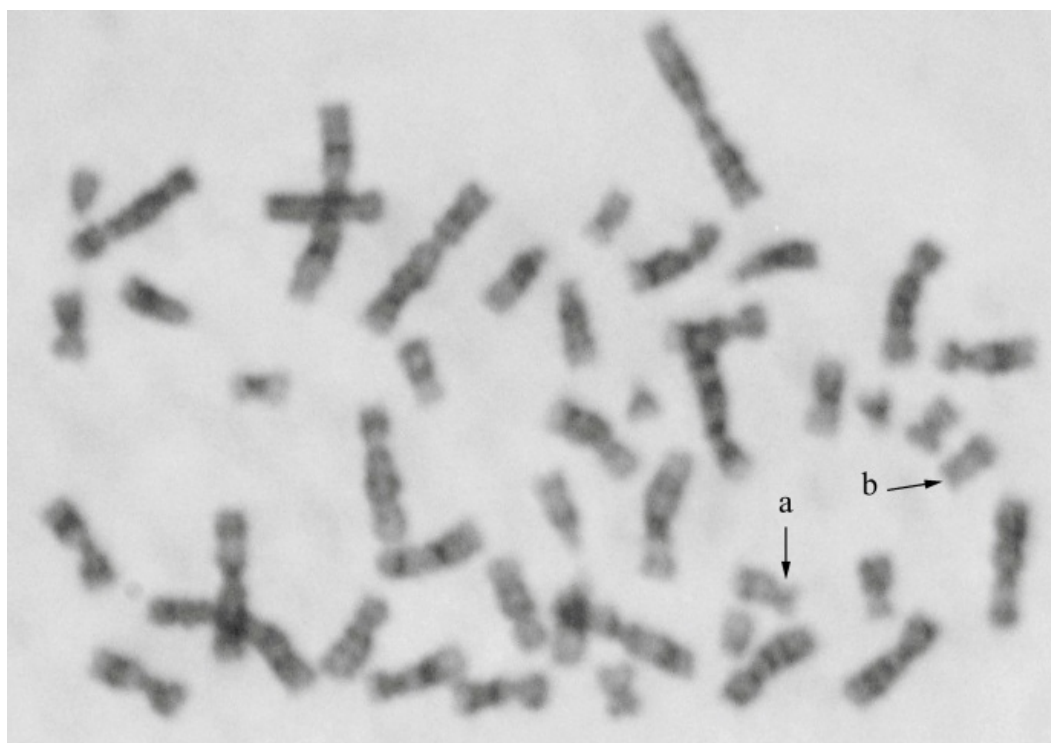


Figure 8. GTG banding of metaphase chromosomes showing the normal chromosome 17 (a) and deleted chromosome 17 (b). Courtesy of the Cytogenetics Laboratory - SAG / IBB-UNESP-Botucatu, SP-BRAZIL

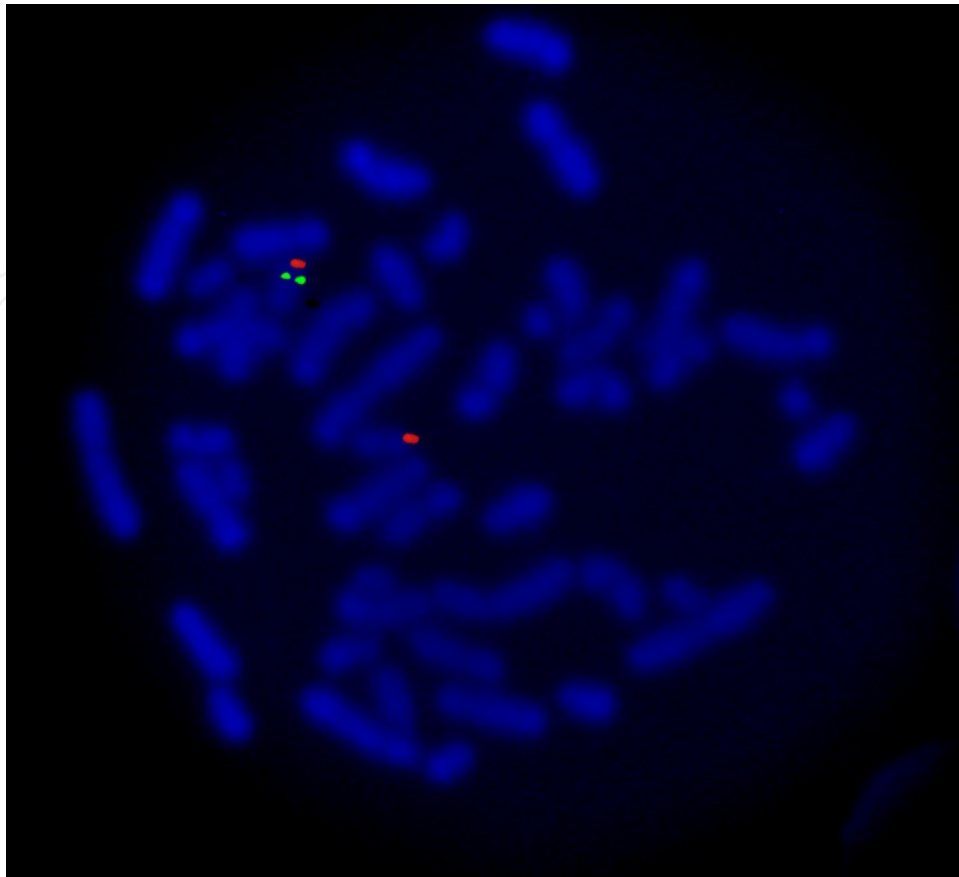


Figure 9. Metaphase FISH using the probe in the Smith-Magenis Cytocell[®] (RAI 1 and Flii) / Miller-Dieker. The red area shows the control the green gene responsible for SMS. *Courtesy of the Cytogenetics Laboratory - SAG / IBB-UNESP-Botucatu, SP-BRAZIL*

Beyond these cytogenetic methods, methods that require only DNA for analysis are newer, cost-efficient, and can be used in a large number of patients at the same time. Additionally, MLPA or qPCR can identify smaller deletions at a higher resolution than FISH or G-banding [45].

6. Differential diagnosis

The differential diagnosis for SMS includes [13, 44].

- 1q36 deletion syndrome
- 9q34 deletion syndrome

As the clinical characteristics of SMS and these syndromes overlap, specific FISH tests are required for establishing a final diagnosis

- 22q11.2 deletion syndrome: velopharyngeal abnormalities and facial characteristics differentiate this syndrome from SMS

- Down syndrome: despite having several overlapping features with SMS, Down syndrome can be diagnosed by simple karyotype analysis
- Williams-Beuren syndrome (WBS): SMS and this syndrome show opposing behavioral characteristics. While WBS patients are overfriendly, loquacious and frequently smiling, SMS individuals are shy, aggressive and restless
- Prader-Willi syndrome (PWS): although obesity may be present in both PWS and SMS, it is always of the morbid type in PWS patients:
- Sotos syndrome (SS): in SS patients, bone age is advanced while in SMS it is normal.

7. Treatment of manifestations

Patients with SMS present functional disturbances (obesity, sleep disturbances) and behavioral abnormalities (aggression, self-injury) which have prompted attempts to medically treat these alterations. Due to the low frequency of SMS, classical placebo-controlled prospective clinical drug trials have not been feasible. Clinical experience to date indicates that no drug is effective in alleviating any SMS symptoms in more than 60% of cases. There are a number of anecdotal reports of successful treatments, however many of unsuccessful treatments are likely unreported.

A review of pharmacological treatments with psychotropic drugs in patients with SMS was reported [46]. The medications were grouped into seven main categories: [1] stimulants; [2] antidepressants; [3] antipsychotics; [4] hypnotics; [5] mood stabilizers; [6] alpha 2 agonists; [7] and benzodiazepines. The stimulant category included methylphenidate, amphetamines, and others (e.g., pemoline). Antidepressants were subdivided into selective serotonin reuptake inhibitors (SSRIs), tricyclics (TCA), and others. The antipsychotic category was divided into typical and atypical. The hypnotic category included melatonin, diphenhydramine, and others. Mood stabilizers included lithium and anticonvulsants used for mood stabilization. Clonidine and guanfacine were grouped under alpha 2 agonists and all benzodiazepines were grouped together. The beta-blockers category was excluded due to a small number of reports. The study was conducted using medical histories of 62 patients with SMS. This study concluded that no consistent results were observed for any medicine or drug group, although the study did not exclude any of the drugs used.

Another elegant work [47,48] tested the effect of administration of B1-adrenergic antagonists together with melatonin in 10 patients with SMS, in an attempt to improve the circadian disturbances. These authors concluded that the administration of acebutolol in the morning and melatonin in the early evening allowed the biological clock reset and restore the normal rhythm of melatonin in SMS patients. The patients had improvements in sleep, diminution of naps during the day, with a higher state of attention and diminution of aggressive behavior.

8. Conclusions

Significant overlap between SMS's clinical features with other similar syndromes does makes it very difficult establish a clinical diagnosis. However, the uniqueness of the behavioral features of this condition should lead health care providers to request specific FISH testing. Treatment for SMS is merely relies on managing the symptoms. Individuals with SMS often require several forms of support, including physical therapy, occupational therapy, speech therapy, and particularly behavioral therapy, which are most effective if started early in life. Therefore, having an early diagnosis can help guide a person's health care through life, and open the doors to a network of information from professionals and other families dealing with the syndrome.

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