Title

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Permalink

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Journal

American Journal of Medical Genetics Part A, 140A(24)

ISSN

1552-4825

Authors

Mikhak, Zamaneh
Kelly, Pamela
Cohen, Tatyana S
et al.

Publication Date

2006-12-15

DOI

10.1002/ajmg.a.31513

Copyright Information

Peer reviewed

Research Letter
Immunoglobulin Deficiency in Stickler Syndrome

Zamaneh Mikhak,[1,2,5]* **Pamela Kelly,**[1] **Tatyana S. Cohen,**[1,3]
Joanne E. Cox,[1,5] **and Virginia E. Kimonis**[4,5]

[1]Healthy Link Asthma Education Program, Children's Hospital, Boston, Massachusetts
[2]Massachusetts General Hospital, Center for Immunology and Inflammatory Diseases, Charlestown, Massachusetts
[3]Massachusetts College of Pharmacy, Boston, Massachusetts
[4]Division of Genetics and Metabolism, Children's Hospital, Boston, Massachusetts
[5]Harvard Medical School, Boston, Massachusetts

To the Editor:

Stickler et al. [1965] first described Stickler syndrome (SS) or hereditary arthro-ophthalmopathy in 1965. This autosomal dominant connective tissue disorder is now recognized in 1 in 10,000 people, a frequency comparable to that of Marfan syndrome [Rose et al., 2001]. Clinical manifestations of SS include the ocular, auditory, oral-facial, cardiac, and musculoskeletal systems. Myopia (90%), retinal detachment (60%), facial abnormalities, such as flat facial features, cleft palate and micrognathia (84%), hearing loss (70%), and early onset joint disease (90%) are common features of SS [Stickler et al., 2001]. In most instances, SS is caused by mutations in *COL2A1*, *COL11A1*, and *COL11A2* procollagen genes, affecting Type II or Type XI collagen, abundant proteins found in the cartilage, the vitreous, nucleus polposus, and in the middle and inner ear [Shpargel et al., 2004; Rose et al., 2005]. There is extensive variability in the phenotypic presentation of SS within and in between families [Liberfarb et al., 2003]. SS is subdivided into three types based on the type of molecular linkage involved and ocular manifestations. Type I is linked to mutations in *COL2A1*. Type II is linked to abnormalities in *COL11A1* while Type III is due to mutations in *COL11A2*. Patients with SSs Types I and II have ocular manifestations while patients with Type III SS have no ocular disease [Rose et al., 2005].

Patients with SS commonly experience recurrent middle ear infections, a phenomenon attributed to the Eustachian tube dysfunction that results from oral-facial abnormalities manifested in this disorder. Here, we report on the first association of SS, due to a novel mutation in the *COL2A1* gene, with humoral immune deficiency. The coexistence of humoral immune deficiency and Eustachian tube dysfunction aggravated the infectious complications in this patient. Recognition and management of the humoral immune deficiency in this patient significantly improved her infectious complications.

The patient is a 4-year-old Caucasian girl born to a 27-year-old G2P1 mother at full term after an uncomplicated pregnancy and vaginal delivery. Birth weight was 3,345 g and birth length was 50 cm. She was born with a cleft palate and experienced feeding difficulties as well as persistent middle ear effusions until the surgical repair of her cleft palate and placement of tympanostomy tubes at 5 months of age. SS was suspected early due to a positive family history and confirmed by genetic testing. The patient had tympanostomy tubes placed three times. She would develop recurrent middle ear infections, once a month to once every other month, with the loss of her tympanostomy tubes. Patient was diagnosed with pneumonia three times, at 12 months, 13 months, and 16 months of age. She began to wheeze at approximately 1 year of age with every episode of upper respiratory or middle ear infection. She suffered from chronic congestion and had a history of penicillin allergy. Environmental allergens included mice, molds, and dust mites.

The patient's father and older brother had SS. Her father required multiple surgeries for retinal detachment beginning at 18 years of age. He also had

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*Correspondence to: Zamaneh Mikhak, M.D., Division of Rheumatology, Allergy and Immunology, Massachusetts General Hospital, Center for Immunology and Inflammatory Diseases, 149 Thirteenth Street, Room 8301, Charlestown, MA 02129. E-mail: zmikhak@partners.org

minimal sensorineural hearing loss in the high range. The 6½-year-old brother had a bifid uvula and submucous cleft palate and myopia. He experienced multiple ear infections and required tympanostomy tubes three times. The grandmother and father's maternal grandmother's sister's son and grandson had retinal detachment. The remainder of the family members presumed to be obligate carriers did not have Stickler-like medical manifestations. Interestingly, her mother was diagnosed with Sturge–Weber syndrome at 1½ years of age when she presented with seizures and an extensive hemangioma. Multiple family members had asthma and allergic rhinitis.

The patient's immunizations were up-to-date. She received one dose of pneumococcal conjugate vaccine at 12½ months of age during the pneumococcal conjugate vaccine shortage. Her growth and development were normal. Her facial features included a flat profile, flat nasal bridge, symmetric and normally placed ears, and mild micrognathia. She had myopia and required corrective lenses since 7 weeks of age. She had no retinal detachment or cataract. Her nasal septum was midline and she had mild turbinate edema. She had a normal cardio-respiratory and neurologic exam. Her musculoskeletal exam was remarkable for generalized ligamentous laxity. She had normal speech. Audiograms demonstrated conductive hearing loss and flat tympanograms due to middle ear effusion when Eustachian tubes were absent or malfunctioning.

DNA testing of the COL2A1 gene showed a heterozygous C to A substitution at position 10 of intron 28 and deletion of G at position 9 of intron 28. This mutation was also identified in her brother and father and not in her mother. The C to A mutation occurs in the polypyrimidine tract important for correct RNA splicing and creates a new cryptic splice site and causes an out of frame insertion of eight nucleotides into the message. This in turns causes a frameshift and therefore a premature termination codon and a null allele. This mutation is considered disease-causing because it has been seen in another family with a Stickler phenotype (unpublished data Prockop D). The consequence of the G deletion is difficult to predict and has not been observed previously.

The sweat test was negative. She had negative serum IgE levels to cat, dog, cockroach, dust, molds (Alterneria, Aspergillus, Candida, and Penicillium), and mites. She had a normal complete blood count and differential, normal complement levels, normal T-cell subsets and normal IgA, IgM, IgE, IgG1, IgG3, and IgG4 levels. She had a low IgG level and a low IgG2 level (10% of IgG). Her response to tetanus was normal while she had low antibody titers to pneumococcal polysaccharide antigens. She was given a 23-valent pneumococcal polysaccharide vaccine at 39 months of age and post-vaccination pneumococcal titers were drawn 4 weeks later. She responded well to this booster pneumococcal vaccine with significant increases in her pneumococcal titers. Table I summarizes the patient's laboratory values at 37 months of age. Table II presents pre- and post-vaccination pneumococcal titers.

Recurrent middle ear and upper respiratory infections are commonly observed in patients with SS and are attributed to the oral-facial abnormalities that lead to Eustachian tube dysfunction. When the severity and/or frequency of these infections are above that expected from the anatomic abnormality alone, patients should be evaluated for other contributing factors. For example, a positive family history of atopy, signs and symptoms of allergic rhinitis or asthma and significant exposure to environmental allergens should prompt an evaluation for allergies. The patient had a low total IgE level and had negative serum specific IgE to multiple allergens. Skin prick testing to multiple allergens were recommended. We next evaluated our patient for immune deficiency given her frequent middle ear infections and isolated episodes of pneumonia. We found that her total IgG was below the lower limit of normal, a significant finding given her frequent infections. Moreover, the level of her IgG2 was low, 10% of her total IgG. She had a normal antibody response to protein antigens. However, despite

TABLE I. Laboratory Values at 37 Months of Age

WBC (1,000×/μl)	7.41	[5.40–11.70]
Hemoglobin (g/dl)	13.0	[10.9–13.0]
Platelet (1,000×/μl)	247	[208–410]
RBC (10^6×/μl)	4.63	[4.10–5.00]
Absolute neutrophil count (1,000×/mm^3)	3.60	[1.80–6.80]
Absolute lymphocyte count (1,000×/mm^3)	2.92	
Absolute eosinophil count (1,000×/mm^3)	0.11	[0.00–0.40]
Neutrophil/band (%)	49	[30–73]
Lymphocyte (%)	40	[16–56]
Monocyte (%)	6	[4–9]
Eosinophil (%)	2	[0–3]
Basophil (%)	1	[0–1]
Atypical lymphocyte (%)	3	[0–6]
C3 (mg/dl)	117	[83–177]
C4 (mg/dl)	22	[14–42]
Percent CD3+	63	[65–75]
Percent CD3+/CD4+	36	[35–50]
Percent CD3+/CD8+	21	[18–30]
Percent CD3−/CD16+ or CD56+	12	[5–15]
Percent CD19+	20	[5–10]
CD4/CD8 ratio	95	[95–100]
Tetanus IgG (IU/ml)	1.00	
IgG (mg/dl)	546	[600–1,500]
IgG1 (mg/dl)	394	[381–884]
IgG2 (mg/dl)	55	[70–443]
IgG3 (mg/dl)	29	[17–90]
IgG4 (mg/dl)	4	
IgA (mg/dl)	51	[50–150]
IgM (mg/dl)	42	[22–100]
IgE (μg/ml)	<5	[0–200]

TABLE II. Pre and Post Vaccination Titers

	Pre-vaccination	Post-vaccination
Pneumococcus Type 1, IgG (µg/ml)	0.11	9.28
Pneumococcus Type 12F, IgG (µg/ml)	0.37	1.21
Pneumococcus Type 14, IgG (µg/ml)	0.27	37.69
Pneumococcus Type 18C, IgG (µg/ml)	0.94	42.93
Pneumococcus Type 19F, IgG (µg/ml)	23.69	27.78
Pneumococcus Type 23F, IgG (µg/ml)	0.95	28.79
Pneumococcus Type 6B, IgG (µg/ml)	1.58	48.48
Pneumococcus Type 3, IgG (µg/ml)	0.02	1.26
Pneumococcus Type 4, IgG (µg/ml)	0.60	11.62
Pneumococcus Type 5, IgG (µg/ml)	0.29	3.10
Pneumococcus Type 7F, IgG (µg/ml)	0.76	0.82
Pneumococcus Type 8, IgG (µg/ml)	0.03	6.82
Pneumococcus Type 9N, IgG (µg/ml)	0.38	20.71
Pneumococcus Type 9V, IgG (µg/ml)	0.87	25.25

numerous middle ear infections, where *Streptococcus pneumoniae* is considered a significant pathogen [Hoberman et al., 2005] and despite having received one dose of pneumococcal conjugate vaccine, her antibody titers against pneumococcal polysaccharide antigens were low. She responded well to a booster immunization with a 23-valent pneumococcal polysaccharide vaccine at 39 months of age. Following this booster vaccination, she was free of middle ear infections and pneumonia for 15 months, the remainder of her follow-up period.

Primary immune deficiencies can be classified into five major categories: antibody deficiency, cellular deficiency, combined deficiency, phagocytic defects, and complement deficiency [Bonilla and Geha, 2003; Bonilla and Geha, 2006]. There is a wide range of manifestations with antibody deficiencies. In one extreme, patients lack B cells completely and have no serum immunoglobulin (agammaglobulinemia). Most patients with antibody deficiency have low serum levels of one or more types of immunoglobulin, such as IgA, IgM, or IgG deficiency with or without IgG subclass (IgG1, IgG2, IgG3) deficiency. Additionally, these patients may be unable to make specific antibodies to polysaccharide or protein antigens [Finocchi et al., 2002]. Another group of patients have normal serum immunoglobulin levels but are unable to make specific antibody responses to polysaccharide or protein antigens [Gross et al., 1992; Orange et al., 2006]. To establish an effective immune response to encapsulated bacteria, such as *S. pneumoniae*, a common pathogen in middle ear bacterial infections [Hoberman et al., 2005], one must be able to generate specific IgG antibodies, mainly in the form of IgG2, to the polysaccharide antigens that coat these bacteria [Sanders et al., 1995]. As a result, *S. pneumoniae* and other polysaccharide-coated bacteria are common bacterial pathogens in patients with IgG and IgG2 deficiency.

Patients with hypogammaglobulinemia often do not become symptomatic until the later part of infancy when maternal immunoglobulin levels wane. A prolonged delay in the ability to generate IgG may result in another form of antibody deficiency, transient hypogammaglobulinemia of infancy, where patients acquire normal immunoglobulin levels and normal specific antibody levels over time. In some patients, serum immunoglobulin levels normalize first while others acquire the ability to make specific antibody first [Cano et al., 1990]. Transient hypogammaglobulinemia of infancy has been shown to last beyond infancy and into early childhood. It is a diagnosis that can be made only in retrospect once patient's antibody deficiency has resolved [McGeady, 1987]. Our patient had IgG deficiency with IgG2 subclass deficiency and normal selective antibody responses. Her normal antibody responses to a 23-valent pneumococcal polysaccharide vaccine may be a manifestation of her maturing immune system. If her hypogammaglobulinemia resolves over time, retrospectively she can be given the diagnosis of transient hypogammaglobulinemia of infancy. Our patient's hypogammaglobulinemia may be a consequence of her *COL2A1* mutation, or it may be a coincidental finding. The patient's older brother also experienced numerous middle ear infections and required tympanostomy tubes three times. A thorough immunologic diagnostic work up was deferred in the patient's brother since at the time of his evaluation, he was no longer experiencing difficulty with repeated infections. However, he did have a low IgG (571 mg/dl) and a low IgA (47 mg/dl) level at 5 years of age. While one case report does not prove an association between SS and humoral immune deficiency, we have reported this patient in order to prompt clinicians that recurrent infections in patients with SS may be due to a humoral immune deficiency.

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