

Allergies in patients with chromosome 22q11.2 deletion syndrome (DiGeorge syndrome/velocardiofacial syndrome) and patients with chronic granulomatous disease

Staple L, Andrews T, McDonald-McGinn D, Zackai E, Sullivan KE. Allergies in patients with chromosome 22q11.2 deletion syndrome (DiGeorge syndrome/velocardiofacial syndrome) and patients with chronic granulomatous disease. *Pediatr Allergy Immunol* 2005; 16: 226–230. © 2005 Blackwell Munksgaard

Humoral immunodeficiencies have a recognized association with atopy. This study investigated the association of a T-cell disorder (chromosome 22q11.2 deletion) and a neutrophil disorder [chronic granulomatous disease (CGD)] with asthma, eczema, and rhinitis using a standardized survey instrument. Patients were recruited from either a national referral center (chromosome 22q11.2 deletion syndrome) or from a registry (CGD). Controls consisted of siblings of patients. Chromosome 22q11.2 deletion syndrome (DiGeorge syndrome/velocardiofacial syndrome) was found to be significantly associated with both eczema and asthma but not allergic rhinitis. CGD was not found to be significantly associated with atopic diseases.

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Key words: allergy; chronic granulomatous disease; DiGeorge syndrome; velocardiofacial syndrome; rhinitis; asthma; eczema

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Accepted 23 December 2004

The association of immunodeficiencies and allergies has long been recognized. Certain immunodeficiencies have an atopic component that is characteristic of the disease. For example, Hyper IgE syndrome is nearly always associated with atopic dermatitis (1). Similarly, atopic dermatitis is often seen in Wiskott Aldrich syndrome (2). In these cases, the underlying immunodeficiency is thought to skew the immune response toward an allergic diathesis, although there is little data to support this presumption. An extreme case of this is in Omenn's syndrome where a few T-cell clones proliferate and populate the body (3). These clones are skewed toward a T helper 2 (Th2) phenotype and classic signs of allergy such as eosinophilia and atopic dermatitis are seen.

In other immunodeficiencies, atopy appears to be increased somewhat over the general population although the mechanism underlying this association is not understood. Some studies suggest that as many as 25% of IgA-deficient individuals have allergies (4–6), while others have not found an increased frequency of atopic diseases (7). Other primary immunodeficiencies

are also associated with allergies and these are often humoral immunodeficiencies. Various IgG subclass deficiencies have been found in populations with severe asthma (8, 9), although a genetic inability to produce IgG2 does not appear to be associated with allergic or infectious disease (10). Transient hypogammaglobulinemia of infancy is associated with food allergies and other signs of atopy (11). Common variable immunodeficiency is associated with a mildly increased risk of allergies (12, 13). Allergies have even been described in boys with X-linked agammaglobulinemia (14).

The cause of atopy is not known and recent genetic analyses suggest that multiple genes contribute to the overall genetic susceptibility (15–17). Studies addressing the hygiene hypothesis have demonstrated that exposures to microbial pathogens early in life confer protection from allergies (18, 19). We wished to further understand the complex relationship between host defense and allergies by studying two patient populations with very distinct immunodeficiencies. Chromosome 22q11.2 deletion syndrome is

a nearly pure disorder of T-cell production (20, 21). Infrequently there can be secondary humoral defects (22). Chronic granulomatous disease (CGD) is a nearly pure disorder of neutrophil function (23–25). There can be a mild T-cell defect, although the mechanism underlying the T-cell defect is not understood (26). These two disorders have not been previously evaluated in terms of their association with atopy.

Methods

The International Study of Asthma and Allergies in Childhood (ISAAC) survey instrument was used to investigate the occurrence of allergy symptoms in patients and unaffected siblings (27, 28). Patients with chromosome 22q11.2 deletion syndrome ($n = 53$) were identified from a large cohort previously described (29). All patients were known to have the chromosome deletion. Patients with CGD ($n = 33$) were identified from a national registry administered by the Immune Deficiency Foundation (NIH 75328). In each case, when the survey instrument was administered, unaffected siblings were recruited to participate as controls. Recruitment was restricted to patients over the age of 5 yr, however, in two cases, there were affected siblings of CGD patients slightly under the age of 5 and those were included. Birth order information was not

collected. This study was approved by the institutional review board.

Statistical analyses were performed using the Fisher's Exact test. No corrections were made for multiple comparisons, however, corrections are noted in the text. The sample sizes were sufficient to detect a 30% difference in prevalence between the chromosome 22q11.2 population and controls and a 40% difference between the CGD population and controls with a power of 0.9 and $\alpha = 0.05$ and $\beta = 0.1$. The sample size for the CGD populations taking and not taking γ -interferon is sufficient to detect a 50% difference in prevalence between the two groups with a power of 0.9 and $\alpha = 0.05$ and $\beta = 0.1$.

Results

Patients and siblings of patients were surveyed for the presence of specific allergy symptoms using a structured validated survey instrument. The instrument allows structured follow-up questions (indented in Tables 1 and 2) when a positive answer is obtained. The demographic data were very similar among all groups. The average age for CGD patients was 16.1 ± 12.4 yr, for CGD siblings it was 15.2 ± 8.7 yr, for patients with chromosome 22q11.2 deletion syndrome it was 13.2 ± 6.4 yr and for their controls it was 14.5 ± 7.4 yr. From 44% to 76% of the children had one or more parents with allergies. In most cases the allergies in the parents

Table 1. Patients with chromosome 22q11.2 deletion syndrome and sibling controls

	No. patients affected	% patients affected	No. controls affected	% controls affected	p-value	Odds ratio (CI)
Maternal history	30/53	57	30/49	61		
Paternal history	29/53	55	29/49	59		
Rural	44/53	83	45/49	92		
Pets with fur	36/53	68	37/49	76		
Wheeze ever	31/53	58	12/49	24	0.0006	4.3 (1.9–10.2)
Wheeze in last 12 months	15/31	48	8/12	67	0.1636	2.0 (0.8–5.3)
Ave no. attacks/yr	5.4		6.5		0.6580	
Wheeze with exercise	11/31	35	6/12	50	0.2954	1.9 (0.6–5.7)
Diagnosed with asthma	19/53	36	11/49	22	0.1919	1.9 (0.8–4.6)
Night cough	18/53	34	14/49	29	0.6702	1.3 (0.6–3.0)
Itchy rash ever	20/53	38	5/49	10	0.0013	5.3 (1.8–15.7)
Itchy rash in last 12 months	17/20	85	5/5	100	0.0084	4.2 (1.4–12.4)
Itchy rash in specific locations	15/17	88	5/5	100	0.0258	3.5 (1.2–10.5)
Diagnosed with eczema	15/53	28	6/49	12	0.0529	2.8 (1.0–8.0)
Runny nose without a cold	24/53	45	23/49	47	1.000	0.9 (0.4–2.0)
Runny nose without a cold in the last 12 months	23/24	96	21/23	91	1.000	1.0 (0.4–2.2)
Runny nose with itchy eyes	14/24	58	18/21	86	0.2915	0.6 (0.3–1.4)
Seasonality to symptoms	17/24	71	18/21	86	0.6792	0.8 (0.4–1.8)
Diagnosed with hayfever	11/53	21	10/49	20	1.000	1.0 (0.4–2.7)
Taking antihistamines	18/53	34	17/49	35	1.000	1.0 (0.4–2.2)

Table 2. Patients with chronic granulomatous disease and sibling controls

	No. patients affected	% patients affected	Number controls affected	% controls affected	p-value	Odds ratio (CI)
Maternal history	9/33	27	6/27	22		
Paternal history	9/33	27	6/27	22		
Rural	17/34	50	15/27	55		
Pets with fur	19/34	56	17/27	63		
Wheeze ever	14/34	41	6/27	22	0.1706	2.5 (0.8–7.6)
Wheeze in last 12 months	8/14	57	2/6	33	0.1624	3.8 (0.7–19.9)
Ave no. attacks/yr	6.2		8.0		0.8889	
Wheeze with exercise	9/14	64	1/6	17	0.0328	9.4 (1.1–79.4)
Diagnosed with asthma	9/34	26	2/27	7	0.0920	4.5 (0.9–23.0)
Night cough	7/34	21	1/27	4	0.0665	6.7 (0.8–58.7)
Itchy rash ever	10/34	29	2/27	7	0.0502	5.2 (1.0–26.3)
Itchy rash in last 12 months	9/10	90	2/2	100	0.0920	4.5 (0.9–23.0)
Itchy rash in specific locations	4/10	40	2/2	100	0.6848	1.7 (0.2–9.9)
Diagnosed with eczema	6/34	18	3/27	11	0.7184	1.7 (0.4–7.6)
Runny nose without a cold	15/34	44	11/27	41	1.000	1.0 (0.4–2.8)
Runny nose without a cold in the last 12 months	15/15	100	11/11	100	1.000	1.1 (0.4–3.2)
Runny nose with itchy eyes	5/15	33	3/11	27	1.000	1.4 (0.3–6.4)
Seasonality to symptoms	10/15	67	9/11	82	0.7861	0.8 (0.3–2.5)
Diagnosed with hayfever	6/34	18	3/27	11	0.7184	1.7 (0.4–7.6)

were limited to rhinitis. Only two parents of CGD patients had eczema. The parents of patients with chromosome 22q11.2 deletion syndrome were more evenly distributed with approximately half of the parents having rhinitis and the others having either asthma or eczema. From 50% to 92% of the respondents identified themselves as rural inhabitants. The majority of patients and controls had a fur-bearing pet in the house (56–76%).

Patients with chromosome 22q11.2 deletion syndrome were far more likely to have wheezing than controls ($p = 0.0006$, corrected $p = 0.0048$). Follow-up questions including queries of recent wheezing, number of attacks and wheezing with exercise were designed to define the likelihood of the symptoms representing asthma as opposed to other disorders. For both patients with the deletion and controls, many of the patients had manifestations such as wheezing with exercise that are more common in asthma. There were no statistically significant differences in patients actually diagnosed with asthma when patients and controls were compared.

Wheezing was almost twice as likely in patients with CGD compared to controls, however, it did not reach statistical significance. There were substantial differences in the answers to the follow-up questions, however, due to smaller sample sizes, these numbers must be interpreted cautiously.

Eczema was seen more frequently in patients with chromosome 22q11.2 deletion compared to

controls ($p = 0.0013$, corrected $p = 0.0104$). Again, the follow-up questions strongly suggest that the rash identified by the parents was indeed eczema. Patients were diagnosed with eczema more than twice as frequently as controls, however, this did not reach statistical significance.

Patients with CGD had an itchy rash more than twice as frequently as controls, however, this did not reach statistical significance due to its infrequent occurrence. The follow-up questions were again suggestive that the itchy rash identified by parents was eczema.

The frequency of rhinorrhea was nearly identical in all patients and controls. The follow-up questions suggested that a significant percentage of people with rhinorrhea had allergies. A minority of patients and controls took antihistamines on a regular basis.

To ensure that our control groups were not skewed, we compared the two control groups. There were no statistically significant differences between the two groups. The p -value for wheezing was 1.000, the p -value for people ever diagnosed with asthma was 0.1203. The p -value for people diagnosed with eczema was 1.000 and the p -value for people with hayfever was 0.3590.

We hypothesized that CGD patients receiving prophylactic γ -interferon might be protected from atopic disease. Eleven CGD patients were on long-term γ -interferon. If anything, the frequencies of patients with allergies were increased in the group receiving γ -interferon, although only the association of asthma with γ -interferon use

Table 3. γ -Interferon in CGD patients and atopic diseases

	CGD patients on IFN, n = 11 (%)	CGD patients not on IFN, n = 23 (%)	p-value
Wheeze ever	54	35	0.4575
Wheeze in past year	36	17	0.3884
Diagnosed with asthma	54	13	0.0328
Itchy rash ever	45	22	0.2318
Itchy rash in past year	36	22	0.4254
Diagnosed with eczema	27	9	0.3627
Runny nose without a cold	45	43	1.000
Runny nose without a cold in past year	36	43	1.000
Diagnosed with hayfever	36	9	0.0703

was statistically significant (Table 3). Four of 11 patients receiving γ -interferon experienced wheezing in the past year compared to 4/23 that were not on γ -interferon. Six of 11 were diagnosed with asthma compared to 3/23 not receiving γ -interferon. Three of 11 were diagnosed with eczema compared to 2/23 not on γ -interferon. Four of 11 were diagnosed with hayfever compared to 2/23 not on γ -interferon.

Discussion

The ISAAC survey instrument has been used to perform epidemiologic analyses of allergies in different settings (28). The initial findings demonstrated that among children aged 13–14 yr of age, the prevalence of asthma ranged from 1.6% (Indonesia) to 36.8% (United Kingdom), with centers in the United States reporting approximately 20% (28). The numbers of patients and controls in our study reporting wheezing in the last 12 months from our study were generally higher (7–28%). The prevalence of a pruritic rash in the past 12 months was approximately 8% in the United States ISAAC study. Again, the numbers in our study were generally higher from both types of patients and both sets of controls (7–32%). The prevalence of rhinitis was approximately 10–20% in the United States. Again, the numbers from our survey were generally higher (41–44%). Additional studies have demonstrated an increased risk of asthma with frequent antibiotic use (30). The reasons for our patients and controls both having higher rates of asthma, rhinitis and eczema might relate to the parents being more medically informed or the overall rising rate of atopy in the United States. A 2003 study of asthma in North Carolina using the same survey instrument revealed recent wheezing in 17% with 11% of the children (12–14 yr of age) actually diagnosed with asthma (31). These numbers are similar to our control populations.

The reasons for the patients with chromosome 22q11.2 deletion syndrome having increased wheezing and eczema compared to their sibling controls is likely to be complex. Surveys were limited to patients over the age of 5 yr in an effort to limit the effects of cardiac disease, nevertheless, residual cardiac disease could contribute to frequent wheezing in the patients (32). Patients are also typically exposed to numerous antibiotics early in life and that too could raise the susceptibility to asthma (30). The most obvious reason is that these patients have a significant defect in T-cell production. The T-cell defect could be associated with increased viral-induced wheezing. Additionally, dysregulated T cells could predispose to allergies, although this has not been frequently described in humans outside of Omenn's syndrome (3). In Omenn's syndrome a few T cells are produced in a patient with severe combined immunodeficiency and are nearly always of a Th2 phenotype. Expansion of these cells leads to eosinophilia, profuse eczema, and other atopic manifestations. Patients with chromosome 22q11.2 deletion have homeostatic expansion of T cells and could conceivably proceed down a similar path (33). Supporting this hypothesis are anecdotal reports of patients with a very severe immunodeficiency and the clinical diagnosis of DiGeorge syndrome who had elevated IgE levels (34). Lastly, children with chromosome 22q11.2 deletion syndrome are often perceived by the family as medically vulnerable. This could bias the reporting of atopic symptoms. Arguing against that is the group of patients with CGD who are also chronically ill but have no increase in atopic symptoms.

The association of allergies with immunodeficiencies is not a new finding. Humoral immunodeficiencies have long been recognized to have an association with allergies (4, 11, 12, 35, 36). Omenn's syndrome, Wiskott Aldrich syndrome, and immunodeficiency, polyendocrinopathy, X-linked (IPEX) syndrome are examples of T-cell disorders associated with atopy (2, 37). Thus, it appears that many types of immunologic defects can be associated with a predisposition to allergies. Additional study of these defects may provide insights into the recent epidemic of allergic disorders.

Acknowledgments

The authors are grateful for the participation of patients, parents, and physicians. The contributions of Melissa Maisenbacher, Michelle Guney, and Mark Henderson are also gratefully acknowledged. This study was supported in part by MO1 RR00240.

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