ARTICLE

Immunodeficiency in Patients With 49,XXXXY Chromosomal Variation

MICHAEL D. KELLER,* TERESA SADEGHIN, CAROLE SAMANGO-SPROUSE, AND JORDAN S. ORANGE

Boys affected with 49,XXXXY sex chromosomal variation have been described to have high incidence of recurrent otitis media and asthma, the cause of which is unknown. We hypothesized that primary immunodeficiency occurs in patients with XXXXY aneuploidy. To investigate this, 31 boys with known 49,XXXXY were evaluated through a multidisciplinary clinic. Screening history was performed using the ''10 Warning Signs of primary immunodeficiency'' (Jeffrey Modell Foundation), as well as by history of atopic and autoimmune conditions. Of the 31 boys, 20 had at least two warning signs of primary immunodeficiency, and five had four or more signs. Sixteen had history of recurrent pneumonia, and 15 carried the diagnosis of asthma. Of the 10 who underwent immunologic screening, eight showed some evidence of impaired antibody responses to polysaccharide antigens, and one was diagnosed with specific antibody deficiency. These preliminary results suggest a high incidence of both atopy and antibody deficiency in boys with 49,XXXXY. © 2013 Wiley Periodicals, Inc.

KEY WORDS: aneuploidy; XXXXY; antibody; immunodeficiency

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INTRODUCTION

Sex chromosome aneuploidy occurs in as many as one in 600 live births. Among these disorders 49,XXXXY is a rare syndrome resulting from double nondisjunction during meiosis. Considered to be a variant of Klinefelter syndrome, affected boys have variable intellectual disability and characteristic facial features (ocular hypertelorism, upslanting palpebral fissures, and flat nasal bridge). It is estimated to occur in one in 85,000 live male births [Gropman et al., 2010; Tartaglia et al., 2011].

Anecdotal reports as well as previous clinical reviews have noted an increased incidence of sinopulmonary infections in the 49,XXXXY population [Tartaglia et al., 2011], though no studies have previously evaluated the immune responses in these patients.

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Recurrent infections have not been reported in Klinefelter syndrome, but there is an elevated rate of autoimmune diseases, which has been theorized to relate to hypoandrogenism [Oktenli et al., 2002]. Since recurrent

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sinopulmonary infections can be indicative of antibody deficiency [Orange et al., 2012], we assessed immunity in 49,XXXXY patients. Here, we provide the first immunologic description of 49,XXXXY and suggest there may be associated deficiencies.

METHODS

Patients and families were interviewed at the Neurodevelopmental Diagnostic Center for Young Children (Davidsonville, MD), and clinical details obtained with verbal consent and IRB approval from the host institution. Patients were screened for a history of "The 10 warning signs of Primary Immunodeficiency" (Jeffrey Modell Foundation, www.info4pi.org), as well as for history of atopic and autoimmune conditions (by prior physician diagnosis). A family history was also obtained.

A retrospective review of vaccine records, prior immunologic testing, or other relevant workups was performed. Recommendations for immunologic screening were made for patients with two or more of the 10 warning signs, or for other history concerning for immunodeficiency, such as severe atopy or autoimmune phenomena. Suggested screening involved measurements of quantitative immunoglobulins (IgG, IgA, IgM), and vaccine titers to *Tetanus*, *Diphtheria*, and *S. pneumoniae*. Following screening, vaccinations and repeat testing were recommended if appropriate.

RESULTS

Clinical Details

Thirty-one patients and families were interviewed. Patient ages varied from 11 months to 17 years (median age 6.5 years). Of the warning signs of primary immunodeficiency, 20 of 31 patients had a history of at least two signs, while five had four or more signs (Fig. 1). Frequent positive warning signs were recurrent pneumonia (many of whom had >5–6 diagnosed episodes), and need for IV antibiotics. Atopic conditions were present in 30 of 31 patients, with asthma (23/31) being most common (Table I). Only one patient had history of autoimmune disease (juvenile idiopathic arthritis), and three patients had first-degree relatives with autoimmune disease. There were no known cases of immunodeficiency in family members.

Immunologic Screening and Chart Review

We recommended immunologic screening for 23 patients (20 with ≥2 signs, and three due to young age or severe persistent asthma). To date, 11 patients have had screening performed. All patients had received all CDC recommended childhood vaccinations, and 10 of 31 had additionally received pneumococcal polysaccharide vaccine (PPSV23) in the past.

Quantitative immunoglobulins were normal for age for all but one reporting patient (Table II). Eight of nine reporting patients had protective serologies to less than 50% of tested serotypes of *S. pneumoniae* (defined as ≥1.3 mcg/ml specific IgG [Orange et al., 2012]), despite all having been previously vaccinated with conjugated pneumococcal vaccine (PCV) and nearly universal histories of upper-respiratory infections. Four patients responded to boosting with PPSV23 (as defined by a fourfold increase in at least 50% of serotypes tested for ≤6 years, or 70% of serotypes for >6 years [Orange et al., 2012]). However, in two of these patients, protection waned significantly at repeat testing (Fig. 2). Titers to *tetanus* and *diphtheria* were modestly protective (defined as ≥0.1 IU) in six of eight patients tested. One patient lacked protection to *H. influenzae* despite receiving conjugated vaccine 4 years prior. Three patients had prior lymphocyte flow cytometry results, and absolute numbers of T-cells, B-cells, and NK cells were within age-matched reference values (Fig. 3).

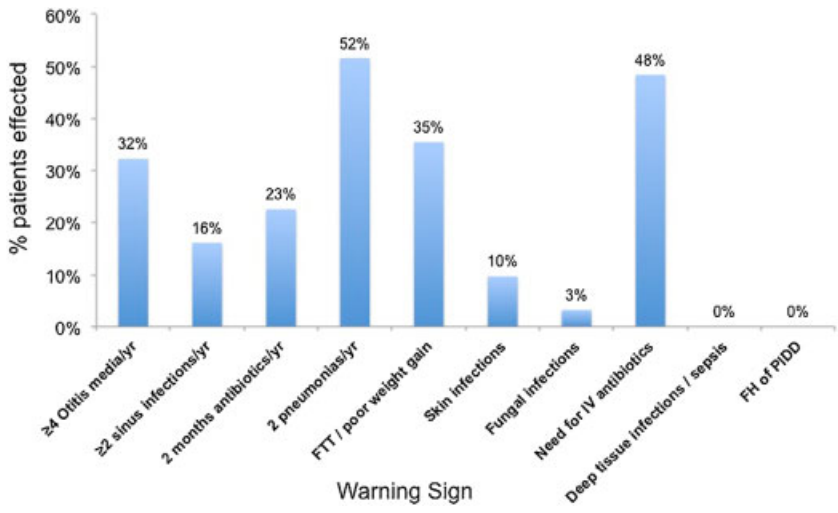

Figure 1. Warning signs of primary immunodeficiency (Jeffrey Modell Foundation) in 49,XXXXY patients.

DISCUSSION

Antibody production is the most commonly affected facet of immunity in the described forms of primary immunodeficiency [Al-Herz et al., 2011]. Humoral deficiency has been described in several forms of aneuploidy. Hypogammaglobulinemia has been reported in trisomy 8 and partial monosomy 22 [Schwanitz and Zerres, 1987; Kurtyka et al., 1988; Yu et al., 2000], while specific antibody deficiency has been reported in Down syndrome [Ram and Chinen, 2011]. The impact of aneuploidy on immunologically active genes of the X-chromosome is not known. A recent genome-wide study in common variable immunodeficiency did not yield any associated X-chromosome copy number variants [Orange et al., 2011]. Interestingly, Xq duplications are associated with facial dysmorphism, cognitive disability, and growth retardation in

TABLE I. Atopic, Endocrinologic, and Autoimmune Characteristics of 49,XXXXY

Clinical manifestations	Number (%)
Allergic	
Asthma	23/31 (74%)
Environmental allergies	11/31 (35%)
Atopic dermatitis	12/31 (39%)
Food allergy	8/31 (26%)
Drug allergy	3/31 (10%)
Endocrine	
Hypogonadism	1/31 (3%)
Hypothyroidism	1/31 (3%)
GH deficiency	2/31 (6%)
Autoimmune	
Juvenile Idiopathic Arthiritis	1/31 (3%)

boys, and recurrent sinopulmonary infections have also been reported [Hou, 2004].

Our cohort of 49,XXXXY patients demonstrated a high incidence of specific antibody deficiency (SAD). Their pattern of response to polysaccharide vaccines followed by waning immunity within months suggests a memory phenotype of SAD [Orange et al., 2012].

Our cohort of 49,XXXXY patients demonstrated a high incidence of specific antibody deficiency (SAD). Their pattern of response to polysaccharide vaccines followed by waning immunity within months suggests a memory phenotype of SAD.

This finding likely explains their high incidence of sinopulmonary infections. A high percentage of atopic conditions including asthma were also seen, though diagnosis of asthma may have been overestimated as many of the patients only have wheezing with infections without day-to-day symptoms. Another contributing factor is the presence of oromotor dysfunction in many patients with 49,XXXXY, as many patients seem to have poor airway clearance and accordingly benefit from airway clearance devices.

Clinical options for management of SAD include use of prophylactic antibiotics and immunoglobulin

TABLE II. Immunologic Data From Reporting 49,XXXXY Patients as Well as Total Warning Signs and Presence of Asthma

				Immunoglobulin quantities				S. Pneumoniae titers[a]				
Patient #	Age (years)	Asthma	Warning signs	IgG[b] (mg/dl)	IgM[c] (mg/dl)	IgA[d] (mg/dl)	IgE[e] (IU)	# Protective (pre-vaccine)	# Protective (post-vaccine)	Diphtheria titer[a]	Tetanus titer[a]	H. Influenzae titer[a]
1	8	Y	3	1,180	355	131	ND	4/14	10/14	0.11	0.81	ND
2	1	Y/viral only	3	679	44	19	8	ND	ND	ND	ND	ND
3	8	Y	2	639	70	20	ND	1/14	ND	0.13	0.11	ND
4	4	Y	3	742	69	42	74	1/14	8/14	ND	ND	2.6
5	8	Y	5	701	94	42	153	4/23	7/23	ND	0.14	0.18
6	4	Y	3	893	195	75	35	7/10	ND	2.44	0.12	ND
7	10	Y/viral only	2	1,030	79	37	ND	ND	ND	ND	ND	ND
8	6	Y/viral only	3	763	87	74	ND	3/12	ND	0.58	0.11	ND
9	7	Y	3	781	82	34	49	2/14	ND	0.152	0.1	1.8
10	3	Y	2	891	89	84	ND	6/14	ND	<0.10	<0.10	ND
11	1.5	Y	3	302	55	15	2	3/14	15/23	ND	<0.1 (0.7 post-booster)	ND

ND, not done.

[a]Protective titers were defined as follows: *S. pneumoniae*, >1.3 mcg/ml; *Tetanus*, >0.1 IU/ml; *Diphtheria*, >0.1 IU/ml; *H. influenza*, >1 mcg/ml.

[b]IgG normal ranges, Age 1 year, 345–1,213 mg/dl; 4 years, 463–1,236; >6 years, 633–1,280.

[c]IgM normal ranges, Age 1 year, 43–173 mg/dl; 4 years, 43–196; >6 years, 48–207.

[d]IgA normal ranges, Age 1 year, 14–106 mg/dl; 4 years, 25–154; >6 years, 33–202.

[e]IgE normal ranges, Age 1 year, 0.8–15 IU/ml; 4 years, 1–69; >6 years, 1–161.

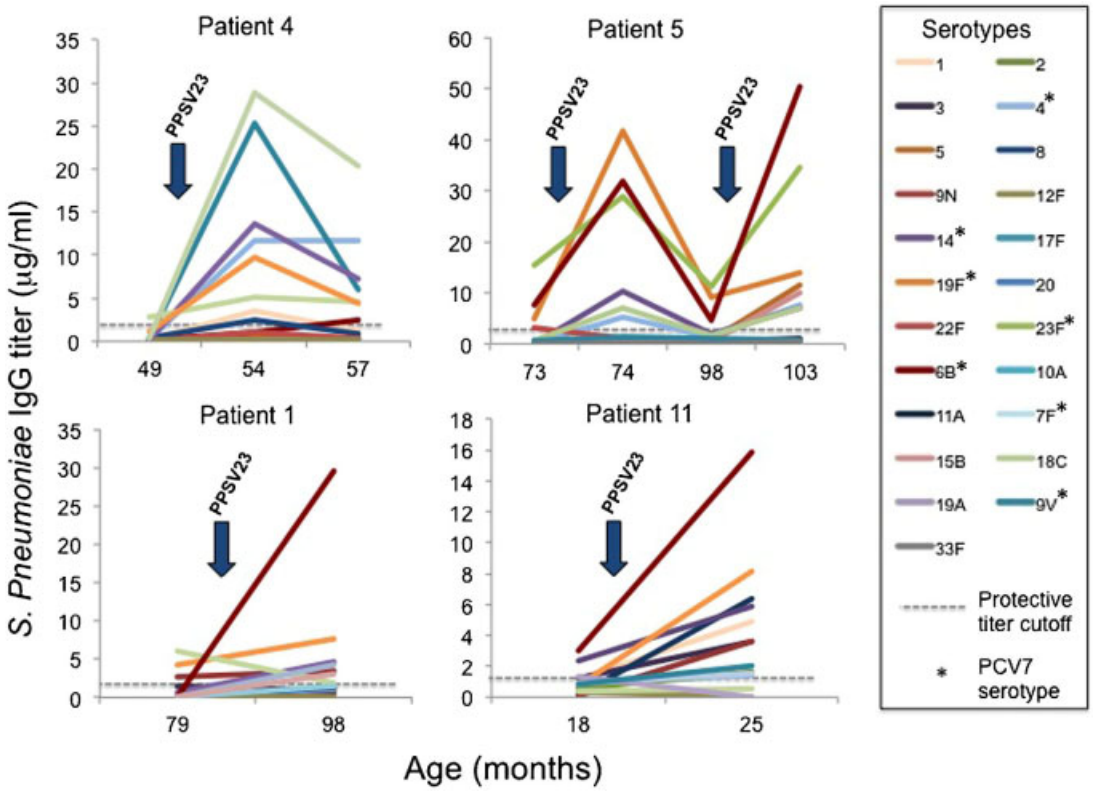

Figure 2. Titers to *S. pneumoniae* serotypes in 49,XXXXY patients showed fair response after vaccination with 23-valent pneumococcal polysaccharide vaccine (PPSV23) but subsequently waned in Patients 4 and 5.

replacement [Bonilla et al., 2005]. Frequently used prophylactic antibiotics include weekly azithromycin (10 mg/kg) or daily amoxicillin (20 mg/kg/day) [Yong et al., 2010]. Use of protein-conjugated vaccines at increased interval may also be beneficial.

In summary, a high incidence of humoral deficiency occurs in patients with 49,XXXXY. The mechanism of this deficiency, including the lyonization pattern and gene dosing of immunologically active genes of the X-chromosome, is unknown and deserving of further investigation. Patients with 49,XXXXY and recurrent respiratory tract infections should be evaluated for antibody deficiency in accordance with current diagnostic guidelines for these disorders [Bonilla et al., 2005; Orange et al., 2012].

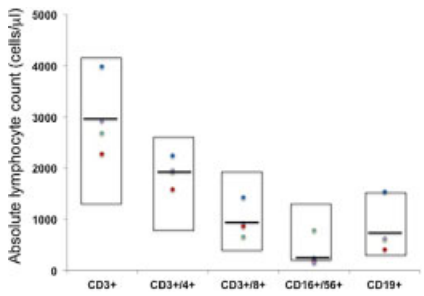

Figure 3. Lymphocyte flow cytometry in patients with 49,XXXXY were within age-matched normal ranges. Normal ranges are denoted by boxes, and the patient mean value is marked by a solid line.

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