Original Article

Smith-Magenis Syndrome Patients Often Display Antibody Deficiency but Not Other Immune Pathologies

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What is already known about this topic? Smith-Magenis syndrome (SMS) is a complex neurobehavioral disorder associated with otitis. Most SMS cases result from chromosome 17p11.2 deletions that encompass the intellectual disability gene *retinoic acid-induced 1* and also genes associated with immunodeficiency, autoimmunity, and/or malignancy.

What does this article add to our knowledge? Description of the immunopathologies and laboratory immunological features of a large cohort of 76 patients with SMS reveals a consistent susceptibly to sinopulmonary infections, including pneumonia, but not to autoimmune, allergic, or malignant diseases.

How does this study impact current management guidelines? As with other genetic syndromes associated with antibody deficiency listed in the American Academy of Allergy, Asthma, and Immunology practice parameters for diagnosis and management of primary immunodeficiency, all SMS patients should receive an immunologic evaluation. Infectious prophylaxis should be considered in selected SMS patients.

BACKGROUND: Smith-Magenis syndrome (SMS) is a complex neurobehavioral disorder associated with recurrent otitis. Most SMS cases result from heterozygous interstitial chromosome 17p11.2 deletions that encompass not only the intellectual disability gene *retinoic acid-induced 1* but also other genes associated with immunodeficiency, autoimmunity, and/or malignancy.

OBJECTIVES: The goals of this study were to describe the immunological consequence of 17p11.2 deletions by determining the prevalence of immunological diseases in subjects with SMS and by assessing their immune systems via laboratory methods.

METHODS: We assessed clinical histories of 76 subjects with SMS with heterozygous 17p11.2 deletions and performed in-depth immunological testing on 25 representative cohort members. Laboratory testing included determination of serum antibody concentrations, vaccine titers, and lymphocyte subset frequencies. Detailed reactivity profiles of SMS serum

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Abbreviations used
BHDS- Birt-Hogg-Dubé syndrome
CVID- Common variable immune deficiency
EMR- Electronic medical records
FLCN- Folliculin
HiB- Haemophilus influenza *type B*
MFI- Mean fluorescence intensity
PRISMS- Patients and the professional advisory board of Researchers Interested in Smith-Magenis Syndrome
RAI1- Retinoic acid-induced 1
SAM- Significance analysis of microarrays
SMS- Smith-Magenis syndrome
TNFRSF13B- Tumor necrosis factor receptor superfamily member 13b
TOM1L2- Target of myb1 like 2 membrane trafficking protein

antibodies were performed using custom-made antigen microarrays.
RESULTS: Of 76 subjects with SMS, 74 reported recurrent infections including otitis (88%), pneumonia (47%), sinusitis (42%), and gastroenteritis (34%). Infections were associated with worsening SMS-related neurobehavioral symptoms. The prevalence of autoimmune and atopic diseases was not increased. Malignancy was not reported. Laboratory evaluation revealed most subjects with SMS to be deficient of isotype-switched memory B cells and many to lack protective antipneumococcal antibodies. SMS antibodies were not more reactive than control antibodies to self-antigens.
CONCLUSIONS: Patients with SMS with heterozygous 17p.11.2 deletions display an increased susceptibility to sinopulmonary infections, but not to autoimmune, allergic, or malignant diseases. SMS sera display an antibody reactivity profile favoring neither recognition of pathogen-associated antigens nor self-antigens. Prophylactic strategies to prevent infections may also provide neurobehavioral benefits to selected patients with SMS.

Key words: *Smith-Magenis syndrome; Chromosome 17p11.2 deletion; Immune deficiency; Autoantibody;* TNFRSF13B*;* FLCN*;* TOM1L2*; B-cell tolerance*

Smith-Magenis syndrome (SMS; Online Mendelian Inheritance in Man [OMIM] #182290; *607642) is a complex genetic disorder, estimated prevalence 1:15,000-25,000. SMS is characterized by intellectual disability, sleep disturbances, self-injurious behaviors, and skeletal abnormalities.[1-3] Although ear infections are commonly described in patients with SMS,[4] it is unclear if the predisposition is due to an anatomic or immunologic abnormality. Diminished antipneumococcal antibodies have been described in SMS sera,[5] but neither a comprehensive clinical evaluation of the SMS immune system nor a detailed account of the full spectrum of infections experienced by patients with SMS has been reported. Similarly, it is unknown if the SMS immune system is prone to the development of autoimmune, malignant, and/or atopic diseases as is the case in many primary immunodeficiencies.[6-9]

Approximately 90% of SMS cases are caused by the heterozygous 3.7 Mb interstitial deletion of 17p11.2, a region encompassing the retinoic acid-induced 1 (*RAI1*) gene locus.[3] In rare cases, SMS may be caused by deleterious *RAI1* point mutations, without deletion of 17p11.2, suggesting that *RAI1* is the gene primarily responsible for the neurodevelopmental features of SMS.[10] *RAI1* serves no known immunologic function,[11] but proximate genes also lost to 17p11.2 deletion, including tumor necrosis factor receptor superfamily member 13b (*TNFRSF13B*), folliculin (*FLCN*), and target of myb1 like 2 membrane trafficking protein (*TOM1L2*), do. *TNFRSF13B* encodes transmembrane activator and CAML interactor (TACI), which controls T-independent humoral responses and B-cell tolerance.[12-15] Heterozygous missense *TNFRSF13B* mutations are associated with common variable immune deficiency (CVID),[16,17] an antibody deficiency disorder often complicated by autoantibody production and hematologic malignancy.[18] Autoimmune disease occurs in 41% of patients with CVID with heterozygous *TNFRSF13B* missense mutations.[19] *FLCN* is a tumor suppressor gene mutated in Birt-Hogg-Dubé syndrome (BHDS).[20] Patients with BHDS accumulate both benign and malignant tumors.[20] *TOM1L2* is not implicated in a human disease, but *Tom1l2*-deficient mice are susceptible to infections and tumors.[21]

Because many patients with SMS are hemizygous for multiple genes associated with immunodeficiency, autoimmunity, and/or malignancy, we hypothesized that they may also be susceptible to these diseases. To test this hypothesis, we surveyed medical histories, spanning 970 person-years, from a large cohort of 76 subjects with SMS aged 6 months to 37 years (mean, 13.8 years) with 17p11.2 deletions. We obtained peripheral blood samples on 25 representative subjects from our cohort, all with deletions encompassing *RAI1, TNFRSF13B, FLCN*, and *TOM1L2*, to create in-depth immunologic profiles via laboratory assessments that included serum immunoglobulin quantification, vaccine titers, lymphocyte flow-cytometry, and custom-made antigen microarrays. Our results indicate that patients with SMS are antibody deficient and frequently experience sinopulmonary infections, including severe bacterial illnesses like pneumonia. Unlike many patients with primary immunodeficiency, subjects with SMS were not more susceptible to autoimmune, allergic, or malignant diseases, nor did they frequently display increased serum autoantibodies or elevated IgE.

METHODS

Study subjects and clinical history evaluations

We enrolled 76 subjects with SMS with heterozygous chromosome 17p11.2 deletions. Subjects ranged from 6 months to 37 years in age (mean, 13.8 years); 52% were female (Table I). Informed consent was obtained for all individuals before study enrollment. The study protocol was approved by the Human Subjects Committee of Yale University, the Institutional Review Board of the Children's Hospital of Philadelphia, and the professional advisory board of Parents and Researchers Interested in Smith-Magenis Syndrome (PRISMS). An immunological diseases questionnaire was distributed to families of subjects with SMS at the international PRISMS family meeting, on the PRISMS website, or in the course of the authors' clinical practice. When subjects were identifiable ($n = 12$), survey responses were secondarily confirmed for accuracy using electronic medical records (EMR). Overall good concordance between survey and EMR data was observed. For survey responses, a recurrent infection was defined as at least 4 infections per year. Peripheral blood samples, paired to survey data, were obtained either at the 2014 International PRISMS Conference and family meeting