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Prevalence of atopic disorders and immunodeficiency in patients with ectodermal dysplasia syndromes

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Abstract

Background—Ectodermal dysplasia (ED) syndromes are a diverse group of disorders that affect multiple ectodermally derived tissues. Small studies and case reports suggest an increase in atopy and primary immunodeficiencies (PIDs) among patients with ED syndromes.

Objective—To determine the prevalence of clinical symptoms suggestive of atopy or immunodeficiency among a large cohort of children with ED syndromes.

Methods—A 9-page questionnaire was mailed to families who were members of the National Foundation for Ectodermal Dysplasias. The surveys were completed by parents of children younger than 18 years with a diagnosis of an ED syndrome or carrier state. Portions of the questionnaire were adapted from previously validated questionnaires developed by the International Study of Asthma and Allergies in Childhood (ISAAC).

Results—We received 347 completed questionnaires (41%). When compared with the 13- to 14-year-old children surveyed by ISAAC, we found both all-aged and age-matched children with ED syndromes, respectively, had significantly higher rates of asthma (32.2% and 37.2% vs 16.4%), rhinitis symptoms (76.1% and 78.3% vs 38.9%), and eczema (58.9% and 48.9% vs 8.2%). The prevalence of physician-diagnosed food allergies (20.7%) and PIDs (6.1%) in these ED patients also exceeded known rates in the general pediatric population.

Conclusion—This large-scale, retrospective study demonstrates a greater reported prevalence of symptoms suggestive of atopic disorders and PIDs among children with ED syndromes than the general pediatric population. A combination of genetic and environmental factors in ED syndromes may contribute to breaches of skin and mucosal barriers, permitting enhanced transmission and sensitization to irritants, allergens, and pathogens.

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Introduction

Ectodermal dysplasia (ED) syndromes include more than 190 disorders that are classified clinically by their unique combinations of ectodermal anomalies. With an estimated prevalence of 7 in 10,000 live births,[1] ED patients typically have at least 2 affected ectodermally derived tissues, including the skin, hair, teeth, nails, and secretory organs (eccrine sweat, salivary, lacrimal, and mucous glands of the respiratory and gastrointestinal tracts). The most common ED syndrome, hypohidrotic ectodermal dysplasia, has been associated with various X-linked mutations of ectodysplasin, which is a tumor necrosis factor ligand within the nuclear factor κB essential modulator (NEMO) pathway. An intact NEMO regulatory protein appears to be critical for both ectodermal development and proper immune function signaling through CD40, interleukin 1 receptor, and Toll-like receptors.[2]

Previous small studies and case reports have demonstrated an apparent increase in atopic disorders and primary immunodeficiencies (PIDs) among patients with ED syndrome.[3,4] NEMO mutations and their resultant dysgammaglobulinemia and altered cellular immune function may be one explanation for this increase.[5] Anatomical abnormalities, including breaches of skin barrier, feeding difficulties, and altered mucous production, may also impair a patient's defense against allergens and pathogens.[6]

With assistance from the National Foundation for Ectodermal Dysplasias (NFED), we sought to assess by questionnaire mailings the prevalence of clinical symptoms suggestive of atopy and immunodeficiencies in children with ED syndromes.

Methods

A study questionnaire was mailed to all parents or guardians of children younger than 18 years with a past diagnosis of either an ED syndrome or an ED carrier state who were in the NFED membership directory as of September 2006. The parents or guardians were asked to complete the questionnaire on behalf of their affected children. These parents or guardians were invited to pass copies of the mailings to other parents or guardians of children with ED syndromes who were non-NFED members for study participation. If the age and diagnostic criteria were met by the non-NFED members, their completed data were included as well.

A second mailing was sent to nonresponding NFED members 2 months after the initial mailing. These nonresponders may have been contacted up to 6 months after the initial mailing. No financial incentive was offered to the children or their parents or guardians.

The questionnaire was developed by the study investigators. Portions of the asthma, allergic rhinoconjunctivitis, and atopic dermatitis sections of this questionnaire were adapted from previously validated written questionnaires developed by the International Study of Asthma and Allergies in Childhood (ISAAC) according to the organization's use policy.[7] Portions of the immunodeficiency section were adapted from the Jeffrey Modell Foundation's published "10 Warning Signs of Primary Immunodeficiency." A retrospective study evaluated the presence of these warning signs in patients with PIDs.[8]

Forty-six children were 13 to 14 years old at the time their questionnaires were completed. Their data, along with data from respondents of all pediatric age groups, were compared with data from the Seattle, Washington, ISAACs, which exclusively surveyed 2,330 children aged 13 to 14 years for asthma, allergic rhinoconjunctivitis, and atopic dermatitis. Both χ^2 and Fisher exact tests were used to assess statistical significance. Significance was determined at $P < .05$.

The institutional review boards of Saint Louis University and Baylor College of Medicine granted approval for this case study. Written informed consent was obtained from all research participants.

Results

Eight hundred thirty-eight questionnaires were mailed to the homes of NFED members. We received 347 completed questionnaires (41%). Demographics regarding age, sex, and specific ED syndromes are given in Table 1.

Patients 13 to 14 years of age with ED syndromes, when compared with same-aged ISAAC patients (Table 2), had a significantly higher prevalence of having ever wheezed; wheezing in the last 12 months; ever having asthma; rhinitis symptoms ever; rhinitis symptoms in the last 12 months; conjunctivitis symptoms in the last 12 months; ever having a relapsing, pruritic rash; a nighttime pruritic rash in the last 12 months; and a history of eczema. Similarly, a significantly higher prevalence for each of these atopic conditions was seen when all-aged patients with ED syndromes were compared with the 13- to 14-year-old ISAAC patients.

Among the 347 patients with ED syndromes, 119 (34.3%) had a history of a reaction to a particular food (Table 3). Sixty-seven patients (19.3%) had a reaction in the last 12 months, and 55 patients (15.9%) nearly always had a similar reaction after eating the suspected food. Seventy-two patients (20.7%) received a physician's diagnosis of a food allergy, including 60 patients (17.3%) whose conditions were diagnosed by blood or skin tests.

Twenty-one of 342 patients with ED syndromes (6.1%) received a physician's diagnosis of an immunodeficiency. These patients included 6 of 335 (1.8%) who were treated with intravenous gammaglobulin. Ten yes/no questions of immunodeficiency warning signs were asked of 335 patients with ED syndromes (Table 4). Fifty-nine percent of individuals with ED syndromes had experienced at least 1 of these warning signs, and 24% had experienced 3 or more.

Discussion

This survey demonstrates a greater reported prevalence of symptoms suggestive of atopic disorders among children with ED syndromes than the general pediatric population. Seven of 8 direct comparisons revealed greater asthma symptom and diagnosis rates for patients of all ages with ED syndromes vs ISAAC patients, who showed only a higher prevalence of wheezing with exercise in the last 12 months. No other asthma, allergic rhinitis, or atopic dermatitis assessments of statistical significance favored the ISAAC patients for all-aged or 13- to 14-year-old patients with ED syndromes. We suspect that a combination of genetic and environmental factors in ED syndromes breach the skin and mucosal barriers, permitting enhanced transmission and sensitization to irritants, allergens, and pathogens. Theoretically, this excessive epidermal permeability may be a primary step in the induction of T_H2 cell responses and initiation of atopic dermatitis and the allergic march. An increased emphasis on barrier creams for patients with both atopic dermatitis and ED syndromes could potentially forestall such a progression.[9]

We have also demonstrated a higher prevalence of reported food allergy in patients with ED syndromes compared with the general pediatric population. Thirty-four percent of patients with ED syndromes report a reaction to a particular food, and 21% report having been diagnosed as having a food allergy by a physician. By comparison, the estimated prevalence of food allergy among US children younger than 3 years was 8% in a 1987 prospective study with masked food challenges.[10] Eight percent was also the reported prevalence of food

allergies in a randomized, cross-sectional survey of 40,104 children in the United States in 2010.[11] Previous surveys of the general US population estimate a food allergy prevalence of approximately 4%.[12]

Our survey reveals an increased risk of immunodeficiency in the ED population, with 6% of patients reporting a physician's diagnosis of an immunodeficiency. By comparison, PIDs have an estimated prevalence of 0.05% of live births.[13] A striking percentage of individuals with ED syndromes reported positive responses to the Jeffrey Modell Foundation's "10 Warning Signs of Primary Immunodeficiency." Those who answered yes to 1 or more, 2 or more, and 3 or more of these questions were 58.5%, 37.9%, and 24.2%, respectively. By comparison, a 2003 medical record review of 41 patients with a known PID found 1 or more, 2 or more, and 3 or more warning signs in 95.1%, 78.0%, and 60.1% of patients, respectively, before the diagnosis of an immunodeficiency.[8] The high rate of immunodeficiency diagnoses and associated warning signs is not unexpected in patients with X-linked hypohidrotic ectodermal dysplasia given their known genetic abnormalities in the NEMO signaling pathway. NEMO mutations may manifest as impaired natural killer cell cytotoxicity and impaired CD40 signaling with resultant hypogammaglobulinemia, diminished antibody response to polysaccharide antigens, and elevated IgM levels.[14,15] The anatomical anomalies, abnormal respiratory mucus, and breeches in skin barriers in patients with ED syndromes may also contribute to the increase in reported frequency of infections.

Our study has some limitations. Questionnaires alone, without clinical or laboratory evaluations, do not constitute a firm diagnosis of atopy or immunodeficiency. Recall bias is a possibility because many questions ask the patients to remember past evaluations, diagnoses, and treatments. There may also be geographic bias because all of the ISAAC patients were from the Seattle region, whereas the patients with ED syndromes were from across North America. The ISAAC patients in our comparison were all 13 to 14 years of age at the time of their participation. Our analysis compared both 13- to 14-year-old patient with ED syndromes and all children with ED syndromes who were younger than 18 years to this age-restricted ISAAC group because there were no other published ISAACs from the United States that specifically reported results in children. The ratio of boys to girls in our study (234:108) matches the known distribution of ED syndromes in children. This 2:1 ratio of boys to girls may skew atopic comparisons with ISAAC patients and the general population. Interestingly, a male predilection for atopy is seen from infancy through adolescence in the general population.[16]

Some larger questions still remain. Are the skin and mucous abnormalities of children with ED syndromes simply mimicking atopic disorders and PIDs? Which genotypes of children with ED syndromes predispose them to atopy and PIDs? The spectrum of ectodermal abnormalities is vast: cleft palates; oligodontia; impaired salivary flow rates and tearing; reduced mucous gland secretion in respiratory and gastrointestinal tracts; diminished sweating; sparse, coarse hair; dystrophic nails; lack of breast development; and absent digits. Other nonectodermal signs may include short stature and cardiac defects. Clearly, the potential atopic and immunodeficiency complications in this population are numerous. We hope that this first, large-scale national survey of ED children, which supports an increase in clinical symptoms suggestive of atopy, may lead to prospective studies to elucidate the clinical effect and biological mechanisms of these disorders in patients with ED syndromes.

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Table 1

Demographics of the study population

Demographic	No. (%) of patients
Age, y	
<5	31 (8.9)
5–8	69 (19.9)
9–12	62 (17.9)
13–14	46 (13.3)
15–18	56 (16.1)
Not reported	83 (23.9)
Sex	
Female	108 (31.1)
Male	234 (67.4)
Not reported	5 (1.4)
Ectodermal dysplasia syndrome	
Hypohidrotic ectodermal dysplasia	194 (55.9)
Hypohidrotic ectodermal dysplasia carrier	8 (2.3)
Clouston syndrome	9 (2.6)
Ankyloblepharon, ectodermal dysplasia, clefting syndrome/Hay-Wells	14 (4.0)
Ectrodactyly, ectodermal dysplasia, clefting	29 (8.4)
Focal dermal hypoplasia syndrome/Goltz	6 (1.7)
Keratitis, ichthyosis, deafness syndrome	1 (0.3)
Rapp Hodgkin syndrome	4 (1.1)
Other	33 (9.5)
Unknown	44 (12.7)
Not reported	5 (1.4)

Table 2

Atopic symptoms in all patients and age-matched patients with ED syndromes vs ISAAC patients

Question	Patients with ED syndrome, all ages, No. (%)	Patients with ED syndrome, 13- to 4-year-olds, No. (%)	ISAAC patients, 13- to 14-year-olds, No. (%)
Child has had wheezing or whistling in the chest at any time in the past	174 (51.0)[a]	26 (57.8)[b]	769 (33.0)
Child has had wheezing or whistling in the chest in the last 12 months	108 (32.0)[a]	15 (34.1)	533 (22.9)
Child has ever had asthma	109 (32.2)[a]	16 (37.2)[b]	382 (16.4)
Child has ever had rhinitis symptoms	261 (76.1)[a]	36 (78.3)[b]	907 (38.9)
Child has had rhinitis symptoms in the last 12 months	246 (72.6)[a]	32 (72.7)[b]	687 (29.5)
Child has had conjunctivitis and rhinitis symptoms in the last 12 months	139 (41.2)[a]	21 (47.7)[b]	312 (13.4)
Child has had a relapsing, pruritic rash	199 (58.4)[a]	25 (54.3)[b]	396 (17.0)
Child has had a nighttime pruritic rash in the last 12 months	24 (7.4)[a]	5 (11.9)[b]	31 (1.3)
Child has a history of eczema	198 (58.9)[a]	22 (48.9)[b]	190 (8.2)

Abbreviations: ED, ectodermal dysplasia; ISAAC, International Study of Asthma and Allergies in Childhood.

[a] $P = .001$ when comparing patients with ED syndromes with ISAAC patients.

[b] $P = .001$ when comparing age-matched patients with ED syndromes with ISAAC patients.

Table 3

Prevalence of food allergies symptoms among patients with ectodermal dysplasia syndromes

Symptom	No. (%) of patients
Has a history of a reaction to a particular food	119 (34.3)
Has had a reaction in the last 12 months to a particular food	67 (19.3)
Nearly always had a similar reaction after eating the suspected food	55 (15.9)
Diagnosed by a physician as having a food allergy	72 (20.7)
Diagnosed by a physician through blood or skin tests	60 (17.3)

Table 4

Prevalence of immunodeficiency symptoms among patients with ectodermal dysplasia syndromes

Symptom	No. (%) of patients
Child has ever had = 8 new ear infections within 1 year	75 (22.4)
Child has ever had = 2 serious sinus infections within 1 year	124 (37.0)
Child has ever had = 2 pneumonias within 1 year	35 (10.4)
Child has ever had = 2 deep-seated infections in lifetime	10 (3.0)
Child has ever had recurrent skin abscesses	23 (6.9)
Child has ever had recurrent deep organ abscesses	0
Child has ever had persistent thrush after 1 year of age	15 (4.3)
Child has ever been on antibiotics for = 2 months with little effect	70 (20.9)
Child has ever needed intravenous antibiotics to clear an infection	53 (15.8)
Child has not, as an infant, gained weight or grown normally	90 (26.9)