

Respiratory Problems in Patients With Ectodermal Dysplasia Syndromes

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The ectodermal dysplasias (EDs) are a heterogeneous group of disorders characterized by a deficiency of ectoderm- and mesoderm-derived tissues and appendages, particularly hair, skin, teeth, and nails. Many of these disorders are associated with a greater risk of respiratory disease than found in the general population. There are no published papers that comprehensively describe these findings and the possible etiologies. Patients have been reported with dramatic decrease in mucous glands in the respiratory tract. Anatomic defects, including cleft palate, that predispose to respiratory infection, are associated with several of the ED syndromes. Atopy and immune deficiencies have been shown to have a higher prevalence in ED syndromes. Clinicians who care for patients affected by ED syndromes should be aware of the potential respiratory complications, and consider evaluation for structural anomalies, atopy and immunodeficiency in individuals with recurrent or chronic respiratory symptoms.

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Key words: ectodermal dysplasia; respiratory; atopy; immunodeficiency

INTRODUCTION

The ectodermal dysplasias (EDs) are a heterogeneous group of disorders characterized by a deficiency of ectoderm- and mesoderm-derived tissues and appendages, particularly hair, skin, teeth, and nails. There are greater than 170 distinct syndromes, with various patterns of inheritance. Many of the disorders are associated with a greater risk of respiratory disease than found in the general population. The aim of this paper is to review possible mechanisms to explain the increased prevalence of respiratory disease in the ectodermal dysplasia syndromes.

One of the first comprehensive reviews of clinical issues in hypohidrotic ectodermal dysplasia (HED), the most common form of ectodermal dysplasia syndromes, was published by Dr. Angus Clarke and colleagues from the University of Wales [Clarke et al., 1987]. HED is characterized by sparse hair, abnormal dentition, and hypohidrosis due to diminished numbers and pathologically abnormal sweat glands. Clarke and his colleagues contacted 56 families with affected individuals, examined the patients in their homes and obtained labs when possible. They reported that 65% of patients reported having asthma or recurrent wheezing; 44% reported recurrent upper respiratory tract infec-

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tions in childhood; 26% reported specific allergies to foods or drugs. At that time mortality in the first year of life was reported as 21%.

A more recent review by Dr. Gert Bluschke and colleagues from the University of Innsbruck, Austria and University Hospital in Erlangen, Germany reported on a postal survey to parents of 100 children affected by HED registered with the German-Swiss-Austrian patient support group from 1999 to 2008. Interestingly, the reported mortality in the first year of life was 2.1%, with the improved survival attributed by the authors to more rapid recognition of affected individuals during infancy. It should be noted that the methodologies of the Clarke study and the Bluschke study are significantly different, such that a direct comparison of mortality rates is not possible. Recurrent respiratory tract infections were reported by 73.5% of individuals with X-linked HED, and 33.3% of individuals with autosomal HED or HED of unknown genetic origin [Bluschke et al., 2010].

Respiratory Pathology

H.R. Clouston in 1939 described an infant with HED who died with otitis media and pneumonia. Autopsy showed “almost amounting to a complete absence of mucous glands in the nasopharynx; a very few small glands were found in the turbinates and a few at the lower end of the trachea, but none in the pharynx, larynx or upper trachea” [Clouston, 1939]. Similarly, in 1965, H. de Jager described a 1-month old child with ectodermal dysplasia who presented with

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pneumonia, otitis media, and mastoiditis who died at 4 months of age. Autopsy showed “The posterior part of the lungs show extensive bronchopneumonia. The most remarkable finding, however, is the total absence of mucous glands in the pharynx, larynx, trachea, and small bronchi... mucous glands are also absent in the posterior part of the mouth and in the upper part of the oesophagus” [de Jager, 1965]. In 1971, John Beahrs and colleagues from Stanford University reported on two adult male siblings with HED and chronic bronchitis. Bronchial biopsy was performed on bronchoscopy which showed “absence of usual bronchial gland hypertrophy seen in chronic bronchitis; relatively inactive appearance of small acinar cells; metaplasia of the gland neck cells to a compact, dense cell type... goblet cells were rare” [Beahrs et al., 1971]. F. Seeliger and colleagues in 2005 reported on a 2-year old German Holstein bull with HED and recurrent coughing and serous nasal discharge. Autopsy showed “a complete lack of mucous glands in the lamina propria from the nasal cavity to the deep bronchi and bronchioli. In the nasal cavity and proximal trachea, there was an increased number of intraepithelial and interstitial leukocytes and focal squamous metaplasia of the epithelial lining, with a loss of cilia and goblet cells” [Seeliger et al., 2005].

W. Roy Smythe and colleagues from Children’s Hospital of Philadelphia published a case report in 2000 on bilateral sequential lung transplant in a sixteen year old patient with HED and a history of frequent, severe lower respiratory infections, hyperexpansion and bronchiectasis. He initially did well without recurrence of significant pulmonary disease. He ultimately succumbed a year later to overwhelming sepsis from a *Pseudomonas* mastoiditis. At the time of his death, his chest radiograph was clear, without evidence of rejection or infection [Smythe et al., 2000].

Margret Casal, from University of Pennsylvania, and colleagues in 2007 reported on postnatal intravenous administration of recombinant ectodysplasin A (EDA), the congenitally-missing protein in X-linked HED, in canine X-linked ectodermal dysplasia. Treatment restored normal lacrimation and resistance to eye and airway infections, and improved sweating, as well as normalization of adult teeth. Mucociliary clearance studies with tagged albumin showed substantial correction of tracheal clearance in the treated HED-affected dogs [Casal et al., 2007]. In a follow-up publication in 2009, Mauldin, Casal and colleagues reported on six dogs with HED injected with recombinant EDA in varying doses and times postnatally. No nasal discharge, sneezing, coughing, or respiratory distress was seen in the treated HED dogs, while the untreated dog had chronic nasal discharge and one episode of bronchopneumonia. At necropsy, dogs who received higher doses had virtually normal numbers of bronchial, tracheal and esophageal mucous glands [Mauldin et al., 2009].

Otolaryngologic Manifestations of Ectodermal Dysplasias

There have been reports of atrophic rhinitis with wide-open nasal cavities, chronic infection and foul odor, with nasal biopsies showing absence of mucous glands and cilia [Sachidananda et al., 2004; Wiesmiller et al., 2005]. Authors have generally recommended saline nasal washes. Wiesmiller and colleagues at University of Ulm, Germany, proposed submucosal cartilage

implants in addition to nasal saline washes [Wiesmiller et al., 2005]. Jennifer Shin and Christopher Hartnick, from Harvard School of Medicine, reported a survey of 69 individuals with various ectodermal dysplasia syndromes in 2004. Twenty one percent of their patients had tympanostomy tubes in place, and 33% had an abnormal hearing screen (vs. 5–15% reported in the general population) [Shin and Hartnick, 2004]. In 2007 Mehta and colleagues from Saint Louis University reported 75 patients with a variety of ED syndromes, noting increased prevalence of hearing loss, otitis media, cerumen impaction in the external ear canal, nasal crusting and concretions, epistaxis, dry mouth, and hoarseness [Mehta et al., 2007a]. Also in 2007 Mehta and colleagues from Saint Louis University and Baylor College of Medicine reported an additional 34 patients with similar findings [Mehta et al., 2007b].

Ankyloblepharon-ectodermal defects-cleft lip/palate syndrome (AEC) is an ectodermal dysplasia characterized by ankyloblepharon filiforme adnatum (eyelid adhesions), sparse wiry hair, skin erosions, nail changes, and cleft lip and/or palate. An international research symposium on AEC was held at Baylor College of Medicine in 2006. Cole and colleagues reported orofacial findings of 18 patients, ranging in age from 4 months to 30 years (mean age 7.5 years). All 18 had cleft palate. Conductive hearing loss was noted in 93% of patients; hoarseness and voice problems in 69%; otitis media or otitis externa in 100%; and 61% had required myringotomy with tubes [Cole et al., 2009].

Ectrodactyly-ectodermal dysplasia-clefting syndrome (EEC) is an ectodermal dysplasia characterized by lobster claw deformity of the extremities, clefting of the primary and secondary palate, atresia of the lacrimal system, repeated infections of eyes and upper respiratory tract, and recurrent urinary tract infections. Christodoulou et al. [1989] from Royal Children’s Hospital in Victoria, Australia noted choanal atresia as a feature of EEC. Obel et al. from University of Aarhus, Denmark in 1993 reported on immunologic function in four patients with EEC and found normal immunoglobulin levels, complement activity, lymphocyte, and granulocyte function. They concluded that recurrent infections in EEC are due to anatomic, rather than immunologic, abnormalities [Obel et al., 1993].

Atopy in Ectodermal Dysplasias

The Clarke study published in 1987 noted a 71% prevalence of eczema, 65% prevalence of asthma or recurrent wheezing, and 26% prevalence of food or drug allergies [Clarke et al., 1987]. NA Vanselow reported on seven males with HED in 1970, with data obtained from the Tecumseh (Michigan) County Health Survey. Fifty-seven percent had evidence of respiratory allergy, with or without eczema. The rate in Tecumseh County at that time was reported to be 8–17% [Vanselow et al., 1970]. In 2012, Barry Mark and colleagues from Saint Louis University, Baylor and the Cleveland Clinic reported on surveys of 347 cases registered by the National Foundation for EDs. They demonstrated a statistically significant ($P \leq 0.001$) increase in asthma, allergic rhinoconjunctivitis, and eczema in ED subjects as compared to cases reported by the International Study of Asthma and Allergy in Childhood (ISAAC). They also demonstrated a dramatically greater prevalence of food allergy (15.9–34.3% as compared to reported 4–8% in the

general US child population) [Mark et al., 2012]. Dr. A Taieb, from the Hopital Pellegrin-Enfants in Bordeaux, France has proposed a theory that atopic disorders might develop due to irritant and allergen exposure through the skin [Taieb, 1999]. Relative to body mass, the skin surface is at its maximum at birth, and it is the main interface with the environment. Skin findings and gastrointestinal tract findings are the earliest related to atopic status. Increased exposure to irritants and allergens through the skin could lead to a specific Th2 cell activation favoring the development of IgE responses to antigens. Since the EDs have significant skin abnormalities, it is conceivable that the increased reports of atopic disease could result from this early activation through the skin surface in patients with EDs. The barrier functions of the respiratory and gastrointestinal tracts are also impaired in various forms of ectodermal dysplasia syndromes, and could contribute to this propensity to atopic disease.

Immunodeficiency in Ectodermal Dysplasias

Feigin et al. [1971] from Washington University in St. Louis published a case report in 1971, describing a patient with ED who had fever, *pneumocystis carinii* pneumonia, osteomyelitis and *E. Coli* sepsis, who was found to have agammaglobulinemia. Melamed et al. from Albert Einstein College of Medicine reported on a male child who died at 16 years of age from *p. carinii* pneumonia. He had had aplastic anemia diagnosed at 8 years of age, bacterial pneumonia at 13 years of age, and recurrent upper respiratory infections. He was shown to have deficient cell-mediated anemia with low T cell numbers, poor in vitro mitogenic responses, negative skin tests for common exposures, and was found to have thymic dysplasia at autopsy [Melamed et al., 1978].

Jonathan Zonana and colleagues in 2000 first described a novel X-linked disorder of immune deficiency and HED that is allelic to Incontinentia Pigmenti and due to mutations in the IKK-gamma (NEMO) gene. These affected males with Hypohidrotic Ectodermal Dysplasia—Immune Deficiency (HED-ID) manifest dysgamma-globulinemia, with recurrent respiratory, skin, bone and gastrointestinal infections, and an excess mortality [Zonana et al., 2000].

Casal et al. in 2005 published a study examining systemic and localized humoral and cellular responses; development and function of T cells; and thymic morphology in dogs with X-linked HED. They did not demonstrate abnormalities in the HED canine immune system [Casal et al., 2005].

Mark et al. [2012] reported a dramatic increase in prevalence of reported immunodeficiencies in individuals with EDs (6% vs. 0.05% in the general population), as measured by the Jeffrey Modell Foundation's questionnaire "10 Warning Signs of Primary Immunodeficiency" and by physician-diagnosed immunodeficiency.

Rare Respiratory Conditions Reported in Ectodermal Dysplasia Syndromes

Frix and Bronson [1986] from Cook County Hospital in Chicago, IL reported on acute miliary tuberculosis in a child with HED. Cankaya reported a Turkish patient with HED and nasopharyngeal rhabdomyosarcoma [Cankaya et al., 2002]. Winter and Bates

[2002] from Radcliffe Infirmary at Oxford, UK reported squamous cell carcinoma of the trachea in a patient with HED.

Conclusions and Recommendations

A number of possible mechanisms appear to contribute to the recurrent or chronic respiratory illnesses observed in the EDs. Treating clinicians must be aware that the patient could have failure of mucous gland development; anatomic abnormalities predisposing to recurrent infection (i.e., cleft palate); atopic disorders (asthma, allergic rhinoconjunctivitis, eczema); or an abnormal immune system. Otolaryngologists recommend use of saline nasal washes to reduce the risk of upper respiratory infection and to decrease allergens in the upper airway. Patients affected by ectodermal dysplasia syndromes should be cautioned not to smoke, and to avoid working unprotected in dusty atmospheres. Presumed bacterial infections may be serious and should be diagnosed and treated aggressively. If symptoms are difficult to manage, recurrent or chronic, consideration should be given to more extensive evaluation for atopy and immune deficiency, or for other more rare conditions. Further research into immune status of individuals with ectodermal dysplasia syndromes is warranted. Similarly, research into the use of increased skin barrier protection in infants with ectodermal dysplasia is reasonable, to ascertain whether this might reduce the incidence of atopy. Further investigation into gene therapy to correct the underlying genetic etiology for the clinical manifestations of the various EDs is also warranted.

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