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Immune Complex-Mediated Autoimmunity in a Patient With Smith-Magenis Syndrome (del 17p11.2)

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Abstract

Smith-Magenis syndrome (SMS) is a sporadic congenital disorder involving multiple organ systems caused by chromosome 17p11.2 deletions. Smith-Magenis syndrome features craniofacial and skeletal anomalies, cognitive impairment, and neurobehavioral abnormalities. In addition, some SMS patients may exhibit hypogammaglobulinemia. We report the first case of SMS-associated autoimmunity in a woman who presented with adult onset of multiple autoimmune disorders, including systemic lupus erythematosus, antiphospholipid antibody syndrome, and autoimmune hepatitis. Molecular analysis using single-nucleotide polymorphism array confirmed a de novo 3.8-Mb deletion (breakpoints, chr17: 16,660,721–20,417,975), resulting in haploinsufficiency for TACI (transmembrane activator and CAML interactor). Our data are consistent with potential loss of function for the BAFF (B cell-activating factor) receptor TACI as a contributing factor to human autoimmune phenomena.

Keywords

Smith-Magenis syndrome; del 17p11.2; systemic lupus erythematosus; autoimmunity; antiphospholipid antibody syndrome; autoimmune hepatitis

Smith-Magenis syndrome (SMS) is a congenital abnormality caused by chromosome 17p11.2 deletions. The most common clinical presentations of SMS include craniofacial and skeletal anomalies, cognitive impairment, circadian rhythm disorder, and self-injurious behaviors.¹ Although uncommonly reported, immunological dysfunction featuring

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hypogammaglobulinemia may develop in SMS patients, potentially due to the haploinsufficiency of TACI (transmembrane activator and CAML interactor).² TACI is located within the SMS core deletion region.^{2–4} TACI is a cognate receptor for BAFF (B cell-activating factor). It plays critical roles in regulating BAFF-mediated B-cell proliferation and antibody production.⁵ TACI-deficient mice develop systemic lupus erythematosus (SLE)-like autoimmunity due to overactivation of BAFF-mediated signaling.⁶ However, in humans, TACI deficiency/mutation is rarely associated with autoimmunity. We present the first case of a 24-year-old female SMS patient with adult onset of SLE, antiphospholipid antibody syndrome, and autoimmune hepatitis.

A 24-year-old white woman with SMS presented with a history of chronic fatigue, shortness of breath, and weight loss, developing over 3 to 4 months. Medical history was remarkable for SMS. The condition had been diagnosed at 14 years of age, based on both clinical presentation and cytogenetic analysis establishing chromosome 17p11.2 deletion. The patient was the 3231-g product of uneventful pregnancy born at 42 weeks by cesarean delivery to a 31-year-old prima gravida mother. Apgar scores were 8 and 9. Psychomotor delays documented at age 18 months prompted initial cytogenetic study that was interpreted as normal (46,XX karyotype), delaying her diagnosis. Review of childhood history was significant for motor and speech delays with referral for early intervention services, recurrent otitis media (onset age 2 years) with bilateral pressure equalizer tube placement 5 times, conductive hearing loss, hypotonia with decreased muscle tone but good strength, hoarse voice, mild decreased visual acuity at age 7 years, wide-based gait pattern, and sensory processing issues, especially touch/tactile, movement/proprioception, and balance/vestibular dysfunction. Maladaptive behaviors consistent with SMS diagnosis included early head banging; teeth grinding, mouthing objects beyond expected age, hitting others, easy distractibility, impulsivity, sensitivity to loud noises, diagnosed attention-deficit/hyperactivity disorder (age 7 years), difficulties with transitioning to change/schedules, attention seeking from adults, mild self-injurious behaviors (putting Q-tips in the ears), and decreased response to pain. Unusual sleep patterns were noted from 1 year of age with difficulties falling and staying asleep, nocturnal awakening, and early sleep offset (4:00–5:00 AM) in childhood.

Determinations of lipid profiles, thyroid-stimulating hormone, and immunoglobulin levels every 2 to 4 years were normal until age 22 years, when her immunoglobulin M (IgM) levels were discovered to be low (tested independently twice). Selective IgM deficiency was diagnosed. In addition, the patient had diffuse, mild enlargement of lymph nodes in abdomen, axilla, and inguinal regions with unclear etiology and no obvious progression based on computed tomography scans at age 20 and 24 years. At 24 years, 6 months prior to presentation, she developed extensive intra-abdominal thrombosis. Workup for causes of a hypercoagulable state ruled out paroxysmal nocturnal hemoglobinuria, dysfibrinogenemia, and lymphoproliferative disorders. Protein S level was mildly low at 42% (56%–158%); anticoagulation had been started for presumed protein S deficiency.

Family history was negative for any genetic abnormalities, neurologic dysfunction, syndromic features, or SLE. Fourteen-point review of systems was negative. The patient was taking no medications other than Coumadin (warfarin sodium).

Physical examination on presentation revealed normal vital signs, dry mucous membranes, and typical body habitus features of SMS: flattened nasal bridge with wide, flat face, tented upper lip, large tongue, and mild scoliosis. In the laboratory, complete blood count showed severe anemia with hemoglobin 5.4 g/dL (hemoglobin had been 9.6 g/dL 4 months earlier), as well as mild leukopenia (white blood cells $3.6 \times 10^9/L$) and thrombocytopenia (platelets $112 \times 10^9/L$). Peripheral blood smear revealed slight thrombocytopenia, severe anemia, and reactive neutrophils. Erythropoietin response was appropriate at 544 mU/mL (4–27 mU/mL). Additional workup indicated no iron, folate, or vitamin B₁₂ deficiency, and no recent parvovirus B19 exposure. Bone marrow biopsy showed hypercellular marrow, without evidence of paroxysmal nocturnal hemoglobinuria, leukemia, lymphoma, or other malignancy. Further testing revealed strongly positive antinuclear antibodies at 14.3 units (<1.0), anticardiolipin IgG at 80 GPL (0–15 GPL), and IgM at 88.7 MPL (0–12.5 MPL); marked elevation of anti-dsDNA at 2655 IU/mL (0–29 IU/mL); positive anti-SSA and antihistone antibodies; markedly decreased C3 at 27 mg/dL (90–200 mg/dL) and C4 at 3 mg/dL (15–30 mg/dL); and undetectable C2 and CH50. Liver function tests were modestly elevated: total bilirubin 1.4 mg/dL (0.2–1.3 mg/dL), alkaline phosphatase 174 U/L (40–150 U/L), aspartate aminotransferase 128 U/L (0–45 U/L), alanine aminotransferase 105 U/L (0–50 U/L), lactate dehydrogenase 1333 U/L (325–750 U/L). Albumin was 3.2 g/dL (3.9–5.1 g/dL). Hepatitis B and hepatitis C serologies were negative, but anti-F-actin was elevated at 47 U (0–19 U). She exhibited polyclonal hypergammaglobulinemia: IgM 290 mg/dL (60–265 mg/dL), IgG 1620 mg/dL (695–1620 mg/dL), and IgA 445 mg/dL (70–380 mg/dL).

The patient was diagnosed with SLE, antiphospholipid antibody syndrome, and autoimmune hepatitis. She was treated with prednisone 40 mg daily with a taper over 3 months; mycophenolate 1.5 g/d was also started. Within 2 weeks of starting treatment, anemia improved, white blood cell and platelet counts normalized, and liver function test abnormalities resolved. However, 3 months after presentation, urinalysis revealed increasing hematuria and proteinuria. Kidney biopsy indicated diffuse proliferative glomerulonephritis. Prednisone and mycophenolate doses were increased to 1 mg/kg per day and 2 g/d, respectively. Three months later, the patient's glomerular filtration rate and urine analysis had normalized. Five months after the presentation, the patient's serum BAFF level was high-normal at 1737 pg/mL (551–1775 pg/mL); CD19⁺ TACI⁺ of B cells was 12.8% (normal, >3.4%). Sequencing of TACI (Fluorescent Sequencing Analysis, Mayo Clinic, Rochester, MN) revealed no heterozygosity and no mutations or deletions.

Molecular Genetics

Whole-genome single-nucleotide polymorphism (SNP) genotyping was performed on the patient and parental genomic DNA using HumanOmniExpress SNP array (Illumina Inc) to determine deletion breakpoints. The genotyping data from these high-density arrays (730,000 SNPs) allowed for analysis of copy number changes at high resolution. Copy number variant analysis and loss of heterozygosity for breakpoint determination were performed for chromosome 17p by analyzing the B-allele frequency and log R ratio tracts with Illumina BeadStudio software.⁷ These results confirmed a de novo 3.8-Mb deletion (Chr 17: 16,660,721–20,417,975; build hg19). The 5' breakpoint is located in CCDC144A,

and the 3' breakpoint just after KRT16P3 (Fig. 1). The observed deletion is commonly observed in SMS patients⁴ and is consistent with TACI haploinsufficiency.

DISCUSSION

Although SMS patients may have immunological dysfunction, association between SMS and clinically apparent autoimmune disease has not been reported. The most commonly noted immune abnormality is hypogammaglobulinemia.^{3,4} A recent study suggests that humoral defects are likely due to the haploinsufficiency of *TNFRSF13B* (TNF superfamily member 13b), otherwise known as *TACI*.² The 17p12.1 deletions in SMS patients range in size from 1.5 to 9 Mb.^{3,8} The critical part of this deletion region is about 1.5 Mb, encompassing over 15 genes, including *TACI*.³ TACI is expressed on B cells and plasma cells. TACI modulates B-cell proliferation, maturation, survival, and homeostasis. TACI-deficient mice exhibit hyperactive B cells that accumulate in peripheral lymphoid tissues and display increased capacity for antigen-specific antibody production.⁹ Moreover, TACI deficiency is associated with a fatal lupus-like autoimmune disease featuring anti-dsDNA and antinuclear antibodies, proteinuria, and autoimmune glomerulonephritis.⁶

TACI likely functions as a negative regulator for BAFF-induced B-cell proliferation and autoantibody production.⁶ Concordant with observations in TACI-deficient mice, overexpression of BAFF renders mice susceptible to autoimmunity reminiscent of human SLE and Sjögren syndrome.¹⁰ Consistent with these results, TACI-immunoglobulin treatment is able to control the progression of the SLE-like disease in BAFF-transgenic mice.¹¹ In addition to its negative regulator role for B-cell activation and proliferation, TACI is also implicated in BAFF-mediated antibody production and class switching.¹²

Mutations of *TACI* have been observed in 2 human diseases: combined variable immune deficiency and IgA deficiency.¹³ Interestingly, *TACI*^{-/-} mice also show reduced IgM and IgA levels.⁵ These studies collectively suggest that TACI has 2 distinct functions in B-cell biology: one is to restrain B-cell activation and keep autoreactive B cells at bay; a second is to promote B-cell differentiation, antibody production and class switching. For reasons that remain unclear, TACI appears relatively more important in controlling autoimmunity in mice but is more crucial for regulating antibody production in humans.

Several clinical features in our patient are consistent with loss of TACI function and dysregulation of BAFF signaling. The well-described 17p11.2 deletion associated with SMS that may affect TACI expression has been documented in our patient. Cross-sectional imaging (computed tomography scanning at ages 19 and 23 years) has repeatedly documented enlargement of lymph nodes in abdomen, axilla, and inguinal regions with unclear etiology. While total immunoglobulin levels were normal at age 20 years, the patient's IgM levels were decreased 2 years prior to the SLE diagnosis, suggesting that defective antibody production is recently acquired. Selective IgM deficiency has been observed in cases of TACI dysfunction in humans.² At age 23 years, high autoantibody titers were noted in the context of transfusion-dependent anemia and thrombocytopenia, SLE-associated nephritis, and autoimmune hepatitis. These data collectively indicate the development of clinical autoimmunity (lymphadenopathy, positive anti-dsDNA,

antinuclear antibodies, proteinuria, and glomerulonephritis) that is paralleled by pathology features observed in TACI-deficient mice. The genome SNP genotyping results confirm the deletion of one TACI allele. In addition, the TACI allele sequencing results show no deletion or mutation of the other copy of the TACI gene. These data reinforce the speculation that haploinsufficiency of TACI plays a major role in developing autoimmunity in our patient.

Interestingly, normal levels of peripheral TACI⁺ B cells and serum BAFF were observed in our patient. However, it is noteworthy that these results were obtained 4 months after institution of the prednisone/mycophenolate treatment and normalization of cytopenias. The effects of medications on BAFF levels and TACI expression have not been studied. The time course of TACI expression levels in relation to the autoimmune disease onset and progression needs to be further elucidated.

Another candidate gene that may contribute to the immunological abnormalities in SMS patients is *TOM1L2*. *TOM1L2* is located in the SMS core deletion region adjacent to the gene *RAI1*. Deletion of *RAI1* accounts for multiple major SMS abnormalities. The SMS patients with *TACI* deletion usually display *TOM1L2* deletion. Recent work suggests that *TOM1L2* localizes in the Golgi apparatus and is involved in endosomal trafficking. Mice with reduced expression of *TOM1L2* are prone to infections and tumors.¹⁴ Lack of *TOM1L2* may contribute to the increased propensity of infection among SMS patients. However, the role of *TOM1L2* in autoimmunity has not been reported.

Our patient had reduced levels of C3, C4 and severe reductions in C2 and CH50. Genetic complement deficiencies, especially C2 and C4, are associated with increased susceptibility to SLE. Possible causes of undetectable levels of C2 and CH50 in this patient are either genetic C2 deficiency or SLE-associated complement consumption. Although we cannot rule out the possibility of genetic complement deficiency, complement consumption is the most plausible explanation for several reasons. First, C2- or C4-deficient patients usually have normal levels of C3.¹⁵ Our patient has a decreased C3 level. Second, complement genes are located in the HLA-III gene cluster of chromosome 6, not in chromosome 17 in the region of described SMS defects. Smith-Magenis syndrome has not been associated with genetic complement deficiencies. Third, our patient has high levels of multiple autoantibodies, including anti-dsDNA; insofar as these autoantibodies exert complement fixing function, extensive complement activation and consumption might be expected. In fact, we observed that while autoantibody levels decreased after the prednisone and mycophenolate treatment, the patient's C3 and C4 levels gradually increased, further supporting the idea that complement consumption is the cause of the patient's hypocomplementemia.

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